GlobalData.

OpportunityAnalyzer: Sepsis and Septic Shock

Opportunity Analysis and Forecasts to 2026

Healthcare

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Table 1 presents the key metrics for sepsis and septic shock in the seven major pharmaceutical markets (7MM) covered in this report—the US, 5EU (France, Germany, Italy, Spain, and the UK), and Japan—during the forecast period from 2016–2026.

Table 1: Sepsis and Septic Shock: Key Metrics in the Seven Major Pharmaceutical Markets

2016 Epidemiology	
Total Incident Population, Sepsis	2.52 million
Total Incident Population, Septic Shock	0.52 million
2016 Market Sales	
US	$2.018.1m
5EU	$629.1m
Japan	$117.1m
Total (7MM)	**$2.764.2m**
Pipeline Assessment	
Number of products in Phase II–III	9
Number of first-in-class products	6
Most Promising Pipeline Drugs	**Peak-Year Sales**
Cefiderocol (Shionogi)	$846.6m
BMS-936559 (anti-PD-L1 mAb, BMS)	$255.8m*
recAP (AM-Pharma)	$197.6m
Thrombomodulin (Asahi)	$193.6m
CYT107 (RevImmune)	$159.9m
Key Events (2016–2026)	**Level of Impact**
Launch of Shionogi's cefiderocol	↑↑
Launch of BMS' BMS-936559	↑↑↑
Launch of AM-Pharma's (Pfizer's) recAP in Japan	↑↑↑
Launch of Asahi's thrombomodulin	↑↑
Launch of new SSC guidelines	↑↑↑
2026 Market Sales	
US	$4.670.7m
5EU	$1,111.5m
Japan	$150.4m
Total (7MM)	**$5,932.6m**

Source: GlobalData, Pharma Intelligence Center [Accessed June 22, 2017]. Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan; SSC = Surviving Sepsis Campaign

*Experts cited a lack of biomarkers as major hurdle in the uptake; GlobalData anticipates that peak sales will be reached after the completion of the forecast period with the development of new biomarkers to stratify patients to this therapy.

2.1 Global Sepsis and Septic Shock Market to Experience Strong Growth on Launch of First-in-Class Pipeline Products

In 2015, GlobalData estimated the overall sales for sepsis and septic shock to be approximately $2.8 billion, comprising annual drug sales of $2.2 billion in sepsis and $0.6 billion in septic shock across the 7MM. Differences in revenue generated by disease area are due to higher incidence rates for sepsis compared with septic shock. GlobalData expects the sepsis and septic shock market to grow by a strong Compound Annual Growth Rate (CAGR) of 7.9% from 2016–2026, reaching annual sales of $5.9 billion by the end of the forecast period.

Some of the main drivers of growth of the sepsis and septic shock marketplace identified by GlobalData include the following:

- The single most important driver of growth in the sepsis and septic shock marketplace will be launch of four new first-in-class pipeline drugs, BMS-936559, recAP, Traumakine, and CYT107; and three improved therapeutic options, Selepressin, thrombomodulin, and cefiderocol. Furthermore, two new first-in-class medical devices will be launched during the forecast period in the US: Toraymyxin and CytoSorb.
- GlobalData anticipates an increased prevalence of sepsis and septic shock across the 7MM that, together with improved awareness of sepsis, will result in a larger treated patient population.
- Drug development in sepsis and septic shock will experience a boost by anticipated improvements in clinical trial design. GlobalData's primary and secondary research identified organ-specific adaptive randomized controlled trials (RCTs) as a future driver for drug development in sepsis and septic shock, as current RCTs struggle to show meaningful outcomes due to heterogeneous patient populations.

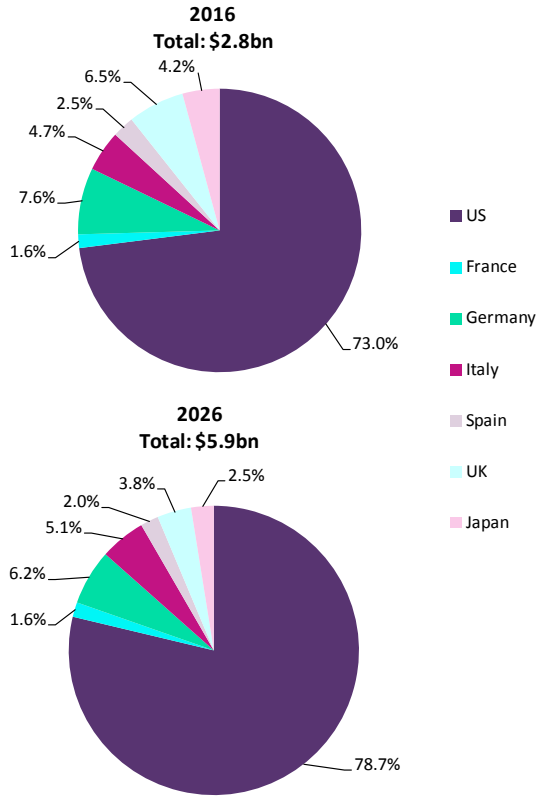
Some of the chief barriers of growth of the sepsis and septic shock marketplace identified by GlobalData include:

- Although biologics have been identified as major drivers for growth, their high annual cost is likely to represent a major barrier for physicians prescribing these medications. Cost-conscious payers are currently putting in place considerable barriers in terms of reimbursement for biologics. However, the critical nature of the disease is anticipated to mitigate barriers to higher expenditure over improvements in the current standard of care (SOC), which features generics that, while inexpensive, are not efficacious in significant proportions of the affected patient populations.

- The complexity inherent to multiple organ involvement in sepsis and septic shock continues to hinder the development of safe and tolerable agents that are effective at treating all manifestations of sepsis.
- In the absence of reliable biomarkers for sepsis, RCTs will continue to recruit over-heterogeneous patient populations. Experts anticipate that adaptive RCTs will assist in reducing the heterogeneity observed in these trials.
- Although considerable improvements in the design of RCTs led to the endorsement of both long term all-cause mortality endpoints (90 day mortality) and the use of composite organ-specific endpoints in early clinical development, late-stage failure continues to be a considerable obstacle in the sepsis drug development landscape.

Figure 1 outlines the global (7MM) sales forecast by country for sepsis and septic shock in 2016 and 2026.

Figure 1: Global Sales for Sepsis and Septic Shock by Country, 2016 and 2026



Source: GlobalData

2.2 Developers Must Leverage Innovative R&D Strategies to Target Appropriate Patients and Achieve Sustained Commercial Success

Despite a high level of engagement in the sepsis and septic shock pipeline, no new sepsis therapeutics reached market approval after Eli Lily withdrew Xigris (drotrecogin alfa [activated]) in October 2011. As drug developers in the last several years routinely failed to show a survival benefit for their pipeline products, clinicians remain sceptical about the validity of clinical studies assessing the safety and efficacy of investigational therapies across a pool of patients with high heterogeneity.

In order to combat these market realities, GlobalData believes developers will have to leverage innovative R&D strategies to establish the strong clinical evidence needed for approval and uptake post-licensure. Some of the key approaches identified by KOLs include adaptive clinical trial design, including interim analyses leveraging multiple clinically relevant biomarkers and companion diagnostics to limit heterogeneity among enrolled patients; targeting highly specific sepsis patient populations based on sepsis-induced conditions; and investigating novel targets with combination therapies that are relevant to sepsis pathophysiology. Specifically, primary research indicated that physicians were most excited about targeting sepsis patients who have become immunosuppressed and treating them with immunostimulatory compounds.

2.3 A High Level of Unmet Need Persists in the Sepsis and Septic Shock Marketplace

GlobalData classifies the overall level of unmet need in the sepsis market as high. KOLs from across the 7MM have cited the absence of licensed sepsis-specific products as the greatest unmet need across the marketplace, agreeing that clinicians would welcome the addition of novel therapies to control all the different disease manifestations observed in sepsis and septic shock patients. Interviewed experts also stressed that improving the medical community's understanding of sepsis pathophysiology will lead to the discovery of more clinically relevant targets and leads, along with novel biomarkers and companion diagnostics that will aid in drug development. Furthermore, experts stressed the importance of the development of new animal models to focus future development in human trials. GlobalData expects there will be ample opportunity for companies to pursue these unmet needs throughout the forecast period.

In the absence of approved medications for sepsis and septic shock patients, experts listed predominantly environmental needs for the pharmaceutical industry, emergency care physicians, and critical care practitioners to improve patient outcomes. A predominant need is the enhancement of efficacy in the use of currently available treatment options in sepsis. GlobalData identified a range of

RCTs examining the role of antibiotic drug monitoring, steroid use, and immunostimulating therapies in sepsis and septic shock. GlobalData's primary research revealed that improved sepsis public awareness campaigns and physician education will help to decrease mortality, primarily due to early recognition and delivery of the current basic treatment options (adequate antibiotics and fluid resuscitation). However, GlobalData believes there is still room to develop products to be delivered to the patients who do not respond to these basic and non-specific initial treatment options.

2.4 Opportunities Remain for Current and Future Players to Develop Therapies Targeting Sepsis-Specific Pathophysiology

While well-established interventions such as antibiotics, fluid resuscitation, and mechanical organ-specific support are poised to reduce sepsis and septic shock mortality and morbidity, experts stressed the importance of improving these treatment options in order to address patients who are not responsive to current SOC. Experts interviewed by GlobalData also welcomed the development of innovative immunomodulatory agents that target sepsis-specific pathophysiology. KOLs were particularly excited about the potential of immunostimulatory agents and their ability to treat the subpopulation of patients with sepsis-induced immunosuppression, but also cited the opportunity to develop agents that correct for the imbalanced inflammatory response that is characteristic to all sepsis patients.

Opportunities will also exist for firms developing novel therapies that target comorbid conditions, with products currently in development targeting sepsis patients with disseminated intravascular coagulopathy (DIC), acute lung injury (ALI), and acute kidney injury (AKI) as examples of this approach. GlobalData ultimately views innovative clinical trial design, companion diagnostics, and proper patient targeting to limit heterogeneity as crucial for the successful licensure of developmental products, particularly those aimed at modulating a patient's immune response.

2.5 Immunomodulating Therapies Poised to Transform Sepsis and Septic Shock Market, but Missing Biomarkers Will Limit Their Utility

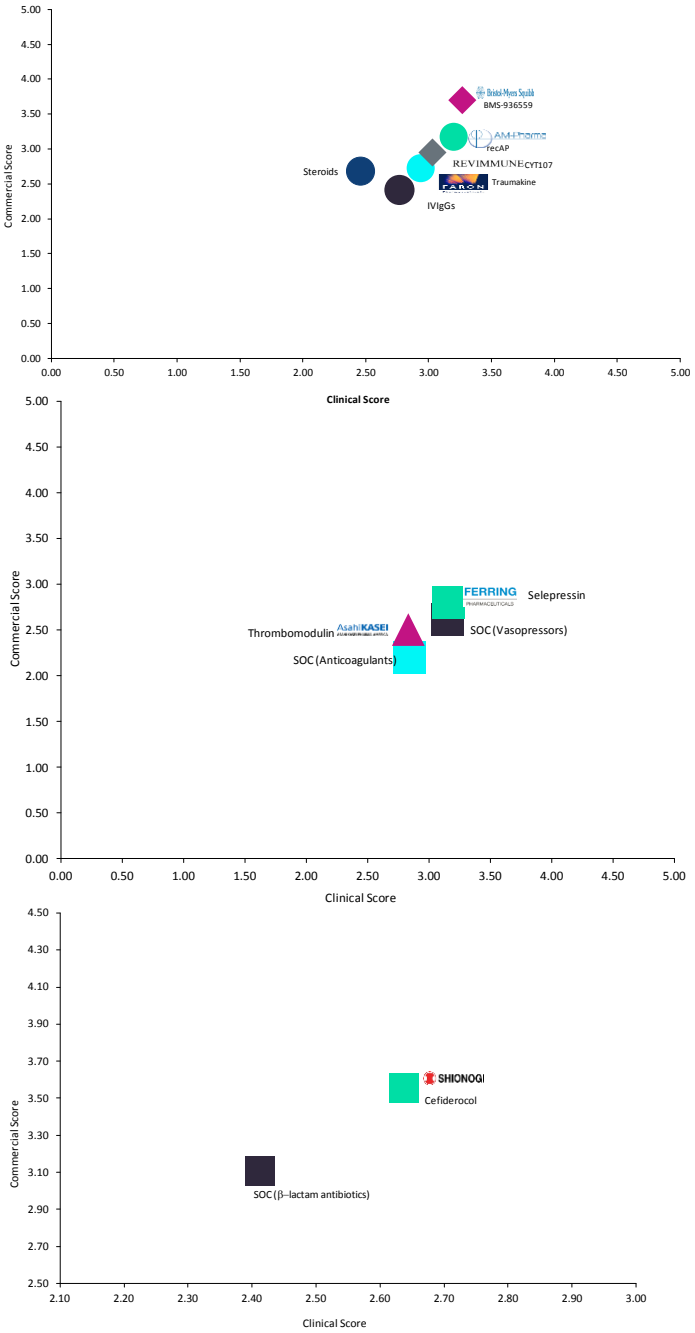
Experts expressed particular enthusiasm about the development of immomodulatory agents to directly intervene with sepsis-induced immune responses. GlobalData anticipates BMS' checkpoint inhibitor, BMS-936559, to be a leading first-in-class therapeutic in the sepsis and septic shock market. While physicians were also very optimistic about RevImmune's IL-7 therapy, CYT107, as a potential first-in-class therapy, GlobalData anticipates CYT107 to be launched after BMS-9356559, as RevImmune is anticipated to initially struggle securing the necessary funding for late-stage clinical development.

In terms of treating specific-organ dysfunctions, experts foresee AM-Pharma's recAP as a very promising approach for sepsis-induced AKI. The currently available clinical data on the bovine alkaline phosphatase (AP) are seen as encouraging in the community, while AM-Pharma's adaptive clinical trial design is highly praised among experts interviewed by GlobalData. Faron's Traumakine, although not currently assessed in sepsis-specific patient populations, is seen as a potential future treatment option for sepsis-induced ALI.

On a basic needs level, experts welcome the launch of Asahi's thrombomodulin and Ferring's selepressin. In the ever-increasing response failures to the currently available vasopressors in septic shock patients, physicians are eagerly awaiting the addition of Ferring's Selepressin to their future treatment armament. However, the majority of physicians interviewed by GlobalData foresee antimicrobial therapy to remain at the forefront in the treatment of sepsis and septic shock patients. GlobalData anticipates that Shionogi's cefiderocol will be a dominant player in the sepsis and septic shock market.

Figure 2 presents the competitive assessment of the marketed and pipeline drugs benchmarked against the closest SOC approaches.

Figure 2: Competitive Assessment of Marketed and Pipeline Agents in Sepsis and Septic Shock, 2016–2026



Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

2.6 What Do Physicians Think?

KOLs from across the 7MM who were interviewed for this report shared their expert insights on the sepsis and septic shock market. The treatment of sepsis and septic shock has experienced a considerable amount of changes in not only an improved understanding of the disease etiology and pathophysiology—as cemented in the updated SEPSIS-3 consensus definitions—but also in improvements in the SOC due to the results of the ARiSE, ProCESS, and ProMISe RCTs, which have been adopted in the updated international SSC guidelines in 2016.

"I think right now we're trying to learn from our mistakes and trying to not do harm.If we've learned anything in the last 25 years in supportive care, it's to not add insult to injury.The standard ventilatory setting 20 years ago was 15 [too high]. It turns out that it seemed fine, and people seemed really comfortable, and it improved their gas exchange. The trouble is, it's overstretching the alveoli, and causing volume trauma to the alveoli, and actually causing ventilator-induced lung injury, right? So, for years and years, we were actually making people worse. It wasn't until the ARDS trials done about ten years ago showed quite convincingly that 6mL is better than 12mL. Now, everybody uses 6mL. So, there's an example where we overdid things."

US Key Opinion Leader

"People speak about SEPSIS-3 definitions, yes, but I wanted the three to be deleted because since Hippocrates sepsis has been putrefaction. That's what it means in Greek:'sepein' means 'putrefaction.' It was very different from just fever and tachycardia and altered white blood cell count. Over the years, people have claimed that the number of sepsis cases has increased over time, but the mortality rate has decreased dramatically. This is just a reporting phenomenon. It's because people were urged to tick the box 'sepsis' for any infection, so they added infections to sepsis. So the numbers increased tremendously and obviously the mortality rates went down because they added minor cases. This is now well recognized as a reporting phenomenon, where sepsis is not as common as sometimes reported."

EU Key Opinion Leader

Physicians are cautiously optimistic—while they are excited about the variety of new pipeline agents currently in clinical development, most experts are also cautious about potential late-stage failure, dampening their hopes to further reduce mortality and long-term morbidity in this devastating disease.

"We hope that the new [SEPSIS-3] definition makes clear that sepsis is reserved as a term for patients with a septic infection and organ dysfunction, that we now address a more severely ill population. This

is also very important for future trials on sepsis, because in the past [trials over the last 25 years] mortality in the control group was much lower than expected….This is because the definition had not been standardized. So, we hope in future trials, that we address a more severely ill population with a hospital mortality rate of 40%."

EU Key Opinion Leader

"I think if you don't invest enough money in the drug and the trials, you will not be able to bring it to market, and so more and more single [Phase III] trials are unlikely to bring a drug to market. If you don't have the money to do a large Phase III trial, then you're going to fail. However, I remain optimistic about a couple of the upcoming clinical results in sepsis."

US Key Opinion Leader

Physicians shared their views about current treatment options and identified the areas where pharmaceutical developers should address in order to launch successful products in this marketplace.

"There's not a single definitive test [for sepsis]. For cancer there's biopsy, and if you've got neoclassic cells, you've got cancer. Or, if we think you might have diabetes, if your blood sugar is over 120, there's a syndrome of diabetes, but there's also a specific diagnostic test.In sepsis, we really don't have that. The diagnosis is a compilation of physiologic abnormalities, laboratory studies, [and] microcirculatory changes; a lot of things are going on, none of which we can say with certainty that a single one of any of those would make the diagnosis. So, yes, I wish it was easier [to diagnose patients with sepsis and septic shock], and people have been trying for a long time to come up with a specific test [for sepsis], but, to date, that hasn't arrived."

US Key Opinion Leader

"Obviously we need new antibiotics. That's absolutely well recognized by everybody. For a number of microorganisms, we no longer have any antibiotic really effective, especially with microorganisms that may become resistant to colistin. It's really a nightmare. We need some new antibiotics. If you go to fluids, well, we need some new crystalloid solutions that would reproduce better the composition of our plasma. That's doable, but the industry is reluctant to such a formula because they are concerned about the fact that the authorities may request some prospective randomized control trials which would be too expensive for them.When you are the Baxter or the Brown Company, you don't want to have to start a big trial to show that your IV fluid is safe and is potentially beneficial."

EU Key Opinion Leader

"I'd say compromised hosts [patients] are our greatest challenge. A patient will experience a temporary reprieve, but in the long term will end up dying from an infection. And in those cases, antibacterial drugs lose their efficacy. That is probably because of some issue with the patient or because of long-term use of antibacterial drugs—an iatrogenic infection—but I do feel our limitations when patients die because of an infection. So, I suppose infection control is our biggest challenge, as patients end up dying from an infection."

Japan Key Opinion Leader

"I think that adaptive response trials are changing the methodology, we need to base clinical trials on bioavailability. You know, a lot of our clinical trials, they didn't even measure the bioavailability of the agents that we were testing."

US Key Opinion Leader

"Sepsis is a syndrome, which makes it hard to talk about a wonder-drug that would cure all the associated symptoms. It is extremely difficult to get a single drug for sepsis, so research needs to focus on specific areas such as bacteria or the source of infection. As part of that, there could be a focus on antibiotics or on boosting immunity levels at certain times. Management of areas such as respiratory circulation is fairly well advanced, but at the end of the day it is infections that are causing patients to die. So it is probably important to have research into immunomodulatory agents and the best timing for having them administered. Or research in to modulation of white blood cell functions. The coagulation system is intrinsically linked to white blood cell function, so it would be helpful to have a drug that supports coagulation functions as well as fighting infections."

Japan Key Opinion Leader

3 Introduction

3.1 Catalyst

Sepsis is a complex disease, which not only involves a wide array of causative agents, but also results in different individual immune responses causing various single or multiple organ dysfunction(s). In late 2016, the sepsis and septic shock market abandoned the concept of a systemic immune response syndrome in the presence of an infection as a potential cause for sepsis; in the new consensus definitions, sepsis is defined as an infection leading to organ dysfunction. Currently, treatment for sepsis relies on the rapid administration of antibiotics and fluid resuscitation in order to fight the infection and regain organ function, along with the use of vasopressors in order to correct for the persistent hypotension seen in septic shock. Past clinical development of drugs has been hampered by late stage failures due to the recruitment of heterogeneous patient populations. Recent advances in clinical trial design, particularly the adoption of adaptive clinical trials, has awakened the hope of new pipeline products entering the sepsis and septic shock marketplace. However, GlobalData's primary research indicated that clinical success will depend on the development of reliable biomarkers to stratify patients to new pipeline drugs. However, physicians remain cautious, as the development of reliable biomarkers to stratify patients to new pipeline drugs are lagging behind the anticipated launch dates of these drugs during the forecast period.

Today, the sepsis and septic shock market is dominated by generic products, as the management of patients with sepsis and septic shock is mainly relying on antimicrobial therapy, fluid resuscitation, vasopressors, anticoagulants, steroids, and immunoglobulin therapy. The competition is high for these therapies, and the market is saturated with many suppliers of inexpensive generics. The sepsis and septic shock market is anticipated to experience the arrival of four new first-in-class pipeline drugs, BMS-936559, recAP, Traumakine, and CYT107; and three improved therapeutic options, selepressin, thrombomodulin, and cefiderocol; as well as two new hemoperfusion devices, Toraymyxin and CytoSorb.

GlobalData projects the global sepsis and septic shock marketplace—which, for the purposes of this report, comprises seven major pharmaceutical markets (7MM: US, France, Germany, Italy, Spain, UK, and Japan)—to experience strong growth during the forecast period, driven by the following dynamics:

- The single most important driver of growth in the sepsis and septic shock marketplace will be launch of four new first-in-class pipeline drugs (BMS-936559, recAP, Traumakine, and CYT107) and three improved therapeutic options (selepressin, thrombomodulin, and cefiderocol).

- GlobalData anticipates an increased prevalence of sepsis and septic shock across the 7MM that together, with improved awareness of sepsis, will result in a larger treated patient population.
- Drug development in sepsis and septic shock will experience a boost by anticipated improvements in clinical trial design. GlobalData's primary and secondary research identified organ-specific adaptive randomized controlled trials (RCTs) as a future driver for drug development in sepsis and septic shock, as current RCTs struggle to show meaningful outcomes due to heterogeneous patient populations.

3.2 Related Reports

- GlobalData (2017). OpportunityAnalyzer: *Clostridium difficile* Infections – Opportunity Analysis and Forecasts to 2026, July 2017, GDHC070POA
- GlobalData (2017). PharmaPoint: Human Immunodeficiency Virus (HIV) – Global Drug Forecast and Market Analysis to 2025, April 2017, GDHC135PIDR
- GlobalData (2016). PharmaPoint: Hepatitis C Virus Therapeutics – Global Drug Forecast and Market Analysis to 2025, December 2016, GDHC129PIDR
- GlobalData (2016). PharmaPoint: Seasonal Influenza Vaccines – Global Drug Forecast and Market Analysis to 2025, October 2016, GDHC130PIDR
- GlobalData (2016). PharmaPoint: Meningococcal Vaccines – Global Drug Forecast and Market Analysis to 2025, May 2016, GDHC115PIDR

3.3 Upcoming Related Reports

- GlobalData (2017). PharmaPoint: Hospitalized Gram-Negative Infections – Global Drug Forecast and Market Analysis to 2026, to be published
- GlobalData (2017). OpportunityAnalyzer: Malaria – Opportunity Analysis and Forecasts to 2026, to be published

4 Disease Overview

4.1 Etiology and Pathophysiology

4.1.1 Etiology

Sepsis is a multifaceted disease that lacks a well-defined etiology and pathology. As a result, the condition's definition is constantly evolving. Bacteria, viruses, fungi, and parasites (alongside their corresponding toxins) are thought to be responsible for causing the physiological changes associated with sepsis, such as activation of both pro- and anti-inflammatory host responses and other non-immunologic coagulation, metabolic, and cardiovascular pathways—all of which can result in organ dysfunction and death if left untreated (Singer et al., 2016). However, it is unclear if these exogenous agents are the sole causes of sepsis. The occurrence of sepsis depends on multiple factors, such as the type of the invading pathogen and its toxins, as well as the host's immune response to the pathogen challenge.

Sepsis is a multifaceted disease that lacks a well-defined etiology and pathology. As a result, the condition's definition is constantly evolving.

4.1.1.1 Disease Definition

Sepsis is a complex disease that not only involves a wide array of causative agents, but also results in different individual immune responses, causing various single or multiple organ dysfunctions. To date, there is no golden standard for sepsis diagnosis or treatment (Singer et al., 2016).

As of February 2017, the sepsis field has experienced three major iterations of refined disease definitions. The first consensus definition for sepsis arrived in 1992 (SEPSIS-1), where the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) defined sepsis as a systemic immune response syndrome (SIRS) in the presence of a known or suspected infection, whereas severe sepsis and septic shock were defined as progressive stages towards organ dysfunction and organ dysfunction plus hypotension, respectively (Bone et al., 1992).

In 2001, the SCCM, the European Society of Intensive Care Medicine (ESICM), the American College of Clinical Pharmacy, the American Thoracic Society, and the Surgical Infection Society recognized the limitations of SEPSIS-1 and introduced the "PIRO" (predisposition, infection, response, and organ dysfunction) staging system, known as SEPSIS-2, to assess risk and predict sepsis outcomes (Levy et al., 2003).

"[The PIRO score system] is not a great discovery; it's just a way to put the elements together. P [stands for] pre-disposing factors like age, immunosuppression, alcoholism, maybe even genetic factors in the future… The I is infections. There are two components. One is the source, when you can define it, being the lungs, the abdomen, the urine, et cetera, and the other one is the type of

microorganisms when you can define it.Then you go to R, that's the response. That would be the C-reactive protein levels, the CRP levels, or the procalcitonin levels, PCT. You could also put fever, the tachycardia, the altered white blood cell count there.Then you have the O, which is the organ dysfunction with the six major organs which are listed in the SOFA [sepsis-related organ failure assessment] score:cardiovascular, respiratory, renal, neural, hematological, and liver."

US Key Opinion Leader

Table 2 highlights the PIRO system introduced by SEPSIS-2.

Table 2: Guidelines for Stratification of Patients with SIRS, Sepsis, Severe Sepsis, and Septic Shock

Variables	Laboratory Results	Clinical Findings
Predisposing factors	Genetic abnormalities	Comorbidities
Infection	Identification of causative microorganisms	Site of infection; specific causative pathogen(s)
Response	WBC, coagulation profile, c-reactive protein levels, and lactate levels	Core temperature, heart rate, blood pressure, and cardiac function
Organ Dysfunction	PaO_2/FiO_2 ratio, bilirubin, creatinine, and CSF chemistry	Glasgow Coma Scale, urine output, and capillary refill

Source: GlobalData; Dellinger et al., 2013; Lyle et al., 2014; Remick, 2007; Sagy et al., 2013; Samraj et al., 2013

CSF = cerebrospinal fluid; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen; WBC = white blood cell

In 2016, the ESICM and SCCM convened a consensus meeting to define sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection (SEPSIS-3) (Singer et al., 2016). GlobalData notes that although internationally endorsed and recognized, to date the SEPSIS-3 definition lacks the support of the ACCP, the Infectious Disease Society of America (IDSA), and the Centers for Medicare & Medicaid Services (CMS), representing the majority of emergency departments (EDs) and intensive care units (ICUs) in the US.

4.1.1.1.1 SEPSIS-3 Consensus Definition

As of February 2016, sepsis is defined by the Third International Consensus Consortium as a life-threatening organ dysfunction caused by a dysregulated host response through both immunological and non-immunological pathways due to an underlying infection, thereby moving away from the concept that sepsis is a result of the host immune response only, as defined by a systemic inflammatory response syndrome (SIRS) to infection (Bone et al., 1992; Singer et al., 2016). In SEPSIS-2, SIRS was used to describe a non-specific inflammatory response to various conditions, including but not limited to: pancreatitis, severe trauma, ischemia/reperfusion injury, burns and sepsis. In SEPSIS-3, the sequential sepsis-related organ failure assessment (SOFA) score is used as a surrogate measure for organ dysfunction, while quick SOFA (qSOFA) was introduced as a clinician-centric tool to identify patients with high mortality risk (Singer et al., 2016). At the same time, SEPSIS-3 simplified the disease

definition by removing the term "severe sepsis," as it already defines sepsis as life-threatening organ dysfunction. Septic shock is now defined as sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of 65mmHg or more and having a serum lactate level of more than 2mmol/L despite adequate volume resuscitation (Singer et al., 2016).

"The first consensus definition conference was in 1991, Dr. Roger Bone put together a concept which has been helpful but not perfect. Sepsis was initially defined as a syndrome that was driven by an infection that was accompanied by [SIRS]. In 2001, there was an attempt to improve upon the definitions, because they'd run into some problems with understanding what exactly was meant by the original criteria.It was found to be overly sensitive, and not very specific. Now, in 2016, they published a paper in Journal of the American Medical Association, the Journal of the American Medical Association, which was the third iteration of an attempt to come up with a consensus definition. Here, there were some changes made which are small, but probably important in the pathophysiology [of sepsis].[SIRS] has been down regulated to not being important, but still helpful."

US Key Opinion Leader

"[With the SEPSIS-3 consensus definition], we wanted to go back to the common use of the word sepsis which is infection plus organ dysfunction attributed to it. If you ask any doctor what a septic patient is, 'Who was the last septic patient you saw?' the doctor will say, 'This patient had an infection plus hypotension,' or oliguria or a low platelet count or something else. If you indeed refer to the true definition of sepsis and the genuine criteria, then in the ICU where I work, we see at least one a day in a big department like ours. So I would say that we see maybe fifteen patients a week or 70 patients a month. It's quite common in a large department such as ours, which includes 35 beds."

EU Key Opinion Leader

"Sepsis is only to be used now when somebody has an infection with a host response which has resulted in organ dysfunction at a site remote from the site of infection. So, there's no such thing as 'severe sepsis.'Any sepsis is severe, so, we did away with the term 'severe sepsis' and just call it 'sepsis' now, and want it to be used when there's a bad infection that's caused a host response, that's actually adding injury to the host.By remote organ dysfunction, whether it's developing disseminated-intravascular coagulation, or decreasing mental status, or causing acute bone injury, or liver injury, whatever. Something has to be happening that tells you the patient's not dealing well with this process and that they need immediate attention."

US Key Opinion Leader

"Then, the term 'septic shock', which require three things. One of which is hypotension, low blood pressure, that's refractory to a simple fluid channel, so it's not just the patient is hypovolemic, because they've had bad diarrhea or had high fever for a long time and become dehydrated. If that's the case, you give them IV [intravenous] fluids and they're better. These are patients who are refractory to standard fluid challenge, and require vasopressors. So, they require artificial, drug-induced vasoconstriction to keep their blood pressure up to a reasonable level, and that is set at a mean arterial blood pressure of 65mL of mercury. Then, they have to have some elevation in their blood lactate level. So, that's the current definition, and the elevated lactate level was debatable, but the long and the short, we decided that, if it's greater than two micromole per liter, then that's too much lactate, and that would be the definition."

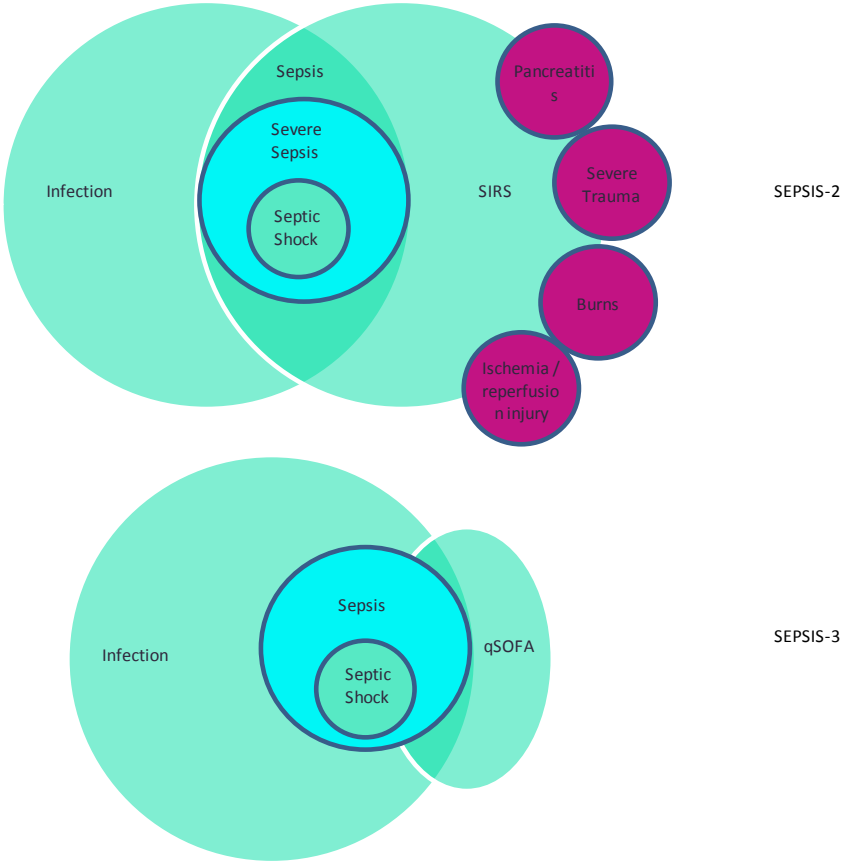
US Key Opinion Leader

"Opinion seems to be split on the subject [sepsis consensus definition], but personally I am impressed with qSOFA. The overriding principle must be to find and treat sepsis as quickly as possible. Of course, speedy diagnosis and speedy treatment is important in every condition, and that is precisely why qSOFA is impressive. However, qSOFA has been criticized by specialists in basic medical sciences, because it cannot be applied to animals."

Japan Key Opinion Leader

Figure 3 highlights the current and past sepsis definitions and their assessment measures.

Figure 3: Sepsis Definition and Diagnosis Criteria as Outlined in SEPSIS-2 and SEPSIS-3



Source: GlobalData

4.1.1.1.2 Motivation for SEPSIS-3

The motivation for updating the 1992 sepsis definition (SEPSIS-2) arose from a high sensitivity and low specificity of the existing SIRS criteria in identifying patients with possible sepsis within ICUs, and an enhanced understanding of sepsis pathophysiology.

The motivation for updating the 1992 sepsis definition (SEPSIS-2) arose from a high sensitivity and low specificity of the existing SIRS criteria in identifying patients with possible sepsis.

"I would say the sepsis numbers have been diluted by patients who had serious signs of infections but not sepsis [SEPSIS-2], so it was named sepsis because of economic reasons, but they had a very low mortality rate, below 5%. This [SEPSIS-2 criteria] diluted all our research on epidemiology, and is one of the explanations why the numbers are so different between countries."

EU Key Opinion Leader

A retrospective database study across 24 European countries identified 93% of all patients admitted to the 198 study ICUs with suspected sepsis based on SIRS criteria (Sprung et al., 2006). A further prospective study on 3,708 patients admitted to three ICUs and three general wards in the US showed that 2,527 patients (68%) met SIRS criteria leading to suspected sepsis. A more recent retrospective analysis outside the ICU at five hospitals in the US showed that about half of all patients met SIRS for suspicion of sepsis (Churpek et al., 2015). Another retrospective research study on nearly 1.2 million patients from 172 ICUs in Australia and New Zealand, from 2000 through 2013, identified 109,663 patients with organ dysfunction and infection using SOFA criteria, whereas only 96,385 patients (87.9%) were identified with sepsis using SIRS criteria as screening tool (Kaukonen et al., 2015).

While these studies have resulted in substantial additional cost burden and potential over- or under-diagnosis of sepsis in clinical practice, SIRS as entry criteria for randomized controlled trials (RCTs) have resulted in recruitment of patient populations that are too heterogeneous for evaluating drug effectiveness, resulting in accrual of late-stage failures in sepsis trials (Kaukonen et al., 2015; Marshall, 2014). In addition, studies on sepsis pathophysiology have shown that sepsis not only involves a complex interplay of both pro- and anti-inflammatory responses, but also results in major modifications of non-immunologic pathways (cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation), which all have prognostic value in determining sepsis, thereby deserving recognition in an updated definition of sepsis (Singer et al., 2016).

4.1.1.1.3 Current State of Sepsis Management in Research and Clinical Practice

The introduction of SEPSIS-3 has resulted in a continuing cleft between research and clinical practice. The new consensus definition of sepsis as outlined in SEPSIS-3 was the result of concerted efforts from the SCCM and the ESICM. Although SEPSIS-3 has been endorsed by all major professional societies in the 5EU and Japan, in the US many societies haven't endorsed this sepsis definition yet. The societies that have endorsed SEPSIS-3 include the American Thoracic Society, the American Association of Critical Care Nurses, and recently the Surviving Sepsis Campaign (SSC) by the release of their updated sepsis guidelines (Rhodes et al., 2017; Singer et al., 2016).

"We hoped to provide clarity to the field [with SEPSIS-3]. I think that the change to infection, sepsis, and septic shock more actually refers to the way clinicians use those terms.So, I do think I'm happy with the way we clarify them.However, because of some of the regulatory agencies in the United States that do not use the new definitions...I worry that it's created more confusion rather than clarification.So, that's a long way of saying I believe that the new definitions are good, but because ICD-10 will change slowly, it creates a lot of problems for clinicians."

US Key Opinion Leader

Many clinicians, particularly those working in EDs and ICUs, are not following the SEPSIS-3 criteria. Indeed, the ACCP, IDSA, and any of the emergency and hospital medicine societies are currently following treatment guidelines from the CMS, which have not yet endorsed SEPSIS-3. Clinical research has already started adopting the new sepsis definition in their patient entry criteria in order to recruit a more homogenous patient population, due to the higher specificity of qSOFA over the SIRS criteria (Churpek et al., 2015; Freund et al., 2017; Societe Française de Medecine d'urgence, NCT02738164). GlobalData believes that the current consensus definitions outlined by SEPSIS-3 will have a considerable impact on future sepsis research, but clinical practice in the US won't adapt to these changes any time soon.

"These problems [adoption in SEPSIS-3 consensus definition] are specific to the US because [CMS] has a nationally mandated sepsis reporting initiative. They have announced that they will not adopt the new definitions. So, in the US, I think it's going to be very slow to adopt these new definitions, because right now the reporting to the federal government has to be in the old definitions."

US Key Opinion Leader

"[Given the new SEPSIS-3 definition], I think you'll see researchers start to just describe clinical trials in terms of sepsis and septic shock [patients]. I think in the same way [as] the Surviving Sepsis campaign guidelines, we adopted sepsis and septic shock as the terminology. I think…when we develop new clinical trials, we will call it sepsis and septic shock, instead of severe sepsis and septic shock. So, I think a lot of the new clinical trials are going to be in [patients with] sepsis, not severe sepsis."

US Key Opinion Leader

"The problem is, if I describe sepsis and not severe sepsis, and I bill for severe sepsis, the third-party payers can reject my claim because they'll say, 'Oh no, you've written sepsis, so you can't up code for severe sepsis.' I get a lot of emails from people who are having their claims rejected because they're billing for severe sepsis, and writing the new definition of sepsis. So, it's creating a lot of confusion. So, what's happening is the ICD-10 code is still severe sepsis, so if you want to be reimbursed, whether as a provider or as a hospital for the higher cost code, you have to bill the ICD-10 code that still says severe sepsis."

US Key Opinion Leader

4.1.1.1.4 SEPSIS-2 Diagnosis Criteria: Infection and SIRS

Table 3 summarizes SEPSIS-2 diagnostic criteria for sepsis, severe sepsis, and septic shock.

Table 3: SEPSIS-2 Diagnostic Criteria (SIRS, Sepsis, Severe Sepsis, and Septic Shock)

SIRS (≥2 meets diagnostic criteria)
Temperature >38°C or < 36°C (>100.4°F or <96.8°F)
Heart rate >90 beats/minute
Respiratory rate ≥20 breaths/minute or $PaCO_2$ ≤32mmHg or mechanical ventilation necessary
WBC ≥12,000/mm^3 or ≤4,000/mm^3 or ≥10% immature forms
Sepsis
SIRS diagnostic criteria met AND suspected OR proven infection
Severe Sepsis
Sepsis diagnostic criteria met
Evidence of organ dysfunction, hypotension, or hypoperfusion
Lactic acidosis (measurement of serum lactate levels — an indication of anaerobic cellular respiration, and that tissues lack oxygen due to organ perfusion dysfunction)
Systolic blood pressure <90mmHg or a systolic blood pressure drop ≥40mmHg of normal
Septic Shock
Severe sepsis diagnostic criteria met
Hypotension persists, despite adequate fluid resuscitation

Source: GlobalData; Dellinger et al., 2013; Remick, 2007

$PaCO_2$ = partial pressure of carbon dioxide; SIRS = systemic inflammatory response syndrome; WBC = white blood cell

KOLs interviewed by GlobalData welcomed the new SEPSIS-3 consensus definition over previous attempts using SIRS criteria. Experts cited SIRS criteria as too sensitive and unspecific to classify a patient as suffering from sepsis or septic shock.

"Sepsis was initially defined as a syndrome that was driven by an infection that was accompanied by [SIRS].So, in other words, if someone has a pneumonia, and they get worse, they have a bad pneumonia but they get pneumonia and then they later develop acute kidney injury, so their kidneys stop working because of the severe lung infection, that would be referred to as 'severe sepsis.' Then septic shock would be a subset of those patients who had cardiovascular dysfunction in such a way that they couldn't maintain their blood pressure without artificial support with a vasopressor."

US Key Opinion Leader

If you define sepsis as being SIRS plus infection, then sepsis equals infection.

"If you define sepsis as being SIRS plus infection, then sepsis equals infection.In other words, it's becoming extremely common, because infection is recognized by fever, associated tachycardia, and the alteration in white blood cell counts. These are three of the four SIRS criteria already, and you need only two plus infection to quality for sepsis."

EU Key Opinion Leader

4.1.1.1.5 SEPSIS-3 Diagnosis Criteria: Infection, qSOFA, and SOFA

Table 4 summarizes SEPSIS-3 diagnostic criteria for sepsis and septic shock.

Table 4: SEPSIS-3 Diagnostic Criteria (qSOFA, SOFA, Sepsis, and Septic Shock)

qSOFA (≥2 meets screening criteria)[a]					
Respiratory rate >22 breaths/minute or more					
Altered mental status					
Systolic blood pressure <10mmHg					
SOFA (≥2 meets diagnostic criteria)					
	Score				
System	0	1	2	3	4
Respiration PaO_2 /FIO_2, mmHg (kPa)	>400 (53.3) or more	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x 10^3 /□L	>150 or more	<150	<100	<50	<20
Liver Bilirubin, mg/dL (□mol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP > 70 mmHg or more	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine < 0.1 or less or norepinephrine < 0.1[b] or less	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
CNS Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal Creatine, mg/dL (□mol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5 (440)
Urine output, mL/day	N/A	N/A	N/A	<500	<200
Sepsis					
qSOFA screening criteria met (or SIRS criteria)					
SOFA diagnostic criteria met (evidence of organ dysfunction) AND suspected OR proven infection					
Septic Shock					
Sepsis diagnostic criteria met					
Lactic acidosis (measurement of serum lactate levels — an indication of anaerobic cellular respiration, and that tissues lack oxygen due to organ perfusion dysfunction), lactate level of >2 mmol/L (18mg/dL)					
Hypotension persists (MAP >65 mmHg or more), despite adequate fluid resuscitation					

Source: GlobalData; Singer et al., 2016; Vincent et al., 1996;

[a]While SIRS played a pivotal role in defining sepsis in SEPSIS-2, qSOFA is not vital in identifying patients with sepsis, but rather a tool to identify patients with an increased mortality risk (Vincent et al., 2016).

[b]Catecholamine doses are given as µg/kg/min for at least 1 hour.

[c]GlasgowComa Scale scores range from 3–15; higher score indicates better neurological function.

CAN = central nervous system; FIO_2 = fraction of inspired oxygen; N/A = not applicable; MAP = mean arterial pressure; $PaCO_2$ = partial pressure of carbon dioxide; SIRS = systemic inflammatory response syndrome; WBC = white blood cell

4.1.1.1.6 Validation of SEPSIS-3

Although qSOFA and SOFA have been assessed in two retrospective and one prospective study for identifying high-risk patients, their clinical validity, in particular outside the ICU, remains uncertain. However, GlobalData notes that qSOFA and SOFA hold great promise for clinical research, as qSOFA criteria have shown a higher specificity in identifying patients with an increased mortality risk (Churpek et al., 2015; Freund et al., 2017; Seymour et al., 2016).

The first retrospective study compared the predictive power of qSOFA, SOFA, and SIRS criteria at determining mortality in 7,932 ICU patients with suspected infection across 130 hospitals in the US from 2009–2013, where the true mortality rate was 16% (1,289 patients). The study showed a lower predictive validity for in-hospital mortality for SIRS (AUROC = 0.64; 95% CI, 0.62–0.66) and qSOFA (AUROC = 0.66; 95% CI, 0.64–0.68) vs. SOFA (AUROC = 0.74; 95% CI, 0.73–0.76; $p < .001$ for both). In less severely ill patients (66,522 non-ICU patients, mortality rate 3%), qSOFA outperformed SOFA and SIRS criteria (Seymour et al., 2016). GlobalData acknowledges that this study strengthens the validity of qSOFA and SOFA in ICU as well as non-ICU patients, however the study did not investigate the use of qSOFA as a screening tool for mortality and SOFA as validation criteria for sepsis, a major shortcoming in the current validation process.

The second retrospective study examined the predictive power of qSOFA, SIRS, modified early warning score (MEWS) and national early warning score (NEWS) at determining mortality or ICU transfer in 30,677 ED and hospital wards in Chicago (US) during November 2008 and January 2016, then the observed mortality rate was 5.4% (1,649 patients). The study showed that outside the ICU, NEWS (AUROC = 0.77; 95% CI, 0.76-0.79), followed by MEWS (AUROC = 0.73; 95% CI, 0.71-0.74), qSOFA (0.69; 95% CI, 0.67-0.70), and SIRS (0.65; 95% CI, 0.63-0.66, $p <0.01$), was most accurate at predicting mortality (Churpek et al., 2015). qSOFA's higherspecificity will be most welcomed by researchers aimed at improving clinical trial outcomes, while its low sensitivity will further alleviate the scepticism in the community about the validity of qSOFA as screening tool for mortality.

A third, more recent prospective study encompassing 879 patients with suspected infection in 30 EDs across France, Spain, Belgium and Switzerland between May and June 2016, supported the use of

qSOFA criteria over SIRS criteria as tool to screen for patients with increased mortality risk. In this study, the overall mortality rate was 8% (70 patients) and qSOFA criteria (qSOFA > 2 or more) performed better at predicting mortality than SIRS (SIRS >2 or more), with AUROCs of 0.80 (95% CI, 0.74-0.85) vs. 0.65 (95% CI, 0.59-0.70), respectively (Freund et al., 2017).

4.1.1.1.7 Future Consensus Definitions

The majority of experts interviewed by GlobalData anticipate further iterations of the sepsis and septic shock definitions in the future. GlobalData believes that future consensus definitions of sepsis will be driven by improvements in the diagnosis of sepsis with biomarkers. However, GlobalData's primary research did reveal a certain polarization in the field, as some KOLs see the current SEPSIS-3 consensus definitions as a step back to the root of sepsis, where the infection is the predominant driver of disease and future manifestations in form of organ dysfunction. GlobalData anticipates the next iteration of guidelines and consensus definitions sometime in 2020.

"[SEPSIS-3] did not address the possibility of using bio-markers as an adjunct to diagnose sepsis.I think this will be addressed in future consensus definitions over the next ten years, as biomarkers very important in the diagnosis and staging of the disease."

EU Key Opinion Leader

"We'll try to keep improving upon [SEPSIS-3] over time when new information becomes available, [for example a] new biomarker that says, 'For sure, this patient is going to die very shortly.' So, if that happens, and it's very specific, we would improve that to future definitions."

US Key Opinion Leader

"I don't think there will be a SEPSIS-4, -5, -6, or -7. I think sepsis has always been infection plus organ dysfunction, and it will remain like that for centuries and forever. Exactly as how myocardial infarction [MI] is a clot in a coronary artery, you may change the criteria, but a MI is a MI. A stroke is a stroke. You will not change that."

EU Key Opinion Leader

4.1.1.2 Risk Factors and Common Causes

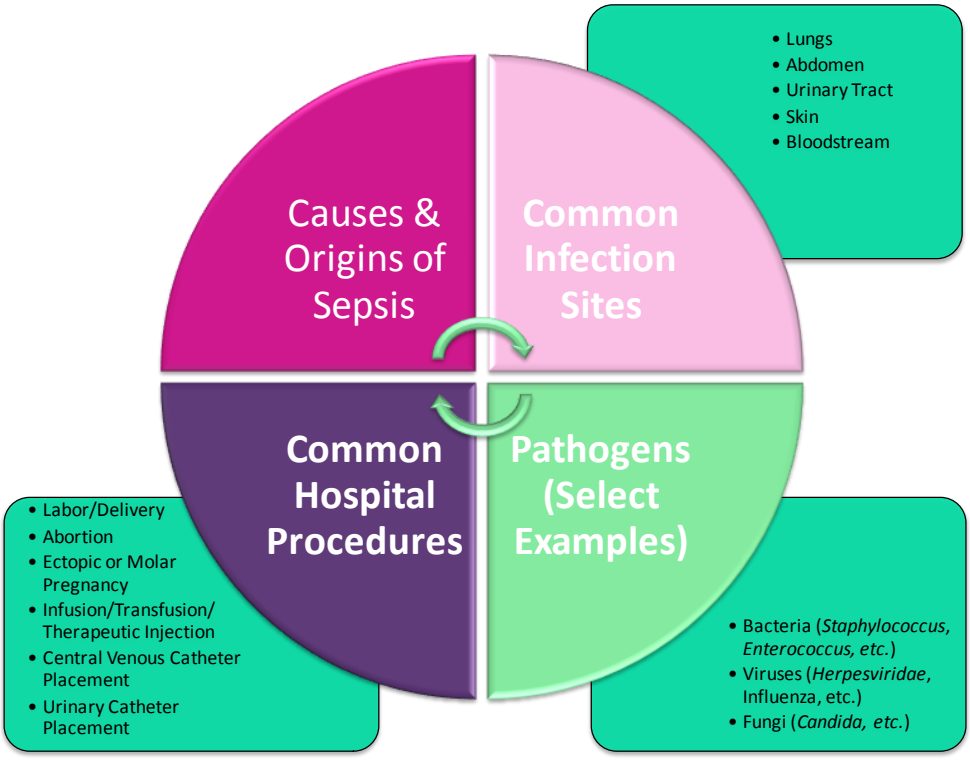
Due to its complex pathophysiology involving various pathogen factors (infectious load, virulence, and toxins) and host factors (environmental, genetics, age, medications, and other illnesses), sepsis is associated with various risk factors, comorbidities, and complications (Uhle et al., 2016). The most frequently observed comorbidities of sepsis are disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and acute liver injury (ALI), while the

most common risk factors are young and old age, diabetes, cancer, and a compromised immune system (Angus et al., 2001; Hiong et al., 2016).

The majority of sepsis-associated infections can be traced back to bacterial origin, where Gram-positive bacteria, such as *Staphylococcus spp*. are among the most predominant causes of sepsis. Gram-negative infections, caused by *Pseudomonas spp*. or *Escherichia coli*, are among the second most common pathogens responsible for sepsis, followed by fungal infections, whereas theincidence rates of viral and parasitic sepsis are very low (de La Rica et al., 2016).

Figure 4 summarizes the common causes of sepsis based on hospital procedures, pathogens, and common infections, and highlights the diversity of potential causative events. This figure is not meant to be an exhaustive list of causative agents, but rather to highlight the heterogeneity of the potential causative pathogens seen in the clinic.

Figure 4: Common Causes and Origins of Sepsis



Source: GlobalData; ICD-10 Codes, 2017

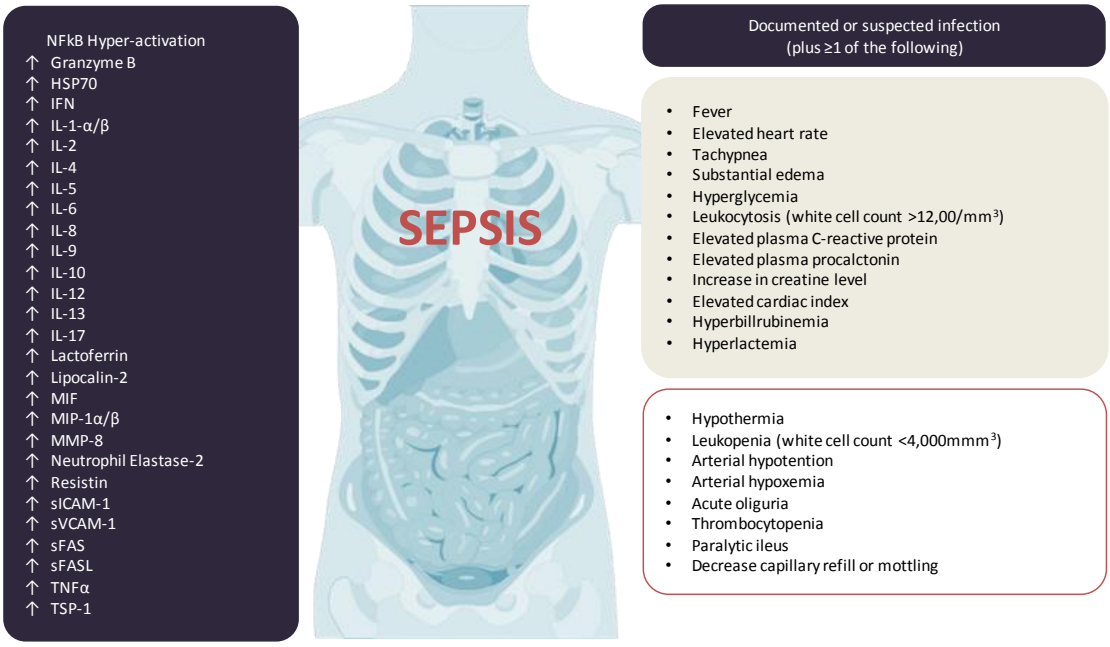
4.1.2 Pathophysiology

Caused by the host's immune response to an invading pathogen and their toxins in the blood stream or tissue, sepsis and septic shock often result in complex manifestations.

Caused by the host's immune response to an invading pathogen and their toxins in the blood stream or tissue, sepsis and septic shock often result in complex manifestations, including life-threatening organ dysfunctions (Singer et al., 2016). In healthy patients, the presence of invading pathogens and their toxins results in activation of the host immune system, triggering a defense mechanism and preventing colonization of the pathogen within the host. After the initial immune response, the host immune system returns to a state of homeostasis, where feedback mechanisms prevent an over- or under-active immune response. In sepsis, this homeostasis is disturbed, resulting in dysfunctioning immune regulation, where the concerted presence of sustained pro- and anti-inflammatory states causes tissue injury, organ dysfunction, anergy (the absence of normal immune response) and/or immunosuppression (Bhan et al., 2016; Okeke and Uzonna, 2016; Uhle et al., 2016).

Figure 5 provides an overview of the most common manifestations of sepsis.

Figure 5: Common Manifestations of Sepsis



Source: GlobalData; adapted from Giza et al., 2016

4.1.2.1 Organ Damage in Sepsis

Figure 6 provides an overview of the most common forms of end-stage organ damage during the pathogenesis of sepsis. The spatial release of pathogenic toxins and mediators in the body can affect how the host responds to infection, as some tissues and organ systems are better equipped to handle it than others, and each may have its own specific set of mediators (Sagy et al., 2013). The most common organ dysfunctions associated with sepsis are DIC, ARDS, AKI, and ALI (Iskander et al., 2013).

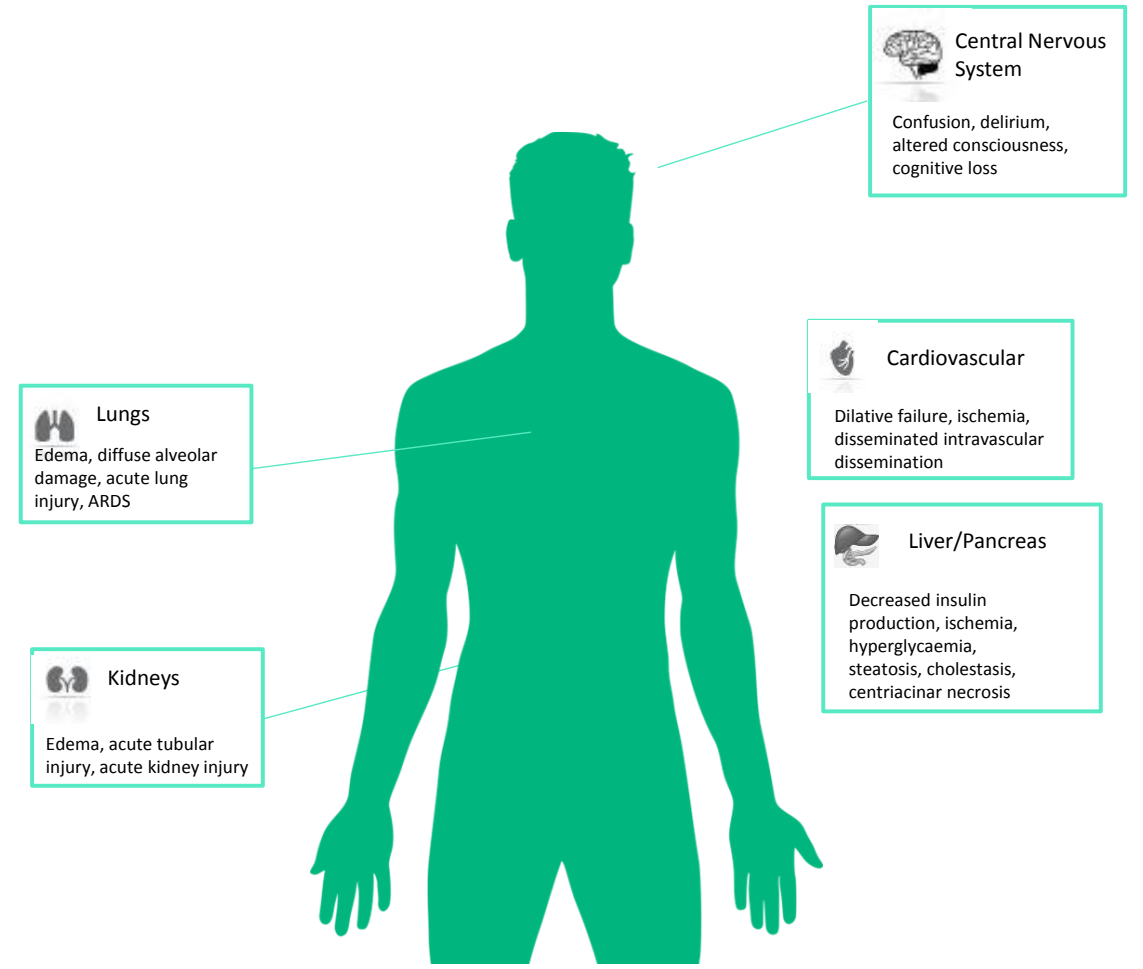
"These are the six organs [cardiovascular, respiratory, renal, neural, hematological, and hepatic] that you should always have in mind because you can quantify the degree of organ dysfunction for these six organs.You may add perhaps sugar levels, but it's difficult to quantify in terms of insulin requirements, for instance. You could try to add the gastrointestinal, but it is also very difficult to quantify it, so we usually limit ourselves to the six organs. These are the six organs which are listed in the SOFA Score."

EU Key Opinion Leader

"There's a hierarchy and a gradation of the degree of organ dysfunction. Typically early events would be cardiovascular events, one of the early findings is an acute confused state. Within a day or two, lung injury occurs, people develop ARDS. Acute kidney injury [can] occur early on, but more commonly it occurs after several days. … The fewer organ dysfunctions, the more likely you're going to survive, because the more organs that are not working, the worse your outcome. Good supportive care tries to spare those organs, and give the rest of the body a chance to recover, and tissue recovery, and function to recover while fighting the infection."

US Key Opinion Leader

Figure 6: The Pathogenesis of Sepsis and End-Stage Organ Damage



Source: GlobalData; adapted from Iskander et al., 2013.
ARDS = acute respiratory disease syndrome

4.1.2.2 Molecular Mechanism of Sepsis

The immune-pathophysiologic mechanism occurring during sepsis is incompletely understood, but it has been shown to involve both pro- and anti-inflammatory pathways simultaneously (Uhle et al., 2016). The imbalance of the net sum of pro- and anti-inflammatory responses can result in sepsis. Typically, this involves a net overactive pro-inflammatory response, followed by a failure of the anti-inflammatory system to regain homeostasis, leading to septic shock and/or immunosuppression (Uhle et al., 2016).

Table 5 summarizes the pathophysiological response causing sepsis and septic shock according to phases and outcomes associated with each one, where sepsis and septic shock are the concerted occurrence of all these phases.

Table 5: Summary of Pathophysiological Events Causing Sepsis and Septic Shock

Phase	Biological Event
Pathogen and detection by immune cells	Pathogens—bacteria, fungi, viruses, or protozoa—invade sterile body compartments through putative entry sites (viruses) or by excretion of exotoxins (by bacteria and fungi) or superantigens (by bacteria) PAMPs are recognized by innate immune system through PRRs
Pro-inflammatory response and septic shock	Activation of NF-kB transcription factor Pro-inflammatory mediators are released to control infection; the "cytokine storm": IL-6, IL-12, TNF-α, and chemokines (IL-8), following activation of neutrophils. During the "cytokine storm," neutrophils engulf pathogens, release antimicrobial compounds, or sacrifice themselves to form NETs to act as a physical antimicrobial barrier (NETosis), thereby causing collateral damage to both pathogens and host tissues. Pyroptosis, NETosis, and necrosis result in loss of membrane integrity and the release of endogenous molecules, triggering so-called damage-associated molecular patterns (heat shock protein 70, S100 proteins, mitochondrial DNA, and metabolic compounds such as ATP).
Anti-inflammatory response and immunosuppression	PRRs bind PAMPs and initiate downstream signaling pathways, mounting an anti-inflammatory response PRRs bind PAMPs, inducing caspases-4/5 activity, causing immunogenic cell death (pyroptosis) Activation of immunosuppressive mechanism results in re-activation of viral or newly developed nosocomial secondary infections and death Exhaustion of immunocompetent cells results in immunoparalysis and death

Source: GlobalData; Uhle et al., 2016

ATP = adenosine triphosphate; DNA = deoxyribonucleic acid; L = interleukin; NET = neutrophil extracellular trap; NF-kB = nuclear kappa-light-chain enhancer; PAMP = pathogen-associated molecular pattern; PRR = pattern recognition receptor; TNF-α = tumor necrosis factor-alpha

4.1.2.2.1 Pathogen and Detection by Immune Cells

The main underlying cause of sepsis is the presence of pathogens (bacteria, fungi, viruses, or protozoa) and their toxins—for example, superantigens (such as enterotoxin B from *S. aureus*); lipopolysaccharides (LPS; endotoxins from Gram-negative bacteria); lipoteichoic acids (LTA; from Gram-positive bacteria), zymosans (D-glucan from fungi), host-adapted surface proteins for entry (viruses), or exotoxins (bacteria, fungi, viruses, or parasites) in the bloodstream of the human host (Uhle et al., 2016). The toxins released by pathogens are collectively called pathogen-associated molecular patterns (PAMPs), and the host immune system has various cell types able to recognize these patterns, including dendritic cells, monocytes/macrophages, and neutrophils equipped with matching pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), C-type lectin receptors, NOD-like receptors (NLR), RIG-I-like receptors, and orphan receptors. The recognition of PAMPs by PRRs triggers the first step in the immune response to infection (Uhle et al., 2016).

4.1.2.2.2 Pro-inflammatory Response

PAMPs are recognized by PRRs in macrophage cell membranes which, in turn, stimulate the macrophage to release pro-inflammatory cytokines that activate the immune system. Toxins also

activate T-lymphocytes, which trigger the production of tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and interferon gamma (IFN-γ). These are important mediators of the inflammatory response cascade and serve to contain an infection when working properly. In sepsis, this response becomes hyperactive because the immune system fails to balance itself through a negative feedback loop.

The major biological events that are characteristic of pro-inflammatory response include:

- Promotion of growth, proliferation, and differentiation of T-cells to become “effector” T-cells with immunological memory
- Promotion of leukocyte migration as well as increased adhesion between endothelial cells and leukocytes
- Production of nitric oxide, resulting in vasodilation and hypotension
- Release of arachidonic acid metabolites—leukotrienes and prostaglandins
- Activation of the complement cascade stimulates the release of anaphylatoxins.
- Increased synthesis and release of tissue factors by the liver, leading to pathological coagulation
- Decreased production of thrombomodulin, which is necessary for the proper anticoagulant response, exacerbates excessive clotting, and results in fibrinolysis inhibition.

4.1.2.2.3 Anti-inflammatory Response

In a normal physiological scenario, the anti-inflammatory response serves as a negative feedback loop to help prevent organ dysfunction and restore homeostasis. However, when a patient develops sepsis, the anti-inflammatory response over-compensates for the pro-inflammatory response. This eventually leads to immunosuppression and the inability of the patient to achieve proper immune regulation. Patients become more susceptible to secondary and opportunistic infections and are also at risk for the reactivation of dormant bacterial and viral infections previously kept in check by a properly functioning immune system (Walton et al., 2014).

When a patient develops sepsis, the anti-inflammatory response over-compensates for the pro-inflammatory response.

The major biological events that are characteristic of an excessive anti-inflammatory response include:

- Excessive production of anti-inflammatory mediators that inhibit TNF-α activity
- Augmentation of acute phase reactants and immunoglobulins
- Inhibition of T-lymphocytes

- Inhibition of mediators that activate the coagulation system

4.1.2.2.4 Sepsis and Septic Shock

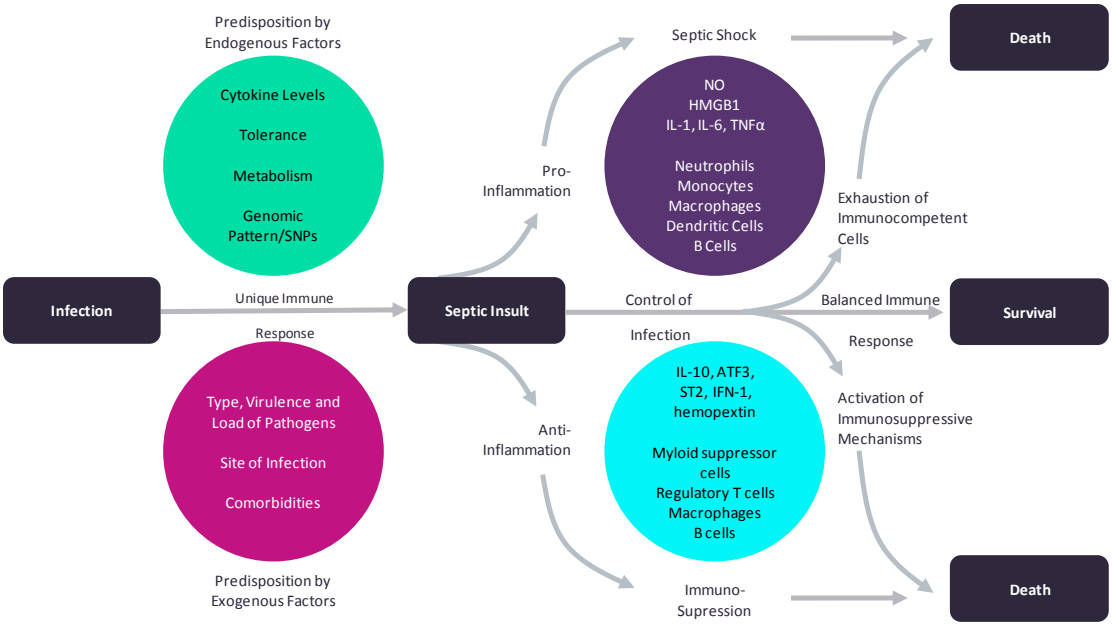
In septic patients, a pathological imbalance between the pro-inflammatory and anti-inflammatory responses during infection leads to an immune system dysfunction. Typically, the imbalance results in a hyper-inflammatory state, followed by either a prolonged pro-inflammatory state or an anti-inflammatory state—both can be the cause of death (Uhle et al., 2016).

The host response typically depends on various predisposing endo- and exogenous factors, such as type of pathogen and its virulence, as well as genomic factors and individual immune tolerance, resulting in an initial increase in the innate immune response and a decrease in the adaptive immune response. The innate immune response drives inflammation to contain the infection and keep it from spreading, where the intensity of the immune responses and inflammation varies, and is dependent on various predisposing endogenous factors (cytokine levels, tolerance, metabolism, and genomic pattern/single nucleotide polymorphisms) and exogenous factors (type, virulence and load of pathogens, site of infection, and comorbidities). Early deaths are due to a cytokine storm, which is characterized by fever, refractory shock, acidosis, and hyper-catabolism. Examples of clinical scenarios that would mirror this would be a patient dying of septic shock syndrome (Hotchkiss et al., 2013a; Hotchkiss et al., 2013b; Uhle et al., 2016).

If a patient survives the initial hyper-inflammatory response, they'll see a restoration of both the innate and adaptive immune systems and the infection will be cleared if homeostasis is reached, otherwise both innate and adaptive immunities fail to control the infection, and patients enter an immunosuppressed state; where the exhaustion of immune-competent cells can lead to a persistent activation of the innate immunity, causing uncontrollable inflammation and organ dysfunction, whereas the activation of immunosuppressive mechanisms can lead to reactivation of viral infection or secondary/opportunistic infections (Hotchkiss et al., 2013a; Hotchkiss et al., 2013b; Uhle et al., 2016).

Figure 7 shows the pathophysiologic mechanism of sepsis.

Figure 7: Current Understanding of Sepsis and Septic Shock Pathophysiology



Source: GlobalData; Uhle et al., 2016.

4.1.2.3 Biomarkers

The complexity of sepsis manifestations is a major reason why accurate diagnostic tools do not currently exist, and also why there is not a gold standard or consensus among physicians with regard to a serum biomarker to diagnose and monitor the condition (Remick, 2007).

Several biomarkers have been investigated in RCTs for the identification of sepsis, however as of February 2017, there is no single biomarker that had a sufficient specificity to be used for sepsis diagnosis. Among the most-studied biomarkers in sepsis are C-reactive protein (CRP) and procalcitonin (PCT), intracellular inflammatory markers that are frequently elevated in the presence of bacterial infections (Prkno et al., 2013). A systemic review of the available literature illustrated a mean sensitivity of 0.77 (95% CI, 0.72–0.81) and a mean specificity of 0.79 (95% CI, 0.74–0.84) for PCT as a marker for bacterial infection (Wacker et al., 2013). GlobalData notes that a biomarker for diagnostic purposes should have a specificity of greater than 0.90, a cut-off no single biomarker has yet achieved in sepsis.

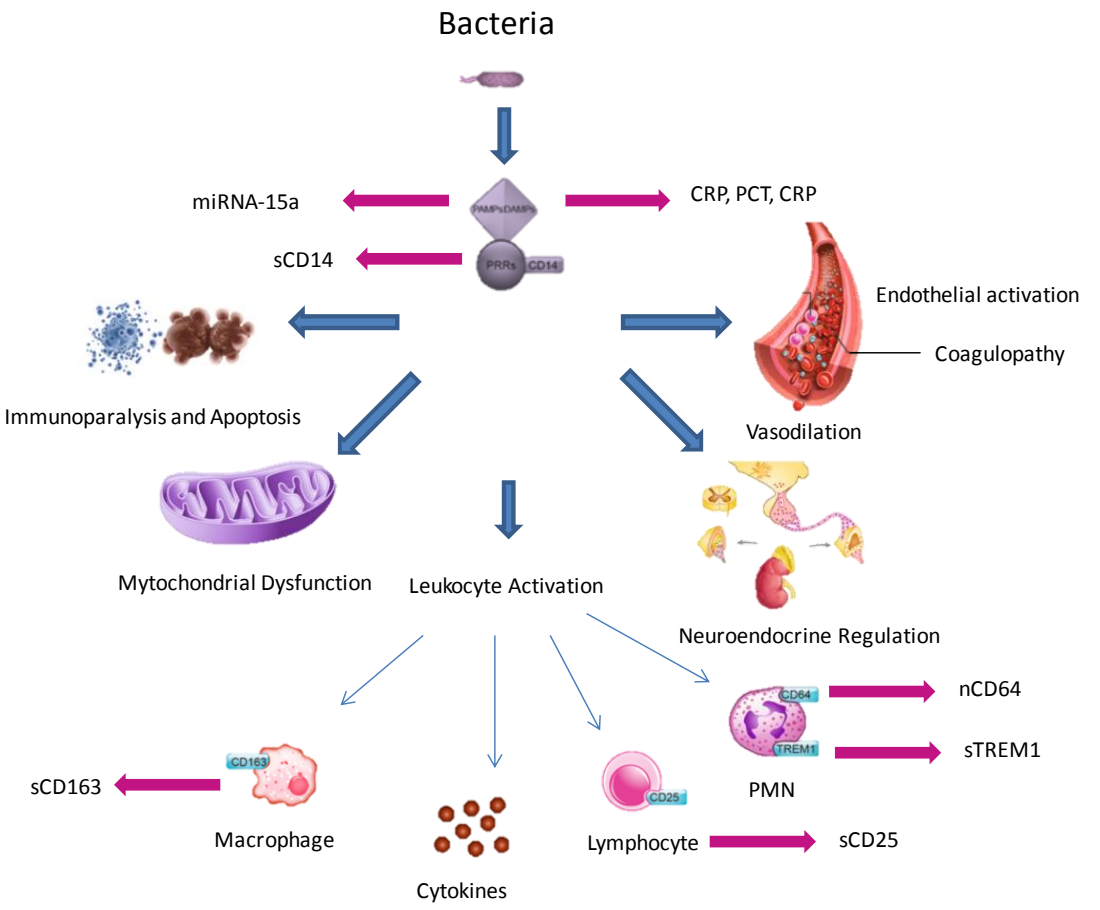
"[CRP] is very useful as a tool for analyzing progress, long-term progress. I get the impression that [PCT] is not dose-dependent. So if, for example, a [PCT] value of 50 goes down to 25 it doesn't

necessarily mean that the level of infection has halved. But CRP does seem to me to be dose dependent. So I don't use just CRP. I use both at the same time."

Japan Key Opinion Leader

Figure 8 shows biomarkers currently being investigated for the diagnosis of sepsis.

Figure 8: Biomarkers in Bacterial Sepsis Diagnosis



Source: GlobalData; adapted from Mearelli et al., 2014

4.1.2.4 Drug Targets

A truly sepsis-specific drug would be one that targets and reverses the underlying immune-pathophysiology within a sepsis patient. One of the major challenges to developing immunomodulatory drugs for sepsis is the incomplete understanding of the complex interplay between pro-inflammatory (cytokine secretion) and anti-inflammatory (anergy/immune paralysis) response pathways. GlobalData believes that an improved understanding of sepsis pathophysiology

and biomarkers will lead to improved stratification of sepsis patients toward more targeted immunotherapies, therefore increasing the chances of companies demonstrating a benefit in a large clinical trial with a drug that targets the underlying sepsis pathophysiology. KOLs interviewed by GlobalData said that academic research is extremely vibrant in sepsis, and they are hopeful that meaningful advancements will be made to ease therapeutic development.

"The [academic] science [focused on sepsis] is still very good. I think this movement clinically is actually great for the field and everyone can benefit from that. I think the basic science on immune system function and organ dysfunction is actually quite healthy. There are lots of papers being written, et cetera, and if you go to clinicaltrials.gov and you type in 'sepsis,' there's almost 1,400 trials registered. Overall, there's lots of energy and enthusiasm in the field. The one place where it looks a bit tired and sad is in new [commercial] therapeutic development. But otherwise, the field is pretty healthy."

US Key Opinion Leader

In the past, developers have attempted to target the pro-inflammatory response, but this approach has yielded high profile late-stage clinical development failures.

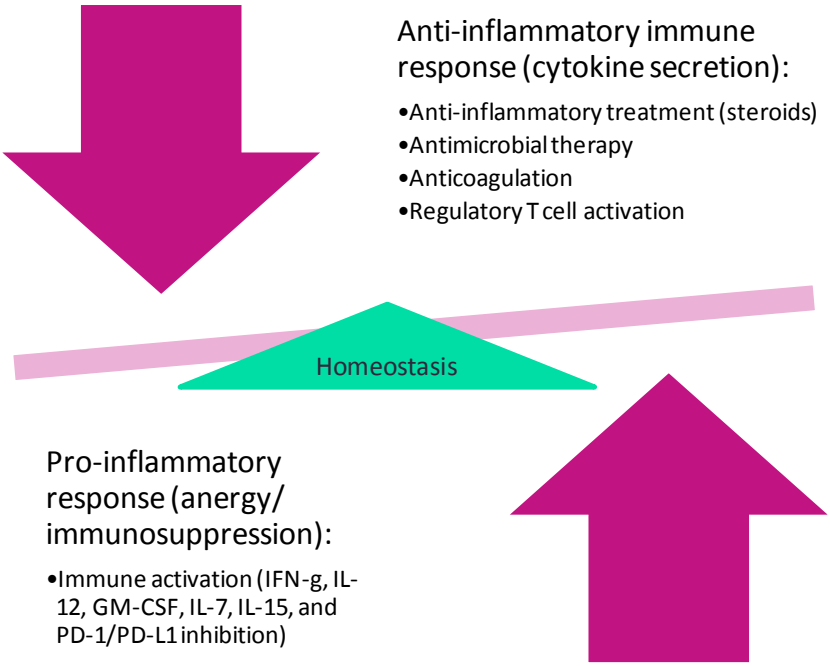
In the past, developers have attempted to target the pro-inflammatory response, but this approach has yielded high profile late-stage clinical development failures. More recently, pharmaceutical companies began targeting anti-inflammatory pathways, but KOLs interviewed by GlobalData tended toward the use of multiple drugs in the treatment of sepsis, as no single agent was proven to be successful in the management of the diverse manifestations of sepsis. Furthermore, experts share the belief that new diagnosis markers will play a pivotal role on stratifying septic patients towards a targeted anti- or pro-inflammatory medications.

