Chapter 3
Epidemiology of Sepsis: Current Data and Predictions for the Future

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Introduction

The history of sepsis is deeply intertwined with advancements in the study of infectious diseases. As far back as Hippocrates (circa 400 BCE), sepsis has been understood to be a destructive process that brings with it the release of systemic toxins, but it was not until the discovery of microorganisms and the consequent recognition of their relationship to infectious pathology that the study of sepsis as a field came into its own. Modern discussions of sepsis have focused on the importance of early recognition and treatment of the disease. In this chapter, we will focus on the epidemiology of sepsis in the light of its changing patterns over time across the globe.

Incidence and Outcome of Sepsis

The consensus definition of sepsis has enabled investigators to study the incidence of the disease through time in different settings. Surveys have been conducted in many, if not most, developed and undeveloped nations and offer a few general points to review before delving into specific cohorts (Table 3.1). First, the incidence of sepsis alone in hospitalized patients may not be as important or easy to quantify as the number of patients who progress to severe sepsis and septic shock (particularly those requiring ICU admission). Many patients requiring hospital admission will meet criteria for the systemic inflammatory response syndrome (SIRS, detailed elsewhere in this volume) and many will have at the very least a suspected infection and will thus qualify for sepsis under traditional definitions. Clearly, if sepsis

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Table 3.1 Key studies of the epidemiology of sepsis

Authors	Methodology	Study period	Selected key findings
Rangel-Frausto et al. [1]	Prospective cohort of patients meeting SIRS criteria in study ICUs and wards in a single academic center	1992–1993	Evolution of SIRS to sepsis in 26%, to severe sepsis in 18%, and septic shock in 4%
Angus et al. [3]	Observational cohort study of patients (hospital-wide) meeting criteria for severe sepsis using state hospital discharge records linked with population data	1995	Severe sepsis incidence of ~2.3/100 hospital discharges, mortality rate of ~29%, estimated annual cost of $16.7 billion
Brun-Buisson et al. (for French ICU group) [22]	Two-month prospective survey of all patients admitted to 170 French ICUs meeting criteria for severe sepsis and septic shock	1994	Severe sepsis in 6.3/100 ICU admissions, ~60% 28 days mortality
Martin et al. [7]	Retrospective cohort study of all hospitalized patients diagnosed with sepsis (per ICD-9-CM codes) using the National Hospital Discharge Survey	1979–2000	Increasing rates of sepsis leading to increasing absolute mortality (with decrease in mortality rate)
Padkin et al. [41]	A retrospective observational cohort study of prospectively-collected data from 91 ICUs in England, Northern Ireland, and Wales. Examined patients meeting criteria for severe sepsis within the first day of their ICU stay	1995–2000	27.1% of patients met criteria for severe sepsis, with mortality rates of 35% during ICU stay and 47% during hospital stay
Vincent et al. (for EPIC II group) [4]	One-day prospective, point-prevalence study of adult patients from 1265 ICUs from 75 countries.	May 8, 2007	51% of ICU patients infected, hospital mortality rate 33% versus 15% in uninfected patients

represents a clinically relevant spectrum of disease from infection to organ dysfunction to shock, then identifying and naming each stage of the disease is important. To that end, a study by Rangel-Frausto in 1995 evaluated the incidence of SIRS and the natural history of the syndrome [1]. The authors found that approximately 68% of patients admitted to their survey units (both wards and ICU) met criteria for SIRS, with 26% of that group developing sepsis, 18% developing severe sepsis, and 4% developing septic shock. Furthermore, large studies of administrative data sets that rely on coding for surrogates of sepsis (e.g., bacteremia) may underreport the true prevalence. The setting of the cohort is also of paramount importance: one would expect to see a high percentage of patients with sepsis in general medical wards or trauma ICUs of large urban hospitals, and would expect to see far fewer in smaller community facilities. One notable attempt to study the epidemiology of sepsis specifically in an academic setting was undertaken by Sands et al. in 1997 [2]. In a study of eight academic medical centers in a prospective observational trial, the

authors found an incidence of sepsis of 2.0 cases per 100 hospital admissions, septic shock in 25% at onset of sepsis, and an overall mortality rate of 34% at 28 days.

Given the inherent difficulties in studying SIRS and sepsis in isolation, far more attention has been paid to patients meeting criteria for severe sepsis and septic shock, a fact that reflects both the incredible amount of resources required to care for these patients, as well as their high risk of death and other complications. A study by Angus et al. in 2001 [3] linked discharge records to U.S. Census data and estimated the incidence of severe sepsis in the United States at 300 cases per 100,000 people (studies of cohorts outside the United States have often found a lower incidence, as discussed below). Over 50% of patients in the cohort who developed severe sepsis required ICU services during the course of their hospital admissions. Several studies have attempted to ascertain the prevalence of sepsis within intensive care units generally. A seminal example of this effort was published in 2009 by Vincent, who led a team of investigators in studying the prevalence of sepsis on 1 day across almost 1300 ICUs in 75 countries, encompassing almost 14,000 patients in the EPIC II trial [4]. In that study, around 70% of patients were infected on arrival to the ICU and infection independently increased the risk of mortality twofold both in the ICU and in-hospital.

