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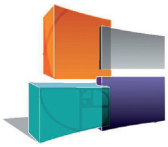

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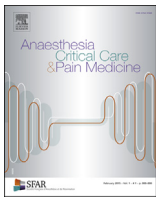

Review article

Update in antibiotic therapy in intensive care unit: report from the 2019 Nîmes International Symposium

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ABSTRACT

The 2019 Nîmes International Symposium in Antibiotic Therapy Optimisation aimed at determining the best approaches of a number of the antibiotic management strategies for critically ill patients. Experts reviewed the latest literature relating to requirements for an optimal antibiotic stewardship program, risks of sub-therapeutic dosing of antibiotics in critically ill patients, persisting issues about efficiency of combination therapy and the value of de-escalation, new perspectives of pharmacokinetics, drug toxicities including collateral damages-associated with antibiotics, the place of nebulisation of antibiotics, management of patients receiving extracorporeal therapies and the place of new antibiotics. In this paper, each of these issues is discussed with key messages presented after a brief review of evidence.

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1. Background

Rapid effective antimicrobial treatment is an absolute necessity in the critically ill patients with sepsis or septic shock [1]. However, various physiological and microbiological challenges are making this treatment very difficult to perform in many cases. The physician in charge should consider the necessary antimicrobial spectrum of activity, dose requirements in patients with multiple organ failure, as well as the risks of multidrug resistant (MDR) pathogen emergence after administration of broad-spectrum antibiotic treatment. We herein provide a summary of the 2019 Nîmes International Symposium on Antibiotic Therapy Optimisation. Experts should respond questions on antibiotic stewardship, including combination antibiotic therapy and de-escalation, dosing in the critically ill patients including new pharmacokinetic (PK) data, the management of patients requiring new organ support and the place of new antibiotics.

2. Emerging antibiotic resistance in Europe

Emergence and spread of MDR pathogens have become a major public health problem and is expected to become a leading cause of death worldwide by 2050 [2]. Inappropriate antimicrobial use represents a major cause of MDR emergence with an estimated cost of around € 75 trillion [3]. MDR pathogens are defined as bacteria resistant to at least one agent in three or more antibiotic categories, extensively drug resistant (XDR) bacteria are resistant to at least one agent in all but two or fewer antimicrobial categories, and pan drug resistant (PDR) organisms are resistant to all antimicrobial agents [4]. In the top 15 "public enemies" selected by the World Health Organisation (WHO), the concept of ESKAPE pathogens has been proposed, which probably present the strongest challenge that healthcare practitioners who treat severe infections are facing today (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*/*Enterobacter cloacae*) [5].

The European Antimicrobial Resistance Surveillance Network has reported the annually increasing prevalence of MDR pathogenic bacteria in 30 European countries [6]. The Network has identified that the third generation cephalosporins-resistant *K. pneumoniae* increased from 15% in 2005 to 31.2% in 2017, especially in Sweden, France and Greece (Table 1) [6]. A similar increase is reported for third generation cephalosporins-resistant *E. coli* (4.2% in 2005 to 14.9% in 2017) [6]. This increased prevalence led to a more frequent use of carbapenems to treat infections due to these pathogens, and thus caused the emergence of XDR and/or PDR Enterobacterales [7]. In Europe, the prevalence of carbapenem-resistant *K. pneumoniae* increased from 2.6% in 2009 to 7.2% in 2017 (Table 1) [6]. The emergence of these carbapenemase producing *K. pneumoniae* (carbapenemase-producing Enterobacterales, CPE) is of particular concern in Italy and Greece (Table 1) [6,8].

Regarding the other ESKAPE bacteria, the prevalence of vancomycin-resistant (VRE) has increased in Europe from 9.1% of the strains in 2009 to 14.9% in 2017. Ceftazidime-resistant *P. aeruginosa* remains stable around 15%, whereas a decrease of methicillin-resistant *Staphylococcus aureus* (MRSA) was observed [6]. However, these findings vary according to the bacterial species and geographical regions. For example, significant increases of VRE have been observed in the United Kingdom and Italy, although they remain almost absent in France (Table 1). Concerning ceftazidime-resistant *P. aeruginosa*, its prevalence decreased in Sweden, UK, Greece and France, whilst it increased in Italy (Table 1) [6].

Although the prevalence of the ESKAPE pathogens is geographically variable, some broad observations can be made:

- ESBL and carbapenemases in Enterobacterales are spreading across all countries;
- a North-South gradient appears to exist for the prevalence of resistance;
- a decrease has been registred for MRSA,notably in France and UK, and ceftazidime-resistant *P. aeruginosa*;
- the spread of VRE between countries is highly variable.