"All these companies tend to have their own pet rock. They have their own drug. But it's probably some kind of combination therapy that will ultimately provide the biggest benefit. Again, unless you specifically hone in on a small population, it's unlikely that one drug is going to help everyone."

US Key Opinion Leader

Figure 9 illustrates potential target pathways for the pro- and anti-inflammatory pathways causing sepsis, thereby restoring immune homeostasis.

Figure 9: Potential Target Pathways for Sepsis Treatment



Source: GlobalData; Okeke and Uzonna,2016

Table 6 summarizes important mediators of both the pro-inflammatory and anti-inflammatory responses and highlights potential drug targets to treat sepsis patients.

Table 6: Mediators of the Pro-inflammatory and Anti-inflammatory Responses

Pro-inflammatory	Anti-inflammatory
TNF-α	Type II IL-1 receptor
IL-1β, IL-2, IL-8, IL-15	IL-4, IL-10, IL-13
Neutrophil elastase	IL-1-receptor agonist
IFN-γ	TGF-β
Thromboxane, platelet-activating factor	Epinephrine phospholipase A_2
Vasoactive neuropeptides	Soluble TNF-α receptor
Plasminogen activator inhibitor-1	Leukotriene B_4-receptor antagonist
Prostaglandins (EX: prostacyclin)	LPS-binding protein
Free radicals	Soluble recombinant CD-14
Soluble adhesion molecules	
Tyrosine kinases	
H_2S	
NO	
HMGB1 protein	
Toll-like receptors	
IL-7	
PD-1/PD-L1 inhibition	

Source: GlobalData; Bone et al., 1997; Sagy et al., 2013
H_2S = hydrogen sulfide; HMGB1 = high-mobility group protein B1;IL = interleukin; LPS = lipopolysaccharide; NO = nitric oxide; TGF = transforming growth factor

4.2 Classification or Staging Systems

Despite the introduction of the new SEPSIS-3 definitions, sepsis classification criteria according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) remain largely unchanged. GlobalData notes that the lack of adaptation is due to the fact that most EDs and ICUs in the US follow CMS core guidelines, which have not yet endorsed the new consensus definitions.

According to CMS and the previous consensus definition of sepsis (SEPSIS-2), sepsis is coded as systemic infection (A41) followed by one or more organ dysfunctions (N17, J96.0, G72.81, G62.81, D65, G93.41, and K72.0) in the case of severe sepsis (R65.10) or septic shock (R65.20), while the SEPSIS-3 consortium recommended to code sepsis as severe sepsis (R65.10) and the corresponding organ dysfunction. In addition, most providers document the origin of the underlying infection (T81.4, T80.2, D85, O03.87, O082.82, O03.37, O04.87, A41.9). GlobalData remarks that the different coding

practices will result in different reimbursement rates for hospitals across the US, thus explaining the lack in adoption of SEPSIS-3 definition practices.

Table 7 outlines sepsis diagnostic codes according to ICD-10-CM standards.

Table 7: ICD-10-CM Diagnosis Codes for Sepsis

Category	Etiology	Details
A41		Sepsis
	0	due to *Staphylococcus aureus*
	1	due to other specified staphylococcus
	2	due to unspecified staphylococcus
	3	due to *Hemophilus influenzae*
	4	due to anaerobes
	5	due to other Gram-negative organisms
	8	Other specified sepsis
	9	Unspecified organism
R65	10	Severe sepsis
	20	without septic shock
	21	with septic shock
N17		Acute kidney failure (kidney)
J96	0	Acute respiratory failure (lung)
G72	81	Critical illness myopathy (muscles)
G62	81	Critical illness polyneuropathy (peripheral nerves)
D65		Disseminated intravascular coagulopathy (clotting)
G93	41	Encephalopathy (brain)
K72	0	Hepatic failure (liver)
T81	4	Infection following a procedure
T80	2	Infection following infusion, transfusion, and therapeutic injections
O85		Puerperal sepsis
O083	87	Sepsis following complete or unspecified spontaneous abortion
O082	82	Sepsis following ectopic and molar pregnancy
O03	37	Sepsis following incomplete spontaneous abortion
O04	87	Sepsis following (induced) termination of pregnancy

Source: GlobalData; ICD-10, 2017

4.3 Symptoms

Symptoms associated with sepsis are diverse and can vary greatly in severity and duration. Patients presenting with sepsis can have vastly different symptoms from case to case, since it can be caused by virtually any pathogen (bacteria, virus, fungi, or parasite) and originate in any tissue or organ system in the body. The situation becomes even more complicated when the infection starts spreading to different tissues, causing more sepsis-induced conditions and symptoms.

Table 8 highlights the symptoms commonly associated with sepsis and septic shock. Due to the absence of drugs marketed specifically for sepsis, clinicians rely on supportive care with fluid therapy, vasopressors, and antibiotics in the management of these symptoms.

Table 8: Symptoms Associated with Sepsis and Septic Shock

Symptom	Description
Suspected or confirmed infection	Infection can be caused by any infectious pathogen (bacteria, virus, fungus, or parasite)
Hyperthermia or hypothermia	Internal body temperature of >38°C or <36°C (>100.4°F or <96.8°F)
Tachycardia	Heart rate >90 beats/minute
Tachypnea	Respiratory rate ≥20 breaths/minute or $PaCO_2$ ≤32mmHg
Abnormal white blood cell count	Characterized by leukocytosis (WBC ≥ 12,000/mm^3) or leukopenia (WBC < 4,000/mm^3).
Positive fluid balance with edema	Fluid gained is greater than fluid lost, which would be suggestive of a renal or cardiovascular issue. This is normally associated with increased secretion of fluid into the interstitial space.
Hemodynamic abnormalities	Characterized by arterial hypotension (BP <90/60), increased cardiac output with vasodilation (low systemic vascular resistance), changes in skin perfusion, decreased urine output, and elevated lactate levels (>4mmol/L or >36mg/dL).
Organ dysfunction	Characterized by hypoxia, altered mental status, hyperglycemia, coagulopathy or disseminated intravascular coagulation, paralytic ileus, acute lung injury, acute respiratory distress syndrome, acute liver failure, and acute kidney disease.

Source: GlobalData; Cawcutt and Peters, 2014; Dellinger et al., 2013; Sagy et al., 2013
BP = blood pressure; $PaCO_2$ = partial pressure of carbon dioxide

4.4 Prognosis

In the absence of a golden standard for sepsis diagnosis or treatment, prognosis for sepsis survival remains a challenge, particularly among the young and elderly populations, as well as in immunocompromised patients or patients with comorbidities, such as those with diabetes and cancer (Angus et al., 2001; Hiong et al., 2016). Sepsis pathophysiology is characterized by the occurrence of three major mortality risk periods in the course of the disease (Delano and Ward, 2016). The first peak is characterized by a failing response to fluid therapy and vasopressors, whereas the second peak between two and three weeks is due to organ dysfunctions caused by infections. The largest upswing

occurs after 60–90 days and continues to rise over the ensuring three years, where persistent immune suppression, catabolism, and inflammation cause chronic deterioration and death (Delano and Ward, 2016). GlobalData notes that current clinical trial efforts in sepsis look mostly at 28 day mortality as clinical endpoint, while some companies started using a 90 day mortality rate endpoint.

4.5 Quality of Life

As of February 2017, there are no systematic studies assessing the quality of life after surviving sepsis. According to experts interviewed by GlobalData, it is unclear how sepsis affects the quality of life of those who survive the acute illness. However, a few retrospective studies on sepsis and related ICU comorbidities show that sepsis survivors suffer from poor long-term mental and physical health (Herridge et al., 2011; Heyland et al., 2000; Kumar et al., 2011; Perl et al., 1995). Moreover, KOLs believe that poor quality of life is also thought to have an economic impact outside of direct healthcare costs, as many survivors are either temporarily or permanently removed from the workforce. GlobalData believes that quality of life and morbidities due to sepsis will be investigated more in future controlled studies throughout the forecast period, and that these will guide the adoption of new efficacy endpoints in clinical trials.

According to experts interviewed by GlobalData, it is unclear how sepsis affects the quality of life of those who survive the acute illness.

A long-term follow-up study included 100 patients with suspected Gram-negative sepsis who were previously stratified to either the monoclonal antibody (mAb) anti-endotoxin or placebo in a double-blind RCT. The results associated physical dysfunction ($p < 0.001$), including problems with work and activities of daily life ($p < 0.02$) and a poor general health ($p < 0.001$), with the long-term survival of sepsis compared to the general population (Perl et al., 1995). Furthermore, a prospective longitudinal cohort study of 109 ICU survivors of ARDS—a common organ dysfunction caused by sepsis—showed that five-year survival among the young participants was associated with ongoing physical and mental health impairments (Herridge et al., 2011). Another cross-sectional study on sepsis survivors' medical charts across university ICU settings in the US showed that long-term health related quality of life (HRQL) among survivors of sepsis was lower ($p < 0.05$) than that of the general US population (Heyland et al., 2000).

Furthermore, a review of the Healthcare Costs and Utilization Project's Nationwide Inpatient Sample (NIS) of US hospitals during 2000–2007 showed an increased incidence of sepsis from 143 incidents in 2000 to 343 incidents in 2007. Although the study registered an overall reduction of sepsis mortality from 39% to 27%, the patient discharge to long-term care facilities increased proportionally in 2007 (Kumar et al., 2011).

5 Epidemiology

5.1 Disease Background

Sepsis is a life-threatening complication arising from an infection, which occurs when the body's response to the infection damages its own tissues and organs. Sepsis can lead to multiple organ failure and death, especially if it is not recognized early and treated promptly (Elfeky et al., 2017; Mayo Clinic, 2016). Anyone can develop sepsis; however, the condition is more common among children less than one year of age, older adults, and those with weakened immune systems (Elfeky et al., 2017; Mayo Clinic, 2016). Although any type of infection (bacterial, viral, or fungal) can lead to sepsis, people suffering from pneumonia, abdominal infection, kidney infection, and bloodstream infection (bacteremia) are more likely to develop sepsis. The most common pathogens for sepsis include bacteria (gram-positive, gram-negative), fungi, viruses, and parasites (Mayo Clinic, 2016).

The disease definitions for sepsis have been revised at regular intervals. The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference defined sepsis as a SIRS (ACCP/SCCM, 1992). The European Society of Intensive Care Medicine and Society of Critical Care Medicine task force members defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Under the new consensus definition (sepsis-3), a patient is diagnosed with sepsis if organ dysfunction can be identified as an acute change in total SOFA score of 2 or more consequent to the infection. Similarly, septic shock occurs when sepsis progresses and in which case profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality. Septic shock is defined as a state of acute circulatory failure characterized by persistent arterial hypotension that cannot be successfully rescued by fluid resuscitation (Shankar-Hari et al., 2016; Singer et al., 2016). It is difficult to identify patients whose organ dysfunction is truly secondary to an underlying infection. Thus, a constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is required for the diagnosis of sepsis and septic shock (Neviere, 2017).

This report provides an overview of the risk factors, comorbidities, and the global and historical trends for sepsis and septic shock in the 7MM. This section includes a 10-year epidemiological forecast for the diagnosed incident cases of sepsis and septic shock, segmented by sex and by age (for all ages). This report also provides an epidemiological forecast for the mortality cases of sepsis and septic shock segmented by age (for all ages). Additionally, the sepsis and septic shock diagnosed incident cases are segmented by causative organism (gram-positive, gram-negative, fungi, viruses, and parasites), and organ dysfunction (renal, respiratory, cardiovascular, critical illness myopathy, critical illness

polyneuropathy, disseminated intravascular coagulopathy, encephalopathy, hepatic, and multiple organ dysfunctions). GlobalData epidemiologists selected nationally representative population-based studies that provided diagnosed incidence and/or mortality rate of sepsis and septic shock in the 7MM. Additionally, the diagnostic criteria for sepsis and septic shock are based on the sepsis-3 definition across all 7MM in this analysis.

5.2 Risk Factors and Comorbidities

The main risk factor for sepsis is any infection, ranging from a bug bite to severe infection like pneumonia or meningitis (Sepsis Alliance, 2017). The tendency to develop sepsis and septic shock is determined by the host response to infection rather than a function of the offending pathogen. People at very young and very old ages are at a higher risk of getting sepsis. People with chronic illnesses with impaired immune systems are also at a higher risk for sepsis (Maloney, 2013).

The epidemiologic literature does not clearly indicate risk factors and comorbidities associated with sepsis. Due to the unpredictable nature and complications involved in the diagnosis and identification of sepsis, which occurs due to a combination of a variety of factors, any condition associated with sepsis can be a complication, comorbidity, or a risk factor. Patients with sepsis/septic shock also suffer from a host of comorbidities. Generally, patients with sepsis/septic shock are frequently identified with underlying comorbidities that have an additive contribution to mortality.

Table 9 presents the risk factors and comorbidities for sepsis and septic shock.

Table 9: Risk Factors and Comorbidities for Sepsis and Septic Shock

Risk Factors	Description		Source
Age	Compared with people ages 15–64 years old, people of ages 85 years and older have 7.8 times higher odds of developing sepsis (95% CI, 6.4–9.6).		Henriksen et al., 2015
Immunosuppression	Immunosuppressed patients are at a 4.5 times higher odds of getting sepsis compared with non-Immunosuppressed people (95% CI, 3.7–5.3)		Henriksen et al., 2015
Alcohol-related conditions	Patients with alcohol-related conditions are at a 2.9 times higher odds of getting sepsis compared with patients with non-alcohol related conditions (95% CI, 2.3–3.7)		Henriksen et al., 2015
Nursing home residence	A significant association was found between patients in nursing home residence and risk of sepsis (residence vs. no residence; OR of 2.60 [95 % CI, 1.2– 5.6]).		Ginde and Moss, 2012
Comorbidities	**Prevalence (%) in Sepsis**	**Prevalence (%) in Septic Shock**	**Source**
Congestive heart failure	23.7	32.6	Kadri et al., 2017; Stoller et al., 2016
Chronic pulmonary disease	25.9	24.1	Kadri et al., 2017; Stoller et al., 2016
Diabetes without chronic complications	25.0	29.4	Kadri et al., 2017; Stoller et al., 2016
Obesity	12.9	-	Stoller et al., 2016
Hypertension	57.4	-	Stoller et al., 2016
Fluid and electrolyte disorders	62.4	-	Stoller et al., 2016

Source: GlobalData, various sources listed above
CI = confidence interval; OR = odds ratio

5.3 Global and Historical Trends

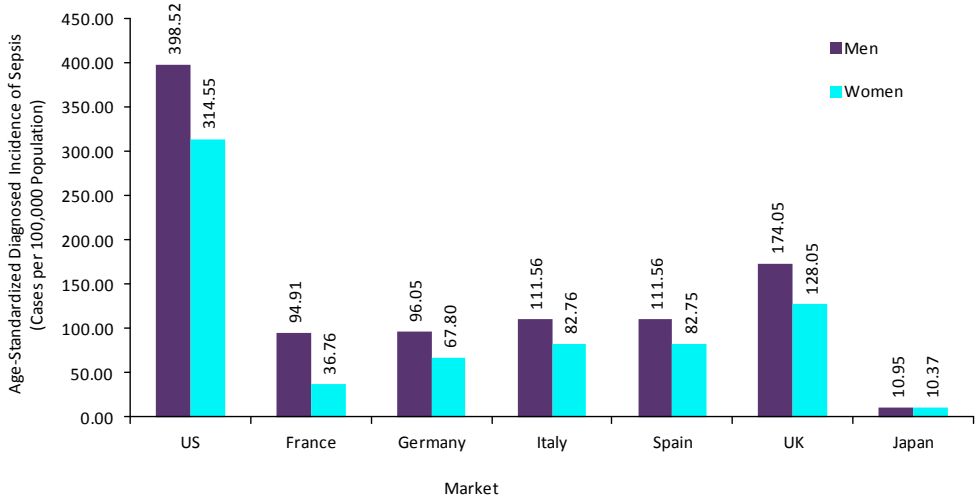
Sepsis is a life-threatening, complex condition and presently, there is a scarcity of data on the burden of sepsis at the global level. Due to the variation in the age composition of the population across markets, GlobalData epidemiologists use the age-standardized incidence of sepsis and septic shock for all ages in the 7MM for international comparison of the incidence across the 7MM. The age-standardized incidence, or the age-adjusted incidence, of a disease is the weighted average of the age-specific incidence rates. Direct incidence comparisons among countries are difficult because the incidence rates may be affected by the varying age distributions of the population in different countries. The use of age-standardized incidence allows for the comparison of incidence among different countries as if they had the same underlying population structure. GlobalData

epidemiologists calculated the age-standardized incidence by multiplying the age-specific incidence proportions from each country by the age-specific world standard population weights (Segi, 1960). However, it is important to note that the age-standardized incidence is an artificial measure used for comparison purposes and should not be used to estimate the number of cases.

In men and women, among the 7MM in 2016, the US had the highest age-standardized diagnosed incidence of sepsis and Japan had the lowest. In the 5EU, the age-standardized diagnosed incidence of sepsis in men ranged between 94.91 cases per 100,000 population in France and 174.05 cases per 100,000 population in the UK in 2016. The age-standardized diagnosed incidence of sepsis in women in the 5EU ranged between 36.76 cases per 100,000 population in France and 128.05 cases per 100,000 population in the UK in 2016. Due to data scarcity, the crude diagnosed incidence of sepsis for Italy is considered to be same as that of Spain and therefore the calculated age-standardized diagnosed incidence rates are also similar in these markets.

Figure 10 presents the age-standardized diagnosed incidence of sepsis in the 7MM for 2016.

Figure 10: 7MM, Age-Standardized Diagnosed Incidence of Sepsis (Cases per 100,000 Population), Both Sexes, All Ages, 2016



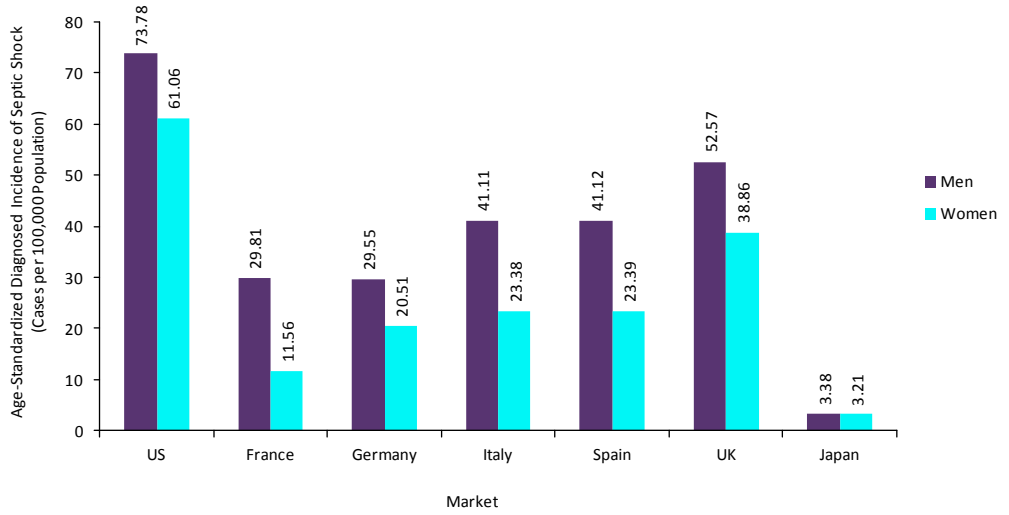
Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016

Among the 7MM, in men and women in 2016, the US had the highest age-standardized diagnosed incidence of septic shock and Japan had the lowest. In the 5EU, the age-standardized diagnosed incidence of sepsis in men ranged between 29.55 cases per 100,000 population in Germany and 52.57 cases per 100,000 population in the UK in 2016. Similarly, the age-standardized diagnosed incidence

of septic shock in women in the 5EU ranged between 11.56 cases per 100,000 population in France and 38.86 cases per 100,000 population in the UK in 2016. Due to data scarcity, the crude diagnosed incidence of septic shock for Italy is considered to be same as that of Spain and therefore, the calculated age-standardized diagnosed incidence rates are also similar in these markets.

Figure 11 presents the age-standardized diagnosed incidence of septic shock in the 7MM for 2016.

Figure 11: 7MM, Age-Standardized Diagnosed Incidence of Septic Shock (Cases per 100,000 Population), Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; de Miguel-Yanes et al., 2015; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016; Walkey et al., 2013

5.4 Forecast Methodology

GlobalData epidemiologists utilized national databases and robust peer-reviewed journal articles to forecast the diagnosed incident cases and mortality cases of sepsis and septic shock in the 7MM. The disease definition for sepsis and septic shock was consistent with the International Classification of Diseases 10th edition (ICD-10) code R65.20 and R65.21 and as per the sepsis-3 guidelines. Whenever available, country-specific sources were utilized and in case of data scarcity, appropriate proxies were used to fill the data gaps.

GlobalData epidemiologists utilized national databases and robust peer-reviewed journal articles to forecast the diagnosed incident cases and mortality cases of sepsis and septic shock in the 7MM.

5.4.1 Sources

Figure 12 to Figure 18 present a summary of the sources used to build the epidemiological forecast for the diagnosed incident cases of sepsis; diagnosed incident cases of septic shock; causative organism cases among the diagnosed incident cases of sepsis and septic shock; organ dysfunction

cases among the diagnosed incident cases of sepsis and septic shock; and the in-hospital mortality cases among sepsis and septic shock diagnosed incident cases in the 7MM.

Data for the diagnosed incidence of sepsis and septic shock from the study by Sakr and colleagues in Italy, and data for the diagnosed incidence of septic shock from the study by Yebenes and colleagues in Spain, were not used in the forecast as the study findings for the diagnosed incidence of sepsis and septic shock from these studies were based on region-specific populations and therefore were not nationally representative (Sakr et al., 2013; Yébenes et al., 2017). Data for the causative agent of sepsis/septic shock from the study by Giorgi-Pierfranceschi and Dentali in Italy were not used in the forecast as this study's findings were based on internal wards only and therefore not representative of all the hospitalized/ICU patients (Giorgi-Pierfranceschi and Dentali, 2016). Data for the organ dysfunction of sepsis from the study by Elfeky and colleagues in the US were not used in the forecast as the definitions of sepsis mentioned in the study are not as per sepsis-3 criteria (Elfeky et al., 2017). Data for organ dysfunction of septic shock from the study by Ferrario and colleagues in Italy were not included in the forecast as the study finding was not nationally representative and the study sample was only 20 (Ferrario et al., 2016). Data for in-hospital mortality of sepsis from the studies by Fedeli and colleagues in Italy and McPherson and colleagues in the UK were not included in our forecast as the definition of sepsis mentioned in the study is not as per sepsis-3 criteria (Fedeli et al., 2016; McPherson et al., 2013).

Figure 12: 7MM, Sources Used and Not Used, Diagnosed Incident Cases of Sepsis

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Dombrovskiy et al., 2007; Lagu et al., 2012; Stoller et al., 2016; **Walkey et al., 2013**	●	●	●	●
France Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Proxy from Spain	●	●	●	●
Spain Bouza et al., 2014; **de Miguel-Yanes et al., 2015**	●	●	●	●
UK Dombrovskiy et al., 2007; Fleischmann et al., 2016b; **Harrison et al., 2006;** Lagu et al., 2012; Padkin et al.,2003; Sakr et al., 2013;	●	●	●	●
Japan Dombrovskiy et al., 2007; Fleischmann et al., 2016b; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; **Ogura et al., 2014**	●	●	●	●
Sources Not Used				
Italy Sakr et al., 2013	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

*Source in bold is the main source used to forecast

Figure 13: 7MM, Sources Used and Not Used, Diagnosed Incident Cases of Sepsis/Septic Shock by Causative Agent

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Dombrovskiy et al., 2007; **Stoller et al., 2016**	●	●	●	●
France **Adrie et al., 2007;** Dombrovskiy et al., 2007; Lagu et al., 2012	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Bouza et al., 2014	●	●	●	●
Spain Bouza et al., 2014	●	●	●	●
UK Dombrovskiy et al., 2007; **Harrison et al., 2006**; Lagu et al., 2012	●	●	●	●
Japan Ogura et al., 2014	●	●	●	●
Sources Not Used				
Italy Fedeli et al., 2016	●	●	●	●
UK McPherson et al., 2013	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

Figure 14: 7MM, Sources Used and Not Used, Organ Dysfunction among Sepsis Cases

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Fleischmann et al., 2016b; **Kadri et al., 2017**	●	●	●	●
France Fleischmann et al., 2016b; **Quenot et al., 2013**	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Proxy from Spain	●	●	●	●
Spain **Bouza et al., 2016;** Fleischmann et al., 2016b	●	●	●	●
UK Proxy from Germany	●	●	●	●
Japan Fleischmann et al., 2016b; **Ogura et al., 2014**	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

Figure 15: 7MM, Sources Used and Not Used, In-Hospital Mortality Cases of Sepsis

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Dombrovskiy et al., 2007; **Stoller et al., 2016**	●	●	●	●
France **Adrie et al., 2007;** Dombrovskiy et al., 2007; Lagu et al., 2012	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Bouza et al., 2014	●	●	●	●
Spain Bouza et al., 2014	●	●	●	●
UK Dombrovskiy et al., 2007; **Harrison et al., 2006**; Lagu et al., 2012	●	●	●	●
Japan Ogura et al., 2014	●	●	●	●
Sources Not Used				
Italy Fedeli et al., 2016	●	●	●	●
UK McPherson et al., 2013	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

*Source in bold is the main source used to forecast

Figure 16: 7MM, Sources Used and Not Used, Diagnosed Incident Cases of Septic Shock

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Dombrovskiy et al., 2007; Lagu et al., 2012; Stoller et al., 2016; **Walkey et al., 2013**	●	●	●	●
France Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Proxy from Spain	●	●	●	●
Spain Bouza et al., 2014; **de Miguel-Yanes et al., 2015**	●	●	●	●
UK Dombrovskiy et al., 2007; Fleischmann et al., 2016b; **Harrison et al., 2006;** Lagu et al., 2012; Padkin et al.,2003; Sakr et al., 2013;	●	●	●	●
Japan Dombrovskiy et al., 2007; Fleischmann et al., 2016b; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; **Ogura et al., 2014**	●	●	●	●
Sources Not Used				
Italy Sakr et al., 2013	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

*Source in bold is the main source used to forecast

Figure 17: 7MM, Sources Used and Not Used, Organ Dysfunction of Septic Shock Cases

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Casserly et al., 2012; and proxy from Italy, Spain, and the UK	●	●	●	●
France Casserly et al., 2012; and proxy from Italy and Spain	●	●	●	●
Germany Engel et al., 2007	●	●	●	●
Germany Casserly et al., 2012; and proxy from Italy and Spain	●	●	●	●
Italy Casserly et al., 2012	●	●	●	●
Italy Latronico et al., 2014; and proxy from Spain	●	●	●	●
Spain Bouza et al., 2016; and proxy from Italy	●	●	●	●
UK Casserly et al., 2012	●	●	●	●
UK Mouncey et al., 2015; and proxy from Italy	●	●	●	●
Japan Proxy from Italy, Spain and the UK	●	●	●	●
Sources Not Used				
Italy Ferrario et al., 2016	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above

Figure 18: 7MM, Sources Used, In-Hospital Mortality Cases of Septic Shock

Sources Used	National Representativeness	Case Definition	Sample Size	Publication Date
US Fleischmann et al., 2016b; **Kadri et al., 2017**	●	●	●	●
France Fleischmann et al., 2016b; **Quenot et al., 2013**	●	●	●	●
Germany Fleischmann et al., 2016b	●	●	●	●
Italy Proxy from Spain	●	●	●	●
Spain **Bouza et al., 2016;** Fleischmann et al., 2016b	●	●	●	●
UK Proxy from Germany	●	●	●	●
Japan Fleischmann et al., 2016b; **Ogura et al., 2014**	●	●	●	●

Legend

National Representativeness
- National sample
- Multi-center study
- Single-center study
- Proxy or assumed value

Case Definition
- Matches definition
- Similar to definition
- Country-specific definition

Sample Size
- >1,000
- 500-1,000
- <500/unknown

Publication Date
- Within last 5 years
- Within last 6-10 years
- Over 10 years ago

Source: GlobalData; various sources listed above
*Source in bold is the main source used to forecast

5.4.2 Forecast Assumptions and Methods

5.4.2.1 7MM

GlobalData epidemiologists obtained the most up-to-date, country-specific total population data from the US Census Bureau's (USCB) International Data Base for each country covered in the forecast.

GlobalData epidemiologists obtained the most up-to-date, country-specific total population data from the US Census Bureau's (USCB) International Data Base for each country covered in the forecast. The USCB was chosen as the source for population data because population estimates are calculated using census and survey data, vital statistics, country-specific administrative statistics, and information from multinational organizations that collect and publish data for these countries. Additionally, the USCB uses a cohort-component projection method that incorporates fertility, mortality, and migration to forecast population estimates (USCB, 2016).

5.4.3 Diagnosed Incident Cases of Sepsis

5.4.3.1 US

To forecast the diagnosed incident cases of sepsis in the US, GlobalData epidemiologists obtained historic data (2008–2012) for the diagnosed incidence of sepsis for both sexes and all ages from the US Healthcare Cost and Utilization Project (HCUP) NIS database study (Stoller et al., 2016). The HCUP NIS database includes data for more than seven million hospital stays across 44 states in the US.

GlobalData epidemiologists applied linear regression to the historical data to forecast the diagnosed incidence of sepsis in the US for both sexes and all ages. Stroller and colleagues did not provide the diagnosed incidence of sepsis by age and sex; therefore, to calculate the age- and sex-specific diagnosed incidence of sepsis in the US, GlobalData epidemiologists used the age- and sex-specific distribution weights for sepsis incidence from a previous NIS database study by Dombrovskiy and colleagues and applied these weights to the projected incidence of sepsis for both sexes and all ages obtained from the regression analysis (Dombrovskiy et al., 2007). Due to a steep increase in the incidence after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists then applied the age- and sex-specific incidence rates to the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in the US (Dombrovskiy et al., 2007; Stoller et al., 2016; USCB, 2016).

Due to a steep increase in the incidence after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026).

5.4.3.2 France

To forecast the diagnosed incident cases of sepsis in France, GlobalData epidemiologists obtained the incidence of sepsis for both sexes and all ages from a nationwide prospective multi-centric survey of patients admitted to French ICUs over two weeks in 2001. Sepsis, being a potentially fatal disease, requires advanced medical attention throughout the hospital stay due to its associated organ dysfunction. The majority of the patients get admitted to the ICU for sepsis management, and ICU-acquired sepsis is common. Hence, GlobalData epidemiologists considered ICU studies are acceptable for forecasting the incidence of sepsis. The researchers did not provide the diagnosed incidence of sepsis by age or sex; therefore, to calculate the age- and sex-specific diagnosed incidence of sepsis in France, GlobalData epidemiologists used the number of sepsis cases obtained from the source for each sex and divided these cases by the respective sex-specific population (Brun-Buisson et al., 2004). GlobalData epidemiologists then calculated the age-specific incidence by using the weights of age- and sex-specific incidence of sepsis provided by Dombrovskiy and colleagues (Dombrovskiy et al., 2007). Due to non-availability of historic data, GlobalData epidemiologists held the age- and sex-specific diagnosed incidence of sepsis constant throughout the forecast period, and applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in France (Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; USCB, 2016).

5.4.3.3 Germany

To forecast the diagnosed incident cases of sepsis in Germany, GlobalData epidemiologists obtained the incidence of sepsis from nationwide discharge records available during 2007–2013 from the Federal Statistical Office. This database provided historic data for diagnosed incidence of sepsis; hence, GlobalData epidemiologists applied linear regression to the historic data to forecast the

diagnosed incidence of sepsis. Researchers provided age-specific diagnosed incidence of sepsis for all the ages but did not provide the sex-specific diagnosed incidence of sepsis; therefore, GlobalData epidemiologists calculated the sex-specific diagnosed incidence of sepsis by applying the sex-specific weights of sepsis (Fleischmann et al., 2016b). Due to a steep increase in the incidence after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in Germany (Fleischmann et al., 2016b; USCB, 2016).

5.4.3.4 Italy

Due to data scarcity for the diagnosed incidence of sepsis in Italy, GlobalData epidemiologists used the age- and sex-specific incidence of sepsis from Spain as a proxy for Italy. GlobalData epidemiologists then applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in Italy (Bouza et al., 2014; USCB, 2016).

5.4.3.5 Spain

To forecast the diagnosed incident cases of sepsis in Spain, GlobalData epidemiologists obtained the age- and sex-specific diagnosed incidence of sepsis from the nationwide records of discharges from acute hospitals during 2006–2011 from the official database of the Spanish Ministry of Health, Social Services and Equality (MSSSI) (Bouza et al., 2014). This database provided historic data for age- and sex-specific diagnosed incidence of sepsis; hence, GlobalData epidemiologists applied linear regression to the historic data to forecast the diagnosed incidence of sepsis. Due to a steep increase after 2016, the projected age- and sex-specific incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists then applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in Spain (Bouza et al., 2014; USCB, 2016).

5.4.3.6 UK

To forecast the diagnosed incident cases of sepsis in the UK, GlobalData epidemiologists obtained historic data for the diagnosed incidence of sepsis for both sexes and ages 16 years and older for the period 1996–2004 from the Case Mix Programme Database, which provides a national comparative audit of critical care for England, Wales, and Northern Ireland; it provides data of sepsis incidence at the time of admission to ICU or within 24 hours after admission to ICU (Harrison et al., 2006). GlobalData epidemiologists applied linear regression to the historic data to forecast the diagnosed incidence of sepsis. Harrison and colleagues did not provide the diagnosed incidence of sepsis by age or sex; therefore, to calculate the age- and sex-specific diagnosed incidence of sepsis in the UK,

GlobalData epidemiologists used the sex-specific distribution weights available from a US study (Lagu et al., 2012). To calculate the age-specific diagnosed incidence for ages 16–85 years and older, GlobalData epidemiologists used the age-specific incidence weights available from a study in the UK (Padkin et al., 2003). Additionally, to calculate the diagnosed incidence of sepsis for ages 0–15 years, age- and sex-specific incidence weights from another US study were used (Dombrovskiy et al., 2007). Due to a steep increase in the incidence of sepsis after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists then multiplied the age- and sex-specific incidence rates by the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in the UK. Because the forecast diagnosed incident cases of sepsis for the UK were for sepsis cases at the time of admission to ICU based on data from the Case Mix Programme Database, GlobalData epidemiologists calculated the ratio of all sepsis cases during the ICU admission/stay to the sepsis cases at the time of admission to ICU from Italy and multiplied this ratio by the forecast age- and sex-specific incident cases of sepsis in the UK for each year to obtain the diagnosed incident cases of sepsis in the UK during the ICU admission/stay (Dombrovskiy et al., 2007; Harrison et al., 2006; Lagu et al., 2012; Padkin et al., 2003; Sakr et al., 2013; USCB, 2016).

5.4.3.7 Japan

To forecast the diagnosed incident cases of sepsis in Japan, GlobalData epidemiologists obtained the number of ICUs and number of patients admitted to ICUs from the Japan Nosocomial Infections Surveillance (JANIS) database for 2008, 2012, and 2015 (JANIS, 2010; JANIS, 2013; JANIS, 2016). Additionally, the number of all ICUs available in Japan was obtained from Ministry of Health, Labour and Welfare (MHLW) and Japanese Society of Intensive Care Medicine statistics (JSICM) (JSICM, 2014; MHLW, 2008). Based on the study sample from the JANIS database, JSICM, and MLHW, GlobalData epidemiologists calculated the number of patients admitted to all the ICUs in Japan. Ogura and colleagues reported the proportion of sepsis cases among the patients admitted in the selected ICUs in Japan (Ogura et al., 2014). Based on the proportion, the sepsis incident cases were calculated by multiplying the proportion by all ICU patients in Japan, and further to obtain the sepsis incidence, the calculated sepsis cases were divided by the Japanese population. To obtain the age- and sex-specific diagnosed incidence of sepsis for Japan, GlobalData epidemiologists applied the age- and sex-specific incidence weights from a US study (Dombrovskiy et al., 2007; Lagu et al., 2012). Due to non-availability of historic data, the age- and sex-specific incidence was held constant for the entire forecast period. GlobalData epidemiologists then multiplied the age- and sex-specific incidence rates by the respective USCB population estimates to forecast the diagnosed incident cases of sepsis in

Japan (Dombrovskiy et al., 2007; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008).

5.4.4 Diagnosed Incident Cases of Septic Shock

5.4.4.1 US

To forecast the diagnosed incident cases of septic shock in the US, GlobalData epidemiologists obtained the diagnosed incidence of septic shock for both sexes for people ages 18 years and older from the NIS HCUP for the period 1998–2009 (Walkey et al., 2013). This source provided historic data of diagnosed incidence of septic shock in the US. The researchers did not provide age- and sex-specific incidence of septic shock in the US, so to calculate the age- and sex-specific diagnosed incidence of septic shock in the US for ages 18 years and older, and ages 0–18 years, GlobalData epidemiologists used the age- and sex-specific distribution weights of the diagnosed incidence of sepsis for ages 18 years and older, and ages 0–18 years, from the US (Dombrovskiy et al., 2007; Stroller et al., 2016; USCB, 2016). GlobalData epidemiologists applied linear regression to forecast the diagnosed incidence of septic shock. Due to a steep increase in the incidence of septic shock after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists then applied the age- and sex-specific incidence rates to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in the US (Dombrovskiy et al., 2007; Stroller et al., 2016; USCB, 2016; Walkey et al., 2013).

5.4.4.2 France

Due to data scarcity, GlobalData epidemiologists used the ratio of the age- and sex-specific diagnosed incidence of septic shock to the age- and sex-specific diagnosed incidence of sepsis from Germany to calculate the age- and sex-specific diagnosed incidence of septic shock in France (Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b). GlobalData epidemiologists then multiplied the age- and sex-specific diagnosed incidence rates of septic shock by the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in France (USCB, 2016).

5.4.4.3 Germany

To forecast the diagnosed incident cases of septic shock in Germany, GlobalData epidemiologists obtained the age-specific diagnosed incidence of septic shock for all ages from nationwide discharge records available during 2007–2013 from the Federal Statistical Office in Germany. This database provided historic data for the incidence of septic shock; hence, GlobalData epidemiologists applied linear regression to forecast the diagnosed incidence of septic shock. Researchers provided age-specific incidence of septic shock but did not provide the sex-specific diagnosed incidence of septic

shock; therefore, to calculate the age- and sex-specific diagnosed incidence of septic shock in Germany, GlobalData epidemiologists used the distribution weights of the age- and sex-specific incidence of sepsis (all forms) in Germany (Fleischmann et al., 2016b). Due to a steep increase in the incidence after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). GlobalData epidemiologists applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in Germany (Fleischmann et al., 2016b; USCB, 2016).

5.4.4.4 Italy

Due to data scarcity, GlobalData epidemiologists applied age- and sex-specific diagnosed incidence of septic shock from Spain as a proxy for Italy. GlobalData epidemiologists applied these rates to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in Italy (Bouza et al., 2014; de Miguel-Yanes et al., 2015; USCB, 2016).

5.4.4.5 Spain

To forecast the diagnosed incident cases of septic shock in Spain, GlobalData epidemiologists obtained the sex-specific diagnosed incidence of septic shock from a cohort-based, retrospective, observational study using the Spanish National Hospital Database (MBDS, minimum basic data set). This database is managed by the MSSSI (de Miguel-Yanes et al., 2015). This database provided historic data for the diagnosed incidence of septic shock for both sexes and all ages for the period from 2008 to 2012; hence, GlobalData epidemiologists applied linear regression to forecast the diagnosed incidence of septic shock. Due to a steep increase in the incidence after 2016, the projected incidence for 2016 was held constant for the remaining forecast period (2016–2026). The source did not provide age- and sex-specific incidence distribution for septic shock; however, the source provided sex-specific distribution of septic shock cases for the combined period 2008–2012. This sex-specific septic shock incidence (calculated from the cumulative period 2008–2012) distribution weight was used to calculate sex-specific incidence of septic shock for respective years for the projected period (2006–2016). Then, to calculate the age-specific incidence of septic shock, GlobalData epidemiologists used the age-specific distribution weights of diagnosed incidence of sepsis for the respective sexes from Spain (Bouza et al., 2014). Then, GlobalData epidemiologists applied this age- and sex-specific rate to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in Spain (Bouza et al., 2014; de Miguel-Yanes et al., 2015; USCB, 2016).

5.4.4.6 UK

Due to data scarcity, GlobalData epidemiologists used the ratio of the age- and sex-specific diagnosed incidence of septic shock to the age- and sex-specific diagnosed incidence of sepsis from Germany to calculate the age- and sex-specific diagnosed incidence of septic shock in the UK. GlobalData epidemiologists then applied these age- and sex-specific diagnosed incidence rates of septic shock to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in the UK (Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; Lagu et al., 2012; Padkin et al., 2003; Sakr et al., 2013, USCB, 2016).

5.4.4.7 Japan

Due to data scarcity, GlobalData epidemiologists used the ratio of the age- and sex-specific diagnosed incidence of septic shock to the age- and sex-specific diagnosed incidence of sepsis from Germany to calculate the age- and sex-specific diagnosed incidence of septic shock in Japan. GlobalData epidemiologists then applied the age- and sex-specific diagnosed incidence rates of septic shock to the respective USCB population estimates to forecast the diagnosed incident cases of septic shock in Japan (Dombrovskiy et al., 2007; Fleischmann et al., 2016b; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; USCB, 2016).

5.4.5 Diagnosed Incident Cases of Sepsis/Septic Shock by Causative Agent

5.4.5.1 7MM

Causative agents for sepsis/septic shock were segmented into the following categories: gram-positive bacteria, gram-negative bacteria, fungi, viruses, and parasites. Gram-positive, gram-negative, and fungi were the major categories among unknown organisms. Hence, the proportions of unknown/other organisms were distributed proportionally across these three categories. GlobalData epidemiologists assumed the proportion of causative organisms among diagnosed incident septic shock cases to be same as that of sepsis and vice versa. The overall proportion of diagnosed incident cases of sepsis/septic shock by causative agent is normalized to 100% in all 7MM. Due to data scarcity in some of the markets, GlobalData epidemiologists assumed the proportion in all ages to be the same as that for ages 18 years and above for those markets.

5.4.5.2 US

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, and fungi from a large hospital-based administrative national dataset, including hospital discharges from 1999–2008 for both sexes and all ages. The data were obtained from the NIS, which was developed as part of the HCUP (Ani et al., 2015). Unknown/other organisms (%) were distributed proportionally across these three

categories. Due to data scarcity, GlobalData epidemiologists obtained the proportion of viruses and parasites among the diagnosed incident cases of sepsis from France (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organism among diagnosed incident cases of septic shock to be same as that of sepsis. GlobalData epidemiologists held the causative agent proportions constant throughout the forecast period, and then applied these proportions to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in the US.

5.4.5.3 France

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in France, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, fungi, viruses, and parasites from a prospective cohort study that included all consecutive adult patients (both sexes and ages 18 years and older) with a diagnosis of septic shock admitted to 14 ICUs in 10 public hospitals in the North-East of France, during the period 2009–2011 (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organism among diagnosed incident cases of sepsis to be same as that of septic shock. GlobalData epidemiologists held the causative agent proportions of sepsis/septic shock constant throughout the forecast period, and then applied these proportions to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in France.

5.4.5.4 Germany

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in Germany, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, and fungi from a prospective cohort, multicenter, epidemiological and longitudinal observational study for both sexes and all ages carried out by the SepNet Critical Care Trials Group (SepNet) in 2013 (SepNet, 2016). Due to data scarcity, GlobalData epidemiologists obtained the proportion of viruses and parasites from France (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organisms among diagnosed incident cases of septic shock to be same as that of sepsis. GlobalData epidemiologists held the causative agent proportions of sepsis/septic shock constant throughout the forecast period, and then applied these proportions to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in Germany.

5.4.5.5 Italy

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in Italy, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, fungi, and viruses from the ALBIOS study—a multicenter, open-label, randomized, controlled trial—in 100 ICUs for both sexes and ages 18 years and older in Italy in 2014 (Caironi et al., 2014). Due to data scarcity, GlobalData epidemiologists obtained the proportion of parasites from France (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organism among diagnosed incident cases of septic shock to be same as that of sepsis. GlobalData epidemiologists held the causative agent proportions of sepsis/septic shock constant throughout the forecast period, and then applied these proportions to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in Italy.

5.4.5.6 Spain

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in Spain, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, and fungi among sepsis cases for both sexes and all ages from nationwide records of discharges from acute hospitals during 2006–2011 from the official database of MSSSI (Bouza et al., 2014). The anaerobic bacterial proportion is distributed equally to gram-positive and gram-negative bacteria. Due to data scarcity, GlobalData epidemiologists obtained the proportion of viruses and parasites from France (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organism among diagnosed incidents of septic shock to be same as that of septic shock. GlobalData epidemiologists held the causative agent proportions of sepsis/septic shock constant throughout the forecast period, and then applied these proportions to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in Spain.

5.4.5.7 UK

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in the UK, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, fungi, viruses, and parasites from a pragmatic, open, multicenter, parallel-group, randomized, controlled trial conducted in NHS hospitals in the UK for both sexes and ages 18 years and older (Mouncey et al., 2015). Mixed and unknown organisms are distributed to equally to gram-positive bacteria, gram-negative bacteria, and fungi. GlobalData epidemiologists assumed the proportion of causative organisms among diagnosed incident cases of sepsis to be same as that of septic shock. GlobalData epidemiologists held the causative agent percentages of sepsis/septic shock constant throughout the

forecast period, and then applied these percentages in the UK to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in the UK.

5.4.5.8 Japan

To forecast the diagnosed incident cases of sepsis/septic shock by causative agent in Japan, GlobalData epidemiologists obtained the proportion of gram-positive, gram-negative, fungi, and viruses from a large population-based database of the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study in ICUs throughout Japan (Hayakawa et al., 2016). Mixed, other, and unknown organisms are distributed equally to gram-positive bacteria, gram-negative bacteria, and fungi. Due to data scarcity, GlobalData epidemiologists obtained the proportion of parasites among diagnosed incident cases of sepsis from France (Quenot et al., 2013). GlobalData epidemiologists assumed the proportion of causative organisms among diagnosed incident sepsis cases to be same as that of septic shock. GlobalData epidemiologists held the causative agent proportion of sepsis/septic shock constant throughout the forecast period, and then applied these proportions in Japan to the respective diagnosed incident cases of sepsis/septic shock to forecast the diagnosed incident cases of sepsis/septic shock by causative organism in Japan.

5.4.6 Organ Dysfunction among Diagnosed Incident Cases of Sepsis

5.4.6.1 7MM

Organ dysfunction among diagnosed incident cases of sepsis was segmented into the following categories: kidney dysfunction, respiratory dysfunction, critical illness myopathy, critical illness polyneuropathy, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more). Due to data scarcity, GlobalData epidemiologists assumed the proportion in all ages to be the same as that for ages 18 years and older.

5.4.6.2 US

To forecast the organ dysfunction among diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data (2008–2012) from the NIS HCUP database from the US (Stoller et al., 2016). Stroller and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction among sepsis patients. Proportion of multiple organ dysfunctions (two organs and more) among sepsis patients was obtained from 2003–2007 NIS databases (Lagu et al., 2012). Critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) proportion among the diagnosed incident

cases of sepsis was calculated from a study by Khan and colleagues, who prospectively enrolled 48 sepsis patients of both sexes and all ages from the two intensive care units during 2003–2004 in the US (Khan et al., 2006). GlobalData epidemiologists then multiplied this organ dysfunctions proportion by the diagnosed incident cases of sepsis to calculate the respective organ dysfunction cases among the diagnosed incident cases of sepsis in the US.

5.4.6.3 France

To forecast the organ dysfunction among diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data from a study by Adrie and colleagues, which provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, and cardiovascular dysfunction among the diagnosed incident of sepsis for both sexes and all ages (Adrie et al., 2007). Encephalopathy proportion among diagnosed incident cases of sepsis was obtained from a retrospective study that analyzed sepsis patients of both sexes and all ages among those hospitalized in the ICU for over 24 hours from 35 ICUs (during 1997–2001) (Guidet et al., 2005). Due to data scarcity, CIM and CIP proportion among sepsis patients was obtained from Italy (Latronico et al., 2014); hepatic dysfunction and multiple organ dysfunctions (two organs and more) among sepsis was obtained from Spain (Bouza et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in France.

5.4.6.4 Germany

To forecast the organ dysfunction among the diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data from a prospective cross-sectional (one-day) study in a representative sample of 454 ICUs and 310 German hospitals during 2003–2004 (Engel et al., 2007). Engel and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, and hepatic dysfunction among the diagnosed incident cases of sepsis for both sexes and all ages. Due to data scarcity, CIM and CIP proportion among sepsis patients was obtained from Italy (Latronico et al., 2014); hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) proportions were obtained from Spain (Bouza et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunctions proportion by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in Germany.

To forecast the organ dysfunction among the diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data from a prospective cross-sectional of 454 ICUs and 310 German hospitals during 2003–2004.

5.4.6.5 Italy

To forecast CIP and CIM proportions among diagnosed incident cases of sepsis, GlobalData epidemiologists calculated data from a prospective observational study conducted in nine medical-surgical Italian ICUs on sepsis patients, which provided the number of CIP and CIM cases among the diagnosed incident cases of sepsis for both sexes and all ages during 2010–2012 (Latronico et al., 2014). Due to data scarcity, proportions of incident cases with kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) were obtained from Spain (Bouza et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in Italy.

5.4.6.6 Spain

To forecast the organ dysfunction among diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data from a study by Bouza and colleagues, which provided the proportions of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among the diagnosed incident of sepsis for both sexes and all ages during 2006–2011 (Bouza et al., 2014). Due to data scarcity, CIP and CIM proportions among sepsis patients were obtained from Italy as a proxy (Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in Spain.

5.4.6.7 UK

To forecast the organ dysfunction among diagnosed incident cases of sepsis, GlobalData epidemiologists calculated the proportion of organ dysfunction among sepsis cases of both sexes and all ages from four quarters of data from the Case Mix Programme Database, which contains data on 162,648 admissions to adult, general critical care units in 181 acute hospitals in the UK, during 2008–2009 (Shahin et al., 2012). The researchers provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among the sepsis patients. Due to data scarcity, CIP and CIM proportions among sepsis patients were obtained from Italy as a proxy, and encephalopathy and hepatic dysfunction proportion among sepsis patients was obtained from Spain (Bouza et al., 2014; Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion

by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in the UK.

5.4.6.8 Japan

To forecast the organ dysfunction among diagnosed incident cases of sepsis, GlobalData epidemiologists obtained data from Ogura and colleagues, who provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among diagnosed incident cases of sepsis cases of both sexes and all ages (Ogura et al., 2014). Due to data scarcity, the average CIP and CIM proportions among sepsis patients from Italy and the US were used as a proxy (Khan et al., 2006; Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of sepsis to get the respective organ dysfunction cases among the diagnosed incident cases of sepsis in Japan.

5.4.7 Organ Dysfunction among Diagnosed Incident Cases of Septic Shock

5.4.7.1 US

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data from the Surviving Sepsis Campaign on 27,836 septic shock patients (both sexes and all ages) from 218 sites across Europe, North America, and South America during 2005–2010 (Casserly et al., 2012). Casserly and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic shock patients. Due to data scarcity, CIP and CIM proportions among the septic shock patients were obtained from Italy as a proxy (Latronico et al., 2014). To calculate the encephalopathy proportion of septic shock cases, GlobalData epidemiologists took the averages of encephalopathy proportions of septic shock cases from Spain and the UK (Bouza et al., 2016; Mouncey et al., 2015). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in the US.

5.4.7.2 France

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data from Casserly and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic

shock cases (Casserly et al., 2012). Due to data scarcity, CIM and CIP proportions among septic shock cases were obtained from Italy as a proxy, and encephalopathy proportion among septic shock cases was obtained from Spain as a proxy (Bouza et al., 2016; Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in France.

5.4.7.3 Germany

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data from Casserly and colleagues that provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, encephalopathy, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic shock patients (Casserly et al., 2012). Due to data scarcity, CIM and CIP proportions among septic shock patients were obtained from Italy as a proxy (Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in Germany.

5.4.7.4 Italy

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data from Casserly and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic shock cases (Casserly et al., 2012). CIM and CIP proportions among septic shock cases were obtained from Latronico and colleagues (Latronico et al., 2014). Due to data scarcity, encephalopathy proportion among septic shock cases was obtained from Spain as a proxy (Bouza et al., 2016). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in Italy.

5.4.7.5 Spain

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data from a retrospective study that used the national MBDS of the Spanish MSSSI of septic shock patients during 2006–2011 (Bouza et al., 2016). Bouza and colleagues provided the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular

coagulopathy, hepatic dysfunction, encephalopathy, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic shock patients (Bouza et al., 2016). Due to data scarcity, CIM and CIP proportions among septic shock patients were obtained from Italy as a proxy (Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in Spain.

5.4.7.6 UK

To forecast the organ dysfunction among diagnosed incident cases of septic shock, GlobalData epidemiologists obtained data of septic shock cases from an open, multicenter, parallel-group, randomized controlled trial from the Case Mix Programme Database at 56 sites in the UK during 2011–2014 (Mouncey et al., 2015). Proportions of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, encephalopathy, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among the septic shock cases were calculated from early, goal-directed therapy, and usual-care septic shock patients (Mouncey et al., 2015). Due to data scarcity, CIP and CIM proportions among septic shock patients were obtained from Italy as a proxy (Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in the UK.

5.4.7.7 Japan

To calculate the proportion of kidney dysfunction, respiratory dysfunction, disseminated intravascular coagulopathy, hepatic dysfunction, encephalopathy, cardiovascular dysfunction, and multiple organ dysfunctions (two organs and more) among septic shock patients, GlobalData epidemiologists took the averages of these organ dysfunction proportions among septic shock cases from the 7MM (Bouza et al., 2016; Casserly et al., 2012; Mouncey et al., 2015). Due to data scarcity, CIP and CIM proportions among septic shock patients were obtained from Italy as a proxy (Latronico et al., 2014). GlobalData epidemiologists then multiplied the organ dysfunction proportion by the diagnosed incident cases of septic shock to get the respective organ dysfunction cases among the diagnosed incident cases of septic shock in Japan.

5.4.8 Sepsis In-Hospital Mortality Cases

5.4.8.1 US

To forecast the sepsis in-hospital mortality cases in the US, GlobalData epidemiologists obtained the historic data (2008–2012) of the proportion of in-hospital mortality among sepsis cases from the

HCUP NIS database from the US (Stoller et al., 2016). The NIS database contains data from more than seven million hospital stays across 44 US states. GlobalData epidemiologists applied linear regression to forecast the in-hospital mortality proportion among the sepsis cases in the US. Due to a steep decline in the in-hospital sepsis mortality proportion after 2016, the projected in-hospital mortality rate for 2016 was held constant for the remaining forecast period (2016–2026). To calculate the in-hospital mortality cases of sepsis, GlobalData epidemiologists first calculated the number of sepsis mortality cases by multiplying the in-hospital mortality proportion of sepsis by the diagnosed incident cases of sepsis. The calculated in-hospital mortality cases of sepsis were divided by the respective year's USCB population (USCB, 2016) to calculate the in-hospital mortality rate of sepsis per 100,000 population for all ages. Stroller and colleagues did not provide the in-hospital mortality rates of sepsis by age; therefore, GlobalData epidemiologists used the age-specific distribution weights of in-hospital mortality rate of sepsis available from the previous NIS database study by Dombrovskiy and colleagues to calculate the age-specific mortality rates of sepsis in the US (Dombrovskiy et al., 2007). GlobalData epidemiologists then multiplied the age-specific in-hospital mortality rates of sepsis by the respective USCB population estimates in the forecast years to forecast the in-hospital death of sepsis cases in the US (Dombrovskiy et al., 2007; Stoller et al., 2016; USCB, 2016).

5.4.8.2 France

To forecast the sepsis in-hospital mortality cases in France, GlobalData epidemiologists obtained data on patients ages 16 years and older from a prospective observational study in a multicenter database (12 French ICUs) during the period 1997–2005 (Adrie et al., 2007). GlobalData epidemiologists calculated the number of sepsis in-hospital mortality cases sepsis by multiplying the in-hospital mortality sepsis proportion by the diagnosed incident cases of sepsis. To calculate the in-hospital mortality rates of sepsis per 100,000 general population, GlobalData epidemiologists divided the calculated in-hospital mortality cases among the sepsis cases ages 16 years and older by the respective year's USCB population (USCB, 2016). Adrie and colleagues did not provide the age-specific in-hospital mortality cases of sepsis in the US. To calculate the age-specific mortality rates of sepsis in France for all ages, GlobalData epidemiologists used the age-specific distribution weights available from the previous NIS database studies by Dombrovskiy and colleagues, and Lagu and colleagues in the US (Dombrovskiy et al., 2007; Lagu et al., 2012). GlobalData epidemiologists then multiplied this age-specific in-hospital mortality rate of sepsis by the respective USCB population estimates to forecast the in-hospital mortality cases of sepsis among the general population in France (Adrie et al., 2007; Dombrovskiy et al., 2007; Lagu et al., 2012; USCB, 2016).

GlobalData epidemiologists calculated the number of sepsis in-hospital mortality cases sepsis by multiplying the in-hospital mortality sepsis proportion by the diagnosed incident cases of sepsis.

5.4.8.3 Germany

To forecast the in-hospital mortality cases of sepsis in Germany, GlobalData epidemiologists obtained the in-hospital mortality proportion of sepsis from nationwide discharge records available during 2007–2013 from the Federal Statistical Office (Fleischmann et al., 2016b). This database provided historic data of age-specific in-hospital mortality proportion of sepsis; hence, GlobalData epidemiologists applied linear regression to forecast the in-hospital mortality proportion of sepsis. Due to a steep decline in the in-hospital sepsis mortality proportion after 2016, the projected in-hospital mortality rate for 2016 was held constant for the remaining forecast period (2016–2026). To calculate the in-hospital mortality cases of sepsis, GlobalData epidemiologists multiplied the in-hospital mortality proportions by the diagnosed incident cases of sepsis for all ages. This study provided age-specific in-hospital mortality of sepsis for the cumulative study period (2007–2013). To calculate the age-specific in-hospital mortality cases for projected years, GlobalData epidemiologists multiplied the in-hospital mortality cases of sepsis of all ages by the distribution weights of age-specific in-hospital mortality of sepsis for the cumulative period (2007–2013) (Fleischmann et al., 2016b; USCB, 2016).

5.4.8.4 Italy

Due to data scarcity, GlobalData epidemiologists applied age-specific in-hospital mortality rate of sepsis from Spain as a proxy for Italy. GlobalData epidemiologists applied these rates to the respective USCB population estimates to forecast the in-hospital mortality cases in Italy (Bouza et al., 2014; USCB, 2016).

5.4.8.5 Spain

To forecast the sepsis in-hospital mortality cases in Spain, GlobalData epidemiologists obtained the in-hospital mortality rates of sepsis from nationwide records of discharges from acute hospitals during 2006–2011 from the official database of MSSI (Bouza et al., 2014). This database provided historic data of in-hospital mortality rate of sepsis per 100,000 population for all ages; hence, GlobalData epidemiologists applied linear regression to forecast the in-hospital mortality rate of sepsis for both sexes in Spain. Due to a steep increase in the in-hospital sepsis mortality rate after 2016, the projected in-hospital mortality rate for 2016 was held constant for the remaining forecast period (2016–2026). To calculate the age-specific in-hospital mortality cases of sepsis, GlobalData epidemiologists applied the age-specific sepsis incidence distribution weights and multiplied by the in-hospital mortality rate of sepsis for the projected period (2006–2016). GlobalData epidemiologists then applied the age-specific mortality rates to the respective USCB population estimates to forecast the in-hospital mortality cases in Spain (Bouza et al., 2014; USCB, 2016).

5.4.8.6 UK

To forecast the sepsis in-hospital mortality cases in the UK, GlobalData epidemiologists obtained the in-hospital mortality rates of sepsis from the Case Mix Programme Database, which provides a national comparative audit of critical care for England, Wales, and Northern Ireland; it provides data of sepsis admissions during 24 hours for the period 1996–2004 (Harrison et al., 2006). This database provided historic data of in-hospital mortality rate (in cases per 100,000 population) of sepsis; hence, GlobalData epidemiologists applied linear regression to forecast the in-hospital mortality rate of sepsis. Due to a steep increase in the in-hospital sepsis mortality rate after 2016, the projected in-hospital mortality rate for 2016 was held constant for the remaining forecast period (2016–2026).To calculate the age-specific in-hospital mortality cases of sepsis, GlobalData epidemiologists multiplied the in-hospital mortality rate of sepsis for 2006–2016 by the age-specific sepsis incidence distribution weights from the NIS database study in the US (Dombrovskiy et al., 2007; Lagu et al., 2012). GlobalData epidemiologists then multiplied the calculated age-specific in-hospital mortality rates of sepsis by the respective USCB population estimates to forecast the in-hospital mortality cases of sepsis in the UK (Dombrovskiy et al., 2007; Harrison et al., 2006; Lagu et al., 2012; USCB, 2016).

5.4.8.7 Japan

To forecast the sepsis in-hospital mortality cases in Japan, GlobalData epidemiologists obtained the in-hospital mortality proportion among the sepsis cases ages 18 years and older from a prospectively conducted multicenter survey at 15 critical care centers in tertiary care hospitals between 2010–2011; all sepsis patients admitted to the ICU were enrolled in this study (Ogura et al., 2014). Due to data scarcity, GlobalData epidemiologists assumed the in-hospital mortality proportion of sepsis in ages 18 years and older to be same as that of all ages. Firstly, to calculate the in-hospital mortality cases of sepsis for all ages and both sexes in Japan, GlobalData epidemiologists multiplied the in-hospital sepsis mortality rate (per 100,000 population) by the USCB population estimates for all ages and both sexes for the forecast period 2006–2026). Secondly, to calculate the age-specific in-hospital mortality of sepsis in Japan, GlobalData epidemiologists applied the distribution weights of age-specific diagnosed incident cases of sepsis with the in-hospital mortality cases of sepsis for the respective years (Ogura et al., 2014; USCB, 2016).

5.4.9 Septic Shock In-Hospital Mortality Cases

5.4.9.1 US

To forecast septic shock in-hospital mortality cases in the US, GlobalData epidemiologists obtained data from a retrospective cohort study using data of septic shock cases of all ages from the University

Health System Consortium from 27 US academic medical centers using electronic health records (EHR) clinical data versus claims data during 2005–2014 (Kadri et al., 2017). This provided 10-year historic data; hence, GlobalData epidemiologists applied linear regression to calculate the in-hospital mortality proportion of septic shock. Due to a steep decline in mortality proportion after 2016, the projected in-hospital mortality proportion of septic shock for 2016 was held constant for the remaining forecast period (2016–2026). To calculate the age-specific in-hospital mortality cases in the US, GlobalData epidemiologists used the age-specific in-hospital mortality cases distribution weights of septic shock from Germany (Fleischmann et al., 2016b). GlobalData epidemiologists then multiplied the age-specific in-hospital mortality proportion of septic shock by the diagnosed incident cases of septic shock to forecast the septic shock in-hospital mortality cases in the US (Fleischmann et al., 2016b; Kadri et al., 2017; USCB, 2016).

5.4.9.2 France

To forecast septic shock in-hospital mortality cases in France, GlobalData epidemiologists obtained data from a prospective cohort study of septic shock patients ages 18 years and older admitted to 14 ICUs in 10 public hospitals in the North-East of France during 2009–2011 (Quenot et al., 2013). The study did not provide age-specific in-hospital mortality of septic shock; hence, GlobalData epidemiologists used the age-specific in-hospital mortality cases distribution weights of septic shock from Germany to calculate age distribution for France (Fleischmann et al., 2016b). GlobalData epidemiologists then multiplied the age-specific in-hospital mortality of septic shock by the diagnosed incident cases of septic shock to forecast the septic shock in-hospital mortality cases in France (Fleischmann et al., 2016b; Quenot et al., 2013; USCB, 2016).

5.4.9.3 Germany

To forecast septic shock in-hospital mortality cases in Germany, GlobalData epidemiologists obtained data from a study of nationwide discharge records available during 2007–2013 from the Federal Statistical Office. This study provided historic data of septic shock in-hospital mortality proportion among septic shock cases; hence, GlobalData epidemiologists applied linear regression to forecast trends in the in-hospital mortality of septic shock. Due to a steep decline in mortality after 2016, the projected in-hospital mortality proportion of septic shock of 2016 was held constant for the remaining forecast period (2016–2026). Researchers provided age-specific in-hospital mortality cases of septic shock for the cumulative period (2007–2013). GlobalData epidemiologists calculated the age-specific septic shock in-hospital mortality cases using age-specific weights (Fleischmann et al., 2016b; USCB, 2016).

5.4.9.4 Italy

Due to data scarcity, GlobalData epidemiologists applied the age-specific, in-hospital mortality proportion of septic shock from Spain as a proxy for Italy. GlobalData epidemiologists then multiplied the age-specific in-hospital mortality proportion of septic shock by the diagnosed incident cases of septic shock to calculate the age-specific septic shock in-hospital mortality cases in Italy (Bouza et al., 2016; Fleischmann et al., 2016b; USCB, 2016).

5.4.9.5 Spain

To forecast the septic shock in-hospital mortality cases in Spain, GlobalData epidemiologists obtained the in-hospital mortality proportion of septic shock cases in ages 18 years and above from the study by Bouza and colleagues (Bouza et al., 2016). Due to data scarcity, GlobalData epidemiologists assumed the in-hospital mortality of septic shock among ages 0–18 years to be same as that among ages 18 years and above. The study did not provide age-specific septic shock in-hospital mortality proportion; hence, GlobalData epidemiologists used the age-specific in-hospital mortality cases distribution weights of septic shock from Germany to segment by age (Fleischmann et al., 2016b). GlobalData epidemiologists then multiplied the age-specific in-hospital mortality proportion of septic shock by the diagnosed incident cases of septic shock to calculate the septic shock in-hospital mortality cases in Spain (Bouza et al., 2016; Fleischmann et al., 2016b; USCB, 2016).

5.4.9.6 UK

Due to data scarcity, GlobalData epidemiologists applied the age-specific in-hospital mortality of septic shock from Germany as a proxy for the UK. GlobalData epidemiologists then multiplied the age-specific in-hospital mortality proportion of septic shock by the diagnosed incident cases of septic shock to calculate the septic shock in-hospital mortality cases in the UK (Fleischmann et al., 2016b; USCB, 2016).

5.4.9.7 Japan

To forecast septic shock in-hospital mortality cases in Japan, GlobalData epidemiologists obtained in-hospital mortality proportion among the septic shock cases ages 18 years and above from a study that prospectively conducted a multicenter survey at 15 critical care centers in tertiary care hospitals between 2010–2011; all septic shock patients admitted to the ICU were enrolled in this study (Ogura et al., 2014). Due to data scarcity, GlobalData epidemiologists assumed the mortality proportion in ages 18 years and above to be same as that of all ages. The study did not provide age-specific data; hence, GlobalData epidemiologists used the age-specific in-hospital mortality distribution weights of septic shock from Germany (Fleischmann et al., 2016b). GlobalData epidemiologists then multiplied

the age-specific in-hospital mortality of septic shock by the diagnosed incident cases of septic shock to forecast the septic shock in-hospital mortality cases in Japan (Fleischmann et al., 2016b; Ogura et al., 2014; USCB, 2016).

5.5 Epidemiological Forecast for Sepsis and Septic Shock (2016–2026)

5.5.1 Diagnosed Incident Cases of Sepsis

GlobalData epidemiologists forecast that the diagnosed incident cases of sepsis in the 7MM will grow by an Annual Growth Rate (AGR) of 2.06% per year over the next 10 years.

GlobalData epidemiologists forecast that the diagnosed incident cases of sepsis in the 7MM will grow by an Annual Growth Rate (AGR) of 2.06% per year over the next 10 years, from 2,594,665 cases in 2016 to 3,129,753 cases in 2026. Additionally, the US will have the highest AGR of 2.34%, while Italy will have the lowest AGR of 0.82%. Of the 7MM, the US had the highest number of diagnosed incident cases with 2,005,428 cases in 2016, while Japan had the lowest number of diagnosed incident cases with 33,791 cases in 2016. Of the 5EU in 2016, Germany had the highest number of diagnosed incident cases with 148,628 cases, while Spain had the lowest number of diagnosed incident cases with 73,170 cases. In 2016, the US accounted for more than 75% of all the diagnosed incident cases of sepsis, while Japan accounted for only 1.30% of diagnosed incident cases of sepsis in the 7MM. In the forecast, changes in the diagnosed incident cases can be attributed to changes in the underlying population structure of each market.

Table 10 presents the diagnosed incident cases of sepsis in both sexes and all ages in the 7MM for select years in 2016 from 2026.

Table 10: 7MM, Diagnosed Incident Cases of Sepsis, Both Sexes, All Ages, Selected Years 2016–2026

Market	2016	2018	2020	2022	2024	2026	AGR (%)
US	2,005,428	2,088,530	2,179,725	2,275,653	2,376,825	2,474,494	2.34%
France	87,912	90,486	92,823	94,889	97,156	99,576	1.33%
Germany	148,628	152,106	155,604	158,417	161,041	163,319	0.99%
Italy	104,339	105,761	107,284	108,949	110,735	112,923	0.82%
Spain	73,170	75,072	76,997	79,138	81,656	84,298	1.52%
UK	141,397	144,810	148,090	151,417	154,420	157,293	1.12%
Japan	33,791	34,955	35,850	36,613	37,187	37,850	1.20%
5EU	**555,446**	**568,235**	**580,798**	**592,810**	**605,008**	**617,409**	**1.12%**
7MM	**2,594,665**	**2,691,720**	**2,796,373**	**2,905,076**	**3,019,020**	**3,129,753**	**2.06%**

Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016

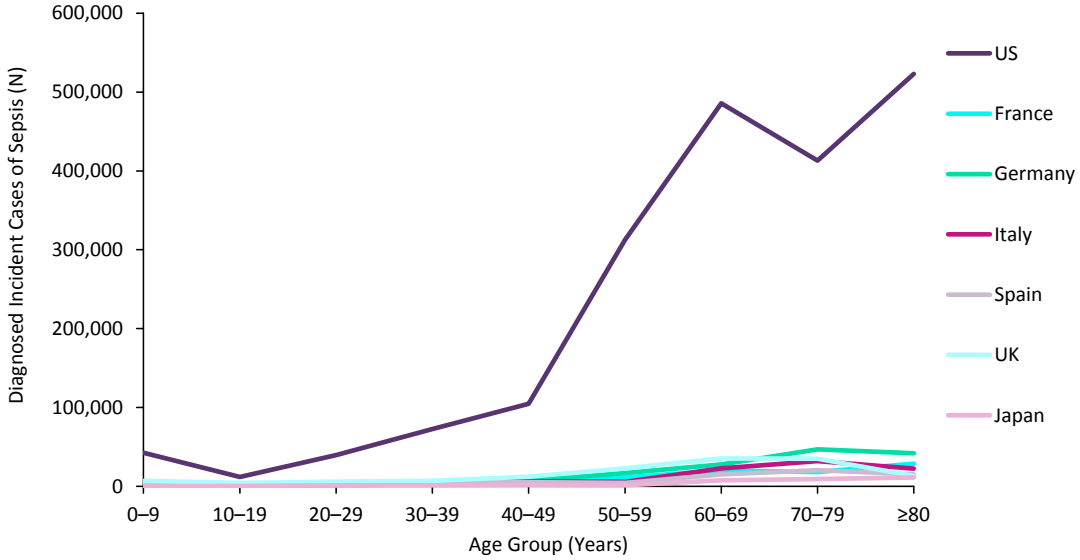
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.2 Age-Specific Diagnosed Incident Cases of Sepsis

Sepsis shows a strong trend of increase in diagnosed incident cases with age that is consistent throughout the 7MM. In 2016, people ages 80 years and above composed the highest proportion (25.24%) of diagnosed incident cases of sepsis, followed by adults ages 60–69 years (23.67%). Children and adolescents ages 10–19 years accounted for the fewest diagnosed incident cases of sepsis (0.93%) in the 7MM. The differences in the number of diagnosed incident cases of sepsis across the various age groups and markets may be attributed to differences in the actual age-specific diagnosed incidence combined with differences in the population demographics in these markets.

Figure 19 presents the age-specific diagnosed incident cases of sepsis in both sexes in the 7MM in 2016.

Figure 19: 7MM, Age-Specific Diagnosed Incident Cases of Sepsis, Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016

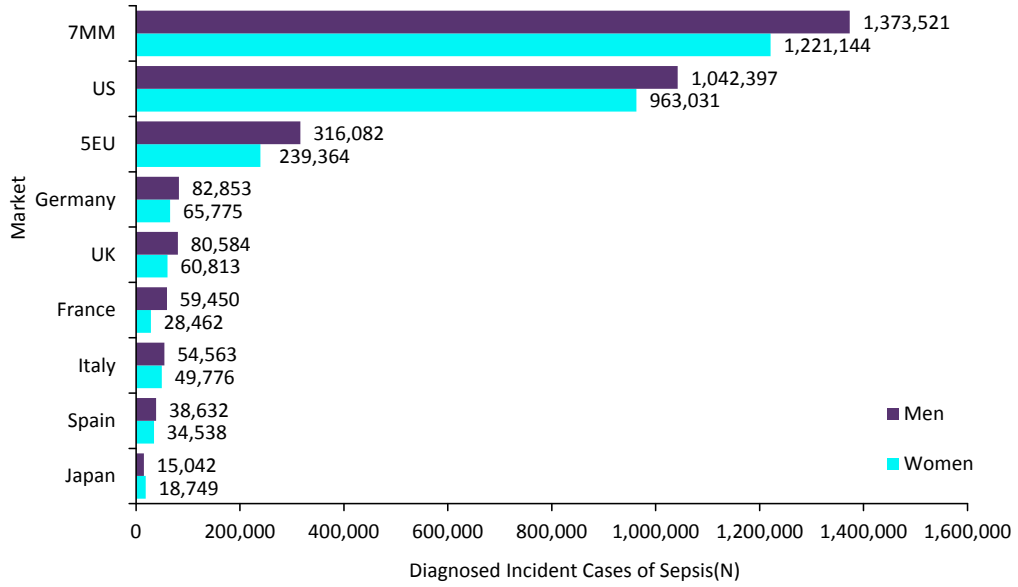
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.3 Sex-Specific Diagnosed Incident Cases of Sepsis

In the 7MM in 2016, the diagnosed incident cases of sepsis occurred almost equally in both sexes, with men being at a slightly higher proportion of 52.94%, with 1,373,521 cases, and women accounting for 47.06%, with 1,221,144 cases. In the US, the number of diagnosed incident cases of sepsis was much higher than in other markets, with 1,042,397 cases in men, while women accounted for 963,031 cases. Japan had the lowest number of cases in men, with 15,042 cases, and in women, with 18,749 cases. Interestingly, among the 7MM, Japan reported more diagnosed incident cases of sepsis in women compared with men. The differences in the numbers of diagnosed incident cases of sepsis across the sexes and markets may be mostly attributed to differences in the underlying demographic differences in each market as well as the significant differences in sex-specific diagnosed incidence.

Figure 20 presents the sex-specific diagnosed incident cases of sepsis in all ages in the 7MM in 2016.

Figure 20: 7MM, Sex-Specific Diagnosed Incident Cases of Sepsis, Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

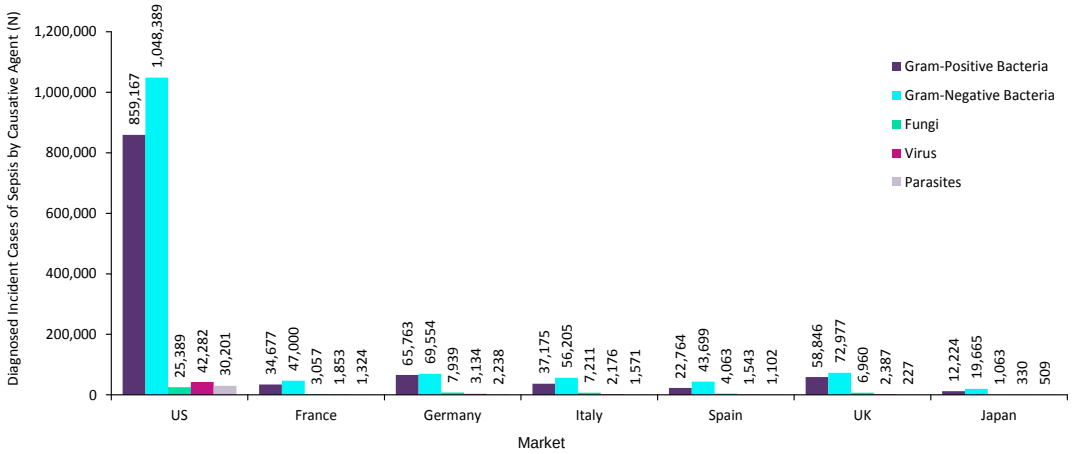
5.5.4 Diagnosed Incident Cases of Sepsis by Causative Agent

In each of the 7MM, gram-negative bacteria caused the highest number of sepsis cases, whereas parasites caused the least number of sepsis cases.

GlobalData epidemiologists reviewed the causative agent distributions in diagnosed incident cases of sepsis, and the pathogens responsible for sepsis are predominantly gram-positive bacteria, gram-negative bacteria, fungi, viruses, and parasites. In each of the 7MM, gram-negative bacteria caused the highest number of sepsis cases, whereas parasites caused the least number of sepsis cases. On the whole, gram-negative and gram-positive bacteria are the major causative agents for sepsis across the 7MM.

Figure 21 presents diagnosed incident cases of sepsis by causative agent in both sexes and all ages in the 7MM in 2016.