Also of note is a recent study by Whittaker et al. [5] that examined the trajectory and outcomes of patients admitted through the emergency department to a non-ICU setting. They found that approximately 45% of patients with severe sepsis were admitted to a non-ICU setting between 2005 and 2009 (with the rate increasing over time) and that 12.5% eventually required transfer to an ICU, particularly oncology patients and patients with markers of higher illness severity on presentation. Another recent study by Rohde et al. [6] examined the rates of recognition of sepsis as well as the predominant organ dysfunctions outside the ICU. Using a random sampling of patients from one tertiary care academic center, the authors found that severe sepsis was documented appropriately in only 47% of cases and that cardiovascular (hypotension) and renal dysfunction were the most common end-organ manifestations in patients admitted to non-ICU settings (66% and 64% of patients, respectively). The authors conclude that severe sepsis on the wards is both poorly documented and that the epidemiology is potentially different from what has been seen previously in the ICU setting.

In terms of incidence over time, Martin et al. found an increase in both sepsis and sepsis-related deaths over the past two decades in the United States using data collected from the National Hospital Discharge Survey between 1979 and 2000 in a study published in 2003 [7]. The incidence increased by approximately 13.7% per year over the 22 year span studied. Importantly, although the overall mortality rate declined over time (from 27.8% to 17.9%), the rising incidence resulted in an increase in number of deaths overall (from 21.9 deaths/100,000 people in 1979 to 43.9/100,000 in 2000). More recently, another study of sepsis trends in the United States by Kumar et al. in 2011 found similar results using the Healthcare Costs and Utilization Project's Nationwide Inpatient Sample, with the number of severe sepsis hospitalizations increasing from 143/100,000 persons in 2000 to 343 in 2007 [8]. Mortality rate decreased from 39% to 27% and hospital length-of-stay decreased

from 17.3 days to 14.9. Many other studies from across the world (some discussed below) have found similar evidence of increasing incidence of sepsis over time as mortality rates continue to decrease. Many explanations have been offered for these findings, notably the increasing use of immunosuppressive medications for organ transplantation and chemotherapy, as well as changes in coding rates of organ dysfunction over time. In any case, these trends are expected to continue for the foreseeable future, particularly in industrialized nations.

While administrative databases do carry the caveats described above, one recent study by Stevenson et al. compared data from the "usual care" arms of severe sepsis clinical trials to data from administrative data sets from 1991 to 2009 and found similar mortality rates between the two groups, suggesting that administrative data may be appropriate for use in monitoring mortality trends over time [9]. Despite that, wide variability exists depending on the method used to study the incidence of sepsis, as shown in a study by Gaieski et al. published in 2013 [10]. The authors studied the period between 2004 and 2009 using several different methods, including ICD-9 codes as well as methods published by Angus [3], Martin [7], Wang [11], and Dombrovskiy [12]. Angus et al. [3] used hospital discharge records from seven states and ICD-9-CM codes for infection and organ dysfunction. Martin et al. [7] made use of the National Hospital Discharge Survey, a database containing the records of a representative sample of hospitals across the United States, and used ICD-9-CM codes for infection and organ dysfunction. Wang et al. [11] based their study on the Compressed Mortality File, a database that contains demographic data and causes for all deaths in the United States, and identified cases based on ICD-10 codes for infection and severe sepsis. The study by Dombrovskiy et al. [12] used the Nationwide Inpatient Sample, a database sponsored by the Agency for Healthcare Research and Quality, along with ICD-9-CM codes for infection and severe sepsis. The incidence of sepsis varied markedly (up to 3.5-fold) depending on the method used, with almost 300 cases/100,000 population using the methods of Dombrovskiy, and 1031 cases/100,000 population using the methods of Wang. Rates of severe sepsis were closer between methods (approximately 13.0–13.3%), but in-hospital mortality rates showed a wider range (14.7% using the method of Wang et al. and 29.9% using the method of Dombrovskiy et al.). In addition, Gaieski et al. noted an increase in the use of sepsis ICD-9 codes by more than double over the 6 year period between 2004 and 2009. Additionally, as billing codes and quality improvement data are increasingly used to identify sepsis, septic shock, and its mortality, incentives to record or not record these data increase.

