Intensive Care Med (2020) 46:1039–1042
https://doi.org/10.1007/s00134-020-05951-5

EDITORIAL

Antimicrobial de-escalation is part of appropriate antibiotic usage in ICU

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Intensive care units (ICUs) are the epicenters of antibiotic resistance, because (a) more than 80% of the patients may receive antibiotic treatment on a given day; (b) the illness severity of the patients and the use of invasive procedures increase the likelihood of successful acquisition of and persistent colonization with new strains; (c) the unstable hemodynamic conditions predispose to establishing suboptimal concentrations of antibiotics at the infection site and (d) the high healthcare workload favors the risk of cross-transmission of resistant strains.

To control the multidrug, extensively resistant microorganisms (MDR/XDR) spread in association with strict infection control programs, antimicrobial therapy must be used wisely and not started inappropriately [1].

The improvement of antibiotic therapy and the antimicrobial stewardship programs in the ICU are multicomponent strategies described in Fig. 1 [1, 2].

Mainly because the available prediction score of MDR/XDR infections is inaccurate, use of broad-spectrum antimicrobials as carbapenems often represent the first choice for empirical antimicrobial therapy in ICU [3] but would be de-escalated in more than 2/3 cases, as they have been repeatedly associated with an increased risk of CPE, *Stenotrophomonas maltophilia* and XDR *P. aeruginosa* infections [4].

In an opinion paper, de Waele and coworkers [5] questioned the role of antimicrobial de-escalation (ADE) as one of the important components of antimicrobial stewardship in critically ill patients.

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We have a different opinion since we consider that the absence of ADE should lead to inappropriate AB management strategies.

In a nutshell [6, 7], the purpose of ADE is to reduce both the spectra of antimicrobial therapy and the selective pressure on microbiota. It is most often not only based on a switch from combination to monotherapy, but also includes early shortening/discontinuing antimicrobial therapies. In the recent ESICM/ESCGIP statement [6], early discontinuation was not included in the definition (low quality of evidence) but the panelists recognized that an early discontinuation aimed at similar objective to reduce the ecological impact of antimicrobials.

Whereas almost all studies to date have agreed on the fact that ADE is safe, one study suggested that ADE may prolong the duration of antimicrobial therapy and ICU length of stay. In an open-labeled randomized controlled trial, Leone et al. [8] reported that a strategy of a systematic decrease of the spectrum of the pivotal antimicrobial failed to be non-inferior to its continuation, in terms of duration of ICU stay. This study was underpowered, non-blinded, there were serious imbalances between groups that have been challenged in an accompanying editorial [9]. Furthermore, in a recently performed multinational cohort study DIANA (ClinicalTrials.gov Identifier: NCT02920463), ADE was associated with an increase in the Day7 clinical cure rate, which is a much more appropriate endpoint (https://healthmanagement.org/c/icu/news/lives2019-findings-from-the-diana-study).

As de Waele et al. [10] point out, the impact of ADE on resistance patterns has not been formerly demonstrated. It clearly depends on the nature of de-escalation chosen. They appropriately highlighted the potential benefit of a step-down strategy from carbapenem to narrow-spectrum antimicrobials in ESBL endemic settings as part of an antibiotic stewardship program. Indeed, such a decrease of the carbapenem use decreases the risk