As emergence of MDR pathogens is a major public health issue in Europe, the "One Health" concept has been proposed to facilitate a worldwide strategy to expand interdisciplinary collaborations in all aspects of antibiotic use in humans, animals and the environment [9,10]. Some strategies for protecting antibiotics including more evidence-based use of antibiotics, better infection control, application of PK/PD-based dosing, development of new antibiotics , expanded vaccination programsand better use of antiseptics [5].

Table 1
Percentages of invasive MDR bacteria in Europe and five European countries since 2009.

Pathogens	Year	Sweden	UK	France	Italy	Greece	Europe
3GC KP[a]	2009	1.7 %	7.2 %	18.7 %	37.1 %	68.7 %	27.5 %
	2017	5.6 % (⟨)[g]	11.4 % (⟨)	28.8 % (⟨)	54.8 % (⟨)	69.2 % (⟨)	31.2 % (⟨)
3GC Ec[b]	2009	2.8 %	9.4 %	6.7 %	17.0 %	10.1 %	7.3 %
	2017	7.4 % (⟨)	10.3 % (⟨)	10.2 % (⟨)	29.5 % (⟨)	18.3 % (⟨)	14.9 % (⟨)
CRKP[c]	2009	< 0.1 %	< 0.1 %	0.1 %	1.3 %	43.5 %	2.6 %
	2017	0.1 % (=)	0.6 % (⟨)	0.7 % (⟨)	29.7 % (⟨)	64.7 % (⟨)	7.2 % (⟨)
MRSA[d]	2009	1 %	27.8 %	22.8 %	37.4 %	40.4 %	19.5 %
	2017	1.2 % (=)	6.9 % (®)	12.9 % (®)	33.9 % (®)	38.4 % (®)	16.9 % (®)
VRE[e]	2009	0.5 %	12.8 %	0.8 %	4.3 %	26.9 %	9.1 %
	2017	0 % (®)	25.8 % (⟨)	0.8 % (=)	14.6 % (⟨)	30.8 % (⟨)	14.9 % (⟨)
CAZRPA[f]	2009	6.9 %	5.5 %	16.8 %	16.5 %	33.7 %	14.8 %
	2017	4.5 % (®)	4.7 % (®)	12.2 % (®)	20 % (⟨)	24.9 % (®)	14.7 % (=)

[a] 3GCKP: third generation cephalosporins resistant *K. pneumoniae*.
[b] 3GCEc: third generation cephalosporins resistant *E. coli*.
[c] CRKP: carbapenem-resistant *K. pneumoniae*.
[d] MRSA: meticillin-resistant *S. aureus*.
[e] VRE: vancomycin-resistant *Enterococci*.
[f] CAZRPA: ceftazidim-resistant *P. aeruginosa*.
[g] Evolution of prevalence of resistance between 2009 and 2017: (⟨) increase; (®) reduction; (=) stabilisation.

3. Antimicrobial stewardship

The purpose of antimicrobial stewardship programs (ASP) is twofold. On the one hand, they intend to optimise patient outcomes by improving the antimicrobial prescription at the bedside and minimising the probability of adverse effects at the individual level, including toxicity and selection of pathogenic organisms (*Clostridium difficile* and fungi, for example). On the other hand, they intend to decrease the emergence and spread of antibiotic resistance, therefore promoting sustainable access to effective antibiotic therapy for all those who need them, including future generations [11,12].

ASP should be performed as a multifaceted strategy, using structural, restrictive and enabling interventions. With the restrictive interventions, one tries to reduce the number of opportunities for inadequate prescription, and with the enabling interventions, one tries to increase the number of opportunities and decrease barriers for optimal prescription. Enabling strategies should be emphasised and used more often, as they are better accepted, produce more sustained effects and synergise all other interventions. ASP should be designed as a quality improvement initiative defining locally customised goals, targets and time-to-targets, selecting interventions on the basis of specific goals, local context/culture and main determinants of prescription, building a dynamic measurement and data collection system with constant feedback to the team, and finally, attaining identification of quality gaps, room for improvement and planning of new interventions [13].

With this design, ASP increases compliance with desired practice and reduces duration of antibiotic treatment, inpatient length of stay antibiotic consumption, individual adverse events and rates of *Clostridium difficile* infections. It also creates synergy in the hospital, improves communication between persons and services, and joins clinical and social sciences, promoting shared goals and changing people and culture.

In the near future, ASP will be viewed as an essential quality improvement strategy in all health institutions, namely in all hospital departments, and it will occur in a much shorter time window, as microbiological tests will become faster and more informative, reducing the duration of empirical antibiotic therapy.