An attempt to validate the use of administrative data in epidemiologic studies of sepsis was published by Iwashyna et al. [13]. The authors used the "Angus" implementation to identify cases of severe sepsis and septic shock (cases with ICD9 codes for severe sepsis and septic shock or codes for infection and associated organ dysfunction are termed "Angus-positive," cases without such codes are termed "Angus-negative") and compared the results to the gold-standard of direct physician review of cases. They found that the Angus method had a positive predictive value of 70.7% and a negative predictive value of 91.5% when compared to direct physician review. Sensitivity was 50.4% and specificity was 96.3%. The authors conclude that

Angus implementation is a reasonable but imperfect method for identifying patients with severe sepsis.

The improvement in mortality rates over time may be due in part to the development of bundled care plans for septic patients. As shown by Barochia et al. in a study published in 2010 that analyzed the use of bundle (i.e., protocolized) care versus non-protocolized care found a consistent benefit to protocolized care ($I^2 = 0\%$, $p = 0.87$) in decreases of time to antibiotics and increases in appropriateness of antibiotics ($p \leq 0.0002$ for both factors) [14]. A more recent study by Miller et al. in 2013 found a decrease in mortality in patients whose care complied with specific sepsis care bundle components: inotropes, red cell transfusions, glucocorticoids, and lung protective ventilation after adjusting for severity of illness [15]. They noted an improvement in all-or-none bundle compliance over time (from 4.9% in 2004 to 73.4% in 2010) and a concomitant improvement in mortality during the study period (from 21.2% in 2004 to 8.7% in 2010).

Another interesting effort to address the changing patterns of sepsis was published by Gaieski et al. [16]. The authors examined the effects of severe sepsis case volume on inpatient mortality and found an inverse relationship, with mortality varying from 18.9% in lower volume centers (<50 cases/year) to 10.4% in higher volume centers (>500 cases/year) over the period between 2004 and 2010 in a nationally representative sample of hospital admissions.

Another recent study that examined the effect of sepsis admissions on overall hospital mortality was published by Liu et al. in 2014 [17]. The study examined two complementary inpatient cohorts, Kaiser Permanente Northern California and the Nationwide Inpatient Sample using both explicit ICD9 codes for sepsis and implicit codes (infection with associated organ dysfunction). Overall, the researchers found that sepsis contributed to one in every two to three deaths, again highlighting both the common and deadly nature of the disease.

Global Cohorts

Outside the United States, several other cohorts deserve mention. A study by Harrison et al. in 2006 of the epidemiology of severe sepsis in the United Kingdom using the Intensive Care National Audit and Research Centre Case Mix Programme Database found a rate of 27% of ICU admissions with severe sepsis (up from 23.6% in 1996 to 28.7% in 2004) [18]. As was seen in the United States, mortality rate decreased (from 48.3% in 1996 to 44.7% in 2004) but absolute number of deaths increased due to the higher incidence (from 9000 to 14,000 over the same period). In 2004, van Gestel et al. examined the point prevalence of severe sepsis in the Netherlands across 47 ICUs and found that it accounted for around 0.6% of hospital admissions and 11% of ICU admissions [19]. Another point prevalence study of severe sepsis in ICUs in Australia and New Zealand found an incidence of around 12% of ICU admissions and around .08% of the population [20]. A more recent study of 171 ICUs in Australia and New Zealand found a decrease in mortality due

to severe sepsis with and without shock in the period between 2000 and 2012 [21]. A French cohort studied by the EPISEPSIS group in 1995 had a prevalence of severe sepsis of 6.5% in ICUs [22], up to almost 15% when the group published findings on a similar cohort in 2004 [23]. An observational cohort of Emergency Department admissions to a University hospital in the West Indies published by Edwards et al. in 2013 found a rate of approximately 1.3% of patients with sepsis, 15.4% of whom had either severe sepsis or septic shock [24]. Overall mortality was 25%, despite a lack of protocols for early goal-directed therapy. One notable study to examine total hospital incidence of [23] sepsis in a prospective cohort in Spain was published by Esteban et al. in 2007. The incidence relative to total hospital admissions was 4.4% and only 32% of patients with severe sepsis were cared for in an ICU [25].

The reasons for such heterogeneity in sepsis incidence around the world are myriad and have been discussed in several recent papers. Adhikari et al., in a study on the global burden of critical illness published in 2010, detailed how different countries have wide ranges of ICU bed availability (e.g., 30.5 beds/100,000 people in the United States versus 8.6/100,000 in the United Kingdom) [26]. Countries with lower numbers of ICU beds will likely admit only the sickest patients, while countries with higher numbers will tend to accept patients who are not as critically ill. As a result, those with fewer ICU beds will tend to under-report the total prevalence of the disease [27]. Other complicating factors include the variety of hospital sizes within a country, the variety of definitions for what constitutes an ICU, and the problematic nature of risk-adjustment models in this setting [28].