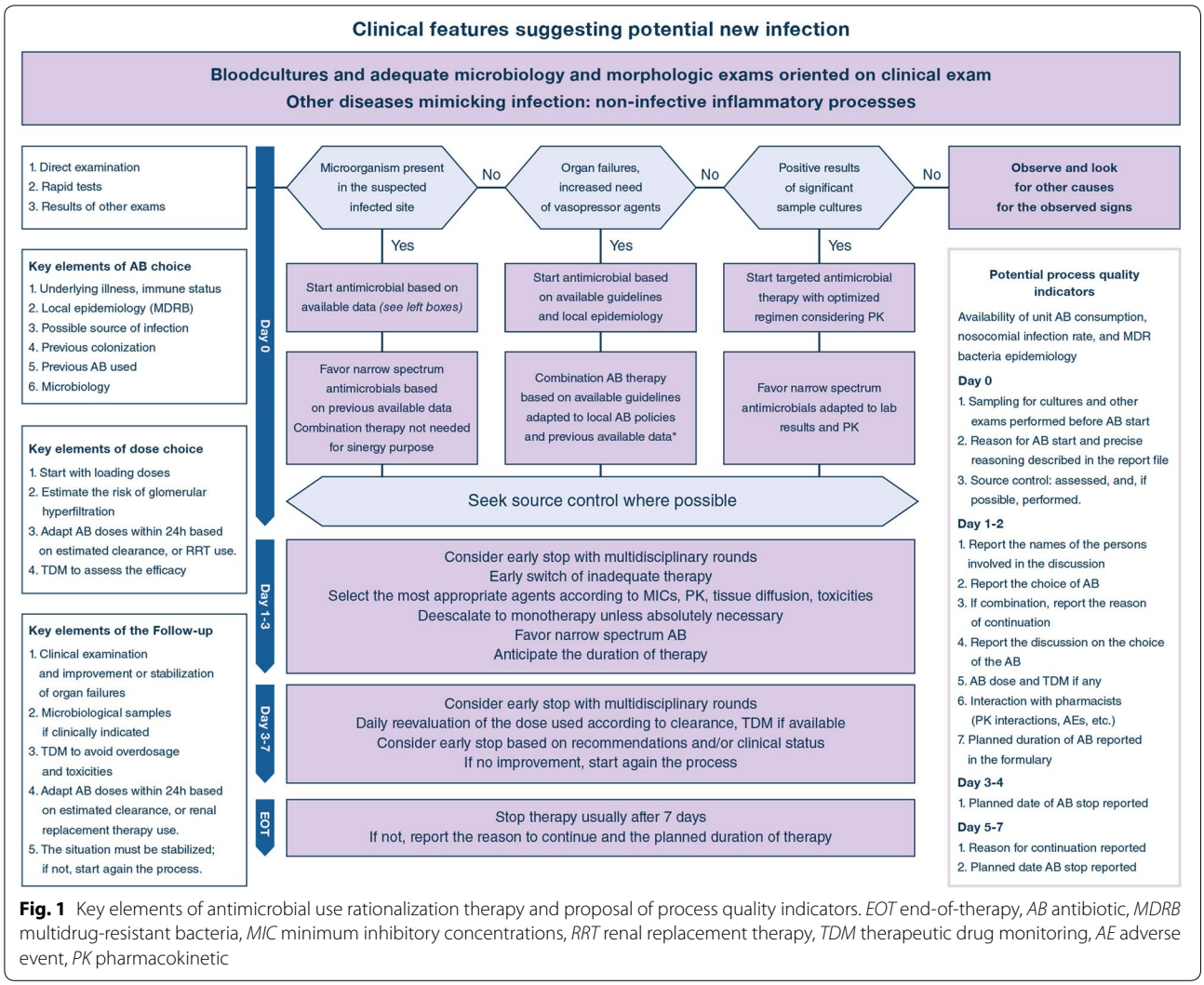

Fig. 1 Key elements of antimicrobial use rationalization therapy and proposal of process quality indicators. *EOT* end-of-therapy, *AB* antibiotic, *MDRB* multidrug-resistant bacteria, *MIC* minimum inhibitory concentrations, *RRT* renal replacement therapy, *TDM* therapeutic drug monitoring, *AE* adverse event, *PK* pharmacokinetic

of breakthrough carbapenem-resistant Gram-negative infections.

We suggest two important processes of care with a third follow-on effect that should be monitored in a quality indicator program.

Broad-spectrum antibiotic therapy is not always needed

First, the inflammatory responses seen in ICUs are very similar to that of sepsis [1]. This can often mean that a watch and wait process where no antibiotics are given, is appropriate. Hranjec et al. in a "before and after study", found that an aggressive immediate antimicrobial therapy when sepsis was suspected resulted in a more rapid antimicrobial initiation, more frequently inadequate therapy and was associated with a higher mortality as compared to a conservative watch and wait strategy [11]. This study showed that the early initiation of antimicrobial therapy in case of sepsis in ICU can often be delayed after a careful examination of patients and the completion of bacteriological and morphological diagnostic exams. As this study was conducted in a surgical (mainly trauma) ICU with a very low observed mortality, we accept that in many ICUs with the most severely ill and immunocompromised patients, it is by far more difficult not to start an antimicrobial therapy on the suspicion of sepsis [1].