Figure 21: 7MM, Diagnosed Incident Cases of Sepsis by Causative Agent, Both Sexes, All Ages, 2016



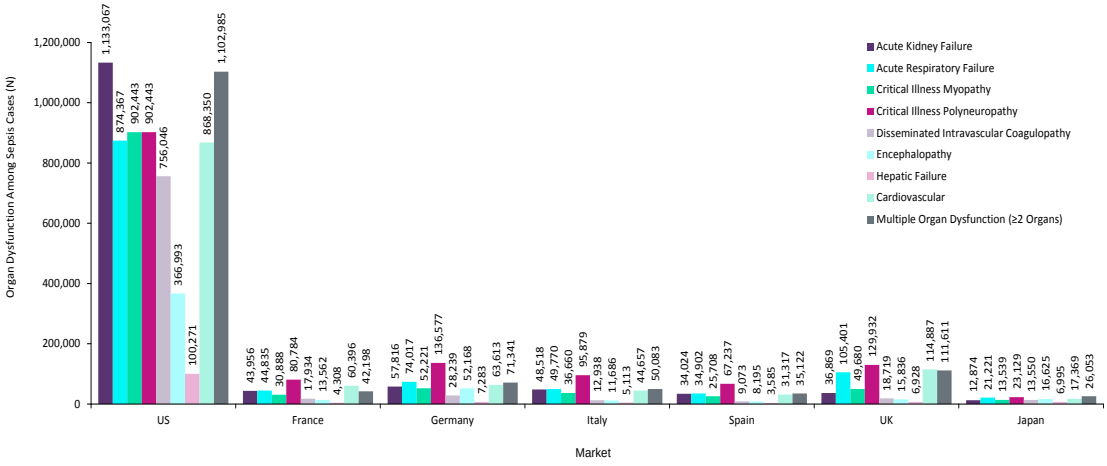
Source: GlobalData; Ani et al., 2015; Bouza et al., 2014; Caironi et al., 2014; Hayakawa et al., 2016; Mouncey et al., 2015; Quenot et al., 2013; SepNet, 2016

5.5.5 Organ Dysfunction among Diagnosed Incident Cases of Sepsis

GlobalData epidemiologists forecast the organ dysfunction among diagnosed incident cases of sepsis. In the 7MM combined, multiple organ dysfunction (two or more organs), and critical illness polyneuropathy among sepsis cases are the predominant organ dysfunction types. This is followed by kidney failure and respiratory failure among diagnosed incident cases of sepsis in the 7MM.

Figure 22 presents the organ dysfunction among diagnosed incident cases of sepsis in both sexes and all ages in the 7MM in 2016.

Figure 22: 7MM, Organ Dysfunction among Diagnosed Incident Cases of Sepsis, Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2014; Engel et al., 2007; Guidet et al., 2005; Khan et al., 2006; Lagu et al., 2012; Latronico et al., 2014; Ogura et al., 2014; Shahin et al., 2012; Stoller et al., 2016

5.5.6 Sepsis In-Hospital Mortality Cases

GlobalData epidemiologists forecast that the sepsis in-hospital mortality cases in the 7MM will grow by an AGR of 2.24% per year over the next 10 years, from 487,814 cases in 2016 to 597,044 cases in 2026. Additionally, Germany will have the highest AGR of 3.15%, while Japan will have the lowest at negative 0.30%. Of the 7MM, the US had the highest number of sepsis in-hospital mortality cases with 290,378 cases in 2016, while Japan had the lowest number of sepsis in-hospital mortality cases with 8,596 cases in 2016. In 2026, the corresponding figures in the US and Japan are forecast to be 363,847 and 8,338 cases respectively. Of the 5EU in 2016, Germany had the highest number of sepsis in-hospital mortality cases with 58,577 cases, while the UK had the lowest number of sepsis in-hospital mortality cases with 27,276 cases. In 2016, the US accounted for 59.53% of sepsis in-hospital mortality cases, while Japan accounted for only 1.76% of sepsis in-hospital mortality cases in the

GlobalData epidemiologists forecast that the sepsis in-hospital mortality cases in the 7MM will grow by an AGR of 2.24% per year over the next 10 years.

7MM. In the forecast, changes in the in-hospital mortality cases can be attributed to trends in the in-hospital mortality rates as well as changes in the underlying population structure of each market.

Table 11 presents the sepsis in-hospital mortality cases in both sexes, all ages in the 7MM for select years from 2016 to 2026.

Table 11: 7MM, Sepsis In-Hospital Mortality Cases, Both Sexes, All Ages, Selected Years 2016–2026

Market	2016	2018	2020	2022	2024	2026	AGR (%)
US	290,378	302,970	316,963	331,974	348,240	363,847	2.53%
France	32,169	33,356	34,413	35,365	36,260	37,055	1.52%
Germany	58,577	71,629	73,678	75,329	76,861	78,163	3.15%
Italy	41,653	42,214	42,817	43,478	44,188	45,055	0.82%
Spain	29,165	29,919	30,679	31,532	32,528	33,575	1.51%
UK	27,276	27,894	28,507	29,242	30,108	31,011	1.37%
Japan	8,596	8,561	8,515	8,463	8,403	8,338	-0.30%
5EU	**188,840**	**205,012**	**210,094**	**214,946**	**219,945**	**224,859**	**1.91%**
7MM	**487,814**	**516,543**	**535,572**	**555,383**	**576,588**	**597,044**	**2.24%**

Source: GlobalData; Adrie et al., 2007; Bouza et al., 2014; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; Lagu et al., 2012; Ogura et al., 2014; Stoller et al., 2016

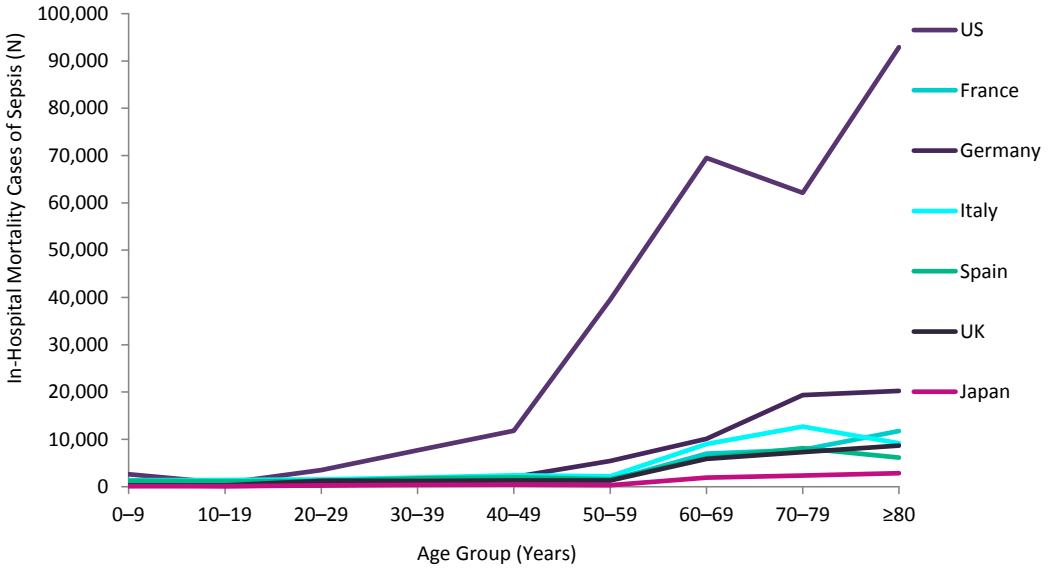
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.7 Age-Specific In-Hospital Mortality Cases of Sepsis

In-hospital mortality cases of sepsis show a strong trend with increasing age that is consistent throughout the 7MM. In 2016, people ages 80 years and older composed the highest proportion (31.11%) of in-hospital mortality cases of sepsis, followed by people ages 70–79 years (24.54%). Children and adolescents ages 10–19 years accounted for the fewest in-hospital mortality cases of sepsis (0.83%) in the 7MM. The differences in the number of in-hospital mortality cases of sepsis across the various age groups and markets may be attributed to differences in the actual age-specific in-hospital mortality rate combined with differences in the population demographics in these markets.

Figure 23 presents the age-specific sepsis in-hospital mortality cases in both sexes in the 7MM in 2016.

Figure 23: 7MM, Age-Specific In-Hospital Mortality Cases of Sepsis, Both Sexes, All Ages, 2016



Source: GlobalData; Adrie et al., 2007; Bouza et al., 2014; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; Lagu et al., 2012; Ogura et al., 2014; Stoller et al., 2016

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.8 Diagnosed Incident Cases of Septic Shock

GlobalData epidemiologists forecast that the diagnosed incident cases of septic shock in the 7MM will grow by an AGR of 2.07% per year over the next 10 years, from 539,085 cases in 2016 to 650,426 cases in 2026. Additionally, the US will have the highest AGR of 2.59%, while Italy will have the lowest at 0.83%. Of the 7MM, the US had the highest number of diagnosed incident cases of septic shock with 351,955 cases in 2016, while Japan had the lowest number of diagnosed incident cases of septic shock with 10,385 cases in 2016. In 2026, the corresponding figures in the US and Japan will be 443,112 and 11,351 cases respectively. Of the 5EU in 2016, Germany had the highest number of diagnosed incident cases of septic shock with 46,233 cases, while Spain had the lowest number of diagnosed incident cases with 23,998 cases. In 2016, the US accounted for 65.29% of all the septic shock cases, while Japan accounted for only 1.93% of diagnosed incident cases of septic shock in the 7MM. In the forecast, changes in diagnosed incident cases can be attributed to changes in the underlying population structure of each market.

Table 12 presents the diagnosed incident cases of septic shock in both sexes, all ages in the 7MM for select years from 2016 to 2026.

Table 12: 7MM, Diagnosed Incident Cases of Septic Shock, Both Sexes, All Ages, Selected Years 2016–2026

Market	2016	2018	2020	2022	2024	2026	AGR (%)
US	351,955	368,846	386,980	405,582	424,293	443,112	2.59%
France	27,490	28,265	28,967	29,587	30,258	30,976	1.27%
Germany	46,233	47,298	48,337	49,156	49,874	50,463	0.91%
Italy	34,175	34,646	35,146	35,695	36,286	37,005	0.83%
Spain	23,998	24,631	25,260	25,965	26,796	27,664	1.53%
UK	44,849	45,899	46,933	47,976	48,925	49,855	1.12%
Japan	10,385	10,689	10,900	11,078	11,203	11,351	0.93%
5EU	**176,745**	**180,739**	**184,643**	**188,379**	**192,139**	**195,963**	**1.09%**
7MM	**539,085**	**560,274**	**582,523**	**605,039**	**627,635**	**650,426**	**2.07%**

Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; de Miguel-Yanes et al., 2015; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016; Walkey et al., 2013

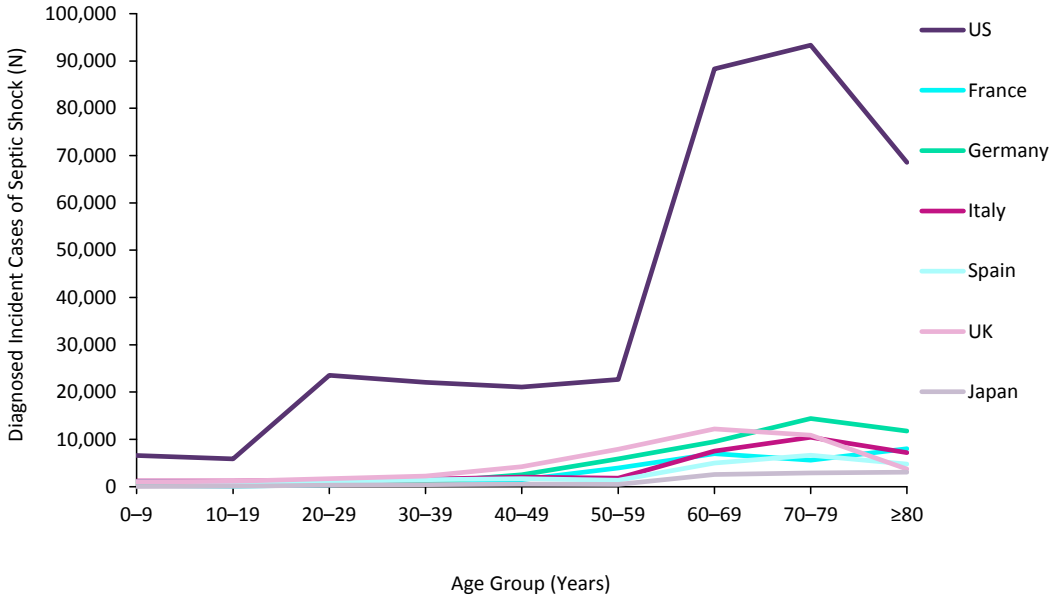
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.9 Age-Specific Diagnosed Incident Cases of Septic Shock

Septic shock shows a strong trend of increase in diagnosed incident cases with age that is consistent throughout the 7MM. In 2016, people ages 70–79 years composed the highest proportion (26.74%) of diagnosed incident cases of septic shock, followed by ages 60–69 years (24.50%) and ages 80 years and older (19.87%). Children and adolescents ages 10–19 years accounted for the fewest diagnosed incident cases of septic shock (1.78%) in the 7MM. The differences in the number of diagnosed incident cases of septic shock across the various age groups and markets may be attributed to differences in the actual age-specific diagnosed incidence combined with differences in the population demographics in these markets.

Figure 24 presents the age-specific diagnosed incident cases of septic shock in both sexes, in the 7MM in 2026.

Figure 24: 7MM, Age-Specific Diagnosed Incident Cases of Septic Shock, Both Sexes, All Ages, 2016



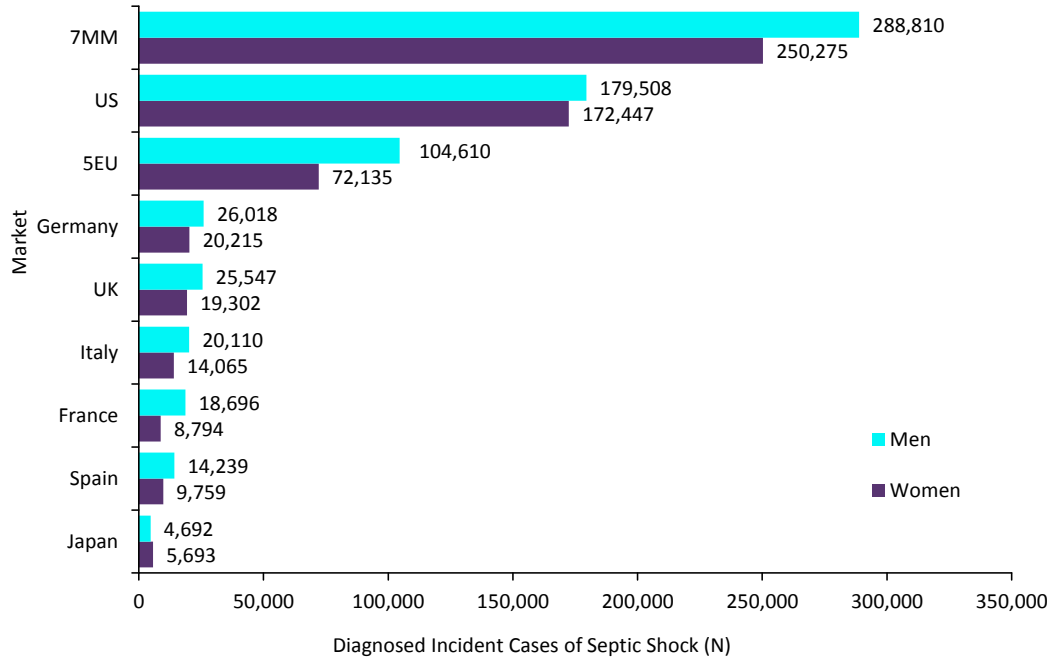
Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; de Miguel-Yanes et al., 2015; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016; Walkey et al., 2013

5.5.10 Sex-Specific Diagnosed Incident Cases of Septic Shock

In the 7MM in 2016, the diagnosed incident cases of septic shock occurred almost equally in both sexes, with men being at a slightly higher proportion of 53.57%, with 288,810 cases, and women accounting for 46.43%, with 250,275 cases. In the US, the number of cases in men was much higher than in other markets, with 179,508 cases, while women accounted for 172,447 cases. Japan had the lowest number of cases in men, with 4,692 cases, and in women, with 5,693 cases. Similar to the diagnosed incident cases of sepsis, among the 7MM, Japan reported slightly higher diagnosed incident cases of septic shock in women compared with men. The differences in the numbers of diagnosed incident cases of septic shock across the sexes and markets can be attributed to the differences in the underlying demographic differences in each market as well as the significant differences in sex-specific diagnosed incidence.

Figure 25 presents the sex-specific diagnosed incident cases of septic shock in all ages, in the 7MM in 2016.

Figure 25: 7MM, Sex-Specific Diagnosed Incident Cases of Septic Shock, Both Sexes, All Ages, 2016



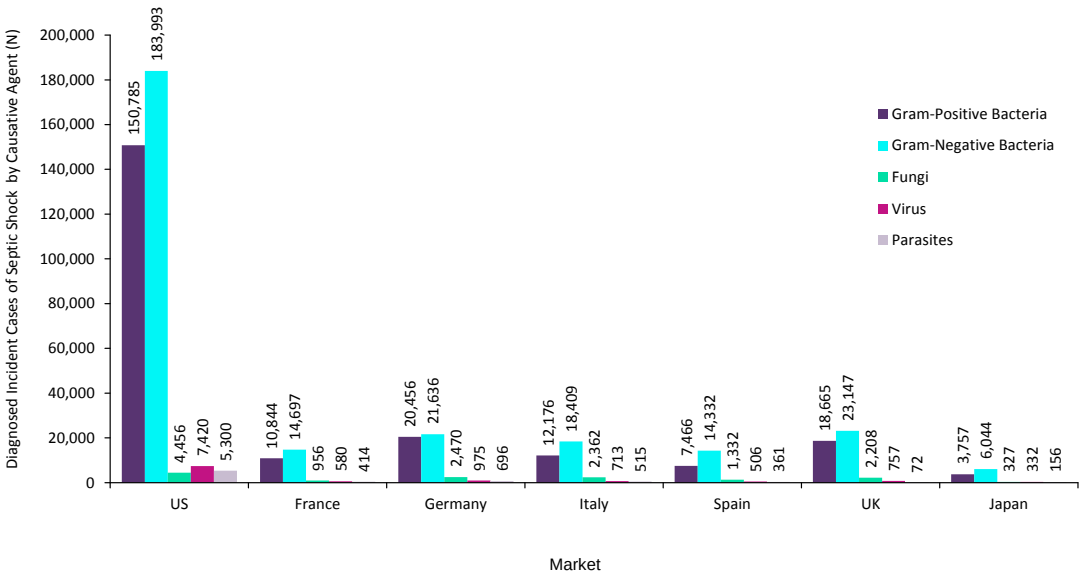
Source: GlobalData; Bouza et al., 2014; Brun-Buisson et al., 2004; de Miguel-Yanes et al., 2015; Dombrovskiy et al., 2007; Fleischmann et al., 2016b; Harrison et al., 2006; JANIS, 2010; JANIS, 2013; JANIS, 2016; JSICM, 2014; Lagu et al., 2012; MHLW, 2008; Ogura et al., 2014; Padkin et al., 2003; Sakr et al., 2013; Stoller et al., 2016; Walkey et al., 2013

5.5.11 Diagnosed Incident Cases of Septic Shock by Causative Agent

GlobalData epidemiologists forecast the causative agent distributions in diagnosed incident cases of sepsis, and the pathogens responsible for sepsis are predominantly gram-positive bacteria, gram-negative bacteria, fungi, viruses, and parasites. In each of the 7MM, gram-negative bacteria caused the highest number of sepsis cases, whereas parasites caused the least number of sepsis cases. Overall, gram-negative and gram-positive bacteria are the major causative agents for sepsis across the 7MM.

Figure 26 presents diagnosed incident cases of sepsis by causative agent in both sexes, all ages in the 7MM in 2016.

Figure 26: 7MM, Diagnosed Incident Cases of Septic Shock by Causative Agent, Both Sexes, All Ages, 2016



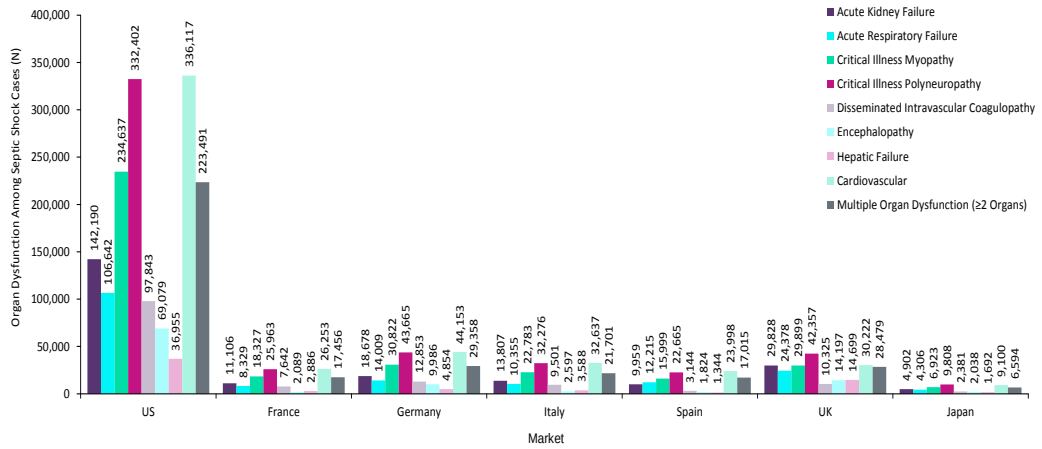
Source: GlobalData; Ani et al., 2015; Bouza et al., 2014; Caironi et al., 2014; Hayakawa et al., 2016; Mouncey et al., 2015; Quenot et al., 2013; SepNet, 2016

5.5.12 Organ Dysfunction among Diagnosed Incident Cases of Septic Shock

GlobalData epidemiologists reviewed the organ dysfunction among diagnosed incident cases of septic shock. In the 7MM, critical illness polyneuropathy and cardiovascular dysfunction among septic shock cases are the predominant organ dysfunctions. This is followed by critical illness myopathy, multiple organ dysfunction (two or more organs), and kidney failure in the 7MM.

Figure 27 presents the organ dysfunction among diagnosed incident cases of septic shock in both sexes and all ages in the 7MM in 2016.

Figure 27: 7MM, Organ Dysfunction among Diagnosed Incident Cases of Septic Shock, Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2014; Casserly et al., 2012; Engel et al., 2007; Latronico et al., 2014; Mouncey et al., 2015

5.5.13 Septic Shock In-Hospital Mortality Cases

GlobalData epidemiologists forecast that the septic shock in-hospital mortality cases in the 7MM will grow by an AGR of 2.28% per year over the next 10 years, from 257,535 cases in 2016 to 316,239 cases in 2026. Additionally, the US will have the highest AGR of 2.88%, while Italy will have the lowest at 1.00%. Of the 7MM, the US had the highest number of septic shock in-hospital mortality cases with 162,197 cases in 2016, while Japan had the lowest number of in-hospital mortality cases of septic shock with 4,364 cases in 2016. In 2026, the corresponding figures in the US and Japan will be 208,904 cases and 4,960 cases, respectively. Of the 5EU in 2016, Germany had the highest number of septic shock in-hospital mortality cases with 26,075 cases, while Spain had the lowest number of diagnosed incident cases with 11,769 cases. In 2016, the US accounted for 62.98% of all septic shock in-hospital mortality cases, while Japan accounted for only 1.69% of septic shock in-hospital mortality cases in the 7MM. In the forecast, changes in the diagnosed incident cases can be attributed to changes in the underlying population structure of each market.

Table 13 presents the septic shock in-hospital mortality cases in both sexes and all ages in the 7MM for select years from 2016 to 2026.

Table 13: 7MM, Septic Shock In-Hospital Mortality Cases, Both Sexes, All Ages, Selected Years 2016–2026

Market	2016	2018	2020	2022	2024	2026	AGR (%)
US	162,197	170,663	179,756	189,269	199,038	208,904	2.88%
France	13,368	13,775	14,143	14,470	14,838	15,242	1.40%
Germany	26,075	26,788	27,501	28,065	28,562	28,962	1.11%
Italy	17,153	17,456	17,783	18,113	18,453	18,863	1.00%
Spain	11,769	12,113	12,451	12,831	13,291	13,777	1.71%
UK	22,609	23,217	23,814	24,423	24,984	25,531	1.29%
Japan	4,364	4,532	4,656	4,769	4,860	4,960	1.37%
5EU	**90,974**	**93,349**	**95,692**	**97,902**	**100,128**	**102,375**	**1.25%**
7MM	**257,535**	**268,544**	**280,104**	**291,940**	**304,026**	**316,239**	**2.28%**

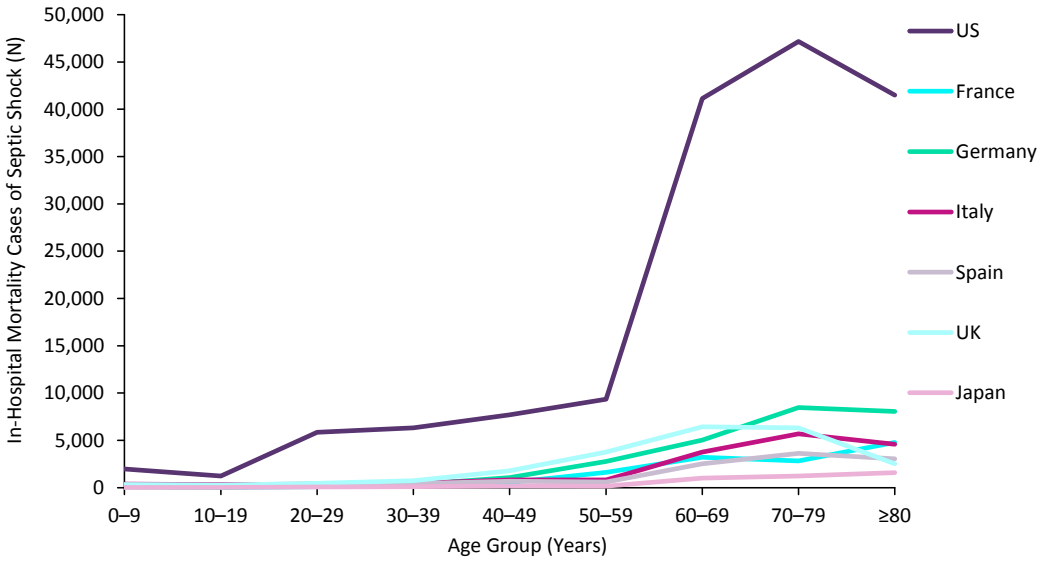
Source: GlobalData; Bouza et al., 2016; Fleischmann et al., 2016b; Kadri et al., 2017; Ogura et al., 2014; Quenot et al., 2013
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.5.14 Age-Specific In-Hospital Mortality Cases of Septic Shock

In-hospital mortality cases of septic shock show a strong trend of increase with age that is consistent throughout the 7MM. In 2016, people ages 70–79 years composed the highest proportion (29.25%) of in-hospital mortality cases of septic shock, followed by people ages 80 years and older (25.65%). Children and adolescents ages 10–19 years accounted for the fewest in-hospital mortality cases of septic shock (0.84%) in the 7MM. The differences in the number of in-hospital mortality cases of septic shock across the various age groups and markets may be attributed to differences in the actual age-specific diagnosed incidence combined with differences in the population demographics in these markets.

Figure 28 presents the age-specific septic shock in-hospital mortality cases in both sexes, in the 7MM in 2016.

Figure 28: 7MM, Age-Specific In-Hospital Mortality Cases of Septic Shock, Both Sexes, All Ages, 2016



Source: GlobalData; Bouza et al., 2016; Fleischmann et al., 2016b; Kadri et al., 2017; Ogura et al., 2014; Quenot et al., 2013
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, Japan

5.6 Discussion

5.6.1 Epidemiological Forecast Insight

Sepsis is one of the oldest and most elusive syndromes in medicine (Angus and van der Poll, 2013). It is a life-threatening complication arising from an infection; it occurs when the body's response to the infection damages its own tissues and organs. Sepsis can lead to multiple organ failure and death, especially if it is not recognized early and treated promptly (Elfeky et al., 2017; Mayo Clinic, 2016). Sepsis, induced by infection, causes a syndrome of physiologic, biologic, and biochemical abnormalities in the body. Sepsis is not a specific illness, but rather a syndrome encompassing a still-uncertain pathobiology. Sepsis and the inflammatory response that ensues can lead to organ dysfunction and death (Elfeky et al., 2017). No specific anti-sepsis treatments exist; as such, management of patients relies mainly on early recognition allowing correct therapeutic measures to be started rapidly (Riviello et al., 2015).

There are inherent challenges in defining sepsis and septic shock. There are no simple clinical criteria or biological, laboratory features or imaging that uniquely identifies sepsis, and sepsis is a broad term applied to an incompletely understood process. Hence, variations in the incidence and mortality rates

of sepsis and septic shock in 7MM are noticed across various literatures. GlobalData epidemiologists addressed this issue by selecting appropriate literatures with similar definitions of sepsis and septic shock as per sepsis-3 criteria.

GlobalData epidemiologists forecast that the diagnosed incident cases of sepsis in the 7MM will grow by an AGR of 2.06% per year over the next 10 years, from 2,594,665 cases in 2016 to 3,129,753 cases in 2026. Additionally, the US will have the highest AGR of 2.34%, while Italy will have the lowest at 0.82%. GlobalData epidemiologists forecast that the diagnosed incident cases of septic shock in the 7MM will grow by an AGR of 2.07% per year over the next 10 years, from 539,085 cases in 2016 to 650,426 cases in 2026. Additionally, the US will have the highest AGR of 2.59%, while Italy will have the lowest at 0.83%. In each of the 7MM, gram-negative bacteria cause the highest number of sepsis/septic shock cases, whereas parasites cause the least number of sepsis/septic shock cases.

Sepsis is an extremely costly medical expenditure, whether it occurs during the initial hospital admission or leads to a readmission. There is an increasing trend of diagnosed incident cases of sepsis and septic shock in all 7MM in the next 10 years. There could be many reasons for the increasing incidence of sepsis, including an aging population, individuals with more comorbid conditions that worsen susceptibility, and increasing resistance to antibiotics by the different kinds of bacteria. Mortality rates from sepsis are also increasing; this could be due to the growth in the population and the increasing incidence of sepsis. Hence, there is need to improve the early detection and management of sepsis and overall reduce mortality rates for patients admitted to the ICU. In the absence of novel sepsis therapeutics, mortality declines may be due to improved processes of care. Potentially effective improvements include earlier antibiotic administration, mechanical ventilation strategies, increased use of early goal-directed therapy, or increased staffing (Stevenson et al., 2014).

Sepsis and septic shock represent one of the oldest and most persistent problems in medicine.

Sepsis and septic shock represent one of the oldest and most persistent problems in medicine. With advances in intensive care, evidence-based guidelines, and increased awareness, doctors have taken huge steps in reducing the risk of imminent death related to sepsis. Strategies are also needed to reach the millions of patients with sepsis who are not reachable by modern intensive care. At the same time, advances in molecular biology have provided keen insight into the complexity of pathogen and alarm recognition by the human host and important clues to a host response that has gone awry. However, harnessing that information to provide effective new therapies has proved to be difficult. To further improve the outcome of patients with sepsis through the development of new therapeutic agents, newer, smarter approaches to clinical-trial design and execution are essential (Angus and van der Poll, 2013). Each hour delay was associated with an additional 4% risk for death, proving that sepsis treatment is time-dependent, with very real consequences for delay. Sepsis bundles have been

shown to decrease mortality, and early antibiotics, especially, are associated with a lower risk of sepsis progressing to septic shock (Seymour et al., 2017). A reliable sepsis surveillance definition based on objective clinical data is needed to more accurately track national sepsis trends and to increase sepsis awareness and prevention (CDC, 2016).

5.6.2 Limitations of Analysis

GlobalData's epidemiological forecast for sepsis and septic shock in the 7MM is limited by the lack of diagnosed incidence data for sepsis and septic shock in Italy. GlobalData epidemiologists assumed the age- and sex-specific diagnosed incidence of sepsis and septic shock in Italy to be the same as that in Spain. This is likely to affect the forecast of the diagnosed incident cases in Italy if the incidence of sepsis and septic shock in the market differs from that in the proxy market. In addition, the historical data needed to understand the future trends in the age- and sex-specific diagnosed incidence of sepsis and septic shock in France and Japan were limited. Therefore, GlobalData epidemiologists used a constant age- and sex-specific diagnosed incidence of sepsis and septic shock in France and Japan for the forecast period. However, there is no noted variation in the diagnosed incidence of sepsis and septic shock in the 5EU markets that have incidence data, so any difference between the forecast incident cases and the actual incident cases of sepsis and septic shock in these markets will be minimal. In France, the UK, and Japan, the ratio of age- and sex-specific septic shock to sepsis incidence from Germany is used to calculate the diagnosed incident cases of septic shock. Due to the lack of country-specific diagnosed incidence data for septic shock, GlobalData epidemiologists believed this to be an appropriate method. Lastly, in Japan, data points were extrapolated to the national level based on data from a subset of ICUs. This approach could be biased if ICUs in the study are not representative of the country. GlobalData epidemiologists will continue to monitor the literature and update the forecast when country-specific epidemiological studies have been published for sepsis and septic shock.

5.6.3 Strengths of Analysis

GlobalData epidemiologists utilized the comprehensive, country-specific data from peer-reviewed journal articles to arrive at a meaningful, in-depth analysis and forecast for the diagnosed incident cases of sepsis and septic shock. In this analysis, GlobalData epidemiologists provide detailed, clinically relevant segmentations for the diagnosed incident cases of sepsis and septic shock.

For all 7MM, the diagnosed incident cases of sepsis and septic shock are segmented by age and sex, causative agent (gram-negative bacteria and gram-positive bacteria, fungi, viruses, and parasites), and organ dysfunction (kidney dysfunction, respiratory dysfunction, critical illness myopathy, critical

illness polyneuropathy, disseminated intravascular coagulopathy, encephalopathy, hepatic dysfunction, cardiovascular dysfunction, and multiple organ dysfunctions). These segmentations are clinically relevant for treatment of sepsis and septic shock cases. Additionally, this forecast provides age-specific in-hospital mortality for sepsis and septic shock for the 7MM, providing detailed characteristics and analysis of the patient population experiencing sepsis and mortality from the disease. The forecast is further strengthened by the use of uniform definition of sepsis as per sepsis-3 criteria across the 7MM. Sepsis and septic shock were defined by ICD-10 codes R65.20 (sepsis) and R65.21 (septic shock). Finally, the forecast methodology was consistent across all markets to allow for meaningful global comparisons of diagnosed incident cases of sepsis and septic shock.

6 Current Treatment Options

6.1 Overview

As of February 2017, there are no marketed drugs specifically aimed at reversing the pathophysiology of sepsis or septic shock. Current treatment options for sepsis and septic shock are limited to infection control (antimicrobial agents) and supportive care (fluid resuscitation, vasopressors, ventilators, and hemodialysis) (Dellinger et al., 2013; Leentjens et al., 2013; Rhodes et al., 2017). The absence of reliable biomarkers and the complexity of sepsis manifestation further add to the challenges seen in sepsis therapy, where reported mortality rates still approach about 30% (Kumar et al., 2011; Remick, 2007). While sepsis mortality has almost halved from the years 2000 to 2007—down from 39% to 27%—sepsis incidence rates have more than doubled in the US during the same time period (Kumar et al., 2011).

Beyond infection control in the form of antimicrobial agents, supportive care measures play a pivotal role in the stabilization of blood pressure. Finally, organ support measures are employed to avoid lasting organ damage; commonly used approaches include mechanical ventilation and hemodialysis. The goal of supportive therapy is to allow antibiotics, along with the patient's immune system, to clear the causative pathogen while organ support keeps the patient alive until the infection is cleared and homeostasis is achieved. Experts interviewed by GlobalData have praised the improvement of supportive care over the years, but have acknowledged more progress needs to be made to push the care for sepsis patients forward and improve upon the current armamentarium and patient outcomes.

"I look at three components of sepsis therapy. One [component] is infection control, one is hemodynamic stabilization, and one is the modulation of the sepsis response. For infection control, it's antibiotics in all cases of course, and source control [surgery] whenever indicated. For the hemodynamic part, fluids and vasopressors manage life-threatening hypotension. In the absence of shock, fluids alone may be sufficient, but sometime an inotropic agent like dobutamine to increase cardiac output and oxygen delivery is needed.Then the third component is the modulation of the sepsis response. There I would put corticosteroids, but that would be only in severe septic shock, when the patient needs high doses of noradrenaline to maintain the blood pressure at an adequate level. I put there also vasopressin, low doses of vasopressin, which would be more endocrine support. I put there glucose control, I put there immunoglobulins (IgGs)."

EU Key Opinion Leader

"All we have [to currently manage patients] is supportive care. Supportive care [has gotten] better [and] we've made progress on how to do that, but we're just still falling short when it comes to agents that target the sepsis cascade itself."

US Key Opinion Leader

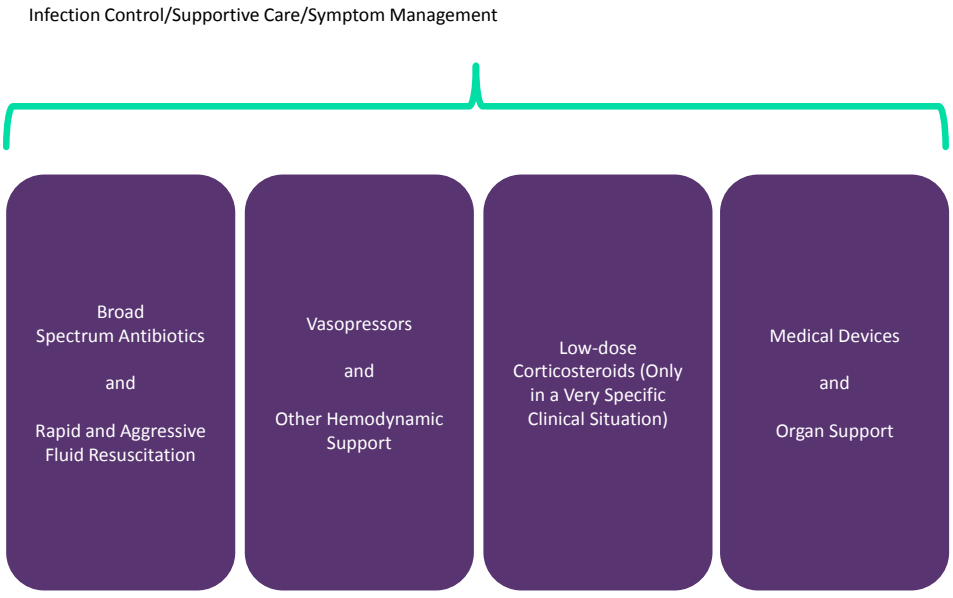
While available treatment options are effective in some patients, other segments of the sepsis population have proven more difficult to manage. For example, patients in the ICU are more vulnerable to secondary infections and are less likely to respond to antibiotic treatment. These patients have the highest mortality risk and have been identified by KOLs as potential candidates for investigative immunostimulatory therapies. As these patients increase their time spent in the ICU, the less effective current treatment options become. Sepsis survivors are subject to continued disease morbidities such as immune paralysis, an area GlobalData identified as underserved with current available treatment options.

"I'm excited about the potential for immune enhancement in improving survival in patients who are in the ICU with sepsis longer than five to seven days, showing symptoms of depleted lymphocyte counts and secondary infections."

US Key Opinion Leader

Figure 29 outlines the current treatment options for sepsis, severe sepsis, and septic shock patients.

Figure 29: Current Treatment Options for Sepsis and Septic Shock, 2017



Source: GlobalData; adapted from ; Dellinger et al., 2013; Leentjens et al., 2013; Rhodes et al., 2017

6.2 Diagnosis and Treatment

Even with the advent of today's advanced broad-spectrum antibiotics, healthcare-associated infections still frequently result in sepsis and septic shock and remain a problem due to their high morbidity and mortality rates (Hall et al., 2011). Diagnosis is a differential exercise, where sepsis suspicion is easily assessed, but confirmation in terms of positive infection and determination of organ dysfunction remains challenging. In practice, sepsis patients present at the ED, where physicians most often start broad-spectrum antibiotic treatment as soon as possible in order to increase the chances of survival, while confirming sepsis diagnosis by ruling out other diseases with similar manifestations.

Even with the advent of today's advanced broad-spectrum antibiotics, healthcare-associated infections still frequently result in sepsis and septic shock and remain a problem due to their high morbidity and mortality rates.

"There is no definitive test [for sepsis] and it's challenging to identify a dysregulated organ response in the absence of a definition for how a regulated organ functions."

Key Opinion Leader

In the past, the SSC guidelines have promoted the use of broad-spectrum antibiotics, but the updated 2016 SSC guidelines for the first time promote antibiotic stewardship—a welcome measure to reduce the incidence of antibiotic-resistant infections. Antibiotic stewardship measures include the use of PCT levels and daily infection assessments to reduce antibiotic exposure and avoid unnecessary antibiotics in non-infectious patients, as well as switching towards more narrow-spectrum antibiotics once pathogens have been identified (Rhodes et al., 2017).

6.2.1 Diagnosis

Currently there are two diagnostic criteria used for the identification of septic patients, namely SIRS and SOFA, where qSOFA is used as a screening tool to identify patients with increased mortality risk. GlobalData's primary and secondary research showed that SOFA and qSOFA are widely used in the 5EU and Japan, while in the US current CMS core measures (SEP-1) still use SIRS criteria to identify septic patients. The move towards updated diagnostic criteria arose from the high sensitivity but low specificity of identifying septic patients using SIRS criteria, and an updated understanding that sepsis pathophysiology involves other non-immunologic pathways (Kaukonen et al., 2015; Marshal, 2014; Singer et al., 2016).

Although not currently used in all guidelines, GlobalData anticipates that the improved specificity of SOFA criteria will aid clinical development by recruiting more homogenous patient populations in RCTs. In addition, GlobalData recognizes that the current understanding of sepsis is still evolving and anticipates that both criteria will be used to aid the diagnosis of sepsis, while the medical and

research communities await the next iteration of the sepsis definition within the next five to ten years (Singer et al., 2016).

Septic patients can present with vastly different symptoms—including hypothermia, hyperthermia, tachycardia, and tachypnea—depending on the infecting pathogen and origin of tissue or organ system in the body. Emergency care practitioners (ECPs) use qSOFA, SIRS, or both screening criteria to identify patients at risk of sepsis. If patients are suspected with sepsis, specific sepsis treatment bundles (SSC, 7MM) or core measures (SEP-1, US only) aimed at source control and supportive care are initiated. Most bundles urge the initiation of broad-spectrum intravenous (IV) antibiotics as soon as possible and to start fluid resuscitation in order to regulate blood pressure. If vasopressors are required to maintain an adequate blood pressure, the patient is diagnosed with septic shock and is transferred to the ICU, where further organ support in the form of ventilators or hemodialysis can be provided.

"SIRS gives us [ECPs] a great handle on inflammation, it provides us with valuable information, but it is not very specific."

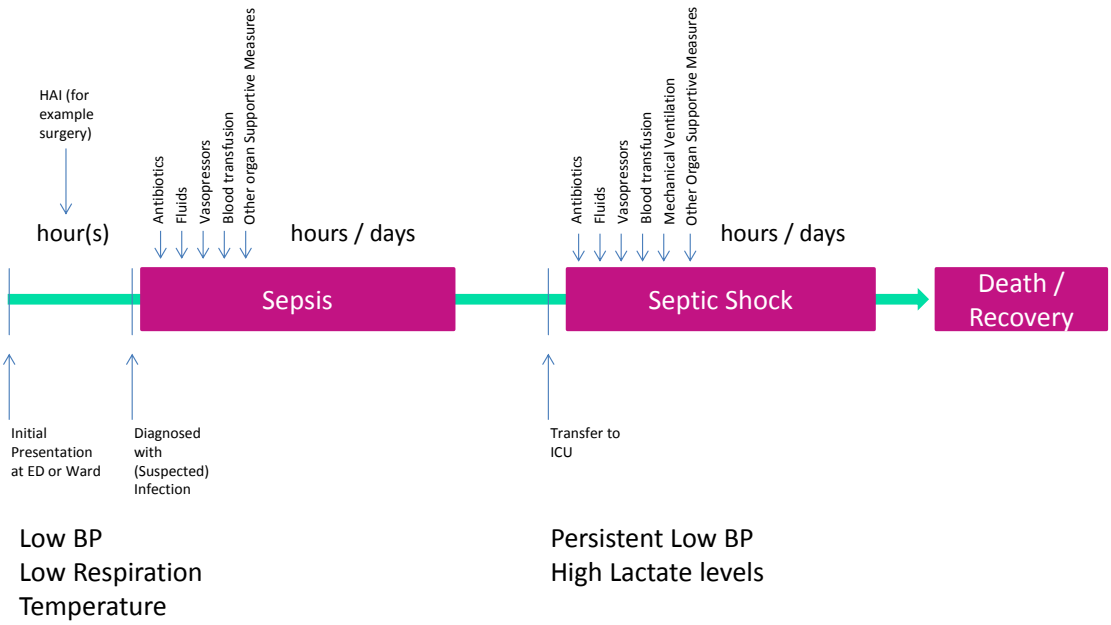
EU Key Opinion Leader

"If you define sepsis as being SIRS plus infection, then sepsis equals infection. In other words, it's becoming extremely common because infection is recognized by fever, associated tachycardia and the alteration in white blood cell counts. These are three of the four SIRS criteria already, and you need only two SIRS plus infection to quality for sepsis. If you use this definition then you see, you know, a very large amount of septic patients a week, and even a GP, a general practitioner, sees a lot every week, but that's not what we call sepsis in our everyday language. The common cold gives you two to four SIRS criteria. SIRS [as a diagnostic tool] is not very specific."

EU Key Opinion Leader

Figure 30 illustrates the disease management timeline for sepsis and septic shock from initial presentation of the patient in the ED or hospital ward (sepsis) to progression to the ICU (septic shock).

Figure 30: Disease Management Timeline for Sepsis and Septic Shock



Source: GlobalData; Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

BP = blood pressure; HAI = healthcare-associated infection

While the use of SIRS is no longer part of the SEPSIS-3 disease definition, GlobalData notes that the SEPSIS-3 consortium still endorses the use of SIRS in raising suspicion of a systemic infection. The new qSOFA criteria were proposed as a more specific screening tool in addition to SIRS in identifying patients with high risk of mortality (Singer et al., 2016). However, their validity remains the subject of healthy discussion among researchers, ECPs, and ICU practitioners. GlobalData's primary and secondary research identified the need for more specific measures to identify patients suffering from sepsis among the main motivators for the proposed changes in the disease definition.

KOLs interviewed by GlobalData acknowledged immense difficulty in identifying sepsis patients and highlighted that the new disease definitions are not to replace current approaches to diagnosis, but to add measures to the repertoire of identifying truly septic patients. Therefore, in the absence of available biomarkers, measures like SIRS, qSOFA, NEWS, MEWS, PIRO, and SOFA are equally valid in raising the suspicion of sepsis and helping to make the diagnosis of sepsis.

"This is one of the fundamental problems with the whole field.It's [sepsis is] a rather vague diagnosis in point of fact, and it is sometimes difficult to say when someone is febrile and, you know, not doing well, because someone who's actually in sepsis, and think about the complexity of this when you are allowing, in your definition, any infection. Any infection—it could be malaria to Ebola, to pneumococcal meningitis, and organs aren't specific either. Sepsis could [be caused by] a myriad of organisms that doesn't have to get limited to a single organ. So, any place in your body could potentially be the source of sepsis…That's a problem because it makes it a very non-descript term."

US Key Opinion Leader

Table 14 describes key differences between the 2012 SEPSIS-2 and the updated SEPSIS-3 diagnosis criteria.

Table 14: Key Differences in Diagnosis Criteria according to new SEPSIS-3

Disease	SEPSIS-2	SEPSIS-3
Sepsis	SIRS and suspected/documented infection	qSOFA and suspected/documented infection
	Two or more SIRS criteria • Temperature >38°C or < 36°C • Heart rate > 90/min • Respiratory rate > 20/min or PaCO2 < 32mmHg (4.3kPa) • WBC count > 12,000/mm^3 or >4,000/mm^3 or >10% immature bands	Two or more qSOFA criteria (Screening) • Respiratory rate > 22/min or more • Altered mental status • Systolic blood pressure of <100mmHg or less Two or more SOFA criteria to assess organ dysfunction
Severe Sepsis	Sepsis with organ dysfunction as measured by • Systolic blood pressure < 90mmHg or MAP < 65mmHg • Lactate > 2mmol/L • Clotting factor dysfunction, INR > 1.5 or PTT > 60s • Bilirubin > 34 mol/L • Urine output < 0.5mL/kg/h for 2h • Creatine > 177mol/L • Platelets < 100x10^9/L • SpO_2 < 90% on room air	Is now covered under sepsis and staging is removed.
Septic Shock	Sepsis with hypotension or lactate levels >1 mmol/L, despite adequate fluid resuscitation	Sepsis patients using vasopressors to maintain a MAP > 65mmHg and have lactate levels > 2mmol/L, after adequate fluid resuscitation

Source: GlobalData; Dellinger et al., 2004; Singer et al., 2016

INR = international normalized ratio; SpO_2 = peripheral capillary oxygen saturation; PTT = partial thromboplastin time

6.2.1.1 SEPSIS-3 Diagnosis Algorithm

Figure 31 outlines the international diagnosis algorithm for triggering suspicion (qSOFA) and diagnosis (SOFA + infection) of sepsis and septic shock according to the new SEPSIS-3 consensus definition (Singer et al., 2016).

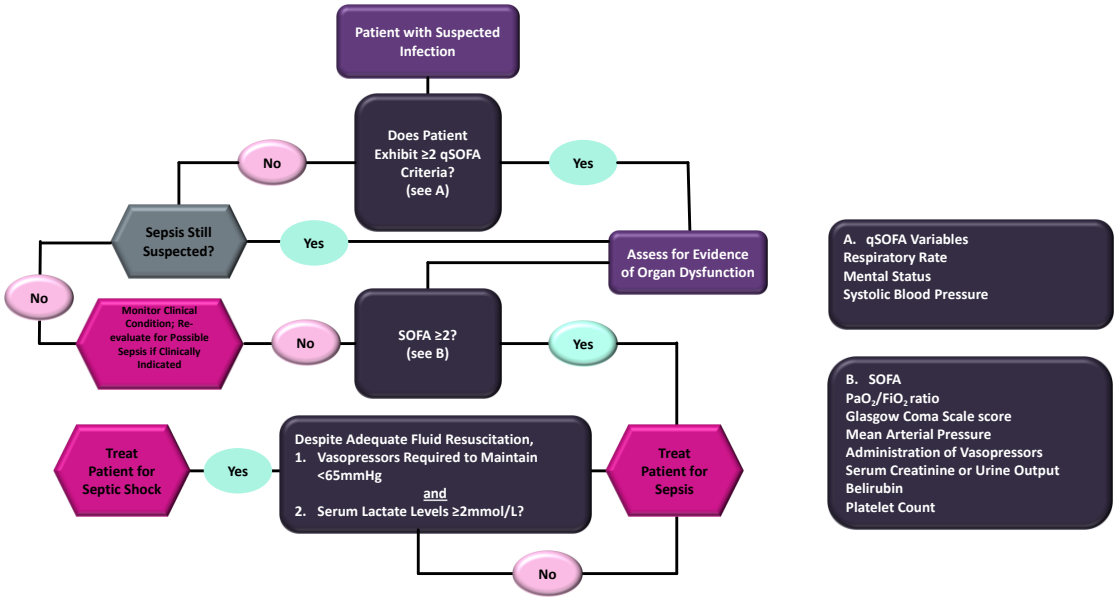
"The SOFA score includes the six organs… cardio circulatory, respiratory, renal, neural, hemato[logic] and liver. It's a score that can quantify the degree of organ dysfunction. It includes the six major organs that we need to consider when we speak about organ failure. If you look at changes over a time it [the SOFA score] is very well correlated with mortality, and can be more sensitive to your therapeutic intervention. Really, I think that's the way to go."

EU Key Opinion Leader

"The SEPSIS-3 definitions were released last year [2016]. And since then a lot of places have been using qSOFA score outside the ICU setting. But qSOFA didn't replace SIRS, and diagnosis is being carried out using a mixture of the two. But for diagnosis of [sepsis] we take blood [smear tests], or biopsies from the area which is suspected as having induced the sepsis."

Japan Key Opinion Leader

Figure 31: Sepsis and Septic Shock SEPSIS-3 Diagnosis Algorithm



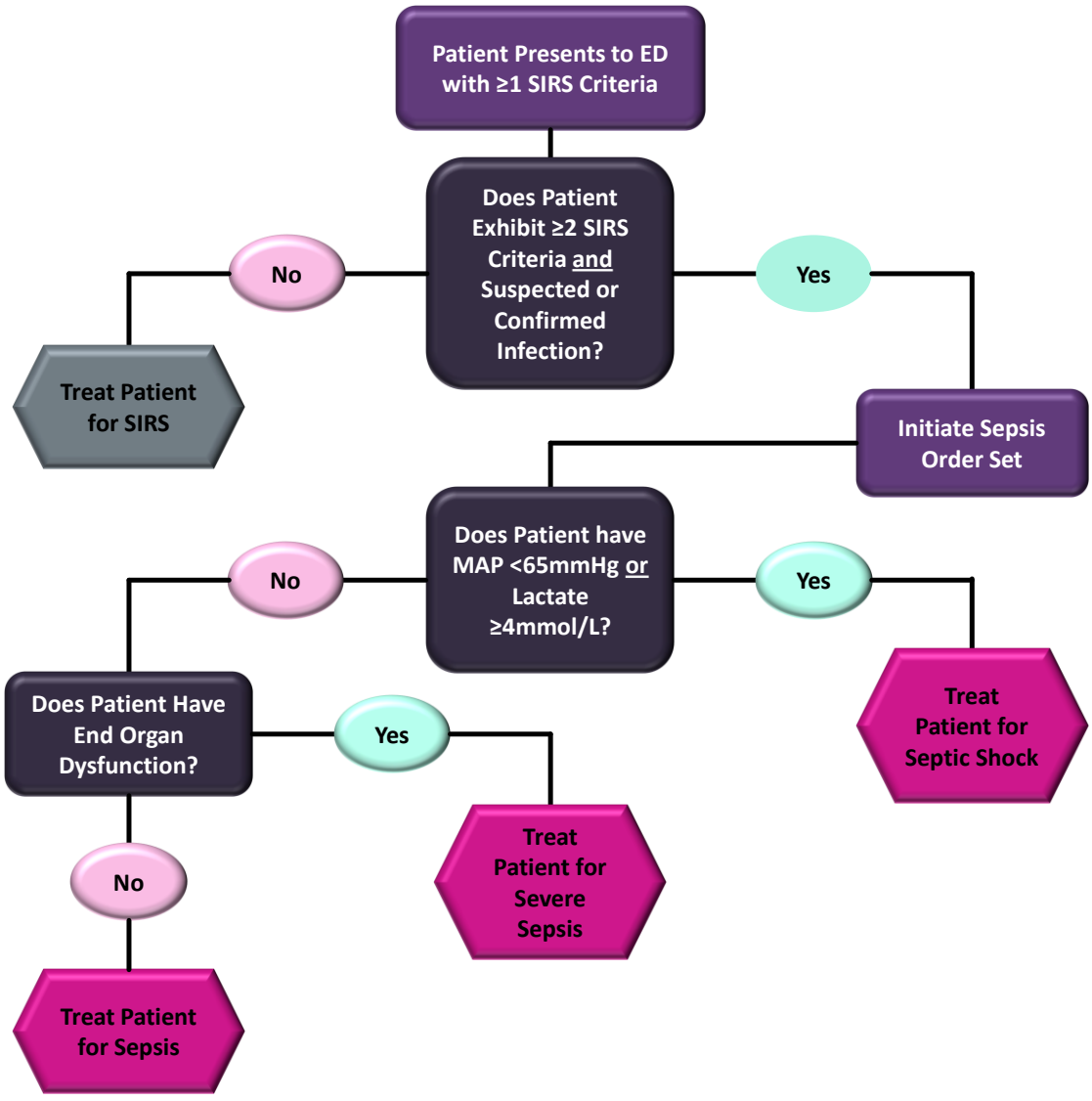
Source: GlobalData; Singer et al., 2016

6.2.1.2 SEPSIS-2 Treatment Algorithm

Figure 32 outlines the previous international diagnosis algorithm for triggering suspicion (SIRS) and diagnosis (SIRS + infection) of sepsis, severe sepsis, and septic shock, according to the new SEPSIS-2 consensus definition (Dellinger et al., 2013). GlobalData's primary and secondary research revealed a healthy skepticism about the validity of the new guidelines, predominantly among US physicians, who are still applying the SEPSIS-2 treatment algorithm in their treatment of patients with sepsis and septic shock.

GlobalData's primary and secondary research revealed a healthy skepticism about the validity of the new guidelines, predominantly among US physicians.

Figure 32: International Treatment Algorithm Overview for Sepsis, Severe Sepsis, and Septic Shock



Source: GlobalData; Dellinger et al., 2013

6.2.2 Treatment Guidelines

Table 15 provides an overview of current sepsis and septic shock guidelines across the 7MM.

Table 15: Treatment Guidelines for Sepsis and Septic Shock, 2017

Country	Guidelines	Publication Date(s)
United States	CMS core measures (SEP-1), SSC guidelines (2016, 2012, 2008, 2004)	2017 (SSC), 2015 (CMS)
France	National guidelinesa, SSC guidelines	2017
Germany	SSC guidelines	2010 (S2K), 2017 (SSC)
Italy	SSC guidelines	2017
Spain	National guidelinesb, SSC guidelines	2016 (national), 2017 (SSC)
United Kingdom	National guidelines[c], SSC guidelines	2016 (national), 2017 (SSC)
Japan	National guidelines[d], SSC guidelines	2014 (national), 2017 (SSC)

Source: GlobalData; [a]Brunkhorst et al., 2010; [b]Gerloni et al., 2016; [c]NICE, 2016; [d]Oda et al., 2014.
SSC = Surviving Sepsis Campaign; CMS = Centers for Medicare & Medicaid Services

"Honestly, I will tell you that from my point of view, it's [SSC is] the only guideline, right. The [SSC] guidelines, even for people who disagree with them, there are no other sepsis guidelines. You can always make them better, but I think that they are as unbiased as we're going to get. They are, I think, well done, and I think that they remain the gold standard for the management of sepsis on a global level."

US Key Opinion Leader

"Guidelines are …very helpful for perhaps very junior doctors or those who sometimes take calls in the ICU but they are not intensivists, they have not been properly trained. In small hospitals you have a cardiologist, a pulmonologist on call during the night, and they must have some guidelines to help them to treat these patients. So I think guidelines are useful, that's a reason why I have been in the guidelines of the Surviving Sepsis Campaign from the very beginning."

EU Key Opinion Leader

In January 2017, the SSC has published updated international consensus guidelines for the management of sepsis and septic shock (Rhodes et al., 2017). Table 10 highlights key changes from the 2012 and 2016 SSC guidelines used in the 7MM, and the CMS Early Management Bundle for Severe Sepsis/Septic Shock (SEP-1), a bundle that makes all EDs by US law liable to deliver specified steps upon the early detection of sepsis.

Table 16:SSC Guidelines Compared

Category	2012 SSC Guidelines recommendations	2016 SSC Guidelines recommendations	CMS's SEP-1
Sepsis Definition	According to SEPSIS-2 (sepsis and severe sepsis), septic shock is defined as severe sepsis with persistent hypotension despite adequate fluid resuscitation.	Endorsed SEPSIS-3, septic shock patients are defined as sepsis patients requiring vasopressors to maintain a MAP of 65mmHg or greater, despite adequate fluid resuscitation and lactate level of 2mmol/L or more	According to SEPSIS-2 criteria, septic shock is defined as severe sepsis + hypotension (MAP <65mmHg, SBP < 90mmHg) OR lactate level of 4mmol/L or more
Infection Control	Achieve within 12 hours, if feasible Achieve as soon as medically and logically feasible Achieve within three hours Blood cultures for pathogen identification One or two antibiotics active against presumed pathogen within first hour Initial broad-spectrum antibiotics/ anti-infectives as soon as possible and within first hour Initial broad-spectrum antibiotics/ anti-infectives within first three hours Combination therapy for neutropenic patients and pseudomonas Combination therapy in patients with septic shock Mono- and/or combination therapy for severe sepsis and septic shock PCT as biomarker PCT to guide de-escalation PCT as biomarker		
Initial resuscitation	At least 30mL/kg in first 3 hours Normalize lactate Crystalloid fluids (no recommendation on 0.9% sodium chloride versus balanced solution) Albumin is recommended in patients in need of substantial fluids Albumin is recommended EGDT (CVP, $ScVO_2$) Use dynamic resuscitation markers (passive leg raise), target MAP of 65mmHg, reassess hemodynamic status EGDT (CVP, $ScVO_2$) or passive leg raise		
Vasopressors	Target MAP of 65mmHg Repeat lactate 1. Norepinephrine 2. Epinephrine as second line 3. Vasopressin to reduce norepinephrine requirement Avoid dopamine is most patients		
Ventilator	6mL/kg tidal volume Prone patients with severe ARDS Prone patients with severe ARDS (P/F < 150) Prone patients with severe ARDS No recommendation Against high frequency oscillatory ventilation No recommendation Weak recommendation for non-invasive ventilation in select patients with sepsis-induced ARDS Unable to make recommendation on non-invasive ventilation Weak recommendation for non-invasive ventilation in select patients with sepsis-induced ARDS		

Source: GlobalData; CMS- SEP1 Measure, 2015; Dellinger et al., 2013; Rhodes et al., 2017

CVP = central venous pressure; $ScVO_2$ = central venous oxygen saturation

6.3 Clinical Practice

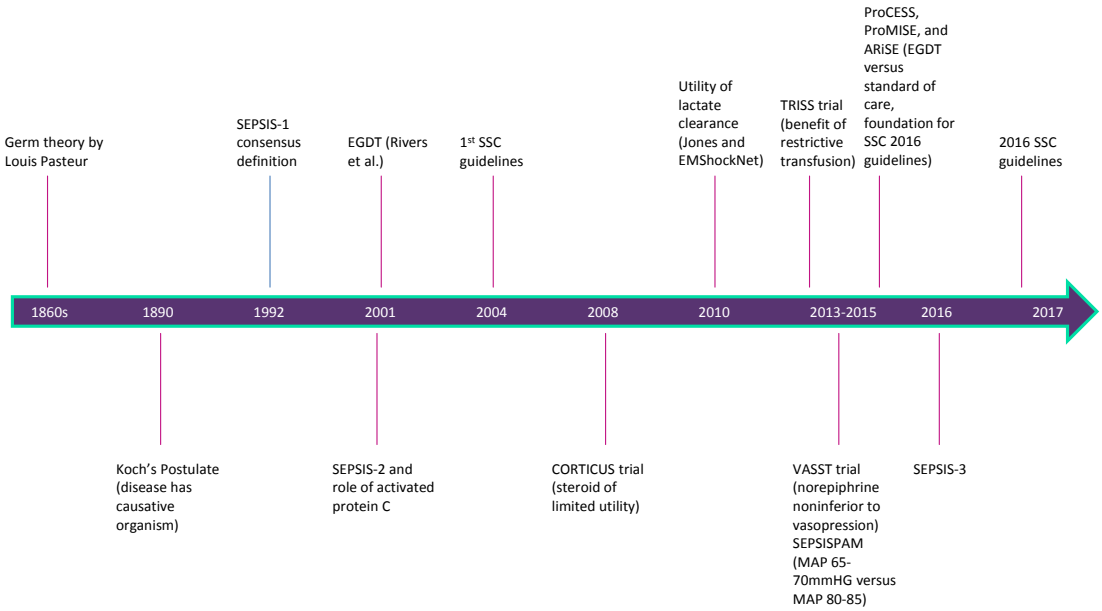
6.3.1 Overview

Clinical practice in management of sepsis and septic shock has evolved considerably since its inception by Louis Pasteur's "germ theory." Today's clinical practice is the result of numerous studies and RCTs aimed at improving infection control and supportive care measures. GlobalData identified River's early goal-directed therapy (EGDT) study as the first landmark event that shaped the treatment of sepsis and septic shock patients; the results of this study were subsequently incorporated into the first 2004 SSC guidelines, and largely persisted in the 2008 and 2012 updates, representing the gold standard of sepsis care at the time (Rivers et al., 2001).

More recent RCTs such as the ProCESS, ProMISe, and ARiSE trials identified early recognition, fluid resuscitation, and antibiotics as key measures for improved survival in the full EGDT therapy regimen, thereby removing unnecessary measures. The results of these studies have subsequently been adopted in the updated 2016 SSC guidelines (Angus et al., 2015; ARISE Investigators and the ANZICS Clinical Trials Group, 2014; Mouncey et al., 2015; Park et al., 2017; Rhodes et al., 2017). Indeed, a systemic analysis of RCTs, observational studies, and investigator-led studies has shown no treatment benefit of EGDT—in particular the use invasive intravenous catheters, measurement of central venous pressure, or central venous oxygen saturation—compared to usual care (physician's discretion), and in addition, EGTD has been associated with increased admission rates to the ICU (Angus et al., 2015). GlobalData notes that the standard of care (SOC) has been influenced tremendously by clinical care physicians, and mortality rates are nowhere near the 46.5% reported in the original Rivers study. Indeed, the protocols of EGDT and SOC have aligned themselves and are almost indistinguishable in terms of initial fluid resuscitation and timing of antibiotic treatment, thereby acknowledging that these factors played the most important role in the EGDT protocol, as they were given to all patients prior to randomization in all studies. In contrast, a central line and carbon dioxide ($PaCO_2$) monitoring as suggested in the EGDT have been shown not to improve the overall mortality outcomes in these trials.

Figure 33 illustrates historical key events that have influenced current clinical practice in the treatment of sepsis and septic shock.

Figure 33: Key Events Shaping Clinical Practice in Sepsis and Septic Shock



Source: GlobalData

6.3.2 Surviving Sepsis Campaign Bundles

Sepsis, largely because of its diverse manifestation, remains an under-diagnosed disease.

Sepsis, largely because of its diverse manifestation, remains an under-diagnosed disease (Singer et al., 2016). Clinical practices in management of sepsis are shaped by bundles and core measures aimed at the early identification of septic patients and the timely and adequate administration of infection control (antibiotics) and supportive measures (fluid resuscitation, vasopressors, and organ support). Among the various national and international bundles, the SSC bundles have been at the cornerstone of improving sepsis survival. GlobalData notes that the SSC bundles have not only proven efficacious in RCTs, but also have been implemented throughout the majority of EDs and ICUs across the 7MM.

GlobalData's primary and secondary research revealed that reducing mortality due to sepsis requires synchronicity among physicians, nurses, pharmacists, and lab personnel, as well as early recognition by the attending physician. Multiple studies across the 7MM have shown that the implementation of this bundle achieved better outcomes in the form of reduced mortality rate and decreased length of stay (LOS) in hospitals (Damiani et al., 2015; Levy et al., 2015; Rhodes et al., 2015). The largest of these studies was performed in 29,470 patients across 218 hospitals in the US, 5EU, and South America. This study noted a 0.7% decrease in sepsis mortality for every three months during the 7.5

year study period (Levy et al., 2015). These bundles, when implemented together, will achieve better outcomes than if implemented individually.

"I like what [the SSC has] done with the latest version [of the guidelines], which is essentially to mirror what we did in [our country] several years ago and to say, 'Look, this care bundle for sepsis is too complex, it's very intensive care-centric, and we need to simplify it and operationalize it and [focus on] the tasks that a non-intensivist can deliver: the antibiotics, the fluid challenges, measuring the lactate, that sort of thing.' Now that they've done that, it makes it a very much more useable care bundle."

EU Key Opinion Leader

Table 17 summarizes the standardized management plan of care for patients with sepsis in terms of the SSC treatment bundles.

Table 17: Treatment Bundles for Sepsis Patients

To Be Completed Within Three Hours:
Measure lactate level
Obtain blood cultures prior to administration of antibiotics
Administer broad-spectrum antibiotics
Administer 30mL/kg crystalloid for hypotension or lactate ≥4mmol/L
To Be Completed Within Six Hours:
Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP ≥65mmHg
In the event of persistent hypotension after initial fluid administration (MAP <65mmHg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion
Re-measure lactate if initial lactate was elevated (target within normalized range)

Source: Global Data; Dellinger et al., 2013

CVP = central venous pressure; $ScvO_2$ = central venous oxygen saturation

6.3.3 Country Differences

KOLs interviewed by GlobalData indicated there are slight differences in how patients are treated in the US, the 5EU, and Japan. Particularly, they cited differences in critical care and intensive care resources from country to country. For example, the US has more critical care beds compared to the UK, which can influence uptake of therapies depending upon where they need to be initiated. Interviewed physicians stressed that new therapies should have the ability to be administered in multiple hospital settings, as time between patient transfers from different areas of the hospital can vary from country to country and can be lengthy in some instances. Furthermore, drug storage locations and the distance drugs need to travel to get to the patient needs to be taken into account as well. These logistical aspects of care are important because the time window in which to initiate

effective therapies in these patients is usually small once the syndrome is recognized, so unnecessary delays in treatment need to be avoided at all costs.

GlobalData's primary research also revealed that some countries are beginning to invest in sepsis-related improvements. KOLs indicated that the NHS in the UK recently invested close to a quarter of a billion pounds ($325,000) in sepsis improvements for the country. One of the aspects of these improvements is to fix the healthcare-system-wide response to sepsis, making it similar to how things have been set up for heart attack or stroke. This includes public awareness campaigns and having paramedic crews or primary care offices alert the hospital that a patient potentially has sepsis. This would trigger a sepsis team to mobilize and assess the patient upon arrival to determine if they continue on the sepsis pathway in order to reduce any delays in treatment.

"The paramedics provide a pre-alert to the hospital, saying we think this patient may have sepsis. They will undertake a standard sepsis screen using, at present, the consensus definitions and these red flag symptoms and signs: systolic [BP] of less than 90, a lactate of more than two, heart rate of more than 130, respiratory rate of more than 25, oxygen saturations of less than 90, and mottled skin or a purpuric rash. I think in February [2015], once the old fashioned definitions have improved, then we'll probably just morph to those international definitions. The sepsis team will be charged with doing the screen for sepsis and determining whether the patient continues on the sepsis pathway… It's a new system, but one which is intended as an operational solution... It's been well-received, actually. I think people have been crying out, particularly people outside critical care, for a better way to understand which patients to identify to initiate therapy."

EU Key Opinion Leader

Japan is at the forefront of using anticoagulant therapy in the management of sepsis and septic shock. GlobalData's primary research identified a combination of thrombomodulin and antithrombin III as particularly effective in patients with sepsis-induced DIC.

"About 60% of patients with severe sepsis or septic shock are diagnosed with septic-associated DIC. In cases where it is diagnosed, we use thrombomodulin and antithrombin III, although Japan may be the only country to use that formulation."

Japan Key Opinion Leader

"A major difference compared to Europe and the US is that here in Japan we are much more proactive in our use of anti-coagulant therapies, not only in the treatment of sepsis-associated blood clotting disorders but also in the treatment of the underlying condition. In some cases, we will even use it as an [anti-infective therapy]."

Japan Key Opinion Leader

6.4 Infection Control – Antibiotics and other Anti-infectives

6.4.1 Overview

Infection control in form of antibiotics and other anti-infective therapies is a major pillar in the treatment of sepsis and septic shock. The majority of sepsis and septic shock cases originate from bacterial origin—GlobalData's survey among emergency care physicians revealed that on average over 54% of sepsis cases are caused by Gram-negative bacteria; Gram-positive bacteria induced sepsis accounts for approximately 40% of cases, whereas on average only 6% of cases were reported due to fungal infections. Intravenous antibiotic therapy during sepsis and septic shock is aimed at enhancing the likelihood of a positive clinical outcome by managing three therapeutic goals:

- Maximize the rate and extent of bacterial eradication
- Minimize possibility of drug toxicity
- Minimize the development of antimicrobial resistance

Although antibiotic therapy is the foundation of sepsis and septic shock therapy, KOLs interviewed by GlobalData noted imperfect timing, dosing, and choice of broad- versus narrow-spectrum antibiotics as major areas of further improvement.

Identification of the pathogen and source of the infection is important because it provides insight into how ill the patient is, as some pathogens are more virulent than others and some sites of infection are more difficult to treat than others. GlobalData's primary research revealed that pathogen identification prior to administration of antibiotics is usually not the case in an actual clinical scenario, because current culture-based lab tests take multiple days to yield confirmatory results, and antibiotics must usually be administered as soon as possible once the patient is recognized as having sepsis. As a result, clinicians frequently prescribe broad-spectrum antibiotics and first-line empiric therapy, which in many cases can lead to antibiotic resistance. The development of rapid, accurate, sensitive, and specific pathogen identification tools would be a welcome addition to the treatment landscape and would help decrease the use of broad-spectrum antibiotics as first-line therapy. Antibiotic resistance has become a worldwide concern due to the lack of novel antibiotics in the pipeline to combat the resistance problem.

"We're still relying on cultures [to identify the pathogens], which are of course are only positive 50% of the time, and take a very long time. So, we're still struggling with the best way to screen and early identify patients who are infected and are likely to develop organ dysfunction."

US Key Opinion Leader

Table 18 highlights the antibiotics frequently used in sepsis patients, broken down by class. GlobalData believes that although antibiotics are currently the cornerstone of sepsis therapy, the opportunity within the market lies in generating a therapy to supplement antibiotics and targeting specific patient populations to reduce mortality and morbidity.

Table 18: Commonly Used Antibiotics in Sepsis and Septic Shock and Important Gaps in Coverage, 2017

Antibiotic Class	Targets/MOAs	Specific Examples of Commonly Used Drugs	Important Gaps in Coverage
Carbapenems	Inhibits bacterial cell wall synthesis through binding to various penicillin-binding proteins.	Imipenem, meropenem, doripenem, ertapenem	Carbapenemase-producing organisms
β-lactams	Inhibits bacterial cell wall synthesis through binding to various penicillin-binding proteins.	Piperacillin-tazobactam, cephalosporins	Carbapenemase- and ESBL-producing organisms
Quinolones	Inhibits bacterial cell division through inhibiting DNA gyrase and topoisomerase IV.	Moxifloxacin, ciprofloxacin, levofloxacin	Quinolone-resistant organisms, which include many of the carbapenemase- and ESBL-producing organisms
Aminoglycosides	Interferes with bacterial protein synthesis, leading to the formation of non-functional or toxic proteins. Irreversibly binds to specific 30S ribosomal subunit proteins and 16S rRNA, which disrupts RNA-dependent protein synthesis.	Gentamicin, tobramycin, amikacin	Most Gram-positive organisms, aminoglycoside-resistant organisms, and most of the carbapenemase- and ESBL-producing organisms
Macrolides	Interferes with bacterial protein synthesis leading to the formation of non-functional or toxic proteins. Irreversibly binds to 50s ribosomal subunit, which disrupts RNA-dependent protein synthesis.	Azithromycin, clarithromycin, erythromycin	Macrolide-resistant organisms, including many Gram-positive organisms and most of the carbapenemase- and ESBL-producing organisms
Glycopeptides (anti-Gram-positive)	Inhibits the incorporation of key peptides (NAM and NAG) into the bacterial cell wall and thus alters bacterial cell membrane permeability and RNA synthesis.	Vancomycin, oritavancin, telavancin	Gram-negative organisms such as Vancomycin-resistant *S. aureus* and *enterococcus spp*. (for vancomycin). Typically used in combination with one of the other classes of antimicrobial agents.
Oxazolidinone (anti-Gram-positive)	Interferes with bacterial protein synthesis leading to the formation of non-functional or toxic proteins. Irreversibly binds to 50s ribosomal subunit, which disrupts RNA-dependent protein synthesis.	Linezolid	Gram-negative organisms. Typically used in combination with one of the other classes of antimicrobial agents.
Cyclic lipopeptides (anti-Gram-positive)	Binds to bacterial cell membranes and causes a rapid depolarization of membrane potential, which causes inhibition of DNA, RNA, and protein synthesis.	Daptomycin	Gram-negative organisms. Typically used in combination with one of the other classes of antimicrobial agents.

Source: GlobalData, Pharma eTrack [accessed September 19, 2016]; Lyle et al., 2014

ESBL = extended spectrum β-lactamase;MOA = mechanism of action

6.4.2 Timing of Antibiotic Therapy

As of February 2017, no large RCT has shown the effect on timing of antibiotic therapy on mortality outcomes in sepsis or septic shock patients. Current clinical practice is the subject of retrospective analysis of small clinical studies (de Groot et al., 2015; Ferrer et al., 2014; Kumar et al., 2006; Sterling et al., 2015). While physicians aim to start antibiotic treatment as early as possible, in alignment with clinical practice, this approach—while aligning with current guidelines—has resulted in the increased usage of broad-spectrum antibiotics and hence the more rapid emergence of multi-drug resistant bacteria. A delay in the introduction of antibiotic treatment could give physicians the chance to assess pathological origin of the infection and prescribe a more targeted antibiotic treatment as the initial therapy, thereby reducing unnecessary drug toxicity and the possibility of antibiotic resistance.

As of February 2017, no large RCT has shown the effect on timing of antibiotic therapy on mortality outcomes in sepsis or septic shock patients.

"You must get antibiotics into [patients with sepsis] as soon as possible, preferably within an hour of them showing up in a hospital care, and then try to support the patient's organ dysfunctions as best you can while you make the diagnosis of what the organism is…That kind of urgency, so, it's the idea that it's a medical emergency and you've got to do these things as quickly as possible, and if you do, you'll have better outcomes. So, the treatment is nothing new or fancy.… if they have an infection, give them antibiotics as quickly as possible."

US Key Opinion Leader

Nevertheless, large RCTs like the ARiSE, ProCESS, and ProMISe trials have shown that early antibiotic treatment (within one hour) and fluid resuscitation have been among the major factors for increased survival of sepsis and septic shock patients. Several small retrospective studies have looked at the mortality outcome upon timing of antibiotic therapy. The results of these studies are highlighted in Table 19. GlobalData notes that these studies provide evidence that introduction of antibiotic therapy could be delayed by up to 3 hours in sepsis patients without affecting the overall mortality rate in this patient population, while septic shock patients are the most likely to benefit from immediate antibiotic therapy (de Groot et al., 2015; Ferrer et al., 2014; Kumar et al., 2006; Sterling et al., 2015). However, current guidelines recommend the start of antibiotic therapy as soon as possible and within the first hour of suspected infection (Rhodes et al., 2017).

