Annals of Intensive Care

REVIEW

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The place of new antibiotics for Gram-negative bacterial infections in intensive care: report of a consensus conference

Pierre-François Dequin[1,2*], Cécile Aubron[3], Henri Faure[4], Denis Garot[2], Max Guillot[5], Olfa Hamzaoui[6], Virginie Lemiale[7], Julien Maizel[8], Joy Y. Mootien[9], David Osman[10], Marie Simon[11], Arnaud W. Thille[12], Christophe Vinsonneau[13] and Khaldoun Kuteifan[9]

Abstract

Introduction New beta-lactams, associated or not with beta-lactamase inhibitors (NBs/BIs), can respond to the spread of carbapenemase-producing enterobacteriales and nonfermenting carbapenem-resistant bacteria. The risk of emergence of resistance to these NBs/BIs makes guidelines necessary. The SRLF organized a consensus conference in December 2022.

Methods An ad hoc committee without any conflict of interest (CoI) with the subject identified the molecules (ceftolozane–tazobactam, ceftazidime–avibactam, imipenem–cilastatin–relebactam, meropenem–vaborbactam and cefiderocol); defined 6 generic questions; drew up a list of subquestions according to the population, intervention, comparison and outcomes (PICO) model; and reviewed the literature using predefined keywords. The quality of the data was assessed using the GRADE methodology. Seven experts in the field proposed their own answers to the questions in a public session and answered questions from the jury (a panel of 10 critical-care physicians without any CoI) and the public. The jury then met alone for 48 h to write its recommendations. Due to the frequent lack of powerful studies that have used clinically important criteria of judgment, the recommendations were formulated as expert opinions as often as necessary.

Results The jury provided 17 statements answering 6 questions: (1) Is there a place in the ICU for the probabilistic use of new NBs/IBs active against Gram-negative bacteria? (2) In the context of documented infections with sensitivity to several of these molecules, are there pharmacokinetic, pharmacodynamic, ecological or medico-economic elements for prioritization? (3) What are the possible combinations with these molecules and in what context? (4) Should we integrate these new molecules into a carbapenem-sparing strategy? (5) What pharmacokinetic and pharmacodynamic data are available to optimize their mode of administration in critically ill patients? (6) What are the dosage adaptations in cases of renal insufficiency, hepatocellular insufficiency or obesity?

Conclusion These recommendations should optimize the use of NBs/BIs in ICU patients.

*Correspondence:
Pierre-François Dequin
pfdequin@gmail.com
Full list of author information is available at the end of the article

Introduction

Bacterial ecology has changed in hospitals over the last few years with the emergence and spread of carbapenemase-producing Enterobacterales and nonfermenting bacteria that have developed resistance to carbapenem antibiotics, either through enzyme production or, more commonly, through altered permeability or efflux [1–6]. New antibiotics may help to control these germs, but they may also induce the emergence of resistant strains [7–11]. Published trials evaluating these antibiotics were generally noninferiority trials, and most did not target the resistant pathogens that are an issue in clinical practice. Some of these antibiotics have been presented as carbapenem-sparing [12], but the relevance of this concept needs to be discussed. Recently, Infectious Diseases Society of America [13] and European Society of Clinical Microbiology and Infectious Diseases [14] have published guidelines on similar topics, but not limited to the intensive care setting. The French Intensive Care Society (FICS, in French: Société de Réanimation de Langue Française, SRLF) organized a consensus conference on "the place of new antibiotics in Gram-negative bacterial infections in intensive care", as there was a need to define recommendations for the use of the new antibiotics available for critically ill patients, given the potentially low level of evidence in the available literature. It focused on newly available beta-lactam antibiotics, including two combinations of a cephalosporin with a beta-lactamase inhibitor (ceftolozane–tazobactam and ceftazidime–avibactam), two combinations of a carbapenem with a beta-lactamase inhibitor (imipenem–cilastatin–relebactam and meropenem–vaborbactam), and a fifth-generation cephalosporin (cefiderocol). Throughout this text, these new antibiotics will be grouped under the abbreviation NBs/BIs (new beta-lactams combined or not with beta-lactamase inhibitors).