As an example, infection-ventilator-associated complications leading to new antimicrobial therapy are associated with microbiological confirmation of an infectious process in only 44% of the cases [12]. However, antimicrobials save lives in case of severe infections and their early empiric use is recommended in recent guidelines of the surviving sepsis campaign and textbooks about sepsis and septic shock. If decided, the antimicrobial

should be started with the most appropriate dosing regimen, adapted on the PK data, and secondarily modified according to drug clearance in this individual patient [13].

De Waele et al. mention ADE should not be a carte blanche for starting a broad-spectrum antimicrobial therapy when an infection is suspected in critically ill patients. This is a sound statement. The decision to start antimicrobial therapy and the selection of the appropriate antimicrobials to administer should be made according to local epidemiology, previous MDR colonization, suspected site of infection, previous antimicrobial use, and available guidelines. A narrow-spectrum antimicrobial will likely be more appropriate for community-acquired infections, in patients without any known previous colonization with MDR bacteria and previous use of antimicrobials; it will also be more logical in region (or ICUs) with a very low risk of MDR (ESBL-producing enterobacterales, MRSA) or XDR (carbapenem-resistant enterobacterales, *Acinetobacter baumannii*). The systematic drawing of bacteriological sampling before starting any antimicrobial therapy is fundamental to guide secondary antimicrobial de-escalation.

In the absence of a documented infection when microbiological culture available, an early stop of antimicrobials should be considered

One key issue is the ability to stop antimicrobials that have been started in case of negative microbiological exams and alternate diagnosis. It requires systematic microbiological sampling before any changes of antimicrobial therapy. There are more and more studies suggesting that this strategy is safe [14, 15], even in immunocompromised patients, including those with leucopenia [16].

When the above-mentioned recommendations have been adopted, the final question on ADE refers to the need to de-escalate from a broad-spectrum antibiotic therapy to a narrowest one with the same efficacy in an attempt to reduce the antibiotic selection pressure

We do recognize that data are insufficient to demonstrate at an individual level that this strategy decreases the emergence of resistant microorganisms; however, it is a sensible strategy to apply together with an appropriate source control if a broad-spectrum antimicrobial therapy has been started.

Conclusions

ADE includes all strategies to stepdown antimicrobial therapies that are not needed, including the early stop of antimicrobial agent(s) administered in the empirical regimen to cover pathogens that are eventually not isolated in the bacteriological cultures, and in case of culture-negative sepsis.

ADE should not be considered alone and take part of the global rationalization of the antimicrobial use conducted, during daily rounds, based on the patient's condition and the microbiological results (Fig. 1). The global strategy is complex and requires a good collaboration of intensivists with microbiologists, ID specialists and pharmacologists. The global rationalization (including ADE) process, more than just the ADE decision, should be included in the continuous quality improvement program (Fig. 1).

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Compliance with ethical standards

Conflicts of interest

JFT declares COI outside of the submitted work: scientific board: Pfizer, Paratek, Nabriva, Merck; MedImune, research grants to my university: Pfizer, Merck, Biomerieux, 3M; lectures fees: Merck, Pfizer, Biomerieux, Gilead. Academic Research program on rapid diagnostic tests (Multicap: NCT 03452826; PHRC 16-0595) and PK optimization in ICU (BICCS PHRC-18-0316). JL has received honoraria from MSD and Pfizer. MB declares outside of the submitted work has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, Bayer, Basilea, Biomerieux, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, Melinta, Shionogi, Tetraphase, VenatoRx and Vifor and has received study grants from Angelini, Basilea, Astellas, Shionogi, Cidara, Melinta, Gilead, Pfizer and MSD.

Publisher's Note

Received: 11 January 2020 Accepted: 23 January 2020
Published online: 20 February 2020

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