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LESS IS MORE IN INTENSIVE CARE

Less empiric broad-spectrum antibiotics is more in the ICU

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Antibiotics are administered in approximately 71% of patients who are admitted to the intensive care unit (ICU) and have helped to save millions of lives [1]. However, up to half of all antibiotic prescriptions may be unnecessary [2]. Antibiotic overuse has contributed to alarmingly high levels of global antibiotic resistance, which is increasing at a rate faster than that at which novel antibiotics are produced. Therefore, finding a fine balance between the appropriate use and avoidance of unnecessary administration is crucial to prevent the renaissance of a new world without antibiotics [2].

Antibiotics clinical effects

Antibiotics largely reduce mortality associated with moderate and severe infections, with a historical number-needed-to-treat estimated in 5.3 for severe pneumonia patients [3]. Infection progressing to sepsis is the leading cause of death in ICU patients and can be potentially treated using antibiotics, along with organ dysfunction support, and infection source control [4]. From the cognitive dimension, the fear of patient deterioration due to sepsis favours the empirical use of antibiotics in ICU patients.

Once a severe infection is diagnosed, the early administration of broad-spectrum antibiotics is recommended to decrease the risk of death [4]. This intuitive recommendation is also based on observational studies that have been carried out in the emergency department [5, 6]. In contrast, a randomized study, showed that the pre-hospital administration of antibiotics in septic patients did not reduce the mortality [7]. Furthermore, in a prospective cohort of ICU patients with bacteremia, early initiation and appropriateness of antibiotic intervention were not found to impact mortality when adequately adjusted for confounders [8]. Additionally, a pooled analysis of the current literature failed to demonstrate a survival benefit related to antibiotic administration within the first hour or within the first 3 h following a diagnosis of sepsis [9].

In surgical and trauma patients, a quasi-experimental before and after study demonstrated that more aggressive antibiotic use had similar outcomes and higher antibiotic exposure compared to conservative use [10]. Interestingly, when antibiotics were administered following the diagnosis of shock (mean arterial pressure < 60 mmHg), the mortality of the aggressively-treated group was higher than that of the conservatively-treated group (66% vs. 25%, $P < 0.0004$). The authors presented several plausible factors to explain these findings. The adequacy of initial antibiotic treatment was lower in the aggressively-treated group, which therefore extended the antibiotics exposure. Moreover, the waiting time for blood cultures and observation of the clinical course may also disclose alternative diagnosis to infections. At last, up to 25% of patients initially diagnosed as septic shock did not have an identified infection 24 h after their initial diagnosis [11].

From the physiological point of view, there is no plausibility that minor time differences in antibiotic administration reduce the intensity of the inflammatory response, and may even be associated with a transient worsening after administration. Lastly, it is difficult to differentiate the effect of early antibiotic use per se from the awareness of critical illness and the timely institution of high quality-of-care [12].

Antibiotics adverse effects

Several adverse effects related to antibiotic use are described in the literature; with acquired multidrug resistance (MDR) being the most concerning effect. Since

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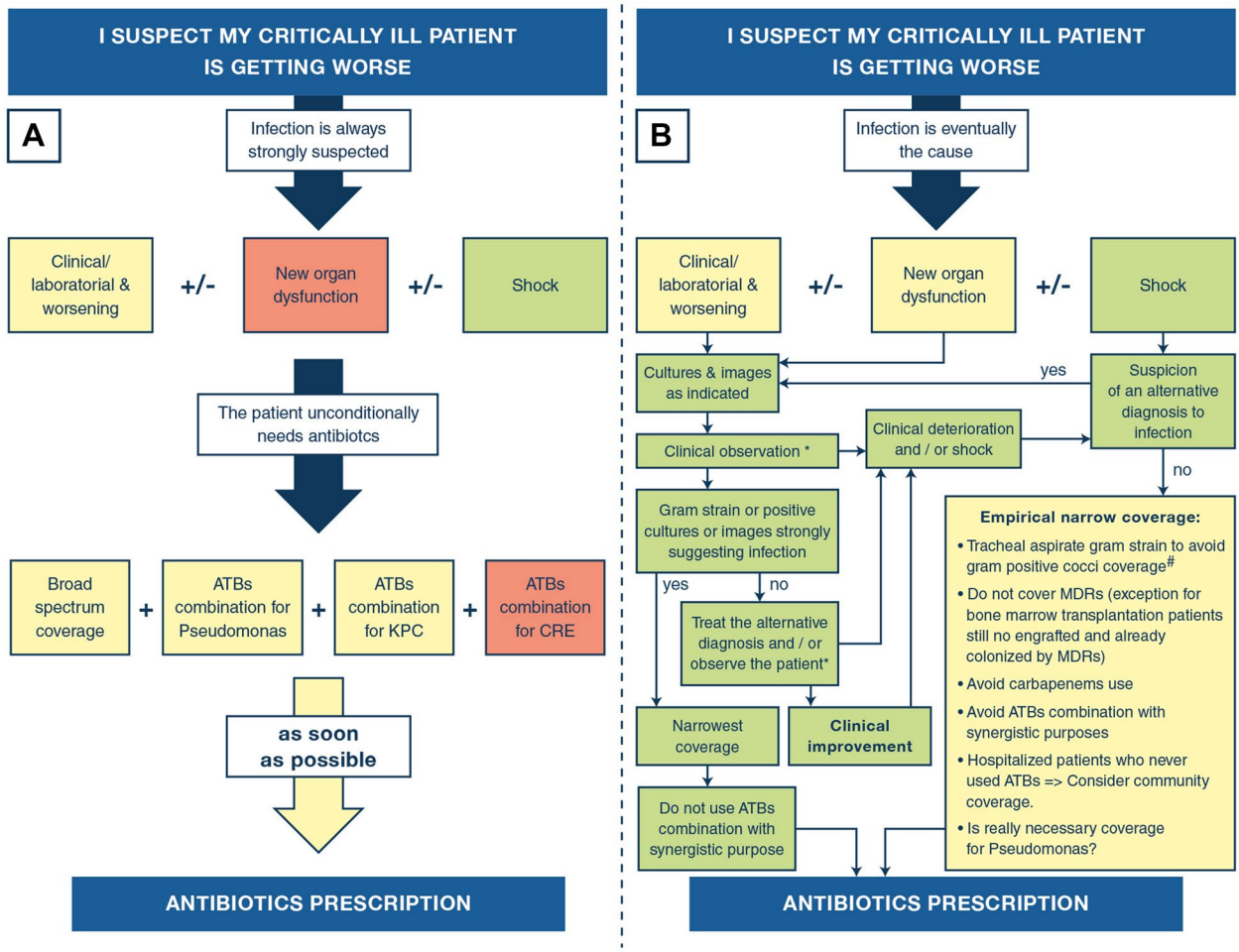