4. Combination antibiotic therapy

Combination antibiotic therapy is defined as the concurrent administration of two or more antibiotics. This definition takes into consideration neither the spectrum of antibacterial coverage nor the fact that two drugs may be included in one formulation. Reasons for choosing antibiotic combinations include broadening of the spectrum, achieving a synergistic effect or reducing the emergence of MDR pathogens. Treatment goals differ between empirical and targeted antibiotic combination therapy. Antibiotic combinations for empirical treatment are mostly used to broaden the spectrum of antibacterial coverage. In this line, antibiotic combination has been advocated in septic shock but combination therapy was not recommended to be routinely used in less severe forms of sepsis [1]. This recommendation is mostly based on an association between inappropriate antibiotic treatment and mortality in septic shock [14]. Data supporting antibiotic combination therapy are however scarce, leading to weak recommendations with some studies suggesting better outcomes using early antibiotic combination [15]. Of note, monotherapy was considered for all patients receiving at least one antibiotic active against the pathogen responsible for the infection. Thus, patients treated with antibiotic combination in which only one antibiotic was active were classified in the monotherapy category. The use of aminoglycoside was also associated with increased survival in neutropenic septic shock patients [16].

A randomised clinical trial (RCT) in septic shock patients, however, failed to show a decrease in organ failure when fluoroquinolones were added to carbapenems [17]. Of note, this trial was performed in a country with a rather low incidence of MDR pathogens. A meta-analysis of RCTs reported no differences in mortality between empirical mono- *versus* combination therapy in adult patients with severe sepsis [18]. The quantity and quality of reported data was low. Toxicity of antibiotic combination was furthermore highlighted in several observational cohort studies, mostly showing an increased risk of renal failure or acute kidney injury (AKI) with the use of aminoglycosides [19], colistin [20] or vancomycin [21]. Lower incidence of recurrent infections using monotherapy compared with antibiotic combinations in patients with sepsis was also reported.

Finally, positive impact of non-antibacterial effects of antibiotics (i.e. anti-inflammatory or anti-toxinic) has been suggested.

Martin-Lœches et al. [22] and Restrepo et al. [23], in two observational studies of patients with severe community-acquired pneumonia, observed lower ICU mortality in patients treated with macrolides than those treated with fluoroquinolones.

To summarise, while inappropriate initial antibiotic treatment appears to be associated with worse outcomes in septic shock, the impact of antibiotic combination on mortality has not yet shown benefit and is likely associated with an increased risk of side effects, mostly AKI.

5. De-escalation

De-escalation is one of the key interventions of ASP. By definition, it consists on narrowing the spectrum of antibiotics, as soon as a pathogen is identified by the microbiological team. The goal is to reduce the selection pressure on pathogens and decrease the cost associated with antimicrobials, while not affecting patient outcomes. De-escalation or streamlining appears in most guidelines of antibiotic management [1]. Although simple, its definition provokes a huge dilemma [24]; some authors suggest that interrupting a companion agent, like aminoglycoside, is part of the definition, whereas others think that the pivotal antibiotic, i.e. the beta-lactam in most cases, should only be considered. Indeed, interrupting aminoglycoside at day 3 is equivalent to administering a complete treatment. However, even de-escalation of the pivotal agent remains unclear, and there is no consensus relating to the ranking of antibiotics according to their spectrum. Two different groups made an attempt to obtain a relevant ranking based on a Delphi process. The two groups were unable to rank several antibiotics, and the two ranking are dissimilar [25,26].

One meta-analysis found that de-escalation is safe in terms of mortality [24]. However, most studies are based on a retrospective analysis of single centre practices. In addition to general biases of retrospective studies, it seems that antibiotics were de-escalated in the less severe patients, i.e. those responding to the empirical treatment [27]. Only two RCTs have assessed the effects of de-escalation [28,29]. Their results suggested that de-escalation might be associated with adverse events, like prolonged increased number of superinfections and prolonged duration of antibiotic exposure.

De-escalation aims to reduce the use of broad-spectrum antibiotics, and hence to decrease the selection pressure exerced on pathogens. The two RCTs did not find a reduction of MDR pathogens in the samples of patients included in the de-escalation group. An observational study specifically explored this issue in 478 antipseudomonal antibiotic prescriptions associated with the emergence of 28.8% of MDR pathogens. The authors concluded that the emergence of antibiotic-resistant bacteria after exposure to antipseudomonal beta-lactam antibiotics was not lower after de-escalation [30]. Due to the large number of variables affecting the emergence of MDR pathogens, we can hypothesise that de-escalation, especially for short duration antibiotic treatments, is probably cosmetic.

In conclusion, de-escalation is a strategy included in ASP, which is based on a weak level of evidence. It is probably the worst strategy, except for all the others. The development of rapid diagnostic tests, the choice of short-duration treatments, and a cautious selection of patients requiring antibiotics should reduce the need for empirical treatment, and then decrease the role of de-escalation in the ASP.