The Cost of Sepsis

Many studies have evaluated the costs of caring for sepsis. A report by the Healthcare Costs and Utilization Project found that sepsis resulted in the highest aggregate costs of any hospital diagnosis in 2009 at 15.4 billion U.S. dollars [29]. The average cost per stay was approximately $18,000 and costs grew at an average annual rate of 11.3%. Sepsis ranked highest among the top three most expensive diagnoses (the others being osteoarthritis and coronary atherosclerosis), with the rate of increase in costs outpacing hospital spending by two to three times. A European trial by Brun-Buisson et al. in 2003 found the total cost of sepsis care to be around Euro 26,000 for sepsis (~USD 36,000), Euro 35,185 (~USD 48,000) for severe sepsis, and Euro 27,083 (~USD 37,000) for septic shock [30]. Importantly, the authors found a significant difference in cost depending on the route of acquisition of sepsis, with ICU-acquired infections approximately 2.5 times as costly as other cases. A UK group found a similar effect, with cost of care rising significantly in patients who acquired sepsis after their second day in the ICU (up to a high of around $18,000 in total costs) [31]. A study of German ICUs published in 2007 estimated that care of the individual sepsis patient accounted for around Euro 1100 ± 400 per day (roughly USD 1500) [32]. It should again be noted that countries with more

ICU beds will tend to admit patients who are on the average less ill than patients in countries with fewer beds and that the cost of care in ICUs is significantly higher than on the wards.

The costs of postoperative sepsis were evaluated in a study by Vaughan-Sarrazin et al. published in 2011 in a cohort of patients treated at 118 Veterans Affairs hospitals in the United States [33]. In the cohort, 564 out of a total of 13,878 patients undergoing general surgery developed sepsis (a rate of 4.1%). Average cost for patients who did not develop sepsis was $24,923 and average cost for patients who did develop sepsis was $88,747, 3.6 times higher. With those data in mind, the authors conclude that a strong financial incentive exists to prevent the development of sepsis (in addition to implications for patient care well-being).

Long-Term Outcomes

It should be noted that many, if not most, studies of the sepsis spectrum report 30-day and/or 90-day mortality. Emerging data suggests that even longer time points may yield important data. A systematic review of long-term mortality and quality of life (>3 months) in sepsis by Winters et al. in 2010 found ongoing mortality beyond short-term end points and consistent impairment in quality of life as well [34]. The authors suggest that longer-term endpoints may paint a more accurate picture of the natural history of the disease and the interventions we use to mitigate it. A study by Iwashyna et al. also published in 2010 supports that conclusion, finding an odds ratio of 3.34 for moderate to severe cognitive impairment among survivors of severe sepsis in a cohort drawn from the Health and Retirement study (mean age 76.9 years old) [35]. The authors also found a high rate of functional impairment among survivors, with a mean increase of 1.57 limitations among those who had no limitations prior to their hospital stay for severe sepsis. Another study by Iwashyna et al. in 2012 of a large Medicare cohort also found that a large portion of survivors suffered from functional disability (almost 480,000 out of the 640,000 patients studied) and moderate to severe cognitive impairment (around 106,000 patients) [36]. There was little change in sepsis mortality, however, from 73.5% to 71.3% over the span of 1996 to 2008. Another study by Storgaard et al. in 2013 found a mortality rate of 33% for severe sepsis and septic shock at 30 days and a hazard ratio of 2.7 in the next 1 year and a ratio of 2.3 over the next 3 years, again pointing to a significant long-term impact of the disease [37]. A more recent study of healthcare utilization in survivors of severe sepsis that made use of Medicare claims found a higher rate of post-discharge mortality in sepsis versus non-sepsis admissions in the year after admission (44.2% versus 31.4%), as well as a steeper decline in days spent at home (−38.6 days), and a greater increase in the proportion of days spent alive in a facility (5.4%) [38]. Another recent study by Liu et al. [39] examined patient-level factors contributing to readmissions and healthcare utilization after sepsis. They found that healthcare utilization increased threefold after admission for sepsis and that most factors leading to increased utilization were present prior to initial sepsis admission (e.g., comorbid disease burden and high pre-sepsis healthcare utilization).