Fig. 1 Two different mindsets in the decision making process to initiate antibiotics to critically ill patients who are getting worse. **a** Aggressive mindset, in which the antibiotics are initiated as soon as possible to avoid further clinical deterioration; and **b** conservative mindset, in which antibiotics are only initiated with the infection diagnosis, or in shock patients without non-infectious alternative suspicion. MDR denotes multidrug resistant bacteria. ATMs denote antimicrobials. KPC denotes *Klebsiella pneumonia* carbapenemase. CRE denotes carbapenem resistant enterobacteriaceae. *In the intensive care unit, patients have 24 h of close clinical observation. #The Gram-positive cocci absence in the tracheal aspirate has a high negative predictive value to *Staphylococcus aureus* growing in patients with high clinical probability of ventilator associated pneumonia and clinical worsening—New fever, hypothermia, unexplained tachycardia and hyperventilation. Laboratorial worsening—leukocytosis, leukopenia, increased C-reactive protein and increased procalcitonin. Red boxes⇒No evidence—no randomized study or cohort evaluation on favor the practice, or randomized study against the practice. Yellow boxes⇒Some evidence—at least one cohort evaluation on favor the practice. Green boxes⇒Clinical evidence—at least one randomized study on favor the practice

1945, antibiotic resistance has been a major fear of Sir Alexander Fleming. Currently, MDR bacteria are largely spread across the world [13]. The real impact of MDRs on the outcomes of ICU patients is debatable, but despite this controversy, the incidence of MDRs is related to poor quality-of-care, as an expression of reduced compliance to hand hygiene [14], and a high burden of antibiotic exposure [15].

The de-escalation approach and single antibiotic dose impact

De-escalation approach, in which the antibiotic spectrum is narrowed or even withdrawn after re-evaluation, has been implemented to reduce exposure to antibiotics. De-escalation has proved to be safe in terms of survival; however, it is associated with an increased ICU length-of-stay, without reducing the incidence of MDRs [16]. De-escalation decreases the time of antibiotic use, but a short exposure still exists; in this way, a single antibiotic dose may be enough to treat severe infections such as

meningococcal meningitis [17], and to promote profound and sustained microbiome unbalances, therefore facilitating opportunistic infections and damping the potential benefit of the de-escalation approach [18].

Stewardship programs, costs, microbiology and outcomes

The main step toward the reduction of antibiotic use is the adequacy of hand hygiene in healthcare professionals [14]. An antibiotic stewardship focusing on feedback, monitoring, persuasion, and audit after each drug prescription is associated with a long term reduction in healthcare associated infections, antibiotic prescriptions, and health care costs, without the deleterious effects on length-of-stay, readmissions, and in-hospital mortality [19]. Furthermore, the decrease in the use of carbapenems, has been associated with an overall reduction in the incidence of MDRs [15]

Antibiotics use mindset

To ensure patient safety, the early aggressive administration of broad-spectrum antibiotics in the ICU setting is common practice [4]. However, maintaining a conservative mindset with respect to antibiotic use and safety is fundamental to both the patient and environment. Mindset modification accomplishes many dimensions; for instance, the RESET model which has been applied to dairy cattle farms resulted in a reduction in antibiotic use in this area [20]. RESET dimensions are (1) (R)ules—an external motivation to reduce antibiotic prescription; (2) (E)ducation—showing that antibiotic prescriptions are unnecessarily excessive, expensive, and paradoxically unsafe; (3) (S)ocial pressure-ensuring societal awareness that unnecessary use of antibiotics is dangerously growing; (4) (E)conomics—the awareness of economic consequences of reduced use of antibiotics to save costs; and (5) (T)ools—ways to spread knowledge regarding the conscious use of antibiotics.

A schematic, aggressive, and conservative mindset to commence antibiotics is presented in Fig. 1.

There are several reasons why aggressive early use of broad-spectrum antibiotics should be avoided in ICU patients. Presence of shock without an alternative diagnosis other than infection, and a diagnosis of infection based on cultures, bacterioscopic examinations, and imaging results for the initiation of antibiotics is currently considered safe practice. Furthermore, clinicians can consider investigating feasible alternative diagnosis for shock in unstable ICU patients before antibiotics initiation. Consideration of antibiotic use in our ICUs is essential, and if necessary; there is great plausibility in changing our mindset to restrict antibiotic use.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest.

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