6. Critically ill patients at risk of suboptimal dosing

Many studies have now defined concentrations or, more accurately, pharmacokinetic exposures of antimicrobials associated with maximal clinical effects. These data exist not only for drugs traditionally subject to dose optimisation, aminoglycosides and glycopeptides, but also beta-lactams, linezolid and tigecycline amongst others [31]. These data have largely been defined in critically ill sub-populations, mostly because of their increased risk of treatment failure, which is partly due to high pharmacokinetic variability that may manifest as sub-therapeutic drug exposures. The prevalence of sub-therapeutic antibiotic exposures in critically ill patients was somewhat defined in the DALI Study, a point prevalence pharmacokinetic study performed in 68 European Intensive Care Units (ICUs) [31]. In the beta-lactam component of this study, nearly 1 in 5 patients were found not to achieve even the most conservative target exposure, and these patients were three times more exposed to treatment failure. Similar data was also found for vancomycin and teicoplanin. It is clear that the lack of verification in critically ill patients before drug licensing means that dosing regimens are not appropriate for all patients.

To this end, post-licensing pharmacokinetic studies in critically ill patients are highly valuable for understanding the disposition of antibiotics in these patients and providing relevant data to design robust and effective dosing regimens. In order to fast track such studies, prioritisation of patient groups at highest likelihood of underdosing is required. Depending on the specific drug, available data currently suggest that under-exposure can be associated with augmented renal clearance (measured creatinine clearance > 130 mL/min), high sickness severity and associated fluid resuscitation, high body weight as well as use of renal replacement therapy and extracorporeal membrane oxygenation. In order to define better empiric dosing regimens for critically ill patients and thsu minimise those who are subject to sub-optimal antibiotic dosing, the above sub-populations are those that should be studied.

7. Pharmacokinetics: new perspective

Adherence to traditional, specifically timed sampling schedules, e.g. “trough” or “peak”, for the purposes of measuring therapeutic drug concentrations to adjust dosing is often exceptionally poor in real-world hospital settings. For example, among 75 hospitalised adults who were not critically ill, of 233 measured plasma vancomycin concentrations that were intended to be trough concentrations sampled 10–12 hours after the previous twice-daily dose, only 84 (36%) were actually sampled within this window [32]. Comparison of concentrations obtained outside the window to a pre-specified target range leads to erroneous conclusions about dosing adequacy. Even when measured correctly, interpatient variability in plasma antibiotic concentrations with standardised dosing is enormous. Of these 84 “true” trough concentrations, 47% were < 10 mg/L, 17% were 10 to < 15 mg/L, 26% were 15 to 20 mg/L, and 10% were > 20 mg/L. Furthermore, only 28% were within the goal trough concentration range for that patient. There is clearly better than standardised dosing for all.

Fortunately, increasingly accessible and user-friendly software tools can implement sophisticated Bayesian approaches to calculate medication doses that are most likely to achieve target drug concentrations. The algorithms that power these software tools are robust to sample timing and more accurate with extremely limited sampling schedules (e.g. one sample) than human intuition, nomograms, or use of pharmacokinetic equations [33]. Fundamental to these tools are population pharmacokinetic/pharmacodynamic models, which are simply collections of equations that relate input (dose) to output (concentration or effect). These equations have one or more unknown variables or parameters (for example clearance), which are distributed with some probability in a population. Knowledge of individual

parameter values permits prediction of individual output at any time for any given input.

When estimating the probability distribution of model parameters in a population, the most common statistical approach is to assume that there is a "typical" value for each parameter that must be estimated, and a random interindividual variability (IIV) around that typical value. This IIV is assumed to be normally distributed with a mean of 0, and a random variance, which must also be estimated. The typical values and IIV are chosen to minimise error in predictions compared with observations. In contrast to this "parametric" approach, the non-parametric approach does not assume typical values and normal IIV. This can be advantageous when characterising unexpected sub-populations or subjects with extreme parameter values [34]. The probability distribution for parameter values in the population model is random. The Bayesian approach then rigorously updates the "prior" population model with newly obtained data from an individual patient to a "posterior" model of that patient. The fewer the data from the patient, the more the posterior model will resemble the prior. Conversely, the richer the data from the patient, the more individual the posterior will be. Essentially, this approach recognises that the pharmacokinetic/pharmacodynamic behaviour of a drug in an individual is not unique, but may be better understood within the context of the behaviour in patient populations.

Such non-parametric population models and Bayesian approach can be used in a freely available software tool called "BestDose", available from the Laboratory of Applied Pharmacokinetics and Bioinformatics at the Children's Hospital Los Angeles and the University of Southern California (www.lapk.org). In addition to presented examples of HIV patients whose outpatient antiretroviral drug dosing was adjusted based on measured drug concentrations to off-label dosing that achieved previously unattained therapeutic success, there are also prospective evaluations of the BestDose software and Bayesian, multiple-model adaptive control algorithm. A recent such evaluation was for vancomycin, comparing traditional trough concentration targeting, BestDose area under the curve (AUC) targeting with trough concentration sampling, and BestDose AUC targeting with optimally timed sampling [32]. With BestDose, patients had fewer blood samples, shorter duration of therapy, and less nephrotoxicity with reduced excessive trough concentrations above 20 mg/L, all without compromising efficacy.