Table 19: Pivotal Studies of Timing of Antibiotic Treatment in Sepsis and Septic Shock

Study	Number of Patients evaluated	Design/ Outcome	Time to antibiotics	Outcome	p
de Groot et al., 2015	1,168 severe sepsis patients (SEPSIS-2)	Prospective study across three Dutch EDs Hazard ratio by disease severity (PIRO)	PIRO 1 to 7 <1h 1–3h >3h PIRO 8 to 14 <1h 1–3h >3h PIRO > 14 <1h 1–3h >3h	11.03 (0.78–1.36) 1.46 (1.05–2.02) 11.02 (0.83–1.25) 1.02 (0.75–1.38) 11.16 (0.86–1.58) 1.40 (0.84–2.34)	0.020 0.824 0.023 0.984 0.863 0.910 0.361 0.366 0.194
Ferrer et al., 2014	17,990 severe sepsis and septic shock patients (SEPSIS-2)	Retrospective analysis of SSC dataset Probability of Mortality	0–1h 1–2h 2–3h 3–4h 4–5h 5–6h >6h	24.6 % (95% CI, 23.2–26.0) 25.9 % (95% CI, 24.5–27.2) 27.0 % (95% CI, 25.3–28.7) 28.8 (95% CI, 25.9–31.7) 28.8 (95% CI, 25.9–31.7) 32.3 (95% CI, 28.5–36.2) 33.1 (95% CI, 30.9–35.3)	N/A 0.165 0.021 0.009 0.006 <0.001 <0.001
Kumar et al., 2006	2,154 septic shock patients (SEPSIS-2)	Retrospective study across fourteen ICUs and ten hospitals in Canada and the US Adjusted odds ratio	<1h >6h	1.67 (95% CI, 1.12–2.48) 92.54 (95% CI 44.92–190.53)	<0.05 <0.05
Sterling et al., 2015	11,017 severe sepsis and septic shockpatients (SEPSIS-2)	Systemic literature review,11 studies identified Odds ratio	<1h 1–2h 2–3h 3–4h 4–5h >5h	1 1.21 (95% CI, 0.84–1.72) 1.42 (95% CI, 0.76–2.67) 1.53 (95% CI, 0.72–3.28) 1.90 (95% CI, 0.72–5.01) 2.47 (95% CI, 0.46–13.36)	>0.05 >0.05 >0.05 >0.05 >0.05 >0.05

Source: GlobalData; de Groot et al., 2015; Ferrer et al., 2014; Kumar et al., 2006; Sterling et al., 2015
h = hour

6.4.3 Dosing of Antibiotic Therapy

As of February 2017, there is no study investigating the combined effect of time to antibiotic administration and optimized dosing of the antibiotic. GlobalData's primary and secondary research has shown that the majority of antibiotics prescribed for the treatment of sepsis and septic shock are delivered intravenously, and these antibiotics possess either bactericidal (killing the pathogen directly) or bacteriostatic (inhibits bacterial growth and proliferation) mechanisms of action.

GlobalData notes that achieving optimal antibiotic dosing in sepsis and septic shock patients is complicated by diverse organ dysfunctions in the disease, which can lead to increased or decreased plasma levels of antibiotics. As a result, the 2016 SSC guidelines recommend that dosing strategies are based on pharmacokinetics/pharmacodynamics (PK/PD) principles in patients with sepsis, provided such tests are available (Rhodes et al., 2017). This recommendation was based on a prospective multinational PK/PD study in 384 patients with infections across 68 hospitals, the results of which showed that an increased volume of distribution of antibiotics due to fluid resuscitation and augmented renal clearance decreased the antibiotic concentration below the minimum inhibitory concentration (MIC) needed to affect the pathogen of interest. The study showed that survival in infected patients receiving antibiotics was correlated with increased antibiotic plasma concentration, where plasma concentrations between 50% and 100% of the MICshowed an increased OR of survival by 1.02 and 1.56 ($p < 0.03$), respectively (Roberts et al., 2014). However, this study was specific to β-lactam antibiotics, which often benefit from prolonged infusion times, and the results can vary from other antibiotics such as aminoglycosides, which act through a concentration-dependent bactericidal mechanism. KOLs interviewed by GlobalData cited the importance of a customized antibiotic dosing approach in order to improve outcomes in patients with sepsis and septic shock.

"Yes, I think we are under-dosing [antibiotics in] sepsis patients."

US Key Opinion Leader

"I don't think we're certain of [the optimal antibiotic] dosage. I don't think we're always sure that we have the right bio-availability, and I don't even think that we're completely certain yet about the best mode of administration…I have to confess, I myself am not 100% sure of the best way to dose antibiotics, so I think I represent many clinicians who are not yet sure about the best way to dose antibiotics, or deliver antibiotics."

US Key Opinion Leader

6.4.4 Antibiotic Resistance

Although the IDSA initially endorsed the SSC 2016 guidelines for the treatment of sepsis and septic shock, it shortly thereafter withdrew endorsement, citing inappropriate antibiotic stewardship recommendations (IDSA, press release, January 2017). While the current SSC 2016 guidelines recommend the use of broad-spectrum antibiotics as soon as possible, their use has been associated with an increased risk of developing *Clostridium difficile* infections and puts the patients at risk of multi-drug resistant bacteria (O'Connor et al., 2004).

GlobalData's primary and secondary research has identified pathogen detection, site of infection (tissue penetration), allergies, organ dysfunction, recent antibiotic exposure, and local resistance patterns as key determinants for choosing the appropriate antibiotic therapy. The 2016 SSC treatment guidelines recommend that blood cultures be obtained prior to the administration of broad-spectrum antibiotics and to guide antibiotic selection on these laboratory results (Rhodes et al., 2017). GlobalData's primary research revealed that current laboratory identification methods take longer than the recommended hour, leading physicians to choose an empiric antibiotic tailored to the local pattern of the most prevalent bacterial species and any recent exposure to antibiotic drugs (Dellinger et al., 2013; Rhodes et al., 2017). The majority of physicians interviewed by GlobalData revealed that they use broad-spectrum antibiotics in everyday clinical practice, but recommended that the initial administration of antibiotics be specific to Gram-negative bacteria (for example piperacillin, meropenem), followed by Gram-positive antibiotics (for example vancomycin, linezolid) after one hour if the patient is not responding, followed by combination therapy if still not responding. In the face of this dire situation, experts cited the development of rapid, accurate, sensitive, and specific pathogen identification tools as a welcome addition to the treatment landscape in order to decrease the use of broad-spectrum antibiotics as first-line therapy.

"[When choosing an antibiotic for a patient] the first question you want to ask yourself is, 'what am I treating and where is the patient coming from?' For instance, if you have a patient that comes back from the Middle East, you know that there is no chance that community-acquired pneumonia is going to be due to something really sensitive, and you have a very high likelihood of getting a patient that is infected with a multidrug-resistant pathogen. What are you treating, who are you treating, and what is the medical history of the patient? These are the important questions to think about when prescribing an antibiotic."

EU Key Opinion Leader

"There are regions of the world where the notion of adequate antimicrobial therapy is a weird concept. In regions where you have a lot of patients with [ESBL-producing] Gram-negative rods, in patients where you have a really high incidence of multidrug-resistant pathogens, then the whole notion of having—and giving—an antibiotic that will be effective is quite difficult."

EU Key Opinion Leader

"They have a very low incidence of MRSA [methicillin-resistant Staphylococcus aureus] and bloodstream infections in Germany compared to the United States or Spain, for instance. Very low, 2% to 3% of patients with sepsis according to the new definition [SEPIS-3], have MRSA infections."

EU Key Opinion Leader

"One of the things that we have to point out is that treating infection has gotten a lot more complicated than it used to be because of multi drug-resistant pathogens. So, this is another area of great concern and of important research: how do we treat the infection most effectively, and when should you do it?Drainage procedure, and when do you just use antibiotics? There's a lot going on now in this field and allied fields that are affecting septic patients, and antibiotic resistance is definitely one of them."

US Key Opinion Leader

GlobalData highlights that antibiotic resistance has become a worldwide concern due to the lack of novel antibiotics in the pipeline.

Current 2016 SSC guidelines recommend daily assessment of antibiotic therapy for antibiotic de-escalation and suggested the use of PCT to reduce the length of antibiotic therapy, thereby reducing the risk of developing antibiotic resistance (Rhodes et al., 2017). GlobalData highlights that antibiotic resistance has become a worldwide concern due to the lack of novel antibiotics in the pipeline.

6.4.5 Other Therapies — Antivirals, Antifungals, and Antiparasitics

While sepsis is caused less frequently by viruses, fungi, or parasites than by bacteria, the use of antivirals, antifungals, and antiparasitics still remains important for the management of some patients. Prior to the administration of these interventions, blood cultures and other relevant tests should be conducted to identify the causative pathogen. If confirmed, therapy should be adjusted accordingly.

Empiric selection of therapy will be similar to the selection of an antibiotic and will be broad enough to cover all suspected pathogens. For example, the SSC recommends the empiric selection of antifungals to be tailored to the local pattern of the most prevalent Candida species and any recent exposure to antifungal drugs. The IDSA guidelines recommend either fluconazole or an echinocandin, with the latter being preferred in most empiric diagnoses, especially in those who have recently been

treated with an antifungal agent (Rhodes et al., 2017). Similar to the approach taken with antibiotics, antiviral and antiparasitic medication should be prescribed according to the susceptibility of the known or suspected virus or parasite.

KOLs interviewed by GlobalData have indicated that about 5% of their patients have their sepsis condition caused by a virus. Fungal infections account for another 5% of the patient population, while less than one percent of cases are due to parasites.

6.5 Supportive Treatment Options for Sepsis and Septic Shock

6.5.1 Overview

In addition to infection control, host-targeting approaches—which currently include careful monitoring and appropriate hemodynamic and organ function support—have been crucial to the successful management of sepsis patients (Dellinger et al., 2013; Leentjens et al., 2013; Rhodes et al., 2017).

The intention in applying supportive therapies is to contribute to improving the care of sepsis patients, which is managing symptoms and comorbidities and keeping them alive until the suspected or confirmed infection can be cleared. GlobalData's primary and secondary research revealed that physicians avoid using certain therapeutic interventions, such as IV immunoglobulins or IV selenium. Furthermore, research indicates against the use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15. The discussion of why these interventions are not used is beyond the scope of this report; however, GlobalData feels it is important to note that the international guidelines for the management of severe sepsis and septic shock specifically point out that these treatments are to be avoided.

Table 20 highlights other frequently employed supportive therapies that target the host in the context of clinically relevant situations.

Table 20: Other Supportive Therapies To Be Implemented When Clinically Relevant

Supportive Therapy	Class/Type	Patient Population
Mechanical ventilation	Lung support	Sepsis and septic shock patients with sepsis-induced lung issues (ARDS or ALI)
Fluid resuscitation	General support	Sepsis and septic shock for stabilization of sepsis-inducedtissue hypo-perfusion
Hemodialysis/RRT	Kidney support	Sepsis and septic shock patients with sepsis-induced acute kidney disease
Blood product administration	Hemodynamic support	Sepsis and septic shock
Vasopressor therapy	Hemodynamic support	Septic shock
DIC and DVT prophylaxis	Hemodynamic support	Sepsis and septic shock
Low-dose corticosteroids	Hemodynamic support	Septic shock patients only when fluid resuscitation and vasopressors are unable to restore hemodynamic stability
Stress ulcer prophylaxis	Hemodynamic support	Sepsis and septic shock
Glucose control	Hemodynamic and general support	Sepsis and septic shock
Sedation, analgesia, and neuromuscular blockade	General support	Sepsis and septic shock
Non-drug related approaches	Nutritional support and setting goals of care	Sepsis and septic shock

Source: GlobalData; adapted from Dellinger et al., 2013; Leentjens et al., 2013; Rhodes et al., 2017
DVT = deep vein thrombosis; RRT = renal replacement therapy

6.5.2 Fluid Resuscitation, Vasopressors, Dobutamine, and Blood Transfusion

From 2001–2017, EGDT was the recommended treatment approach for sepsis and septic shock patients. As of January 2017 and in face of the results from the ARiSE, ProCESS, and ProMISe landmark studies, the SSC 2016 guidelines no longer recommend EGDT in the management of sepsis and septic shock patients (Angus et al., 2014; ARISE Investigators and the ANZICS Clinical Trials Group, 2014; Mouncey et al., 2015; Rhodes et al., 2017; Rivers et al., 2001). GlobalData notes that the major differences between EGDT and physicians' SOC are the need for a central venous line to monitor carbon dioxide (CO_2) and SvO_2. If antibiotics represent the primary cornerstone of sepsis and septic shock therapy, KOLs highlighted initial fluid resuscitation and vasopressors as the second and third most important supportive measures in sepsis and septic shock therapy, respectively.

"The treatment of [patients with] septic shock [involves] giving fluids, and if they have an infection, give them antibiotics as quickly as possible. It's just now that it's [been] demonstrated how important the timing is, and how you can lose people very early on if you didn't do that early resuscitation correctly or you didn't give an appropriate antibiotic correctly."

US Key Opinion Leader

Table 21 presents an overview of landmark studies in the treatment of sepsis and septic shock.

Table 21: Evolution of the Standard of Care in Sepsis and Septic Shock, 2017

Study or Author	Patients, N		Fluid resuscitation, mL		Vasopressors, %		Dobutamine, %		Blood transfusion, %		Primary mortality	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control		
Rivers et al., 2001	130	133	4,981 ± 2,984	3,499 ± 2,438	27.4	30.3	13.7	0.8	64.1	18.5	29.2	44.4
Jones et al., 2010	150	150	4,300 ± 2,210	4,500 ± 2,360	75.3	72.0	5.3	3.3	3.3	7.3	22.7	16.7
ProCESS	439	902	2,805 ± 1,957	2,783 ± 1,880	54.9	48.1	5.7	1.0	14.4	7.9	21.0	18.5
ARiSE	196	804	1,964 ± 1,415	1,713 ± 1,401	66.6	57.8	15.4	2.6	13.6	7.0	18.6	18.8
ProMISe	630	630	2,226 ± 1443	2,022 ± 1,271	53.3	46.6	18.1	3.8	8.8	3.8	29.5	29.2

Source: GlobalData; Angus et al., 2014; ARISEInvestigators and the ANZICS Clinical Trials Group, 2014; Mouncey et al., 2015; other sources listed above; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

Among the first measures in the treatment of sepsis and septic shock patients is the administration of up to 30mL/kg of balanced IV crystalloids or saline solution, followed by frequent assessment of hemodynamic status to determine improvement or deterioration to septic shock. Furthermore, the guidelines recommend dynamic over static variables to predict fluid responsiveness; recommended dynamic measures include passive leg raises, fluid challenges against stroke volume measurements, and variations in systolic pressure, pulse pressure, or stroke volume induced by mechanical ventilation. CVP alone can no longer be used alone to guide fluid resuscitation. For septic shock patients requiring vasopressors, the guidelines recommend a MAP of 65mmHg and a normalization of lactate levels, if they were elevated, as resuscitation targets (Rhodes et al., 2017). Experts interviewed by GlobalData shared their concern about the use of lactate levels as guidance for resuscitation because in some sepsis patients vasopressors elevate lactate levels, therefore potentially masking a positive response to fluid resuscitation. The use of albumin in addition to crystalloids is reserved for patients requiring substantial (unspecified) amounts of fluids, whereas the use of hydroxyethyl starch (HES) for IV fluid therapy is not recommended (Rhodes et al., 2017).

"In the large surveys, national surveys around the globe, it's shown repeatedly that the point estimate of mortality due to a specific episode of septic shock is getting lower, is improving. Recognizing that septic shock in particular is a medical emergency, and should be treated as such, [is the reason for the lower mortality]. Which means that you've got to get their left ventricular filling pressure, you have to, even though they don't respond well to fluid, you have to give them enough fluids to maintain filling

pressure in the heart. You must re-establish their blood pressure through early intervention with vasopressors."

US Key Opinion Leader

The third pillar of supportive care in the management of sepsis and septic shock is the regulation of blood pressure by vasopressors. The 2016 SSC guidelines recommend the use of norepinephrine as first-line medication, with vasopressin and epinephrine as second-line agents. The use of dopamine is only suggested in patients with low risk of tachyarrhythmia and in patients with persistent hypoperfusion despite adequate fluids and vasopressors (Rhodes et al., 2017). KOLs interviewed by GlobalData noted that while norepinephrine is a good vasopressor, its recommendation as a first-line drug is based on sparse evidence, thereby the ideal drug selection and dosage remain largely unknown and should be adjusted on an individual basis.

"I think vasopressin can cause excessive gut ischemia sometimes, but in our hands vasopressin is a good agent."

US Key Opinion Leader

Other supportive measures include red blood cell (RBC) transfusions, but these are recommended only when hemoglobin concentration in sepsis patients decreases to 7.0g/dL or less, and in the absence of extenuating circumstances such as myocardial ischemia, severe hypoxemia, or acute hemorrhage. Furthermore, the 2016 SSC guidelines recommend the use of erythropoietin for the treatment of anemia in sepsis patients, whereas fresh frozen plasma to correct for clotting abnormalities is not suggested (Rhodes et al., 2017). Platelet transfusions as a prophylactic measure are suggested when platelet counts are less than 10,000/mm^3 ($10x10^9$/L) and in the absence of apparent bleeding, and when counts are less than 20,000/mm^3 ($20x10^9$/L) if the sepsis patient has a significant risk of bleeding (Rhodes et al., 2017).

6.5.3 Mechanical Ventilation and Hemodialysis

When patients develop sepsis-induced comorbidities, they are treated with organ support therapies such as dialysis or mechanical ventilation. The supportive use of mechanical ventilators is particularly recommended in adult sepsis and septic shock patients suffering from sepsis-induced ARDS. The 2016 SSC guidelines recommend a target tidal volume of 6mL/kg, going up to 12mL/kg for patients suffering from ARDS. Furthermore, the use of a higher positive end-expiratory pressure (PEEP) over lower PEEP is recommended in sepsis patients with moderate to severe ARDS, where upper plateau pressures are recommended not to exceed 30cm H_2O (Rhodes et al., 2017). In addition, the guidelines recommend the use of recruitment maneuvers in patients with ARDS, where a sustained continued

positive airway pressure has been shown to improve survival and occurrence of severe hypoxia. Intubation of ARDS patients with a PaO_2/FIO_2 ratio of 150 or higher should occur with the patient lying on his or her face (prone) rather than on his or her back (supine), whereas the use of high-frequency oscillatory ventilation in sepsis patients with ARDS is not recommended. The use of facilitating neuromuscular blocking agents to further support mechanical ventilation is restricted to 48 hours or less in ARDS patients and a PaO_2/FIO_2 of less than 150mmHg, in order to avoid neuromuscular weakness, myopathies, or neuropathies. The use of β-2 agonists and peripheral arterial catheters in sepsis patients with ARDS and bronchospasm is not recommended. Further breathing facilitating measures and weaning measures are recommended, and are detailed in the 2016 SSC guidelines (Rhodes et al., 2017).

"Supportive care and the ICU has definitely gotten better, and the ventilators are better, dialysis machines are better, they're more functional. They're easier to use, and we've learned not to hurt people with our technologies, and our overstretching their alveoli, and dialysing before they really needed it, and giving them blood products when they really didn't need it. So, we've learned that early resuscitation is important, and then careful supportive care without adding iatrogenic injury to their already disordered physiology. So, we're getting better, but what's getting better is, the background care is getting better, not necessarily some new, wonderful treatment."

US Key Opinion Leader

The 2016 SSC guidelines do not recommend the use of blood purification devices, including high-volume hemofiltration and hemoadsorption, as well as other coupled plasma filtration and adsorption techniques. Renal replacement therapy (RRT), on the other hand, is suggested in patients suffering from AKI in order to support fluid balance in hemodynamically unstable sepsis patients, whereas the use of RRT in the absence of other definitive indications for dialysis, such as for increase in creatine or oliguria, is not recommended (Rhodes et al., 2017).

Renal replacement therapy (RRT), on the other hand, is suggested in patients suffering from AKI in order to support fluid balance in hemodynamically unstable sepsis patients.

6.6 Other Therapeutic Approaches to Sepsis and Septic Shock

Other therapeutic measures are frequently used in the treatment of sepsis and septic shock, but they are either very specific to selected patient populations or, in the case of steroids, immunoglobulin G (IgG), and anticoagulants, evidence of their use has not been assessed in large RCTs (Rhodes et al., 2017). Table 22 highlights other commonly used therapeutic treatment options for sepsis and septic shock patients.

"We've learned [that] what not to do, what to do, and how much to do it is still a big deal [to treat sepsis].We overfed people. You could increase their nutrition, but you'd also add all that CO_2 you've

generated that now needs to be blown off by the lung.So, you're actually making their respiratory situation worse by over-feeding them. In fact, if you overfeed people, they actually do worse, and if you let them have enough nutrition to keep their gastrointestinal tract viable but not trying to force-feed them. We overstretched the alveoli by adminisering too much oxygen, we gave too much blood. We did a lot of stuff that was contributing to the illness, in our effort to help."

US Key Opinion Leader

Table 22: Summary of Minor Supportive Measures, 2017

Therapeutic Class	Major Marketed Drugs	Target Patients
Source control (surgery)	Surgical intervention by removing of infectious tissue	
Steroids	IV hydrocortisone	Not recommended in sepsis patients. In septic shock patients, not responding to adequate fluid resuscitation and vasopressor therapy, a daily dose of 200mg per day is suggested
Immunoglobulins	IV immunoglobulins (IVIg, IVIgGM, or IVIgG)	Guidelines recommend against the use of immunoglobulins due to weak evidence of efficacy. Immunoglobulins are used in immune-suppressed sepsis and septic shock patients.
Anticoagulants	Antithrombin	Not recommended in patients with sepsis and septic shock
Sedation and Analgesia	Propofol, dexmedetomidine and benzodiazepines	Minimized continuous or intermittent sedation of ventilatedsepsis and septic shock patients
Glucose control	IV insulin	In sepsis and septic shock patients under a protocoled approach
Bicarbonate therapy	Sodium bicarbonate	Not recommended in patients with sepsis and septic shock
VTE prophylaxis	heparin	In sepsis and septic shock patients, low molecular weight heparin is recommended to prevent VTE
Stress ulcer prophylaxis	Proton pump inhibitors or histamine-2 receptor antagonist	In patients with sepsis and septic shock, who have risk factors for gastrointestinal bleeding
Nutrition	Enteral feeding orin combination with IV glucose	Administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feeding not recommended in critically ill patients with sepsis and septic shock.
Setting goals of care	N/A	Sepsis and septic shock patients, family relatives, and physicians

Source: GlobalData; Rhodes et al., 2017; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

VTE = venous thromboembolism

7 Unmet Needs Assessment and Opportunity Analysis

7.1 Overview

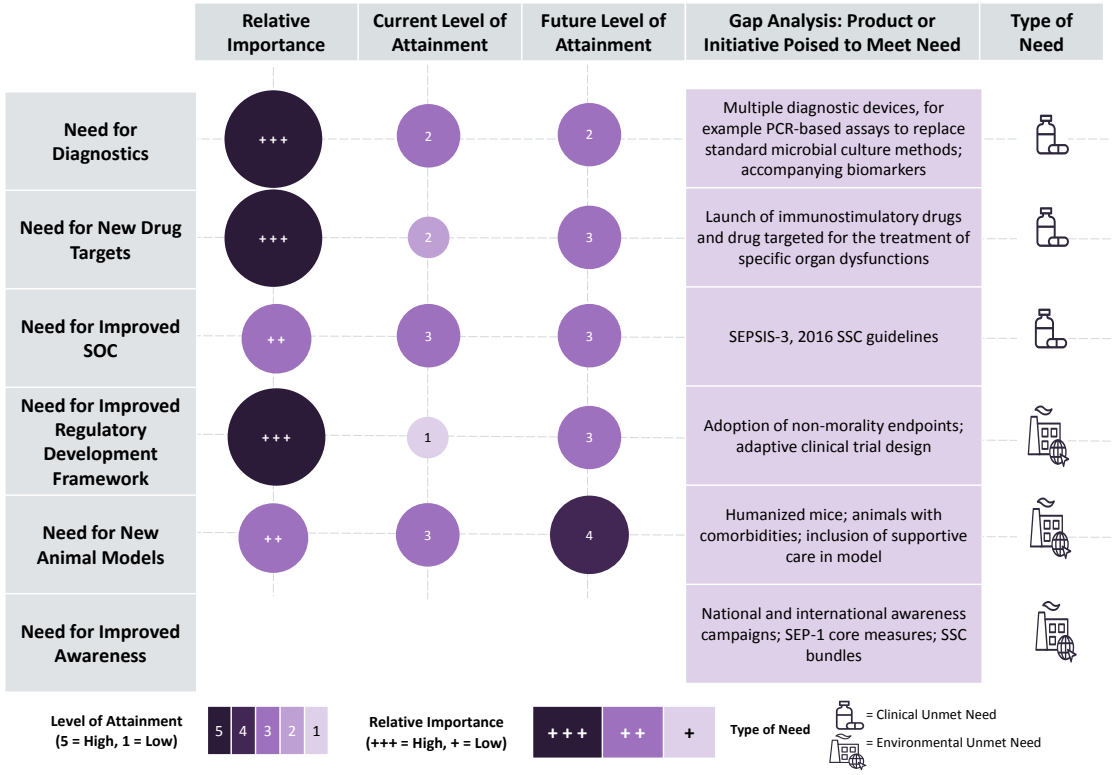
GlobalData assesses the current level of unmet need in the sepsis and septic shock market as high. There are no approved drugs to impede the course of the disease, and the current management is limited to early infection control measures such as administration of antibiotics to help clear the infection, along with organ support measures in the form of fluid resuscitation, vasopressors, ventilators, and RRT—which in Japan and the 5EU includes the hemoperfusion column Toraymyxin—to stabilize patients.

Key environmental unmet needs include the current development framework that companies encounter when seeking market approval for new drugs for sepsis and septic shock patients, while key clinical unmet needs deal with characteristics that these new therapeutics must fulfill in order to be successful within this disease indication. In the absence of approved medications for sepsis and septic shock patients, experts listed predominantly environmental needs for the pharmaceutical industry, emergency care physicians, and critical care practitioners to improve patient outcomes.

Figure 34 highlights the aforementioned key clinical and environmental unmet needs in the sepsis and septic shock market, which GlobalData identified through extensive primary and secondary research across the 7MM. Unmet needs will be discussed according to each need's relative level of importance (high, moderate, or low) and their current and future levels of attainment (1 = low attainment, 5 = high attainment). Following a detailed description of the unmet need, GlobalData provides a gap analysis of each unmet need, which will reveal the current products and strategies that are positioned to satisfy these needs during the forecast period. Importantly, the clinical and commercial positioning of all pipeline products discussed in this report will be assessed in the context of how well they address these unmet needs. Each section will be concluded with an opportunity analysis, where GlobalData highlights remaining opportunities for developers to exploit these unmet needs throughout the forecast period.

At the end of the forecast period and after the successful launches of all eight pipeline agents (Shionogi's cefiderocol, Ferring's Selepressin, Asahi's thrombomodulin, Spectral's Toraymyxin, Am-Pharma's recAP, Faron's Traumakine, RevImmune's CYT107, and BMS' anti-PD-L1 mAb BMS-936559), GlobalData expects the majority of unmet needs to be only partially addressed, leaving developers with considerable opportunity to address challenges in the diagnosis and management of sepsis patients, as well as the possibility to address new opportunities for development of sepsis-specific treatment options to directly interfere with sepsis pathophysiology.

Figure 34: Unmet Need and Opportunity in Sepsis and Septic Shock, 2017



Source: GlobalData

7.2 Improved Biomarkers to Guide Treatment Decisions and Support Drug Development

7.2.1 Unmet Need

GlobalData's primary and secondary research revealed the need for quantitative and clinically relevant biomarkers to guide treatment decisions and to support clinical drug development.

GlobalData's primary and secondary research revealed the need for quantitative and clinically relevant biomarkers to guide treatment decisions and to support clinical drug development.

From a clinical perspective, biomarkers currently available to diagnose sepsis lack the necessary specificity and sensitivity to characterize the presence of infection. In the absence of reliable biomarkers, sepsis diagnosis remains a subjective exercise, where certain clinical criteria raise the suspicion of sepsis and septic shock. Experts cited diagnostic tools for quick infection and pathogen identification as a primary unmet need in current clinical practice To confirm bacterial infections, clinicians are still relying on culture-based techniques, which not only take up to 24 hours, but also have a high false negative rate. Furthermore, traditional laboratory cultures lack antibiotic

susceptibility testing (AST), an increasingly important feature in an environment with growing resistance to almost every known antibiotic.

"We still don't have a good mechanism for screening for infection, and identifying early patients who are infected. We're still relying on cultures, which are of course only positive 50% of the [time], and the SIRS criteria, which are not very good at all, [to make a diagnosis for sepsis]. So, we're still struggling with the best way to rapidly screen and identify patients who are infected and are likely to develop organ dysfunction. I think that we're going to develop biomarkers for identifying patients early before we develop a new therapeutic agent."

US Key Opinion Leader

"It would be extremely helpful to have some kind of simple method that clinicians can use to quickly diagnose the type of bacteria in a bacterial infection."

Japan Key Opinion Leader

"There's not a single definitive test [for sepsis]. For cancer there's biopsy, and if you've got neoclassic cells, you've got cancer. Or, if we think you might have diabetes, if your blood sugar is over 120, there's a syndrome of diabetes, but there's also a specific diagnostic test. In sepsis, we really don't have that. The diagnosis is a compilation of physiologic abnormalities, laboratory studies, [and] microcirculatory changes; a lot of things are going on, none of which we can say with certainty that a single one of any of those would make the diagnosis. So, yes, I wish it was easier [to diagnose patients with sepsis and septic shock], and people have been trying for a long time to come up with a specific test [for sepsis], but, to date, that hasn't arrived. Not that people aren't trying, but it's just not that easy to do."

US Key Opinion Leader

From an R&D perspective, the complexity of the inflammatory and immune processes within the host in response to specific pathogens makes it difficult to stratify patients into specific treatment groups in current RCTs. Consequently, experts cited new diagnostics to reduce heterogeneous patient populations currently enrolled in RCTs as a key unmet need. Specifically, experts would like to leverage diagnostic tools to not only identify sepsis or septic shock patients, but also to inform about the host's immune status at the time of enrollment. The immune response during sepsis and septic shock is known to fluctuate between hyper-inflammation and immune paralysis, resulting in various types of organ dysfunctions. Therefore, current and future treatment options must rely on the reliable identification of the patients' immune status in order to administer targeted interventions.

Furthermore, experts highlighted a potential selection bias in current RCTs, where physicians can identify patients with high certainty to survive or die based on existing comorbidities.

"The problem in our patient population is that the host response changes quite quickly over time. By the time you get your evaluation and you start the drug the next day, the situation may be different. It's very different from cancer, where you can use precision medicine because the cell receptors will not change so rapidly. So you characterize your cancer cells and you look at receptors, and then you use the drug which is most suitable for this type of alteration. That makes a lot of sense. In sepsis, things change so quickly that we are facing a major challenge. Nevertheless, we need to characterize the host response better than in the past, where people were looking at just SIRS plus organ dysfunction, and that's it. That was really too naïve. We should no longer do that."

EU Key Opinion Leader

"There is still the activated protein C [Elli Lilly's Xigris], which was on the market [but was withdrawn by the manufacturer]. I think it [Xigris] works. Some people say it doesn't work, because there was another negative trial, and I agree that the second prospective [RCT] was totally negative, but the drug was already on the market. The second trial failed to enroll patients likely to benefit from this intervention, if you enroll very heterogeneous patient populations, you risk diluting your efficacy signal. To make a long story short, I think that other companies than Eli Lilly will actually restart studies on it because it works very well in animals, the clinical data is quite compelling as well."

EU Key Opinion Leader

"Sure, I would love one [biomarker], the problem with the immunosuppressed stage is we don't know when it starts, and so using lymphocyte count is still just a rough surrogate for the immunosuppressed phase. So what you really want is a better marker for when the immunosuppressed phase starts, and we don't really have that yet."

US Key Opinion Leader

"I think, another thing that we've learned, is that the days of just treating everybody with an anti-sepsis drug are pretty much over. You've got to have some way of figuring out whether the patient you're about to treat is likely to respond to the treatment [besides just using vital signs]. You have to do something to say that 'The drug I'm going to give you is likely to benefit the patient with some type of biomarker, or some kind of pure diagnostic.' I'm relatively optimistic that we'll find something sooner or later."

US Key Opinion Leader

7.2.2 Gap Analysis

At the end of the forecast period, GlobalData anticipates that the need for new diagnostics will remain high. Experts complained that current culture-based methods have both a high false positive rate—mostly due to contaminations—and a high false negative rate, where pathogens of interest cannot be cultured under laboratory conditions. Novel pathogen identification methods, such as polymerase chain reaction (PCR)-based techniques, suffer from high sensitivity and low specificity and don't usually inform about antibiotic susceptibility patterns for the pathogens of interest.

KOLs interviewed by GlobalData see particular promise in sequencing techniques, which can be used for diagnostic purposes for pathogen identification and can also assess the antibiotic susceptibility of the pathogen of interest. For example, AsTrID—a diagnostic instrument developed by Q-linea—combines newer amplification techniques such as rolling circle amplification (RCA) for the sequencing of bacterial probes, which allow the identification of both the pathogen and its antibiotic susceptibility pattern in under three hours (Jarvius et al., 2016).

"We're still relying on [culture-based methods], which are of course are only positive 50% of the time, and take a very long time [to yield results]. So, we're still struggling with the best way to screen and early identify patients who are infected and are likely to develop organ dysfunction."

US Key Opinion Leader

"New methods to define infection in the bloodstream and in other body fluids are important. Culture- and PCR-based methods have failed to help us so far, because they cannot give us information regarding [antibiotic] susceptibility. There is one very promising method approaching the market now, [ASTrID from q-linea], which is very interesting and offers completely new aspects in guiding treatment, where you get a very fast susceptibility test within five or six hours."

5EU Key Opinion Leader

A survey among high-prescribing physicians indicated that current sepsis and septic shock diagnosis is dominated by PCT and CRP biomarkers to identify infection. Experts cited physicians' familiarity and low cost of execution as primary drivers for the widespread use of PCTs and CRPs. Furthermore, KOLs expressed great promise for genomic profiling techniques, where certain risk genes will not only be used to identify patients with an increased mortality risk, but will also be used to guide therapy in terms of commencing an immunosuppressing or immunostimulating intervention in the sepsis pathophysiology.

"I think that's one of the great unmet medical needs, is a rapid, accurate diagnosis. The next big thing is trying to do a rapid genomics, if you can do a rapid gene screen for certain high-risk genes, if you could pick that up, maybe that would be better than, you know, clinical assessments, or measuring their lactate, and so on and so forth. So, I would say, that's one of the great unmet medical needs, is making a rapid diagnosis, despite the fact we've been trying to convince people this is important. It doesn't necessarily get people fired up, but if you had a test where you, say, had a rapid genomics test and said 'This set of genes tells you that there's a 95% chance this patient is going to be in the ICU within the next 24 hours in septic shock,' then that would be great. People are working at it, there's actually some evidence that this might prove to be useful."

US Key Opinion Leader

In the absence of reliable and accurate biomarkers for sepsis and septic shock, current RCTs stratify patients based on surrogate measures such as a low lymphocyte counts, low human leukocyte antigen, antigen D related (HLA-DR) levels, decreased inotropic requirements, or specific organ dysfunctions. GlobalData anticipates that during the forecast period—with the exception of Toraymyxin, which features a companion diagnostic—no other pipeline agent will leverage biomarkers to identify patients most likely to benefit from specific treatments. Experts consistently drew parallels to other therapeutic fields such as oncology and hepatitis C, where the development of biomarkers has sparked major innovations and improvements in disease outcomes, such as a cure in the case of hepatitis C. While KOLs see the future long-term treatment landscape for sepsis and septic shock shifting towards a personalized medicine approach, GlobalData notes that this change is not likely to be implemented during the period of the forecast.

7.2.3 Opportunity

GlobalData anticipates that major opportunities to develop and leverage new diagnostics for sepsis and septic shock will remain after the launch of the forecasted pipeline drugs from 2016–2026. Particularly from an economic perspective, GlobalData anticipates that mAbs, such as BMS' anti-PD-L1 mAb, BMS-936559, will be limited to patients with a positive PD-L1 signature in order to justify the associated high therapeutic cost. For example, in Japan, the use of Merck & Co's anti-PD-1 mAb Keytruda (pembrolizumab) is subject to a positive PD-L1 signature in the treatment of non-small cell lung cancer, and a similar approach is pushed for BMS' anti-PD-1 mAb Opdivo (nivolumab) (Katsuya et al., 2016; Pharma Japan, press release, March 22 2017). While the development of biomarkers for mAbs will be driven foremost by economic incentives, GlobalData believes that other diagnostics such as low IL-7 cytokine levels and thrombo-elastometry—a technique that detects changes in the fibrinolytic activity in whole blood samples, which raise suspicion of DIC and guide physicians in the

use of anti-coagulation therapies—will be used for improved stratification of patients who receive the pipeline agents CYT107 and thrombomodulin therapy, respectively(Kuiper et al., 2016).

In terms of novel diagnostics for sepsis and septic shock, GlobalData anticipates that the need for faster and more reliable methods will remain high. A particularly innovative approach is the use of Raman spectroscopy to detect individual pathogens and their antibiotic susceptibility patterns (Liu et al., 2016). However, GlobalData notes that current developing efforts are limited to academic settings, and the lack of standardization among different research groups further hinders commercialization of this technology in the near future.

7.3 Novel Therapeutic Interventions Targeting Sepsis Pathophysiology

7.3.1 Unmet Need

GlobalData's primary and secondary research revealed a lack of sepsis-specific therapies to supplement the current SOC and improve patient outcomes as a key clinical unmet need in the sepsis and septic shock marketplace.

Experts cited the need to develop new interventions that target sepsis pathophysiology, in particular the immune host response, in order to buy physicians time to identify the cause of the infection and prescribe a pathogen-specific antimicrobial agent. Ideally, new therapy sepsis-specific interventions could be administered in patients diagnosed with sepsis or septic shock, thereby preventing sustained organ damage.

Experts cited the need to develop new interventions that target sepsis pathophysiology, in particular the immune host response.

"We've been trying for a very long time to come up with strategies to re-establish the normal physiology of organs, by giving [the sepsis and septic shock patients] anti-inflammatories, or maybe immuno-adjuvants. We still haven't succeeded…We need some new ideas and new treatments to try to either prevent organ dysfunction, or more rapidly improve organ function once it's become dysfunctional. I think there's still room for that, with a number of different strategies that people are trying."

US Key Opinion Leader

"Either modifying the immune response of the patient, but using biomarkers to guide that, or protecting the endothelium because to protect the endothelium, the microvasculature, the cells in the periphery, you may not need so much to select the right patient population, it may work in all septic patients. These are the two strategies I would certainly consider the most [promising]."

EU Key Opinion Leader

"I think it's primarily the modulation of the sepsis response, as I call it. You may call it adjunct therapies, if you like. That's where the focus should be. I would say that there are many options there, but one important one is to try to preserve the endothelial cell function, thereby limiting edema formation as we know that edema is very bad for all the organs."

EU Key Opinion Leader

"I'd say compromised hosts are our greatest challenge. A patient will experience a temporary reprieve, but in the long term will end up dying from an infection. And in those cases, antibacterial drugs lose their efficacy. That is probably because of some issue with the patient, or because of long-term use of antibacterial drugs—an iatrogenic infection—but I do feel our limitations when patients die because of an infection. So, I suppose infection control is our biggest challenge, because patients end up dying from an infection."

Japan Key Opinion Leader

7.3.2 Gap Analysis

Experts interviewed by GlobalData are particularly excited about the potential of immune-stimulating agents to interfere with late-stage sepsis and septic shock morbidity and mortality. During the forecast period, GlobalData anticipates the launch of two novel immunostimulatory drugs, namely BMS' anti-PD-L1 mAb BMS936559 and RevImmune's CYT107. However, based on current enrolment criteria for RCTs, the usage of these two drugs will be limited to patients with distinct immunosuppression symptoms, such as a low lymphocyte count. KOLs interviewed by GlobalData cited the need for new biomarkers for an immunosuppressed state in sepsis and septic shock patients in order to broaden the application of these drugs.

"I do think immune-adjuvants are a big deal. I think, whether they're able to do a PD-1 [mAb], or interleukin 7, I think, there are a number of things that are coming after that. So, I think that's an interesting approach."

US Key Opinion Leader

"We need to be targeting the immunosuppressed phase of sepsis and improve it, enhancing the immune system response in patients with sepsis who have a low lymphocyte count."

US Key Opinion Leader

"I'd like to see an antibiotic that can be used in a bundle, but I don't think that is feasible. Not even in the future. Or a vasopressor that has limited adverse side effects. Or a drug that can return an

immunosuppressed system to its original state. I'd rather have something that can return the system to its original state than something that induces increased activity."

Japan Key Opinion Leader

In addition to novel immune-boosting drugs to more effectively address sepsis-induced immunosuppression, KOLs expressed increasing interest in novel drugs to support organ functions, in particular to protect the microvascular function of endothelial cells in sepsis and septic shock patients. AM-Pharma, Asahi, Faron, Ferring, and Spectral are developing unique anti-inflammatory treatment options to prevent or ameliorate organ dysfunction. For example, AM-Pharma and Faron are developing recAP and TraumaKine, respectively, for the treatment of sepsis-induced kidney and lung dysfunction. Although both pipeline drugs are targeting distinct organ dysfunctions, GlobalData notes that the similar molecular pathways of these two pipeline drugs could make these products future competitors in the sepsis and septic shock marketplace. Meanwhile, Asahi and Ferring are developing thrombomodulin and selepressin, respectively, as novel anti-coagulation treatment options to predominantly target patients with sepsis-induced DIC. In particular, selepressin's dual mechanism of action (MOA) as anti-coagulant and endothelial cell stabilizing agent resonated well with interviewed experts.

"If we could find a way to protect the microvasculature by protecting the endothelial cells, then we could limit edema formation and protect the organs. That's what researchers are doing with selepressin, which is a vasopressin derivative.We may already do it with vasopressin, and actually we and others published some data on this, but perhaps with selepressin it may be practically effectively with a V1 agonist substance."

EU Key Opinion Leader

"The Faron company is working on a substance that could potentially protect the lung endothelium in ARDS, so in acute respiratory failure. This is a study which is ongoing now, that will enroll 200 patients with ARDS, and they will try to elucidate this product's effect on adenosine production, potentially helping the patients to recover more quickly."

EU Key Opinion Leader

"The near future in sepsis and septic shock treatment will be shaped by new entrants to the market. There may be some different compounds without anti-coagulant activity that could be protective in sepsis. If we look in the long term, yes, there are some other options that could clearly be considered in the future. Stem cells could also be considered in respiratory failure and other forms of organ failure. There is a lot in the pipeline, and some of them are really very exciting."

EU Key Opinion Leader

Lastly, KOLs cited recent research on mesenchymal stem cell (MSC) therapy as promising approaches to treating sepsis and septic shock patients. GlobalData notes that stem cells are not only able to directly modify a host immune response, but also possess proven anti-infective properties (Heming et al., 2016; Kingsley and Bhat, 2016). Early clinical safety studies of mesenchymal stem cells in healthy volunteers demonstrated a good safety profile, while Phase I trials in septic shock patients are still ongoing (Ottawa Hospital Research Institute, NCT02421484; TiGenix S.A.U., NCT02328612).

"There's also some work with mesenchymal stem cells, and could you potentially treat patients who are in a pro-apoptotic state, where they're losing cells and they're losing [organ] function. If you could give them some help to tide them over with some stem cells until they recover, it's a fascinating idea, and I think sounds a bit pie in the sky, but in actuality, it's not such a crazy idea. It may actually work, so, yes, I'm optimistic [about this approach]."

US Key Opinion Leader

7.3.3 Opportunity

GlobalData anticipates future opportunities to develop new therapeutic interventions for sepsis and septic shock to remain after the forecast period. The sepsis market is still very immature in terms of available treatment options, and although any new approved drug will be welcomed by both physicians and patients alike, many other therapeutic interventions, such as modified T cells, remain unexplored in sepsis. Transfusion of cytomegalovirus (CMV)-resistant T cells is currently being investigated as a treatment option for CMV infection after allogenic hematopoietic stem cell transplantation (Atara Biotherapeutics, NCT01646645). For sepsis, T cells could be engineered to be resistant to apoptosis and specifically target bacterial, viral, parasitic, or viral pathogens. These specific T cells could be transfused during the immunosuppressed disease stage to restore immunity in immunosuppressed sepsis patients, and could be inactivated through an integrated suicide gene when no longer needed (Boomer et al., 2014).

Furthermore, experts highlighted that with the exception of Spectral's Toraymyxin, which is paired with an endotoxin analysis assay (EAA) in recent Phase III RCTs, developers have failed to leverage diagnostic biomarkers for directing the usage of their investigational pipeline drugs (Spectral, NCT01046669). In a market like sepsis and septic shock, where diagnosis and current guidelines for disease management are very vague, GlobalData anticipates that a clear diagnostic biomarker to guide physicians towards the use of a new drug is an essential undertaking if that drug is to be successful.

"Our guidelines for sepsis are not directive, we overly base our recommendations on prospective randomized control trials while dismissing accumulated success of sepsis therapy in clinical practice. Everybody wants prospective randomized control trials, but these trials are all negative, [one] after the other, primarily because the patient populations are very heterogeneous. Some patients may improve by a therapy, but some patients may be harmed by the same therapy, so that at the end there is no difference in survival rates."

EU Key Opinion Leader

7.4 Enhancing Effectiveness of Currently Available Interventions to Help Improve Clinical Outcomes

7.4.1 Unmet Need

GlobalData's primary and secondary research revealed a need for clinicians to more effectively leverage the currently available interventions for treating patients with sepsis and septic shock. Specifically, KOLs cited the need to improve antibiotic selection and dosing depending on the underlying infection(s). An example is the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA)-induced sepsis and septic shock, where experts highlighted that inappropriate choice of antibiotics and short courses of treatment frequently fail to clear the underlying infection. Indeed, experts acknowledged that up to 30% of patients diagnosed with sepsis or septic shock receive inadequately dosed antibiotics. GlobalData notes that the administration of sub-MIC doses of antibiotics will frequently fail to clear the bacterial infection and increases the risk of developing resistance to the administered antibiotic, while concentrations above the MIC but beyond the therapeutic window increase the risk of host toxicity.

"[MRSA] is a major pathogen in sepsis patients. We make a lot of mistakes in treating S. aureus infections, in terms of diagnostic testing, not adequately addressing the problem of prolonged antibiotic treatment in these patients, and not adequately eradicating the focus of infection. I think we have to think of S. aureus as only one example, where we have to look more on the infectious aspects of sepsis. This is really because critical care physicians are very good at treating organ dysfunction, but not at infectious disease convergence in treating infection, to the point that infectious disease specialists should be involved in the treatment [of sepsis and septic shock patients]."

EU Key Opinion Leader

"Therapeutic drug monitoring [TDM] has shown us that up to 30% of patients [with sepsis or septic shock] do not receive adequate dosages of antibiotics. This problem is discussed in every critical care

congress since, I would say, the last three years or so. TDM is not a bedside test yet and cannot be done in every ICU. So, I think it's a future task of the industry to develop simple diagnostic therapeutic drug monitoring devices."

EU Key Opinion Leader

"I think we have to focus more on antibiotics, with the upcoming [emergence of] multi-[drug] resistant bugs. I think we have to deal more on this infection side. Sepsis experts are normally interested in supportive treatments, mechanical ventilation, shock treatment, but less on the treatment of the underlying infection."

EU Key Opinion Leader

KOLs identified the inability to incorporate expert opinion in current guidelines as a major drawback in improving patient outcomes in sepsis and septic shock. For example, the 2016 SSC guidelines for sepsis and septic shock are largely based on evidence collected from RCTs, and expert opinions are not incorporated. While the incorporation of only high quality data from RCTs is very encouraging, KOLs highlighted that the majority of trials fail to achieve statistical significant outcomes in terms of overall mortality. GlobalData notes that the reasons for the failures are multitude, but experts agree that too-heterogeneous patient populations and inconsistent medical interventions in terms of antibiotic and supportive care are among the major causes.

KOLs identified the inability to incorporate expert opinion in current guidelines as a major drawback in improving patient outcomes in sepsis and septic shock.

Therefore, a therapy that could be beneficial for a certain patient population could be deemed harmful to another. A prime example is steroid therapy in septic shock patients refractory to fluid resuscitation and vasopressors. While large RCTs for steroids in septic shock patients have failed to achieve statistically significant outcomes in overall 28 day all-cause mortality, steroid usage in clinical practice remains a popular treatment option to reduce duration of septic shock (Annane et al., 2002; Hadassah Medical Organization, NCT00147004). Furthermore, experts criticized the guidelines for being not very specific, as critical choices of optimal antibiotic dosing and resuscitation fluid volume remain unknown. While the failure to specify exact quantities is understandable—in past guidelines, too-high recommended ventilator settings had caused lung damage in patients—ineffective antibiotics or too low concentrations of antibiotics can have severe consequences for patients. Lastly, experts identified the need to replace crystalloid fluids with new formulations that are more similar to human plasma.

"I think right now we're trying to learn from our mistakes and trying to not do harm [to patients with sepsis or septic shock]. If we've learned anything in the last 25 years in supportive care, it's to not add insult to injury.The standard ventilator settings twenty years ago were similar to what we are using

nowadays. In between this 25 year period, we used tidal volume per kilogram and people seemed really comfortable. It improved their gas exchange but it's also overstretching the alveoli, causing volume trauma to the alveoli, and actually causing ventilator-induced lung injury. So, for years and years and years, we were actually making people worse. It wasn't until the EGDT trials done about ten years ago showed quite convincingly that 6mL is better than 12mL.Now, everybody uses 6mL.So, there's an example where we overdid things."

US Key Opinion Leader

7.4.2 Gap Analysis

According to GlobalData's primary research, the current SOC in sepsis and septic shock is the result of a constant effort of government-sponsored RCTs aimed at improving patient outcomes. GlobalData identified several measures and RCTs aimed to improve the use of available treatment options for sepsis and septic shock patients throughout the forecast period. The most recent multinational effort of the ARiSE, ProCESS, and ProMISe RCTs has shown that invasive procedures such as EGDT do not impact overall all-cause mortality, and that early antibiotic administration, fluid resuscitation, and hemodynamic stabilization are essential for favorable clinical outcomes. The SSC endorsed these findings in their 2016 SSC guidelines (Angus et al., 2015 ARISE Investigators and the ANZICS Clinical Trials Group, 2014; Mouncey et al., 2015; Rhodes et al., 2017; Rivers et al., 2001).

GlobalData expects that RCTs will continue to play a pivotal role in shaping the treatment landscape in sepsis and septic shock. In particular, RCTs aimed at improving infection control, supportive care, and the use of steroids in sepsis and septic shock patients will influence the treatment protocol (The George Institute, NCT01448109; University of Aarhus, NCT02569086; Aarhus University Hospital, NCT02478073; CAMC Health System, NCT02764359; Southeast University China; NCT02616354; Medical University of Lublin, NCT03034174; Zhongda Hospital, NCT02508350). While most of the anticipated RCTs are aimed at specific interventions, KOLs highlighted an upcoming adaptive RCT investigating various therapeutic interventions in the treatment of community-acquired pneumonia (CAP), where multiple of the previous mentioned interventions are to be assessed in improving patient outcomes in this patient population (UMC Utrecht, NCT02735707). GlobalData expects the results of this RCT in CAP to be the most influential in improving the current management of sepsis and septic shock, as pneumonia is known as a leading cause of sepsis.

"There is a consortium, I'm part of the European consortium, but we have consortia in the United States, Canada, Australia, and Europe. We will start to build up an international trials group in patients with a very specific sepsis focus, community-acquired pneumonia, and including patients in

the registry, and then embedding multifactorial interventions at the same time. The idea is to recruit large patient populations with very specific focus in sepsis over short periods of time and large geographical areas in order to find the best possible treatment approach."

EU Key Opinion Leader

"In Japan, awareness campaigns, SSC guidelines, as well as local guidelines have contributed to a decline in critically ill sepsis and septic shock patients."

Japan Key Opinion Leader

7.4.3 Opportunity

Despites efforts by clinicians and researchers to improve on currently available interventions, GlobalData anticipates needs for improved SOC to remain for the duration of the forecast period. While results from large RCTs will eventually improve some aspects of the current SOC, most notably steroid use and antibiotic selection and dosing, the problems of demonstrating statistically significant outcomes in large heterogeneous patient populations will remain challenging and slow the progress of clinical research. After the results of the adaptive RCT in CAP are published, experts anticipate similar adaptive RCTs in sepsis and septic shock patients, where SOC measures will be further optimized in terms of dosing and timing. In addition, experts anticipate that an increased understanding of sepsis and septic shock pathophysiology will further guide timing and dosing of treatment options. GlobalData anticipates that improvements to the treatment protocol for sepsis and septic shock patients will further reduce overall mortality, allowing pharmaceutical companies to focus development on drugs aimed at reducing organ dysfunction and treatment approaches that directly interfere with the sepsis-induced immune response.

GlobalData foresees opportunities to develop drugs for specific organ dysfunctions in sepsis and septic shock patients. Pharmaceutical developers are advised to concentrate their clinical development programs to specific sepsis and septic shock patient populations in order to facilitate market approval and the development of specific diagnostics to guide physicians in their future use.

7.5 Streamlined Regulatory Framework to Stimulate Clinical Research and Drug Development

7.5.1 Unmet Need

The absence of a sepsis-specific, regulatory-approved product in the 7MM provides evidence of the difficulty of entering the sepsis and septic shock marketplace. GlobalData's primary and secondary research identified limited funding opportunities from small-cap biotech firms and the currently endorsed clinical endpoints as two key challenges to current drug development efforts.

Firstly, drug development in the sepsis and septic shock market is conducted predominantly by small-cap biotech firms, which lack the financial backing of Big Pharma to fully support late-stage clinical development. Big Pharma is represented in the sepsis and septic shock therapy area, but these efforts are either very early in the development process—BMS is leveraging its success with PD-(L)1 checkpoint inhibitors (the anti-PD-L1 mAb BMS-936559 and the anti-PD-1 mAb Opdivo [nivolumab]) in oncology by exploring the relevance of these therapeutics in sepsis pathophysiology—or are contingent on the success of early development by small-cap biotech firms: for example, Pfizer is planning to acquire AM-Pharma's recAP after successful completion of Phase II clinical development. The fact that most of the sepsis and septic shock pipeline is being advanced by small-cap biotech firms highlights the high risk associated with the clinical development of drugs in this disease indication. Furthermore, the high costs associated with Phase III studies represent a major barrier to market entry. In January 2017, InflaRx halted development of its anti-inflammatory drug IFX-1 for sepsis due to a failure to secure the necessary funding for large-scale Phase III studies, instead choosing to focus future development efforts of IFX-1 for various chronic and acute inflammatory indications, such as infection prevention after cardiac surgery (InflaRx, press release, January 4, 2017).

Secondly, experts believe that current clinical endpoints, endorsed by regulatory agencies, are no longer appropriate to measure a treatment benefit in a disease with decreasing mortality and increasing long-term morbidity due to sepsis and septic shock. The current regulatory framework demands that pipeline drugs being evaluated to treat sepsis patients demonstrate a mortality benefit in their pivotal clinical trials in order to support future market approval. KOLs interviewed by GlobalData highlighted the need for regulatory agencies to move away from all-cause mortality endpoints towards other non-mortality endpoints, such as improvement in organ dysfunction. Furthermore, experts encouraged the use of single Phase III trials to support new drug applications (NDAs) in the sepsis and septic shock market.

"It's important that we have data [concerning quality of life post-sepsis]. If we had this we could understand the true fiscal costs of sepsis, and that might persuade governments, budget holders, and grant makers to actually appropriate funds towards sepsis improvement and research."

EU Key Opinion Leader

"[Funding has] been a big problem in the field now. There's been so many failures that to get investors is kind of a big deal, especially when you are going to narrow down the patient populations to try to maximize the chances for success in the trial."

US Key Opinion Leader

"These small companies are interesting, but the CEO is more dedicated to the money problem than the trial design…We need to perform research of the literature first, then feasibility trials, then maybe efficacy trial, or an efficacy trial not covered on mortality, but on other surrogates of co-mortality and co-morbidity. Find a group of dedicated people caring for the patients, who want to collaborate with you, and both will win. So, the physicians will win for the patients and the CEO will win for the company, if they develop a good process, how to bring their drug on to the market. It's not only for drugs, pharmaceutical companies, it's much more true for medical devices."

EU Key Opinion Leader

"I think if you don't invest enough money in the drug and the trials, you will not be able to bring it to market, and so more and more single stage [Phase] III trials are unlikely to bring a drug to market. If you don't have the money to do a large Phase III trial, then you're going to fail. As everybody else has done."

US Key Opinion Leader

7.5.2 Gap Analysis

During the forecast period, GlobalData anticipates the need for an improved regulatory environment to persist. Small-cap biotech firms will continue to struggle in late-stage clinical development, both in terms of fund raising and in demonstrating mortality benefits in heterogeneous patient populations with decreasing mortality and increasing long-term morbidity outcomes. Experts foresee an increase in the use of composite and organ-specific endpoints for early stages of clinical development, while later Phase III RCTs will shift from short-term mortality (28 day all-cause mortality) towards longer time mortality endpoints (90 day all-cause mortality). GlobalData expects that biomarkers and improved patient stratification by organ dysfunction will have the highest impact on positive clinical development during the forecast period, where more homogeneous patient populations will ensure

lower recruitment targets in RCTs to achieve statistically significant outcomes. Thereby small-cap developers will be able to conduct smaller pivotal RCTs in specific sepsis and septic shock patient populations. GlobalData believes that this will further reduce the cost of developing sepsis products in the near term, while in the long term drug development will hinge on improved incentives from regulatory agencies and/or the entry of Big Pharma to fill the financial void of late-stage clinical development in the sepsis and septic shock marketplace.

"Improvement in organ function is a better endpoint than mortality, which is influenced by so many factors including comorbidity. Elderly patients suffering from comorbidities have a higher mortality risk than young patients, but we recruit them both in RCTs. In these trials looking at differences in mortality, for about 75% of these patients [based on age], you already know whether they will survive or not. With your new form of therapy, you may influence a maximum [of] one quarter of this population. It's becoming really very difficult to show that any strategy could really make a patient survive when he or she would have otherwise died. Whereas, if your drug has a real beneficial effect, it can be measured by an improved organ function. We can see now a trend in the field towards a focus on organ function."

EU Key Opinion Leader

7.5.3 Opportunity

GlobalData anticipates major opportunities for regulatory agencies to invigorate drug development in the sepsis and septic shock marketplace. KOLs interviewed by GlobalData believe that companies should look to take advantage of expedited review pathways offered by regulatory agencies, and should seek to work more closely with regulatory agencies when designing late-stage trials. Furthermore, regulatory bodies can increase financial incentives for developing companies, such as extended patent lives for products, to spur companies to re-join the pipeline. Experts foresee a shift towards the adoption of improvement in organ function as primary efficacy endpoints for pivotal late stage clinical trials. However, in the absence of positive stimuli from regulatory agencies and governments, and a lack of innovation to establish other non-mortality endpoints for pivotal clinical trial, GlobalData expects slow progress in bringing innovative drugs to the sepsis and septic shock marketplace. Big Pharma will continue to leverage positive clinical results from small-cap biotech developers in potential merger and acquisition deals to stimulate drug development. AM-Pharma, the small-cap developer of recAP has agreed to a potential acquisition deal with Pfizer upon completion of their adaptive Phase IIa/IIb RCTs for sepsis-induced AKI (AM-Pharma, press release, May 11 2015).

GlobalData anticipates major opportunities for regulatory agencies to invigorate drug development in the sepsis and septic shock marketplace.

7.6 More reliable animal models to facilitate effective screening of lead candidates

7.6.1 Unmet Need

Experts interviewed by GlobalData noted that future drug development efforts in the sepsis and septic shock market will hinge on reliable and meaningful animal models in order to prioritize potential therapies to be advanced into humans studies. However, the validity of animal models for sepsis and septic shock in the pre-clinical evaluation of potential drug targets has been the subject of debate among researchers as an increasing number of sepsis pipeline drugs show therapeutic benefits in animals, which then did not translate into the human physiology of the disease. A particularly concerning study, which compared the gene expression profiles of peripheral blood leukocytes in mice and humans after severe injury (sepsis), trauma, and burns, identified considerable dissimilarities among mice and human gene profiles (Seok et al., 2013; Takao and Miyakawa, 2015). While these studies show potential limitations of animal models in sepsis and septic shock research, experts stress that similarities remain and that multiple different animal models, in the form of surgical, non-surgical, rodent, and non-human primate models are needed to adequately reflect human sepsis pathophysiology (Lakshmikanth et al., 2016).

"Our animal models for testing new agents are still really inadequate for predicting the response in humans.Our methodology for clinical development in sepsis is still not adequate for testing the therapeutic agents."

US Key Opinion Leader

"Drugs work in [animal] models, but the problem is, again, for all these adjunctive treatments now, we need biomarkers to inform us about the inflammatory and anti-inflammatory course of the individual patients, at which point we should intervene, and whether this patient might be a responder for this specific drug. Without this, I'm 100% convinced we will not show any benefit. These compounds are interesting, and this is also not fair for the industry and for us, from our perspective, we have to develop, with the industry, new ideas, how to define responders, how to create new study designs. These companies spend so much money into trials without any success. This is one of the reasons why they give up on us."

EU Key Opinion Leader

Table 23 highlights the current drawbacks of animal models used in sepsis and septic shock research.

Table 23: Key Facts About Currently Used Animal Models in Sepsis

Animal Model	Drawbacks	Suggestions for Improvements	Impact on Clinical Development
Endotoxemia model	Differences in nature of initiating agent: LPS-induced endotoxemia showed no correlation between genes expressed inhumans and murine animals	Prolonged infusion of LPS or intraperitoneal administration of LPS induces symptoms like human endotoxemia in mice.	Endotoxin removal has been investigated in multiple RCTs after being proven beneficial in animal models (Tifacogin and TAK-242). Model is representative of immediate early cytokine storm, best suited for anti-inflammatory drug evaluation.
Bacterial infusion model	Non-uniform response (timing of disease development, no infection site source) by bacterial challenge dependent on mode of infection	This model is good to study infection by single pathogen. Infection by mixed bacterial communities would resemble more likely scenario encountered in patients.	Believed to be representative of septic shock and early pro-inflammation (cytokine storm) (used in anti- TNF-α and IL-1 receptor agonists). High doses of bacteria lead to DIC (used in activated protein C and antithrombin development). Well suited to study host response to pathogen.
Cecal ligation and puncture (CLP) Model	The model has been predominantly applied to young mice, whereas in humans the old and newborn populations are at increased risk of sepsis mortality.	Apply resuscitation to mice and allow for inclusion of aged mice with potential co-morbidities.	Believed to be closed model to human sepsis (golden standard). Used for complement 5a, anti-TNF antibody, and IL-12 research, showing good correlation to human response. Well suited for intra-abdominal infections. CLP results in AKI organ dysfunctions.
Colon ascendens stent peritonitis (CASP) model	Variation by different colon size of animal and invading fecal content (pathogens). The model does not differentiate between a pro- and anti-inflammatory immune response.	Use of CASP in combination with CLP to rule out different effects of inflammatory mediators (TNF, IFN-γ). Use of higher numbers to reduce noise through heterogeneous response.	CASP model resembles shock and organ dysfunction (ARDS, AKI). Used in anti-TLR-4 antibody research and to study the compliment C3 pathway Well suited for diffuse peritonitis.
Polymicrobial peritoneal contamination and infection (PCI) model	Severity is controlled by amount of injected human fecal matter, causing variable results.	PCI involves low cost and combines advantages of both CLP and CASP models.	PCI allows the study of polymicrobial infections and is well suited as replacement for CLP and CASP models.
Implantation model	Although implantation of fibrin clots showed higher reproducibility, the model shows differences in hyperdynamic response and leukopenia.	Model gains from increased survival rates and is a good compliment to CLP and CASP models to assess early systemic inflammation.	Implantation of *E.coli* fibrin clotsinto canine peritoneum showed resemblance to human septic shock with immediate hyperdynamic response. Well suited to study systemic inflammation.
Pneumonia model	Not all animals will develop sepsis, introducing variability. Lack of supportive care.	Increased survival by inhibiting anti-inflammatory cytokines with increased mortality by inhibiting pro-	Intranasal or tracheal route infection with *Streptococcus pneumoniae, Klebsiella pneumoniae,* or *Pseudomonas*

	inflammatory cytokines.	*aeruginosa* for lung infection. Well suited to study lung infection. Delayed mortality suited to study later sepsis onset and development of MODS.

Source: GlobalData; Hawiger et al., 2015; Kingsley and Bhat, 2016; Lakshmikanth et al., 2016; based on primary research interviews with sepsis specialists.
MODS = multiple organ dysfunction syndrome

7.6.2 Gap Analysis

GlobalData identified multiple efforts for improving current sepsis and septic shock animal models. Table 23 highlights the most commonly used animal models in preclinical research for sepsis and septic shock, and provides experts' suggestions to make them more physiologically relevant for the human form of the disease. Experts interviewed by GlobalData highlighted that previous sepsis animal models have been overly focused on the pro-inflammatory immune response and that newer models, and in particular biomarker-guided interventions in animal models, will hold great promise to translate early-stage development efforts into tangible success in late-stage human trials. A particular milestone in developing more relevant animal models are so-called "humanized mice"—mice with transplanted human stem cells that express a fully operational human innate and adaptive immune system—in cecal ligation and puncture (CLP) models, which showed very close resemblance to human sepsis in terms of lymphocyte apoptosis and elevated cytokine levels (Unsinger et al., 2009). However, GlobalData anticipates that the high cost of humanized mice and failure to mimic human epithelial cells and human plasma will limit their widespread use over cheaper non-surgical models such as endotoxemia and bacterial infusion models.

Further promising improvements to existing animal models will come through inclusion of old mice, mice with existing co-morbidities, and the administration of supportive care including antibiotics to closer mimic sepsis in humans. Drug developers of sepsis-specific drugs have the potential opportunity to find similar benefits of these drugs in trauma, burn injury, and acute endotoxemia patients, as changes in gene expression in humans have shown a high degree of similarity (Fink and Warren, 2014).

"Let's face it, we're not going to take patients in the ICU and just give them drug X without giving them antibiotics. It's almost silly to do an animal model that way, and pretend that it's going to tell us anything about what happens in actual patients."

US Key Opinion Leader

"So, adjusting the animal model is very important. I think that we're already talking about different animal models, different mouse models, looking at keeping mice alive longer, and treating them after they develop sepsis not before they develop sepsis."

US Key Opinion Leader

"I think we should be studying old animals, with core morbidity, it's just like our patients. I think the humanized mouse is a good model. It's not perfect, you know, because the epithelial cells are still mice, whereas with the lymphocyte populations that are human, they try various ways to get some interaction between human-human cells and lymphocytes. So, I think it's a good idea. I think some chimeric mouse experiments, I think are very helpful. So, yes, there are ways of making them better, and we should spend some time doing that."

US Key Opinion Leader

7.6.3 Opportunity

GlobalData anticipates further opportunities for improvements of existing animal models for sepsis and septic shock to remain for the duration of the forecast period, and beyond. Experts anticipate animal models of sepsis to remain important for guiding preclinical research. Some experts argued that future preclinical research should focus on animal models other than mice, and cited mammals such as sheep, pigs, or chimpanzees as possible alternatives. While the nature of the best suited animal model remains to be seen, experts agree that future preclinical animal models will have to include supportive care in terms of fluid resuscitation, antibiotics, and hemodynamic stabilization measures.

"I think you learn a lot by studying animal models. I think it's of value. I'm not one of these people that say 'forget it'; however, you have to say that the track record of how predictive a response in a mouse is going to say how it's going to do in an ICU for a human is one gigantic leap. We've not done a very good job with translational research, and the animal models are definitely part of the problem."

US Key Opinion Leader

7.7 Improved Awareness among Healthcare Workers and the Public

7.7.1 Unmet Need

GlobalData identified a high environmental unmet need for improving sepsis and septic shock awareness across the 7MM. KOLs have indicated to GlobalData that improving both the public's and healthcare-worker's awareness and education on sepsis will increase early recognition and accurate diagnosis, which are crucial to the success of currently available treatment options. Experts reiterated

that delayed diagnosis and late administration of anti-infectious and other supportive measures increase the risk of developing severe complications, increasing the patient's mortality risk, while also placing a high financial burden on the 7MM's healthcare systems and resources. Furthermore, KOLs explained that early diagnosis and treatment of sepsis requires a highly coordinated effort among primary care physicians, nurses, emergency care physicians, and ICU physicians, who need to communicate efficiently and be educated and aware of sepsis, its signs, and how to treat it.

"People could do a better job applying our current repertoire. Right now if you look at compliance with their own standards, it's about 50% to 60%. People can give antibiotics faster, they can give fluids more quickly. They can measure lactates more appropriately. So, we're still not there, even with what little we know, we're not doing it frequently enough."

US Key Opinion Leader

"One of the most important signs of sepsis are very sensitive changes in hemodynamics, intracerebral blood vessels…a lot of scoring systems to make early recognition of sick people in the emergency room include confusion…CURB-65, which is a standard mnemonic for recognizing severe pneumonia, looks at 'confusion,' then the 'respiratory rate,' poor urine output, and rapid breathing. Confusion is very interesting, and the problem we run into in the hospital too, one of the problems with recognizing septic patients that are admitted for some other problem is that their manifest is often difficult to assess. They're often given sedative hypnotic agents to help them sleep, or pain meds to deal with the pain. So, the confusion becomes more difficult, but in the emergency room it's very reliable.We've got to recognize that people don't [always] have elevated body temperatures, some of them are very, very ill and we should be paying attention to them."

US Key Opinion Leader

7.7.2 Gap Analysis

During the forecast period, GlobalData anticipates an increase in the awareness of sepsis and its early diagnosis. Measures such as the anticipated updated 2017 sepsis bundles from the SSC, the SEP-1 core measures in the US, and various national awareness campaigns in the 5EU and Japan will help to educate the general public as well as ED and ICU practitioners about sepsis and septic shock, thereby further reducing sepsis and septic shock mortality.

During the forecast period, GlobalData anticipates an increase in the awareness of sepsis and its early diagnosis.

"What's really needed is a clinical index of suspicion. We need to have awareness raised, we need to have education, and we need to have the public aware of some of the signs and symptoms of sepsis… What we need is good old-fashioned education, campaigning, and lobbying."

EU Key Opinion Leader

"I think [the SSC has] changed the way that the healthcare community views sepsis. I think they've provided a platform for sepsis and a platform for people like me who are trying to initiate sepsis improvement. Their job in that has been transformational. I think the guidelines are sound. However, they were not communicated outside the critical care community, and that's a common problem with healthcare professionals."

EU Key Opinion Leader

7.7.3 Opportunity

GlobalData anticipates the need for improved sepsis and septic shock awareness to remain after the forecast period. While continued awareness campaigns are an effective tool to momentarily raise awareness for sepsis and septic shock, GlobalData estimates that the development of new biomarkers will have the biggest impact on long-term future sepsis and septic shock diagnosis and disease outcomes. Furthermore, monetary penalty measures such as the SEP-1 core measures in the US will continue to play pivotal roles in the adherence to sepsis and septic shock care bundles.

8 Research and Development Strategies

8.1 Overview

Past research and development efforts to find new drugs to interfere with the early pro-inflammatory immune response in sepsis have all but failed, after the approved drug Xigris was voluntarily withdrawn by Eli Lilly in October 2011 (Eli Lilly, press release, October 25 2011). The challenges that led to Eli Lilly's Xigris demise continue to haunt drug developers to date. Among the most important challenges, GlobalData identified the difficulty of demonstrating statistical significant efficacy in short-time mortality, such as the commonly used 28 day all-cause mortality endpoint, in a disease where supportive care and early source control in the form of antibiotics have increased survival by almost 50% in recent years, while long-term morbidity and mortality remain largely unchanged (Ranieri et al., 2012).

"I would say that the most important thing is not over-claiming your results. What Eli Lilly did that sunk them is they tried to overgeneralize the drug, and they over-marketed it. I think rather than flood the market with advertising, I think a more carefully thought out approach is better."

US Key Opinion Leader

Current developers have recognized that this initial hyper-inflammatory host response is very short-lived and therefore difficult to target with drug-based interventions. Newer strategies are aimed at interfering with the longer-lived and later-occurring immunosuppressed state of sepsis, or are targeted at patients with specific organ dysfunctions accompanying the sepsis, such as DIC, AKI, or ARDS. The majority of pipeline drugs are being investigated by small-cap biotech companies, where developers are increasingly moving towards the adoption of adaptive clinical trial designs, allowing them to reduce the lead time to bring medications earlier to the market, while also allowing for changes in the clinical trial protocol to stratify patients to more targeted interventions. GlobalData believes that the move towards adaptive clinical trial designs not only increases the chances for future market approval, but also results in considerable cost savings in clinical development, an area that is of particular interest for small-cap biotechnology firms (Perner et al., 2017).

As of April 2017, GlobalData identified three pipeline drugs—AM-Pharma's recAP, Ferring's anti-coagulant selepressin, and BMS' anti-PD-L1 mAb BMS-936559—which are being investigated in adaptive clinical trials (AM-Pharma, NCT02182440; BMS, NCT02576457; Ferring, NCT02508649). KOLs interviewed by GlobalData acknowledged companies' efforts aimed at improving the clinical trial design and stratification of patients to more targeted interventions; however, the majority of KOLs remain convinced that developers have room for further improvement. In order to reduce the

heterogeneity in the recruited patient populations, KOLs interviewed by GlobalData cited the need for the increased use of biomarkers by sepsis and septic shock drug developers.

While the majority of clinical-stage drug development in sepsis is being carried out by small-cap biotechnology firms, GlobalData anticipates that Big Pharma is targeting these firms for potential acquisitions in order to gain a foothold in the sepsis and septic shock market while minimizing upfront risk. For example, in May 2016, Pfizer secured the rights to acquire all assets of AM-Pharma upon successful completion of AM-Pharma's current Phase IIb clinical development program of recAP (AM-Pharma, press release, May 11 2016; AM-Pharma, NCT02182440).

"In the next five years, I can see sepsis product development trying to improve early recognition of sepsis and its underlying causative pathogen. I can also see treatments that are specific to the evolution of the inflammatory process. Specifically, products that can determine the pro- or the anti-inflammatory status of the patient so interventions can be directed to turn the inflammation up or down, whichever is needed."

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Table 23 highlights strategies pursued by developers to gain market approval for their pipeline drugs.

Table 23: Key Strategies Pursued by Current Sepsis and Septic Shock Drug Developers

Strategy	Companies and Pipeline Drugs	Phase of clinical development	Primary endpoint	Key Patient Selection Criteria	Study Design
Implement SEPSIS-3 consensus definition	Most companies have utilized the more stringent SEPSIS-3 definition by recruiting sepsis patients with organ dysfunction (formerly known as severe sepsis).				
Immunostimulatory drugs	BMS' BMS936559 (BMS, NCT02576457) RevImmune's CYT107 (RevImmune, NCT02640807)	Phase Ia/IIb Phase IIa	Safety, 90 day all-cause mortality Immune reconstitution by lymphocyte count	Sepsis-induced immunosuppression Sepsis-induced lymphopenia (less than 900 lymphocytes/mm^3)	Adaptive Phase Ib/IIa Traditional design
Seeking approval for end organ-specific or pathogen-specific treatment options	Ferring's selepressin (Ferring, NCT02508649) Asahi's thrombomodulin (Asahi, NCT01598831) AM-Pharma's recAP (AM-Pharma, NCT02182440) Shionogi's cefiderocol (Shionogi, NCT02714595) Faron Pharmaceutical's Traumakine (Faron Pharmaceuticals, NCT03119701)	Phase IIb/III Phase III Phase IIa/IIb Phase III Phase II	Composite endpoint of vasopressor- and ventilator-free days (Up to Day 30 with 90 day mortality as secondary endpoint) 28 day all-cause mortality Renal function at Day 7 (SOFA, SAPS2 scores) Test of cure (bacterial infection) 30 day all-cause mortality	Septic shock (SEPSIS-2) Sepsis with cardiovascular dysfunction (INR of higher than 1.40) Sepsis-induced AKI Gram-negative sepsis Open heart surgery	Adaptive Phase IIb/III design Traditional design Adaptive Phase IIa/IIb design Traditional design Traditional design
Anti-inflammatory drugs	InflaRx's IFX-1 (InflaRx, NCT02246595) Spectral's Toraymyxin (Spectral, NCT01046669)	Phase IIa (discontinued due to financial reasons) Phase III	PK/PD and Safety, with 28 day all-cause mortality as secondary endpoint 28 day all-cause mortality	Sepsis (SEPSIS-3) with early intervention (<3.5 hours) Sepsis (SEPSIS-3) with endotoxin activity assay of 0.60 EAA units	Traditional design Biomarker guided traditional design

Source: GlobalData, Pharma Intelligence Center [Accessed Month Day, 2017]; Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

In terms of common organ dysfunctions, drug developers have been focusing their development efforts on the comorbidities listed in Table 24 as strategies to enter the sepsis and septic shock market. Developers are attempting to demonstrate a mortality benefit of their therapy when it is used in parallel with the current treatment options.

Table 24: Common Sepsis Comorbidities Being Targeted by Drug Developers

Comorbidity	Example of Historical or Pipeline Drug or Therapy Targeting Comorbidity
Coagulopathy	Xigris, thrombomodulin, ALT-836
Low blood pressure	Selepressin, arginine vasopressin, arginine vasopressin analogs
Acute kidney injury	recAP, hemodialysis
Autodigestion	LB-1148
Acute lung injury/ARDS	Mechanical ventilation, thrombomodulin
Acute liver failure	N/A
Endotoxemia	Eritoran, Toraymyxin hemoperfusion device

Source: GlobalData, Pharma Intelligence Center [Accessed December 16, 2016]; based on primary research interviews with sepsis specialists.
N/A = not applicable

8.1.1 New SEPSIS-3 Consensus Definition to Guide Future R&D Efforts

As of February 2016, multinational efforts to change the current understanding of sepsis have resulted in updated consensus definitions for sepsis and septic shock (Singer et al., 2016). While these efforts have been aimed at both clinical practice and R&D, the authors of these new consensus definitions anticipated their biggest impact to be on clinical development (Singer et al., 2016). Previous SEPSIS-2 definitions of sepsis and septic shock used SIRS criteria—known to have a high sensitivity and low specificity for sepsis and septic shock diagnosis—resulting in the recruitment of very heterogeneous patient populations into RCTs (Churpek et al., 2015). Indeed, some critics argued that the use of SIRS diagnosis criteria have contributed to an inflated sepsis incidence rate, with reduced mortality rates among sepsis and septic shock patients (Azkárate et al., 2016; Iskander et al., 2013).

some critics argued that the use of SIRS diagnosis criteria have contributed to an inflated sepsis incidence rate, with reduced mortality rates among sepsis and septic shock patients.

On the other hand, the new SEPSIS-3 definitions have great potential to influence patient recruitment in RCTs, as sepsis under the new definition demands an organ dysfunction due to the underlying infection—a patient population with an inherently higher mortality risk—thereby increasing the chances of measuring a survival benefit in terms of a mortality endpoint. Although the majority of ongoing RCTs were initiated before the release of the new consensus definitions, these trials were already aimed at a severe sepsis patient population. GlobalData's extensive primary and secondary research indicated that future clinical trials, in particular for septic shock, will benefit from the new definition, as previous trials have used different diagnosis criteria for septic shock.

