

The quadruple burden of sepsis

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Over 2000 years ago, Hippocrates introduced the term σψις (sipsi), which loosely translates to “make rotten.” Subsequent health practitioners observed an association between “blood putrefaction” and fever, and around 150 years ago, Louis Pasteur linked putrefaction to tiny organisms (or microbes). Since then, researchers have expanded our knowledge of sepsis, including the role of infectious microbes, accompanying host response and antimicrobial therapies. From initially being considered a condition in which “flesh rots,” sepsis is now formally defined as a “life-threatening organ dysfunction caused by a dysregulated host response to infection.”¹

The quantification of the global burden of sepsis is patchy and incomplete, especially in low- and middle-income countries (LMICs), where sepsis is concentrated and delivery of health care is generally suboptimal. Despite this uncertainty, sepsis is conservatively estimated to claim over 8 million lives annually, including 420 000 newborns.^{1,2}

Recognizing this burden and with strong global advocacy from the Global Sepsis Alliance, the United Nations World Health Assembly (WHA) passed a landmark resolution in May 2017 that urged World Health Organization (WHO) member states to recognize sepsis as a global challenge and to improve measures to prevent, diagnose and manage it.³

However, the real challenge lies ahead as the global community embarks on achieving the United Nations Sustainable Development Goals (<https://sustainabledevelopment.un.org/>), which among the 17 goals and 169 targets, clearly encapsulates the complex interplay of factors that contribute to the quadruple burden of sepsis: medical, social, economic and political.

Factors contributing to sepsis do not lend themselves to solutions crafted in silos. Instead, success relies on the combined and sustained efforts of providers and recipients of health care, pharmaceutical companies and policy-makers. For example, the WHA resolution urging states to improve infection prevention and control strategies can be achieved by universal public health, vaccine programs and adherence to hygiene, whereas those with sepsis can be screened at the bedside using simple clinical features and treated with simple, effective treatments such as oxygen, intravenous fluid, antimicrobial agents and possibly cardiotoxic agents. However, this resolution cannot be achieved if vaccinations, drugs and personnel are in short supply in LMICs⁴ and even in some high-income countries. To address the low availability of antimicrobial agents, the WHO List of Essential Medicines incorporated new anti-

KEY POINTS

- Sepsis accounts for about 8 million deaths annually.
- In May 2017, the United Nations World Health Assembly passed a resolution urging World Health Organization member states to recognize sepsis as a global threat and to improve measures to prevent, diagnose and manage sepsis.
- Addressing the quadruple burden of sepsis — medical, social, economic and political — will require a concerted approach by stakeholders, including providers and recipients of health care, and policy-makers.
- Use of antimicrobial treatments for sepsis must be balanced against the problem of rising antimicrobial resistance.
- Management of sepsis will require robust, resilient health systems to educate health care providers, monitor antimicrobial delivery and resistance, and develop or evaluate interventions.

microbial agents, which could increase availability and affordability in LMICs.⁵ However, the use of antimicrobial treatments must be balanced against rising antimicrobial resistance, which could make it more challenging to manage infections.^{4,6}

Although the management of sepsis involves effective treatments, it also requires effective communication with patients and families. The WHA resolution urges states to promote public awareness and to use the term “sepsis” while communicating with its citizens. Public advocacy, notably by the Global Sepsis Alliance (which includes World Sepsis Day), UK Sepsis Trust and Canadian Patient Safety Institute, has raised awareness of sepsis.^{1,7} Educating people about signs and symptoms of sepsis will prompt them to seek medical care early, which is particularly relevant to those living in poverty and with low health literacy who may hesitate to seek care. The Global Sepsis Alliance created infographics to explain maternal and neonatal sepsis, and encourages patients and families to ask their providers, “Is this sepsis?”

In addition to appropriate medical treatments and advocacy, effective management of sepsis also requires infrastructure and financing. The Service Delivery Indicators program compared availability of medicines and infrastructure at health facilities in seven countries in Africa: 22% to 93% had appropriate equipment (e.g., thermometers, refrigerators) and 19% to 64% had appropriate infrastructure (e.g., water, electricity).⁸ A separate study of 101 hospitals from 41 countries showed that 20% lacked triage services and 70% did not apply protocols for sepsis.⁹

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To build robust, resilient health systems that educate health care providers, monitor delivery of antimicrobial agents and resistance and evaluate or develop interventions, financial investment from governments or private–public partnerships is critical. Without such investment, the global agenda for sepsis will not succeed. Incentives to control sepsis are complicated by reimbursement modalities; a study in the United States showed that postsurgical complications were associated with a higher per-encounter hospital contribution margin for patients covered by Medicare and private insurance.¹⁰

Health systems also need to support patients with postsepsis sequelae, including higher cognitive decline, depression and post-traumatic stress disorder.⁷ Sepsis affects individuals, but the burden is shared by their families and caregivers. Sepsis affects newborns disproportionately in LMICs and threatens to stall gains made in child survival. Sepsis in adults who are in hospital also has devastating economic consequences to societies that can least afford it. Therefore, appropriate systems are required to support patients and families during and after the episode of critical illness.

Sepsis cannot be adequately addressed without global support and political will. The UN Sustainable Development Goals include social determinants of sepsis, such as environmental degradation, climate change, overcrowding and lack of education, all of which must be addressed to reduce sepsis. The WHA resolution urges states to improve coding in the *International Statistical Classification of Diseases and Related Health Problems* to quantify the burden of sepsis and antimicrobial resistance. In addition, the Global Sepsis Alliance has advocated for the development of international registries to monitor the burden and outcome of sepsis.

The WHA resolution was adopted by all UN member states, and underscores that this is a global issue requiring a global commitment to improve care. Although the WHA resolution is a

step in the right direction, executing this will be challenging, particularly if countries move toward a nationalistic agenda that excludes people in LMICs. We remain optimistic that we can build global consensus for addressing this issue.

In the last five minutes you spent reading this article, at least 75 people died from sepsis. To decrease the ravages of sepsis will require a strong global health agenda, sharing of successful endeavours across nations and strong political will to work across country borders. The WHA resolution is a reminder that we can achieve great outcomes. With a concerted evidence-based effort that links local initiatives with regional and global programs, we will be able to reduce the substantial global burden of sepsis.

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