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EDITORIAL

Empirical antimicrobials in the intensive care unit

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Critically ill patients frequently present with infection, potentially leading to sepsis or septic shock, where timely and appropriate antimicrobial treatment is paramount [1, 2]. We aim to provide a step-by-step approach for prescribing empirical antimicrobials in intensive care unit (ICU) patients with a suspected infection.

Assessing the need and urgency

The need

Antimicrobial therapy is vital for treating most infections, yet it poses potential harm when overused, making proper diagnostic assessment crucial. Diagnostic evaluation includes clinical examination, imaging and laboratory testing [3]. Intensivists have a key role in interpreting these results, integrating each test into the broader decision-making process on a case-by-case basis. Complex patients may necessitate a multi-disciplinary strategy involving ICU physicians, referring physicians, surgeons, microbiologists and infectious disease specialists [4].

Despite extensive research, no gold standard biomarker exits to distinguish infection from other inflammatory states. The 2021 Survival Sepsis Campaign Guidelines (SSCG) advise against using procalcitonin for diagnosing sepsis and initiation of antimicrobials, compared to clinical assessment alone [3].

Microbiological sampling is essential in both diagnosis and to allow targeted therapy at a later stage and should be performed before starting antimicrobials while ensuring it does not significantly delay treatment [3]. At a minimum, blood cultures and samples from suspected infection sites should be taken. For more guidance, see Fig. 1. Rapid microbiological and molecular techniques can support earlier and tailored antimicrobial regimens [5, 6]. Numerous commercial tests are now accessible, enabling faster identification of potentially implicated pathogens. Emerging clinical evidence generally indicates that these tests offer superior sensitivity and specificity compared to traditional culture-based diagnostics [6]. However, several caveats persist, including limitations to detecting only predefined pathogen panels, overly sensitive identification of non-viable pathogens and costs [7]. Prompt and accurate interpretation will demand in-depth knowledge and expertise to ensure appropriate action is taken. Further research is crucial to understand the impact on antibiotic stewardship and patient outcomes.

The urgency

Sepsis and septic shock are medical emergencies requiring prompt action. The SSCG advocate for immediate antimicrobial administration within 1 h of recognizing possible septic shock or a high likelihood of sepsis [3]. To mitigate the risks associated with the overuse of antimicrobial agents [8], the diagnostic assessment window is extended in patients presenting with possible sepsis without shock, allowing for a more thorough evaluation. A weak recommendation exists for deferring antimicrobials in patients with low infection likelihood and no shock, with careful patient observation. Previous research even indicates that, in certain well-monitored ICU environments, postponing the start of antimicrobial treatment until preliminary microbiological findings are accessible may be justifiable in the less severely ill, allowing for more precise targeting of therapy [9]. However, definitive conclusions remain elusive. The advent of rapid diagnostics is set to revolutionize this field.

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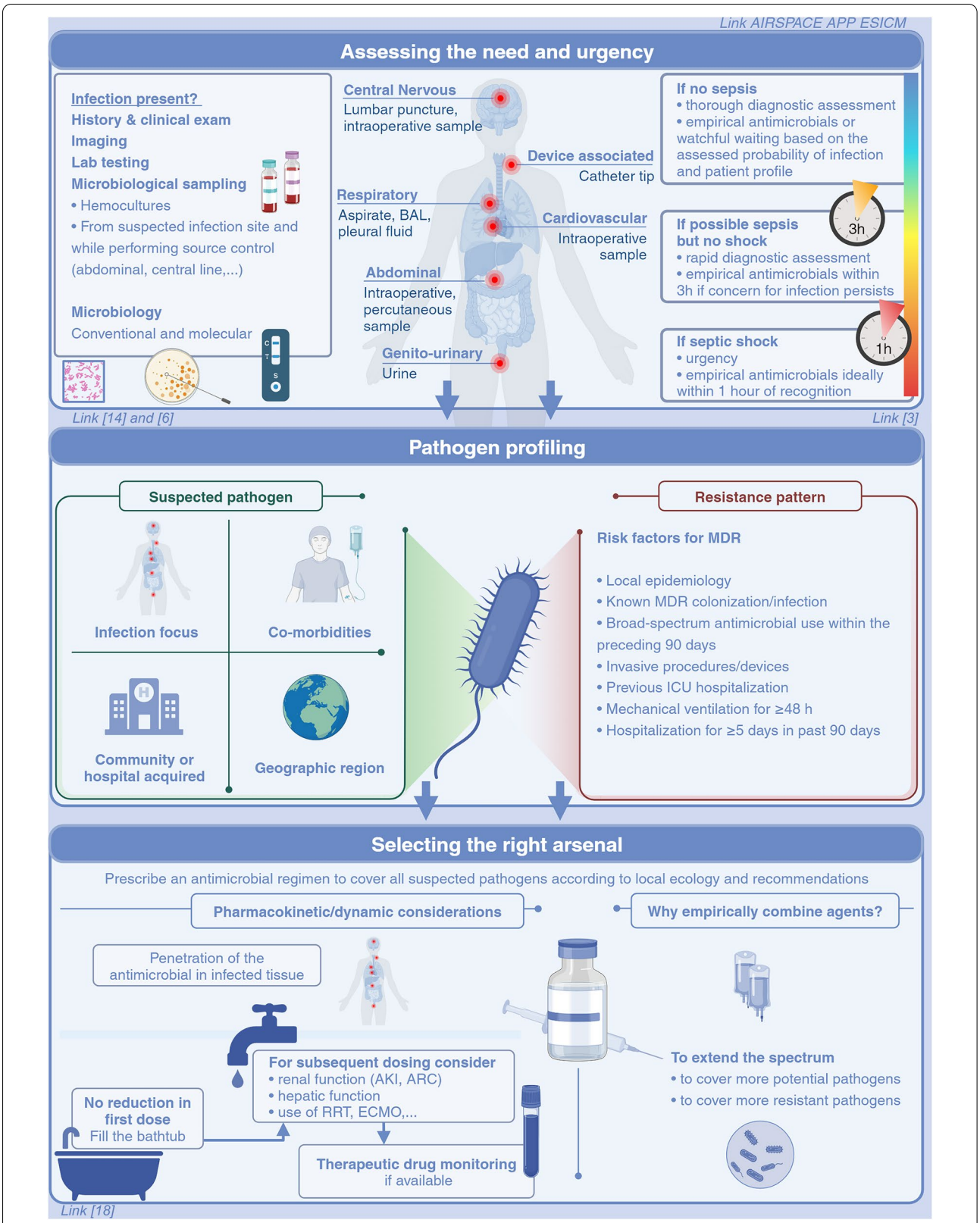