"We hope that the new [SEPSIS-3] definition makes clear that sepsis is reserved as a term for patients with a septic infection and organ dysfunction, that we now address a more severely ill population. This is also very important for future trials on sepsis, because in the past [trials over the last 25 years] mortality in the control group was much lower than expected….This is because the definition had not

been standardized. So, we hope in future trials that we address a more severely ill population with a hospital mortality rate of 40%."

EU Key Opinion Leader

"In the future, we have to address more severely ill patients as defined by the new sepsis definition [SEPSIS-3]. When you look for past trials on septic shock [patients] and use the new definitions, you now define a subgroup of septic shock patients who have a mortality of 60% [with SEPSIS-3] and not 35% [with SEPSIS-2]."

EU Key Opinion Leader

8.1.2 Immuno-stimulatory Drugs for Late-Step Intervention

8.1.2.1 Overview

An increased understanding of sepsis pathophysiology has led to the concept of sepsis as an immune imbalance, where both pro- and anti-inflammatory responses are responsible for disease course and outcome (Delano and Ward, 2016). Sepsis typically involves an initial state of an excessive pro-inflammatory response, which is thought to be short-lived and difficult to target (Boomer et al., 2014). This initial state, also known as cytokine storm is followed by a immunosuppressant state, which is thought to be responsible for the late-onset sepsis mortality, particular death due to secondary infections after prolonged time spend in an ICU setting (Boomer et al., 2011; Drewry et al., 2016). Experts expressed particular excitement about BMS's anti-PD-L1 mAb BMS-936559 for reversing the immunosuppressant state of sepsis and septic shock pathophysiology.

Experts interviewed by GlobalData cited the inability to quickly and reliably identify the status of a patient's immune response as major limiting factor of immune-modulatory therapies, where an immunostimulatory drug might be exaggerating an already excessive pro-inflammatory response and thereby increasing the risk and magnitude of organ dysfunction(s), or where an immune-dampening drug reduces the immune response of an immunosuppressed patients who is already at high risk for potential fatal secondary infections.

"We need to be targeting the immunosuppressed phase of sepsis and [reverse] it, enhancing the immune system response in septic patients who have a low lymphocyte count."

US Key Opinion Leader

"Well I think there are good preclinical data that show that [anti-]PD-1 is a potent immunosuppressant, and that people die with the lymphocyte depletion. It's is a marker of mortality, and that secondary infection is a common cause of mortality in patients with sepsis for longer than

five to seven days. So I'm excited about the potential for immune enhancement in improving survival in patients who are in the ICU with sepsis longer than five to seven days."

US Key Opinion Leader

"Let's take patients who have been through their first experience with the inflammatory process [for RCTs], and now are somewhat stabilized. They've got fluids, they've got their ventilator if needed. If there are some individuals whose immune response, particularly their adapt[ive] immune response is really diminished, could you potentially give them an immune-adjuvant? The nice thing about this idea is that it doesn't have to be done immediately. It's not like you have to get in there within the first few minutes of the onset of illness in order to be effective. So, there is time to do an assessment of what their immune functions actually look like, either through genomics or through dynamic testing, where you take the patient's blood ex vivo and then stimulate it with LPS, and then measure various inflammatory markers. If it turns out that they are quite immunosuppressed, they might be a good patient to treat with an immune adjuvant. So, the other beauty about doing this is that it would be tailoring the treatment to what the patient needs."

US Key Opinion Leader

"It's not an insignificant number of [immunosuppressed] patients. In some recent papers, it's suggested that maybe close to 50% of patients who are in the [ICU] with a septic process are in a state of relative immune suppression. You really do need to get, you know, what's called a 'liquid biopsy.' You have to actually get the patient's blood, and then measure what's going on in their cells. That would be a good strategy. Then, at least you could say, 'Well, we tailor the treatment towards the indicators within the patient of who should respond to this treatment.'

US Key Opinion Leader

"I do think immune-adjuvants are a big deal [for sepsis]. Whether they're able to do a PD-1 antibody or interleukin 7, I think, there are a number of things that are coming after that. So, I think it's an interesting approach."

US Key Opinion Leader

8.1.2.2 Potential Biomarkers to Assess Immune Status

Table 25 highlights potential clinically relevant biomarkers that could be used by companies to identify and stratify patients who experience a state of immune paralysis. Among the different biomarkers, experts cited HLA-DR expression as the most advanced indicator for a patient's immune state. Indeed, a small prospective RCT study in 83 septic patients, which compared HLA-DR to TNF-α

as outcome predictors for sepsis mortality, identified HLA-DR as a more accurate predictor of mortality and acquisition of secondary infections (p = 0.04 and 0.054 for HLA-DR and TNF-α, respectively; Drewry et al., 2016). However, cost and missing familiarity with flow cytometry instruments to assess patients' HLA-DR levels have been identified as major barriers for its widespread use in an ICU setting (Demaret et al., 2014).

"There are good markers currently available to determine if the patient is in an immunocompromised state. You could look at things like absolute lymphocytopenia if you wanted something that's easily measured. In Germany and other places, they've used HLA-DR expression on monocytes and that's a good marker of immunosuppression. There are actually licensed kits and machines that can do that. In the past, the trouble has always been in standardizing the assay across clinical sites. Standardization across sites is crucial. If each hospital has its own assay you [are] going to have too much variability."

US Key Opinion Leader

Based on the heterogeneity of the immune response in sepsis patients, a panel of biomarkers or transcriptomic biomarkers is thought to be most suited to an individualized, goal-directed therapeutic approach (Bauer et al., 2016; Leentjens et al., 2013). GlobalData notes that current entry criteria in RCTs for immunostimulatory drugs are mainly based on absolute lymphocyte counts, HLA-DR levels, or surrogate markers for sepsis-induced immunosuppression such as sepsis or septic shock with decreased inotropic requirements (BMS, NCT02576457; Hospices Civils de Lyon, NCT02361528; Radboud University, NCT01649921; Revimmune, NCT02640807).

While all these biomarkers hold great promise for future drug development efforts, GlobalData sees particular value for PD-L1 biomarkers—assessed by flow cytometry—to identify patients likely to benefit from an anti-PD-L1 mAb intervention. Furthermore, elevated plasma levels of soluble IL-7 receptor (sCD127 cytokine) are associated with an increased mortality risk in septic shock patients, and could be a good complementing biomarker for RevImmune's CYT107 upcoming Phase III RCT (Demaret et al., 2014).

"Developing a panel of biomarkers that would guide [sepsis and septic shock] therapy would be a huge advance in the field."

US Key Opinion Leader

Table 25 highlights common biomarkers used in sepsis and septic shock diagnosis.

Table 25: Biomarkers for Assessment of Immune Status

Marker	Mode of action	Recent studies
HLA-DR expression on monocytes	Marker of reduced APC capacity of monocytes	Landelle et al., 2010
PD-1 and PD-L1	Marker of T-cell exhaustion	Guignant et al., 2011
IL-10	Marker of anti-inflammatory cytokine response	Suárez-Santamaría et al., 2010
TNF-alpha/ IL-10 ratio	Marker of anti-inflammatory cytokine balance	Gogos et al., 2000
sCD163	Marker of anti-inflammatory cytokines	Gaini et al., 2008
sFas, FasL, and sFas/FasL ratio	Marker of lymphocyte apoptosis	Huttunen et al., 2012
Attenuated TNF-alpha production by *ex vivo* LPS stimulated monocytes	Marker of reduced capacity of pro-inflammatory cytokine production	Appoloni et al., 2002

Source: GlobalData; adapted from Leentjens et al., 2013
APC: antigen presenting cells
Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

8.1.2.3 Academic-driven Research into Immunostimulatory Therapy Options Sets the Premise for the Industry

GlobalData identified two late-stage Phase III clinical development efforts sponsored by academic institutions, which represent the first proof-of-concept studies of immunostimulating drugs in sepsis and septic shock patients (Hospices Civils de Lyon, NCT02361528; Radboud University, NCT01649921).

The earliest therapeutic intervention of this kind goes back to April 2007 with the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF)—a major immune modulator and hematopoietic growth factor—in sepsis and septic shock patients with immune-paralysis. A small prospective, multicenter, German government-sponsored Phase II RCT in 38 sepsis or septic shock patients with a monocytic HLA-DR of < 8,000/cell for two days showed that GM-CSF at 4ug/kg/day randomized 1:1 with placebo over 28 days was able to achieve its primary endpoint of immune reconstitution in all patients treated with GM-CSF, whereas the placebo arm achieved immune-reconstitution in only three out of 19 participants ($p < 0.001$). However, the study did not show statistical significant differences in hospital or ventilator-free days (Meisel et al., 2009, Charite University [Berlin, Germany], NCT00252915). As of March 2017, sargramostim—a generic recombinant GM-CSF manufactured by Genzyme—is in Phase III clinical development with a targeted patient population of 488 patients with sepsis- or septic shock-induced immunosuppression, as assessed by a HLA-DR of smaller than 8,000 mAbs per cell at Day 3 (Hospices Civils de Lyon, NCT02361528). The primary endpoint of this study is the number of patients presenting with at least

one ICU-acquired infection at Day 28 or ICU discharge. The completion date of this study is estimated as September 2018.

The second most advanced academic effort towards immune-stimulating therapy in septic shock is an intervention with recombinant IFN-γ, which is currently investigated in a RCT in about 20 patients with septic shock patients presenting with leukocytosis or leucopenia (Radboud University, NCT01649921). The primary endpoint of this study is TNF-alpha secretion by *ex vivo* LPS-stimulated leukocytes as a marker for a restored immune response at Days 0, 2, 7, 14, and 28. GlobalData notes that previous trials of this sponsor have not been updated and results have been published later, therefore it is anticipated that results of this study will be published sometime during 2017 (Radboud University, NCT01270490; Radboud University, NCT00441753; Radboud University, NCT00740740; Radboud University, NCT01449695).

"The pendulum has moved away from these [anti-inflammatory strategies] and right now we are more excited by immune-stimulating strategies because it is clearly evidenced that the patients often have immunosuppression rather than an excessive pro-inflammatory response. We are exploring the possibility to use an anti-PD-1 or anti-PD-L1 drug, or IFN-γ *maybe, to try to stimulate the immune response with GCSF, granulocyte colony-stimulating factor. Granulocyte macrophage colony-stimulating factor (GCMF) it should be, not the granulocyte colony-stimulating factor (GCSF).We tried it [GCSF] already, it didn't work. So it's not just increasing the number of white blood cells. That didn't work in our study a number of years ago, but GCMF has maybe. That could be, perhaps, a better option."*

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8.1.2.4 Industry-Driven Research for the Development of Immuno-stimulating Drugs

As of April 2017, there are two commercial developers for immunologic adjuvants in sepsis and septic shock patients. RevImmune, a small-cap biotechnology company, is developing CYT107, a recombinant human IL-7 cytokine for sepsis-induced lymphopenia (RevImmune, NCT02640807). In addition, BMS is currently developing its blockbuster drug Opdivo—a human IgG4 anti-PD-1 mAb, which has shown high remission rates in the treatment of locally advanced or metastatic squamous non-small cell lung cancer after prior chemotherapy in adults—and an anti-PD-L1 mAb BMS-936559 for sepsis-induced immunosuppression (BMS, NCT02960854; BMS, NCT02576457). While RevImmune is following the trajectory of a traditional clinical trial design, BMS is applying a novel adaptive clinical trial design, which not only saves time in combining a Phase Ia and Phase IIb study but also allows for changes in therapeutic doses of their anti-PD-L1 mAb BMS-936559, increasing the chances for a good outcome for their 90-day all-cause mortality endpoint (BMS, NCT02576457).

As of April 2017, there are two commercial developers for immunologic adjuvants in sepsis and septic shock patients.

"There anti-PD1, PD-L1, and there's IL-7, that are in clinical trials now, that we're about to get involved in, that I'm very excited about."

US Key Opinion Leader

"The idea would be to jump-start the patient's own immune system to fight off the infection along with the antibiotics we provide. I think that these strategies haven't had the testing and have been neglected. I think if something's likely to work it's going to fall in this group of drugs."

US Key Opinion Leader

Experts interviewed by GlobalData exuded great optimism about immune-stimulating drugs for sepsis therapy. KOLs were particularly excited about the ability to harness biomarkers such as HL-DR, PD-L1, and sCD128 levels for the successful stratification of patients towards these therapeutic interventions. However, current entry criteria in these RCTs are largely based on either lymphocyte counts or a timing of the disease, where a prolonged exposure results in an immunosuppressed state, an approach criticized by experts. Nevertheless, GlobalData notes that these entry criteria are targeting a larger potential patient population, thereby attracting a higher potential return for the companies and their investors.

"There's a whole bunch of immunostimulatory molecules that are in some pilot studies. There are molecules targeting IFN-γ, *interleukin-7, and interleukin-15 that are in small studies. The one that's probably going to go forward is the anti-PD-1 antibody. I think immunostimulatory molecules are the hot area now. It's been a hypothesis. It's been around for more than 20 years but people focus so much on the anti-inflammatory molecules that they've forgotten about this immunosuppression. I think this is the next group of drugs you're going to see going to trials."*

US Key Opinion Leader

8.1.3 Other Specific Development Strategies

If challenged to create an effective strategy to bring new drugs to the sepsis and septic shock patients, experts interviewed by GlobalData said they would either focus their efforts on the biomarker-guided selection of subsets of the sepsis patient population, or would try to target molecular pathways or comorbidities common to a broad range of sepsis patients. The later strategy is currently being pursued by Asahi, Ferring, AM-Pharma, and Shionogi. Ferring and Asahi are developing anti-coagulation therapies for sepsis and septic shock patients (Asahi, NCT01598831; Ferring, NCT02508649). By leveraging the causative links of inflammation and activation of the coagulation

cascade for sepsis-induced DIC and fibrinolysis, developers hope to prevent further organ damage such as AKI, ALI, or ARDS (Toh and Hoots, 2007).

Indeed, GlobalData's primary and secondary research suggested that anti-coagulants can potentially benefit patients with sepsis-associated DIC (Tagami et al., 2015a). AM-Pharma, which is set to be acquired by Pfizer upon successful completion of its current adaptive Phase IIa/IIb RCT, targets sepsis-induced AKI (AM-Pharma, NCT02182440). The primary endpoint of AM-Pharma's adaptive RCT is renal function as assessed by SOFA and SAPS2 scores; however, GlobalData anticipates that recAP will have to demonstrate a survival benefit in terms of a 28 day or 90 day all-cause mortality endpoint once it progresses into Phase III clinical development. Finally, Shionogi is developing a next-generation cephalosporin antibiotic, cefiderocol, which not only shows a high hydrolytic stability against β-lactamases, but also utilizes the bacterial iron transport mechanism to gain undetected cell entry (Ito et al., 2016; Shionogi, NCT02714595). With the inevitable emergence of bacterial resistance, GlobalData believes that this antibiotic will show utility in treating Gram-negative sepsis and septic shock patients.

Developers tend to target specific organ dysfunction, such as DIC or AKI, or are developing agents aimed at specific pathogens in terms of antibiotic infection control. This strategy is very well suited for small-cap pharmaceutical companies, as these pipeline agents usually focus on a particular organ dysfunction in sepsis, allowing for recruitment of small patient sub-populations, while endpoints are based on organ improvement or ventilator- or vasopressor-free days. However, experts interviewed by GlobalData expect that in addition to organ improvements, these pipeline drugs have to demonstrate a survival benefit in the form of a primary mortality endpoint, such as 28 day or 90 day all-cause mortality, thereby encouraging these developers to conduct larger Phase III clinical trials in order to achieve statistically significant results and to gain market approval. GlobalData believes that the necessity to demonstrate a survival benefit makes these small-cap companies targets for potential takeovers from Big Pharma.

"There's a hierarchy and a gradation of the degree of organ dysfunction…it's usually cardiovascular [dysfunction] first, lung second, then kidneys, neck, stem, liver dysfunction and then gastrointestinal dysfunction… the DIC or the coagulopathy tends to be relatively late…So, yes, of course, the fewer organ dysfunctions that you have, the more likely you're going to survive…That's basically what's done with supportive care, to try to spare those organs, and give the rest of the body a chance to recover, and tissue recovery, and function to recover while you get rid of the infection, then they should be better."

US Key Opinion Leader

"There are some new vasopressors that might be helpful, and I think, you know, doing something that's relatively straightforward, like just going after the blood vessels, forget trying to change the milieu of every organ in the body, but it just targets the blood vessels, I think is actually a good idea. I think that approved vasopressors is a good idea, and maybe something we should think about, just tackling one problem at a time. Just vascular is enough."

US Key Opinion Leader

8.1.4 Anti-inflammatory Drugs for Early Intervention (IFX-1, Toraymyxin)

Past drug discovery efforts have largely been focused on the development of drugs targeting the hyper-inflammatory state of the sepsis host's immune response. Although over 100 clinical trials aimed at targeting sepsis and septic patients with elevated levels of pro-inflammatory cytokines such as TNF- α, IL-1β, or IL-6 failed to show statistical significant survival benefits in the tested patient populations, experts interviewed by GlobalData noted that these trials have been conducted in too heterogeneous patient population and less severe cases of sepsis. The key message from these failed RCTs was that anti-inflammatory drugs target a very short-lived disease state and have to be applied very early in the course of the disease. Furthermore, the intervention in the hyper-inflammatory disease state must leverage quantitative, rapid, and ideally point-of-care diagnostics to maximize the chances of successfully targeting the patients most likely to respond positively to these experimental therapeutic agents (Boomer et al., 2014). However, KOLs interviewed by GlobalData believe that the redundancy of molecular signaling pathways in the pro-inflammation cascade will further dampen this approach; therefore, these experts recommended a combination of multiple anti-inflammatory drugs in order to intervene with the hyper-inflammatory activation cascade. As of June 2017, there is no company developing a combination therapy to intervene in the pro-inflammatory disease pathophysiology in sepsis and septic shock patients.

"All these companies tend to have their own pet rock. They have their own drug. But it's probably some kind of combination therapy that will ultimately provide the biggest benefit. Again, unless you specifically hone in on a small population, it's unlikely that one drug is going to help everyone."

US Key Opinion Leader

"We need to find an agent that works in the early stages of sepsis, and the hyper-inflammatory phase. Find a way to change, to immune-modulate. That's something that we'd all like to see."

US Key Opinion Leader

"During the hyper-inflammatory state, so, the first 24 hours or so, when a person's come to the hospital, if you're going to give these agents [anti-inflammatory drugs], you have to give them very quickly. You have to administer them very early in order to have an effect, and usually it's too late. So, in the animal lab, we're able to give these things because we know exactly when the injury took place, and we could dose correctly also, but when patients are coming in from the community, you don't know how long they've been ill, how long they've been percolating their problem before they show up. So, undoubtedly, by the time it becomes evident to the patient and their family and the people in the emergency room, this patient really is sick, it's perhaps too late to intervene with an early anti-LPS antibody or something. If you're going after something that occurs very early on, it's so early that it may not be even picked up by anybody until such time as they're already fully responding to for example [LPS]."

US Key Opinion Leader

"Well, right now, we have to admit, first, that our anti-inflammatory strategies have not been very successful targeting tumor necrosis factor, TNF, or interleukin-1 or whatever. Even corticosteroids have not been very effective. We must accept that giving an anti-inflammatory agent to large patient populations may not be the best way to go."

EU Key Opinion Leader

As of June 2017, two small-cap biotechnology companies were developing anti-inflammatory drugs to intervene in this part of sepsis pathophysiology. Both companies used different strategies in order to stratify patients likely to benefit from their therapeutic intervention. InflaRx is developing IFX-1, an inhibitor of complement response, that was last in Phase IIa of clinical development before its discontinuation due to the high cost of late-stage development (InflaRx, press release, January 4 2017; InflaRx, NCT02246595). The company enforced a very strict time window of 3.5 hours—the minimum time for the consent procedure prior to enrollment into the trial in Germany—for the administration of IFX-1 in sepsis patients in order to increase the likelihood of encountering patients in a hyper-inflammatory disease state (InflaRx, NCT02246595). Furthermore, InflaRx measured a panel of pro-inflammatory cytokines in blood of patients before administration of the study drug and identified a very narrow window of opportunity for anti-inflammatory drugs. IFX-1 is currently being investigated as pre-emptive treatment option for pro-inflammatory complications after cardiac surgery (InflaRx, NCT02866825).

Spectral is developing Toraymyxin, but predominantly due to its high cost and lack of efficacy data from RTCs, it is not an established treatment option for managing sepsis and septic shock patients in the 5EU and Japan. In the US, Toraymyxin is currently being reviewed by the FDA for market approval

for septic shock patients. Spectral leveraged a companion EAA diagnostic in order to identify patients likely to benefit from endotoxin removal by the hemofiltration device. The trial results indicated no statistically significant impact on 28 day all-cause mortality, but identified patients with high endotoxin levels as most likely to benefit from this therapeutic intervention. While experts interviewed by GlobalData praised the clinical trial design with the companion diagnostic, they are not convinced that endotoxin removal holds promise in the course of the disease.

"The study [EUPHRATES] was very well done. The results will be discussed in Brussels in a couple of weeks. They have not been published yet. The study's totally, totally negative. There is absolutely nothing there, so that's a shame, but it shows that endotoxin alone may not be the answer and just eliminating endotoxin with a hemoperfusion system may not work. It's not a failure of the conduct of the trial. The trial was well done. It's clearly something that doesn't work. We have to admit it, but I was not very positive before it started, because we did a study, you may have seen it, a multi-centric controlled system which was already very negative. I was not too positive about that particular study."

EU Key Opinion Leader

Furthermore, previous attempts to target bacterial endotoxin by targeting its cell receptors (TLR-4), mAbs such as nebacumab (HA-1A), and now Toraymyxin have failed to demonstrate a therapeutic benefit (Heming et al., 2016).

"The most significant challenge [for drug developers] is the redundancy of the inflammatory response.We had so many failed trials in part because the inflammatory response is so redundant that choosing a single target as a therapeutic agent, as a therapeutic intervention, is really unlikely to succeed."

US Key Opinion Leader

"One thing we have learned from all these trials with anti-mediator strategies is that, it's not going to be easy to do.It's a multi-component problem. So, let's say we're going after inflammation, you've got IL-1, you've got IL-8, IL-12, IL-18, IL-33. IL-17, I mean, there are a lot of pro-inflammatory events that are running in parallel, and interacting with each other.So, the idea of going in with a single agent, like, a single monoclonal against one, and ignoring all the rest of them, I think, is not a good idea, and probably should be not put on the shelf.I think, with few exceptions, now, there may be some very specific syndromes that it is really driven, just by IL-1, or just by IL-12. There are a lot of interesting states in macrophage activation syndrome.It is possible there's a subset of patients that, if you could identify them quickly, you could potentially go with a very narrow strategy, but that's not the vast majority of patients, but it's certainly an idea."

One thing we have learned from all these trials with anti-mediator strategies is that, it's not going to be easy to do.It's a multi-component problem.

US Key Opinion Leader

8.2 Clinical Trial Design

8.2.1 Overview

In the absence of approved drugs which interfere with the sepsis pathophysiology, clinical trials in sepsis and septic shock are traditionally designed as superiority RCTs, where an investigative drug is compared to a placebo control arm with both arms receiving standard source control measures such as antibiotics and where applicable supportive interventions in form of fluid resuscitation, vasopressors, and ventilator support. This trial design has been applied in over 100 RCTs for sepsis and septic shock patients, and with the exception of Eli Lilly's Xigris, has not led to the approval of new drugs in this indication. Xigris, which was initially been able to show a benefit on patient survival in form of a 28 Day all-cause mortality,has been voluntarily withdrawn after a subsequent RCT failed to confirm Xigris' mortality benefit in sepsis patients (Eli Lilly, NCT00568737).

All KOLs interviewed by GlobalData agreed that the reason for these past failures lies in the desire to broadly target all sepsis and septic shock patients. The resulting heterogeneous patient populations in these trials potentially masked most therapeutic effects, as in many instances a specific patient population may have responded to the treatment, while the majority of patients did not respond.

"Heterogeneity [of the sepsis patient population] is a key issue. We are definitely mixing apples and oranges on many of the clinical trials we are trying to conduct."

EU Key Opinion Leader

More recently, developers have been focused on adaptive clinical trial designs. GlobalData identified three late-stage RCTs in sepsis and septic shock that use an adaptive clinical trial design. Adaptive clinical trial design allow the developer to adjust pivotal clinical trial protocol parameters, such as dose of the intervening drug, as well as biomarker-guided stratification of specific patient populations, and furthermore benefits from time and resource savings by having continuous clinical trial phases (Zhang and Lee, 2014).

"I think that adaptive response trials are changing the methodology, we need to base clinical trials on bioavailability. You know, a lot of our clinical trials, they didn't even measure thebio availability of the agents that we were testing."

US Key Opinion Leader

BMS is currently assessing the safety, efficacy, and PK/PD of a novel anti-PD-L1 inhibitor in an adaptive Phase Ia/IIb study (BMS, NCT02576457). Ferring's novel anti-coagulant, selepressin, is

currently being evaluated in a Phase IIb/III RCT with adaptive clinical trial design (Ferring, NCT02508649). Lastly, AM-Pharma is developing a recombinant alkaline phosphatase, which is currently in a Phase IIa/IIb adaptive clinical trial (AM-Pharma, NCT02182440).

8.2.2 Traditional Clinical Trial Design

Traditional clinical studies are designed to evaluate a single hypothesis in a predetermined plausible patient population size, where randomization guarantees an unbiased outcome of the treatment and placebo arms. Unlike many other diseases, where clinical evaluation of therapy candidates is aided by well-studied biomarkers and quantitative diagnostic criteria for patient selection in RCTs, sepsis and septic shock present with non-specific diagnostic criteria and reliable biomarkers are not available.

"There are a lot of [agents] out there that probably should have been positive. [Their trials] were just designed incorrectly. The way you design the trial all depends on how you think the drug works... you want to pick up the patients who are at risk and you don't want to [enroll participants across] a bunch of countries where the background care is suspect."

US Key Opinion Leader

"Companies are failing with trials because they're trying to generalize their treatments to a [sepsis] patient population that is too large…. [Developers] used to go for the billion dollar indication, the 750,000 US patients with severe sepsis. I think that's dreaming, and no therapy is going to get approved for every single severe sepsis patient. I think [firms] have to set their sights on the 25% [of sepsis or septic shock patients] that their particular agent may be able to benefit. They want the whole pie, but that's not who their drug is going to work in."

US Key Opinion Leader

In an effort to reduce the heterogeneity of this patient population, developers utilize quantitative inclusion criteria in order to exclude patients with mild symptoms, likely to improve upon application of infection control and supportive measures alone. Asahi's thrombomodulin Phase III clinical trial is specifically recruiting patients with sepsis-induced cardiovascular dysfunction by demanding an INR of greater than 1.40 for their pivotal RCT (Asahi, NCT01598831). Spectral's Toraymyxin used an EAA companion diagnostic for recruitment in their Phase III RCT (Spectral, NCT01046669). Furthermore, Shionogi's cefiderocol, a next-generation cephalosporin antibiotic, is focusing on sepsis patients with Gram-negative bacterial infections (Shionogi, NCT02714595). InflaRx's now-halted IFX-1 used an early time point for the therapeutic intervention as criteria for the trial enrollment. While the emphasis on specific patient sub-populations is welcomed by experts, they suggested a much narrower focus

where patients are stratified by pathogen, infection site, organ dysfunction, and existing co-morbidities.

"First, we have to address more severely ill patients, because many compounds are promising, but used in a less severe population where it will not work. Second, we have to address the heterogeneity of patients with different pathogens, and then we have to address the problem of different sites of infection… for instance, focus on pneumonia patients, or abdominal infections."

EU Key Opinion Leader

The endpoints in sepsis and septic shock RCTs can vary between various composite measures of an improved organ function, immune reconstitution by lymphocyte counts, or days off the ventilator, but most pivotal Phase III RCTs have an all-cause mortality endpoint. While experts interviewed by GlobalData agreed that drugs need to show some kind of mortality benefit in order to gain market approval by regulatory agencies, they indicated that the 28 day all-cause mortality is no longer clinical relevant and longer mortality endpoints, such as 90 day all-cause mortality, should be pursued.

"I think surrogate outcomes are reduction of organic dysfunction, a prevention of regression of organ dysfunction. I think ultimately, in order for a therapeutic agent to be licensed, it's going to have to be mortality-based outcomes though."

US Key Opinion Leader

8.2.3 Adaptive Clinical Trial Design

Adaptive clinical trials offer several potential advantages compared with traditional RCTs; among the most relevant of these advantages for sepsis is the ability to improve the study's statistical power by enriching a subpopulation of patients in specific treatment arms either by drug dose or according to biomarkers (Ahuja and Birge, 2016). Adaptive clinical trials are most commonly executed within a Bayesian framework model, which uses Bayes' theorem of statistical distribution to determine likely outcomes such as superiority, noninferiority, or futility of certain treatment regimens, thereby allowing the developer to focus its efforts on specific treatment arms or patient sub-populations, reflecting real-world medical practice. Consequently, the development cost and time can be reduced, making this approach particularly enticing for small pharmaceutical companies.

Developers in sepsis are increasingly employing adaptive clinical trial designs to allow for changes in clinical trial protocols, such as the enrichment of a sub-patient population shown to benefit particularly from therapy, and reducing the discovery process by combining multiple clinical development phases in one trial (Perner et al., 2017). By applying adaptive clinical trial designs to a

heterogeneous disease such as sepsis, developers have the opportunity to assess their drugs against all sepsis or septic shock patients first, and to narrow their focus to a very specific sub-patient population, either through biomarkers or other pathogen- or organ dysfunction-related indicators, thereby further increasing the chances for a successful market approval.

"[RCTs] in sepsis are dead. We did all these [RCTs], comparing compounds with placebo, or noninferiority trials comparing two different agents. Many, many of these trials have been so-called negative. So, we spent billions of dollars, and we've spent so much time waiting for the right [RCT]. Nothing influenced our guidelines."

EU Key Opinion Leader

GlobalData identified three late-stage pipeline drugs that are in trials with adaptive clinical trial design. BMS' BMS-936559, an anti-PD-L1 mAb, is currently in a Phase Ia/IIb adaptive clinical trial. In this trial, BMS will be able to assess both safety and efficacy of their anti-PD-L1 mAb in a continuous RCT. In the first part of the adaptive RCT, the safety of a single dose of BMS-936559 will be assessed, and then the trail will subsequently evaluate the impact of BMS-936559 on the survival of sepsis-induced immunosuppressed patients using a 90 Day all-cause mortality endpoint (BMS, NCT02576457). The second pipeline drug currently in a Phase IIb/III adaptive clinical trial design is Ferring's selepressin. While the endpoint for the first part of the pivotal RCT is a composite measure of vasopressor-free and ventilator-free days, the following second part of the RCT is assessing selepressin's efficacy using a 90 day all-cause mortality endpoint (Ferring, NCT02508649). The third pipeline drug in a Phase IIa/IIb clinical trial with an adaptive design is AM-Pharma's recAP, which will utilize essential PK/PD information from the first part of the study to inform clinical relevant doses of recAP for the efficacy part of the study. The endpoint of the Phase IIb part of the study is renal function as assessed by SOFA and SAPS2 scores (AM-Pharma, NCT02182440). While the Phase IIb/III adaptive design by Ferring is arguably a smarter move towards earlier approval, GlobalData believes that AM-Pharma is more focused on achieving a positive efficacy profile of recAP at this point in time, in order to proceed with the potential acquisition of their assets by Pfizer (AM-Pharma, press release, May 11 2015).

While KOLs interviewed by GlobalData welcomed the industry's move towards adaptive clinical trial design in sepsis, they believe that the broader sepsis community isn't taking full advantage of the potential benefit of adaptive clinical trial design. Experts cited large efforts such as the REMAP-CAP adaptive trial initiatives in CAP and the I-SPY 2 adaptive trial in oncology as examples of the future direction to improve SOC in sepsis and septic shock patients (Park et al., 2016; UMC Utrecht, NCT02735707; QuantumLeap, NCT01042379).

The REMAP-CAP study stratifies patients with severe CAP to various treatment domains, where an algorithm randomizes patients to the treatment arm with the best outcomes, while closing down unfavorable domains with futile or indifferent outcomes in 60 day all-cause mortality (UMC Utrecht, NCT02735707). GlobalData notes that the results of the REMAP-CAP study can influence the future treatment of sepsis and septic shock patients, as over 35% of patients who participated in Eli Lilly's Phase III RCT of Xigris suffered from sepsis as a result of severe CAP (Eli Lilly, NCT00604214; Laterre et al., 2005; UMC Utrecht, NCT02735707). Experts interviewed by GlobalData indicated that similar adaptive clinical trials in sepsis are likely to be conducted during the forecast period.

over 35% of patients who participated in Eli Lilly's Phase III RCT of Xigris suffered from sepsis as a result of severe CAP.

"We will start to build up an international trials group in patients with a very specific sepsis focus, [severe] community-acquired pneumonia, and include patients in our city in the registry, and then enroll patients to many multifactorial interventions. We look for organ function, looking at five domains. We have an antibiotic treatment domain, with different interventions; we have an anti-inflammatory treatment domain with hydrocortisone; we have a mechanical ventilation bundle domain, where we test different procedures, how to ventilate. And then we put more patients in the winner group during the interim analysis, [closing down the inactive intervention arm]. This has never been performed in the field of infectious diseases, as far as I know, for just inpatients [patients administered to the emergency department], never."

EU Key Opinion Leader

In the I-SPY 2 adaptive clinical trial, multiple novel pipeline drugs for stage II/III breast cancers are assessed in addition to standard chemotherapy, where biomarkers guide the decision making to close-down or increase recruitment to effective treatment regimens (Park et al., 2016; Quantum Leap, NCT01042379).

"Response-adaptive randomized trials, which have been performed in the field of oncology and breast cancer, are the future. Breast cancer, it's a disease which is much simpler to diagnose compared to sepsis, but it's also heterogeneous, there are different subtypes, receptor positive/negative, biomarker positive/negative. So, this is, yes, comparable to sepsis, a very, very, very complicated heterogeneous disease, such as sepsis."

EU Key Opinion Leader

8.2.4 Participant Enrolment Criteria

8.2.4.1 Overview

Sepsis patients frequently present with non-specific diagnostic criteria; consequently, RCTs in sepsis and septic shock have tried to evaluate drugs in a very heterogeneous patient population. Developers are pursuing different strategies to guide their selection of patients into RCTs. The most commonly utilized entry criteria in sepsis drug development are entry criteria based on stratification strategies by mortality risk, by biomarkers, by organ dysfunction(s), or by infection.

8.2.4.2 Patient Stratification by Mortality Risk

GlobalData's primary and secondary research showed that past drug development efforts in sepsis have been hampered by heterogeneous patient populations, with less severely ill patients already responding to source control and supportive measures, making the study drug irrelevant for the overall outcome. Therefore, it is not surprising that current developers aim to study their pipeline agents in more severely ill patients. For example, Ferring's adaptive Phase IIb/III trial of selepressin is recruiting septic shock patients, a sepsis patient group not responsive to vasopressor therapy and with increased lactate levels, both of which are also indicators of an increased mortality risk. BMS is assessing their anti-PD-L1 mAb BMS936559 in a sepsis patient population with sepsis-induced immune suppression, an immunity state that is correlated with an increased risk of secondary infection and viral reactivation, both of which contribute to a higher mortality risk.

KOLs noted that certain inclusion criteria such as mortality risk can result in more predictable outcomes, where baselineage and existing comorbidities as assessed by an increased SOFA score were correlated with a statistical significant mortality risk ($p = 0.041$ and $p = 0.026$, respectively), While this results of this study are not too surprising—an increased SOFA score is known to correlate with an increased mortality risk—the implications for RCTs in sepsis patients stratified by mortality risk hold great promise to improve the chances of achieving a favorable outcome (Demaret et al., 2014).

"I think we've over-generalized and had too much population heterogeneity in our trials.We need to power trials for a lower mortality in the control group and focus on specific sub-population. I think surrogate outcomes such as reduction of organic dysfunction, prevention of regression of organ dysfunction are useful. But I think ultimately, in order for a therapeutic agent to be licensed, it's going to have to be mortality-based outcomes. I don't think in the US the FDA would license a new drug just based on a surrogate outcome."

US Key Opinion Leader

"We historically have on the shelf really quite a large number of therapeutic trials with equivocal results, and to my mind the main issue with that is that we're putting a very heterogeneous cohort of patients into one pot, naively assuming that we can treat them all the same. They're heterogeneous, of course, in the origin of their disease, but more importantly for me in terms of the stage of progression of their disease. We are not working in the public sector to try and get patients to the hospital quickly, we're not working on how we can identify sepsis in its early stages, and only until we've done that, until we've reduced the heterogeneity of the disease, then we're going to continue to see equivocal therapeutic trials."

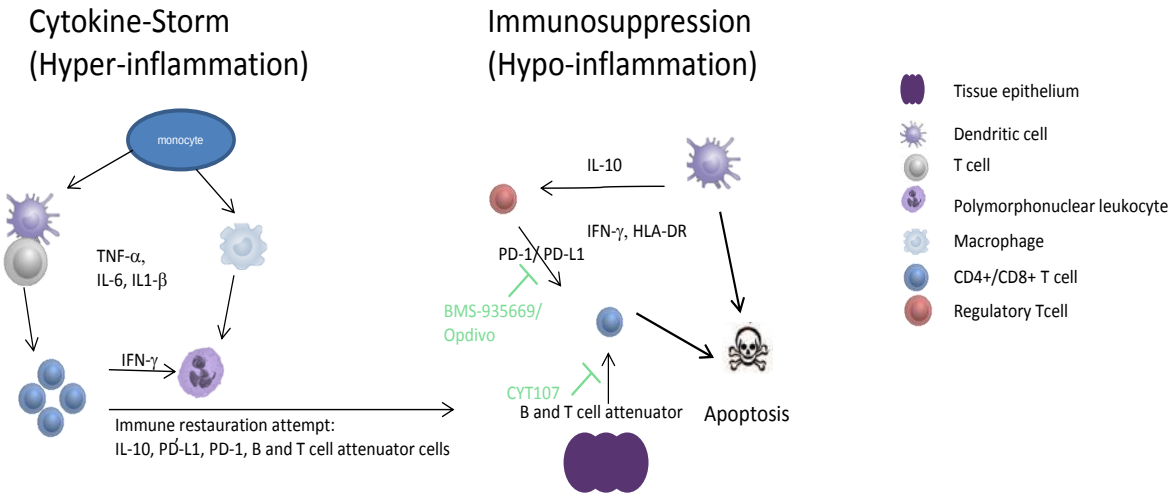
EU Key Opinion Leader

8.2.4.3 Patient Stratification by Biomarker

GlobalData's primary research identified biomarker-guided entry criteria for RCTs in sepsis and septic shock as one of the most innovative approaches to tackle an overly heterogeneous patient population.

Figure 29 outlines treatment options alongside the associated biomarkers for optimal patient stratification in RCTs (Boomer et al., 2014).

Figure 35: Current Treatment Options and Associated Biomarkers for Sepsis and Septic Shock, 2017



Source: GlobalData; Boomer et al., 2014

"There are a lot of biomarkers now available in Europe. Calcitonin is very, very often used, it's a good biomarker and it's the champion so far, but it [biomarker research] must improve because specificity is not good. So, in many patients without any infection, PCT has increased, levels are increased, [in] major surgery patients, for instance."

EU Key Opinion Leader

GlobalData identified two late-stage developers which use biomarkers as entry criteria for their RCTs.The prime example of a biomarker-guided patient stratification strategy is represented by Spectral's use of their companion diagnostic EAA to identify patients with high levels of endotoxin, who are most likely to benefit from therapeutic intervention with their endotoxin hemoperfusion device, Toraymyxin (Spectral, NCT01046669). The second developer is RevImmune, which is developing CYT107, an immunostimulatory recombinant version of the cytokine IL-7; RevImmune is utilizing a low lymphocyte count as an entry criterion for their current Phase IIa RCT to identify patients with sepsis-induced lymphopenia (RevImmune, NCT02640807).GlobalData notes that sCD127, the receptor for IL-7, could be an ideal biomarker to identify patients for IL-7 supplementation therapy, as an increased level of sCD127 has been shown to be associated with an increased mortality risk (Demaret et al., 2014). However, from a strategic perspective, a low lymphocyte count might select for a larger potential patient population than high levels of sCD127, thereby increasing potential future sales of CYT107.

Another biomarker is human leukocyte antigen-DR (HLA-DR), which is employed in the patient stratification of GM-CSF immunostimulation therapy (Meisel et al., 2009). However, a technological barrier—acquisition and operation of a flow-cytometry instrument—limits its widespread use (Demaret et al., 2014).

"Look at the success we had in viral hepatitis, it's a curable disease now, and this is only because we developed PCR technologies which can give us information whether the virus load is low or high, and whether it's [the patient is] a responder. This is only possible by diagnostic tools, and this is what I always underline, we are better off developing biomarkers, in order to define responders to that treatment."

EU Key Opinion Leader

"Whatever your inclusion criteria were, that's the patient population you're going to market to. The problem is, the critical care community had the experience with [Xigris] where Lilly tried to generalize it. If you studied it in a population, and the inclusion criteria were a lymphocyte count less than 100, that's the only population you're going to be able to use it in, and if you try to flood the market and convince people that you can just use it 'widely,' it's doomed to failure."

US Key Opinion Leader

8.2.4.4 Patient Stratification by Organ Dysfunction

Another strategy to homogenize the patient populations enrolled in sepsis and septic shock trials is the stratification of patients by organ dysfunction. GlobalData identified two late-stage developers who are stratifying their patients in their RCTs by specific organ dysfunctions. The first developer is Asahi, who is stratifying their patients based on an international normalized ratio (INR) for blood clotting of greater than 1.40 to select for sepsis-induced DIC patients for the treatment with their investigational anticoagulant, thrombomodulin (Asahi, NCT01598831). Although this strategy will result in the recruitment of patients which are most likely to benefit from this therapeutic intervention, GlobalData notes Asahi's chosen endpoint of 28 day all-cause mortality might not be long enough to demonstrate a statistically significant benefit on the survival.

"[Asahi] is running a clinical trial right now on thrombomodulin that is specifically for patients with DIC and an elevated INR and organ dysfunction. Once that trial is successful, you can't then suddenly say, 'Well, it worked in the patient population with DIC, so we suggest its use in all patients.' If a company that's making thrombomodulin is trying to decide what their market's going to be, they should calculate that based on the population in which it was studied. One of the main challenges for pharmaceutical companies is that they invest a lot of money into drug development; if they're lucky, they then prove that a drug is efficacious in sepsis, and they try to generalize that to a larger patient population. That is always going to get them in trouble. I think that Lilly did that with [Xigris]. They overestimated their patient population."

US Key Opinion Leader

The second developer, AM-Pharma, is developing recAP for the treatment of sepsis-induced AKI. Specifically, AM-Pharma is recruiting patients with stage 1 AKI who present with an increased serum creatinine of greater than 26.2µmol/L, equaling an increase of more than 1.5-fold over the reference value 28 hours prior to screening. In addition, stage 1 AKI patients are required to have a urinary output of less than 0.5mL/kg for over six hours following adequate fluid resuscitation. The primary endpoint of AM-Pharma's adaptive Phase IIa/IIb study is normalization of renal function at Day 7 of the intervention with recAP (AM-Pharma, NCT02182440). GlobalData expects that AM-Pharma—or Pfizer, if the later proceeds with acquisition of AM-Pharma after the successful completion of the current clinical development stage—will have to demonstrate a survival benefit for recAP therapy in the form of a mortality endpoint in order to support a possible market approval by the FDA.

8.2.4.5 Patient Stratification by Pathogen

A last patient stratification strategy, which is currently being pursued by Shionogi, is the focus on sepsis caused by Gram-negative bacterial infections. Shionogi is developing a novel cephalosporin antibiotic, cefiderocol, which not only demonstrates improved hydrolytic activity against b-lactamases, but also utilizes the bacterial iron uptake-transporter to gain entry into the bacterial cell (Ito et al., 2016). Cefiderocol is in Phase III clinical development and is recruiting patients with documented infection, such as hospital-acquired pneumonia (HAP), ventilator associated pneumonia (VAP), healthcare associated pneumonia (HCAP), complicated urinary tract infection (cUTI), or blood stream infection (BSI) caused by Gram-negative pathogens with evidence of carbapenem resistance (Shionogi, NCT02714595). Experts interviewed by GlobalData identified this strategy as a major opportunity for successful clinical development of novel drug candidates, as different pathogens require potentially unique therapeutic interventions. In addition to Shionogi microbiological identification of pathogens, GlobalData identified several other promising approaches based on PCR, Raman spectroscopy, and mass spectrometry techniques to identify the causative pathogens in sepsis, with transcriptomic techniques as the leading choice among experts interviewed by GlobalData, as this technique not only allows the identification of infections leading to sepsis but also distinguishes a normal infection from infections leading to sepsis (Bauer et al., 2016).

Shionogi is developing a novel cephalosporin antibiotic.

"E. coli sepsis infections can't be compared with a patient with a S. aureus sepsis. S. aureus needs a prolonged, very complicated treatment, you have to go into soft tissue, into bones, with your antibiotic, which is really, really difficult sometimes and this is not true [with] a sepsis E. coli infection."

5EU Key Opinion Leader

"First, we have to address more severely ill patients, because many compounds are promising, but used in a less severe population where it will not work. Second, we have to address the heterogeneity of patients with different pathogens, and then we have to address the problem of different sites of infection… for instance, focus on pneumonia patients, or abdominal infections."

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8.2.5 Endpoints

Firms developing late-stage products in sepsis and septic shock use a variety of endpoints to demonstrate clinical efficacy. For example, Ferring is using both a composite endpoint of vasopressor- and ventilator-free days, as well as a 90 day all-cause mortality endpoint for their adaptive Phase IIb/III study of selepressin in septic shock patients (Ferring, NCT02508649). Similarly, AM-Pharma, which is developing recAP in sepsis patients with sepsis-induced AKI, is using renal function as

assessed by SOFA criteria and SAPS2 (simplified acute physiology score) as their primary endpoints in their adaptive Phase IIa/IIb study (AM-Pharma, NCT02182440). Companies in late-stage clinical development such as Spectral, Asahi, BMS, and Ferring are using traditional mortality endpoints of either 28 day or 90 day all-cause mortality (Asahi, NCT01598831; BMS, NCT02576457; Ferring, NCT02508649; Spectral, NCT01046669).

Indeed, KOLs interviewed by GlobalData had the unifying belief that while drug developers can and should be leveraging composite or organ-specific endpoints in early clinical development, novel pipeline drugs in the pivotal phase of development will have to demonstrate a survival benefit, preferably using long-term mortality endpoints of 90 days or longer, in order to be granted market approval by the FDA, EMA, or Japan's Pharmaceuticals and Medical Devices Agency (PDMA).

"We're trying to get regulatory agencies to move away from [28 day mortality], because it's not the optimal endpoint…there was no particular reason why it was chosen. If you look at the Kaplan Meier plot of survival, there is a more rapid decline in the first several months, and then it sort of begins to level off, but there isn't a break point at 28 days, or for that matter any other day. So, I think [28 day mortality] is too short…I think a better indicator is 90 day mortality, because I think allows enough time for those patients who are not going to recover to manifest."

US Key Opinion Leader

"I mean, it's hard to not want to study mortality in a disease that has high mortality, but you can make an argument for looking at non-mortality endpoints that would be patient-centered, and important in healthcare delivery and healthcare expenses, other than just mortality. A lot of people are now trying to talk the [FDA] into a composite endpoint. Cardiologists, for a long time, have said, 'Well, our end point is going to be death for a myocardial infarction'. A need for another [MI] endpoint was coronary stenting, they were looking at other events that are important to the patient that are non-mortal but still important, and then they did a composite end point, which includes several things, not just mortality. So, maybe people can work on that in sepsis research as well, where they say, 'Well, you know, mortality's important, but so is being on a ventilator is important,' I personally think that's a good trend, to try to move away from just mortality."

US Key Opinion Leader

"The primary endpoint in most Phase II and III studies is 28 day mortality; 28 days is short-term, which is wrong. It is absolutely wrong... I think long-term outcome is the variable we should look at and it should be 90 day mortality."

EU Key Opinion Leader

9 Pipeline Assessment

9.1 Overview

The sepsis pipeline has undergone a paradigm shift over the past several years. Previously, drug development in sepsis and septic shock was focused on the discovery of early interventions in the anti-inflammatory immune response during sepsis pathophysiology. Today, the majority of current pipeline drugs are aimed at the treatment of sepsis-specific organ dysfunctions or the treatment of the immunosuppressed state of sepsis and septic shock. Developers and physicians remain shaken from Eli Lilly's discontinuation of Xigris in 2011—to date, Xigris was the only sepsis-specific treatment option receiving FDA approval since November 2001. Since then, many developers have tried and failed to gain marketing approval in sepsis and septic shock. Among the most prominent late-stage clinical failures were Eisai's Eritoran, Agennix's talactoferrin alfa, and AstraZeneca/ BTG's Cytofab. The collective consensus among KOLs interviewed by GlobalData was cautious optimism. The critical care community is not overly confident that these products will display benefits in their selected trial patient populations, but they would welcome any of their approvals if they display convincing results.

Despite these recent setbacks, smaller companies have stayed on course and invested a considerable amount of money to develop potentially effective products. These firms are fueled by the idea of being the only sepsis-specific therapy on the market and seek to fit their products into the generalized treatment algorithm for specific patient populations. Currently, there are eight products in late-stage development (Phase IIb and Phase III) to treat sepsis and septic shock, with three pipeline drugs indicated for sepsis, three agents for septic shock, and one indicated for both sepsis and septic shock. The most promising pipeline candidates include anti-coagulants, hemofiltration devices, immunomodulatory agents, and vasopressors. The active pipeline marks the beginning of Big Pharma's return to the sepsis and septic shock marketplace. Both Pfizer and BMS are committing substantial resources in the development pipeline. While BMS is entering the development landscape with early Phase I and Phase II clinical development programs, Pfizer has entered into an acquisition agreement with AM-Pharma pending a successful completion of AM-Pharma's Phase IIb clinical development program. Furthermore, with six remaining small-cap pipeline players, GlobalData anticipates more licensing and acquisition agreements as a viable option for Big Pharma to catapult back into the sepsis and septic shock market when a product is further along and there isn't as much risk associated with development.

GlobalData notes that this licensing and acquisition approach is beneficial for both small-cap companies and big Pharma, as small-cap companies are struggling to secure the necessary funding for

pivotal Phase III clinical development programs. InflaRx halted development of their lead pipeline product IFX-1 because it failed to secure the necessary funding for Phase III clinical development in sepsis; the company is now pursuing development of this drug for infection prevention in patients undergoing cardiac surgery (InflaRx, press release, January 4 2017).

InflaRx halted development of their lead pipeline product IFX-1 because it failed to secure the necessary funding for Phase III clinical development in sepsis.

9.2 Promising Drugs in Clinical Development

Table 26 outlines the promising late-stage pipeline agents that GlobalData expects to be licensed for the treatment of sepsis and septic shock across the 7MM during the forecast period.

Table 26: Key Late-Stage Pipeline Agents for Sepsis and Septic Shock, 2017

Product Name	Therapy class	Company	Developmental Stage
ART-123	Anti-coagulant	Asahi Kasei Pharma America	Phase III
Selepressin	Cardiovascular, Vasopressor	Ferring International Center SA	Phase III
Cefiderocol	Antibiotic	Shionogi & Co Ltd.	Phase III
Toraymyxin	Hemofiltration Device	Spectral Medical Inc	Phase III
CYT107	Immuno-stimulatory	Cytheris SA / RevImmune LLC	Phase IIa
recAP	Immuno-suppressive	AM-Pharma	Phase IIa/b
Traumakine	Immuno-suppressive	Faron	Phase III
BMS-936559	Immuno-stimulatory/ anti-PD-L1 antibody	Bristol-Myers Squibb Company	Phase II

Source: GlobalData, Pharma Intelligence Center [Accessed June 23, 2017].

Table 27 provides a comparison of the therapeutic classes in development for sepsis and septic shock during the forecast period.

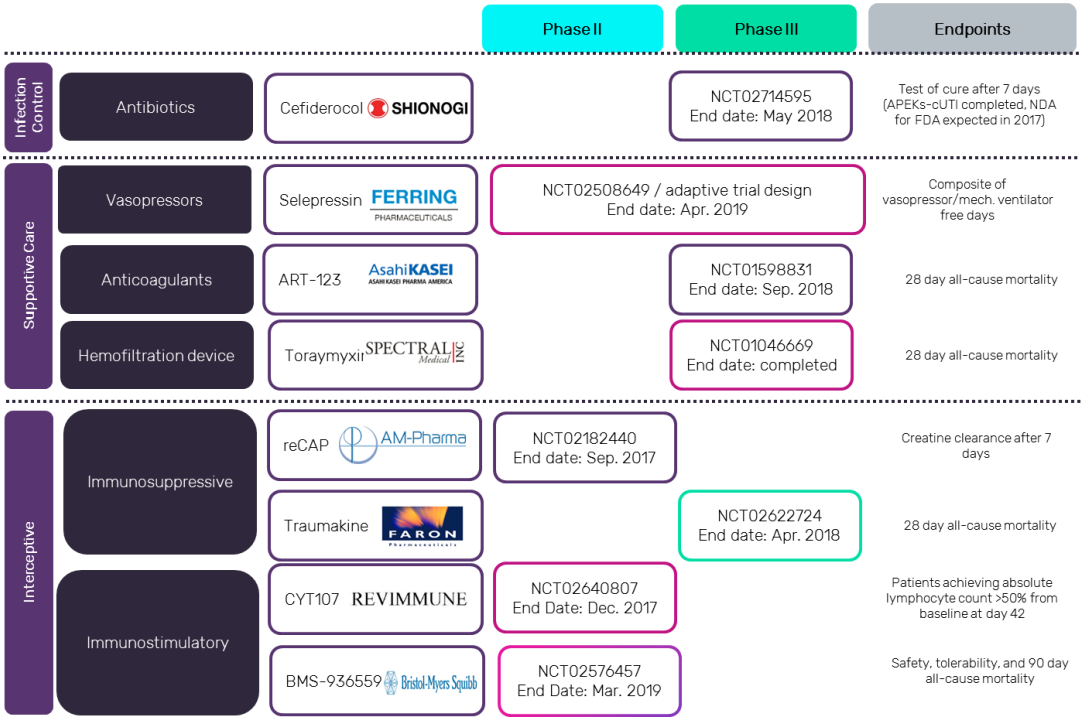
Table 27: Comparison of Therapeutic Classes in Development for Sepsis and Septic Shock, 2016–2026

Therapeutic Class	Advantages	Disadvantages
Antibiotics	Targets the etiological pathogen	Does not change the course of the immune-response in sepsis patients
Immunosuppressive agents (Dampening immune response)	Suppresses an overactive immune response, thereby protecting organ integrity Acts directly on sepsis pathophysiology in the host	Difficult to time treatment in the absence of biomarker; potentially harmful in sepsis patients with immune paralysis; previous RCTs have failed to show efficacy
Immunostimulatory agents (Stimulating immune response)	Activates immune response to prevent secondary infections or viral reactivation Acts directly on sepsis pathophysiology in the host	Difficult to time treatment in the absence of biomarker; potentially harmful in sepsis patients with anti-inflammatory response;, pathogen is not cleared by immune response
Anti-coagulants	Supportive care, improves organ dysfunctions	Does not directly interfere with sepsis pathophysiology
Vasopressors	Supportive care, improves organ dysfunction by increasing blood flow (counteracting hypotension)	Does not directly interfere with sepsis pathophysiology

Source: GlobalData; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

Figure 36 outlines the key Phase II and Phase III trials for the promising late-stage pipeline agents that GlobalData expects to be licensed for the treatment of sepsis and septic shock in the 7MM during the forecast period.

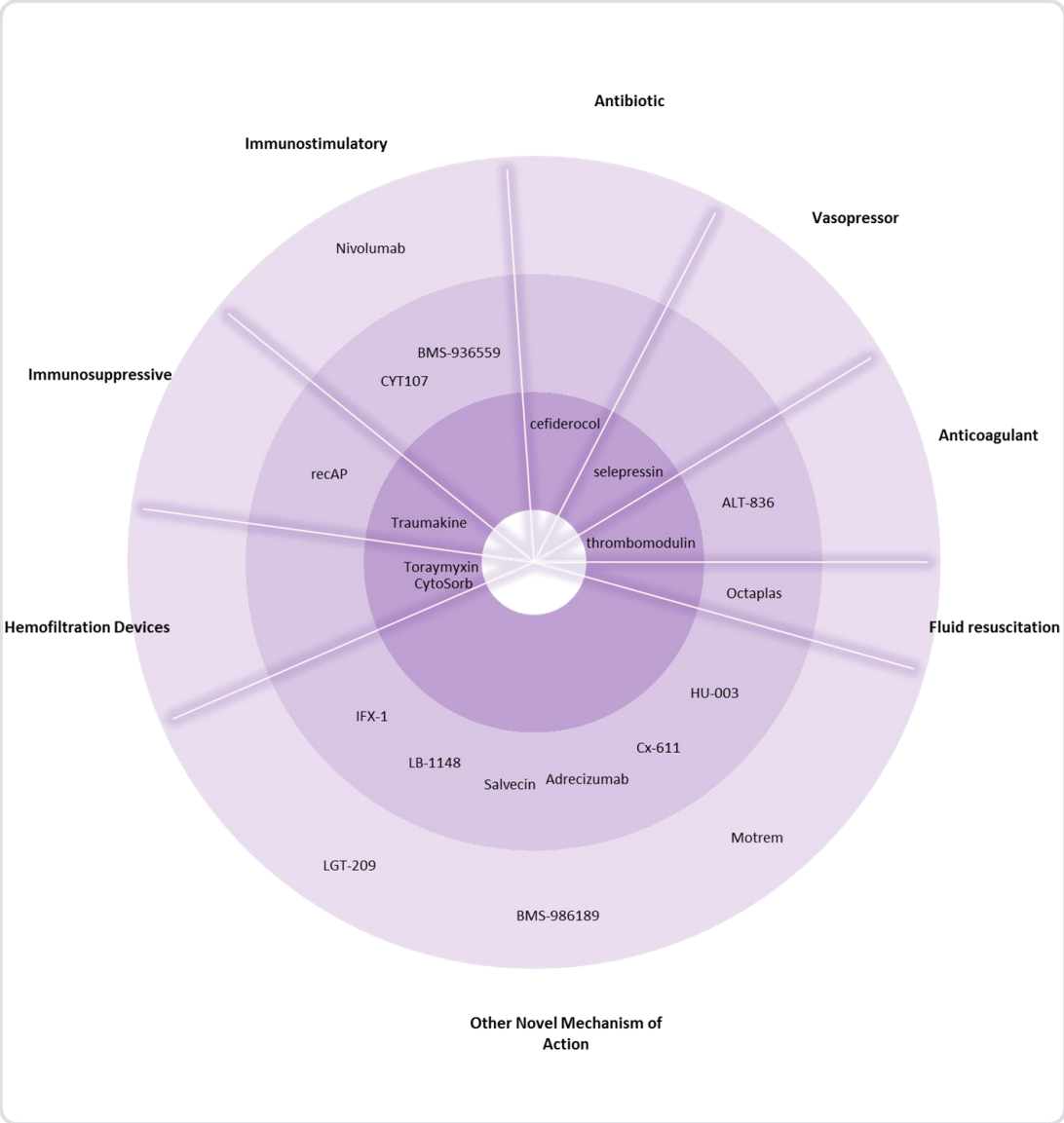
Figure 36: Sepsis and Septic Shock – Phase II–III Pipeline, 2017



Source: GlobalData, Pharma Intelligence Center [Accessed May 5 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

Figure 37 displays the products currently in development for the treatment of sepsis and septic shock as a bullseye diagram.

Figure 37: Bullseye Diagram of Products in Clinical Development for Sepsis and Septic Shock, 2017



Source: GlobalData, Pharma Intelligence Center [Accessed May 5 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

9.2.1 Selepressin

9.2.1.1 Overview

Selepressin is a novel hypotension treatment option being developed by Ferring to replace norepinephrine and vasopressin in the treatment of septic shock patients.

Selepressin is a novel hypotension treatment option being developed by Ferring to replace norepinephrine and vasopressin in the treatment of septic shock patients. Selepressin belongs to the class of antidiuretic vasopressin hormones consisting of nine amino acids that regulate water retention at low concentrations, as well as blood pressure at higher concentrations, by constricting blood vessels (Sharman and Low, 2008).

Unlike vasopressin—which functions by interaction with type 1a and type 2 oxytocin-type receptors, and can also bind to type 3 oxytocin-type receptors—selepressin is a selective vasopressin type 1a receptor agonist and has been shown to affect hemodynamic blood pressure control with reduced vascular and capillary leakage in animal models compared with vasopressin (Laporte et al., 2011; Maybauer et al., 2014; Sharman and Low, 2008). Because studies have shown that type 2 receptor interactions with vasopressin are not beneficial for septic shock patients, as they promote fluid accumulation and increase the risk of microvascular thrombosis and pulmonary edema, experts view selepressin's selectivity for type 1a receptors as potentially beneficial for patients suffering from septic shock (Asfar, 2014; Vincent, 2015).

As of June 2017, selepressin is in Phase IIb/III clinical evaluation in septic shock patients across 50–60 sites in the EU and the US as part of an adaptive double-blinded RCT. In the initial part of the study (Phase IIb), its safety and efficacy are being evaluated in four treatment arms of selepressin, with doses ranging from 1.7–5.0ng/kg/min, compared with placebo. In the second part of the trial (Phase III), the most effective dosing regimen will be evaluated for safety and efficacy against a placebo control arm. The primary endpoint of each phase is a composite measure of mortality, vasopressor-free days, and mechanical ventilator-free days (Ferring, NCT02508649). GlobalData estimates a primary completion date of November 2018, with completion of all secondary endpoints by April 2019.

Based on this completion date, GlobalData anticipates the earliest selepressin could achieve market approval in early 2020 in the 5EU and the US. Based on company press releases, Ferring has not initiated any clinical studies in a Japanese patient population and is most likely going to conduct an independent Phase III RCT for Japan. GlobalData expects Ferring to out-license selepressin's commercialization rights for the Asian market and therefore anticipates market approval for Japan at the earliest in 2026.

"We used to think that vasopressin could be some kind of a last resort agent that you could add in patients with profound hypotension, who require high doses of noradrenaline. We actually revisited this opinion as it seems that it could protect the endothelium and limit edema formation. We should perhaps use vasopressin derivatives [like selepressin] very early in the process, perhaps even before we need a vasopressin agent, to try to act quickly at this practical level. So it would no longer be a drug that you administer when it's usually late. It would be a compound that you would give relatively early. Of course, that has to be shown effective in clinical trials and the idea remains that we should use only low doses because vasopressin derivatives at high doses could have harmful effects by inducing an excessive vasoconstriction."

EU Key Opinion Leader

Table 28 presents a product profile for selepressin.

Table 28: Product Profile – Selepressin

Molecule	Selepressin
Anticipated Launch Date	US: 2020; 5EU: 2021; Japan: 2026.
Therapeutic Class	Vasopressor
Developer	Ferring International Center SA, a key subsidiary of Ferring Holding SA (Switzerland)
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	Septic shock, cardiovascular (hypotension)
Targeted Patient Pool (based on clinical trials)	Septic shock patients of 18 years or older with proven or suspected infection and hypotension requiring vasopressors to maintain MAP of 65mmHg or more
Potential Clinical Positioning	Replacement therapy for norepinephrine and other vasopressors in the regulation of hypotension in septic shock patients. Selepressin is thought to increase arterial pressure while reducing vascular leakage and pulmonary edema by selective binding to the vasopressin type 1a receptor.
Potential Commercial Positioning	GlobalData anticipates potential licensing opportunities for big and small Pharma for expansion into the Japanese market, as Ferring is currently not conducting any studies in Japanese volunteers Ferring Holding is an established privately owned biotechnology company that has a rich history of collaborations and licensing agreements. In the past, Ferring has used licensing agreements to expand their products to the Japanese (Astellas Pharma) and greater Asian markets (I-MAB), and to out-license drugs for potential orphan drug designation (Levo Therapeutics).
Formulation and Dosing	Currently in Phase II/III adaptive clinical trial; doses evaluated range from 1.7ng/kg/min to 5.0ng/kg/min
Pricing and Reimbursement	GlobalData anticipates selepressin to be priced at a 25% premium compared to marketed vasopressin.

Source: GlobalData, Pharma Intelligence Center [Accessed May 8, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

5EU = France, Germany, Italy, Spain, and UK; N/A = not applicable

9.2.1.2 Efficacy

As of February 2017, Ferring has not released any statistical analysis of the Phase II study results of selepressin in septic shock patients (Ferring, NCT01612676; Ferring, NCT01000649). Therefore, GlobalData bases the efficacy analysis of selepressin on available unprocessed Phase II data, preliminary released conference reports, review papers, and extensive primary research among experts in the field (Albers, 2015; Asfar et al., 2016; Ferring, NCT01612676; Hajjar et al., 2017; Heming et al., 2016; Hessler et al., 2016; Russel et al., 2013; Vincent, 2015; Vincent and Post, 2016).

Both Phase II clinical trials enrolled a total of 84 septic shock patients combined, where selepressin was assessed in an open-label study and in an RCT as replacement therapy for norepinephrine at doses of 1.25 and 2.50ng/kg/min, respectively (Asfar et al., 2016). According to a preliminary report, both selepressin doses accelerated weaning of vasopressor support, decreased cumulative fluid balance, and decreased ventilator-free days (Ferring, NCT01612676; Ferring, NCT01000649; Russel et al., 2013). As of July 2015, selepressin is being investigated in an adaptive Phase IIb/III RCT enrolling 1,800 planned septic shock patients. The study features a composite endpoint composed of mechanical ventilator-free days, vasopressor-free days, and all-cause mortality (Ferring, NCT02508649). GlobalData believes that this trial design will strengthen the company's ability to demonstrate the effectiveness of selepressin in septic shock patients compared with the use of norepinephrine.

"The study is conducted in patients with early septic shock. If the study's positive, we hope so of course, then the drug will be very widely used. It has a great potential. It may be relatively difficult to show the efficacy.That's a challenge, and I'm not so sure that the study protocol is the best with the adaptive design, but okay, let's hope, in any case, that it will work. Let's see the results. I'm relatively positive. I think it has good chances to show a benefit, and if so, oh yes. It will be widely used. That's a huge market, for this in the world."

EU Key Opinion Leader

According to GlobalData's primary and secondary research, selepressin's ability to selectively bind to type 1a oxytocin-type receptors increases its potency over traditional arginine vasopressin therapy while also offering a potentially safer alternative to less-selective catecholamines such as norepinephrine, which have been identified as an independent risk factor for increased mortality in septic shock patients (Hessler et al., 2016).

Furthermore, treatment failure rates are increasing among septic patients on catecholamines where, despite high doses, the patients' hemodynamics are not improving. Further details about the

pathophysiology of catecholamines in septic shock patients are outside the scope of this report, but have been extensively reviewed in the literature (Hessler et al., 2016).

Alternative blood pressure regulating medications such as arginine vasopressin—a mixed type 1a:type 2 (1:1) receptor antagonist—have been investigated as add-on therapy to norepinephrine in septic shock patients in the VASST trial, but no additional benefit was observed than compared to norepinephrine alone (Russel et al., 2008). *Post hoc* analyses of this trial have identified a reduced mortality rate among patients with concomitant steroid therapy, and a reduced need for RRT for patients with low acute kidney injury (Vincent and Post, 2016). The following VANISH RCT, aimed at evaluating arginine vasopressin alone or in combination with steroids as a first-line drug in 409 septic shock patients, showed no difference in overall mortality or kidney failure-free days for arginine vasopressin compared to noradrenaline alone; but the study did show a lower plasma creatine level and a lower incidence of RRT requirements among patients in the arginine vasopressor treatment arm.An analysis of the VANISH study suggested that while overall mortality and kidney failure-free days were not able to demonstrate significant treatment benefits for vasopressins, the researchers were able to differentiate the treatment arms by using incidence of AKI as a primary endpoint (Vincent and Post, 2016).

9.2.1.3 Safety

GlobalData assessed the safety profile of selepressin based on the reported frequency of AEs from Ferring's completed Phase II study in early septic shock patients (Ferring, NCT01612676). Due to the trial's open-label design and the absence of a comparator group, the safety of selepressin must be further evaluated in larger RCTs.

Table 29 shows the most commonly reported serious adverse events (SAEs) during selepressin therapy.

Table 29: Reported SAEs of selepressin During Phase II Study

	Infusic Regimen 3.75ng/kg/m	Infusion Regimen 2: 5.0ng/kg/min	Infusion Regimen 3: 7.5ng/kg/min	Infusion Regimen 4: Modified 3.75ng/kg/min	Total
Total SAEs	1/5 (20.00%)	4/7 (57.14%)	2/5 (40.00%)	3/13 (23.08%)	10/30 (33.33%)
Cardiac disorders	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Cardiac failure	0/5 (0.00%)	0/7 (0.00%)	0/5 (0.00%)	1/13 (7.69%)	1/30 (3.33%)
Cardiogenic shock	1/5 (20.00%)	0/7 (0.00%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Myocardial ischemia	0/5 (0.00%)	0/7 (0.00%)	1/5 (20.00%)	0/13 (0.00%)	1/30 (3.33%)
Right ventricular failure	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Rectal hemorrhage	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	1/13 (7.69%)	2/30 (6.67%)
Intestinal ischemia	0/5 (0.00%)	0/7 (0.00%)	1/5 (20.00%)	0/13 (0.00%)	1/30 (3.33%)
Hepatic congestion	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Endocarditis	1/5 (20.00%)	0/7 (0.00%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Septic shock	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Cerebral hemorrhage	0/5 (0.00%)	0/7 (0.00%)	0/5 (0.00%)	1/13 (7.69%)	1/30 (3.33%)
Respiratory failure	0/5 (0.00%)	0/7 (0.00%)	1/5 (20.00%)	0/13 (0.00%)	1/30 (3.33%)
Colostomy	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)
Distributive shock (Vascular disorder)	0/5 (0.00%)	0/7 (0.00%)	1/5 (20.00%)	0/13 (0.00%)	1/30 (3.33%)
Peripheral ischemia	0/5 (0.00%)	0/7 (0.00%)	1/5 (20.00%)	0/13 (0.00%)	1/30 (3.33%)
Shock	0/5 (0.00%)	1/7 (14.29%)	0/5 (0.00%)	0/13 (0.00%)	1/30 (3.33%)

Source: GlobalData; Ferring, NCT01612676

9.2.1.4 SWOT Analysis

Table 30 presents a SWOT analysis for selepressin.

Table 30: Selepressin SWOT Analysis, 2017

Strengths	Selective type 1 vasopressin agonist; potentially superior to arginine vasopressin in terms of occurrence of vascular leakage and lung edema. Selepressin is a potential safer vasopressor than norepinephrine in the treatment of hypotension in septic shock by increasing the blood circulation without affecting cardiac output.
Weaknesses	Although catecholamines have been shown to be associated with an increased mortality risk, physicians are very familiar with their safe use. Vasopressins such as arginine vasopressin are currently not recommended as first-line therapeutic for treating hypotension in septic shock patients. Therefore, adoption to this therapy might be initially slow. Selepressin is anticipated to be sold at a price premium, therefore competition from affordable generic alternatives will dampen initial uptake.
Opportunities	Ferring could seek a label extension of selepressin for other cardiovascular diseases. Ferring has the opportunity to promote norepinephrine dosage reductions as a potential benefit of this drug.
Threats	Unforeseen (S)AEs could threaten the successful market penetration of selepressin. The safety profile of selepressin needs to be further evaluated in larger cohorts. Hypotension is currently successfully managed by affordable generic norepinephrine. Selepressin will face increasing competition from affordable, generic vasopressors.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

9.2.2 Thrombomodulin (ART-123)

9.2.2.1 Overview

Building on Eli Lilly's past success of Xigris (activated protein C [activated drotrecogin alfa]), Asahi Kasei Pharmais developing thrombomodulin alpha (ART-123), a novel anticoagulant for the treatment of blood clotting.

Building on Eli Lilly's past success of Xigris (activated protein C [activated drotrecogin alfa]), Asahi Kasei Pharma—a Japan-based biotechnology company—is developing thrombomodulin alpha (ART-123), a novel anticoagulant for the treatment of blood clotting caused by excessive thrombin formation, defective fibrinolysis, and defective natural anticoagulants, resulting in fibrin deposits and DIC in sepsis patients (Yamakawa et al., 2015). Whereas Xigris is a recombinant exogenous source of human activated protein C, which actively inhibits tissue factors responsible for clot formation, thrombomodulin activates endogenous protein C as a cofactor through thrombin-catalyzed conversion of protein C to activated protein, thereby inhibiting clot formation (Yamakawa et al., 2015). Protein C activation results in an anti-coagulation effect through association with downstream protein C targets, such as Factor Va and VIIIa (Hoppensteadt et al., 2014).

In addition to targeting the same biological pathway as Xigris, thrombomodulin also demonstrates cytokine-suppressing effects by inhibiting monocyte and macrophage activation, resulting in an additional anti-inflammatory action. Thrombomodulin has also been reported to exhibit its anti-

inflammatory effect through binding and degradation of human high mobility group box 1 protein (HMGB-1), an important cytokine mediator in the inflammation, and through direct binding to LPS, thereby preventing recognition through CD-14 and subsequent immune activation by macrophages or dendritic cells (Ito et al., 2008; Ma et al., 2015).

"[Thrombomodulin is] a new drug that has a similar mechanism of action [to Xigris]. It's an anti-coagulant and at the same time it's an anti-inflammatory agent."

EU Key Opinion Leader

"Thrombomodulin acts very closely to activated protein C. Our study uses a biomarker to select patients with a coagulopathy and is progressing slowly, but I prefer that to a big trial ending quickly but with negative data because the population was so heterogeneous and 1,000 patients were treated to achieve a negative result. It's a lot of energy, expense for nothing [like with Xigris]. We hope that this will be a valuable intervention.The drug is already available in Japan. Looking at their data, it seems the data analysis supports the use of thrombomodulin, but these are not prospective randomized control trials any longer, because the drug is on the market in Japan. Reviewing the data available, it's in favor of thrombomodulin."

EU Key Opinion Leader

"So the data demonstrates it [thrombomodulin] to be somewhat effective. And my own view is that it is extremely good, but it [thrombomodulin] doesn't seem to be quite as effective as an anti-coagulant. So in severe cases of sepsis-associated DIC, I would keep an eye on the data and in cases where the anti-coagulant effect was insufficient I would administer an antithrombin III formulation in addition to thrombomodulin."

EU Key Opinion Leader

Xigris was withdrawn from the market after a post-marketing Phase III RCT in septic shock patients showed no statistically significant difference in the Xigris- and placebo-treated groups in terms of overall 28 day and 90 day mortality. In comparison, thrombomodulin is currently marketed in Japan under the brand name Recomodulin for the treatment of sepsis induced DIC, and as of March 2017 is additionally being evaluated in DIC subjects with renal impairment (Asahi Kasei Pharma Corporation, NCT01704001; Eli Lilly, press release, October 25, 2011; Ranieri et al., 2012). In order to gain regulatory approval in the US and 5EU, Asahi is currently conducting a Phase III RCT in sepsis patients who present with clinical evidence of a bacterial infection and a known site of infection with cardiovascular dysfunction (coagulopathy) or respiratory failure due to sepsis (Asahi, NCT01598831). In contrast to Xigris, thrombomodulin is being tested in a more homogenous sepsis patient population

in their pivotal Phase III RCT; however, GlobalData anticipates that the 28 day all-cause mortality endpoint might not prove adequate in showing a statistically significant treatment benefit for ART-123 compared with placebo, as many companies have moved towards composite endpoints of mortality and other treatment benefits such as ventilator-free days or other indicators of organ improvement. ART-123's pivotal Phase III trial is expected to reach completion of its primary endpoint in September 2017, with completion of all secondary endpoints in September 2018 (Asahi, NCT01598831).

GlobalData expects the launch of thrombomodulin for the treatment of sepsis with coagulopathy or ALI/ARDS in the US and 5EU in late 2018. Based on Asahi's past history of striking deals with major companies to help maximize commercial potential, GlobalData anticipates that Asahi will seek a marketing partner to help commercialize thrombomodulin within the US and 5EU. Until February 2016, Asahi and Pfizer Japan were co-promoting Recomodulin in Japan, before both parties decided to end this agreement (Asahi, press release, February 15, 2016).

"I am skeptical [about thrombomodulin and its similar MOA to Xigris] for two reasons. First, I'm not sure that intervening on the pro/anti-inflammatory balance is appropriate in these patients. Second, the problem [with] activated protein C was not [the] side effects. The incidence of serious bleeding episodes in patients treated with activated protein C was not relevant or frequent enough to interfere with the clinical views of the drug. As a doctor, I used activated protein C and my skepticism was because I had concern about the efficacy. I was not afraid of the side effect."

EU Key Opinion Leader

Overall, GlobalData sees great promise for anticoagulant therapy of sepsis-induced coagulopathy to reduce sepsis mortality, as DIC and microvascular thrombosis are associated with an increased risk for multiple organ dysfunction syndrome and a poor survival prognosis (Fourrier, 2012). Experts interviewed by GlobalData expressed no concerns about excessive bleeding as a potential risk of thrombomodulin therapy, citing physicians' ability to control bleeding risks with similarly difficult-to-administer anticoagulants such as heparin. In addition, RCTs have shown that the risk of bleeding complications is particularly low among coagulation disorder diseases such as sepsis (Meziani et al., 2017). However, experts did express concerns about identifying sepsis patients likely to benefit from this intervention. In the absence of reliable biomarkers to identify sepsis-induced DIC, KOLs are concerned about Asahi's Phase III trial design, as it is very similar to previous failed RCTs in terms of chosen patient population and primary outcome measures. GlobalData believes that biomarkers such as endothelial- and leukocyte-derived particles will have great relevance for early detection of sepsis-induced DIC in future RCTs (Delabranche et al., 2016).

"[Asahi is] targeting sepsis patients with coagulopathy and in terms of the molecules in development they are the furthest along. They'd be specifically for the population with sepsis-induced DIC… I think the clinical trial is not optimal. I don't think the clinical execution is optimal. What I feel bad about is I think soluble thrombomodulin has the potential to be an effective molecule, but I don't think the way the clinical development's being done is going to lead to a success."

US Key Opinion Leader

"I know about [thrombomodulin]. I'll be very interested in looking at the results. I'm still puzzled by the protocol of the study. I would say it's similar to the protocol of most of the drugs that have been tested so far... It seems like they're making the same mistakes Eli Lilly did with Xigris. And many others have, with many other drugs."

EU Key Opinion Leader

Table 31 presents a product profile for thrombomodulin (ART-123).