Demographic and Genetic Factors

Gender

A number of demographic factors have been found to affect a person's risk of developing sepsis. In the previously mentioned EPISEPSIS study, men were more likely to develop sepsis by a ratio of almost 2:1 with an average age of around 65 [22]. Although the authors saw no difference in mortality between men and women, survivors tended to be younger than non-survivors (61 versus 70 years, $p < .001$). After adjusting for sex in the population-at-large, Martin et al. showed a significantly higher risk of sepsis in men as well, with a relative risk of 1.28. In addition, sepsis developed later in life for women than men (62.1 versus 56.9 years), and the age of the overall population increased over the duration of the study (from 57.4 in the period between 1979 and 1984 to 60.8 years of age in the period between 1995 and 2000) [40]. A study by Padkin et al. of ICUs in the United Kingdom found an increased rate of sepsis in men (54% of patients admitted to the ICU) and the median age was 65 years [41]. A multicenter Italian study published in 2013 also found an increased risk of sepsis in men (63.5% of patients admitted to ICUs with severe sepsis), but interestingly found an increase in mortality among women with severe sepsis (OR 2.33) despite similar rates of overall ICU mortality between men and women [42]. The increased mortality in women may be explained at least partially by experimental evidence that women demonstrate more robust inflammatory responses to LPS than men [43]. Interestingly, an Austrian study of resource utilization by men and women in the ICU found that, despite more severe illness among women, men accounted for much greater levels of resource utilization and a higher number of invasive procedures, neither of which translated into improvement in mortality rate [44]. Both age and gender might be mitigated as risk factors by a study of comorbid conditions (discussed below), but the fact remains that both factors correlate well with the risk of sepsis in many different populations.

Race

The contribution of race to sepsis risk has been difficult to tease out, likely due to the myriad variables complicating the equation. Race itself is a difficult concept to study, owing to its changing definition over time. In addition, what was once considered a biological category influenced by genetics and ancestry is now thought to be primarily a social construction of culture, class, and environment. Given the complex nature of the terminology itself, it becomes difficult to study the epidemiology of a particular disease within a specific racial group (as opposed to a particular ethnic group, for example). That said, comorbid conditions such as end-stage renal disease are more prevalent in certain ethnic groups than others, and competing demographic factors such as socio-economic status (SES) certainly play an important role in the overall burden of disease in a particular community (due to access to

healthcare, etc.). For the purposes of this review, we will use the terminology adhered to by the authors of the individual studies we discuss. In most larger cohorts, whites have significantly lower rates of sepsis. In the cohort of Martin et al., blacks and other non-whites had a relative risk of approximately 2.0 for the development of sepsis. Blacks had the highest mortality rate from sepsis (23.3%) and developed sepsis at the youngest ages (47.4 years on average). In a study by Mayr et al. of seven US states and infection-related Emergency Department visits, black patients had a 67% higher risk of severe sepsis when compared to white patients and an 80% higher mortality rate. The authors also found an increased rate of infection in black patients (47.3 versus 34.0 per 1000 population) and an increased risk of associated organ dysfunction (OR 1.29), both of which help to explain the racial disparities [45]. Barnato et al. found similar disparities in studying a cohort of six hospital referral areas in the United States using data from the US Census that showed an incidence of severe sepsis of 6.08/1000 population in black patients (versus 4.06 and 3.58/1000 for Hispanics and whites, respectively) [46]. After adjusting for SES, black patients still had an adjusted rate ratio of 1.44 for the development of severe sepsis. In addition, blacks had a higher case fatality rate than Hispanics and whites (with rates of 32.1%, 30.4%, and 29.3% respectively). Slightly conflicting data were found by Dombrovskiy et al. in a study of a New Jersey database published in 2008 [47]. In that cohort, black and white patients had similar case fatality rates from severe sepsis, but black patients were of significantly lower age (61.6 versus 72.8 years), at significantly higher risk of comorbidities such as HIV and diabetes, and were at much higher risk of poor health care coverage (3.96 times white patients). Taken together, it is likely that black patients do indeed have a greater predisposition to severe sepsis, but it is as yet unclear whether that predisposition results from specific genetic factors, environmental factors, or comorbid conditions. In terms of the level of care provided to patients of different races within the same hospital, a study by Mayr et al. found no differences between the care received by blacks and whites for pneumonia, but did note that hospitals that served primarily black patients were less likely to provide timely antibiotics (OR .84) [48].

Interestingly, a study by Mendu et al. found improved survival in all-cause critical illness among patients in Boston, Massachusetts who did not speak English as their primary language (30-day odds ratio 0.69) [49]. The effect was not confounded by indicators of severity of disease, specific language spoken, and neighborhood poverty index (a proxy for SES). While the authors did not report the specific difference in mortality rate for sepsis alone, they did note that controlling for sepsis as an admitting diagnosis did not alter their primary conclusions.

Socioeconomic Status

In terms of SES itself, many studies have noted the relationship between SES and access to ICU care, as well as overall intensity of care. A systematic review by Fowler et al. noted that patients without health insurance are less likely to receive critical care services (odds ratio 0.56) and may experience worse clinical outcomes [50].