Fig. 1 A step-by-step approach for prescribing empirical antimicrobial therapy. Created with BioRender.com. *AKI* acute kidney injury, *ARC* augmented renal clearance, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *MDR* multidrug resistant, *RRT* renal replacement therapy [3, 6, 14, 18]. AIRSPACE ESICM https://airspace.esicm.org/login

Pathogen profiling

Profiling the suspected causative pathogen(s), by making an informed estimation of the species and susceptibility pattern is mandatory when determining empirical treatment. This process considers the presumed infection source, underlying comorbidities, local ecology and the risk of multidrug-resistant (MDR) organisms (Fig. 1) [10]. ICUs are known to have a high prevalence of MDR infections due to high antimicrobial pressure and extensive barrier breaching interventions [11]. Additional classical risk factors to be evaluated include history of colonization or infection with MDR pathogens, hospitalization for 5 days or longer within the past 90 days and recent antimicrobial treatment [12]. MDR prevalence thresholds have been proposed to guide empirical antimicrobial choice. However, these thresholds are largely based on expert opinion, using heterogeneous criteria, and with wide ranges that limit uniform applicability [13]. For more severely ill patients, a lower threshold (5–10%) for covering difficult-to-treat bacteria is generally accepted [13].

Selecting the right arsenal

No single empirical antimicrobial regimen is recognized as the gold standard. Once more, an individualized assessment is crucial, taking into account the severity of illness, the presumed source of infection, immunosuppressive status and patient-related risk factors for MDR [3, 14, 15]. Incorporating local ecological patterns into international guidelines presents significant challenges [3]. As a result, the development of hospital-specific guidelines should be encouraged to better address unique environmental factors and needs. The chosen agent should offer a spectrum that covers the majority of suspected causative pathogens. In this context, beta-lactams are one of the most commonly utilized classes [1]. Combining multiple agents to include a broader range of species and resistance patterns is generally accepted when deemed essential. The use of a combination of different drug classes, targeting the same (susceptible) pathogen to accelerate pathogen clearance or prevent the emergence of resistance, is more controversial [16]. In patients at low risk for MDR infection or when susceptibilities are known, the SSCG recommend against combination therapy [3]. In certain cases, specific agents are proposed as adjunctive therapy and available guidelines should be followed [17]. It is essential to incorporate the regular reassessment of both spectrum and duration of treatment into the daily workflow to mitigate ecological pressure.

In addition, choosing the appropriate empirical arsenal requires careful consideration of pharmacokinetic/pharmacodynamic factors to guarantee sufficient antimicrobial concentration at the infection site while reducing potential toxic effects. Precise dosing, including the amount, method of administration, and dosage frequency, is important to ensure effective treatment. During the initial phase, patients with sepsis, as a rule, have a larger volume of distribution and/or augmented drug clearance necessitating larger initial doses or more frequent dosing intervals, depending on the characteristics of the agents used. Once a steady state level has been reached, subsequent dosing should be adjusted according to the patient's clinical status (presence of end organ failure, use of extra corporeal techniques) and the way of elimination of the antimicrobials (renal, hepatic). Therapeutic drug monitoring has been suggested as a valuable tool for optimizing doses and reducing adverse effects [18].

Future perspectives

Advancements in diagnosing sepsis and identifying its causative microorganisms are key to increasing the effectiveness of treatments and simultaneously minimizing antimicrobial exposure. Decision tools incorporating patient, setting, and microbiology data, interpreted by artificial intelligence, represent a promising area currently under exploration.

There's a need for well-designed trials to establish timeframes for ICU physicians to commence or defer empirical therapy and to determine whether combination therapies are more effective than single-agent regimens, and if so, identify the most suitable types and settings for their use. Additionally, studying the ecological impact of various antimicrobial choices at the patient, institutional, and global levels is necessary.

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Declarations

Conflicts of interest

The authors confirm that they have no conflicts of interest to declare.

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