In summary, the time has come to move beyond treating all patients as simply average, and use modern, capable software tools like BestDose and others to consider each patient as an individual, with an equally individual drug dosage regimen.

8. Risks of antibiotics in the ICU: toxicities and collateral damage

Beta-lactams are widely used as first-line therapy because of their broad-spectrum coverage of different pathogens, their bactericidal properties and few drug-related complications. Thus, beta-lactams are commonly considered as safe drugs. However, as monitoring of beta-lactam plasma concentrations has become increasingly available, the risk of over-exposure is now better identified in critically ill patients. Moreover, the need for higher than conventional dosing regimens for less susceptible strains and reduction in glomerular filtration rate may lead to accumulation and adverse events. There is compelling evidence that toxicity occurs in ICU patients even with beta-lactams.

8.1. Beta-lactam related neurotoxicity

Neurotoxicity has been reported in 10–15% of ICU patients and associated with significantly higher beta lactams trough concentrations [35]. A Cmin/minimal inhibitory concentration (MIC) ratio > 8 has been correlated with an incidence of neurological deterioration above 60% [36]. The underlying mechanism of beta-lactam neurotoxicity seems related to a decrease of GABA release from nerve terminals for cephalosporins, whereas a competition between beta lactam core and GABA on GABA A receptors occurs for penicillin and carbapenems. Renal dysfunction has been identified as a major risk factor of overdosing and neurotoxicity. In several retrospective studies, cefepime has been incriminated in the occurrence of encephalopathy [37]. The diagnosis of neurotoxicity is highly challenging in ICU patients, as there is no specific sign (confusion, myoclonus, convulsions). Electroencephalogram and therapeutic drug monitoring (TDM) could help to diagnose beta-lactam related neurotoxicity [38]. Discontinuation of the offending drug is the best approach to retrospectively diagnose beta-lactam induced neurotoxicity.

8.2. Beta-lactam related nephrotoxicity

Acute interstitial nephritis is a quite rare adverse event, but it is associated with poor renal outcome, as only half of the patients fully recover at 6 months [39]. Increasingly, piperacillin/tazobactam has been incriminated in the occurrence of AKI, especially while it is co-administered with vancomycin. In a retrospective study of 11,650 patients, around 27% of patients receiving the combination therapy of piperacillin/tazobactam and vancomycin developed AKI compared with 15.4% of patients receiving the combination therapy of meropenem and vancomycin ($P = 0.001$) [40]. However, interestingly, the increased risk of nephrotoxicity is no longer observed neither when piperacillin/tazobactam is administered as extended infusion nor when administered as short course therapy. The combination of several nephrotoxic drugs (vancomycin, piperacillin, aminoglycoside) should be used carefully, especially in patients presenting pre-existing kidney disease, older patients or patients with septic shock.

8.3. Strategies to reduce antibiotic induced-kidney injury

TDM has been advocated to optimise beta-lactam therapy and to minimise toxicity [41]. For vancomycin, different pharmacokinetic targets have been considered. However, area under the AUC-guided dosing strategy is independently associated with less nephrotoxicity than trough concentration-guided dosing strategy [41]. For aminoglycosides, the use of renal replacement therapy associated with high-dose of aminoglycoside could decrease nephrotoxicity [42].

8.4. Clostridium difficile *infections*

Finally, antibiotics not only induce toxicity but also may cause harm to the intestinal microbiota, leading to an increased risk of *Clostridium difficile* infections. However, all antibiotics do not have similar impact on the intestinal flora.

8.5. In practice

The use of antibiotics, in "at risk" patients (renal dysfunction), should consider the benefice-risk ratio for efficacy/toxicity, especially when no alternative exists. Where possible, TDM may help minimising toxicity but exposure thresholds should be clearly identified.

8.6. What is next?

In the near future, antimicrobial optimal dosing regimens should not only be defined based on PK/PD targets associated with

clinical and microbiological efficacy, but also on PK/toxicodynamics targets. The use of dosing softwares may help achieving these goals.

9. New mechanisms causing collateral damages

The human body is estimated to host over 100 trillion bacterial cells divided into more than 10.000 different microbial species. In serious infections leading to sepsis or septic shock, a single bacterial species is generally responsible for the disease, and this single bacterium should be treated with antibiotics. There is no single antibiotic, not even a narrow-spectrum antibiotic that acts over only one bacterium, meaning that any antibiotic treatments would affect a large proportion of the human commensal flora. The human microbiome is essential for the human wellbeing, and the effects caused by the disturbance of the bacterial balance, sometimes referred to as the collateral damage of antibiotic treatment, are just starting to emerge more clearly.