Methods

The SRLF appointed its Reference and Evaluation Committee to organize a consensus conference to better define the indications and conditions of use for these new antibiotics. The members of the committee defined six generic questions (Table 1), and then Patient, Intervention, Control, Outcome (PICO) questions were submitted to experts (Additional file 1) [15]. One expert was appointed for each generic question asked. A group of intensive care fellows and members of the committee carried out the bibliographic research in PubMed (contributors are listed in Additional file 1). Keywords were defined based on PICO questions. Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables of published data were drawn up [16]. The level of evidence was assessed according to the type of study for each of the quoted references and then reassessed (increased or decreased) according to the quality of the study's methodology. References were grouped according to each judging criterion. An overall quality of evidence was determined for each judging criterion based on the quality of evidence of each individual reference, the coherency of results between the different studies, whether the evidence was direct or indirect, and cost analysis. A "high" quality of evidence led to a "strong" recommendation (must, must not… GRADE 1 + or 1-). A moderate, low or very low quality of evidence led to an "optional" recommendation (probably should, probably should not… GRADE 2 + or 2-). In the absence of evidence, the issue was recommended in the form of an expert opinion.

The panel was made up of 10 members coordinated by a chairperson. All practiced or had practiced in intensive care, and two were also qualified in infectious diseases. They were chosen by the organizers on the one hand for their clinical interest in the topic, but on the other because they had no related potential conflicts of interest. At the end of the conference, the role of the panel was to provide a consensus text with the conclusions and recommendations of the conference in the form of a clear answer to each of the questions. The experts wrote a text for the panel members debating the assigned question, including the most recent scientific data, their opinions and arguments. A meeting was held for the experts, the panel members and a large audience of intensive care

Table 1 Questions put to the conference experts and panel

Question 1: Is there a place for the empirical use of the new beta-lactams active against Gram-negative bacteria in the intensive care setting?
Question 2: In the context of documented infections with susceptibility to more than one of these antibiotics, is there any pharmacokinetic, pharmacodynamic, ecological, or cost-effectiveness evidence for priorization?
Question 3: What are the possible combinations with these antibiotics, and in what context?
Question 4: Should these new antibiotics be included in a carbapenem-sparing strategy?
Question 5: What pharmacokinetic and pharmacodynamic data are available in critically ill patients to optimize the mode of administration, particularly continuous infusion, dose increase, and administration strategy guided by measurement of plasma antibiotic concentration?
Question 6: How should doses be adjusted in renal or hepatocellular failure or obesity?

physicians. The experts presented their analyses and the specific scientific data for the question they were responsible for, and they answered the questions and comments of the panel and the public. After the public meeting, the panel met privately to draft the text answering the questions. Recommendations were formulated according to GRADE methodology. The proposed recommendations were presented and discussed individually. The aim was not necessarily to obtain a convergent opinion of the panel members for all of the proposals but to uncover points of agreement and points of disagreement or indecision. Each recommendation was then assessed by each panel member and scored individually from 1 (totally disagree) to 9 (strongly agree). The panel score was defined using a GRADE grid [17]. To achieve a strong recommendation, at least 70% of the participants had to agree. If there was no strong agreement, recommendations were reworded and then rescored to achieve consensus. Two recommendations required rewriting and a second round of voting to reach consensus. The final text contains the conclusions and recommendations of the conference.

Question 1

Is there a place for the empirical use of the new beta-lactams active against Gram-negativeGram bacteria in the intensive care setting?

Recommendation 1A These antibiotics should probably not be used empirically in critically ill patients (grade 2-, moderate quality of evidence, strong agreement)

Recommendation 1B The panel suggests that the use of these antibiotics should only be considered in the exceptional case of septic shock occurring in a patient with known colonization by carbapenemase-producing Enterobacterales or Pseudomonas aeruginosa resistant to any antipyocyanic antibiotic or in the event of an outbreak of one of these bacterial infections (panel opinion, strong agreement).