Table 31: Product Profile – Thrombomodulin (ART-123)

Brand (Molecule)	ART-123 (thrombomodulin alfa)
Anticipated Launch Date	US: late 2018; 5EU: late 2018;Japan: marketedsince 2008
Therapeutic Class	Anticoagulant – hematological disorders
Alternative Brand Names	Thrombomodulin (5EU and US); Recomodulin (Japan)
Developer	Asahi Kasei Pharma Corp
Marketing Partner	Asahi Kasei Pharma America Corp. (former Artisan, now American key subsidiary of Asahi)
Targeted Indication (based on clinical trials)	Sepsis-induced DIC, ALI, and ARDS
Targeted Patient Pool (based on clinical trials)	Sepsis patients ages 18 years or older with proven or suspected infection and cardiovascular dysfunction or respiratory failure due to sepsis and coagulopathy characterized by an INR > 1.40 without other known causes.
Potential Clinical Positioning	Thrombomodulin will target sepsis patients with DIC, excluding patients with severe renal failure with chronic or acutef hemodialysis, or patients requiring hemofiltration, or peritoneal dialysis, as this is one of the major exclusion criteria for the current ART-123 Phase III trial. Asahi will have the aspiration of making ART-123 the leader in the class of anti-coagulants specifically marketed for patients with sepsis or septic shock with sepsis-associated coagulopathy, cardiovascular dysfunction, or respiratory failure.
Potential Commercial Positioning	As there are currently no marketed products for sepsis and septic shock, when Asahi brings thrombomodulin to market they will have no direct competition. GlobalData expects Asahi to leverage its dominant position to drive the market penetration of thrombomodulin in the 7MM, specifically in sepsis patients with sepsis-associated coagulopathy, cardiovascular dysfunction, or respiratory failure. Asahi could see off-label use in sepsis and septic shock patients with coagulopathy. Despite its expected entrance into a sepsis marketplace with few competitors, GlobalData believes that Asahi must partner with a larger firm in order to maximize the commercial potential of thrombomodulin.
Formulation and Dosing	GlobalData expects ART-123 to be administered as an IV injection; 0.06mg/kg/day up to a maximum dose of 6mg/day for six days.
Pricing and Reimbursement	GlobalData assumed a comparable pricing and reimbursement strategy as in Japan, where thrombomodulin is currently marketed.

Source: GlobalData, Pharma Intelligence Center [Accessed June 23, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

9.2.2.2 Efficacy

In 2007, Asahi completed their pivotal Phase III RCT of thrombomodulin in 234 patients with DIC with and without infectious cause, randomized 1:1 to either thrombomodulin or heparin, leading subsequently to its market approval in Japan in 2008.

In this study, thrombomodulin showed an 11.8% treatment resolution difference (95% CI, -7.3–30.9%) in the thrombomodulin treatment group compared with the heparin treatment arm (Saito et al., 2007). Thrombomodulin treatment of DIC as a result of infection or any other hematologic malignancy demonstrated a DIC resolution effect of 66.1%, compared with 49.9% in the heparin treatment group. The overall treatment benefit for DIC of infectious and non-infectious cause was 16.2% (95% CI, 3.3–29.1%) for the thrombomodulin treatment. Although this study showed no treatment difference between the thrombomodulin and the heparin treatment arms in terms of all-cause 28 day mortality (difference -6.6%, 95% CI, -24.6–11.3), thrombomodulin treatment significantly reduced the rate of bleeding at Day 7 ($p = 0.0271$) and demonstrated a higher rate of anti-coagulation as measured by rate of change in D-dimer, thrombin–anti-thrombin complex (TATc), and Plasminogen activator inhibitor-1(PAI-1) compared with heparin (Saito et al., 2007).

A retrospective analysis using modified DIC criteria, as defined by the Japanese Association for Acute Medicine (JAAM) instead of the original DIC entry criteria from the Japanese Ministry of Health and Welfare (JMHW), showed that the mortality rate in patients with resolved DIC and infection (4/47 patients, 8.5%) was improved compared with the mortality rate in unresolved DIC patients with infection (13/29, 44.8%, $p = 0.0004$). This study identified DIC patients complicated by severe infection as most likely to benefit from thrombomodulin intervention in terms of overall survival (Aikawa et al., 2011). GlobalData notes that this study was underpowered to detect a statistically significant improvement in overall all-cause 28 day mortality rates.

A Phase IIb RCT, which was aimed at sepsis patients complicated by DIC, failed to achieve its primary endpoint of statistically significant efficacy in terms of all-cause 28 day mortality compared with SOC, which includes heparin. A *post hoc* analysis identified patients with respiratory or cardiac dysfunction and coagulopathy characterized by a prothrombin time international normalized ratio (PT-INR) of greater than 1.4 at baseline with a platelet count in the range of 30–150x10^9/L as having the greatest benefit of survival, with a 28 day mortality rate of 26.3% compared with 38.2% in the placebo arm (Vincent et al., 2013). GlobalData notes that this sub-patient population formed the entry criteria for the currently ongoing Phase III RCT.

“I think in the next years, we will make really some changes. There is the activated protein C [Xigris], which was on the market. I think it works. Some people say it doesn’t work, because there was another

negative trial. Now we have a new one [thrombomodulin]. I think that other companies than Eli Lilly will be actually restart studies on it [Xigris], because it works very well in animals, the clinical data is quite compelling as well."

EU Key Opinion Leader

"Thrombomodulin is already available in Japan and the available data is in support of this intervention. The RCT (Phase III) on biomarker-proven [sepsis] patients with coagulopathy is very well designed and we hope this will be a valuable intervention. Let's see, but I think that trial is carefully done."

EU Key Opinion Leader

Table 32 summarizes the key outcomes in DIC patients treated with thrombomodulin, heparin, or placebo (SOC).

Table 32: Thrombomodulin Clinical Efficacy Outcomes from RCTs

Study	Endpoint	Outcome	Number of Patients (%)
Saito et al., 2007 (Phase III, Japan)	**DIC resolution** in DIC patients without infection	Thrombomodulin	42/64 patients (65.6%)
		Heparin	28/61 patients (45.9%)
		Difference 95% CI	19.7% (2.6—36.8%)
	DIC resolution in DIC patients with infectious background	Thrombomodulin	32/48 patients (66.7%)
		Heparin	28/51 patients (54.9%)
		Difference 95% CI	11.8% (-7.3—30.9%)
	Disappearance of bleeding symptoms at Day 7 in DIC patients without infection	Thrombomodulin	14/43 patients (32.6%)
		Heparin	6/45 patients (13.3%)
		Difference 95% CI	19.2% (2.1—36.4%)
	Disappearance of bleeding symptoms at Day 7 in DIC patients with infection	Thrombomodulin	17/45 patients (37.8%)
		Heparin	13/46 patients (28.3%)
		Difference 95% CI	9.5% (-9.7—28.8%)
	28 day mortality in DIC patients without infection	Thrombomodulin	11/64 patients (17.2%)
		Heparin	11/61 patients (18.0%)
		Difference 95% CI	-0.8% (14.2--12.5)
	28 day mortality in DIC patients with infection	Thrombomodulin	14/50 patients (28.0%)
		Heparin	18/52 patients (34.6%)
		Difference 95% CI	-6.6% (24.6--11.3%)

Aikawa et al., 2011 (Retrospective analysis of Phase III, Japan)	**28 day mortality** using modified DIC criteria (Japanese Association for Acute Medicine, JAAM)for DIC patients with infection **DIC resolution** in JAAM DIC patients with infection	Thrombomodulin Heparin Difference 95% CI Thrombomodulin Heparin Difference 95% CI	9/42 patients (21.4%) 12/38 patients (31.6%) -10.2% (-9.1—29.4%) 27/40 patients (67.5%) 20/36 patients (55.6%) 11.9% (-9.8—33.7%)
Vincent et al., 2013; Artisan Pharma, NCT00487656 (Phase IIb, global)	**28 day mortality** in sepsis patients complicated by DIC **28 day mortality** in sepsis patients complicated by DIC and PT-INR of 1.4 at baseline	Thrombomodulin Placebo (SOC) Thrombomodulin Placebo (SOC)	66/371 patients (17.8%, p = 0.17) 79/370 patients (21.6%) 21/80 patients (26.3%) 29/76 patients (38.2%)
Tagami et al., 2015a (Retrospective analysis of JDPCD)	**28 day mortality** in sepsis-induced DIC patients after intestinal perforation	Thrombomodulin Control (SOC) Difference 95% CI	184/726 patients (25.3%) 346/1476 patients (23.4%) 1.9% (-1.9—5.7%)
Tagami et al., 2015b (Retrospective analysis of JDPCD)	**28 day mortality** in sepsis-induced DIC patients diagnosed with severe pneumonia	Thrombomodulin Control (SOC) **Odds ratio**	429/1,280 patients (37.0%) 1,866/5,062 patients (36.9%) **1.00 (95% CI, 0.98—1.03)**

Source: GlobalData; Aikawa et al., 2011; Saito et al., 2007; Tagami et al., 2015a; Tagami et al., 2015b; Vincent et al., 2013
JDPCD = Japanese Diagnosis Procedure Combination Inpatient Database

9.2.2.3 Safety

Thrombomodulin possesses a strong safety profile based on available safety data from completed Japanese Phase III and global Phase IIb studies (Artisan, NCT00487656; Saito et al., 2007; Vincent et al., 2013). While the intervention of thrombomodulin as an anti-coagulant in sepsis pathophysiology carries the risk of bleeding, this risk is reduced compared with alternative anticoagulants such as heparin (Saito et al., 2007). In the global Phase IIb RCT, 19 patients (5.1%) in the thrombomodulin group and 17 patients (4.6%) in the placebo group, which was treated with SOC including heparin, experienced serious major bleeding, with four patients from each group having a fatal bleed. Blood chemistries were comparable across the study treatments, with no statistical differences between the groups in the number of patients with laboratory results outside of normal at any time point.

Thrombomodulin possesses a strong safety profile based on available safety data from completed Japanese Phase III and global Phase IIb studies.

Furthermore, there were no differences between thrombomodulin and placebo in terms of prevalence of thromboembolic complications—defined as deep-vein thrombosis, pulmonary embolism, ischemic stroke, and acute coronary syndrome (Vincent et al., 2013). The most commonly occurring AEs in the thrombomodulin treatment group were hypokalemia, anemia, and pyrexia, but no statistically significant differences between the treatment and the placebo arms have been observed.

Table 33 highlights clinically relevant treatment emergent adverse events (AEs) and SAEs that were observed during the thrombomodulin global Phase IIb study (Artisan, NCT00487656).

Table 33: ART-123 Phase IIb Trial—Important Treatment-Emergent AEs and SAEs Monitored

Event	ART-123 (n = 370) (%)	Placebo (n = 371) (%)
AE	91.4	92.4
SAE	37.5	34.1
Serious major bleeding event	5.1	4.6
AEs leading to permanent study discontinuation	8.9	10.3
Development of new infections	43.0	42.0
Positive result for anti-ART-123 antibody	1.6	1.3
Positive result for neutralizing ART-123 antibody	0.0	0.0
AEs related to anti-ART-123 antibodies	0.0	0.0

Source: GlobalData; Hoppensteadt et al., 2014; Vincent et al., 2013
CI = confidence interval

9.2.2.4 SWOT Analysis

Table 34 presents a SWOT analysis for thrombomodulin.

Table 34: Thrombomodulin SWOT Analysis, 2017

Strengths	Already marketed for use in patients with DIC in Japan.
	Demonstrated rapid resolution of overt DIC compared to placebo in sepsis patients.
	Mortality rate of 17.8% compared to 21.6% in the placebo group is clinical evidence suggestive of efficacy based on predetermined statistical tests prior to initiation of Phase IIb trial.
	No increase is apparent in the incidence of serious bleeding events.
	The overall safety profile of thrombomodulin is very strong according to publically available data when compared to placebo.
	Use of the recombinant protein does not generate a clinically relevant immune response.
	Lowers serum biomarkers indicative of coagulation abnormality (DD, F1.2, and TATc) compared to placebo group over the course of the first 14 days on treatment.
Weaknesses	Current indication being sought is severe sepsis with coagulopathy, a specific subpopulation of the overall sepsis patient population. This therapy may not fit into the generalized treatment algorithm for all sepsis and septic shock patients.
	GlobalData anticipates thrombomodulin will not be indicated for use in patients with severe renal failure requiring chronic or acute need of hemodialysis, hemofiltration, or peritoneal dialysis, as this is one of the major exclusion criteria for the current thrombomodulin Phase III trial.
	Does not treat the underlying cause of the condition, which is a hyperactive immune response to infection. The therapy treats a symptom of the sepsis condition: coagulopathy.
Opportunities	There are currently no marketed products to treat patients with sepsis and septic shock. Therefore, when approval is reached to treat sepsis with coagulopathy, considerable coverage should be given to the product launch.
	Expand indication in the 7MM by conducting post-marketing studies outside patients with sepsis, colon cancer, and idiopathic pulmonary fibrosis.
Threats	Altor BioScience's ALT-836, an anti-coagulant being developed to treat sepsis patients, is currently in Phase II of development).
	Thrombomodulin's MOA is very similar to that of Xigris, as it activates endogenous protein C rather than introducing exogenous protein C. Asahi will have to carefully market this product to circumvent the stigma and press associated with Xigris and its failure to show any benefit in increasing survival in sepsis patients.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

9.2.3 recAP

9.2.3.1 Overview

recAP (recombinant human alkaline phosphatase) is an engineered human hybrid alkaline phosphatase (AP), which combines the crown-domain of the long half-life placental human isoform of AP with the improved catalytic domain of the intestinal human isoform of AP. recAP is being developed by the private Dutch company AM-Pharma for the treatment of sepsis-induced AKI. Am-Pharma's recAP interferes in the damaging effect of extracellular adenosine triphosphate (ATP) and inactivation of LPS, two essential triggers of an organ-damaging immune response during sepsis. In an

in vitro assay of human proximal tubular epithelial cells (PTEC)—cells whose damage is pivotal in AKI pathophysiology—isolated from healthy volunteers, AM-Pharma was able to induce a pro-inflammatory response (increased TNF-alfa, IL-6, and IL-8, $p < 0.05$) upon challenge with the bacterial endotoxin LPS, the addition of recAP was able to significantly reduce ($p < 0.05$) the inflammatory response by de-phosphorylation of.LPS, thereby preventing further downstream activation of TLR4 mediated inflammatory response(Wilmer et al., 2010). Furthermore, recAP has been shown to reduce tissue damage through de-phosphorylation of extracellular ATP—tissue-damaging ATP is released during an excessive inflammatory response by neutrophils—to adenosine, which has been shown to both have a tissue protective role and to be beneficial for the recolonization of a healthy microbiota (Peters et al., 2015; Vallon et al., 2006).

"A small study showed that giving alkaline phosphatase [recAP] could prevent the development of renal dysfunction in septic patients. That was published in Critical Care a few years ago. In Brussels, in a few weeks' time, we have the big International Symposium on Intensive Care, and there will be some very nice data presented on new therapies of sepsis including alkaline phosphatase as well."

EU Key Opinion Leader

As of May 2017, recAP has not only received the FDA's coveted Fast Track designation, but its adaptive Phase IIa/Phase IIb clinical trial design has also been shortlisted for the most innovative clinical trial design by the inaugural Clinical & Research Excellence Awards in Boston (AM-Pharma, press release, April 26, 2016). Currently, AM-Pharma is well supported by various industry investors including AbbVie and Pfizer, which invested an upfront payment of $87.5m for a minority equity interest in AM-Pharma, with Pfizer reserving the rights to acquire AM-Pharma with a potential one-time payment of up to $512.5m after the expected successful completion of its adaptive Phase IIa/IIb RCT at the end of 2017 (AM-Pharma, press release, May 11, 2016; AM-Pharma, NCT02182440).

"The alkaline phosphatase [approach] is interesting…They have some good data about the molecule in preventing sepsis-induced acute kidney injury."

US Key Opinion Leader

"Acute kidney injury is a very common finding in people with sepsis. And we know that if you get acute kidney injury you are much more apt to die. As the kidneys go, so goes whether you live or die, often. I think [recAP] does have its niche there. Even if you didn't necessarily demonstrate a mortality benefit, if you showed decrease in progression of renal dysfunction or decrease in the need for hemodialysis in a clinical trial in a critically ill population, I think that would be taken as a very exciting thing by the critical care [community]."

US Key Opinion Leader

Table 35 presents a product profile for recAP.

Table 35: Product Profile – recAP

Brand (Molecule)	recAP (recombinant human alkaline phosphatase)
Anticipated Launch Date	US and 5EU – 2021; Japan – 2025*
Therapeutic Class	Anti-inflammatory
Alternative Brand Names	AP; CIAP
Developer	AM-Pharma – with the potential acquisition by Pfizer upon successful completion of Phase IIa/IIb
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	GlobalData expects recAP to be indicated for the treatment of sepsis and septic shock patients with sepsis-induced AKI.
Targeted Patient Pool (based on clinical trials)	GlobalData expects recAP to be indicated for sepsis-induced AKI.
Potential Clinical Positioning	GlobalData expects recAP to be predominately prescribed in sepsis and septic shock patients with AKI. AM-Pharma will be looking to offer physicians an option to treat patients with acute kidney failure and those who require routine or constant dialysis, as this patient population is excluded by the majority of sepsis pipeline products. This patient population has also been identified by KOLs as a major unmet need. Furthermore, experts indicate a drug would be clinically useful even if it only demonstrates improvement in kidney function or decreases the need for dialysis and could see potential use as a prophylactic to help patients avoid kidney dysfunction. Furthermore, GlobalData expects that physicians will use recAP in other sepsis-induced organ dysfunctions, in particular ARDS.
Potential Commercial Positioning	When AM-Pharma brings recAP to market, it will have no direct competition within the sepsis market space because it will be the only drug to specifically target sepsis and septic shock patients that have AKI. GlobalData expects AM-Pharma—and at this stage most likely Pfizer--to leverage its position in the market by highlighting that the product is the only option to treat patients with kidney issues. AM-Pharma will want to use this approach to drive the market penetration of its product in the 7MM.
Formulation and Dosing	GlobalData expects recAP to be administered as an IV injection once daily for three days at 0.4, 0.8, or 1.6mg/kg.
Pricing and Reimbursement	GlobalData anticipates a similar pricing strategy to Traumakine, which is priced on other marketed interferon-β-1a therapies.

Source: GlobalData, Pharma Intelligence Center [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

*There are currently no clinical trials performed in a Japanese patient population

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan; N/A = not applicable

9.2.3.2 Efficacy

The first clinical in-human data of bovine AP—collected during AM-Pharma's Phase I study on 67 healthy volunteers challenged with LPS and in 36 sepsis and septic shock patients with evidence of sepsis-induced AKI—showed improved renal function and no significant innate immune response, but the drug was found to exhibit a short half-life (Pickkers et al., 2009). In the following Phase II studies,

AM-Pharma showed that bovine AP resulted in statistically significant improvement of renal creatinine clearance, and a reduction in RRT-requirements and a general reduction of ICU and hospital stay for the bovine AP treatment groups (Heemskerk et al., 2009; Pickkers et al., 2009).

The results of these studies are summarized in Table 11.

Table 36: Reported Efficacy of Bovine AP in Phase II Studies

Study	Measure	Drug (dosage)	Treatment	Placebo
Phase II	RRT-requirement in sepsis-induced AKI patients at Day 28	Bovine AP (67.5U/kg body weight)	4/11 patients (36%)	4/5 patients (80%)
	AKI incidence in non-AKI sepsis patients at Day 28		4/14 patients (29%)	4/6 patients(66%)
	28 day overall mortality		6/25 patients (24%, p = 0.45)	4/11 patients (36%)
	Difference in serum creatinine clearance from baseline (mL/min)		+22 (n = 10, 95% CI, 25–101,p < 0.05)	-24 (n = 5, 95% CI, 45–59)
Phase II	RRT-requirement in sepsis-induced AKI patients at Day 28	Bovine AP (bolus 67.5U/kg, maintenance 132.5U/kg/day for two days)	3/16 patients (19%, p = 0.29)	7/19 patients (37%)
	Serum creatinine (mean +/- SD, mL/min)		164+/-48 (p = 0.11)	214+/-120
	28 day overall mortality		7/16 patients (44%; p = 0.25)	6/20 patients (30%)

Source: GlobalData;Heemskerk et al., 2009; Pickkers et al., 2012

The initial positive results of bovine AP resulted in AM-Pharma pursuing the design of recAP, a recombinant human AP shown to have a longer half-life and a higher enzymatic phosphatase activity than bovine AP (Peters et al., 2015). As of May 2016, recAP has cleared Phase I development, showing peak concentration at 1 hour of infusion with rapid clearance of about 10% and 5% recAP remaining after 4h and 24h, respectively (AM-Pharma, press release, May 10, 2016; Peters et al., 2016). Furthermore, the study showed that a single administration of recAP of 2,000U/kg, or after multiple administrations over three days at 1,000U/kg, was sufficient to achieve up to 20 times the AP activity than from baseline. AM-Pharma assessed recAP at doses of250, 500, and 1,000U/kg (0.4mg/kg, 0.8mg/kg, and 1.6mg/kg), with the 250U/kg (0.4mg/kg) dose achieving less AP activity than bovine AP, and the 500U/kg (0.8mg/kg) dose arm exceeding the latter in total AP activity (Peters et al., 2016). AM-Pharma's Phase IIa study has been completed and the Phase IIb part proceeded with an undisclosed dosing of recAP (AM-Pharma, press release, May 10, 2016). GlobalData expects the results of the second part of the Phase IIa/IIb study at the end of 2017.

As of May 2017, recAP is undergoing a Phase II adaptive RCT that aims to assess its safety and optimal dosing in 120 sepsis-induced AKI patients stratified to placebo and three different doses of recAP during the initial Phase IIa stage, followed by a proof-of-concept Phase IIb study in 170 sepsis-induced AKI patients, randomized 1:1 to placebo and chosen recAP dosage from the Phase IIa part.As of May

2016, AM-Pharma has completed the Phase IIa part of the clinical evaluation of recAP and is proceeding to the Phase IIb trial without adjustments to the treatment protocol. GlobalData notes that based on the outlined adaptive trial design, un-blinding and analysis of the initial Phase IIa could have resulted in early termination in the case of recAP showing no treatment effects, the futility disclosure, or in the event of SAEs (AM-Pharma, press release, April 19 2016; AM-Pharma, NCT02182440; Peters et al., 2016). The primary endpoint of the Phase IIb part of the adaptive RCT is creatinine clearance, and the secondary efficacy measure is incidence of RRT with time on renal support as additional endpoint (Peters et al., 2016).

"The alkaline phosphatase is interesting… They've got some good data about the molecule's ability to prevent sepsis-induced [AKI]."

US Key Opinion Leader

"I could see a scenario where a therapy could be initiated to prevent the onset of kidney disease. You'd have critically ill patients at risk and you might go prophylactic and try to prevent the onset of renal dysfunction."

US Key Opinion Leader

9.2.3.3 Safety

The safety profile of AP from its Phase I and Phase II trials presented with similar treatment-emergent AEs in the treatment and the placebo arms (Heemskerk et al., 2009, Pickkers et al., 2009; Pickkers et al., 2012). As for the safety data of recAP in healthy volunteers, AM-Pharma concluded that doses up to 2,000u/kg of recAP—twice the concentration currently administrated in AM-Pharma's Phase IIa/IIb trial—was well tolerated and safe, without evidence of anti-drug antibodies. The occurrence of AEs was not significantly different from the placebo group in healthy volunteers, however the most commonly observed AEs for the recAP treatment groups included headaches (3/33 patients, 9%); postural dizziness (2/33 patients, 6%) in the single dose regimen; and infusion-site reaction (3/18 patients, 17%) and local swelling (2/18 patients, 11%) in the multiple dose regimen (Peters et al., 2016). In addition, AM-Pharma reported that recAP was well tolerated and safe at the unspecified clinically relevant dose in the first part of the Phase IIa/IIb RCT (AM-Pharma, press release, May 10, 2016).

The safety profile of AP from its Phase I and Phase II trials presented with similar treatment-emergent AEs in the treatment and the placebo arms.

9.2.3.4 SWOT Analysis

Table 37 presents a SWOT analysis for recAP.

Table 37: recAP SWOT Analysis, 2017

Strengths	AM-Pharma's recAP is a first-in-class treatment alternative for sepsis-induced AKI, a condition that is only treated by RRT and steroids.
	Upon successful completion of the current Phase IIa/IIb study, AM-Pharma will have financial backing of Pfizer to fund pivotal Phase III clinical development.
Weaknesses	AM-Pharma's recAP and its bovine AP haven't shown any benefit on overall 28 day mortality, a clinical endpoint that experts still see as crucial in order to obtain drug approval from the FDA.
Opportunities	AM-Pharma could extend the application of recAP as adjunctive therapy to antibiotics in order to prevent colonization against pathogenic bacteria, such as *C. difficile*. Mice challenged with *C.difficile* and antibiotics showed a higher survival in the AP treatment arm. It is believed that this mode of action is accelerated through reduction of ATP to adenosine, which is thought to promote the colonization of gut microbiota.
	Seeking label extension to other organ tissue dysfunction treatments in sepsis and septic shock, such as ARDS; a potential clinical endpoint would be ventilator-free days.
Threats	Unforeseen long-term AEs and SAEs of recAP treatment in sepsis-induced AKI patients
	The barrier to entry for competing drug manufacturers is relatively low in terms of generating modified APs for the treatment of sepsis-induced AKI or other tissue organ dysfunctions.
	Leading Bioscience's tranexamic acid is an alternative medication potentially indicated as treatment for organ dysfunction, with particular interest in gastrointestinal dysfunctions and MODS.
	Faron's Traumakine is targeting ARDS patients and is in Phase III clinical development. If AM-Pharma/ Pfizer is aiming for this patient population, it won't be first to market and has to compete with potentially already established treatment option for ARDS.

Source: GlobalData,Pharma Intelligence Center [Accessed May 10, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report Vallon et al., 2006

MODS = multiple organ dysfunction syndrome

9.2.4 Traumakine (Recombinant Human IFN-β-1a)

9.2.4.1 Overview

Traumakine (FP-1201), a human recombinant interferon-beta-1a (IFN-β-1a) receptor agonist, is being developed by Faron Pharmaceuticals together with China Medical System Holdings, Maruishi Pharmaceuticals, and Pharmbio Korea as development partners. As of May 2017, Traumakine is in Phase III clinical development for ARDS in Europe and Japan, whereas clinical development for the US will hinge on a planned Phase II RCT to evaluate the investigational product's safety and efficacy (Faron, NCT00789685; Maruishi, JapicCTI-163320). Faron retained full commercialization and development rights of Traumakine for Europe and has out-licensed future development and commercialization for the Japanese market to Maruishi Pharmaceuticals (Faron, press release, December 28 2010).

Although Traumakine is currently not indicated for the treatment of sepsis and septic shock patients, experts interviewed by GlobalData expressed optimism about IFN-β-1a therapy and its potential on

reducing ALI in sepsis and septic shock patients with ARDS. Similarly to AM-Pharma's recAP, Traumakine functions by taking advantage of the anti-inflammatory and endothelial cell stabilizing effect of adenosine. However, in contrast to recAP, which dephosphorylates ATP, Traumakine binds to the IFN-β receptor and induces expression of CD73—a cell surface enzyme with 5'-ectonucleotidase activity—which catalyzes the conversion of AMP to adenosine (Bellingan et al., 2014).

"Adenosine is a substance that may be protective against the harmful effects of infections. The nice thing about it is that you could measure the adenosine levels in the blood. There is now a small company working on this approach. It makes sense."

EU Key Opinion Leader

Table 38 presents a product profile for Traumakine.

Table 38: Product Profile – Traumakine

Brand (Molecule)	Traumakine (recombinant human **IFN-β**-1a receptor agonist)
Anticipated Launch Date	US and 5EU – 2022; Japan – 2025*
Therapeutic Class	Anti-inflammatory
Alternative Brand Names	
Developer	Faron
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	GlobalData expects Traumakine to be indicated for the treatment of sepsis and septic shock patients with sepsis-induced ALI.
Targeted Patient Pool (based on clinical trials)	GlobalData expects Traumakine to be indicated for sepsis-induced ALI.
Potential Clinical Positioning	GlobalData expects Traumakine to be predominately prescribed in sepsis and septic shock patients with ALI. Faron will be looking to offer physicians an option to treat patients with acute respiratory disease syndrome and those who require routine or constant ventilator support, as this patient population is excluded by the majority of sepsis pipeline products. This patient population has also been identified by KOLs as a major unmet need. Furthermore, GlobalData expects that physicians will use Traumakine in other sepsis-induced organ dysfunction, in particular AKI.
Potential Commercial Positioning	When AM-Pharma brings recAP to market, they will have no direct competition within the sepsis market space because they will be the only drug to specifically target sepsis and septic shock patients who have ALI. GlobalData expects Faron to leverage its position in the market by highlighting that their product is the only option to treat patients with lung issues. Faron will want to use this approach to drive the market penetration of its product in the 7MM.
Formulation and Dosing	GlobalData expects Traumakine to be administered as an IV injection once daily for one day at 10ug/kg.
Pricing and Reimbursement	GlobalData anticipates the pricing of Traumakine to be based on currently marketed IFN-β-1a therapies, such as Avonex and Rebif.

Source: GlobalData, Pharma Intelligence Center [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

*There are currently no clinical trials performed in a Japanese patient population

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan; N/A = not applicable

9.2.4.2 Efficacy

Evidence supporting the clinical efficacy of Traumakine is derived from small, open-label Phase II studies. GlobalData notes that due to the open-label nature of these studies, no major conclusions on the efficacy of Traumakine can be drawn, as comparisons to other historic treatment approaches are dependent on multiple independent factors such as baseline patient characteristics, local pathogen prevalence, and particularly for sepsis, different SOC approaches.

In the first open-label Phase I/II PK/PD, safety, and efficacy (dose-escalation and dose-expansion) study of Traumakine, Faron recruited 96 ARDS patients across eight ICUs in the UK, of whom 37 patients were enrolled into the study, while the remaining 59 patients formed the control group, as these patients were recruited during periods of non-recruitment or failed to submit consent paperwork before the 48-hour deadline (Faron, NCT00789685). The optimal dose of Traumakine was assessed to be 10µg/mL IV Traumakine once daily for six days; a similar dose has been shown *ex vivo* to be associated with a four and 14.3 times higher expression of CD37 in lung culture cells than compared to untreated cells at Day 1 ($p = 0.04$) and Day 4 ($p = 0.004$), respectively. The primary endpoint of all-cause mortality at Day 28 was observed in three patients (8% mortality rate) in the treatment arm and in 19 patients (32% mortality rate) in the control cohort (Bellingan et al., 2014).

In the second open-label Phase II study of Traumakine in a Japanese patient population, licensing partner Maruishi recruited 18 ARDS patients across 15 ICUs in Japan from February to December 2015. Faron reported no AEs in 18 ARDS patients at doses of IV 2.5µg/ml, 5.0µg/mL, and 10µg/mL for six days. The primary efficacy endpoint of all-cause mortality at Day 28 was met in four patients, representing a mortality rate of 22.2% (Faron, press release, January 7 2016).

As of May 2017, Traumakine is being evaluated in two prospective Phase III RCTs in order to gain market approval in Europe and Japan (Faron, NCT02622724; Maruishi, JapicCTI-163320). The studies have 28 day all-cause mortality as a pivotal efficacy endpoint. A Phase II RCT to support drug approval in the US is planned for H2 2017 (Faron, press release, February 9 2017).

9.2.4.3 Safety

Based on the reported Phase II data, Traumakine seems to be well tolerated and safe at doses up to 10µg/mL daily for six days (Bellingan et al., 2014; Faron, press release, January 7 2016). During Faron's Phase I/II open-label study of Traumakine, the company reported no drug-related AEs at doses of 0.44µg/mL, 4.4µg/mL, or 10µg/mL. However, during the dose escalation phase of the study, two of the five patients receiving 22µg/mL reported fever, rigors, and tachycardia (Bellingan et al., 2014).

The most common AEs associated with the use of other IFN-β-1a antagonists for multiple sclerosis (Avonex, Rebif) are headache, insomnia, diarrhea, nausea, vomiting, itching, rash, muscle and joint pain, fatigue, fever, chills, and hair loss (Avonex, summary of product characteristics, 2015; Rebif, summary of product characteristics, 2013). Although Avonex, Rebif, and Traumakine contain the same active ingredient, Avonex and Rebif are administered at SC doses of 15µg/mL, 22µg/mL, or 44µg/mL, while Traumakine is formulated as an IV drug in concentrations of 10µg/mL, a difference that could explain the observed discrepancy in the occurrence of AEs.

9.2.4.4 SWOT Analysis

Table 39 presents a SWOT analysis for Traumakine.

Table 39: TraumaKine SWOT Analysis, 2017

Strengths	Faron's Traumakine is a first-in-class treatment alternative for sepsis-induced ALI, a condition that is only treated by ventilator support and steroids.
	Faron's out-licensing for the development of Traumakine in Japan has mitigated the risk of late stage failure and has allowed the company to penetrate both the European and Japanese markets in the near future.
Weaknesses	As of May 2017, Faron hasn't started clinical development of Traumakine in the US. GlobalData anticipates that Faron will miss potential revenue streams from the most lucrative market.
	As of May 2017, Faron holds the only patent on the IV formulation of IFN-β-1a in Finland, which it hopes to expand worldwide under the Patent Co-operation Treaty.
Opportunities	Seeking label extension to other organ tissue dysfunction treatments in ischemic conditions, multi organ failure, and AKI
Threats	Unforeseen long-term AEs and SAEs of Traumakine treatment in sepsis-induced AKI patients.
	The barrier for entry for competing drug manufacturers is relatively low in terms of IP protection, Faron only holds the IP for the IV formulation of IFN-β-1a. Landsteiner Scientific markets IFN-β-1a as an IV formulation under the brand names Pheroliz and Xerfelan for the treatment of multiple sclerosis in Mexico.
	AM-Pharma's recAP is thought to be beneficial for sepsis-induced ARDS and could potentially compete for market share in this indication.

Source: GlobalData, Pharma Intelligence Center [Accessed May 10, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report; Faron, press release, March 1, 2016

IP = intellectual property

9.2.5 BMS-936559

9.2.5.1 Overview

BMS-936559, an anti-PD-L1 mAb for the treatment of sepsis and septic shock, was originally developed by Medarex, before the company was acquired by BMS in July 2009.

BMS-936559, an anti-PD-L1 mAb for the treatment of sepsis and septic shock, was originally developed by Medarex, before the company was acquired by BMS in July 2009 (BMS, press release, July 22, 2009; Peggs et al., 2009). PD-L1 surface protein—a highly expressed and potent inducer of T-cell apoptosis—dampens the immune response by binding to T cells and inhibiting their proliferation, their ability to produce cytokines, or their ability to perform other cytotoxic defense functions.

Excessive and persistent antigenic exposure to PD-L1 as commonly seen in chronic viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV); cancer; and sepsis leads to exhausted T cells, therefore mAb-targeted binding and inactivation of these proteins holds great promise in re-activating an immune response (Sharpe et al., 2007).While anti-PD-L1 mAbs have been increasingly popular in the treatment of various cancers, this is the first time one of these mAbs has been evaluated in immunosuppressed patients and in particular sepsis patients (Brahmer et al., 2012; Topalian et al., 2012).

BMS continues to develop BMS-936559 for sepsis and various cancer targets, whereas ViiV Healthcare retained developing rights for BMS-936559 in HIV after acquiring BMS' HIV assets in February 2016 (BMS, press release, February 22, 2016).As of March 2017, BMS-936559 is in Phase I//IIa of clinical development in a planned patient population of 225 sepsis patients with sepsis-induced immunosuppression. The primary endpoints of this early stage clinical trial are safety, tolerability, and all-cause mortality at Day 90 (BMS, NCT02576457).

Experts interviewed by GlobalData were very optimistic about this novel aspect of interfering with the PD-L1 axis by stimulating T cell responses in immunocompromised sepsis and septic shock patients, resulting in a decreased risk of secondary infections and viral reactivation in these patients (Wang et al., 2015). In patients suffering from sepsis-induced immunosuppression, neutrophils express excessive PD-L1, which bind to receptors on T cells and prevent immune system responses.

GlobalData believes that the key opportunity for anti-PD-L1 mAbs lies in the simultaneous use of PD-L1 levels to classify the patients' immune response as pro-inflammatory (cytokine storm) versus anti-inflammatory (immune paralysis). Ideally, PD-L1 levels would serve as biomarkers for anti-PD-L1 therapy (Guignant et al., 2011).

Table 40 presents a product profile for BMS-936559.

Table 40: Product Profile – BMS-936559

Molecule	BMS-936559 (MDX-1105, Anti-PD-L1)
Anticipated Launch Date	US and 5EU -- 2021; Japan -- 2023
Therapeutic Class	Immuno-stimulatory mAb
Developer	BMS
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	Sepsis-induced immune suppression in sepsis and septic shock patients
Targeted Patient Pool (based on clinical trials)	Sepsis and septic shock patients with 24 hours of previous history of disease
Potential Clinical Positioning	BMS' anti-PD-L1 mAb has the potential to become the SOC in sepsis and septic shock therapy in the later progression of the disease, after antibiotics and fluid administration have stabilized the patients, where BMS-936559 will help reduce mortality due to sepsis-induced immune suppression by boosting the immune response against secondary infections.
Potential Commercial Positioning	BMS-936559 has the potential to become the first-in-class therapy for sepsis-induced immunosuppression, over other immune stimulatory treatment options in sepsis and septic shock patients as previous IgG, GM-CSF, and G-CSF therapies have not shown satisfactory results in large RCTs.
Formulation and Dosing	Unspecified IV dose of BMS-936559. Based on previous RCTs of BMS-936559 in cancer patients, GlobalData anticipates a dosing range between 0.3 to 10mg/kg for an unspecified length of time.
Pricing and Reimbursement	GlobalData anticipates a similar pricing strategy to other marketed anti-PD-L1 mAbs, such as AstraZeneca's Imfinzi (durvalumab) in oncology.

Source: GlobalData, Pharma Intelligence Center [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

5EU = France, Germany, Italy, Spain, and UK; N/A = not applicable

9.2.5.2 Efficacy

Advances in the understanding of sepsis pathophysiology have led to the conclusion that the host immune response to pathogens is guided by both pro- and anti-inflammatory processes. Indeed, immunological studies on the immune cells of sepsis patients have shown a decreased production of pro-inflammatory cytokines and an increased expression of PD-1 and PD-L1 receptors on innate and adaptive immune cells, leading to T cell exhaustion (Chang et al., 2014; Ertel et al., 1995; Rigato and Salomao., 2003). *In vitro* studies analyzing the blood of critically ill patients with or without sepsis not only showed increased levels of PD-L1, but also showed that exposing cells to anti-PD-L1 mAbs overnight results in increased levels of lymphocytes, as well as CD4+ and CD8+ T cells, and increased production of anti-inflammatory cytokines such as IFN-γ and IL-2 (Chang et al., 2014).

As of March 2017, GlobalData could not find any efficacy information of BMS-936559 in sepsis-induced immunosuppression. However, the effects of anti-PD-L1 mAbs in sepsis animal models and *in*

vitro studies of human blood isolates are very similar to the immune pathology seen in many patients with cancer, leading sepsis experts to believe that anti-PD-L1 therapies can positively interfere with sepsis pathophysiology.

Relevant efficacy information for BMS-936559 in sepsis was derived from the clinical evaluation of BMS-936559 in advanced cancer patients (BMS, NCT00729664; Brahmer et al., 2012). *Ex vivo* PK/PD studies of blood samples from advanced cancer patients receiving up to 10mg/kg BMS-936559 showed that more than 65% of the expressed PD-L1 from peripheral-blood T cells was bound by the anti-PD-L1 mAb BMS-936559 *in vivo*. Because of the complex nature of the tumor microenvironment, it remains unclear how this may correlate with the overall objective response rate of 6–17% with prolonged stabilization of advanced cancers including non-small cell lung cancers, which have not been considered responsive to immunotherapy previously (Brahmer et al., 2012). GlobalData anticipates results from the Phase I/IIa RCT for BMS-936559 in sepsis-induced immunosuppression to be obtained by early 2019 (BMS, NCT02576457).

9.2.5.3 Safety

BMS-936559 presented with an overall good safety profile in patients with advanced cancer, with treatment-related SAEs reported in 19 out of 207 patients (9%) during the 12-week treatment period. Although prolonged exposure to BMS-936559 carried an increased risk of severe autoimmune reactions, GlobalData notes that sepsis patients will require a shorter treatment period (BMS, NCT00729664; Brahmer et al., 2014).

Experts cited the administration of anti-PD-L1 mAbs to patients suffering from a pro-inflammatory disease state as most concerning, as BMS-936559 could further accelerate the excessive immune response, potentially causing harm to this patient group. Furthermore, PD-L1 signaling through neutrophils, which migrate from injury sites to the lymph nodes, is essential to inducing apoptosis of B and T cells in an effort to rebalance the humeral immune response to future challenges with these pathogens (Hampton et al., 2015; Kamenyeva et al., 2015).

Table 41 shows the most commonly reported SAEs during therapy.

Table 41: Most Frequently Reported AEs and SAEs of BMS-936559*

Drug-related AEs	0.3mg/kg(n =3)		1mg/kg (n = 37)		3mg/kg (n = 42)		10mg/kg (n = 125)		Total (n = 207)	
	AEs	SAEs	AEs	SAEs	AEs	SAEs	AEs	SAEs	AEs	SAEs
Any event	1 (33%)	-	24 (65%)	3(8 %)	37 (88%)	17 (40%)	116 (93%)	59 (47%)	126 (61%)	19 (9%)
General disorders										
Fatigue	1 (33%)	-	10 (27%)	-	7 (17%)	-	15 (12%)	3 (2%)	33 (16%)	3(1%)
Pyrexia	-	-	2 (5%)	-	3 (7%)	-	1 (1%)	-	6 (3%)	-
GI disorders										
Diarrhea	1 (33%)	-	4 (11%)	-	6 (14%)	-	8 (6%)	-	19(9%)	-
Nausea	-	-	3 (8%)	-	2 (5%)	-	8 (6%)	-	13 (6%)	-
Skin and SC disorders										
Rash	-	-	5 (14%)	-	1 (2%)	-	8 (6%)	-	14 (9%)	-
Pruritus	-	-	6 (16%)	-	3 (7%)	-	3 (2%)	-	12 (6%)	-
Musculoskeletal and connective tissue disorders										
Arthralgia	-	-	3 (8%)	-	3 (7%)	-	9 (7%)	-	15 (7%)	-
Myalgia	-	-	1 (3%)	-	3 (7%)	-	3 (2%)	-	7 (3%)	-
Pain in extremity	-	-	-	-	2 (5%)	-	4 (3%)	-	6 (3 %)	-
Nervous system disorder										
Myasthenia gravis	-	-	-	-	-	-	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Headache	-	-	3 (8%)	-	2 (5%)	-	4 (3%)	-	9 (4%)	-
Dizziness	-	-	3 (8%)	-	-	-	4 (3%)	-	7 (3%)	-
Procedural complications										
Infusion-related reaction	-	-	-	-	2 (5%)	-	19 (15%)	1 (1%)	21 (10%)	1 (1%)
Eye disorders										
Eye pruritus	-	-	1 (3%)	-	4 (10%)	-	1(1%)	-	6 (3%)	-
Metabolism and nutrition disorder										
Decreased appetite	-	-	3 (8%)	-	1(2%)	-	2(2%)	-	6 (3%)	-
Blood and lymphatic system disorders										
Lymphopenia	-	-	-	-	1 (2%)	-	6 (5%)	1 (1%)	7 (3%)	1 (1%)
Endocrine disorders										
Hypothyroidism	-	-	-	-	1 (2%)	-	5 (4%)	-	6 (3%)	-
Adrenal insufficiency	-	-	-	-	1 (2%)	1 (2%)	1 (1%)	-	2 (1%)	1 (1%)
Cardiac disorders										
Myocarditis	-	-	1 (3%)	-	-	-	-	-	1 (1%)	-
Immune system disorder										
Sarcoidosis	-	-	-	-	-	-	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Infections										
Endophtalmitis	-	-	-	-	1 (2%)	1 (2%)	-	-	1 (1%)	1 (1%)

Source: GlobalData; Brahmer et al., 2012
* reported in at least 3% of all drug-treated cancer patients (dose range 0.3-10mg/kg)

9.2.5.4 SWOT Analysis

Table 42 presents a SWOT analysis for BMS-936559.

Table 42: BMS-936559 SWOT Analysis, 2017

Strengths	BMS-936559 is targeting a novel pathway in sepsis pathophysiology, which, in contrast to the short-lived early pro-inflammatory pathway, is longer lived and occurs later in the disease progression.
	BMS-936559 is currently evaluated without the use of companion diagnostics and biomarkers, therefore BMS can broaden its application to a bigger patient population in sepsis and septic shock.
Weaknesses	BMS-936559 will likely also be used in oncology and based on the high price tag of nivolumab, GlobalData expects that the treatment option will be as expensive as for patients with solid cancers.
	Treatment is not guided by specific biomarkers and it remains unknown which sepsis and septic shock patients are most likely to benefit from therapy. In cancer patients, anti-PD-L1 monotherapy has been shown to induce hyperprogressive tumor growth. PD-L1 levels did not correlate to response in all studies in oncology.
Opportunities	BMS is exploring the efficacy and safety of BMS-936559 in the treatment of solid cancers.
	BMS could promote the cost savings of preventing patient readmission to the hospital—a cost estimated to be up to $30,000 per patient visit—in order to justify the high upfront cost ofBMS-936559.
	BMS can use PD-L1 levels as an indicator to initiate immunostimulatory therapy with BMS-936559.
Threats	There is a risk of developing immunity against the administered mAb.
	BMS-936559 will be competing against RevImmune's CYT107 for patient share, as both drugs are targeting a similar sepsis and septic shock patient population.

Source: GlobalData, Pharma Intelligence Center [Accessed May 10, 2017]; Brower, 2016; Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

9.2.6 CYT107

9.2.6.1 Overview

CYT107 is a glycosylated recombinant human IL-7 being developed by RevImmune (formerly known as Cytheris), a small-cap private biotechnology company with presences in the US and France.

IL-7 is a pluripotent, essential, and non-redundant cytokine that inhibits both B and T cell apoptosis, thereby inducing proliferation of naïve and memory T cells (Th1 [CD4] and Th2 [CD8] effector T cells), without affecting regulatory T cells, leading to replenished lymphocyte pools (Boomer et al., 2011; Hotchkiss et al., 2001; Rosenberg et al., 2006). In addition, IL-7 increases T cell receptor diversity, thereby boosting immunity against infections by increasing the ability of T cells to recognize pathogens; furthermore, IL-7 enhances the expression of cell-adhesion molecules, resulting in faster trafficking of T cells to sites of infection (Levy et al., 2012; Pellegrini et al., 2011; Venet et al., 2012). During sepsis pathophysiology, particular in the immunosuppressant state of the disease, patients

present with characteristically low levels of IL-7 and depleted lymphocyte pools, therefore, replenishing IL-7 levels with recombinant IL-7 is thought to be beneficial in this patient population (Boomer et al., 2011).

CYT107 is currently in Phase II of clinical development in sepsis patients (RevImmune, NCT02797431; RevImmune, NCT02640807). The primary endpoint of these studies is the reconstitution of immune response in sepsis and septic shock patients with lymphocytopenia, and is assessed by an increase in absolute lymphocyte count of 50% or more at Day 42 (Centre Hospitalier Universitaire à Limoges, NCT02797431; RevImmune, NCT02640807). Based on published results of CYT107 therapy in cancer and HIV patients, and a general optimism expressed by KOLs across all 7MM, GlobalData expects CYT107 to be able to achieve its primary endpoint and start evaluating CYT107 in a larger sepsis patient population with lymphopenia to demonstrate efficacy. However, RevImmune's previous history of bankruptcy demonstrates that further progression of CYT107 will depend on establishing deals with other players in the field in order to secure the necessary funding of late stage clinical development. Upon successful completion of its current Phase II study, GlobalData sees RevImmune as an attractive acquisition target for large Pharma to enter the sepsis and septic shock marketplace.

Based on published results of CYT107 therapy in cancer and HIV patients, and a general optimism expressed by KOLs across all 7MM..

Table 43 presents a product profile for CYT107.

Table 43: Product Profile – CYT107

Molecule (Brand)	CYT107
Anticipated Launch Date	US and 5EU – 2022; Japan – 2025*
Therapeutic Class	Immuno-stimulatory intervention
Alternative Brand Names	Recombinant human IL-7
Developer	RevImmune
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	GlobalData expects CYT107 to be indicated for sepsis and septic shock patients with lymphopenia, presented by an absolute lymphocyte count of <900 cells/mm^3 or less.
Targeted Patient Pool (based on clinical trials)	GlobalData expects CYT107 to be administered to sepsis and septic shock patients 48–120 hours after hospital admission, with a SOFA score of at least 2 or more, and presence of an immune-compromised state (absolute lymphocyte count of <900 cells/mm^3 or less).
Potential Clinical Positioning	RevImmune's CYT107 will be reserved for the treatment of the immune-compromised state of sepsis and septic shock patients, which typically occurs 48–120 hours after ICU admission and is characteristic of a low absolute lymphocyte count.
Potential Commercial Positioning	As there are currently no marketed immunostimulatory drugs for sepsis and septic shock patients, with the exception of less frequently used IgGs, CYT107 will mainly compete with BMS' anti-PD-L1 mAb BMS-936559 for patient share. Diagnosis of an immune-compromised state in sepsis
Formulation and Dosing	GlobalData expects two CYT107 in either high (twice a week dose for four weeks) or low frequency (twice for week for first week, followed by weekly doses for next three weeks) formulation of 10µg/mL
Pricing and Reimbursement	GlobalData anticipates a similar pricing than to BMS-936559, which is based on commercially available Imfinzi (durvalumab).

Source: GlobalData, Pharma eTrack [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

*There are currently no clinical trials performed in a Japanese patient population

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan; N/A = not applicable

9.2.6.2 Efficacy

As of March 2017, there are no published results on human clinical trials for IL-7 therapy in sepsis. However, GlobalData leveraged findings from CYT107's clinical development programs in HIV, HEP-C/HEB-B, and cancer patients to estimate efficacy in sepsis and septic shock patients. However, most of these studies were terminated due to Cytheris filed bankruptcy in June 2013 and evidence for clinical relevance of this therapy in sepsis and septic shock patients requires further investigation (Cytheris SA, NCT01190111; Cytheris SA, NCT01027065; Cytheris SA, NCT01025297; Cytheris SA, NCT01024894; Cytheris SA, NCT00492440; NIAID, NCT00839436; Hotchkiss et al., 2013b; Trédan et al., 2015).

The premise of IL-7 therapy in sepsis and septic shock patients is based on encouraging results from animal studies of fungal sepsis, where animals undergoing a cecal ligation and puncture wound—a

common technique to induce peritonitis (an abdominal infection)—and challenged with *Candida albicans* showed an increase in global immunity and increased survival (Unsinger et al., 2012). Furthermore, *ex vivo* analysis of CD4+ and CD8+ cytokines upon T cell stimulation in healthy volunteers and septic shock patients showed unaltered, responsive IL-7 pathway responses, with the ability to restore normal lymphocyte function by reconstitution of IL-7 (Venet et al., 2012).

The most recent RCTs of CYT107 were conducted in 20 patients with metastatic breast cancer (Phase II) and 26 patients with HIV infections receiving antiretroviral therapy (Phase I/IIa) (Levy et al., 2012; Trédan et al., 2015). Both studies failed to achieve statistical significant improvements in their respective disease area, but both studies reported a statistical significant increase in CD4+ and CD8+ cytokines upon CYT107 treatment. Experts interviewed by GlobalData highlighted similar results in animal models of sepsis upon IL-7 therapy and were therefore very optimistic about this therapeutic intervention. In the absence of actual clinical efficacy data in sepsis patients, the results of RevImmune's Phase II study are highly anticipated (Centre Hospitalier Universitaire à Limoges, NCT02797431).

Table 44 highlights the effect of CYT107 on CD4+ and CD8+ in cancer and HIV patients.

Table 44: Immunological Effects of CYT107 in Cancer and HIV Patients

Study	Measure		CYT107		Placebo
			20ug/kg, n = 10	30ug/kg, n = 8	n = 6
EUDRACT2006-00624-20A (HIV)	CD4+ at week 0 (baseline) CD4+ at week 12 CD4+ at week 52 CD8+ at week 0 (baseline) CD8+ at week 12 CD8+ at week 52*	268 (95% CI, 152–373) 419 (p < 0.002) 422 (p < 0.005) 761 (95% CI, 530–857) 1081 (p < 0.002) <1081 (p < 0.01) 10ug/kg, n = 10	240 (95% CI, 197–323) 563(p < 0.002) 412 (p < 0.005) 659 (95% CI, 376–1090) 1210 (p < 0.002) <1210 (p < 0.01) NA	276 (95% CI, 207–370) 799 (p < 0.002) 897 (p < 0.005) 415 (95% CI, 209–1524) 1011 (p < 0.002) <1011 (p < 0.01) NA	280 (95% CI, 203–344) 259 >259 502 (95% CI, 393–1123) 487 >500 n = 10
NCT01362107	CD4+ (Day 0 to Day 21, before chemotherapy) CD4+ (Day 57 to Day 78, during chemotherapy) CD8+ (Day 0 to Day 21, before chemotherapy) CD8+ (Day 57 to Day 78, during chemotherapy)	+148.1 (95% CI, +41.8--+763.9, p = 0.002) +58.6 (95% CI, -15.2--+281.5, p = 0.121) +104.3 (95% CI, -17.2--+900, p = 0.006) +66.8 (95% CI, +8.4--+245.7, p = 0.083)	NA NA NA NA	NA NA NA NA	+9.9 (95% CI, -50.3--+102.2) -2.4 (95% CI, -27.6--+112.5) -3.4 (95% CI, -33.5--+59.6) +1.8 (95% CI, -36.2--+37.9)

Source: GlobalData; Levy et al., 2012
*numeric value not provided in supplementary material (extrapolated from graph)
N/A: Not applicable

9.2.6.3 Safety

GlobalData's extensive primary and secondary research showed that of IL-7 therapy was well tolerated in four multinational clinical trials in patients with HIV, cancer, hepatitis C, and sepsis (Levy et al., 2009; Monneret et al., 2014; Rosenberg et al., 2011; Sportès et al., 2008; Unsinger et al., 2010). Unlike the pro-inflammatory cytokine IL-2, IL-7 has been shown to lead to less incidences of fever, capillary leak syndrome, or other clinical abnormalities associated with excessive pro-inflammatory cytokine stimulation (Unsinger et al., 2012). In patients with HIV, CYT107 was well tolerated at doses of 10 and 20μg/kg, whereas at the higher dose of 30μg/kg, dose-limiting toxicity was observed in 2/8 patients (25%), resulting in transient grade 3 alanine aminotransferase increase and a grade 2 rash (Levy et al., 2012).

9.2.6.4 SWOT Analysis

Table 45 presents a SWOT analysis for CYT107.

Table 45: CYT107 SWOT Analysis, 2017

Strengths	CYT107 is targeting a novel pathway in sepsis pathophysiology in a specific patient population of sepsis and lymphopenia.
	In the absence of reliable biomarkers for sepsis and septic shock diagnosis, absolute lymphocyte counts are a good indicator for CYT107 therapy.
Weaknesses	To date no clinical data on CYT107 in sepsis patients are publically available.
	RevImmune has a history of failing to secure funding for late-stage clinical development programs.
Opportunities	RevImmune can leverage the general optimism about the molecular pathway and its promise in sepsis therapy.
	Measurement of sCD127 (IL-7 receptor) levels—by ELISA techniques—to identify the septic shock patients most likely to respond to therapy.
	Combination therapy of immunostimulatory therapies, as seen in oncology, could be a great opportunity to promote exposure of CYT107 therapy. Furthermore, anti-PD-1 and IL-7 therapy have shown marked interferences within the immune response in a mouse animal model of sepsis, supporting the premise of combining different immunostimulatory agents, such as BMS' BMS-936559 and RevImmune's CYT107.
	Increasing incidence of fungal infections in ICU settings is an opportunity, as CYT107 has shown a combined activity of improving immune response and fungal clearance through an up-regulation of IFN-γ in mouse sepsis models, thereby reducing the risk of invasive fungal infection.
Threats	Altor is currently exploring an IL-15 agonist against solid tumors that activates the immune response similarly to IL-7; however, it activates not only T cells, but also natural killer cells and dendritic cells. Should Altor decide to pursue development of their IL-15 agonist in sepsis, experts argue that it could be a more potent immune-stimulatory agent, whereas IL-7 is thought to be more T cell-specific.
	Another potential threat is BMS' anti-PD-L1 agonist, which is exploiting a similar molecular mechanism.

Source: GlobalData, Pharma Intelligence Center [Accessed May 10, 2017]; Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report; Boomer et al., 2014; Demaret et al., 2014; Hotchkiss et al., 2013b; Shindo et al., 2015; Unsinger et al., 2012

ELISA = enzyme-linked immunosorbent assay

9.2.7 Cefiderocol

9.2.7.1 Overview

Cefiderocol (also known as S-649266) is a novel siderophore cephalosporin antibiotic, which carries an iron-chelating catechol moiety in addition to its improved β-lactamase-resistant cephalosporin core structure. Cefiderocol is designed to exploit the essential bacterial iron siderophore uptake system by hijacking this transporter to gain entry to the bacterial cell, where the cephalosporin part of the molecule binds to penicillin-binding proteins, leading to disruption of bacterial cell wall synthesis and lysis of the bacteria. Furthermore, cefiderocol has been shown to have a high stability against all clinically relevant β-lactamases—bacterial enzymes conferring multi-drug resistance (Ito et al., 2016; Ito-Horiyama et al., 2016; Kohira et al., 2016).

Originally co-developed by Shionogi and GSK, in November 2015 both companies decided to end this collaboration agreement and to independently develop and commercialize this class of novel cephalosporin antibiotics. As of March 2017, both companies are advancing cefiderocol for use against Gram-negative bacterial infections for the global market, with Shionogi's cefiderocol in Phase III, and GSK's GSK3342830 in a first-in-human Phase I clinical trial in healthy volunteers in Australia (GlaxoSmithKline, NCT02751424; Shionogi, NCT02714595). GlobalData assumes that GSK is conducting independent Phase I clinical trials of GSK3342830 in order to market it in Europe, China, and the US, while Shionogi is likely to target all 7MM excluding China. Indeed, based on Shionogi's successful Phase II RCT, where S-649226 met all pre-specified endpoints and showed superiority to imipenem/cilastatin at test of cure (TOC) criteria, the company is planning on submitting a NDA to the FDA in 2017 (Shionogi, press release, January 12, 2017).

Table 46 presents a product profile for cefiderocol.

Table 46: Product Profile – Cefiderocol

Molecule	Cefiderocol
Anticipated Launch Date	US: 2019; 5EU: 2020; Japan: 2019
Therapeutic Class	Siderophore cephalosporin
Alternative Brand Names	S-649266, GSK3342830
Developer	Shionogi
Marketing Partner	N/A (Royalty agreement with GSK)
Targeted Indication (based on clinical trials)	Gram-negative bacterial infections
Targeted Patient Pool (based on clinical trials)	Patients with sepsis caused by Gram-negative bacteria
Potential Clinical Positioning	First-line treatment alternative to other Gram-negative antibiotics
Potential Commercial Positioning	Shionogi is a Japan-based pharmaceutical company with various marketed products in Japan and the US, but no marketed products in the 5EU. S-649226, due to its high stability against β-lactamases and the increasing incidence of carbapenem multidrug resistant Gram-negative bacteria, has the potential to gain significant market share.
Formulation and Dosing	Based on current Phase III clinical trial design, cefiderocol will be administered via IV at 2g over 3 hours every 8 hours for a period of 7 to 14 days
Pricing and Reimbursement	GlobalData anticipates a similar pricing strategy to the marketed antibiotics Zerbaxa (ceftolozoane/tazobactam) and ceftazidime.

Source: GlobalData, Pharma Intelligence Center [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

5EU = France, Germany, Italy, Spain, and UK; N/A = not applicable

9.2.7.2 Efficacy

As of January 2017, Shionogi's cefiderocol has completed Phase II clinical evaluation, showing superiority over imipenem/cilastatin.

As of January 2017, Shionogi's cefiderocol has completed Phase II clinical evaluation, showing superiority over imipenem/cilastatin in its non-inferiority trial in 452 patients with complicated Gram-negative urinary tract infections (cUTIs) (Shionogi, press release, January 12 2017; Shionogi, NCT02321800). Shionogi's S-649226 met its primary efficacy endpoint of composite over clinical cure and microbiologic eradication TOC in 252 patients (72.6%), showing superiority over the comparator imipenem/cilastatin, which achieved a TOC in 119 patients (54.6%), a weighted difference of 18.58% (95% CI, 8.23—28.92). While these trial results are very encouraging for cefiderocol's future clinical development, GlobalData notes that cefiderocol is being evaluated in a broader patient population in its pivotal Phase III RCT, including patients with healthcare-associated pneumonia, bloodstream infections, cUTI, sepsis, and ventilator-associated pneumonia (Shionogi, NCT02714595). GlobalData anticipates the results of this study sometime early 2018.

9.2.7.3 Safety

Based on Shionogi's Phase II RCT in patient with cUTI, cefiderocol presented a favorable safety profile, as fewer patients in the cefiderocol treatment arm experienced AEs than in the imipenem/cilastatin arm, with 40% and 50% of patients experiencing AEs, respectively (Shionogi, press release, January 12 2017; Shionogi, NCT02321800). Shionogi reported the occurrence of SAEs in 14 patients (4.7%) in the cefiderocol treatment arm, compared to 12 patients in the comparator treatment arm (8.1%). As of March 2017, Shionogi hasn't released any further results on the safety of cefiderocol in the Phase II RCT.

9.2.7.4 SWOT Analysis

Table 47 presents a SWOT analysis for cefiderocol.

Table 47: CefiderocolSWOT Analysis, 2017

Strengths	Novel cephalosporin with unique Trojan-horse-like uptake ability and high stability against β-lactamase.
	Cefiderocol is directly evaluated in sepsis patients, making it more likely that it might become a first-line treatment option for bacterial infection control.
Weaknesses	Entry into the bacterial cell is dependent on iron binding and uptake through iron transport channels, therefore high doses of antibiotic are potentially required to saturate *in vivo* iron levels.
	Cefiderocol is administered in very high doses (2g every 8 hours), therefore large quantities of this molecule need to be synthesized.
	Because of its activity against multi-drug-resistant bacteria, cefiderocol is not likely to be used as first-line antibiotic from an antibiotic stewardship perspective—withholding antibiotics against difficult-to-treat bacterial infections reduces the chances of evolving resistance.
Opportunities	The biggest opportunity for cefiderocol lies in the increasing incidence of Gram-negative pathogens causing sepsis.
Threats	Gram-negative bacteria becoming resistant to this treatment.
	GSK could start competing in the same markets as Shionogi if royalty payments are lower than potential commercial gain through sales.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

9.2.8 Toraymyxin (PMX-20R)

9.2.8.1 Overview

Toraymyxin (also known as PMR-20R) is an extracorporeal direct hemoperfusion adsorption column of polystyrene fibers coated with the antibiotic polymyxin B designed to bind and remove bacterial endotoxin from the bloodstream in patients diagnosed with sepsis and septic shock. The product is currently marketed in Japan and the 5EU by Japan-based Toray Industries. Marketing and commercialization rights of Toraymyxin for the US are currently being pursued by Spectral Medical, which holds an exclusive distribution agreement in North America (Spectral Medical, press release,

March 25, 2009; Spectral Medical, press release, November 22, 2010). Spectral is leveraging its own EAA—the only FDA-approved diagnostic to aid in the risk assessment of sepsis patients on their first day of ICU admission—to specifically target patients that are most likely to benefit from using the hemoperfusion device.

In the 5EU and Japan, GlobalData's primary research indicated that Toraymyxin is not an established treatment option for managing sepsis and septic shock patients, despite being approved for this indication. Experts cited the product's high cost and the lack of a large, well-controlled clinical trial in a specific sepsis patient population as major reasons for its slow uptake. GlobalData's extensive primary and secondary research identified Italy as major market for Toraymyxin, which became popular after the release of the positive results of the early-terminated EUPHAS RCT, which included 64 patients, 1:1 randomized to Toraymyxin and SOC (Antonelli et al., 2015; Cruz et al., 2009; St. Bortolo Hospital, NCT00629382).

"The lack of a large, properly-controlled clinical trial is the reason why [Toraymyxin] hasn't picked up widespread use."

EU Key Opinion Leader

Although the preliminary results of Spectral's pivotal Phase III trial (EUPHRATES) indicated that Toraymyxin failed to show statistically significant treatment benefit in terms of 28 day mortality compared with placebo, a correlation of reduced mortality as a function of the amount of endotoxin removed, as well as improvement in overall cardiovascular function, motivated Spectral to pursue FDA approval for septic shock patients with endotoxemia (Spectral Medical Inc, press release, 23 February 2017; Spectral Diagnostic Inc, NCT01046669). As of May 2017, Toraymyxin is FDA-approved in select hospitals under the expanded access program; final decisions about a potential market approval for the US are outstanding (Spectral Medical Inc, press release, May 31, 2016). Experts interviewed by GlobalData were not optimistic about the future prospect of this intervention in sepsis and septic shock patients.

"I'm intrigued with the prospect of removing endotoxin [using Toraymyxin]. What I like about their trial is they specifically target people with high endotoxin activity. I think that's a strong aspect of their clinical trial. I don't know how important it is to actually remove endotoxin. The reason why I say that is the previous 2,000-patient trial with Eisai's Eritoran, which is a very potent inhibitor of endotoxin, saw absolutely no benefit at all…I think the Toray filter does what it's supposed to do and I like the design [of the RCT, specifically targeting people with high endotoxin activity,] but at the end of the day I've become more cynical of how important endotoxemia is because of my clinical experience with a trial [investigating a] drug with very potent ability to block endotoxins. It didn't work."

US Key Opinion Leader

"Timeline [of disease progression] is also extremely important. By the time you get patients on the filter it may not matter because downstream cascades have already happened and they are already in a hyper-inflammatory state. The other thing is often when you give antibiotics and fluids the endotoxin levels come down quite quickly so your target is actually no longer there. That being said, all the open label and small clinical trial data that was comprised in the meta-analysis showed a statistically significant benefit to the Toraymyxin filter. So I think I'm definitely happy that the trial's been done and I'm going to stay tuned."

US Key Opinion Leader

Table 48 presents a product profile for Toraymyxin.

Table 48: Product Profile – Toraymyxin

Brand (Device)	Toraymyxin (polymyxin B extracorporeal direct hemoperfusion adsorption column)
Anticipated Launch Date	US: early 2018; 5EU and Japan: marketed
Therapeutic Class	Hemofiltration device
Alternative Brand Names	PMX-20R
Developer	Spectral Diagnostics (US — licensed from Toray Industries); Estor (Italy — licensed from Toray Industries); Ferrer Farma (Spain — licensed from Toray Industries)
Marketing Partner	N/A
Targeted Indication (based on clinical trials)	GlobalData expects Toraymyxin to be indicated for the treatment of septic shock patients with endotoxemia, which is caused by Gram-negative infections.
Targeted Patient Pool (based on clinical trials)	GlobalData expects Toraymyxin to be predominately prescribed in Gram-negative bacterial-induced septic shock patients who have an EAA of greater than or equal to 0.60 EAA units. Patients who have end stage renal disease that require chronic dialysis will not qualify to receive treatment, as this is one of the major exclusion criteria in the pivotal Phase III trial.
Potential Clinical Positioning	Toray Industries' partners will be looking to position Toraymyxin as the first product in the sepsis space that directly targets an underlying cause of the disease—endotoxins that induce the hyper-inflammatory immune response that drives organ failure.
Potential Commercial Positioning	As there are currently no marketed products for sepsis and septic shock, when Toraymyxin gains approval it will not have any direct competition in the hemofiltration therapy class that treats septic shock patients with high amounts of endotoxin in the blood. GlobalData expects Toray Industries' partners will want to leverage their dominant position to drive the market penetration in the 7MM, specifically in septic shock patients with endotoxemia.
Formulation and Dosing	GlobalData expects two Toraymyxin PMX-20R cartridges (PMX cartridges) to be administered approximately 24 hours apart. Each treatment will target two hours with a minimum of one and half hours, at a flow rates of approximately 100mL/minute (range 80 to 120mL/minute).
Pricing and Reimbursement	GlobalData expects Spectral Diagnostics to seek premium pricing because Toraymyxin satisfies a major unmet medical need.

Source: GlobalData: Pharma eTrack [Accessed March 1, 2017]; primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan; N/A = not applicable

9.2.8.2 Efficacy

A pivotal Phase III study comparing the safety and efficacy of Toraymyxin with a sham comparator control, more commonly referred to as the EUPHRATES trial, was initiated in 2010 by Spectral Diagnostics in the US and Canada (Spectral Diagnostics Inc., NCT01046669). This trial, which enrolled 450 patients randomized to receive either Toraymyxin hemoperfusion treatment or SOC, measured all-cause 28 day mortality in subjects with septic shock who had high levels of endotoxin (defined as EAA ≥0.60 EAA units). As of May 2017, the results of this RCT have not been published, but Spectral announced that Toraymyxin failed to show statistically significant treatment benefit in terms of all-cause 28 day mortality compared with placebo (Spectral Medical Inc, press release, February 23, 2017; Spectral Diagnostic Inc, NCT01046669). However, the study did show reduced mortality in subjects with high endotoxin levels, as well as an improved cardiovascular health. Experts interviewed by GlobalData expressed their disappointment with the study results reported thus far.

Experts interviewed by GlobalData expressed their disappointment with Toraymyxin's study results reported thus far.

"The study's totally, totally negative. There is absolutely nothing there, so that's a shame, but it shows that endotoxin removal alone is not the answer and just eliminating endotoxin with an filtration system may not work. It's not a failure of the conduct of the trial. The trial was well done. It's clearly something that doesn't work."

EU Key Opinion Leader

"Toraymyxin is not cheap! …. But there is evidence to show that it [Toraymyxin] is effective in stabilizing blood pressure and relieving shock. I use it [Toraymyxin] in cases where blood pressure cannot be stabilized. In cases where blood pressure does not stabilize even after using fluid resuscitation or norepinephrine, but that is probably in less than 10% of cases."

Japan Key Opinion Leader

Up until the EUPHRATES trial, most clinical efficacy evidence relied on retrospective, meta-analyses, or small RCTs that failed to achieve statistical significant results (Antonelli et al., 2015; Cruz et al., 2007; Cruz et al., 2009; Mitaka and Tomita, 2011).

A 2007 meta-analysis, which included prospective and retrospective observational studies, pre-and post-intervention design, and RCTs, was performed to evaluate the effectiveness of Toraymyxin in sepsis (Cruz et al., 2007). The study concluded that Toraymyxin appears to have favorable effects on MAP, dopamine use, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio, and mortality. There was significant inter-trial heterogeneity for the MAP and dopamine/dobutamine requirements, which become non-significant when analysis was stratified for baseline MAP.

Publication bias, lack of blinding, and suboptimal method quality were identified as failures in all publications reviewed.

Table 49 summarizes the efficacy of Toraymyxin based on physiological end points by treatment group at baseline and 72 hours.

Table 49: EUPHAS Trial — Toraymyxin Physiological End Points by Treatment Group at Baseline and 72 Hours

Clinical Outcomes	Toraymyxin Mean (n = 34) (95% CI)			Conventional Therapy Mean (n = 30) (95% CI)		
	Baseline	72 Hours	P-value	Baseline	72 Hours[A]	P-value
MAP, mmHg	76 (72–80)	84 (80–88)	0.001	74 (70–78)	77 (72–82)	0.37
Inotropic score	29.9 (20.4–39.4)	6.8 (2.9–10.7)	<0.001	28.6 (16.6–40.7)	22.4 (9.3–35.5)	0.14
Vasopressor dependency index, mm Hg-1	4.3 (2.7–5.9)	0.9 (0.3–1.5)	<0.001	4.1 (2.3–6.0)	3.3 (1.3–5.3)	0.26
PaO2/FiO2	235 (206–265)	264 (236–292)	0.049	217 (188–247)	228 (199–258)	0.79

Source: GlobalData; adapted from Cruz et al., 2009

A In the conventional therapy group, 3 patients died before 72 hours (n = 27)

Table 50 summarizes change in SOFA scores by treatment group after 72 hours.

Table 50: EUPHAS Trial — Change in SOFA Scores by Treatment Group After 72 hours

Δ in mean SOFA score	Toraymyxin (n = 34) (95% CI)	Conventional Therapy (n = 30) (95% CI)	P-value
Total	-3.4 (-4.4 to -2.4)	-0.1 (-1.7 to 1.5)	< 0.001
Cardiovascular	-1.7 (-2.4 to -1.0)	-0.7 (-1.2 to -0.2)	= 0.04
Renal	-0.3 (-0.7 to 0.1)	0.06 (0.1 to 1.1)	= 0.01
Respiratory	-0.1 (-0.4 to 0.2)	-0.1 (-0.5 to 0.3)	= 0.97

Source: GlobalData; Cruz et al., 2009

Table 51 summarizes event-free days and days spent in hospital by treatment group.

Table 51: EUPHAS Trial – Event-Free Days and Days Spent in Hospital by Treatment Group

Finding	Toraymyxin Mean Days (n = 34) (95% CI)	Conventional Therapy Mean Days (n = 30) (95% CI)	P-value
RRT-free	31.6 (24.6–38.6)	26.7 (13.4–40.3)	= 0.61
Mechanical ventilation-free	21.4 (15.4–27.3)	17.0 (8.5–25.3)	= 0.47
Length of ICU stay	20.3 (15.0–25.5)	18.3 (8.8–27.8)	= 0.72
Length of Hospital stay	37.2 (29.6–44.8)	32 (18.0–46.0)	= 0.53

Source: GlobalData; Cruz et al., 2009

The EUPHAS trial suggested that this hemofiltration device could potentially significantly reduce mortality in sepsis and septic shock patients with endotoxemia; however, no structured data collection had been carried out to determine which patient populations the device holds the most promise to treat. The results from this study jumpstarted the use of the hemofiltration device in Italy and also kick-started a collaborative registry of clinical data where investigators can submit data for patients they have treated with the device. This data collection was named the Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock 2 (EUPHAS2) project (Antonelli et al., 2015). No inclusion and exclusion criteria or therapeutic constraints were imposed to highlight the borderline practice in the selection of patients for Toraymyxin and to capture all available clinical data for sepsis patients who received hemofiltration with this device. The EUPHAS2 project agreed with the outcomes of the EUPHAS trial that the device would benefit sepsis patients with Gram-negative infections in the abdomen. The project also concluded that specific studies focused on patients with Gram-negative infections of non-abdominal origin are needed before recommending treatment with Toraymyxin.

A 2011 meta-analysis was performed to evaluate the efficacy and mechanism of Toraymyxin in patients with septic shock (Mitaka and Tomita, 2011). This literature review identified that the hemofiltration device adsorbed monocytes, activated neutrophils, anandamide, and endotoxin through direct covalent bonding, hydrophobic and ionic interactions, and hydrodynamics. Furthermore, the device reduced blood concentrations of inflammatory cytokines, plasminogen activator inhibitor 1, and adhesion molecules. The following clinically relevant outcomes were also reported to be improved in patients receiving Toraymyxin hemoperfusion: increased blood pressure, reduced requirements for vasopressive/inotropic agents, increased pulmonary oxygenation, and reduced mortality, endothelial damage, pro-apoptotic activity, and immunosuppression. The study concluded that the beneficial effects may be attributable to the direct adsorption of endotoxin, monocytes, activated neutrophils, and anandamide, as well as to an indirect decrease in inflammatory cytokines and other mediators.

A major issue with meta-analyses is that trials with positive results are more likely to be published than those with negative or neutral results. Furthermore, in Japan, where Toraymyxin has been available since 1994, only a fraction of the patients treated have been included in clinical research publications (Cruz et al., 2007). Therefore the results of any review are limited by the quality of the data obtained in the smaller studies. Also, the subset of patients studied in the published reports is extremely diverse. This is why the EUPHRATES trial and its results are pivotal to the widespread use of Toraymyxin, as there has not been a large-scale, well-controlled trial in specific patient populations with clinically relevant endpoints to date.

"It's not widely used because the level of evidence we have is minimum [and] it's quite expensive. Another reason is the fact that you have to use it when LPS is around and you don't know when LPS is around. [Furthermore], if the LPS that you test for is around, [you don't know if it] is biologically active and biologically responsive for the treatment... The [EUPHRATES] trial is a step in the right direction. I think the treatment will [get] more attention with a clinician because the companion diagnostic will tell you when the endotoxin is around… It would be more user-friendly and the cost would be justified."

EU Key Opinion Leader

"[After the failure of Eritoran] I'm at a loss. I really thought that endotoxemia and endotoxin was a major player in sepsis. [Eritoran] is extremely biologically active in vitro… The trials were designed and run well and I was quite hopeful. I'm just at a loss to why there's no benefit [when patients were given Eritoran]. Unless endotoxin doesn't matter all that much... I thought the trial was conducted well. I think it answered the questions [it was supposed to answer], which raises the question about endotoxin."

US Key Opinion Leader

9.2.8.3 Safety

Overall, Toraymyxin possesses a strong safety profile when considering data obtained from meta-analyses and the EUPHAS trial (Antonelli et al., 2015; Cruz et al., 2007; Cruz et al., 2009; Mitaka and Tomita, 2011). Furthermore, the device has been used safely in Japan for over two decades and in the 5EU since 2002. The 2007 meta-analysis paper stated that very few AEs were reported among the included publications. The publication specifically stated that only two studies reported AEs, suggesting that the treatment is generally well tolerated. However, these publications included small sample sizes, which impair the ability to observe any rare but serious AEs (Cruz et al., 2007).

Specific AEs reported included clotting of the device in 4 out of 21 cartridges and hypersensitivity (erythema) in 2 out of 35 patients (Cruz et al., 2007). Potential AEs include thrombocytopenia and hypotension during hemofiltration, but the observed AEs associated with the device were minimal and similar to those that would be encountered for any extracorporeal therapy in the ICU (Cruz et al., 2007; Cruz et al., 2009). Polymyxin B has known nephrotoxic and neurotoxic effects, however these are theoretically avoided because the polymyxin B is not released into the circulating blood; this was indirectly corroborated since no AEs have been reported indicative of nephrotoxicity (cellular casts) or neurotoxicity (irritability and progressive weakness) (Cruz et al., 2007).

Overall, these data strongly suggest that Toraymyxin is safe in septic shock patients with associated endotoxemia.

9.2.8.4 SWOT Analysis

Table 52 presents a SWOT analysis for Toraymyxin.