Apart from direct action on bacteria, certain antibiotics also have other side effects. Fluoroquinolones have long been known to affect the collagen synthesis that may cause weakening of tendons and risk of tendon rupture. As a consequence, the vessel walls, which are mainly structured of collagen, can also be weakened. In a recent study, researchers compared propensity-matched patients who received an antibiotic treatment with either fluoroquinolones or penicillin and evaluated the risk of admission due to aortic aneurysm or dissection. Within 60 days after the intake of the antibiotic, there was an increased hazard ratio of 1.66 (95% CI, 1.12 to 2.46) for fluoroquinolones users compared with amoxicillin [43]. As a result, the U.S. Food and Drug Administration (FDA) recommends not using fluoroquinolones in patients at risk for aortic aneurysm or dissection.

Apart from the main role of energy metabolism, mitochondria are now known to be involved in many other cellular processes like apoptosis and regulation of inflammation during viral and bacterial infections. Infection-induced mitochondrial dysfunction has been put forward as one pathogenic mechanism of organ failure in sepsis. However, another mechanism could also contribute to mitochondrial dysfunction in severe infections. According to the endosymbiotic theory, the mitochondrion is of bacterial origin and their molecular and structural components of the protein expression system are very similar. Many antibiotics target protein synthesis via interaction with bacterial ribosomes and can thus also interfere with mitochondrial protein synthesis, leading to mitochondrial dysfunction [44]. Kalghatgi et al. investigated the difference between bacteriostatic and bactericidal antibiotics and found that bactericidal antibiotics (represented by ciprofloxacin, ampicillin and kanamycin) reduced mitochondrial respiration profoundly compared with bacteriostatic antibiotics (tetracycline). Interestingly, they found that the negative effects seemed to be mediated by increased reactive oxygen species production and that mitochondrial respiration could be restored by the administration of N-Acetyl Cysteine, a well-known anti-oxidant [45].

10. Is there a place for nebulisation of antibiotics in critical care?

Nebulisation of anti-infective agents is a common practice in bronchiectasis and cystic fibrosis chronic infections and became an un-standardised practice in mechanically ventilated patients as salvage therapy. Two global international surveys [46,47] reported that 50% of the responding intensivists never conducted this practice, which is mainly due to the lack of protocolisation or experience. According to the same surveys, colistin and aminoglycosides were the commonest antibiotics being aerosolised, with a great heterogeneity of dosages, and in indications ranging from pneumonia, ventilator-associated tracheobronchitis, or colonisation by MDR organisms. It is remarkable that only 1/3 adhered to recommendations and the most frequent device was jet nebuliser, which delivers particles whose size do not allow them to be distributed to the alveoli. A systematic review of 1435 studies in adults receiving invasive mechanical ventilation identified only 11 studies on nebulised antibiotics [48]. Two different administration strategies (“Adjunctive” or “Substitute”) were considered clinically relevant. Five studies included had small sample size ($<$ 50 patients) and only six were randomised. Diversity of case-mix, dosage and devices were a source of bias. Only a few patients had severe hypoxemia. Aminoglycosides and colistin were safe regarding nephrotoxicity and neurotoxicity, but significantly increased respiratory complications in 9%, particularly when administered to hypoxemic patients. For tracheobronchitis, a significant decrease in emergence of resistance was evidenced (relative risk at 0.18; 95% CI, 0.05 to 0.64, I = 0%). Similar findings were observed in pneumonia by susceptible pathogens, without improvement in mortality or ventilation duration. In pneumonia caused by resistant pathogens, higher clinical resolution (odds ratio at 1.96; 95% CI, 1.30 to 2.96, I = 0%) was evidenced. These findings were not consistently evidenced in the assessment of efficacy against pneumonia caused by susceptible pathogens. Performance of RCTs evaluating the impact of nebulised antibiotics with more homogeneous populations, standardised drug delivery, pre-determined clinical efficacy and safety outcomes is urgently required. Opportunities of research are reported in Table 2. Without concomitant systemic administration of the drug, nebulisation may reduce nephrotoxicity, but may also be associated with higher risk of respiratory complications. Recommendations from the European Society of Clinical Microbiology and Infectious Diseases were released in November 2017 [49], suggesting that administration of antibiotics by aerosolisation in mechanically ventilated adults should be a practice restricted to salvage therapy in pneumonia by difficult-to-treat organisms following a strict protocol of administration [50].

Table 2
Five remaining questions on nebulisation.

Number	Clinical questions still remaining
1	How is the delivered dose dispersed in the lung?
2	How much is absorbed into the blood?
3	How does the resulting serum PK:PD profile mimic an intravenous dose of the same drug?
4	How specific formulations might impact on efficacy?
5	How much is removed from the site by suctioning?

11. Optimising anti-infective therapy in patients with Extracorporeal Membrane Oxygenation

Extracorporeal Membrane Oxygenation (ECMO) is a life support technique used to treat patients with cardiac and/or respiratory failure who are refractory to conventional therapies. Survival for adults supported with ECMO showed continuous improvement over time, with survival rates reported of 50% in patients with veno-arterial ECMO and up to 70% in patients with veno-venous ECMO [51]. However, more than half of adult patients receiving ECMO will develop nosocomial infections, especially pneumonia, and these infections are associated with an increased morbidity and mortality [52].