Arguments

These recommendations are supported by the following data: first, for carbapenem-susceptible bacteria, no randomized controlled trial has shown a superiority of NBs/BIs over meropenem or the best available treatment [18–22]; second, colonization by Gram-negative bacteria resistant to carbapenems due to the production of carbapenemase is currently exceptional. In France, ertapenem-resistant Enterobacterale isolates vary between 0.02 and 0.2% [23]. A 2019 study in 11 Parisian hospitals found that only 1.2% of patients were colonized with carbapenemase-producing Enterobacteriales [4]. In an intensive care setting, REA-REZO 2018 data showed that 14.4% of health care-associated infections were attributed to *Pseudomonas aeruginosa*, with 23.3% of carbapenem-resistant strains, without specifying the mechanism of resistance [24]. Moreover, *P. aeruginosa* often combines several mechanisms of resistance, including an efflux system or lack of permeability due to porin inactivation, mutations in the penicillin-binding protein, and the overproduction of natural cephalosporinase [25]. Beta-lactams other than NBs/BIs may be active against all of these mechanisms. Third, less than 10% of patients colonized with multidrug-resistant (MDR) bacteria will develop an infection due to these bacteria, and the absence of colonization by MDR bacteria is an excellent negative predictive factor for MDR bacterial infection [26–28]. Fourth, similar to other beta-lactams, NBs/BIs exert selection pressure. For example, exposure to ceftazidime–avibactam led to the emergence of 20% resistance in Enterobacterales [7], and exposure to ceftolozane–tazobactam led to 15–50% resistance in *P. aeruginosa* [8, 9]. After exposure to ceftolozane–tazobactam, cross-resistance to ceftazidime–avibactam has also been reported [9, 10]. Rapid emergence of resistance has been reported with cefiderocol and, in addition, has been associated with excess mortality of patients infected with *Acinetobacter baumannii* [11].

Thus, given the lack of superiority of NBs/BIs over carbapenems, the low risk of MDR bacterial infection in the absence of prior colonization or an ongoing epidemic, the risk of the emergence of resistance, and the need to keep these antibiotics as a last resort, the panel suggests that their empirical use should be reserved for exceptional situations combining septic shock and known colonization by either carbapenem-resistant bacteria or *P. aeruginosa* resistant to other antipyocyanic antibiotics or in the event of a local epidemic of one of these germs. There are no data to support empirical use of NBs/BIs in the sole presence of risk factors for MDR bacterial colonization. Prior carbapenem therapy is a risk factor for the selection of carbapenem resistance in *P. aeruginosa* but is not sufficient to support the empirical use of NBs/BIs.

In exceptional cases where empirical administration of one of these antibiotics has been initiated, it is imperative that this therapy be reassessed and reduced if possible. This assumes that bacteriology laboratories reduce the time needed to determine antibiotic susceptibility, and to test available antibiotics without incorporating a priori strategies for sparing certain molecules.

Question 2

In the context of documented infections with susceptibility to more than one of these antibiotics, is there any

pharmacokinetic, pharmacodynamic, ecological, or cost-effectiveness evidence for prioritization?

Recommendation 2A There is insufficient evidence to prioritize ceftazidime–avibactam, meropenem–vaborbactam or imipenem–cilastatin–relebactam for carbapenem-resistant Enterobacterales infections when strains are susceptible to these antibiotics. (no recommendations, insufficient quality of evidence, strong agreement).

Arguments

All three antibiotics are active against class A carbapenem-resistant Enterobacterales (*e.g.,* KPC). Ceftazidime–avibactam is the only compound active against class D carbapenem-resistant Enterobacterales (*e.g.,* OXA-48). None of these three antibiotics are active against carbapenem-resistant Enterobacterales carrying metallo-β-lactamases (*i.e.,* NDM or VIM). The intrinsic susceptibility profiles of each molecule are summarized in Table 2.

No randomized controlled trial has compared these three new antibiotics in patients with carbapenem-resistant and non-carbapenem-resistant Enterobacterales infections. There are no pharmacokinetic, pharmacodynamic, ecological or cost-effectiveness arguments in favor of one of these antibiotics over the others if they are active in vitro.

Most randomized controlled trials assessing the efficacy of these three antibiotics did not target carbapenem-resistant Enterobacterales and most often used a carbapenem as a comparator [20, 21, 29–33]. Only two small randomized controlled trials specifically included patients infected with carbapenem-resistant Enterobacterales [34, 35].

Only one retrospective study compared ceftazidime–avibactam and meropenem–vaborbactam for carbapenem–resistant Enterobacterales infections. This study found no significant difference in mortality, clinical success at 30 and 90 days, or adverse events [36]. In this study, strains from patients receiving ceftazidime–avibactam developed resistance more often than those from patients receiving meropenem–vaborbactam, but not significantly so.