Table 52: Toraymyxin SWOT Analysis, 2017

Strengths	Toraymyxin is the first product to target an underlying causative agent of the hyper-inflammatory response that causes sepsis, severe sepsis, and septic shock and is not just more supportive therapy. Toraymyxin has been marketed in Japan and the 5EU since 1994 and 2002, respectively. Since its approval in Japan two decades ago, Toraymyxin has possessed a strong safety profile. Clinical studies and meta-analyses provide additional evidence of its safety. Spectral Diagnostics leverages an EAA companion diagnostic, which can increase the use of the device and aid in proper patient identification once it's licensed in the US. Dialysis and extracorporeal therapies have been routinely used, therefore it is clinically feasible that this technique can be safely and routinely applied to remove harmful endotoxins from the blood that drive the underlying septic condition.
Weaknesses	Target patients would include only be those with sepsis, severe sepsis, and septic shock who have endotoxemia—those who are septic due to a Gram-negative bacterial infection and have elevated levels of endotoxin. Therefore, therapy would not fit into the generalized sepsis treatment algorithm. GlobalData anticipates Toraymyxin will not be indicated for use in patients with end-stage renal disease that requires chronic dialysis, because this is one of the major exclusion criteria for the current Toraymyxin Phase III trial being performed by Spectral Diagnostics. Eisai's Eritoran, which blocks endotoxin-activated TLR-4 signaling, was unsuccessful in a pivotal Phase III trial. GlobalData's primary research indicated that this may mean endotoxin is not as important in sepsis patients as it once was thought, and therefore may not bode well for Toraymyxin demonstrating a mortality benefit in the current EUPHRATES trial.
Opportunities	There are currently no marketed products to treat patients with sepsis, severe sepsis, and septic shock—this would be the first therapy to treat an actual underlying cause of the septic condition, rather than being a supportive therapy. Therefore, when approval is reached, considerable coverage will be given to the product launch, generating a buzz in the overall sepsis market to help drive sales and carve out market share. Spectra Diagnostics may leverage its EAA companion diagnostic to increase the use of Toraymyxin once it is licensed in the US. Toray and its partners can expand the device's indication in Japan and the 5EU by conducting post-marketing studies in additional patient populations. Increase uptake in the 5EU by demonstrating efficacy in specific patient populations.
Threats	Gambro-Lundia's Cascade Device/Oxiris is a hemofiltration device being developed to treat sepsis patients. Toraymyxin has been available in the 5EU since 2002, and hasn't seen widespread use. GlobalData expects this to change only if the EUPRHATES trial sees positive Phase III results, as this will be the first large, well-controlled clinical trial in a specific and clinically relevant sepsis patient population. Cytosorb is planning to release a CytoSorb XL column that is able to bind and remove endotoxin from the patients' bloodstream.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report
5EU = France, Germany, Italy, Spain, and UK

9.2.9 CytoSorb

9.2.9.1 Overview

CytoSorbents is marketing CytoSorb, an extracorporeal hemoadsorbing column designed to bind hydrophobic substances with an average molecular weight in the range of up to 55kDa—a molecular mass range thought to be representative of the majority of cytokines—which is CE-marked in over 32 countries, including the 5EU, but not in Japan or the US (CytoSorbents, 2017a).

CytoSorb's major market is Germany, where the company reported sales of almost $5m in 2016.

CytoSorb's major market is Germany, where the company reported sales of almost $5m in 2016 (CytoSorbents, 2017b). CytoSorb is marketed for life-threatening inflammation including trauma, burn injury, cytokine release syndrome, liver failure, surgical complications, pancreatitis, lung injury, influenza, and sepsis. In the US, CytoSorbents is seeking FDA approval for CytoSorb in cardiac surgery (CytoSorbents, NCT02566525). As of May 2017, CytoSorbents is not pursuing clinical development for CytoSorb in sepsis or septic shock patients, indicating that the company disapproves of the FDA's insistence on the demonstration of a mortality benefit in order gain marketing approval for sepsis and septic shock (CytoSorbents, 2017a).

Table 53 presents a product profile for CytoSorb.

Table 53: Product Profile – CytoSorb

Brand	CytoSorb
Anticipated Launch Date	TBD
Therapeutic Class	Hemoadsorption column
Developer	CytoSorbents
Marketing Partner	Aferetica SRL (Italy), Fresenius Medical Care (France), L.IN.C. Medical Systems (UK), Palex Medical SA (Spain), Direct (Germany)
Targeted Indication (based on clinical trials)	Septic shock, cardiac surgery
Targeted Patient Pool (based on clinical trials)	CytoSorb is indicated for the prevention and treatment of life-threatening inflammation in the ICU, including septic shock, and in addition is indicated for cardiac surgery.
Potential Clinical Positioning	CytoSorbents is continuing to promote the use of its hemoadsorption column CytoSorb in the 5EU, while it is planning for further clinical efficacy studies for cardiac surgery in the US in order to gain market approval from the FDA.
Potential Commercial Positioning	GlobalData anticipates that CytoSorbents will focus on the 5EU, where it is competing with Spectrals' Toraymyxin hemoperfusion column. However, unlike Toraymyxin, which is limited to the treatment of Gram-negative sepsis and septic shock, CytoSorb can be beneficial in all sepsis and septic shock patients, as it is removing both pro- and anti-inflammatory cytokines from the bloodstream.
Formulation and Dosing	CytoSorbents indicated that one treatment for sepsis or septic shock would involve the usage of up to three cartridges.
Pricing and Reimbursement	GlobalData estimated pricing for CytoSorb based on investor presentations and primary research with KOLs across the 7MM.

Source: GlobalData, Pharma Intelligence Center [Accessed June13, 2017]; primary research interviews and surveys conducted with KOLs and high-

prescribing physicians in the countries included in this report
N/A = not applicable
5EU = France, Germany, Italy, Spain, and UK; 7MM = US, 5EU, and Japan

9.2.9.2 Efficacy

In Europe, the approval of medical devices with similar function as already approved instruments is warranted by a simple CE certification, and the manufacturer is not obliged to demonstrate efficacy in RCTs (Gehling and Tryba, 2016). Clinical efficacy of CytoSorb usage in septic shock patients derives from case series, however GlobalData notes that definitive conclusions about CytoSorb's efficacy can't be drawn without properly conducted RCTs. Experts urge the medical community to use scientific judgement about efficacy drawn from these studies before using CE approved medical devices for sepsis and septic shock (Gehling and Tryba, 2016; Kogelmann et al., 2017).

While these case studies are not sufficient to draw conclusions about CytoSorb's effect on mortality, the available evidence seem to indicate that CytoSorb therapy lowers vasopressor requirements and furthermore seems to improve vascular barrier function, thereby reducing vascular leakage (David et al., 2017; Kogelmann et al., 2017). Human plasma samples from septic shock patients taken before and after treatment with CytoSorb showed an improved vascular endothelial integrity when applied to human umbilical vein endothelial cells *ex vivo* (David et al., 2017).

9.2.9.3 Safety

Based on observational case studies, CytoSorb is well tolerated and no device-related AEs were reported (Kogelmann et al., 2017). GlobalData notes that CytoSorb's safety profile should be further validated in large RCTs; in particular, its effect on plasma levels of antibiotics warrants further studies (David et al., 2017).

9.2.9.4 SWOT Analysis

Table 54 presents a SWOT analysis for CytoSorb.

Table 54: CytoSorb SWOT Analysis, 2017

Strengths	CytoSorb has been marketed in 32 countries, including the 5EU. Although CytoSorb has not been assessed in RCTs, physicians, particularly in Germany, are very familiar with this therapeutic in the treatment of septic shock. CytoSorb is designed to easily integrate within existing RRT therapy devices. CytoSorb is more cost-efficient than competitors such as Toraymyxin, which is 10 times more expensive. Dialysis and extracorporeal therapies have been routinely used, therefore it is clinically feasible that this technique can be safely and routinely applied to remove the harmful endotoxins that drive the underlying septic condition from the blood.
Weaknesses	Therapy with the CytoSorb column is not supported by clinical evidence in controlled RCTs. Efficacy was only demonstrated in case studies and in the absence of control cohorts. CytoSorb was been shown to reduce the plasma concentration of merepenem (76%), piperacillin (58%), and clindamycin (15%) in one case study. GlobalData notes that this observation might result in additional drug monitoring to ensure sufficient antimicrobial plasma concentrations are achieved during CytoSorb therapy.
Opportunities	CytoSorbents is currently exploring a new column, called CytoSorb XL, which is designed to bind endotoxin from the bloodstream. GlobalData expects this device to compete for patient share with Spectral's Toraymyxin once approved. Experts recommend the use of surrogate endpoints over the traditional 28 day mortality. Specifically, experts recommend the use of white blood cell counts, C-reactive protein, PCT levels, and indices of organ dysfunction such as SOFA, SAPS II, and APACHE scores to gauge the clinical efficacy of this intervention in RCTs.
Threats	CytoSorbents has not been validated in large RCTs for sepsis and septic shock, and physicians might not be inclined to use a device with unproven efficacy. Application of CytoSorb justifies the use of therapeutic drug monitoring to ensure appropriate concentrations of antibiotics. The extra cost of monitoring might defer physicians to use this device.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report; David et al., 2017

9.3 Other Innovative Early-Stage Approaches

Table 55 highlights innovative early-stage pipeline drugs, which are not included in our forecast but which experts interviewed by GlobalData have identified as particularly innovative in the treatment of sepsis and septic shock patients.

Table 55: Innovative Early-Stage Therapies for Sepsis and Septic Shock, 2017

Product Name	Therapy class	Mechanism of Action	Company	Latest Developmental Stage
IFX-1	Anti-C5a mAb	Anti-inflammatory	InflaRx	Phase IIa for sepsis
LB-1148	Serine protease inhibitor	Autodigestion inhibitor	Leading BioSciences	Phase II
ALT-836	Anti-tissue factor mAb	Anti-coagulant/anti-inflammatory	Altor BioSciences	Phase II
Salvecin (tosatoxumab)	mAb to *S. aureus* alpha toxin	Binding and inactivation of *S. aureus* alpha toxin	Aridis	Phase I/IIa
Nivolumab		PD-1 antagonist	BMS	Phase I
LGT-209	Lipid modulator	Clearance of endotoxins, anti-inflammatory	Cyon	Phase I
Adrecizumab	anti-adrenomedullin mAb	Stabilization of circulation and renal function	Adrenomed AG	Phase II

Source: GlobalData, Pharma Intelligence Center [Accessed May 3, 2017]; Wang et al., 2015

9.3.1 IFX-1

IFX-1, a first-in-class anti-human C5a mAb targeting activation products of the complement system, is being developed by the Germany-based InflaRx GmbH. Although activation products, such as C5a play essential roles in the initial defense against pathogens, in sepsis, a disproportionate activation of the complement system leads to a multitude of organ dysfunctions. The most potent of these inflammatory response triggering products is C5a, which binds to neutrophils through C5aR receptors and induces a strong immune response, contributing to cardiovascular shock, DIC, ALI, AKI, ARDS, and multiple organ dysfunction syndrome (MODS) through generation of oxygen-radicals and the release of granular digestive enzymes (Guo and Ward, 2006).

After InflaRx's successful Phase IIa clinical evaluation of IFX-1 in sepsis patients in December 2015, the company decided to halt clinical development in sepsis and focus its development efforts in cardiac surgery, severe CAP, hidradenitis suppurativa, and another undisclosed chronic inflammatory auto-immune disease (InflaRx, press release, January 4, 2017; InflaRx, NCT02246595).

GlobalData notes that InflaRx's decision to hold development of IFX-1 in septic shock patients was guided by insufficient funding for larger Phase III trials in sepsis patients, a common problem of the

current clinical trial design, which evaluates mortality endpoints in a disease with overall decreasing mortality rates, leading to higher patient recruitment rates in order to show statistically significant efficacy over placebo groups. Furthermore, experts interviewed by GlobalData expressed a general pessimism about therapeutic approaches interfering with the anti-inflammatory immune response in sepsis, as over 100 clinical trials aimed at anti-inflammatory drugs in a span of over 40 years have failed to show statistically significant efficacy in sepsis and septic shock patients (Marshall, 2014).

Although InflaRx's Phase IIa trial was only aimed at the safety and PK/PD of IFX-1 in sepsis patients, IFX-1 achieved statistically significant C5a inhibition without affecting C5b compliment—an essential complement factor of the terminal membrane attack complex (MAC) in the lysis of encapsulated pathogens such as meningococci—when IFX-1 was administrated 3.5 hours after initial screening (InflaRx, press release, January 28 2016). Furthermore, IFX-1 was reported as well tolerated, with a favorable PK/PD profile and no evidence of auto-antibody generation (InflaRx, press release, January 4, 2017; InflaRx, NCT02246595).

GlobalData notes that InflaRx's Phase IIa study of IFX-1 in sepsis patients not only demonstrated its potential benefit as an anti-inflammatory drug in sepsis therapy, but also showed that timing of administration of the drug is essential, as measurements of a panel of pro-inflammatory cytokines (IL-6, IL-8,IL-12, and TNF-alfa) showed a narrow time window of opportunity for the administration of anti-inflammatory therapeutics in sepsis patients. GlobalData notes that the 3.5 hour window of administration of IFX-1 presented the minimal time to complete the consent paperwork to participate in this clinical trial in Germany. As early administration of IFX-1 intervention is essential for this therapeutic to show benefit, it is not surprising that InflaRx is exploring IFX-1 as a prophylactic intervention for infection after cardiac surgery (InflaRx, NCT02866825). Sepsis following surgical intervention is one of the most common causes of death; GlobalData expects that IFX-1, while not directly indicated for sepsis treatment, will help to reduce the incidence of sepsis and septic shock resulting from complications due to cardiac surgery if IFX-1 is approved for this indication as pre-emptive medication.

9.3.2 LB1148 (tranexamic acid)

Leading BioSciences' Phase II RCT of LB1148 (tranexamic acid), a serine protease inhibitor formerly known as InflammaGen Shok-Pak, in patients with septic shock, failed to recruit patients and was terminated in June 2016 (Leading BioSciences, NCT02317549). Leading BioSciences has since started a Phase II trial of LB1148 in patients undergoing bowel resection. GlobalData anticipates that the autodigestive enzyme inhibitor LB1148 treatment will not be indicated for sepsis and septic shock during the forecast period.

KOLs interviewed by GlobalData have identified LB1148 as an exciting new approach to inhibit the phenomenon known as "autodigestion," which occurs during sepsis and septic shock when the mucosal barrier and lining of the intestine break down due to extended periods of ischemia and hypoperfusion in the gut. The escaping digestive enzymes come into contact with the organs and tissue outside the digestive tract, the bloodstream, and the lymphatic system, and the patient essentially begins to digest themselves. This phenomenon can occur during septic shock and multi-organ failure (Leading BioSciences, 2014a; Lee et al., 2012).

Along with developing LB-1148, Leading BioSciences is also developing a rapid-use, handheld, point-of-care breath or blood diagnostic shock assay known as AnaZyme. The company has aspirations of launching this as a tandem diagnostic to be used in combination with LB-1148 (Leading BioSciences, 2014b). The firm is looking to use blood or breath samples to measure the presence and severity of inflammatory activity so it can be diagnosed prior to the onset of shock.

"I think the autodigestion that occurs in the gut is a novel mechanism. In the setting of septic shock, they have some pilot data and it's a hypothesis that blocking those proteases is going to help... I'm excited. I can't say I think it's going to work or it's not going to work. That's why we do these experiments, to get the answer. I think it is at least a novel attempt."

US Key Opinion Leader

"I frankly had to go do the literature search to digest the autodigestion theory. I've been involved in sepsis research for 16 years and I had never heard of it. I follow the pathophysiologic story. There aren't really any good biomarkers [for autodigestion], which will complicate things. But it's a scientifically plausible hypothesis. You've got to test it with an agent that would reverse it. There's lots of intriguing animal data, which is always good, but that's been true for a lot of things. It certainly deserves to be tested."

US Key Opinion Leader

9.3.3 ALT-836

ALT-836, a recombinant chimeric anti-tissue factor (anti-TF) antibody, was originally developed by Sunol Molecular Corporation under the name of Sunol cH36 as part of their tissue factor antagonist program for the treatment of inflammatory diseases and cancer. In March 2005, Tanox acquired Sunol's tissue factor antagonist program and continued development of Sunol cH36 under the acronym TNX-832 (Tanox, press release, March 28, 2005). After the subsequent buyout of Tanox by Genentech, development and commercialization rights for TNX-832 were acquired by its current developer Altor BioSciences (Altor, press release, February 12, 2008).

As an anti-TF antibody, ALT-836 exerts its anti-coagulative and anti-inflammatory activity by binding and inactivating human TF or TF-factor VIIa complex, thereby preventing initiation of the extrinsic coagulation pathway, which otherwise would result in the abnormal coagulation and systemic inflammation commonly seen in sepsis patients (Altor BioScience Corporation, 2014; Morris et al., 2012).

As an anti-TF antibody, ALT-836 exerts its anti-coagulative and anti-inflammatory activity by binding and inactivating human TF or TF-factor VIIa complex.

As of January 2013, ALT-836 has completed Phase II clinical evaluation in 60 patients with ALI or ARDS, and although Altor announced the initiation of second Phase II follow-up study funded by a National Heart Lung and Blood Institute (NHLBI) Phase II Competing Renewal Grant, GlobalData could not find evidence of any further development of ALT-836 in sepsis or cancer patients (Altor, press release, May 23, 2011; Altor, NCT00879606). Based on extensive primary and secondary research, GlobalData infers that Altor is concentrating its efforts on the development of ALT-803, an IL-15 agonist aimed at natural killer (Nk) and T cell stimulation in cancer and HIV patients.

Early Phase I clinical development efforts of ALT-836 across a range of 0.06 to 0.1mg/kg in 18 patients with suspected or proven bacterial infection and infection-induced ALI or ARDS—where ALI/ARDS was defined as acute bilateral pulmonary infiltrates on a chest X-ray consistent with the presence of pulmonary edema, a PaO_2/FiO_2 of 100 to 300mm Hg, and the clinical absence of left atrial hypertension—showed a dose-dependent exposure to ALT-836 across the infusion range, and no major bleeding events or anti-ALT-836 antibody responses (Altor, NCT01438853; Altor, NCT00879606; Morris et al., 2012).

"The preliminary work clearly shows that tissue factor is at the center place in the early pathophysiology of acute lung injury or ARDS."

EU Key Opinion Leader

"We tried activated protein C in ARDS. It didn't have any benefit. That's a good blocker of coagulation. I guess I would say I'm not very excited about [ALT836's ability to demonstrate a benefit in ARDS patients]."

US Key Opinion Leader

"The tissue factor antibody might be interesting because it's really an important key point in the pathophysiology of acute lung injury or ARDS."

EU Key Opinion Leader

Table 56 outlines key hospital indices from ALT-836's Phase I study.

Table 56: Hospital Indices — ALT-836

Hospital	Placebo Mean (SD) (n = 3)	0.06mg/kg ALT-836 Mean (SD) (n = 5)	0.08mg/kg ALT-836 Mean (SD) (n = 5)	0.10mg/kg ALT-836 Mean (SD) (n = 5)
Days on ventilator	25.5 (± 25.7)	14.1 (± 23.1)	15.5 (± 10.4)	6.4 (± 2.6)
Days in ICU	29.2 (± 26.5)	15.2 (± 22.1)	16.4 (± 10.1)	7.1 (± 2.4)
Days in hospital	33.3 (± 29.1)	29.9 (± 45.6)	25.4 (± 12.6)	16.7 (± 10.5)
ICU free days at study day 28[a]	8.7 (± 8.1)	17.4 (± 9.8)	8.4 (± 9.0)	20.0 (± 2.4[C])
Ventilator free days at study day 28[b]	11.0 (±9.8)	18.8 (± 10.6)	8.4 (± 11.2)	21.0 (± 3.1)

Source: GlobalData; adapted from Morris et al., 2012
SD = standard deviation
[a] Mean number of days to study day 28 that the patients were not admitted to the ICU. Patients that did not survive to study day 28 were assigned zero ICU-free days.
[b] Mean number of days to study day 28 that the subjects achieved unassisted breathing. Patients that did not survive to study day 28 were assigned zero ventilator-free days.
[C] P < 0.05 compared to placebo group

Data from Altor's Phase I study demonstrated that ALT-836 could be safely administered to patients with sepsis-induced ALI/ARDS. The most frequently observed AE across both the ALT-836 and placebo treatment arms was anemia (Altor BioScience Corporation, NCT014338853; Morris et al., 2012).

Table 57 outlines the key safety data for ALT-836.

Table 57: Safety Profile – ALT-836

Adverse Event	Placebo (n = 3)	0.06mg/kg ALT-836 (n = 5)	0.08mg/kg ALT-836 (n = 5)	0.10mg/kg ALT-836 (n = 5)	Total (n = 18)
Mortality by study day 28 (treatment related)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)
Patients with non-fatal SAEs (treatment related)	2 (1[A])	1 (0)	0 (0)	1 (1[B])	5 (2)
Total number of AEs (treatment related)	20 (2)	18 (3)	29 (5)	20 (6)	87 (16)
Patients with hematuria AEs (treatment related)	0 (0)	2 (2)	2 (2)	5 (4)	9 (8)
Patients with anemia (treatment related)	2 (2)	1 (1)	2 (2)	3 (0)	8 (5)

Source: GlobalData; adapted from Morris et al., 2012
[A] Worsening anemia and empyema reported as possibly related to placebo treatment.
[B] Hypoxic respiratory failure (study day 23) secondary to hospital-acquired pneumonia reported as possibly related to study drug treatment.

9.3.4 Salvecin

Salvecin (tosatoxumab; also known as KBSA301), a human IgG1 mAb targeting *S. aureus* alpha-toxin, was previously developed by Kenta biotech with manufacturing assistance from Rentschler Biotechnologie, before Kenta and all its assets, including KBSA301, was acquired by the privately held biotechnology company Aridis Pharmaceuticals LLC (Aridis, press release, May 10, 2013). The human IgG mAb Salvecin exerts its antimicrobial activity through binding and inactivation of *S. aureus* alpha-toxin, thereby preventing the toxin from forming functional pores for host cell invasion (Aridis, press release, January 5 2017). GlobalData notes that current resistance genes won't provide the bacteria with protection from this antibiotic, as this therapeutic intervention involves a new protective mechanism; therefore, Salvecin is a potential treatment option for MRSA infections.

As of January 2017, Salvecin successfully completed Phase I/IIa of clinical development in 42 patients with hospital-acquired pneumonia or ventilator-associated pneumonia caused by *S. aureus* as adjunctive to current used antibiotics (Aridis, NCT01589185). Aridis announced that Salvecin has met all primary endpoints and no safety concerns were reported (Aridis, press release, January 5, 2017). Based on the positive results from this study, Aridis is planning on proceeding with plans for late-stage development in H2 2017 (Aridis, press release, January 5, 2017).

9.3.5 Opdivo (nivolumab)

In addition to developing an anti-PD-L1 mAb (BMS-936559) for sepsis-induced immunosuppression, BMS is developing its PD-1 mAb blockbuster drug Opdivo (nivolumab) for sepsis-induced immunosuppression in sepsis and septic shock patients. As of December 2016, Opdivo is in Phase I clinical development to assess its safety, tolerability, and pharmacokinetics in 30 patients with sepsis or septic shock and sepsis-induced immunosuppression (BMS, NCT02960854). GlobalData anticipates the completion of this study in H2 2017.

Initial efficacy results of Opdivo in sepsis were derived from a case study where a combination therapy of Immukine (IFN-γ) and Opdivo (nivolumab) showed promising results in reversing fungal sepsis-induced immunosuppression in a woman suffering from severe abdominal mucormycosis (Grimaldi et al., 2017). Physicians in this case study used a panel of biomarkers, including absolute lymphocyte count, HLA-DR expression, and increased PD-1 on T cells to confirm an immunosuppressed state in the patient. GlobalData notes that the entry criteria for Opdivo's Phase I study are stated very broadly as sepsis-induced immune suppression, allowing the use of all the aforementioned biomarkers. Experts emphasized the need to accurately and reliably detect patients in an immunosuppressed state with the use of a panel of biomarkers. The generic Immukine, on the

other hand, has been in Phase III clinical development in sepsis and septic shock patients since November 2012 (Radboud University, NCT01649921). In this trial, Immukine intervention is initiated after noradrenalin dose has been adjusted by over 50%—which is thought to be characteristic of a sepsis-induced immunosuppressed state—in 20 sepsis or septic shock patients. As of April 2017, the trial status remains unchanged with an estimated completion date of December 2016. Based on previous trials by the sponsor and reporting of the previous results, GlobalData anticipates the results of this small RCT sometime in late 2017.

"There is a study starting now from BMS looking at the effects of one of these components [immune-stimulatory drugs like Opdivo] in patients with sepsis. There is a very nice case report of a patient who had mucormycosis, who was about to die from this fungal infection, who totally recovered with this strategy. So we are very excited. It's just one case, but it's a very explicit case. It's quite convincing evidence for this.You may argue that we need to better monitor the degree of inflammatory response in the patient. So, yes, we should do that. We should try to look at pro-inflammatory markers like interleukin-6, like CRP, which is much cheaper, or others, and we should also look at the degree of immunosuppression, HLE or lymphocyte count, for instance. That could help to characterize the patient populations. It is not so easy, although it would be more precision medicine and I can only applaud that. We need to go into what I call personalized medicine and then precision medicine."

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9.3.6 Adrecizumab

Adrecizumab is currently developed by German-based Adrenomed AG and has completed Phase I clinical development in March 2017. Adrenomed is planning a Phase II study in septic shock patients, which GlobalData expects to start in H1 2017, with an estimated completion date of March 2019 (Adrenomed, NCT03085758). Adrenomed is planning to recruit 300 septic shock patients, who are receiving vasopressor therapy for no longer than 12 hours. The primary endpoint of this Phase II study is safety, tolerability, and all-cause 90 day mortality of Adrecizumab administered in two doses (2mg/kg or 4mg/kg) compared with placebo.

Adrecizumab is a first-in-class humanized IgG1 mAb against adrenomedullin, a vasodilator peptide hormone implicated in hemodynamic homeostasis, targeting vascular regulation through maintaining of endothelial integrity and preventing vascular leakage (Adrenomed, press release, March 8 2017; Caironi et al., 2017).

In animal models of sepsis, adrenomedullin therapy remains controversial with both supplementation of exogenous adrenomedullin or reduction of adrenomedullin by mAbs resulting in improved survival

and disease outcome (Caironi et al., 2017). In humans, adrecizumab administered at three doses (0.5, 2.0, and 8.0mg/kg) has been shown to increase the plasma concentration of adrenomedullin while preventing its vasodilatory and blood pressure reducing activity (Adrenomed, press release, March 8, 2017; Adrenomed, NCT02991508). Adrenomed reported no AEs during adrecizumab therapy over a period of 90 days. Adrecizumab's early Phase I evaluation in 24 healthy volunteers demonstrated a good safety profile and the drug was well tolerated (Adrenomed, press release, March 8, 2017; Adrenomed, NCT02991508).

GlobalData notes that past RCTs on endotoxin-lowering interventions, such as Spectral's Toraymyxin, have failed to demonstrate a survival benefit associated with endotoxin clearance. Furthermore, positive results of endotoxin clearance in animal models in terms of increased survival have not translated in human trials. Researchers participating in the ALBIOS study, which examined outcomes of fluid resuscitation with albumin than compared them to resuscitation with crystalloids fluids, showed that a subgroup of acutely critically ill septic shock patients showed high plasma levels of adrenomedullin (Caironi et al., 2017; Fondazione IRCCS Ca' Granda [Ospedale Maggiore Policlinico], NCT00707122). The study demonstrated a correlation of mortality and high levels of adrenomedullin , suggesting the use of adrenomedullin as a biomarker for disease severity, where fluid therapy reduces adrenomedullin to levels correlated with increased survival (Caironi et al., 2017). GlobalData expects that adrenomedullin will be used as biomarker guiding the therapeutic intervention with adrecizumab.

9.3.7 LGT-209

In August 2016, Cyon Therapeutics secured worldwide rights for Novartis' anti-proprotein convertase subtilisin kexin type 9 (anti-PCSK9) mAb LGT-209 for use in SIRS and the prevention and treatment of sepsis. The licensing deal includes regulatory and commercial milestones with undisclosed financial details (Cyon, press release, August 23 2016). Novartis stopped development of LGT-209 due to increasing competition from other PSCK9 mAbs, such as Amgen's evolocumab and Regeneron's alirocumab. LGT-209 has completed Phase I clinical development for hypercholesterolemia, demonstrating a good safety profile and efficacy profile in lowering cholesterol, supporting the hypothesis of increased LPS clearance upon PSCK9 therapy (Novartis, NCT01859455; Novartis NCT01979601). Cyon has initiated a private venture capital round to fund its upcoming Phase II clinical development of LGT-209, and GlobalData expects initiation of clinical development in H2 2017 (Cyon, press release, August 23 2016).

As an anti-PCSK9 mAb, LGT-209 is believed to decrease the plasma concentration of available PCSK9—a key regulator of serum cholesterol levels through targeting liver low-density lipoprotein (LDL)

receptors—thereby increasing hepatic clearance of cholesterol and, most importantly, pathogenic lipids such as LPS by increasing the number of available LDL receptors (Momtazi et al., 2017). Multiple studies have implicated PCSK9 levels with symptoms of sepsis and septic shock, where patients with a partial deletion of the PCSK9 allele showed an increased survival rate (Walley, 2014). Conversely, PCSK9 overexpression in mice has been shown to decrease LPS clearance, increase inflammatory cytokines, and induce sepsis in animal models (Momtazi et al., 2017).

Multiple studies have implicated PCSK9 levels with symptoms of sepsis and septic shock, where patients with a partial deletion of the PCSK9 allele showed an increased survival rate.

9.4 Other Drugs in Development

This section highlights the remaining early stage clinical development pipeline for sepsis and septic shock. Table 58 outlines pipeline products currently in Phase I or Phase II clinical development for sepsis and/or septic shock.

Table 58: Drugs in Development for Sepsis and Septic Shock, 2017

Latest Phase of Development	Company	Product	Indication
PHASE II	TiGenix NV	Cx-611	Sepsis
	Huons Co Ltd	HU-003	Sepsis and septic shock
	Octapharma AG	Pooled plasma (human)	Sepsis and septic Shock
PHASEI	BMS	BMS-986189	Sepsis
	Inotrem SA	Motrem	Septic shock

Source: GlobalData, Pharma Intelligence Center [Accessed May 3, 2017]. Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

9.4.1 Cx-611

TeGenix is developing Cx-611, an allogenic adipose-derived stem cell treatment for sepsis due to community-acquired bacterial pneumonia. As of March 2015, Cx-611 has successfully completed Phase I clinical development in human volunteers, where Cx-611 demonstrated a good safety and tolerability profile with no reported SAEs (TeGenix, press release, March 12 2015; TeGenix, NCT02328612). TeGenix started a Phase Ib/IIa study of Cx-611 for sepsis and severe CAP in January 2017. GlobalData estimates that the study, which is assessing the safety and efficacy of Cx-611 in 180 sepsis patients, will be completed by H2 2017 (TeGenix, EudraCT-2015-002994-39). The efficacy endpoints of this study include a composite of ventilator and vasopressor-free days, and survival at day 28.

Cx-611, as an adult MSC-derived treatment option for sepsis, is thought to derive its beneficial effects through modulation of the immune response by inducing an immunomodulatory effect, while also having a direct antimicrobial effect through the release of antimicrobial peptides (Lombardo et al, 2015). Animal models have shown that MSCs reduce the initial pro-inflammatory response by the

release of anti-inflammatory IL-10 and in addition reduce the bacterial burden through the release of antimicrobial peptides. The effect on the immunosuppressive state of sepsis remains unknown and needs to be further investigated (Lombardo et al., 2015).

9.4.2 HU-003

HU-003—a purified extract from *Lonicera japonica* plant—is developed by South-Korea based Huons. As of May 2017, the purified extract has completed Phase I development and is currently undergoing Phase II evaluation in development for sepsis. GlobalData could not obtain any information about its MOA or results of its efficacy and safety in clinical trials.

9.4.3 Pooled Human Plasma

OctaPharma is currently developing an improved resuscitation fluid, solvent/detergent-based formulations of human plasmacalled Octaplas and OctaplasLG. As of January 2017, Octaplas is in Phase II clinical development for septic shock. In this Phase II RCT, 40 septic shock patients were assigned to either Octaplas or a crystalloid comparator group. The primary endpoint of this study is change in microvascular perfusion from baseline and change in biomarkers indicative of endothelial barrier function (Rigshospitalet [Denmark], NCT03092245). GlobalData expects completion of clinical Phase II development in H2 2017.

Octaplas is a replacement therapy to traditional crystalloid therapy, and is thought to be more representative of human plasma with coagulation factors within normal ranges, thereby preventing further organ dysfunction.

"We need some new crystalloid solutions that would reproduce better the composition of our plasma. That's doable, but the industry is reluctant to develop such a formula because they are concerned about the fact that the authorities may request some prospective randomized controlled trials which would be too expensive for them."

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9.4.4 BMS-986189

BMS is developing BMS-986189, a therapy with an undisclosed mechanism, for sepsis patients. The pipeline drug is currently being assessed in 31 human volunteers for PK/PD parameters and other safety parameters (BMS, NCT02739373). The trial was initiated in December 2016 and GlobalData expects results to be released in H2 2017.

9.4.5 Motrem

France-based Inotrem is developing Motrem, an antagonist of the triggering receptor expressed on myeloid cells (TREM-1), for the treatment of septic shock. By competing for TREM-1 binding, Motrem dampens the inflammatory disease response in septic shock patients. First in human Phase I trials demonstrated efficacy in line with preclinical studies and presented a good safety profile with no reported AEs (Inotrem, press release, September 13, 2016). As of May 2017, Inotrem is planning a Phase Ib study of Motrem in healthy volunteers challenged with endotoxin.

Motrem is derived from the TREM-like Transcript-1 protein and shares the first 12 amino acid units of this protein. Upon binding of Motrem to the TREM-1 receptor on myeloid cells, Motrem prevents a toll-like receptor-initiated response against pathogens, which otherwise would trigger the secretion of pro-inflammatory cytokines. Although TREM-1 levels have been suggested as a possible biomarker to differentiate SIRS from sepsis, clinical studies have shown mixed results on correlating disease severity and TREM-1 levels. While some studies showed higher levels of TREM-1 among sepsis patients than compared to healthy volunteers, other studies showed higher TREM-1 levels in survivors of sepsis and septic shock than compared to non-survivors, with no difference of TREM-1 levels upon initial presentation to the ED (Marioli et al., 2014; van Bremen et al., 2013). TREM-1's role on the pro- and anti-inflammatory immune response is the subject of further research. GlobalData anticipates that Inotrem's planned Phase I study of Motrem in healthy volunteers who are challenged with endotoxin will establish TREM-1's role in the early pro-inflammatory response to sepsis and septic shock.

10 Pipeline Valuation Analysis

In this accompanying section to the forecast model, GlobalData discusses each pipeline drug against comparable measures currently pursued in the treatment of sepsis and septic shock. In order to rate new pipeline products compared with the existing SOC, GlobalData used weighted clinical and commercial attributes ranging from one (1) to five (5), with 1 being the least favorable score and 5 being the most favorable. The weighted percentage for each attribute refers to its importance in sepsis and septic shock, based on primary and secondary research in form of interviews, surveys, and literature research. Each clinical and commercial score is shown as a raw and a weighted score that reflects the clinical and commercial strength for that drug in the sepsis and septic shock market.

10.1 Clinical Benchmark of Key Pipeline Drugs

The clinical benchmark for pipeline drugs varies based on the drug's MOA and placement in the current treatment protocol for sepsis and septic shock patients. In order to facilitate the comparison of pipeline products with the available SOC options, GlobalData has categorized the pipeline products set to be launched during the forecast period into three categories. The categories are listed in the order of importance to interviewed KOLs.

Experts were most excited about sepsis-specific treatment options that are able to directly interfere with sepsis and septic shock pathophysiology. Physicians are hopeful that these agents will have a great impact on the course and outcome of sepsis and septic shock. Current treatment options include the use of IV steroids and IV immunoglobulins, which benefit from decades of experience with their use and from being available as affordable generics. However, these interventions have low specificity in interference with the sepsis-induced immune response, as physicians continue to struggle in the identification of patients likely to respond to these treatment options. Therefore, KOLs put a particular importance on the use of diagnostics, biomarkers, and clinical trials demonstrating efficacy in the selected patient population.

Table 59 presents the clinical scores of pipeline drugs being developed to directly interfere with the pathophysiology in sepsis and septic shock, compared with the clinical scores of current SOCs.

Table 59: Clinical Benchmark of Key Sepsis-Specific Treatment Options – Sepsis and Septic Shock

Attributes	Weighting	SOC (Steroid)		Am-Pharma's recAP		Faron's Traumakine		SOC (IVIgGs)		BMS' BMS-936559		RevImmune's CYT107	
		R	W	R	W	R	W	R	W	R	W	R	W
Efficacy (based on available clinical data)	25.0%	2.75	0.69	2.25	0.56	2.00	0.50	2.25	0.56	2.75	0.69	2.25	0.56
Diagnostics/biomarkers/patient selection	20.0%	2.00	0.40	3.00	0.60	3.00	0.60	3.75	0.75	3.75	0.75	3.75	0.75
Safety and tolerability Profile	15.0%	2.50	0.38	4.25	0.64	4.25	0.64	3.50	0.53	2.75	0.41	3.00	0.45
MOA (novelty of approach)	7.5%	2.50	0.19	5.00	0.38	5.00	0.38	2.50	0.19	5.00	0.38	5.00	0.38
Duration of treatment	5.0%	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13
Physician familiarity	12.5%	3.25	0.41	3.00	0.38	3.00	0.38	2.75	0.34	2.75	0.34	2.75	0.34
Route of administration	5.0%	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13	2.50	0.13
Clinical trial design	10.0%	1.50	0.15	4.00	0.40	2.00	0.20	1.50	0.15	4.50	0.45	3.00	0.30
Total Clinical Score	**100.0%**	**19.50**	**2.46**	**26.50**	**3.20**	**24.25**	**2.94**	**21.25**	**2.77**	**26.50**	**3.27**	**24.75**	**3.03**

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report
R = raw score; w = Weighted score

Physicians and KOLs interviewed by GlobalData stressed the importance on preventing organ damage in sepsis and septic shock patients. The current armamentarium of physicians is composed of rapid fluid resuscitation, vasopressors, the administration of anticoagulants, and mechanical devices such as respirators and renal replacement therapies in the prevention/reversal of organ dysfunction(s). KOLs placed particular importance on efficacy, followed by safety and the novelty of approach. Compared to sepsis-specific pipeline drugs, KOLs rated diagnostic biomarkers for patient stratification as secondary to efficacy and safety, as the expectation is that these interventions benefit all patients with sepsis and septic shock. A detailed valuation of medical devices was outside the scope of this report, as devices discussed in this report were already available in some of the 7MM.

Table 60 presents the clinical scores of pipeline drugs being developed for supporting care in sepsis and septic shock, compared with those of the current SOCs.

Table 60: Clinical Benchmark of Key Supportive Care Treatment Options – Sepsis and Septic Shock

Attributes	Weighting	SOC (Vasopressors)		Ferring's Selepressin		SOC (Anticoagulants)		Asahi's Thrombomodulin	
		R	W	R	W	R	W	R	W
Efficacy endpoints (based on available clinical data)	30.0%	3.75	1.13	3.00	0.90	3.25	0.98	3.00	0.90
Diagnostics and biomarkers	15.0%	4.00	0.60	4.00	0.60	3.00	0.45	3.00	0.45
Safety and tolerability profile	22.5%	2.25	0.51	3.00	0.68	2.00	0.45	2.75	0.62
MOA (novelty of approach)	17.5%	2.25	0.39	2.75	0.48	2.50	0.44	2.50	0.44
Physician familiarity	10.0%	4.00	0.40	3.50	0.35	4.00	0.40	3.50	0.35
Clinical trial design	5.0%	2.50	0.13	3.00	0.15	2.50	0.13	1.50	0.08
Total Clinical Score	**100.0%**	**18.75**	**3.15**	**19.25**	**3.16**	**17.25**	**2.84**	**16.25**	**2.83**

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

R = raw score; W = weighted score

The majority of KOLs interviewed by GlobalData believe infection control will remain a major aspect of sepsis and septic shock treatment throughout the forecast period.

The majority of KOLs interviewed by GlobalData believe infection control will remain a major aspect of sepsis and septic shock treatment throughout the forecast period. New pipeline agents entering the sepsis and septic shock market are most heavily weighted on the current prevalence of pathogens (efficacy and spectrum of activity), followed by diagnostic biomarkers to identify the causative pathogens, and physician familiarity with available generic anti-infective drugs).

Table 61 presents the clinical scores of pipeline drugs being developed for infection control in sepsis and septic shock, compared with the current SOCs.

Table 61: Clinical Benchmark of Key Infection Control Treatment Options – Sepsis and Septic Shock

Attributes	Weighting	SOC (β-lactam antibiotics)		Shionogi's Cefiderocol	
		R	W	R	W
Efficacy/activity spectrum	30.0%	2.50	0.75	3.50	1.05
Safety profile	15.0%	2.50	0.38	2.50	0.38
Diagnostics/biomarker	22.5%	1.50	0.34	1.50	0.34
Physicians familiarity	17.5%	3.00	0.53	3.00	0.53
Antibiotic stewardship/development of resistance	10.0%	3.00	0.30	2.00	0.20
Clinical trial design	5.0%	2.50	0.13	3.00	0.15
Total Clinical Score	100.0%	15.00	2.41	15.50	2.64

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

R = raw score; W = weighted score

10.2 Commercial Benchmark of Key Pipeline Drugs

Although most of the anticipated pipeline drugs for the sepsis and septic shock market are anticipated to encounter similar commercial barriers for successful market penetration, GlobalData decided for the purpose of this report to evaluate each pipeline drug against its most relevant SOC measure, as the clinical and commercial weightings will differ slightly depending on the type of intervention.

KOLs anticipate developers of drugs that interfere with a sepsis-induced host immune response to be very successful commercially, as the currently available treatment options are limited to steroids and immunoglobulins, which are both unspecific in restoring immune homeostasis. Experts assigned the size of the targeted population as the most important commercial attribute, as it will determine future market share. The current clinical trial designs for AM-Pharma's recAP and Faron's Traumakine target sepsis and septic shock patients with sepsis-induced AKI and ALI organ dysfunction, respectively. However, GlobalData foresees increasing competition between the two companies. During the forecast period, the battle for market share will be dependent on the each company's marketing resources. GlobalData anticipates a similar scenario for BMS' BMS-936559 and RevImmune's CYT107. Other clinical attributes such as novelty of approach, relative price, manufacturing, and molecule type were weighted by experts as equally important for future commercial success.

Table 62 presents the commercial scores of the pipeline drugs being developed to directly interfere with the sepsis pathophysiology compared with the current SOC.

Table 62: Commercial Benchmark of Key Sepsis-Specific Treatment Options – Sepsis and Septic Shock

Attributes	Weighting	SOC (Steroid)		Am-Pharma's recAP		Faron's Traumakine		SOC (IVIgGs)		BMS' BMS-936559		RevImmune's CYT107	
		R	W	R	W	R	W	R	W	R	W	R	W
Size of targeted patient population	30.0%	2.50	0.75	1.75	0.53	1.50	0.45	2.00	0.60	2.00	0.60	2.00	0.60
Degree of competition in targeted patient population	15.0%	2.50	0.38	3.00	0.45	3.00	0.45	2.50	0.38	4.50	0.68	4.50	0.68
Company's marketing and sales force strength	15.0%	2.50	0.38	3.00	0.45	2.50	0.38	4.00	0.60	5.00	0.75	2.00	0.30
Reimbursement/relative price and cost effectiveness	10.0%	4.50	0.45	4.50	0.45	2.50	0.25	4.00	0.40	2.50	0.25	3.50	0.35
Manufacturing/product availability across 7MM	10.0%	5.00	0.50	3.75	0.38	3.00	0.30	2.00	0.20	5.00	0.50	2.00	0.20
Molecule type/ manufacturing cost	5.0%	4.00	0.20	3.50	0.18	3.00	0.15	4.00	0.20	3.50	0.18	4.50	0.23
Novelty	15.0%	0.25	0.04	5.00	0.75	5.00	0.75	0.25	0.04	5.00	0.75	4.00	0.60
Total Commercial Score	100.0%	21.25	2.69	24.50	3.18	20.50	2.73	18.75	2.41	27.50	3.70	22.50	2.95

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report
R = raw score W = weighted score
7MM = US, France, Germany, Italy, Spain, UK, and Japan

Similarly to pipeline drugs aimed at interfering with the host immune response, for novel therapies targeting current supportive care in the form of novel anticoagulants and vasopressors, the major commercial benchmark is the size of the targeted patient population compared to affordable, well established generic SOCs. Furthermore, experts highlighted that currently used vasopressors and anticoagulants are well suited to manage organ dysfunctions in sepsis and septic shock patients. GlobalData values lack of competition as another major commercial attribute in the successful penetration of the sepsis and septic shock market.

Table 63 presents the commercial scores of the pipeline drugs being developed for supporting care in sepsis and septic shock compared with the current SOC.

Table 63: Commercial Benchmark of Key Supportive Care Treatment Options – Sepsis and Septic Shock

Attributes	Weighting	SOC (Vasopressors)		Ferring's Selepressin		SOC (Anticoagulants)		Asahi's Thrombomodulin	
		R	W	R	W	R	W	R	W
Size of targeted patient population	25.0%	3.25	0.81	3.25	0.81	1.50	0.38	1.00	0.25
Competition	20.0%	2.50	0.50	1.00	0.20	2.50	0.50	2.75	0.55
Company's marketing and sales force strength	15.0%	2.50	0.38	3.00	0.45	2.50	0.38	4.00	0.60
Reimbursement	5.0%	4.50	0.23	1.00	0.05	2.50	0.13	2.50	0.13
Novelty	12.5%	0.25	0.03	2.00	0.25	0.25	0.03	1.50	0.19
Manufacturing/product availability across 7MM	12.5%	3.00	0.38	4.75	0.59	4.75	0.59	4.75	0.59
Clinical trial design	10.0%	3.00	0.30	4.50	0.45	2.00	0.20	2.00	0.20
Total Commercial Score	**100.0%**	**19.00**	**2.62**	**19.50**	**2.81**	**16.00**	**2.20**	**18.50**	**2.51**

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

R = raw score; W = weighted score

7MM = US, France, Germany, Italy, Spain, UK, and Japan

Pipeline agents targeting infection control in sepsis and septic shock patients also have the size of the targeted patient population, as compared to currently available generic antibiotics, as the major commercial benchmark. Experts cited clinical trial design as major opportunity to promote future commercial success.

Table 64 presents the commercial scores of the pipeline drugs being developed for infection control in sepsis and septic shock compared with the current SOC.

Table 64: Commercial Benchmark of Key Infection Control Treatment Options – Sepsis and Septic Shock

	Weighting	SOC (β-lactam antibiotics)		Shionogi's Cefiderocol	
		R	W	R	W
Size of targeted patient population	25.0%	1.50	0.38	3.50	0.88
Competition	20.0%	3.50	0.70	3.50	0.70
Company's Marketing and Sales Force Strength	15.0%	2.50	0.38	2.50	0.38
Reimbursement	5.0%	4.50	0.23	4.50	0.23
Novelty	12.5%	4.50	0.56	4.50	0.56
Manufacturing/product availability across 7MM	12.5%	4.75	0.59	4.75	0.59
Clinical Trial Design	10.0%	2.75	0.28	2.25	0.23
Total Commercial Score	**100.0%**	**24.00**	**3.11**	**25.50**	**3.56**

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

R = raw score; W = weighted score

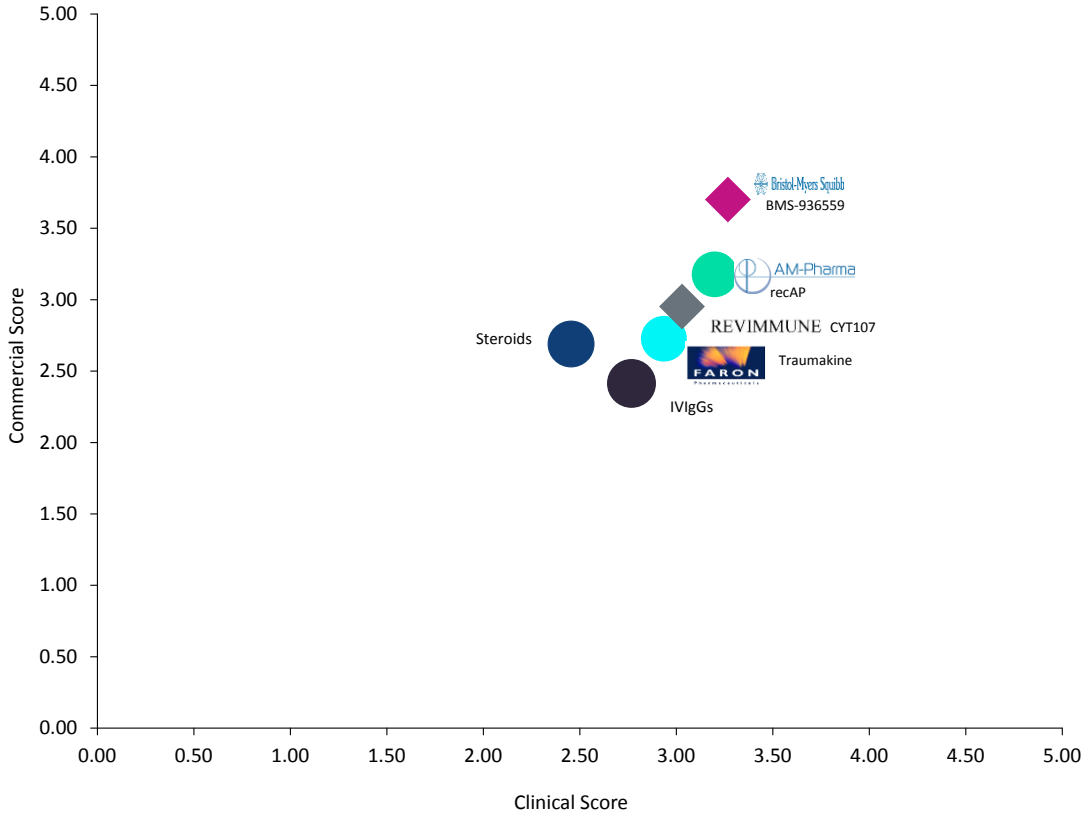
7MM = US, France, Germany, Italy, Spain, UK, and Japan

10.3 Competitive Assessment

Based on the previously discussed clinical and commercial attributes of upcoming pipeline drugs for sepsis and septic shock, GlobalData anticipates BMS' anti-PD-L1 mAb BMS-936559 to dominate the market among the sepsis-specific agents aimed at interfering with the host immune response. Although BMS-936559 has very similar clinical scores to AM-Pharma's recAP, BMS has a higher commercial score, mainly attributed to BMS' stronger sales and marketing force compared to AM-Pharma. Although experts expressed a high interest in RevImmune's IL-7 therapy CYT107, GlobalData identified the company's market capitalization, the potential struggle to secure funding for pivotal Phase III clinical development, and its past history of bankruptcy as limiting factors to securing future commercial success. Faron's Traumakine will be positioned at the bottom in terms of its clinical and commercial scores in this category; Traumakine is currently not being assessed in a sepsis or septic shock patient population and experts foresee initial usage of Faron's IFN-β-1a therapy CYT107 in sepsis-induced ALI. GlobalData expects that Traumakine will be competing with AM-Pharma's recAP, which will see uptake predominantly in sepsis-induced AKI, during the forecast period.Experts expect all pipeline agents in this category to exceed currently available treatment options in terms of clinical and commercial attributes at the end of the forecast period.

Figure 38 presents the competitive assessment of the marketed and pipeline drugs for sepsis-specific treatment options benchmarked against the SOC.

Figure 38: Competitive Assessment of Marketed and Pipeline Agents for Sepsis-Specific Treatment Options – Sepsis and Septic Shock, 2016–2026



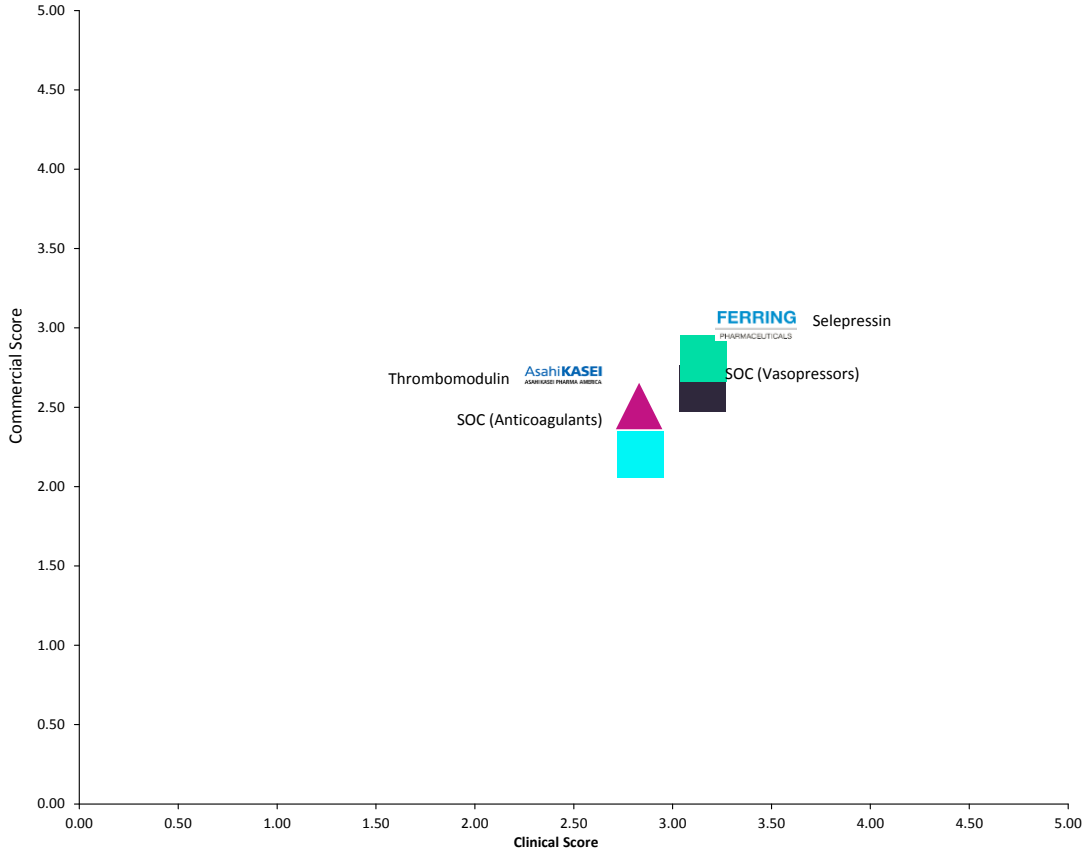
Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

For the category of pipeline agents aimed at improving currently available SOCs for the supportive care of sepsis and septic shock patients, experts foresee a marginal benefit of pipeline drugs over marketed generic drugs. Experts approved of Ferring's adaptive clinical trial design for the pivotal clinical development of Selepressin, but were cautiously optimistic about selepressin's efficacy profile in face of vasopressin's past failure to demonstrate clinical efficacy in sepsis and septic shock patients. Thrombomodulin, which is currently marketed in Japan, underwhelmed KOLs interviewed by GlobalData. Experts expressed concerns about Asahi's current clinical trial design in terms of recruitment of a highly heterogeneous patient population, but also in terms of its short-term 28 day all-cause mortality endpoint. Developers are increasingly adopting longer 90 day all-cause mortality as the primary endpoint of their pivotal RCTs.

Experts approved of Ferring's adaptive clinical trial design for the pivotal clinical development of Selepressin.

Figure 39 presents the competitive assessment of the marketed and pipeline drugs for supportive care treatment options benchmarked against the SOC.

Figure 39: Competitive Assessment of Marketed and Pipeline Agents for Supportive Care Treatment Options – Sepsis and Septic Shock, 2016–2026

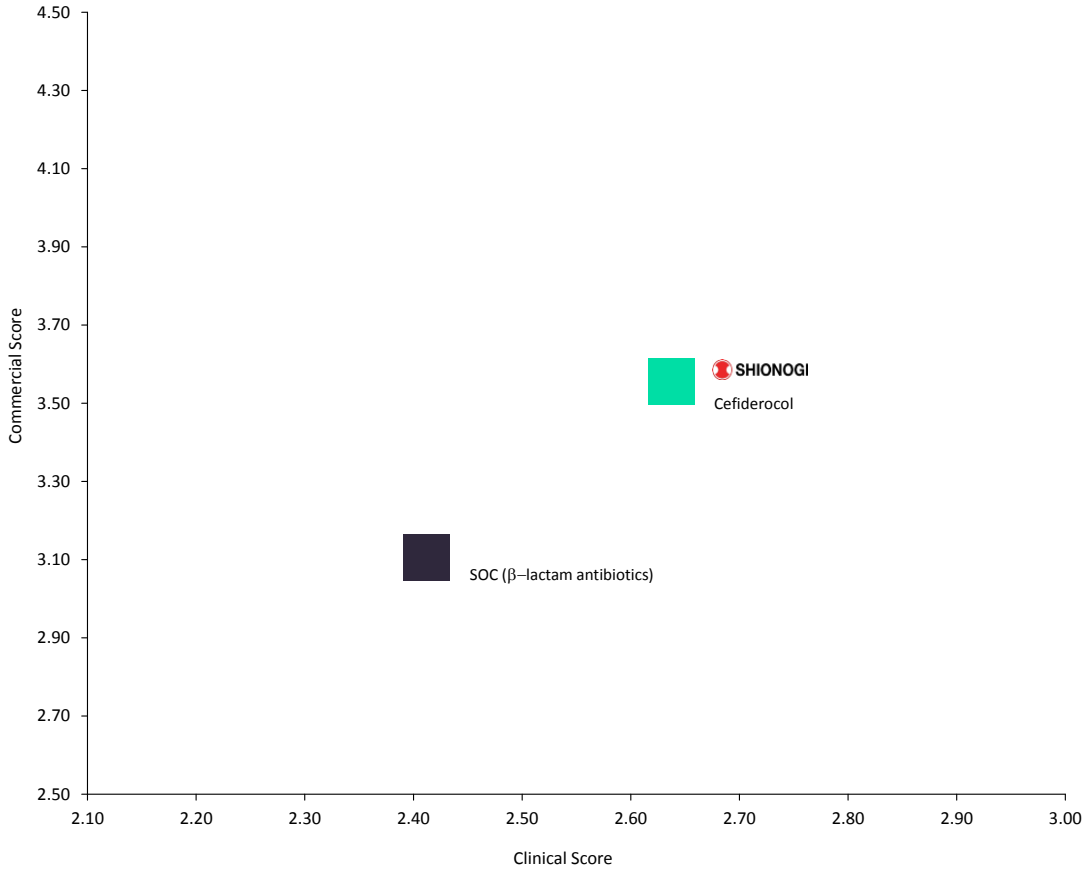


Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

KOLs anticipate infection control to remain the most important therapy for sepsis and septic shock patients. The sepsis and septic shock market for anti-infectives is dominated by affordable generic drugs. GlobalData anticipates that any new anti-infective entering the market will face considerable competition from cheaper generics, as well as physicians' familiarity with the prescription of well-established anti-infectives. For the scope of this report, GlobalData included Shionogi's cefiderocol as the only new antibiotic entering the sepsis and septic shock market. As of June 2016, cefiderocol was the only antibiotic specifically evaluated in a sepsis and septic shock patient population in its pivotal clinical trials. GlobalData anticipates a moderate uptake of cefiderocol due to its high cost in addition to high competition with generic antibiotics.

Figure 40 presents the competitive assessment of the marketed and pipeline drugs for infection control treatment options benchmarked against the SOC.

Figure 40: Competitive Assessment of Marketed and Pipeline Agents for Infection Control Treatment Options – Sepsis and Septic Shock, 2016–2026



Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

10.4 Top-Line 10-Year Forecast

For the purpose of this report, GlobalData defines the global sepsis and septic shock market as encompassing the sales of infection control drugs; supportive care drugs, including fluids, vasopressors, and anticoagulants; and immunosuppressive and immunostimulatory drugs, including steroids and immunoglobulins, prescribed for the treatment of sepsis and septic shock in the 7MM. Sepsis is a heterogeneous disease that can affect multiple organs, and as such, sepsis treatment typically relies on drugs to control the causative infection, drugs to control organ function, and therapies that directly interfere with the host immune response. Modern drug discovery for sepsis and septic shock is still in its infancy and has thus far only resulted in the market approval of Xigris, which was later recalled from the market by Eli Lilly. The majority of currently available treatment options for sepsis and septic shock are derived from the treatment of other infectious diseases and organ supportive measures; revenues generated by these products outside of the aforementioned countries, patient populations, and clinical scenarios are beyond the scope of this analysis.

Historically, the treatment of sepsis and septic shock relied on early administration of anti-infective drugs with the addition of other drugs to support vital organ function. Experts place antibiotics, antifungals, and antivirals at the forefront of treatment; organ supportive measures were rated as important, but are thought of as drugs to ensure survival while antibiotics clear the life-threatening infection. In 2016, GlobalData estimated the global market for sepsis and septic shock to exceed $2.0 billion in annual sales across the 7MM. The US dominated global sales, generating over $2.0 billion (a 73.0% market share) in annual sales in 2016. The 5EU, led by Germany ($210.0m), generated almost $630.0m (a 23.0% market share) in annual sales, whereas Japan trailed the global sales in 2016, generating approximately $117.1m (a 4.2% market share). The difference in country-specific revenue is primarily explained by higher disease prevalence in the US; 75.6% of global sepsis and septic shock patients resided in the US in 2016, whereas the 5EU and Japan experienced lower disease incidence rates of 23.0% and 1.4%, respectively. The majority of drugs used in the treatment of sepsis and septic shock are generic and therefore GlobalData noted no significant difference in the annual cost of therapy (ACOT) for these drugs across the 7MM.

By 2026, GlobalData expects this market to double in size, reaching $5.9 billion dollars in annual sales, which represents a compound annual growth rate (CAGR) of 10.8% from 2015–2025.

During the forecast period, GlobalData anticipates strong growth for the sepsis and septic shock market across the 7MM. By 2026, GlobalData expects this market to double in size, reaching $5.9 billion dollars in annual sales, which represents a compound annual growth rate (CAGR) of 10.8% from 2015–2025. From a regional perspective, the US will remain the overall market leader across the 7MM, generating $4.6 billion by 2026, which represents an overall market share of approximately 78.7%. Growth during the forecast period will be predominantly driven by the launch of new pipeline

drugs, while disease incidence is estimated to grow at an annual rate of 1.6% across the 7MM. Despite considerable improvement in clinical trial design with the adoption of adaptive RCTs, experts identified late-stage failure as a continuing barrier to market entry. GlobalData expects that Shionogi's cefiderocol to be the market leader among the new pipeline agents, generating 14% of the overall annual sales in 2026. Innovative new treatment options such as BMS' BMS-936559, RevImmune's CYT107, AM-Pharma's recAP, and Faron's Traumakine are expected to represent 23.2% of the overall market share. Experts foresee antibiotics and other anti-infective measures at the forefront of treatment in sepsis and septic shock throughout the forecast period, citing missing biomarkers for stratifying patients towards innovative treatment options that directly interfere with the sepsis pathophysiology as major a hurdle to their uptake.

Table 65 presents the top-line sales forecast for products used to treat sepsis and septic shock in the 7MM from 2016–2026.

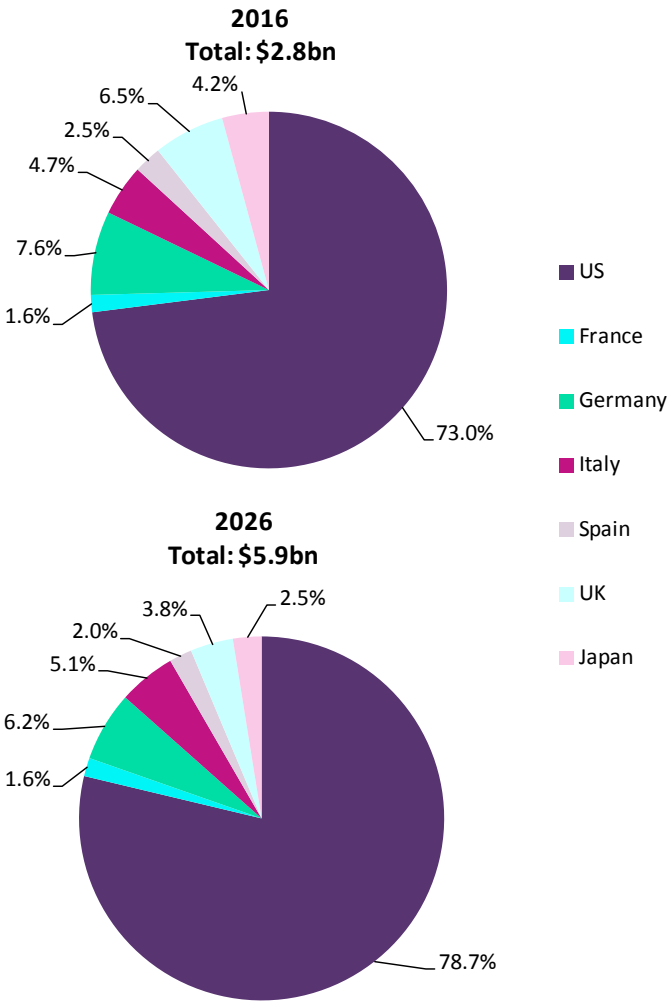
Table 65: Top-Line Sales Forecast ($m) for Sepsis and Septic Shock, 2016–2026

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2016–2026) (%)
US	1,680.41	1,718.25	1,950.67	2,121.85	2,271.70	2,596.53	2,935.39	3,270.83	3,734.91	3,779.61	3,893.43	8.8%
5EU	414.36	430.12	444.10	457.87	490.59	538.38	569.90	603.86	656.82	673.30	701.95	5.4%
Japan	77.65	79.16	80.62	86.36	88.21	90.40	92.91	95.47	99.47	100.97	105.69	3.1%
Total	2,172.42	2,227.53	2,475.40	2,666.07	2,850.50	3,225.30	3,598.20	3,970.16	4,491.20	4,553.88	4,701.07	8.0%

Source: GlobalData
5EU = France, Germany, Italy, Spain, and UK

Figure 41 outlines the top-line sales forecast by country/region for sepsis and septic shock across the 7MM in 2016 and 2026.

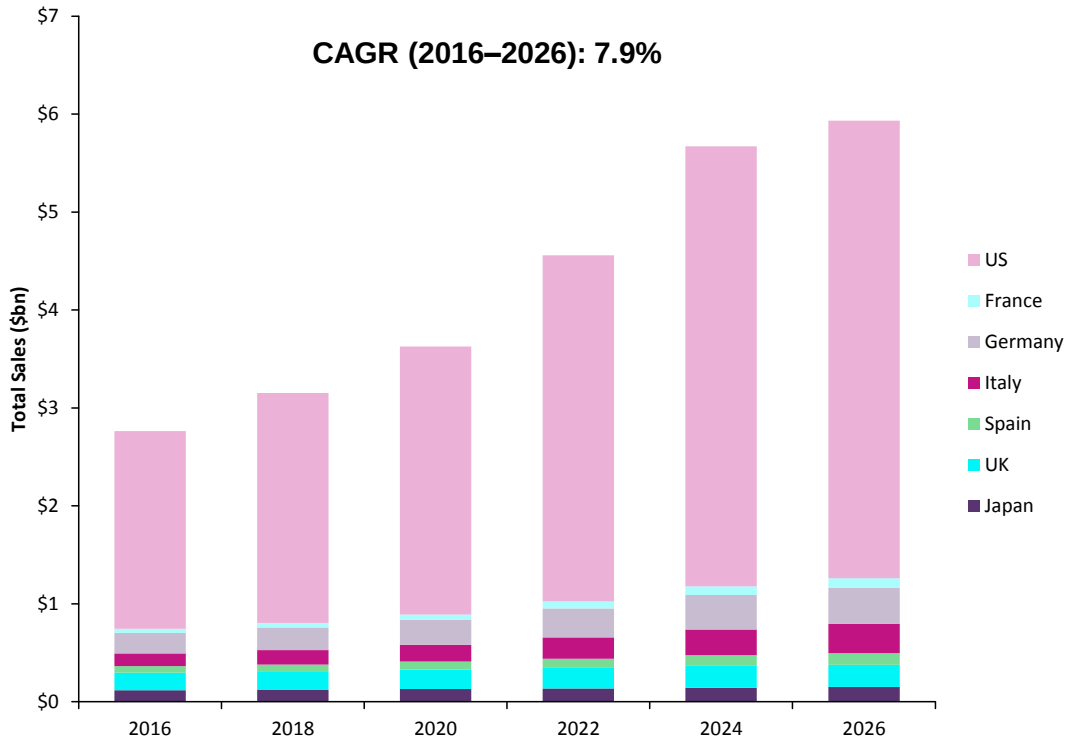
Figure 41: Top-Line Sales for Sepsis and Septic Shock by Country/Region, 2016 and 2026



Source: GlobalData

Figure 42 outlines the top-line sales forecast by markets for sepsis and septic shock across the 7MM from 2016–2026.

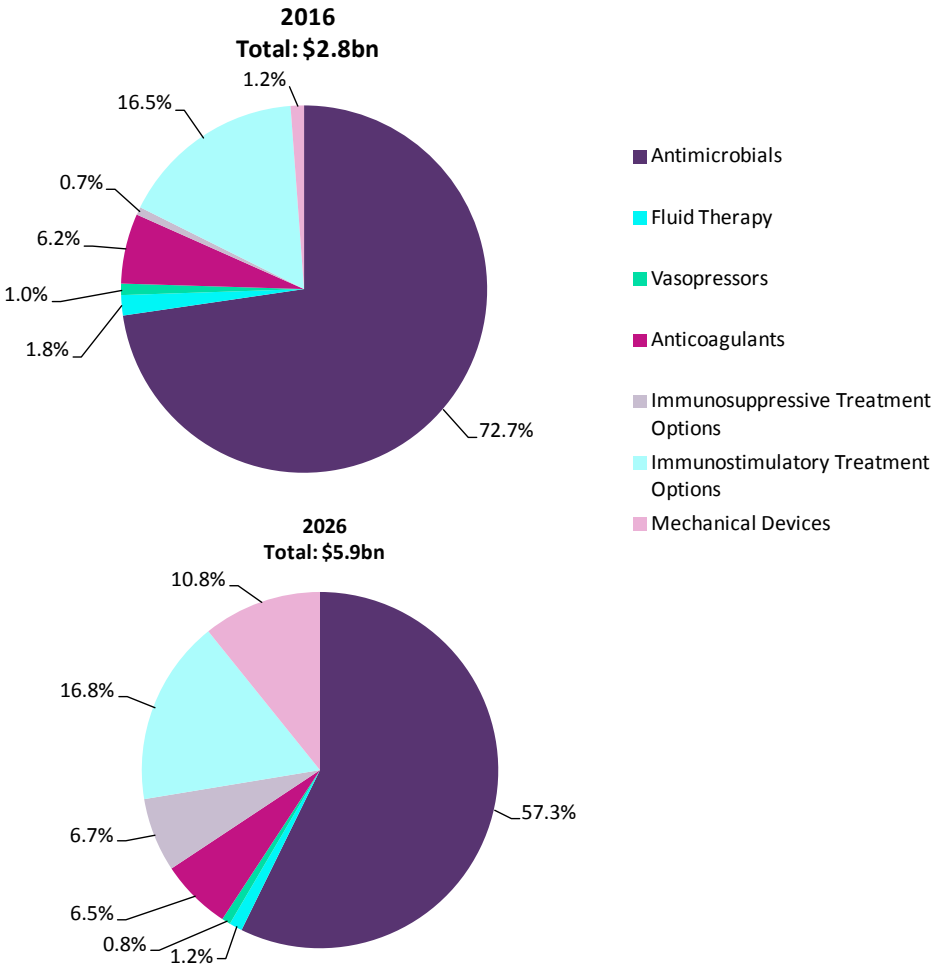
Figure 42: Top-Line Sales for Sepsis and Septic Shock by Region, 2016–2026



Source: GlobalData

Figure 43 outlines the top-line sales forecast by drug class for sepsis and septic shock in 2016 and 2026.

Figure 43: Global Sales for Sepsis and Septic Shock by Drug Class, 2016 and 2026



Source: GlobalData

Table 66 lists the key events that GlobalData expects to impact the sales of products for the treatment of sepsis and septic shock during the forecast period.

Table 66: Key Events Impacting Sales for Sepsis and Septic Shock, 2016–2026

Year	Event	Level of Impact	Type of Impact
2017	Pfizer to execute exclusivity deal to acquire AM-Pharma	High	↑↑↑
2020	Launch of new SSC guidelines/ consensus definitions	High	↑↑↑
2020	Launch of Shinogi's cefiderocol	Medium	↑↑
2024	Launch of BMS' BMS-936559	High	↑↑↑
2025	Launch of RevImmune's CYT107	High	↑↑↑
2025	Launch of Faron's Traumakine	Medium	↑↑
2025	Launch of AM-Pharma/Pfizer's recAP	High	↑↑↑
2026	Launch of Ferring's selepressin	Medium	↑↑
2017	Pfizer to execute exclusivity deal to acquire AM-Pharma	High	↑↑↑
2020	Launch of new SSC guidelines/ consensus definitions	High	↑↑↑
2020	Launch of Shinogi's cefiderocol	Medium	↑↑
2024	Launch of BMS' BMS-936559	High	↑↑↑
2025	Launch of RevImmune's CYT107	High	↑↑↑
2025	Launch of Faron's Traumakine	Medium	↑↑
2025	Launch of AM-Pharma/Pfizer's recAP	High	↑↑↑
2026	Launch of Ferring's selepressin	Medium	↑↑
2017	Pfizer to execute exclusivity deal to acquire AM-Pharma	High	↑↑↑
2020	Launch of new SSC guidelines/ consensus definitions	High	↑↑↑

Source: GlobalData, Pharma eTrack [Accessed June 21, 2017], primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

Table 67 lists the global (7MM) drivers and barriers that GlobalData anticipates will most heavily influence sepsis and septic shock market dynamics from 2016–2026.

Table 67: Sepsis and Septic Shock Market – Global Drivers and Barriers, 2016–2026

Drivers
The most important driver of growth in the sepsis and septic shock marketplace will be the arrival of the first therapies targeting specific segments of the sepsis population.
An aging population is one of the dominant factors in the increased incidence rate of sepsis and septic shock during the forecast period.
Innovations in R&D strategies and the implementation of adaptive clinical trial designs that feature long-term all-cause mortality outcomes will continue to drive the launch of clinical pipeline drugs throughout the forecast period.
Improvements in the management of sepsis and septic shock patients will result in decreased mortality rates and an increased number of patients in need of immunostimulatory or immunosuppressive treatment options to restore immune homeostasis.
The launch of Asahi's thrombomodulin will foster increased participation in the development pipeline of novel sepsis and septic shock therapies.
Continued awareness campaigns of sepsis and septic shock at the national and international levels will result in earlier diagnosis and improved outcomes for patients.
Improvements in patient stratifications with novel biomarkers will result in a strengthened uptake of immunomodulation therapies. However, experts interviewed by GlobalData anticipate that the launch of novel biomarkers for sepsis diagnosis and stratification to fall outside the forecast period
Barriers
Although sales of biologic agents have contributed substantially to other disease markets, these drugs' high prices reduce uptake. Furthermore, reliable patient stratification via biomarkers will limit their future use.
Late-stage clinical failure will remain a major hurdle to market entry. Experts highlighted the need for new biomarkers to stratify patients to specific therapeutic interventions.
Austerity measures will continue to stifle growth in the pharmaceutical markets within the 7MM. Many countries have seen blanket drug price cuts and freezes since 2008; numerous country-specific pricing and reimbursement policies and laws have been introduced, that negatively impact the global pharmaceutical market.
Despite the increased availability of novel antibiotics with potent activity against multi-drug-resistant bacteria, generic antibiotics have remained the cornerstone of therapy primarily due to a high level of clinician familiarity with prescribing these antibiotics.
Physician education will be a critical barrier to the growth of the global sepsis and septic shock marketplace over the forecast period, particularly for novel agents with unusual dosing schedules or unique MOAs that are unfamiliar to prescribers.
Inadequate awareness, both on the part of the public and healthcare providers, will likely hinder the uptake of novel therapeutics throughout the forecast period. Firms can potentially circumvent this obstacle by becoming actively involved in efforts to improve the level of sepsis awareness and education. This is particularly important in the post-Xigris marketplace, as firms will benefit from a proactive approach to promoting new products.

Source: GlobalData, primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report

7MM = US, France, Germany, Italy, Spain, UK, and Japan

10.4.1 US

In 2016, GlobalData estimated the sepsis and septic shock marketplace in the US to have reached $2.0 billion in annual sales (73% of overall sales across 7MM). GlobalData's primary research identified an increased incidence rate of sepsis and septic shock as the predominant driver of sales growth in the

US in 2016. The annual sales in the sepsis and septic shock market are dominated by antimicrobial therapies, which GlobalData estimates to have accounted for 78.8% of the revenue generated in 2016. Organ supportive measures and drugs to modulate the host immune response were estimated to account for 10.1% and 10.9% of market share, respectively.

In 2026, GlobalData anticipates the sepsis and septic shock market to reach $4.7 billion in annual sales, representing a CAGR of 9%. The major driver of the growth of the sepsis and septic shock market will be the launches of new pipeline drugs; GlobalData estimates that 46% of the market share will be generated by new entrants to the market. However, antimicrobials, including Shionogi's cefiderocol ($780.7m), will remain the dominant therapy option in sepsis and septic shock, mainly due to their broad use across all patient populations, generating annual sales of $2.1 billion as a class in 2026. Sepsis-specific treatment options will experience the largest CAGR of 14%, accounting for $206.5m of the overall sales in 2026. Among the sepsis-specific treatment options, AM-Pharma's recAP will dominate the market, with annual sales reaching $195.6m, closely followed by Faron's Traumakine, and BMS' BMS-936559, which are estimated to generate $174.8m and $150.8m in annual sales by 2026, respectively. Sales in this category are mainly driven by increased incidence of AKI and ALI organ dysfunctions, whereas use of BMS' BMS-936559 will be limited to sepsis-induced immunosuppression in sepsis and septic shock patients. Experts viewed missing biomarkers to stratify patients to these therapies as a major barrier for future uptake.

In 2026, GlobalData anticipates the sepsis and septic shock market to reach $4.7 billion in annual sales, representing a CAGR of 9%.

