EDITORIAL

Infection, Antibiotics, and Patient Outcomes in the Intensive Care Unit

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Infection is a major cause of admissions and prolonged stays in intensive care units (ICUs). Epidemiological information on the underlying source of infections, associated microorganisms, treatment, and eventual outcomes is essential for identifying gaps and opportunities to optimize patient management. Systematic and harmonized data collection across institutions allows for geographical comparisons and tracking of temporal trends and also enhances the generalizability of findings. However, such large-scale patient-level data are scarce, likely due to the immense logistical demands for coordinating such a study.

Related article

Building on previous work (the European Prevalence of Infection in Intensive Care [EPIC I] study in 1992 and the Extended Prevalence of Infection in Intensive Care [EPIC II] study in 2007),[1,2] and as reported in the Extended Study on Prevalence of Infection in Intensive Care III (EPIC III) in this issue of *JAMA*, Vincent and colleagues[3] collected comprehensive data on the global epidemiology of infections in ICUs from point prevalence surveys at 1150 centers in 88 countries spanning 6 continents. All cause in-hospital mortality within 2 months was also recorded. The majority of the ICUs were from academic medical centers in upper-middle to high-income countries. Among 15 165 patients with infection data, 8135 (54%) patients had suspected or proven infection and 10 640 (70%) received at least 1 antibiotic. Gram-negative bacteria were the predominant microorganisms isolated in those with positive cultures (3540/5259 [67%]). The in-hospital mortality was 30% among patients with suspected or proven infection.

The most striking finding of EPIC III is how little has changed in terms of the prevalence of infection and the associated mortality over 3 decades. The EPIC I study[1] was based on data from 1992 and reported that 45% of the participants had infections. The EPIC II study[2] was based on data from 2007 and reported that 51% of the participants had infections with an in-hospital mortality rate of 33%. These estimates are close to those from other similar studies performed during the past decade.[4] Although it could be argued that these studies vary in case definitions and durations of follow-up, and it may not be possible to draw conclusions based on direct comparisons, it is disappointing that mortality remains so high despite the focus on the early recognition and management of sepsis over the years. This could raise concerns about possible stagnation in investments by governments and pharmaceutical companies in antibacterial therapeutics and diagnostics, especially with multidrug-resistant bacteria becoming more common.

In the current report by Vincent et al,[3] the high prevalence of gram-negative bacteria among the positive microbiological cultures, especially among patients with hospital- and ICU-acquired infections, likely reflects the overall microbial ecosystem in the participating ICU units and is a cause for concern. This is because of the ability of gram-negative pathogens to acquire antibiotic-resistance genes, especially in the presence of antibiotic selection pressure.[5] This global trend has been recognized as a major challenge with a limited range of therapeutic options available. Two recent reports commissioned by the World Health Organization highlight the limited pipeline for antibiotic agents. The 60 potential therapeutics in development consist of 50 antibiotics and 10 biologics and provide little benefit over existing treatments because only a few target the most concerning multidrug-resistant gram-negative bacteria.[6]

Another important finding of this study is the persistently high rate of antibiotic use relative to the prevalence of infections, which is similar to that reported in 2007 by the EPIC II study.[2] Although appropriateness for the use of antibiotics was not assessed in the 15 165 patients, the data reveal that a substantial proportion of antibiotic use was either for prophylaxis (28%; n = 4217) or empirically prescribed (51%; n = 7723) and only 35% (n = 5259) had positive microbiological cultures. Antibiotic use is likely to be even higher in ICUs in low- to middle-income countries, with an increasing trend mirroring the economic resources available in these countries.[7] Given the emphasis on antibiotic stewardship programs in recent years, persistently high antibiotic consumption in the ICU highlights the challenges in implementing effective stewardship interventions in this setting.

Imprecise clinical and microbiological diagnostics are often slow or inadequate to explain the rapid changes in the physiological status of patients, contributing to the physicians' hesitancy to de-escalate or discontinue antibiotics in this high-stakes patient population.[8] Recent efforts to discontinue antibiotics have focused on procalcitonin use, diagnostic stewardship, and computerized decision support systems among others. However, these types of efforts have not been shown to have a lasting effect on antibiotic use or antibiotic resistance among patients in the ICU.[8] Even though major infectious disease societies and international expert groups have published recommendations and checklists for general antimicrobial stewardship programs,[9,10] there is a lack of guidance for both the utility and implementation of antimicrobial stewardship specific to the ICU. There is a need for novel approaches to optimize antibiotic use in these critically ill patients to enable better outcomes while minimizing the collateral harms associated with antimicrobial resistance.

It is encouraging to observe continued expansion of the EPIC I study since 1992, with increasing representation from

various geographical and resource settings. This reflects the unprecedented connectivity that the medical and scientific communities now exploit to form global networks. To improve participation from low- to middle-income countries, active support can be offered for specialized research tasks such as ethics applications and data collection. Capacity building through research can potentially promote successful collaborations and bring about sustained benefits to the local health care system. Another advantage of a wide collaborative network is the opportunity to engage local investigators in survey design to prioritize information for data collection and to enhance applicability of data and analysis with the aims of strengthening monitoring systems and designing interventions to improve patient care.

A limitation in the interpretation of EPIC III,[3] especially when considered together with other similar point prevalence surveys conducted in ICUs, is the inconsistent method of data collection. The ambiguity in diagnosing and treating infections, compounded by the diverse underlying pathologies among ICU patients, contribute to uncertainties around the identification of infections and classification of their sources. Compared with sepsis, which is usually identified by standardized criteria according to international consensus,[11] diagnosis of infections is more nuanced. In addition, nonsterile sites such as the respiratory tract and the urinary tract can potentially be overestimated as sources of infection because true infection cannot be confidently discriminated from colonization. These uncertainties threaten the reproducibility of the findings and limit the ability of these data to detect temporal trends. Carefully designed serial point prevalence surveys with core components to maintain comparability, and optional variables adapted for local interests, can better evaluate the clinical effects of developments in critical care and sepsis management.

The EPIC III study by Vincent et al[3] is an impressive report that highlights a high prevalence of infections and antibiotic use in ICUs globally. This will likely motivate further research to fill the gap in the design and implementation of antibiotic stewardship interventions specifically targeting ICU settings. Given that these 3 point prevalence studies spanning almost 30 years have consistently reported high and stable mortality rates,[1-3] it is imperative that continued development of novel diagnostics and therapeutics be encouraged. The infectious disease and critical care communities cannot remain complacent in the face of such high levels of infection-related ICU mortality.

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