Several single-center or multicenter observational cohort studies have reported the efficacy of ceftazidime–avibactam or meropenem–vaborbactam, alone or in combination, for severe carbapenem-resistant Enterobacterales infections [37–48]. However, there are no published clinical data on the efficacy of imipenem–cilastatin–relebactam for KPC-producing Enterobacterales infections.

The size of the bacterial inoculum may impact the in vitro activity of these new antibiotics on carbapenem-resistant Enterobacterales [49], but the clinical significance remains unknown.

Table 2 Spectrum of new beta-lactams with or without beta-lactamase inhibitors

	Carbapenemase-producing Enterobacterales			Nonfermenting gram-negative bacilli	
	Ambler classification				
	Class A (prototype: KPC)	Class B = MβL (prototype: NDM)	Class D (prototype: OXA-48)	*Pseudomonas aeruginosa* XDR	Imipenem-resistant *Acinetobacter baumanii*
Ceftolozane-Tazobactam					
Ceftazidime-Avibactam					
Imipenem-cilastatine-Relebactam					
Meropeneme-Vaborbactam					
Cefiderocol					
Avibactam + Aztreonam					

KPC = *Klebsiella pneumoniae* carbapenemases; MβL = metallo-beta-lactamases; NDM = New-Delhi MβL; OXA-48 = oxacillinase-48; XDR = extensively drug-resistant [113]

Green boxes: mainly susceptible species

Red boxes: mainly resistant species

Orange box: despite being highly susceptible in vitro, clinical efficacy remains uncertain, with excess mortality in a subgroup of the credible trial [11]

Recommendation 2B The panel suggests that cefiderocol should be used only if other therapies have failed (or are poorly tolerated) in documented infections with class A or D carbapenememase-producing Enterobacterales (panel opinion, strong agreement).

Arguments

Cefiderocol is effective against class A or D carbapenemase-producing Enterobacterales and is the only antibiotic also effective against metallo-β-lactamase-producing Enterobacterales.

Clinical data on the efficacy of cefiderocol against carbapenem-resistant Enterobacterales infections are limited [11, 35, 50, 51]. An increase in the minimum inhibitory concentration of cefiderocol was reported in 15% of patients treated in the cefiderocol arm of the CREDIBLE-CR trial [11, 50].

Given the risk of emergence of cefiderocol-resistant strains, even though it is the only NB/BI with activity against metallo-β-lactamase-producing Enterobacterales, the panel did not recommend cefiderocol as first-line therapy.

Recommendation 2C There is insufficient evidence to prioritize cefiderocol over the combination of ceftazidime–avibactam plus aztreonam in documented infections with metallo-β-lactamase-producing Enterobacterales, especially NDM-producing strains (no recommendations, insufficient quality of evidence, strong agreement).

Arguments

Cefiderocol is intrinsically active against metallo-β-lactamase-producing Enterobacterales. Another option for treating these infections is a combination of avibactam and aztreonam [52] (Table 2). Aztreonam is a monobactam that is not hydrolyzed by class B metallo-β-lactamases. However, it is hydrolyzed by the majority of other beta-lactamases, including KPC and AmpC. Additionally, most metallo-β-lactamase-producing Enterobacterales also produce other enzymes, notably class A serine-β-lactamases. Avibactam restores the activity of aztreonam against most carbapenem-resistant Enterobacterales. Thus, the combination of aztreonam and avibactam is active against bacteria that are resistant to either of these antibiotics individually [53]. No aztreonam–avibactam combination is currently marketed in France; therefore, aztreonam must be combined with ceftazidime–avibactam.

Available data suggest that these two options (cefiderocol and aztreonam–avibactam) are more efficient and cause less kidney injury than the use of older antibiotics [54, 55]. However, no comparison is currently available between these two options.

Recommendation 2D There is insufficient evidence to prioritize ceftolozane–tazobactam, ceftazidime–avibactam, and imipenem–cilastatin–relebactam in documented infections caused by Pseudomonas aeruginosa resistant to other antibiotics (no recommendations, insufficient quality of evidence, strong agreement).

Arguments

In infections caused by *P. aeruginosa* resistant to carbapenems and other usually active beta-lactams (piperacillin–tazobactam, ceftazidime, cefepime, aztreonam), there are currently no randomized controlled trials or pharmacodynamic, pharmacokinetic, clinical, ecological, or cost-effectiveness arguments in the literature to favor one NB/BI over another in this indication.

