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Challenges in combating sepsis in Germany—Learning from others and the COVID-19 pandemic

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Sir William Osler, one of the most influential and beloved physicians of all time, pointed out in 1898: "Humanity has but three great enemies: fever, famine, and war; of these the greatest, by far the most terrible, is fever." For most parts of the world, where over 80% of mankind live, this still holds true.

Sepsis remains as a major global health threat, and a leading cause of death, disability, and healthcare spending around the world, annually accounting for approximately 20% or 1 in every 5 deaths [1, 2]. Sepsis-related deaths might be even higher, up to 13.7 million, based on the Global Burden of Disease Study, estimating that 7.7 million deaths associated with 33 pathogens would rank as the second leading cause of deaths globally in 2019 [3]. In accordance with the updated sepsis definition and the World Health Organization (WHO)/World Health Assembly (WHA) Sepsis Resolution from 2017, most of the estimated 14.9 million excess deaths during the COVID-19 pandemic are also to be attributed to viral sepsis as the final common pathway to death from most infectious diseases [4–6].

Sepsis disproportionally affects low- and middle-income countries (LMICs), with 85% of cases occurring in LMICs, but it is also a leading cause of hospital death and major driver of healthcare expenditures in high-income countries (HICs; [1, 2]). According to the Global Burden of Sepsis Study, both the age-standardized sepsis incidence and sepsis-associated morality rate decreased between 1990 and 2017 by 37.0% and 52.8%, respectively. Recent health record-based estimates of the incidence of sepsis in Germany, Sweden, and the United States suggest that it is higher than 700 per 100,000 population in these countries and 3–4 times higher than prior estimates, which were derived from inpatient administrative health data (IAHD; [7–9]).

Hospital mortality in Germany [8–10] seems to be up to twice as high as in other health economies such as Australia, England, Sweden, and the United States [11, 12]. In addition, according to data from Australia and England derived from nationwide ICU registries, hospital mortality for severe sepsis between 2000 and 2012 decreased from 35.0% to 18.4% and from 45.5% to 32.1%, respectively [11, 12]. However, in Germany between 2014 and 2018 the German Quality Network Sepsis (GQNS)—which offers quality reporting based on IAHD data, peer reviews, and support for establishing continuous quality management and staff education—reported no impact on the course and level of risk-adjusted hospital mortality for the 74 participating hospitals. Observed mortality was 43.5% during the baseline period and 42.7% in the intervention pe-

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riod (April 2016–June 2018). The same was true for the level and course of risk-adjusted hospital mortality for sepsis for all German hospitals. The respective interrupted time-series analyses were based on the national DRG statistics. This comparison found no statistically significant difference between 2014 and 2018 for the national and the GQNS control and study cohorts. The authors of this report concluded: "Voluntary quality initiatives may not be able to achieve adequate priority among pertinent stakeholders among hospital board and department leadership. Therefore, sepsis needs to become part of the mandated external quality assurance for all German hospitals to end preventable suffering from sepsis and reduce the burden for the German health care system." The failure of this voluntary quality improvement initiative, although it had the formal support of the hospital and hospital boards of directors, is fully in line with results of the cluster randomized controlled MEDUSA trial. This publicly funded trial, which comprised 40 German hospitals with over 4000 enrolled patients and aimed to improve sepsis care by fostering early recognition and management of sepsis as an emergency, also failed to increase the number of patients who received antibiotic therapy within the first hour of exhibiting the signs of sepsis. Only 30% of these patients received antibiotics within 1 h of showing signs of sepsis, and this remained unchanged over the 4-year study period. This explains why the hospital mortality rate remained unchanged.

In concordance with the change team leaders who were established in the participating hospitals of the MEDUSA trial [13], the local quality improvement leaders of the GQNS collaborative reported the following significant barriers to effective quality management at the hospital level: (1) lack of time and resources for quality improvement activities; (2) failure to generate hospital-wide improvement efforts due to general staff shortage; (3) lack of involvement of all relevant departments; and (4) insufficient engagement of the hospital leadership [14].

Given that there is plenty of room for improvement for a better understanding of the true burden and optimal prevention and management of sepsis in Germany, we are very pleased that several internationally highly esteemed clinical researchers accepted our invitation to share the latest scientific evidence on the progress that has been made over the past few years in this poorly recognized field, but also to provide information on the existing knowledge gaps that hamper further advancements in the acute management as well as in the long term-care of sepsis and it sequelae [15–18].