Supportive treatment options for sepsis and septic shock patients will benefit from the launch of Ferring's new vasopressor, selepressin, and Asahi's new anticoagulant, thrombomodulin. GlobalData estimated supportive care option sales to grow at a CAGR of 8%, reaching annual sales of $444.7m by the end of the forecast period. GlobalData estimated that generic vasopressors and anticoagulants will continue to dominate this market segment, as new entrants are expected to struggle against generic price competition and physician familiarity with the use of conventional therapies. In particular, Ferring's selepressin will have to demonstrate significant advantages over norepinephrine, epinephrine, and vasopressin in order to penetrate this market. Experts foresee that selepressin will struggle to compete in this market share, reaching annual sales of $9.2m by 2026.

GlobalData notes that although septic shock patients are receiving additional medication in the form of vasopressors, their low cost of therapy mean that the overall market sizes of sepsis and septic shock is not affected. Annual sales are primarily driven by the higher incidence of sepsis, compared to the low incidence of septic shock; when corrected for incidence rate, the generated annual sales of sepsis and septic shock are very similar.

Table 68 presents the sales forecast for selected products used to treat sepsis and septic shock in the US from 2016–2026.

Table 68: Sales Forecasts ($m) for Sepsis and Septic Shock in the US, 2016–2026

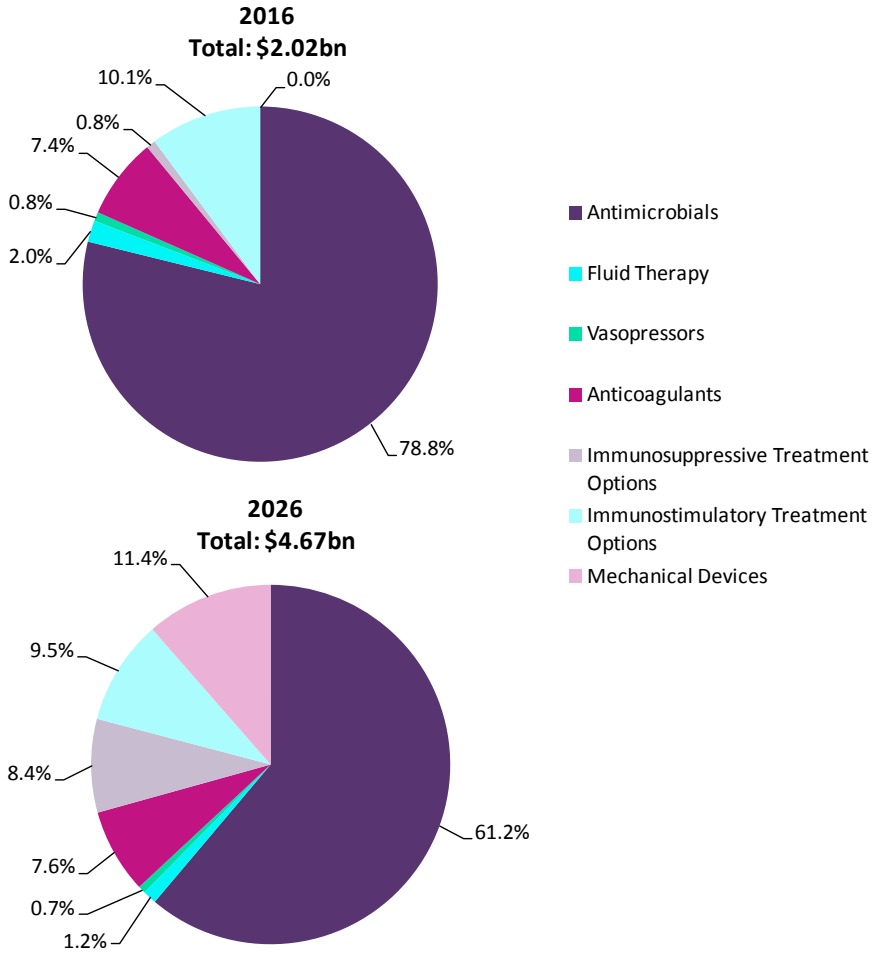
Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2016–2026) (%)
Antimicrobials	**1,591.23**	**1,634.25**	**1,677.31**	**1,851.91**	**1,955.01**	**2,096.69**	**2,288.42**	**2,500.58**	**2,659.55**	**2,776.36**	**2,856.89**	**6.0%**
Antibiotics	**1,570.34**	**1,612.74**	**1,655.18**	**1,829.15**	**1,931.56**	**2,072.57**	**2,263.59**	**2,475.00**	**2,633.24**	**2,749.31**	**2,828.99**	**6.1%**
Cefiderocol	-	-	-	130.12	185.84	280.07	422.32	582.31	691.22	756.36	780.74	N/A
Fluid Therapy	**39.53**	**41.21**	**42.79**	**44.42**	**46.15**	**47.90**	**49.73**	**51.65**	**53.55**	**55.51**	**58.02**	**3.9%**
Vasopressors	**16.35**	**16.99**	**17.59**	**18.22**	**22.16**	**23.34**	**24.93**	**26.90**	**28.55**	**29.89**	**31.04**	**6.6 %**
Norepinephrine	1.48	1.50	1.53	1.56	1.56	1.59	1.61	1.63	1.65	1.68	1.70	1.4 %
Epinephrine	0.85	0.87	0.89	0.91	0.93	0.96	0.98	1.00	1.03	1.05	1.07	2.3 %
Vasopressins	13.96	14.55	15.10	15.68	15.67	16.19	16.67	17.12	17.61	18.18	19.00	3.1 %
Dobutamine	0.06	0.06	0.07	0.07	0.07	0.08	0.08	0.08	0.09	0.09	0.09	4.5 %
Selepressin	-	-	-	-	3.92	4.53	5.60	7.06	8.18	8.89	9.16	N/A
Anticoagulants	**149.37**	**152.55**	**285.72**	**292.89**	**301.34**	**310.51**	**320.90**	**331.03**	**340.11**	**348.44**	**355.69**	**9.1 %**
Heparin	11.17	11.46	11.76	12.06	12.39	12.72	13.06	13.42	13.76	14.11	14.50	2.6 %
Antithrombin	138.20	141.08	144.12	147.26	150.61	153.95	157.42	161.09	164.55	168.11	171.47	2.2 %
Thrombomodulin	-	-	129.84	133.57	138.34	143.85	150.43	156.52	161.80	166.21	169.72	N/A
Immunosuppressive Treatment Options	**16.80**	**17.27**	**17.74**	**18.22**	**18.74**	**103.52**	**172.30**	**230.19**	**519.87**	**366.71**	**392.49**	**37.0 %**
Steroids	16.80	17.27	17.74	18.22	18.74	19.26	19.80	20.36	229.98	21.47	22.09	2.8 %
recAP	-	-	-	-	-	84.26	97.77	121.47	153.61	178.33	195.61	N/A
Traumakine	-	-	-	-	-	-	54.74	88.36	136.29	166.91	174.79	N/A
Immunostimulatory Treatment Options	**204.78**	**202.42**	**201.48**	**200.44**	**199.45**	**302.73**	**338.81**	**368.50**	**409.49**	**436.91**	**442.21**	**8.0 %**
IgGs	204.78	202.42	201.48	200.44	199.45	198.18	196.83	195.46	193.56	191.53	184.40	-1.0%
CYT107	-	-	-	-	-	-	31.15	52.40	82.73	102.09	107.01	N/A
BMS-936559	-	-	-	-	-	104.55	110.83	120.65	133.20	143.30	150.79	N/A
Mechanical Devices	**-**	**-**	**104.58**	**123.78**	**193.37**	**252.83**	**338.28**	**419.27**	**481.88**	**519.13**	**534.35**	**N/A**

Toraymyxin	-	-	104.58	123.78	158.38	206.84	272.36	325.75	367.47	391.84	402.78	N/A
CytoSorb	-	-	-	-	34.99	45.99	65.92	93.52	114.40	127.29	131.57	N/A
Total	**2,018.05**	**2,064.69**	**2,347.21**	**2,549.88**	**2,736.21**	**3,137.52**	**3,533.39**	**3,928.13**	**4,493.00**	**4,532.95**	**4,670.68**	**8.8%**

Source: GlobalData

Figure 44 outlines the sales forecast by drug class for sepsis and septic shock in the US in 2016 and 2026.

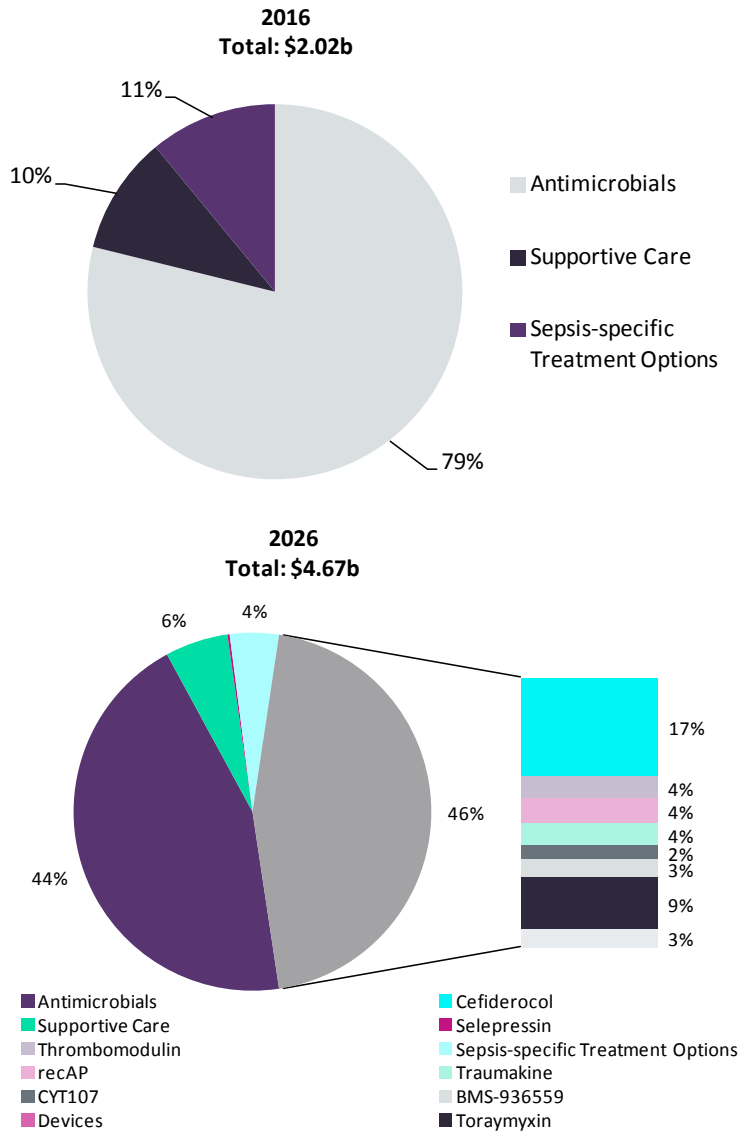
Figure 44: Sales for Sepsis and Septic Shock by Drug Class in the US, 2016 and 2026



Source: GlobalData

Figure 45 outlines the sales forecast by pipeline drugs compared to conventional therapies for sepsis and septic shock in the US in 2016 and 2026.

Figure 45: Sales for Sepsis and Septic Shock by Drug Class in the US, 2016 and 2026



Source: GlobalData

"Supportive Care" includes fluid resuscitation, vasopressors, and anticoagulants.

"Sepsis-Specific Treatment Options" include steroids and IVIgGs.

10.4.2 5EU

In 2016, GlobalData estimated that the overall sales in the 5EU sepsis and septic shock market reached $629.1m, with Germany as the country with the largest contribution, generating 33.4% of overall annual sales across the 5EU. GlobalData identified a larger patient population as the major reason for the higher sales in Germany compared to the rest of the 5EU. With the exception of France, the overall annual sales for sepsis and septic shock are in line with each country's disease prevalence. GlobalData's primary and secondary research identified an overall cheaper ACOT across all drugs used in the treatment of sepsis and septic shock as the major cause of France's lower contribution to the overall 5EU annual sales in 2016. In line with this analysis, France is expected to experience the second strongest growth (a CAGR of 8.5%) with the launch of seven new pipeline drugs during the forecast period, closely led by Italy with a CAGR of 8.9%. Compared to existing therapeutics for the treatment of sepsis and septic shock, new pipeline drugs are expected to be priced similarly across all the 5EU, thereby explaining the increased growth in these countries. At the end of the forecast period, GlobalData anticipates the 5EU to reach annual sales of $1.1 billion, representing a CAGR of 5.9%. The UK is expected to lag behind in terms of overall annual sales in 2026: GlobalData expects a moderate CAGR of 2.4%. Experts cited restrictions placed by the UK's oversight committee, the National Institute for Health and Care Excellence (NICE), as the major barrier of growth in this market; GlobalData anticipates novel biologic treatment options to initially struggle for reimbursement in this market.

At the end of the forecast period, BMS' anti-PD-L1 mAb BMS-936559 is expected to dominate the market across the 5EU, reaching annual sales of $98.31m in 2026. Experts interviewed by GlobalData expressed enthusiasm about BMS-936559's MOA and its potential to interfere with the late onset of sepsis-induced immunosuppression. GlobalData anticipated that BMS-936559's uptake will be limited to patients with clear immunosuppression symptoms, as experts expressed concerns about the usage of currently existing biomarkers, such as GM-CSF counts, to stratify patients to this treatment.Therefore, GlobalData anticipates that BMS-936559 won't have reached its peak sales at the end of the forecast period and will grow in line with the development of new tools to identify patients with sepsis-induced immunosuppression.

At the end of the forecast period, BMS' anti-PD-L1 mAb BMS-936559 is expected to dominate the market across the 5EU, reaching annual sales of $98.31m in 2026.

Table 69 presents the sales forecast for selected products used to treat sepsis and septic shock in the 5EU from 2016–2026.

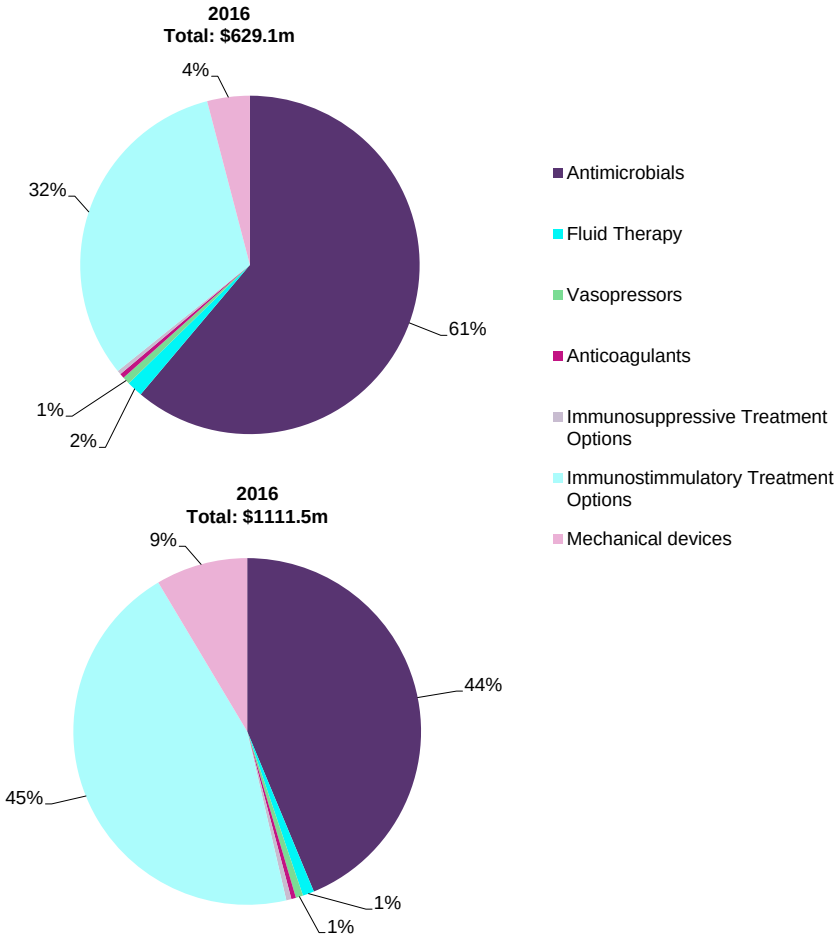
Table 69: Sales Forecast ($m) for Sepsis and Septic Shock in the 5EU, 2016–2026

Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2016–2026) (%)
Antimicrobials	**384.60**	**389.72**	**394.70**	**399.67**	**431.96**	**439.82**	**450.00**	**462.08**	**472.30**	**480.19**	**486.13**	**2.4%**
Antibiotics	**321.58**	**326.45**	**331.09**	**335.73**	**367.75**	**375.39**	**385.38**	**397.30**	**407.36**	**415.13**	**421.29**	**2.7%**
Cefiderocol	-	-	-	-	**$27.45**	**$30.58**	**$36.07**	**$43.49**	**$48.97**	**$52.19**	**$53.16**	N/A
Fluid Therapy	**9.60**	**9.84**	**10.05**	**10.27**	**10.49**	**10.70**	**10.91**	**11.12**	**11.33**	**11.55**	**11.84**	**2.1%**
Vasopressors	**4.55**	**4.59**	**4.63**	**4.68**	**4.72**	**6.04**	**6.32**	**6.76**	**7.19**	**7.44**	**7.53**	**5.2%**
Norepinephrine	0.95	0.96	0.96	0.97	0.98	0.99	0.99	1.00	1.00	1.01	1.01	0.6%
Epinephrine	0.14	0.14	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.8%
Vasopressins	3.41	3.45	3.49	3.52	3.56	3.59	3.62	3.66	3.69	3.72	3.74	0.9%
Dobutamine	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	-0.9%
Selepressin	-	-	-	-	-	1.28	1.52	1.92	2.31	2.53	2.58	N/A
Anticoagulants	**2.82**	**2.82**	**3.56**	**3.65**	**3.80**	**4.00**	**4.27**	**4.48**	**4.64**	**4.73**	**4.76**	**5.4%**
Heparin	0.89	0.90	0.90	0.90	0.91	0.91	0.91	0.91	0.91	0.92	0.91	0.2%
Antithrombin	1.92	1.93	1.94	1.94	1.95	1.96	1.97	1.97	1.98	1.99	1.99	0.3%
Thrombomodulin	-	-	0.72	0.80	0.94	1.14	1.39	1.59	1.75	1.83	1.86	N/A
Immunosuppressive Treatment Options	**2.40**	**2.42**	**2.43**	**2.45**	**2.47**	**3.03**	**3.42**	**3.93**	**29.23**	**5.10**	**5.32**	**8.3%**
Steroids	2.40	2.42	2.43	2.45	2.47	2.48	2.49	2.50	27.12	2.51	2.51	0.4%
recAP	-	-	-	-	-	0.55	0.71	1.00	1.39	1.68	1.87	N/A
Traumakine	-	-	-	-	-	-	0.23	0.43	0.72	0.90	0.94	N/A
Immunostimulatory Treatment Options	**199.56**	**215.50**	**228.59**	**241.96**	**255.53**	**315.34**	**349.62**	**386.12**	**431.61**	**467.39**	**500.94**	**9.6%**
IgGs	199.56	215.50	228.59	241.96	255.53	269.32	283.28	$297.49	$312.10	$327.05	$350.94	5.8%
CYT107	-	-	-	-	-	-	$13.92	$24.84	$40.27	$49.70	$51.68	N/A
BMS-936559	-	-	-	-	-	$46.03	$52.42	$63.79	$79.24	$90.64	$98.31	N/A
Mechanical devices	**25.56**	**33.30**	**39.52**	**45.89**	**52.36**	**58.91**	**65.54**	**72.28**	**78.92**	**85.07**	**$95.01**	**14.0%**
Toraymyxin	19.51	24.22	28.04	31.95	35.92	39.93	44.00	48.12	52.33	56.59	63.66	12.6%
CytoSorb	6.05	9.08	11.48	13.94	16.44	18.98	21.55	24.15	26.58	28.48	31.35	17.9%
Total	**629.08**	**658.19**	**683.50**	**708.57**	**761.33**	**837.84**	**890.09**	**946.76**	**1,035.22**	**1,061.47**	**1,111.53**	**5.9%**

Source: GlobalData, Pharma eTrack [Accessed June 21, 2017]. Primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

Figure 46 outlines the sales forecast by drug class for sepsis and septic shock in the 5EU in 2016 and 2026.

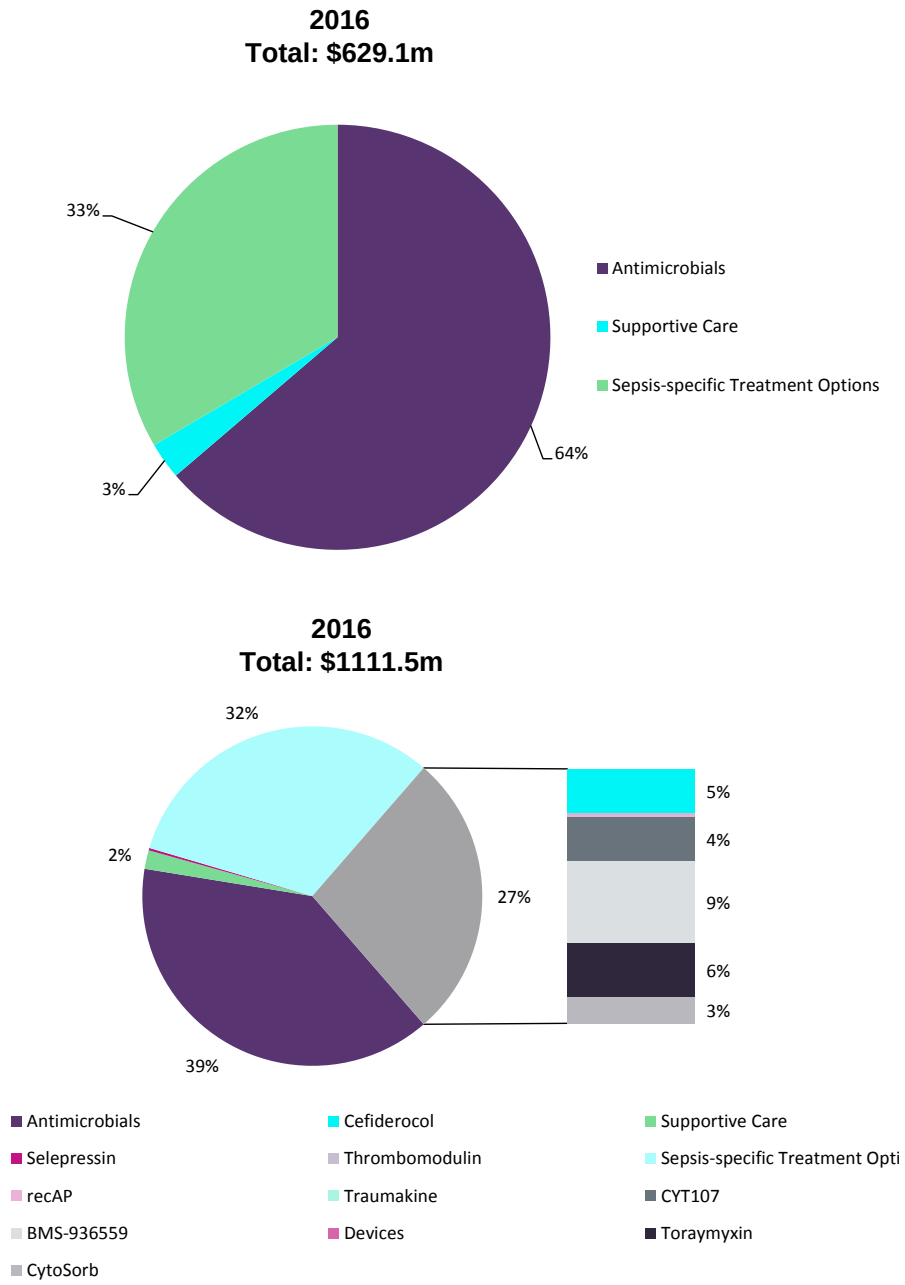
Figure 46: Sales for Sepsis and Septic Shock by Drug Class in the 5EU, 2016 and 2026



Source: GlobalData

Figure 47 outlines the sales forecast of pipeline drug sales compared to conventional therapies for sepsis and septic shock in the 5EU in 2016 and 2026.

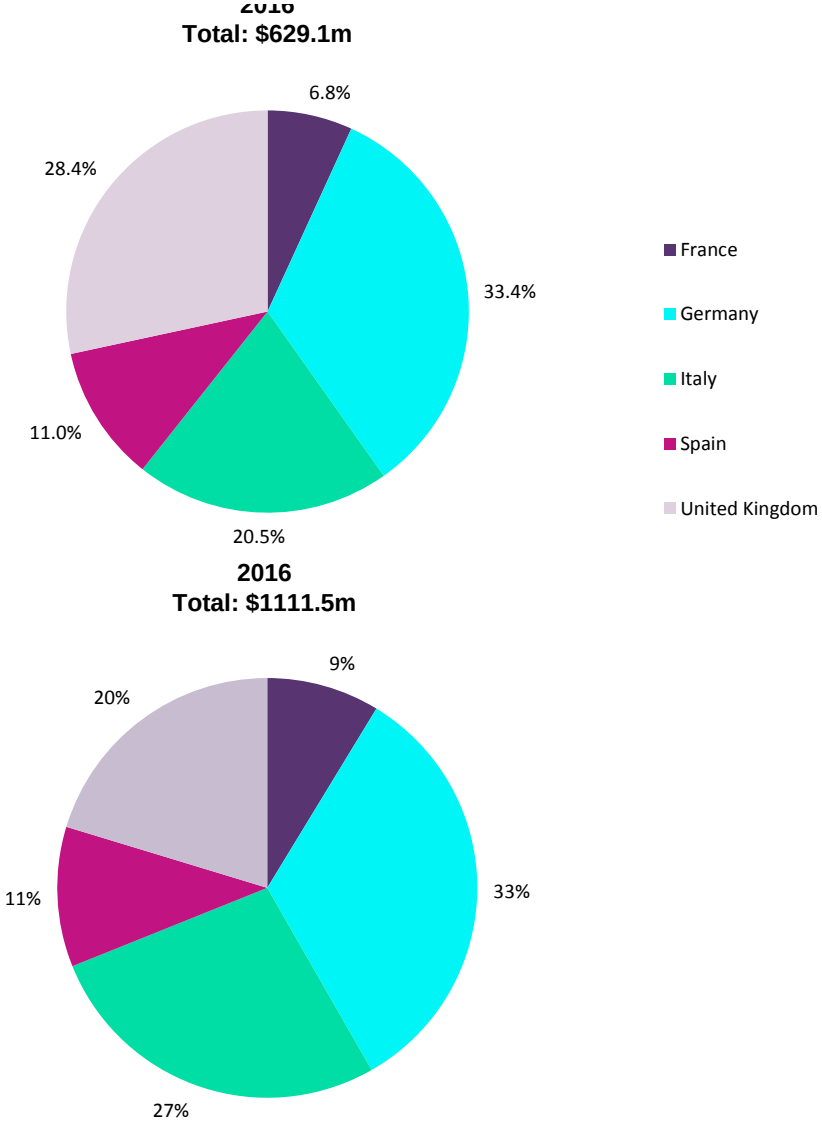
Figure 47: Sales for Sepsis and Septic Shock by Drug Class in the 5EU, 2016 and 2026



Source: GlobalData

Figure 48 outlines the sales forecast by country for sepsis and septic shock in the 5EU in 2016 and 2026.

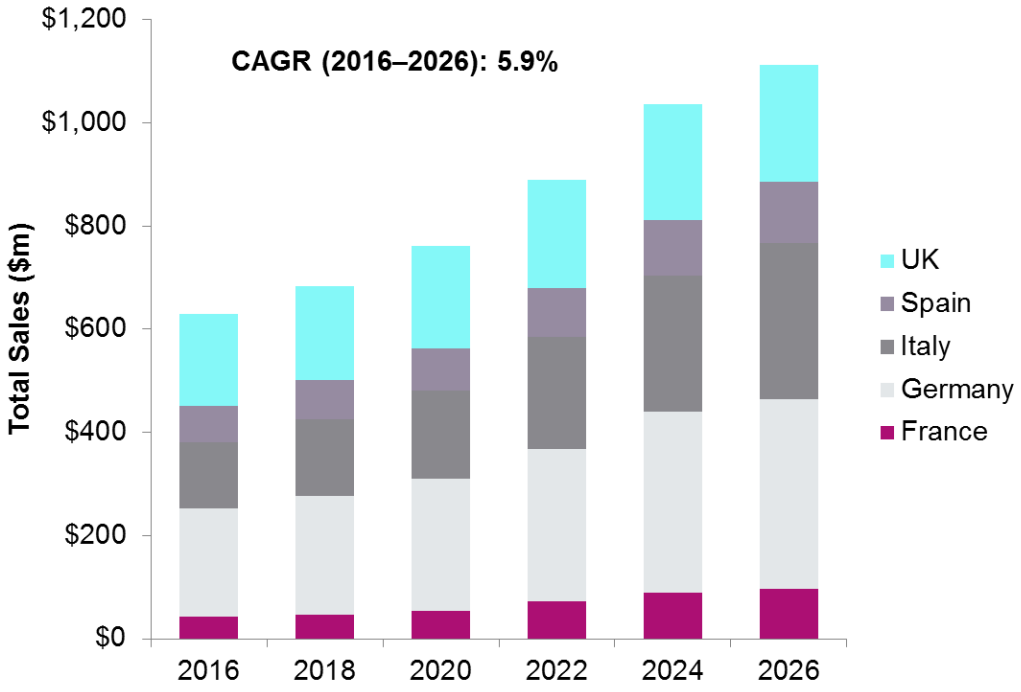
Figure 48: Global Sales for Sepsis nd Septic Shock by Country in the 5EU, 2016 and 2026



Source: GlobalData

Figure 49 outlines the sales forecast by country for sepsis and septic shock in the 5EU from 2016–2026.

Figure 49: Global Sales for Sepsis and Septic Shock by Country in the 5EU, 2016–2026



Source: GlobalData

10.4.3 Japan

Experts anticipate a slight increase in total incidence cases over the forecast period, which will be predominantly associated with an aging population..

GlobalData's primary and secondary research has indicated a very low incidence rate of sepsis and septic shock in Japan compared to the rest of the 7MM. Experts anticipate a slight increase in total incidence cases over the forecast period, which will be predominantly associated with an aging population. In Japan, the main vasopressor used in clinical practice for the treatment of sepsis and septic shock is thrombomodulin. Furthermore, Japanese physicians are more familiar with the use of blood purification devices, such as Toraymyxin, which is already marketed in Japan.

GlobalData estimates the 2016 Japanese sepsis and septic shock market to have reached $117.1m in annual sales. Immunoglobulin treatment contributed the most to overall sales, representing 43% of the overall sales in 2016.

In 2026, GlobalData anticipates the sepsis and septic shock market to experience moderate growth at a CAGR of 2.5%, reaching annual sales of $150.4m. GlobalData identified an overall low incidence rate of sepsis and septic shock as a major hurdle for growth in this market. At the end of the forecast

period, Shionogi's cefiderocol will be the dominant drug, with estimated annual sales of $12.7m. However, GlobalData anticipates BMS' BMS-936559 and RevImmune's CYT107 to remove significant market share from expensive immunoglobulin therapy in the first years after the forecast period. GlobalData expects BMS-936559 and CYT107 to enter the Japanese market in late 2024 and 2025, respectively. The initial uptake of these therapies will be limited due to missing biomarkers to stratify patients. Furthermore, GlobalData anticipates that physicians will be initially cautious in the prescription of immunostimulating drugs; experts cited safety concerns about the administration of immunostimulating drugs to patients suffering from an initial hyperinflammatory response as major hurdle for uptake.

Table 70 presents the sales forecast for selected products used to treat sepsis and septic shock in the 5EU from 2016–2026.

Table 70: Sales Forecasts ($m) for Sepsis and Septic Shock in Japan, 2016–2026

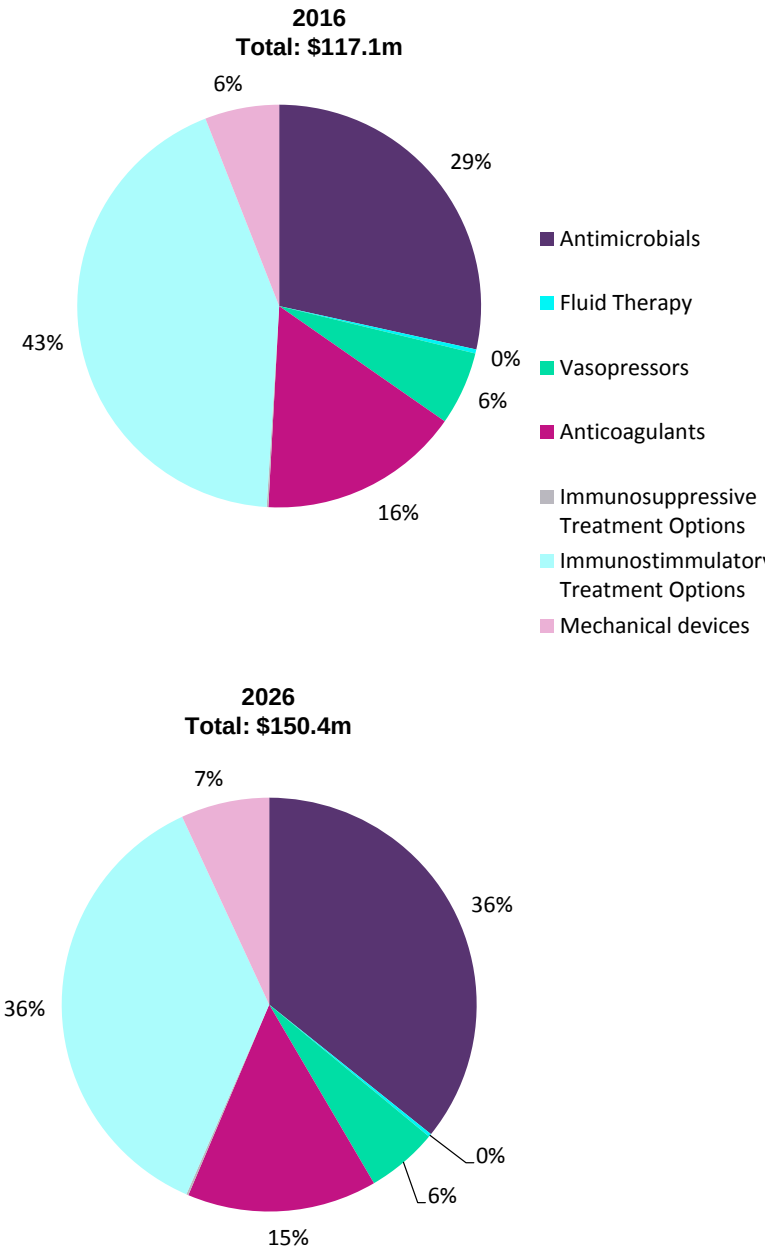
Year	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	CAGR (2016–2026) (%)
Antimicrobials	**33.33**	**34.34**	**35.19**	**41.11**	**42.60**	**44.52**	**46.92**	**49.44**	**51.27**	**52.61**	**53.80**	**4.9 %**
Antibiotics	**33.17**	**34.19**	**35.04**	**40.96**	**42.45**	**44.38**	**46.78**	**49.30**	**51.13**	**52.47**	**53.67**	**4.9 %**
Cefiderocol	-	-	-	5.14	5.86	7.04	8.76	$10.62	$11.83	$12.51	$12.73	N/A
Fluid Therapy	**0.38**	**0.38**	**0.38**	**0.38**	**0.38**	**0.38**	**0.38**	**0.37**	**0.37**	**0.37**	**0.36**	**0.5 %**
Vasopressors	6.92	7.11	7.27	7.41	7.55	7.68	7.80	7.91	8.02	8.14	8.37	1.9 %
Norepinephrine	5.60	5.77	5.90	6.02	6.15	6.26	6.37	6.47	6.57	6.67	6.82	2.0 %
Epinephrine	1.30	1.33	1.35	1.37	1.38	1.40	1.41	1.43	1.44	1.45	1.47	1.2 %
Vasopressins	0.02	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	-3.8%
Dobutamine	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.4 %
Selepressin	-	-	-	-	-	-	-	-	-	-	0.07	N/A
Anticoagulants	**18.93**	**19.39**	**19.79**	**20.13**	**20.47**	**20.80**	**21.10**	**21.37**	**21.62**	**21.89**	**22.27**	**1.6 %**
Heparin	0.33	0.33	0.32	0.32	0.31	0.31	0.30	0.30	0.29	0.28	0.27	-2.0%
Antithrombin	-	-	-	-	-	-	-	-	-	-	-	N/A
Thrombomodulin	18.60	19.06	19.46	19.82	20.16	20.50	20.79	21.07	21.33	21.61	22.00	1.7 %
Immunosuppressive Treatment Options	**0.15**	**0.15**	**0.15**	**0.15**	**0.15**	**0.15**	**0.15**	**0.15**	**1.64**	**0.20**	**0.25**	**4.7 %**
Steroids	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	1.64	0.15	0.14	-

												0.7%
recAP	-	-	-	-	-	-	-	-	-	0.04	0.08	N/A
Traumakine	-	-	-	-	-	-	-	-	-	0.01	0.02	N/A
Immunostimulatory Treatment Options	**50.43**	**50.37**	**50.37**	**50.21**	**50.02**	**49.78**	**49.42**	**49.01**	**50.61**	**52.05**	**55.00**	**0.9 %**
IgGs	50.43	50.37	50.37	50.21	50.02	49.78	49.42	49.01	48.53	48.09	47.11	-0.7%
CYT107	-	-	-	-	-	-	-	-	-	0.79	1.15	N/A
BMS-936559	-	-	-	-	-	-	-	-	2.08	3.17	6.74	N/A
Mechanical devices	**6.97**	**7.21**	**7.56**	**7.89**	**8.22**	**8.56**	**8.88**	**9.20**	**9.51**	**9.84**	**$10.37**	**4.1 %**
Toraymyxin	6.91	7.06	7.33	7.58	7.83	8.09	8.33	8.56	8.79	9.04	9.42	3.2 %
CytoSorb	0.06	0.16	0.23	0.31	0.39	0.47	0.55	0.63	0.72	0.80	0.94	31.0 %
Total	117.11	118.96	120.71	127.29	129.39	131.88	134.65	137.46	143.03	145.08	150.42	2.5 %

Source: GlobalData

Figure 50 outlines the sales forecast by drug class for sepsis and septic shock in Japan in 2016 and 2026.

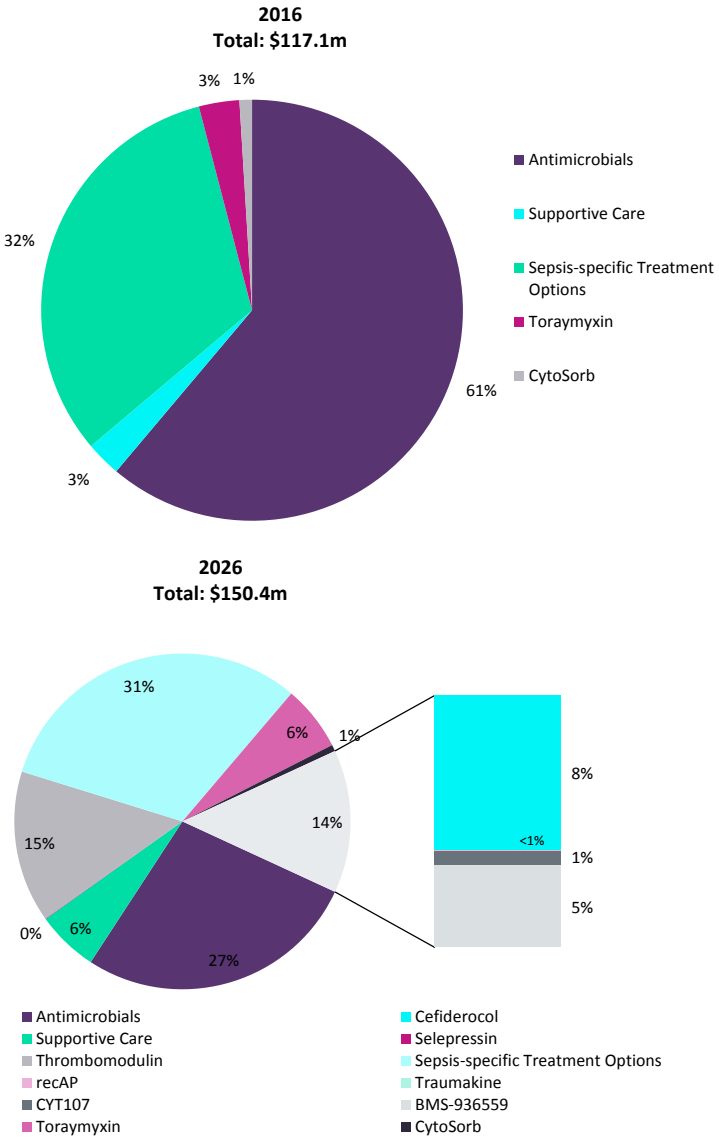
Figure 50: Sales for Sepsis and Septic Shock by Drug Class in Japan, 2016 and 2026



Source: GlobalData

Figure 51 outlines the sales forecast of pipeline drugs compared to conventional therapies for sepsis and septic shock in Japan in 2016 and 2026.

Figure 51: Sales for Sepsis and Septic Shock by Drug Class in Japan, 2016 and 2026



Source: GlobalData

11 Appendix

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11.2 Abbreviations

5EU	the five major European pharmaceutical markets (France, Germany, Italy, Spain, and the UK)
7MM	the seven major pharmaceutical markets (US, France, Germany, Italy, Spain, the UK, and Japan)
ACA:	Affordable Care Act
ACCP/SCCM:	American College of Chest Physicians/Society of Critical Care Medicine
ACOT:	annual cost of therapy
AE:	adverse event
AGR:	Annual Growth Rate
AKI:	acute kidney injury
AKP-A:	Asahi Kasei Pharma America
ALI:	acute lung injury
AP:	alkaline phosphatase
APC:	antigen presenting cell
APACHE II:	acute physiology and chronic health evaluation II
ARDS:	acute respiratory distress syndrome
ASC:	expanded adipose-derived stem cell
AST:	antibiotic susceptibility testing
ATP:	adenosine triphosphate
AUROC:	areas under the receiver curve
AVP:	arginine vasopressin
BIAP:	bovine intestinal alkaline phosphatase
CAGR:	compound annual growth rate
CAP:	community-acquired pneumonia
CARS:	compensatory anti-inflammatory response

CASP:	colon ascendens stent peritonitis
CDC:	Centers for Disease Control and Prevention
CE:	Conformité Européene
CLP:	cecal ligation and puncture
CMS:	Centers for Medicare and Medicaid Services
CMV:	cytomegalovirus
CRP:	C-reactive protein
cUTI:	complicated urinary tract infection
CI:	confidence interval
CIP:	critical illness polyneuropathy
DIC:	disseminated intravascular coagulation, or disseminated intravascular coagulopathy
DVT:	deep vein thrombosis
EAA:	endotoxin activity assay
EMA:	European Medicine Agency
ECG:	electrocardiogram
ECMO:	extracorporeal membrane oxygenation
ECP:	emergency care practitioner
ED:	emergency department
EGDT:	early goal-directed therapy
EMA:	European Medicines Agency
EphMRA:	European Pharmaceutical Marketing Research Association
ESICM:	European Society of Intensive Care Medicine
EUPHAS:	Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock randomized controlled trial
EUPHAS2:	Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock 2 project

EUPHRATES:	pivotal Phase III clinical trial investigating the use of Toraymyxin in septic shock patients
F1.2:	prothrombin fragment
GI:	gastrointestinal
GCSF:	Granulocyte colony stimulating factor
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
HLA-DR:	Human leukocyte antigen - antigen D related
HBV:	hepatitis B virus
HCUP:	US Healthcare Cost and Utilization Project
HCV:	hepatitis C virus
HES:	hydroxyethyl starch
HIV:	human immunodeficiency virus
HLA-DR:	human leukocyte antigen, antigen D related
HMGB1:	high mobility group box-1
ICD-10:	International Classification of Diseases, Tenth Revision
ICU:	intensive care unit
IDSA:	Infectious Diseases Society of America
IFN-γ:	interferon gamma
IgG:	immunoglobulin G
IL-1:	interleukin-1
IL-1β:	interleukin-1 beta
IL-2:	interleukin-2
IL-6:	interleukin-6
IL-18:	interleukin-18
INR:	international normalized ratio (also known as prothrombin time)
ISTH:	International Society on Thrombosis and Hemostasis

IV:	intravenous
JAAM:	Japanese Association for Acute Medicine
JANIS:	Japan Nosocomial Infections Surveillance
JSICM:	Japanese Society of Intensive Care Medicine
KOL:	key opinion leader
LDL:	low-density lipoprotein
LeoPARDS :	Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis
LCOS:	low cardiac output syndrome
LPS:	lipopolysaccharide
LWMH:	low weight molecular heparin
mAb:	monoclonal antibody
MAP:	mean arterial pressure
MAMPs:	microbial-associated molecular patterns
mDIC:	modified disseminated intravascular coagulation
MEWS:	modified early warning score
MHLW:	Ministry of Health, Labour and Welfare (Japan)
MIC:	minimum inhibitory concentration
MOA:	mechanism of action
MRSA:	methicillin-resistant *Staphylococcus aureus*
MSC:	mesenchymal stem cell
NDA:	new drug application
NEWS:	national early warning score
NHDS:	National Hospital Discharge Survey
NHLBI:	National Heart Lung and Blood Institute
NICE:	National Institute for Health and Care Excellence (UK)
NMBAs:	neuromuscular blocking agents

NIS:	Nationwide Inpatient Sample
NO:	nitric oxide
PAMP:	pathogen-associated molecular pattern
PaO_2/FiO_2:	arterial partial pressure of oxygen/fraction of inspired oxygen
PCI:	polymicrobial peritoneal contamination and infection
PCR:	polymerase chain reaction
PCSK9:	proprotein convertase subtilisin kexin type 9
PCT:	procalcitonin
PDMA:	Pharmaceuticals and Medical Devices Agency
PD-1:	Programmed death 1 protein
PD-L1:	Programmed death ligand 1
PEEP:	positive end-expiratory pressure
PIRO:	predisposition, infection, response and organ dysfunction
PK/PD:	pharmacokinetics/pharmacodynamics
PRR:	pattern recognition receptor
PT-INR	prothrombin time international normalized ratio
qSOFA:	quick sequential organ failure assessment
RCT:	randomized clinical trial
recAP:	recombinant human alkaline phosphatase
ROI:	return on investment
RRT:	renal replacement therapy
SA-AKI:	sepsis-associated acute kidney injury
SAE:	serious adverse event
SAPS2:	simplified acute physiology score
SEP-1:	Sepsis core measure
SEPSIS-2:	2nd sepsis consensus definition

SEPSIS-3:	3rd sepsis consensus definition
SCCM:	Society of Critical Care Medicine (US-based)
SCIENS:	Phase IIa trial involving IFX-1 being conducted by InflaRx
sCD163:	soluble CD163
sFas:	Soluble factor associated suicide
SIRS:	systemic inflammatory response syndrome
SOC:	standard of care
SOFA:	sequential organ failure assessment
SSC:	Surviving Sepsis Campaign
TATc:	thrombin-antithrombin complex
TF:	tissue factor
TLR-4:	toll-like receptor 4
TNF-α:	tumor necrosis factor alpha
TOC:	test of cure
UCSD:	University of California, San Diego
USCB:	United States Census Bureau
UTI:	urinary tract infection
$V_{1a}R$:	vasopressin type 1a receptor
$V_{1b}R$:	vasopressin type 1b receptor
V_2R:	vasopressin type 2 receptor
VAP:	ventilator-associated pneumonia
vWF:	von Willebrand factor
WBC:	white blood cell count

11.3 Methodology

GlobalData's dedicated research and analysis teams consist of experienced professionals with marketing, market research, and consulting backgrounds in the pharmaceutical industry, and advanced statistical expertise.

GlobalData adheres to the codes of practice of the European Pharmaceutical Marketing Research Association (EphMRA, ephmra.org).

All GlobalData databases are continuously updated and revised. The following research methodology is followed for all databases and reports.

11.4 Forecasting Methodology

GlobalData uses a patient-based forecast to determine the market size for therapeutic indications. Estimates for the 2016 market for sepsis and septic shock in the 7MM are based on a number of sources, including KOL interviews, prescriber surveys, company reports, press releases, published articles, proprietary databases, and general news media.

For sepsis and septic shock, total patient share exceeds 100% when patients are prescribed more than one drug; many patients are concomitantly treated with a combination of antibiotics to extend antibiotic spectrum or increase antibiotic activity with synergies between antibiotics. The estimated number of compliant days for each drug is determined from prescriber surveys, KOL interviews, and internal estimated compliance rates based on the drug's profile.

GlobalData's proprietary forecast model does not account for inflation and is in 2016 dollars. The following paragraphs outline the underlying assumptions for the forecast.

11.4.1 Diagnosed Sepsis and Septic Shock Patients

The total sepsis and septic shock population is the same as the diagnosed population, as this is a life-threatening critical illness, requiring immediate therapy and hospitalization.

Sepsis and septic shock patients are segmented by organ dysfunction (DIC, AKI, ALI, and any other organ dysfunction, including hepatic and neurologic manifestations) in each major market. Percentages in each segment were obtained from secondary literature resources. GlobalData did not segment patients by causative pathogen, but has provided information on the prevalence of bacterial (Gram-negative and Gram-positive) and fungal infections. The causative pathogen was instrumental to the chosen patient shares of all treatment options in the sepsis and septic shock market.

11.4.2 Percent Drug-Treated Patients

Percent drug-treated patients were calculated using both primary and secondary research. GlobalData estimates the percentage of drug-treated patients to change depending on drug and disease indication (sepsis or septic shock). The moderate uptake of new pipeline drugs is mainly driven by the absence of reliable biomarkers to stratify patients. GlobalData expects a slow gradual change away from current steroids and non-specific immunostimulants (immunoglobulins) towards specific immunosuppressant biologic treatment options (BMS-936559, CYT107, recAP, and Traumakine) over the forecast period.

11.4.3 Drugs Included in Each Therapeutic Class

The sepsis and septic shock drugs included in GlobalData's market forecast can be broadly classified into the following therapeutic classes. Representative members of the classes were chosen based on primary research among physicians across the 7MM:

Antimicrobials (only IV formulations were considered)

- **Antimicrobials** include antibiotics and antifungal therapies
- **Aminoglycosides** include gentamycin and streptomycin
- **Fluoroquinolones** include ciprofloxacin and levofloxacin
- **Carbapenems** include meropenem, imipenem, and imipenem with cilastatin
- **Extended spectrum β-lactams** include ampicillin, amoxicillin/clavulanic acid, and piperacillin/tazobactam
- **Macrolides** include azithromycin, clarithromycin, and erythromycin
- **Glycopeptides** include vancomycin and Targocid (teicoplanin)
- **Oxazolidinones** include Zyvox/Zyvoxid/Gabriox (linezolid) and Sivextro (tedizolid phosphate)
- **Lipopeptides and polymyxins** include Cubicin (daptomycin) and colistin
- **Antifungals** include amphotericin B and nystatin

Fluid Therapy

- **Crystalloids** include Ringer's solution
- **Albumin** include human albumin

Vasopressors (only IV formulations were considered)

- **Norepinephrine**
- **Epinephrine**
- **Vasopressin**
- **Dobutamine**

Anticoagulants

- **Heparin** includes low molecular weight heparin (LMWH) only
- **Antithrombin** includes antithrombin III only

Immunosuppressive Treatment Options

- **Steroids** include hydrocortisones only

Immunostimulatory Treatment Options

- Immunoglobulins (IVIgGs)

Mechanical devices

- **Toraymyxin**
- **CytoSorb**

11.4.4 Launch and Patent Expiry Dates

Table 71 summarizes the projected launch dates for sepsis and septic shock across the 7MM. The launch dates were estimated based on primary and secondary research.

Table 71: Key Projected Launch Dates for Sepsis and Septic Shock

Product – Brand Name(s) (Drug Name)	US	5EU	Japan
BMS-936559	2021	2021	2024
Cefiderocol	2019	2020	2020
recAP	2021	2021	2025
Traumakine	2022	2022	2025
CYT107	2022	2022	2025
Selepressin	2020	2020	2026
Thrombomodulin	2018	2018	Marketed
Toraymyxin	2018	Marketed	Marketed
CytoSorb	2020	Marketed	Marketed

Source: GlobalData, Pharma eTrack [Accessed June 22, 2017], primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report.

11.4.5 General Pricing Assumptions

GlobalData uses national formularies to gather pricing information. Prices presented in formularies can represent prices at different stages in the supply chain. As such, when ex-factory wholesale prices are not available, GlobalData uses conversion formulas—which remove taxes and pharmacy and wholesale margins—in order to obtain estimated ex-factory wholesale prices for each country. In Japan, wholesale and pharmacy margins added to manufacturer prices are unregulated, and as such an estimated ex-factory pharmacy price is utilized in our forecasts.

Currency conversion to US dollars utilized the 2016 yearly average from OANDA (www.oanda.com).

The following references were used as price sources, backing-out formulas, and discount rates for each market covered in this report, to estimate ex-factory wholesale pricing:

- US: Prices were obtained from Thomson Reuters' Red Book.
- France: Prices were obtained from Ministère des Affaires Sociales et de la Santé.
- Germany: Prices were obtained from Rote Liste, and conversion formulas were determined based on information from the Patented Medicine Prices Review Board (PMPRB) (PMPRB, 2013).
- Italy: Prices were obtained from L´Informatore Farmaceutico, and conversion formulas were determined based on information from the Patented Medicine Prices Review Board (PMPRB) (PMPRB, 2013).
- Spain: Prices were obtained from Organización Farmacéutica Colegial.
- UK: Prices were obtained from the British National Formulary (BNF), and conversion formulas were determined based on information from the European Parliament (European Parliament, 2011) and National Institute for Health and Care Excellence (NICE) (NICE, 2014).
- Japan: Prices were obtained from the SSRI's NHI drug price database (April 2012). Conversion formulas were determined based on information from the Japan Pharmaceutical Manufacturers Association (JPMA) (JPMA, 2012) and *The Wall Street Journal* (Mochiziku, 2014).

GlobalData used data on national adult weight averages to price drugs that are dosed based on weight. The following references were used as sources to estimate the national average weights:

- US: Fryar et al., 2012
- France: Castetbon et al., 2009
- Germany: Mensink et al., 2013; Scheidt-Nave et al.,, 2012

- Italy: Leclercq et al., 2009
- Spain: Rodríguez-Rodríguez et al., 2009
- UK: Sutton R, 2011
- Japan: Lin Y et al., 2004

11.4.6 Individual Drug Assumptions

This section provides a concise overview of the clinical positioning, number of treatment days, ACOT, and compliance for each drug in the forecast.As there are currently no marketed drugs directly indicated for sepsis or septic shock, and currently branded antibiotics used in infection control are outside the scope of this report, this section will be primarily focused on pipeline drugs expected to be launched during the forecast period. Based on GlobalData's primary and secondary research, sepsis and septic shock coincide very often with more than one organ dysfunction. If more than two organ systems are involved in sepsis and septic shock, patients are diagnosed with MODS. In order to adjust for comorbidities and the involvement of multiple organ dysfunctions across sepsis and septic shock patients, GlobalData multiplied patient shares with the reported rate of MODS across the 7MM for drugs prescribed in all organ dysfunctions. For specific drug classes, such as anticoagulants and special medical devices, GlobalData applied no factor for the adjustments, but adjusted the corresponding patient shares. Sepsis and septic shock are life-threatening diseases and treatment requires hospitalization across all 7MM, therefore GlobalData assumes a compliance rate of 100% for all products used in the treatment protocol.

11.4.6.1 Aminoglycosides (numerous drugs available):

- **Clinical positioning:** Aminoglycosides are a class of antibiotics with Gram-negative bactericidal activity.
- **Treatment days:** The average number of treatment days per course of aminoglycosides is 10.
- **Average cost of therapy:** US: $207.48; France: $71.11; Germany: $207.48; Italy: $72.74; Spain: $12.02; UK: $111.24; Japan: $62.56. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.2 Fluoroquinolones (numerous drugs available):

- **Clinical positioning:** Fluoroquinolones are a class of antibiotics with broad-spectrum bactericidal activity against both Gram-negative and Gram-positive bacteria.
- **Treatment days:** The average number of treatment days per course of fluoroquinolones is 10.
- **Average cost of therapy:** US: $120.49; France: $18.47; Germany: $802.06; Italy: $168.64; Spain: $45.95; UK: $372.91; Japan: $440.68. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.3 Carbapenems (numerous drugs available):

- **Clinical positioning:** Carbapenems are a class of antibiotics with broad-spectrum bactericidal activity against both Gram-negative and Gram-positive bacteria.
- **Treatment days:** The average number of treatment days per course of carbapenems is 10.
- **Average cost of therapy:** US: $1,127.70; France: $568.03; Germany: $1,079.96; Italy: $423.82; Spain: $1,346.27; UK: $826.80; Japan: $820.67. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.4 Extended spectrum β-lactams:

- **Clinical positioning:** Extended spectrum β-lactams are a class of antibiotics with broad-spectrum bactericidal activity against both Gram-negative and Gram-positive bacteria.
- **Treatment days:** The average number of treatment days per course of extended spectrum β-lactams is 10.
- **Average cost of therapy:** US: $438.60; France: $189.64; Germany: $344.49; Italy: $173.10; Spain: $131.39; UK: $973.09; Japan: $266.17. GlobalData only used IV formulations of antibiotics in this class. Generics are available.

- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.5 Macrolides (numerous drugs available):

- **Clinical positioning:** Macrolides are a class of antibiotics with broad-spectrum bacteriostatic activity against both Gram-negative and Gram-positive bacteria (mostly Gram-positive).
- **Treatment days:** The average number of treatment days per course of macrolides is 10.
- **Average cost of therapy:** US: $65.66; France: $22.21; Germany: $271.35; Italy: $62.06; Spain: $21.73; UK: $443.02; Japan: $35.77. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.6 Glycopeptides (numerous drugs available):

- **Clinical positioning:** Glycopeptides are a class of antibiotics with bactericidal activity against Gram-positive bacteria.
- **Treatment days:** The average number of treatment days per course of glycopeptides is 10.
- **Average cost of therapy:** US: $324.94; France: $440.22; Germany: $676.92; Italy: $290.29; Spain: $231.39; UK: $276.93; Japan: $445.97. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.7 Oxazolidinones (numerous drugs available):

- **Clinical positioning:** Oxazolidinones are a class of antibiotics with bacteriostatic activity against Gram-positive bacteria.
- **Treatment days:** The average number of treatment days per course of oxazolidinones is 10.

- **Average cost of therapy:** US: $1,711.71; France: $771.42; Germany: $133.54; Italy: $746.04; Spain: $825.97; UK: $1,380.14; Japan: $1,649.84. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.8 Lipopeptides and polymyxins (numerous drugs available):

- **Clinical positioning:** Lipopeptides and polymyxins are two classes of antibiotics with bacteriostatic activity against Gram-positive (lipopeptides) and Gram-negative (polymyxins) bacteria.
- **Treatment days:** The average number of treatment days per course of lipopeptides and polymyxins is 10.
- **Average cost of therapy:** US: $3,191.33; France: $848.07; Germany: $1,393.64; Italy: $653.33; Spain: $749.46; UK: $595.86; Japan: $487.54. GlobalData only used IV formulations of antibiotics in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.9 Antifungals (numerous drugs available):

- **Clinical positioning:** Antifungals are a class of antimicrobials with activity against fungal pathogens.
- **Treatment days:** The average number of treatment days per course of antifungals is 10.
- **Average cost of therapy:** US: $159.12; France: $1,174.50; Germany: $3,450.51; Italy: $10.09; Spain: $74.19; UK: $1,163.22; Japan: $45.24. GlobalData used both oral and IV formulations of drugs in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The

adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.10 Crystalloids:

- **Clinical positioning:** Crystalloids are the first-line treatment options for fluid resuscitation in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of crystalloids is one.
- **Average cost of therapy:** US: $10.04; France: $2.71; Germany: $44.07; Italy: $14.00; Spain: $3.99; UK: $10.33; Japan: $4.98. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.11 Albumin:

- **Clinical positioning:** Albumin solutions are frequently used for fluid resuscitation in sepsis and septic shock patients. However, their higher cost and the non-inferiority of crystalloids in RCTs limits their use.
- **Treatment days:** The average number of treatment days per course of albumin is one.
- **Average cost of therapy:** US: $353.76; France: $1.59; Germany: $103.54; Italy: $158.06; Spain: $130.70; UK: $123.81; Japan: $179.97. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.12 Norepinephrine (numerous brand names):

- **Clinical positioning:** Norepinephrine is the first-line treatment option to treat persistent hypotension in septic shock patients.
- **Treatment days:** The average number of treatment days per course of norepinephrine is one.
- **Average cost of therapy:** US: $3.81; France: $1.08; Germany: $15.76; Italy: $1.05; Spain: $0.17; UK: $1.19; Japan: $410.28. Generics are available.

- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.13 Epinephrine (numerous brand names):

- **Clinical positioning:** Epinephrine is a second-line therapy for the treatment of hypotension in septic shock patients.
- **Treatment days:** The average number of treatment days per course of epinephrine is one.
- **Average cost of therapy:** US: $9.44; France: $5.58; Germany: $0.88; Italy: $5.58; Spain: $1.31; UK: $14.55; Japan: $529.78. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.14 Vasopressins:

- **Clinical positioning:** Vasopressin is a third-line and beyond treatment option in the treatment of non-responsive hypotension in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of vasopressins is one.
- **Average cost of therapy:** US: $79.07; France: $48.09; Germany: $48.09; Italy: $48.09; Spain: $1.26; UK: $94.91; Japan: $5.65. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.15 Dobutamine:

- **Clinical positioning:** Dobutamine is a third-line therapy for the treatment of hypotension in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of dobutamine is one.

- **Average cost of therapy:** US: $1.03; France: $1.07; Germany: $1.69; Italy: $0.48; Spain: $0.47; UK: $1.32; Japan: $1.00. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.16 Heparin:

- **Clinical positioning:** LMWH is a first-line treatment option for sepsis-induced DIC.
- **Treatment days:** The average number of treatment days per course of heparin is six.
- **Average cost of therapy:** US: $20.22; France: $0.36; Germany: $3.58; Italy: $0.04; Spain: $5.45; UK: $18.75; Japan: $75.10. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis and septic shock were assumed to be 100% in all markets, because this product is for a specific organ dysfunction so any adjustments are already reflected in the patient share assigned.

11.4.6.17 Antithrombin:

- **Clinical positioning:** Antithrombin III is a second-line anticoagulant used in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of antithrombin is six.
- **Average cost of therapy:** US: $1,164.00; France: $97.60; Germany: $147.42; Italy: $66.39; Spain: $78.98; UK: $97.60; Japan: $128.95. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis and septic shock were assumed to be 100% in all markets, because this product is for specific organ dysfunctions and so any adjustments are already reflected in the patient share assigned.

11.4.6.18 Steroids:

- **Clinical positioning:** Although steroid treatment has not been shown efficacious in RCTs, steroids are frequently used as immunosuppressant therapy in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of steroids is three.

- **Average cost of therapy:** US: $49.63; France: $7.40; Germany: $85.93; Italy: $5.90; Spain: $2.30; UK: $9.26; Japan: $26.69. GlobalData used only IV formulations of drugs in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.6.19 IgGs:

- **Clinical positioning:** Although IVIgG treatment has not been shown efficacious in RCTs, IgGs are frequently used as immunostimulant therapy in sepsis and septic shock patients.
- **Treatment days:** The average number of treatment days per course of IgGs is 2.
- **Average cost of therapy:** US: $10,806.37; France: $170.00; Germany: $7,629.89; Italy: $10,363.12; Spain: $4,267.38; UK: $4,891.68; Japan: $19,937.25. GlobalData used only IV formulations of drugs in this class. Generics are available.
- **Adjustments for comorbidities:** The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.7 Generic Erosion

While in general the prices of drugs experiencing a loss of market exclusivity decrease upon the entry of generic competition, GlobalData assumed that the majority of antibiotic classes are already dominated by generic drugs, thus upcoming patent expiries are thought not to influence the overall pricing as a class.

11.4.8 Pricing of Pipeline Agents

11.4.8.1 Cefiderocol

GlobalData assumes a dose of 2g of cefiderocol every 8 hours, totaling 6g/day over a course of 10 days. GlobalData expects an average dosing adjusted pricing based on ceftazidime pricing and Zerbaxa, deriving ACOTs of US: $5,749.20; France: $3,139.50; Germany: $4,232.22; Italy: $3,328.75; Spain: $225.68; UK: $4,771.34; Japan: $5,749.20. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%.

The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.2 Selepressin

GlobalData assumed a 25% premium over generically available vasopressin in order to effectively compete for market share in this treatment category across the 7MM. GlobalData expects ACOTs of US: $98.84; France: $60.11; Germany: $60.11; Italy: $60.11; Spain: $1.58; UK: $118.64; Japan: $512.85. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.3 Thrombomodulin

GlobalData assumed a similar 7MM pricing strategy for thrombomodulin to that in Japan, where the drug is currently marketed. GlobalData expects ACOTs of US: $3,927.94; France: $329.34; Germany: $497.47; Italy: $224.03; Spain: $266.52; UK: $329.34; Japan: $435.14. The adjustments made for comorbidities in sepsis and septic shock were assumed to be 100% in all markets, because this product is for specific organ dysfunction and so any adjustments are already reflected in the patient share assigned.

11.4.8.4 Traumakine

GlobalData based the pricing for Traumakine on the marketed IFN-β-1a therapies such as Avonex and Rebif. GlobalData assumed a dose of 10µg over the course of treatment. GlobalData assumed the following ACOTs: US: $2,095.67; France: $72.81; Germany: $98.19; Italy: $76.26; Spain: $86.30; UK: $57.57; Japan: $103.91. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.5 recAP

GlobalData assumed a similar pricing strategy for recAP to that for Traumakine. Both therapies have similar modes of action and are set up to be potential future competitors. GlobalData assumes the following ACOTs: US: $2,095.67; France: $72.81; Germany: $98.19; Italy: $76.26; Spain: $86.30; UK: $57.57; Japan: $103.91. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made

for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.6 BMS-936559

GlobalData assumed a similar pricing for BMS-936559 to AstraZeneca's anti-PD-L1 checkpoint inhibitor Imfinzi (darvalumab), assuming that prices across different disease indications will not be significantly different. Compared to the treatment of various cancer targets, mAb therapy in sepsis and septic shock is assumed to be at a lower dose and for shorter periods. GlobalData assumed an average dose of 10mg/kg for BMS-936559 for sepsis and septic shock patients, over a treatment period of two days. GlobalData used average weight adjustments across the 7MM to derive at the final ACOT (US: $11,402.22, France: $8,539.44, Germany: $8,539.44, Italy: $8,539.44, Spain: $3,417.16, UK: $2,955.30, Japan: $3,256.90). The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.7 CYT107

GlobalData assumes pricing of CYT107 to be similar to BMS-936559, as both drug target a similar patient population, and are both of biological origin. GlobalData assumes an ACOT of US: $11,402.22, France: $8,539.44, Germany: $8,539.44, Italy: $8,539.44, Spain: $3,417.16, UK: $2,955.30, Japan: $3,256.90. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.8 Toraymyxin

Toraymyxin is already marketed in the 5EU and Japan. GlobalData based pricing of this pipeline drug on primary research with KOLs across the 7MM. GlobalData assumes an ACOT of $10,000 for the US, 5EU, and Japan. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.4.8.9 CytoSorb

CytoSorb is already marketed in the 5EU and Japan. GlobalData based pricing of this pipeline drug on primary research with KOLs across the 7MM. GlobalData assumes an ACOT of US: $4,000.00; France:

$4,000.00; Germany: $4,000.00; Italy: $4,000.00; Spain: $4,000.00; UK: $4,000.00; Japan: $4,000.00. The adjustments made for comorbidities in sepsis are – US: 55.0%; France: 48.0%; Germany: 48.0%; Italy: 48.0%; Spain: 48.0%; UK: 78.9%; Japan: 77.1%. The adjustments made for comorbidities in septic shock are – US: 63.5%; France: 63.5%; Germany: 63.5%; Italy: 63.5%; Spain: 70.9%; UK: 63.5%; Japan: 63.5%.

11.5 Primary Research – KOLs Interviewed for this Report

Mayuki Aibiki, MD

Chairman and Vice-President, Emergency Medicine

Department of Emergency Medicine, Ehime University

Shitsukawa, Japan

Derek C. Angus, MD, MPH, FRCP

University of Pittsburgh School of Medicine

University of Pittsburgh Schools of the Health Sciences

UPMC Health System

Professor and Chair, Critical Care Medicine

Distinguished Professor and Mitchell P. Fink Endowed Chair

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Professor of Critical Care Medicine, Medicine, Health Policy and Management, and Clinical and Translational Science

Director, CRISMA Center, Department of Critical Care Medicine

Pittsburgh, Pennsylvania, US

Frank M. Brunkhorst, MD

Professor of Anesthesiology and Critical Care Medicine

Director, Center for Clinical Studies, University of Jena

Head, Paul Martini Research Unit Clinical Septomics / Department of Anesthesiology and Intensive Care

Senior Physician, Internal Medicine

Jena, Thuringia, Germany

Jean-Daniel Chiche, MD

Full Professor of Critical Care Medicine

Hopital Cochin

Executive Committee Co-Chair: Surviving Sepsis Campaign

Immediate Past- President of the ESICM

Paris, France

Ron Daniels, MB, ChB, FRCPEd, FRCA, FFICM

Consultant, Critical Care and Anesthesia

Heart of England NHS Foundation Trust

CEO: Global Sepsis Alliance

Chair: United Kingdom Sepsis Group

Principal Trustee: UK Sepsis Trust

Founding Director: Survive Sepsis

Birmingham, UK

Toru Kotani, MD

Anesthesiology; Critical Care Medicine

Tokyo Women's Medical University

Tokyo, Japan

Mitchel Levy, MD

Professor of Medicine and Division Chief, Pulmonary and Critical Care Medicine

Alpert Medical School of Brown University

Medical Director, MICU, Rhode Island Hospital

Providence, Rhode Island, USA

Steven M Opal, MD

Professor of Infectious Disease and Internal Medicine

Professor, Medicine

Chief of the Infectious Disease Division

Director, Infectious Disease Division

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Jean-Louis Vincent, MD

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Consultant, Head, Department of Intensive Care, Erasme Hospital

Chairman, International Sepsis Forum

Clinical Instructor, Departments of Anesthesiology and Critical Care, University of Southern California

President, European Society of Intensive Care Medicine

Brussels, Belgium

11.6 Primary Research – Prescriber Survey

In addition to the KOLs cited above, high-prescribing physicians (non-KOLs), including critical care medicine, intensive care medicine, and Internal Medicine represented the seven markets covered in this report. All of the non-KOL responses were obtained through an electronic survey created by the report authors in collaboration with the GlobalData primary research team. The survey was launched in April 2017 and completed in May 2017.

A summary of high prescribers surveyed for this report can be found in Table 72.

Table 72: High-Prescribing Physicians (non-KOLs) Surveyed, By Country

Country	Total Number of Prescribers Surveyed
US	20
France	10
Germany	11
Italy	10
Spain	11
UK	10
Japan	10
Market 8	0
Market 9	0
Total (7MM)	**82**

Source: GlobalData

11.7 About the Authors

11.7.1 Analyst

Sebastian S. Gehrke, PhD is an Analyst in the Infectious Disease team at GlobalData in London (UK). Sebastian constructs syndicated market research reports for the pharmaceutical health care sector. Since joining GlobalData in 2016, Sebastian has provided in-depth scientific analysis of products within the pharmaceutical sector, constructed market forecast models based on extensive primary and secondary research, using this business intelligence to formulate potential market access strategies. Sebastian's key areas of expertise span the fields of immunology and infectious diseases. Sebastian holds a PhD in medicinal chemistry/biochemistry, which he was awarded from the University of East Anglia during his multidisciplinary doctoral studies at King's College London, the John Innes Centre Norwich and the University of East Anglia (UK). Sebastian's PhD studies dealt with the discovery of novel drugs for neglected parasitic diseases, such as African sleeping sickness, Chagas disease, and leishmaniosis. After his PhD in 2012, Sebastian did his postdoctoral studies in the Institute for Infectious Disease Research at McMaster University (Canada). At McMaster University, Sebastian worked on high-throughput screens of small molecules and natural products to identify novel antibacterial targets and drug classes to combat the Gram-negative antibiotic drug crisis.

11.7.2 Therapy Area Director

Christopher J. Pace, PhD is the Director of Infectious Diseases at GlobalData in Boston, where he oversees the infectious diseases portfolio of syndicated market research reports. Since joining

GlobalData in 2013, Dr. Pace has extensively researched and provided in-depth analysis and commentary on a wide range of topics within the infectious diseases space and across the pharmaceutical and healthcare industries, with areas of expertise including hepatitis C and HIV therapeutics, vaccine R&D and immunization policy (specifically dengue, meningococcal disease, and hepatitis B), and market access strategies for antibiotics. Dr. Pace holds a PhD in Chemistry from Boston College and a BS in Chemistry from Fairfield University. Dr. Pace's doctoral research focused on the use of unnatural amino acids as tools for examining the fundamental energetics of aromatic interactions in proteins. While at Boston College, Christopher tutored college-level chemistry and biochemistry in the greater Boston area, and he also served as the Boston College Campus Representative for the Northeastern Section Younger Chemists Committee (NSYCC).

11.7.3 Epidemiologist

Thirumugam M., MHA is a Senior Epidemiologist at GlobalData in Hyderabad, India. His responsibilities include producing epidemiological reports for major disease indications, monitoring and maintaining the company's state-of-the-art epidemiology database. Prior to joining GlobalData, Thirumugam worked as a Scientist-B (Research Scientist) in the Indian Council of Medical Research (ICMR) funded epidemiology research project at German Leprosy and TB Relief Association India. He worked as Consultant, Public Health in Regional Resource Centre of North Eastern States, under the aegis of Ministry of Health and Family Welfare, Govt. of India; Christian Medical College (CMC) Vellore in the Department of Physical Medicine and Rehabilitation as a Tutor in the past. He is a certified Operational Research expert and scientific writer by TB UNION, World Health Organization and also certified in conducting Cochrane systematic reviews by South Asian Cochrane Network. During his career, he has published several research articles in various international peer-reviewed journals. Thirumugam holds a Master of Public Health Administration degree from the School of Health System Studies, Tata Institute of Social Sciences, Mumbai, and a Bachelor of Occupational Therapy degree from CMC, Vellore. Besides, he also holds a Master Degree in Health Care and Hospital Management from Anna University, Coimbatore.

11.7.4 Managing Epidemiologists

Lizzy Sunny, PhD is the Practice Head of the Epidemiology Division at GlobalData in Hyderabad, India. Dr. Sunny has worked with various national-level cancer registries, well-respected academic institutions, and pharmaceutical consulting companies around the globe. She is experienced in the design and execution of many large-scale population-based epidemiological studies, including breast cancer screening studies, and in analyzing epidemiological research data. During her career, she has published several research articles in various international peer-reviewed journals, and has written

several reports and monographs related to cancer epidemiology. Additionally, she has worked for top pharmaceutical companies in the US and Europe on epidemiology consulting projects. She has received large project grants from national and international organizations, and has headed various national-level epidemiology projects in India. Dr. Sunny holds a Master's degree in Science from MG University, India; a Doctoral Programs in Public Health (DPPH) degree from the Tampere School of Public Health at Tampere University in Finland; and a PhD in Epidemiology from Tampere University. She completed her post-doctoral research in clinical cancer epidemiology at Gothenburg University in Sweden.

Kasey Fu, MPH is the Director of Epidemiology at GlobalData in Boston, where her primary responsibilities include producing descriptive and analytical epidemiological reports for major drug indications, monitoring and maintaining the company's state-of-the-art epidemiology database, liaising with other company units in developing new products, and completing global consulting projects. Prior to joining GlobalData, Kasey worked as a Wilbur G. Downs Global Health Fellow at the Instituto Nacional de Salud of Colombia analyzing dengue epidemic trends, risk factors, and the effects of climate change using multivariate regression and spatial modeling. She also worked as a staff writer for the Yale-Tulane Virtual Medical Operations Center producing public health and epidemiology reports for US military operations and international aid efforts during catastrophic disasters. Kasey holds a Master of Public Health in the Epidemiology of Microbial Diseases from the Yale School of Public Health. She is also fluent in Chinese and proficient in Spanish.

11.7.5 Global Director of Therapy Analysis and Epidemiology

Claire Herman, MPH is the Global Director of Therapy Analysis and Epidemiology at GlobalData in Boston. She has more than 15 years of experience in the healthcare industry, during which she has led teams in the development and delivery of industry-leading competitive intelligence product offerings. Claire began her career at Decision Resources, where she worked as an Analyst and Epidemiologist evaluating disease markets across therapeutic areas, assessing the potential of pipeline drugs in the context of current medical practice, and developing patient-based prescription drug sales forecasts. Prior to her current role, Claire was the Director of Autoimmune/Inflammation, CNS, and Ophthalmology for Citeline/Informa's Trialtrove database, where she managed her team's daily operations and was involved in various product enhancement initiatives. Previously, she was a Manager in Citeline's consulting division, where she developed customized analyses of the clinical trials competitive landscape. Claire holds a Bachelor's degree from Wellesley College and a Master of Public Health degree in epidemiology from Boston University.

11.7.6 Global Head and EVP of Healthcare Operations and Strategy

Bornadata (Bonnie) Bain, PhD is the Global Head and EVP of Healthcare Operations and Strategy. Bonnie has almost 20 years' experience in the healthcare sector and a proven track record of developing innovative solutions on both the client and agency sides of the business. Bonnie was GlobalData Healthcare's first western analyst and under her leadership, the company launched a number of premium syndicated reports, analytical tools and databases in the pharmaceuticals and medical devices space. Prior to GlobalData, Bonnie was Vice President and Global Research & Analysis Director for Informa's Pharma Division, which includes Datamonitor Healthcare, Scrip Group, and Business Insight. Bonnie also worked for several years at Decision Resources as an Analyst and Project Manager. On the client side of the industry, Bonnie worked for several years as a Senior Manager in Marketing Strategy and Analytics at Boston Scientific where her work contributed to the successful commercialization of the first ever Access and Visualization Platform at the company. Bonnie has a PhD in Biochemistry and Molecular Biology from Purdue University and completed a Post-Doctoral Fellowship in Molecular Pharmacology at the University Of Miami School Of Medicine. She also has a graduate certificate in Applied Management Principles from Purdue University Krannert School of Management.

11.8 About GlobalData

GlobalData is a leading global provider of business intelligence in the Healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

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