A Danish cohort studied by Koch et al. in 2013 found a strong association between bacteremia and 30-day mortality (crude hazard ratio 1.38 between low and high levels of education and 1.58 between low versus high income tertile) [51]. Substance abuse rates, social support, pre-existing comorbidities, location of acquisition of infection, and infectious agent were all significantly different between SES groups. Correcting for those differences attenuated much of the difference in mortality between SES groups (adjusted hazard ratio 1.15 between low and high levels of education and 1.29 between low versus high income tertile).

A multicenter observational study by Mendu et al. [52] of almost 15,000 critically ill patients examined the relationship between neighborhood poverty rate and the development of bloodstream infections. After multivariate analysis, neighborhood poverty rates in the two highest quintiles (20–40% and >40%) were strongly associated with an increased risk for bloodstream infection (26% and 49%, respectively) relative to the lowest quintile (neighborhood poverty rate < 5%).

Biological Factors

Genetics also play a significant role in the development of sepsis and susceptibility to infections and are discussed fully in a separate chapter. A study by Sørenson et al. published in 1998 looked at genetic susceptibilities to a range of diseases by following a cohort of children in Denmark adopted between 1924 and 1926 [53]. Environmental factors seemed to play a role in the development of cancers and vascular disease (odds ratio 5.16 and 3.02, respectively, for death of adoptee when an adoptive parent died of one of those diseases), and genetic factors played a role in cardio/cerebrovascular disease (OR 4.52) and infections (OR 5.81) when the authors studied the frequency of adoptee death when the biologic parents died of one of the above. More recently, Henckaerts et al. reviewed the DNA of 774 MICU patients and found that polymorphisms in NOD2 and TLR4 (both important for innate immunity) were associated with an increased risk of bacteremia and increased in-hospital mortality (OR 4.26 and 2.27, respectively) [54]. Another study of genetics in critically ill patients by Sutherland et al. found a significantly increased risk of infection in patients with single nucleotide polymorphisms of CD14, mannose-binding lectin, and TLR2 [55]. A polymorphism of Mal, an adaptor protein downstream of TLR2 and TLR4, was found by Kohr and colleagues to provide protection against bacteremia and certain specific infectious pathogens [56]. A study by Agnese et al. found a significantly increased risk of gram-negative infections in ICU patients with specific TLR4 polymorphisms (79% versus 17%, $p > .004$) [57]. While mutations in the pathways listed above have been well studied in the literature, it is important to note that not every study evaluating them has shown consistent results. In addition, a great many other genetic pathways are under investigation, more fully detailed in a recent review by Waterer et al. [58]. Genetic polymorphisms have not yet cracked the code for vulnerability to sepsis, but they hold out the promise of a more specific biomarker in the near future.

Comorbidities

Many diseases predispose patients to the development of sepsis, but a few specific entities deserve special attention for their significant effects on overall rates and outcomes. In particular, malignancy, HIV infection, obesity, and diabetes mellitus all appear to increase susceptibility to infection.

Malignancy

Malignancy, particularly hematologic malignancy, seems to be the most significant risk factor. A cohort study by Williams et al. in 2004 found, in a survey of hospital data from six states in 1999, around 30,000 cases of severe sepsis out of a total of around 606,000 total cancer cases (a rate of around 5%) [59]. Nationally, they estimated around 126,000 cancer patients would develop sepsis (around 16 cases per 1000 cancer patients). The relative risk of hospitalization for severe sepsis in patients with cancer was approximately 3.96, with a mortality rate of 8.5%, and a cost of 3.4 billion dollars annually. Analysis of the National Hospital Discharge Survey in 2006 by Danai et al. found even more dramatic results, with 1465 cases per 100,000 cancer patients, and a relative risk of 9.77 compared to patients without underlying malignancy [60]. When the data were analyzed in terms of race, they found that blacks and other non-white races had a higher incidence of sepsis relative to whites (with relative risks of 1.28 and 1.47, respectively). Male cancer patients were more likely to develop sepsis than female cancer patients with a relative risk of 1.98. In addition, multivariate analysis found that the presence of cancer independently increased the risk of death from sepsis with an adjusted odds ratio of 1.98. In terms of specific cancer types, pancreatic cancer caused the greatest increase in the risk of sepsis (with 14,468 cases/100,000 patients), followed by multiple myeloma, leukemia, lung cancer, and lymphoma.