It should be noted that meropenem–vaborbactam is intrinsically inactive against meropenem-resistant strains of *P. aeruginosa*.

Defining the minimum inhibitory concentrations (MICs) of *P. aeruginosa* could help in selecting the most appropriate NB/BI. Unfortunately, molecular diagnostic methods for the rapid identification of antibiotic resistance of *P. aeruginosa* do not allow for a definitive determination of which molecule to use, as this pathogen often has multiple resistance mechanisms. In the APECT-NP trial, the emergence of *P. aeruginosa* strains resistant by enzymatic mechanisms was comparable in the ceftolozane–tazobactam and meropenem groups; however, in the meropenem group, more second infections occurred with a different strain, resistant by mutation through efflux mechanisms [56].

Recommendation 2E The panel suggests that cefiderocol be used only in cases of treatment failure or intolerance to other therapies, for documented infections with Pseudomonas aeruginosa resistant to other antibiotics (panel opinion, strong agreement).

Arguments

Cefiderocol is active against over 90% of carbapenem-resistant strains of *P. aeruginosa*, including strains resistant to the other three NBs/BIs mentioned above [57–60]. In a post hoc analysis of the CREDIBLE-CR trial, an increase in the MIC of cefiderocol was observed in 15% of patients receiving cefiderocol, without exceeding the susceptibility threshold of the molecule [11].

To preserve the efficacy of cefiderocol while minimizing the risk of emergence of resistant strains, the panel

recommends limiting its use to cases for which there is no other alternative.

Recommendation 2F Cefiderocol should probably not be used for documented infections caused by carbapenem-resistant Acinetobacter baumannii unless there are no other treatment options available (grade 2-, moderate quality of evidence, strong agreement).

Arguments

Despite its in vitro activity against the majority of carbapenem-resistant strains of *Acinetobacter baumannii*, currently available clinical data do not support the efficacy of cefiderocol for this indication. In the cefiderocol arm of the CREDIBLE-CR trial, the majority of deaths attributed to treatment failure occurred in patients with *A. baumannii* infections [11]. These results could be due to a phenomenon of heteroresistance to cefiderocol [61].

The treatment of severe infections due to carbapenem-resistant *A. baumannii* involves a combination of antibiotics, including colistin, aminoglycosides, tigecycline, and ampicillin–sulbactam, depending on the susceptibility profile of the strain, the site of infection, and the characteristics of the patient, after consultation with an infectious disease specialist. Ceftazidime–avibactam, meropenem–vaborbactam, imipenem–cilastatin–relebactam, and ceftolozane–tazobactam are not active against this pathogen.

Question 3

What are the possible combinations with these antibiotics, and in what context?

Recommendation 3 There is insufficient evidence to recommend combining these antibiotics with aminoglycosides or any other antibiotics (no recommendations, insufficient quality of evidence, strong agreement).

Arguments

In vitro, synergy appears to exist between ceftazidime–avibactam or ceftolozane–tazobactam and aminoglycosides [62–68]. There are no available clinical data showing a benefit of these combinations, particularly with regard to survival [68–72]. As with older beta-lactams, a few clinical cases and retrospective studies have tested NBs/BIs combined with an aminoglycoside to broaden the antibiotic spectrum. These studies, of insufficient quality of evidence, did not show increased toxicity or any particularity compared to the combination of aminoglycosides with other beta-lactams.

Regarding colistin, the synergistic effect is variable in vitro [73–83]. The combination of ceftazidime–avibactam and colistin may have an antagonistic effect in vitro [79, 84]. Only in vivo cases emphasize the known nephrotoxicity of colistin [80].

For tigecycline [65, 74, 75, 85] and fosfomycin [77, 86, 87], synergy has been inconsistently observed in vitro. The clinical data are of very poor quality [69, 88].

Question 4

Should these new antibiotics be included in a carbapenem-sparing strategy?

Recommendation 4 The panel suggests that these new antibiotics should not be used as a part of a carbapenem-sparing strategy (panel opinion, strong agreement)

Arguments

See the arguments in question 1 for recommendations on exceptional empirical use of NBs/BIs.