Fleischmann-Struzek and Rudd in their contribution [15] stress that according to the Global Burden of Sepsis Study [1], "both the age-standardized sepsis incidence and sepsis-associated morality rate decreased between 1990 and 2017 by 37.0% and 52.8%, respectively." These encouraging findings confirm the rationale for the WHA/WHO sepsis resolution, "that sepsis follows a unique and time-critical clinical course, which in the early stages is highly amenable to treatment through early diagnosis and timely and appropriate clinical management," and that "sepsis can often be prevented through appropriate hand hygiene, access to vaccination programmes, improved sanitation and water quality and availability, and other infection prevention and control best practices" [4].

In regard to Germany, the authors discuss several flaws that most likely contribute to the ongoing underestimation of the true burden of sepsis, for example: (1) "In Germany [in] the system of the death statistics, sepsis is considered an immediate or intermediate, not the underlying cause of death. Thus sepsis-related deaths often 'hide behind' deaths coded due to pneumonia or other underlying causes"; (2) "the lack of information on out-of-hospital sepsis deaths, which comprise around one out of ten sepsis deaths according to a US study"; and (3) "in 2020, one out of three coronavirus disease 2019 (COVID-19) patients treated on general wards fulfilled the clinical criteria for sepsis according to a systematic review." Taking into account the current flaws in the assessment of the true burden of sepsis, even the most recent estimates on sepsis incidence and sepsis-related death for Germany may reflect a considerable underestimation of its true burden. Although current estimates of more than 500,000 sepsis cases annually and more than 140,000 sepsis-related deaths are based on chart review information from a sample of 10,334 inpatient cases aged ≥ 15 years treated during 2015–2017 in ten German hospitals, which is considered the gold standard [8]. The authors conclude: "To improve knowledge, reliable data and ways to operationalize sepsis definitions, which are applicable in all resource settings, are urgently needed. This requires sepsis to be included in national research and health care agendas."

Hallie Prescott and Marlies Ostermann provide an excellent update on what is new and different in the 2021 Surviving Sepsis Campaign Guidelines [16]. Among several updates on fluid resuscitation and use of vasopressors in patients with septic shock, they emphasize that: (1) "While qSOFA provides prognostic information, it is neither sensitive nor specific for sepsis. As such, the guidelines now include a strong recommendation against using qSOFA as a single screening tool for sepsis"; (2) "as before, there is a strong recommendation to initiate antimicrobials within 1 h of sepsis and septic shock. For patients without shock, the guideline recommends a rapid assessment of infectious versus noninfectious causes of illness, and administration of antimicrobials within 3 h if concern for infection persists." And they stress that: (3) "There are 12 new recommendations addressing long-term outcomes from sepsis, including strong recommendations to screen for economic and social support and to make referrals for follow-up where available; use shared decision-making in post-intensive care unit (ICU) and hospital discharge planning; reconcile medications at both ICU and hospital discharge; provide information about sepsis and its sequelae in written and verbal hospital discharge summary; and to provide assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge".

Evangelos Giamarellos-Bourboulis, in his contribution on what we learned through the assessment of immunomodulatory approaches during the COVID-19 pandemic [17], concluded that the positive results from several of these studies reinforced the concept of immunotherapy for sepsis and concluded that: "The end result is that sepsis immunotherapy should rely on the use of biomarkers which provide information on the activation of a specific

prevailing mechanism in order to enable the selection of the appropriate drug." Likewise, Antoni Torres and coworkers in their review of the evidence on corticosteroids in sepsis and community-acquired pneumonia [18] concluded that: "Future research should be conducted guided by a precision medicine approach in order to identify adequate dosage and duration of corticosteroid treatment for the appropriate patients."

Indeed, it is one of the encouraging lessons from the pandemic that four immune modulators have received emergency use authorization (EUA) by the Food and Drug Agency of the United States (FDA; [19]), one of which was run by a German company and had also received financial support by the German Ministry for Education and Science (BMBF; [20]). Three of these immune modulators also received EUA by the European Medical Agency (EMA; [21]).

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