HIV

Despite the great advances made in the treatment of HIV with anti-retroviral therapies, patients with HIV continue to be at increased risk of developing sepsis. A study by Greenberg et al. found that 13.7% of ICU patients were HIV seropositive. Of that group, the majority of their acute infections were nosocomial (112 out of a total of 194 infections) [61]. The inpatient mortality rate was 42% for HIV patients with severe sepsis in the ICU. Interestingly, in a multivariate regression model, markers associated with HIV were not independently predictive of hospital mortality (e.g., CD4 count, use of HAART), but APACHE II score was (OR 1.12). A cohort of patients studied by Coquet et al. found an increase in annual admissions of HIV

patients to the ICU from 1996 to 2005, but a steady decrease in ICU and 90-day mortality between 1996 and 1997 and between 2004 and 2005 from 25% and 37.5%, respectively, to 8.6% [62]. Severe sepsis was among the strongest predictors of mortality in HIV patients admitted to the ICU (behind specific organ failures and coma) with an OR of 3.67. Those data were corroborated by another study by Japiassú et al. of 88 HIV-infected patients admitted to the ICU of an infectious diseases research center [63]. The rate of severe sepsis in that population was 50% and severe sepsis was the strongest independent predictor of mortality, both 28-day (OR 3.13) and 6-month (OR 3.35). Respiratory infections accounted for the majority of cases of severe sepsis, as discussed further below.

Obesity

Obesity, defined as a body-mass index (BMI) $\geq$ 30 kg/m^2, is a tremendous public health problem throughout the developed world. According to a recent systematic review of the 2013 Global Burden of Disease Study, the proportion of adults with a BMI of 25 kg/m^2 or higher increased from 28.8% to 36.9% between 1980 and 2013 in men and 29.8% to 38.0% in women [64]. The proportion of obese children and adolescents in developed countries also increased substantially. In addition to the well-established cardiovascular risks of obesity, patients are also at increased risk of a range of other diseases, including malignancies of multiple types. Obese patients also appear to be at significantly increased risk for infection. While the mechanism of susceptibility is not fully understood, adipose tissue does appear to contribute actively to inflammation, with both leptin and adiponectin playing important roles in the balance of immune functions. A retrospective study by Yaegashi et al. in 2004 of obese medical ICU patients found that morbid obesity (BMI $\geq$ 40 kg/m^2) increases the risk of sepsis from 6.1% to 26.7% over obese patients [65]. A matched cohort study published the same year by Bercault et al. found similar results, with mechanically ventilated obese patients being significantly more likely to acquire a diagnosis of septic shock during their ICU than their non-obese counterparts (8% versus 3%, $p < 0.05$) [66]. In a more recent population-based cohort study by Wang et al., the morbidly obese were more likely than the non-obese to develop sepsis (HR 1.57) [67]. They also found increased waist circumference (>102 cm in men and >88 cm in women) to be a better predictor for the risk of sepsis than BMI (HR 1.34).

Interestingly, a large multinational cohort study by Arabi et al. published in 2013 found that obese patients had a lower mortality rate due to sepsis than non-obese patients (OR 0.80 for obese patients, 0.61 for morbidly obese patients), but that the association between obesity and survival disappeared when they controlled for variations in sepsis management [68]. Specifically, obese patients seem to receive less intravenous fluid per kilogram and lower antibiotic doses per kilogram than the non-obese. A recent retrospective cohort study by Gaulton et al. corroborated those data, finding no difference between mortality rates in the obese and non-obese due

to sepsis. Another recent study by Prescott et al. again found that obesity conferred a protective effect against mortality at 1 year (OR 0.59 for obese patients and 0.46 for morbidly obese patients) [69].

Diabetes

Diabetes mellitus (DM), defined as a fasting glucose ≥126 mg/dL, a 2-h glucose of ≥200 mg/dL after a 75 g oral glucose challenge test, and/or a hemoglobin A1c level of ≥6.5, carries with it an increased risk of infection and sepsis. In a prospective cohort study published in 2005, Muller et al. found a higher risk of lower respiratory tract infection (OR for patients with type I DM of 1.42 and for type 2 DM of 1.32) and urinary tract infection (DM1 OR 1.96 and DM2 OR 1.24) as well as increased risks of both mucus membrane and skin infections [70]. The incidence rate for sepsis in diabetes patients in the cohort of Danai et al. mentioned above was found to be 700.8/100,000 [60] and Stegenga et al. found that 22.7% of all septic patients were diabetic in a retrospective analysis of a clinical trial [71]. That cohort also showed no increase in the mortality rate of sepsis in patients with underlying diabetes. Other studies have found conflicting data, however [72], and the true impact of sepsis on diabetic patients is as yet unclear.