Optimisation of antibiotic therapy for ECMO patients remains a pharmacological challenge. Increase in the volume of distribution, altered clearance or drug extraction by the circuit could induce

significant changes in antibiotics pharmacokinetics under ECMO assistance, as shown in children [53]. However, recent studies in adult populations did not confirm these results [54]. Indeed, achievement of target concentrations is poor in critically ill patients for commonly used antibiotics (beta-lactams, glycopeptides, fluoroquinolones and aminoglycosides) [55] but seems to be similar in ECMO and non-ECMO patients. Therapeutic drug monitoring, alternative drug choices or alternative regimens could help to increase achievement of target concentrations in tissues in ECMO patients.

For the future, dose optimisation, choice of drugs or route of administration should improve antibiotic administration in ECMO patients.

12. New antibiotics

12.1. New antibiotics: needs and expectations

In the last 15 years, intensivists and infectious diseases consultants have started to face novel peculiar challenges in the treatment of severe infections in critically ill patients in ICU, due to the selection and diffusion of MDR Gram-negative bacteria [56,57].

Indeed, although the development of resistance has accompanied antibiotic therapy since its dawn, Gram-negative bacteria have only started in the recent years in non-negligible numbers to manifest concomitant resistance to all commonly used classes of antibiotics. Fortunately, this situation has started to change very recently, owing to the introduction into the market of novel drugs with potent activity against some MDR Gram-negative bacteria such as carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant Pseudomonas aeruginosa (CRPA) [58].

Nonetheless, the availability of novel agents does not automatically imply an easy and always successful treatment, for several reasons:

- most of available novel agents have still suboptimal activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB);
- activity against CRE of novel β-lactam/β-lactamase inhibitors (BL-BLI) is dependent of the type of carbapenemase conferring resistance to carbapenems;
- resistance to novel antibiotics has already started to emerge, and widespread use of novel antibiotics should thus be avoided, in order to relieve selective pressure for further development of resistance;
- on the other hand, adequate coverage for MDR should be empirically guaranteed in critically ill patients with severe infections and risk factors for MDR, in order not to delay active treatment [59].

With so many factors at stake, treatment of MDR Gram-negative bacteria infections in critically ill patients is becoming a very complex task, which requires dedicated expertise, as well as an always updated knowledge of the patients' medical history, local microbiology and epidemiology, in order to promptly recognise the risk of MDR Gram-negative bacteria and also the most likely resistance mechanisms involved.

This latter factor is particularly important in light of the renewed possibility of treating severe MDR-GNB infections with beta-lactams (some already available such as ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam, and others that will be available in the near future), which inevitably raises the question as to whether the type of suspected resistance determinant (e.g., the type of carbapenemase) should not only guide the choice of the better agent/s to be administered, but also the decisions about escalation and de-escalation, in order to follow antibiotic stewardship purposes including at the enzyme-level.

12.2. Ceftazidime/avibactam

Ceftazidime/avibactam is a recently marketed beta-lactam/beta-lactamase inhibitor (BL-BLI) combination active against class A (e.g. KPC) and class D (e.g. OXA) carbapenemase-producing CRE and demonstrated activity against some CRPA isolates [60]. Ceftazidime/avibactam is approved by FDA and EMA for complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP) and VAP. Furthermore, ceftazidime/avibactam received approval by the European Medical Agency (EMA) for infections due to Gram-negative bacteria in adults with limited treatment options. Although efficacy of ceftazidime-avibactam in randomised clinical trials was demonstrated against ceftazidime-resistant isolates, whereas CRE were not included, its activity against the latter is supported by the favourable results of observational studies. Consequently, ceftazidime/avibactam is an important, effective, and already available option for the treatment of CRE, whose use should be necessarily optimised according to antibiotic stewardship principles. Indeed, some cases of resistance to ceftazidime/avibactam, conferred by blaKPC mutations have already been reported [60].

12.3. Meropenem/vaborbactam

Meropenem/vaborbactam is another novel BL-BLI, exerting potent and specific activity against class A (e.g. KPC) carbapenemase-producing CRE. After having received approval by FDA for cUTI, meropenem/vaborbactam was recently approved by EMA for cUTI, cIAI, HAP, VAP, and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. Because of demonstrated superiority of meropenem/vaborbactam, the open-label TANGO-II trial, in which meropenem/vaborbactam was compared with the best therapy available for CRE infections, was terminated early. Against this backdrop, meropenem/vaborbactam is another novel and very effective option for KPC-producing CRE. In this light, future therapeutic algorithms for CRE infections should carefully take into account the peculiar characteristics and spectrum of activity of each of these two novel compounds, in order to maximise the effectiveness of anti-CRE therapies in each selected situation and preserve the activity of both drugs in the long-term.