For documented infections with carbapenem- and NB/BI-susceptible pathogens (but those resistant to older beta-lactams), the panel's recommendations are based on 4 arguments: first, with the exception of an ancillary study of a pivotal trial on ventilated-associated pneumonia [55], all the trials were in favor of simple noninferiority of NBs/BIs compared with carbapenems for Gram-negative infections sensitive to both types of antibiotics [18–21, 29]; second, health care cost data did not support the promotion of one class of antibiotics or the other [89]; third, the ecological impact of these antibiotics has not been fully assessed because their use is recent. However, some clinical trials have shown a rapid emergence of cross-resistance following the use of ceftolozane–tazobactam [8, 10], affecting up to 14% of *P. aeruginosa* strains. The emergence of resistance following exposure to ceftazidime–avibactam for infections with carbapenem-resistant Enterobacterales has been demonstrated in two clinical trials and has involved up to 15% of *Klebsiella pneumoniae* strains [38, 79]. A rapid increase in the MIC has been reported during treatment with cefiderocol [11]. All these data raise the fear of a rapid emergence of resistance to NBs/BIs if their use is not restricted. Fourth, these antibiotics appear to be the only antibiotics of last resort for infections with carbapenemase-producing Enterobacterales or with *P. aeruginosa* resistant to other antipyocyanic antibiotics.

Under these conditions, the panel considers it essential to preserve the use of NBs/BIs.

Question 5

What pharmacokinetic and pharmacodynamic data are available in critically ill patients to optimize the mode of administration, particularly continuous infusion, dose increase, and administration strategy guided by measurement of plasma antibiotic concentration?

Recommendation 5A To increase the time that plasma levels of the antibiotic exceed the target concentration, these antibiotics should be administered as a prolonged infusion (2 to 4 h) (grade 1+,high quality of evidence, strong agreement).

Recommendation 5B The panel suggests increasing the dose of some of these antibiotics in situations where there is a risk of underdosing, including increased renal clearance, high body mass index, and potentially difficult-to-reach infection sites (panel opinion, strong agreement).

Recommendation 5C There is no evidence for routine plasma monitoring to guide the use of these antibiotics (no recommendations, insufficient quality of evidence, strong agreement).

Arguments

To use beta-lactams properly, their mode of administration must be adapted to increase exposure to the antibiotic (percentage of time spent above the target concentration, calculated according to the MIC). Prolonged infusion and continuous infusion following a bolus are two modes that increase this exposure and have been shown to be superior, in pharmacokinetic and pharmacodynamic terms, to nonprolonged intermittent infusion [90–93]. No randomized clinical trial has shown the superiority of continuous infusion over prolonged infusion. In contrast, under some circumstances (high body mass index, hard-to-reach tissues, high volume of distribution, and increased renal clearance), plasma levels could, with continuous infusion, be permanently stabilized at an insufficient concentration [93]. Intermittent administration by prolonged infusion theoretically reduces this risk since each new injection generates a peak plasma concentration, thus avoiding the risk of permanent underdosing.

The use of a prolonged infusion optimizes the time during which the plasma concentrations of NBs/BIs are above the MIC [94–98]. The duration of prolonged infusion should be adapted to the stability of the molecule. All NBs/BIs except imipenem–cilastatin–relebactam are stable at 25 °C for more than 4 h, and 4-h infusions are recommended [99, 100]. For imipenem–cilastatin–relebactam, 3-h infusions ensure its stability at 25 °C [100].

As with other beta-lactams, certain clinical situations carry a risk of NB/BI underdosing: high body mass index, hard-to-reach infection site (especially the lungs, central nervous system, bones and joints), and high renal clearance (creatinine clearance > 130 ml/min/1.73 m^2) [101, 102]. The marketing authorizations for certain antibiotics already provide an increased dosage for pulmonary infections. In other situations where there is a risk of NB/BI underdosing, increasing the daily dose of some of these antibiotics increases the time of exposure of the pathogen to an effective dose of the drug [103].

The assay of these different antibiotics is not available in all hospitals; for drugs combining a beta-lactam and a beta-lactamase inhibitor, the assay of the latter is not systematically available. The time required to obtain results may be long and not well suited to real-time drug administration. In addition, an NB/BI has a high therapeutic index. For these reasons, the panel did not select routine plasma monitoring to tailor NB/BI dosing.

If it is possible to obtain the results in time to adapt doses, it could be interesting, in situations where there is a particular risk of underdosing, to confront the residual plasma concentration of the molecule of interest with the MIC for the pathogen.

Question 6

How should doses be adjusted in renal or hepatocellular failure or obesity?