Etiology and Source of Infection

In the cohort of Martin et al., gram-negative organisms dominated as the primary etiology of sepsis between 1979 and 1987 [7]. After that period, gram-positive organisms became the dominant bacteria. By 2000, gram-positive organisms accounted for 52.1% of infections, gram negatives for 37.6%, and fungi for 4.6%. Polymicrobial and anerobic organisms accounted for the rest of the infections in the cohort. Overall, the rate of gram-positive infections increased by the highest relative amount, an average of 26.3% per year in the period studied. In addition, the rate of fungal infections increased 207%, from 5321 cases in 1979 to 16,042 in 2000. The shift in etiologic agent may be due to increases in invasive procedures and hospital infection rates. In contrast, the EPIC II point prevalence study found a higher prevalence of gram-negative infections than gram positive (62% versus 47%, with the overlap representing polymicrobial infections) [4]. An etiologic agent was isolated in 70% of the total cohort. *Staphylococcus aureus* alone accounted for 20.5% of total infections and *Pseudomonas* accounted for around 20%. Several agents were independently associated with hospital mortality in multivariate logistic regression analysis: *Enterococcus*, *Pseudomonas*, and *Acinetobacter* [4]. A recent study by Ani et al. [73] that made use of the Nationwide Inpatient Sample database found that between 1999 and 2008, the most common causes of severe sepsis were gram-negative organisms, particularly *Escherichia coli*, but that *S. aureus* had the highest mortality hazard ratio (1.38).

In most cohorts, the lungs are the most common site of infection leading to sepsis. In the EPIC II cohort, the lungs accounted for approximately 64% of the total infections, followed by abdominal (20%), bloodstream (15%), and renal/GU infections (14%). The first EPISEPSIS cohort found similar numbers, with respiratory infections responsible for more cases of severe sepsis than any other site (41%) [22]. In the cohort published by Angus et al. in 2001, respiratory infections accounted for 45.8% of all severe sepsis, with bacteremia of unspecified site causing the highest relative mortality (41.2%) [3]. The cohort of community-acquired sepsis published by Storgaard found that urinary infections accounted for the highest percentage (36%) [37]; the discrepancy may be due to the selection of community-acquired sepsis in particular, as the weight of evidence strongly supports the notion that respiratory infections are the most common cause of sepsis by a wide margin.

A retrospective observational study of Canadian hospitals and ICUs by Leligdowicz published in 2014 found an association between the etiologic agent and the mortality rate [74]. With around 70% culture positivity in the cohort overall, gram positives were the most common etiologic agent (34.2% versus 25.7% gram negatives). As in prior cohorts, the lung was the most common site of infection for the development of sepsis. After adjusting for a number of factors known to affect mortality in sepsis, disseminated infections and intra-abdominal infections accounted for the highest risk of mortality by source.

An interesting attempt to find the underlying connection between organism, site of infection, and mortality rate was published in 2004 by Cohen et al. In a meta-analysis of 510 articles encompassing over 55,000 patients with microbiologic confirmation of infection, the authors demonstrated the importance of stratifying clinical trials not just by source of infection and etiologic agent, but also by the interaction between the two. They note, for example, that catheter-related bloodstream infection due to coagulase negative *Staphylococcus* is a wholly different process than the same site of infection due to *Candida* [75].

Conclusions

Sepsis has been recognized as a severe inflammatory response to infection since the days of the Ancient Greeks. Through the work of pioneering scientists and physicians, the connection between causative agents and the response of the host came to the fore. More recent advances in epidemiology have led to an understanding of sepsis as a common disease with potentially catastrophic complications. Consensus definitions have allowed sepsis to be studied as a global problem, with coordinated networks analyzing trends in incidence and outcome and giving insights into demographic trends and comorbidities associated with the development of the disease. Persons of non-white races appear more vulnerable to the disease, as do patients with underlying malignancy, HIV, obesity, or diabetes. Despite improvements in sepsis care, the rising incidence of the disease has resulted in an increase in mortality in the last few decades. Respiratory infections remain the primary source of

infection, and gram-positive organisms appear to be eclipsing gram-negatives as the primary etiologic agents driving the disease.

Advances in epidemiology have greatly improved our ability to understand who is most vulnerable to the continuum of sepsis. These advances will point the way toward ever more sophisticated mechanistic questions regarding the development of the disease process. As our understanding of the disease improves and our treatments become more targeted, these epidemiologic tools will help us understand the effect of our interventions on the overall incidence and mortality of sepsis. The recent increase in the number of sepsis cases has shown no sign of abating, and we have every reason to expect the trend to continue into the future. We expect that mortality rate will continue to decline, though, as advances in medical knowledge enter the clinical arena. Concomitant advances in other fields will undoubtedly change the spectrum of infectious source and agent, but coordinated networks will balance those shifts by offering a greater understanding of the dynamics of the disease across the world.

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