12.4. Ceftolozane/tazobactam

Ceftolozane/tazobactam is probably the novel, available BL-BLI with the most potent in vitro activity against CRPA (although not against carbapenemase-producing strains), whereas it is not active against CRE [61]. Ceftolozane/tazobactam is approved by FDA for the treatment of cIAI, cUTI and HAP/VAP [62]. However, the most attractive use of ceftolozane/tazobactam at the present time is perhaps the treatment of CRPA infections, also for off-label indications. Finally, the possibility of using ceftolozane/tazobactam as a carbapenem-sparing option for infections due to extended-spectrum β-lactamases (ESBL)-producing Enterobacterales has also been proposed, that might be useful in selected scenarios pending confirmatory clinical and economic data [61].

12.5. What is next

In conclusion, novel treatment options have become available in recent years, providing some much-awaited resources for effectively counteracting some severe MDR Gram-negative bacteria infections. However, their optimal use should be guaranteed in

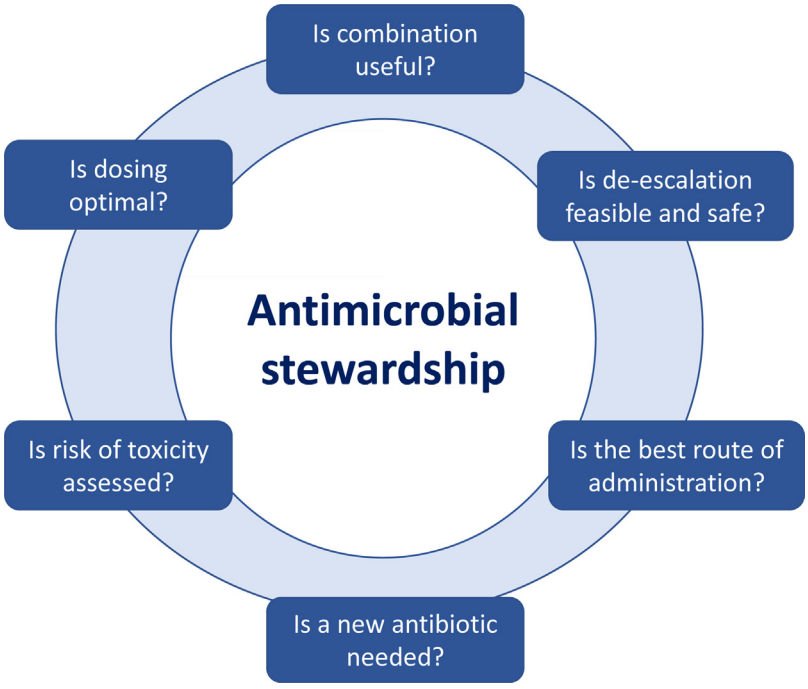

Fig. 1. Six routine questions related to antimicrobial stewardship.

the long term, for delaying as much as possible the emergence and diffusion of resistance to novel agents. Despite important progresses, PK/PD optimisation of dosages and treatment duration in critically ill patients still have some areas of uncertainty requiring further study that should also take into account resistance selection as a major endpoint.

13. Conclusion

Important landmark studies examining different questions about antibiotic administration have modified the way intensivists should administer antibiotics in the ICU. The 2019 Nîmes International Symposium has permitted world-renowned experts to share their vision on how intensivists can improve patient outcomes (Fig. 1). Pharmacokinetic studies have identified high-risk patients for under or overdosing. While underdosing may put the critically ill patients at higher risk of mortality, overdosing exposes them to potential severe brain or kidney dysfunction. Therapeutic drug monitoring and maybe a dedicated software with online machine learning will probably help the intensivists optimising and personalising the dose through the difficult journey of the critically ill patient, and will hopefully be an important player in improving our patient survival in the future. At an institutional level, an ASP should be implemented as a quality improvement initiative to avoid unnecessary broad-spectrum antibiotic treatments and guarantee adequate antibiotic treatments. Antimicrobial stewardship may also help intensivists considering de-escalation, combination therapy reassessment, antibiotic duration shortening and even antibiotic treatment discontinuation when infection is unlikely. Recent progresses in rapid microbiological diagnosis (there are more to come without any doubt) will likely facilitate the implementation of antimicrobial stewardship, paving the way towards better outcomes and perhaps less MDR pathogens emergence. Recently developed antibiotics mostly designed to target MDR Gram negative bacilli, as well as nebulised route, should also be considered as precision weapons to fight life-threatening bugs in the ICU.

Disclosure of interest

AB: lecturer for Aspen and consultant for LFB.
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MLeo: lecturer for 3 M, Aspen, MSD, Octopharma, Pfizer and consultant for Aguettant, Amomed.
The other authors declare that they have no competing interest.

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