Recommendation 6A In acute kidney injury, dosing should probably not be adjusted within the first 24 h of treatment (grade 2-, moderate quality of evidence, strong agreement).

Recommendation 6B After the first 24 h of treatment, the dosage of these antibiotics should be adjusted according to the creatinine clearance or renal replacement therapy modalities if appropriate (grade 1+, high quality of evidence, strong agreement).

Arguments

Beta-lactams have a high therapeutic index, which means that the risk of antibiotic toxicity is limited compared to the risk of underdosing during the first days of a serious infection. Furthermore, in septic shock patients with acute kidney injury, the renal function usually improves, as shown in the trial by Gaudry et al., in which nearly 50% of patients had improved kidney function by the 72nd hour [104]. Thus, early dose adjustment of these antibiotics puts the patient at risk of underdosing in the first 24–48 h, justifying this delay before lowering the dose [105–107]. In one trial, the risk of emerging resistance

to ceftazidime–avibactam was higher in cases with renal replacement therapy, possibly due to underdosing [108].

After 24-48 h, if the severity of kidney injury is confirmed, dose adjustment is warranted to avoid overdosing. This adjustment should be based on an estimate of the glomerular filtration rate by measuring the creatinine clearance and on the type of renal replacement therapy. Dose-adjustment depends on the molecule. In the case of intermittent hemodialysis, the dose of antibiotic must be injected again after each session to compensate for the elimination of the antibiotic during the session. In the case of continuous renal replacement therapy, dose-adjustment schedules are often imperfect because antibiotic elimination is correlated with the effluent flow rate, which varies frequently. Plasma monitoring seems relevant in this situation.

Recommendation 6C The panel suggests that doses of these antibiotics should not be decreased in patients with liver failure (panel opinion, strong agreement).

Arguments

These antibiotics are all exclusively eliminated via the kidneys, without hepatic metabolism. Thus, impairment of liver function does not affect the elimination of these antibiotics. Therefore, there is no need to change the dosage of these antibiotics in case of impaired liver function. To our knowledge, no clinical trials have evaluated these antibiotics in patients with hepatocellular impairment.

Recommendation 6D The panel suggests that the dose of these antibiotics not be increased in obesity (panel opinion, strong agreement).

Arguments

There are few published data on the administration of these antibiotics to obese patients. However, as with other beta-lactams, the hydrophilic nature of these antibiotics means that the change in volume of distribution is small in this population [109–111]. A trial using simulation (Monte Carlo model) for obese patients (body mass index between 35 and 65 kg/m^2) treated with ceftolozane–tazobactam for complicated intra-abdominal or urinary tract infection achieved the target plasma concentration without requiring a change in the recommended dose schedule [112].

Additional data are needed to refine the dosing schedule for this specific population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13613-023-01155-4.

Additional file 1. members of the bibliography group; PICO questions (Patient, Intervention, Comparator, Outcome).

Acknowledgements

The authors thank the members of the bibliography group for their commitment and work: Pierrick Bauduin (médecine intensive réanimation, CHU, Caen, France), Sylvain Le Pape (médecine intensive réanimation, CHU, Poitiers, France), Lionet Tchatat-Wangueu, Hélène Messet-Charrière, Misylias Bouaoud (médecine intensive réanimation, CHU, Tours, France) and Dima Siblani (médecine intensive réanimation, CH, Mulhouse, France).

Author contributions

JYM, MS, AWT, and KK prepared the consensus conference and defined the questions. PFD, CA, HF, DG, MG, OH, VL, JM, DO, and CV constituted the jury, chaired by PFD. The answers to the questions were drafted jointly. Each person wrote the argument for the question(s) he or she was responsible for and had it validated by the group. PFD harmonized the writing of the different parts. All authors reviewed, corrected and approved the final text.

Funding

The organization of this consensus conference was funded by the French Intensive Care Society.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

PFD reports receiving research support through the loan of medical equipment from Fisher & Paykel Healthcare and Aerogen and personal funding from Aridis Pharmaceuticals as a consultant.

Author details

[1]Inserm UMR 1100, Centre d'Etudes des Pathologies Respiratoires, Université, Tours, France. [2]Médecine Intensive Réanimation, Hôpital Bretonneau, 37044 Tours cedex 9 Tours, CHU, France. [3]Médecine Intensive Réanimation CHU de Brest, Université de Bretagne Occidentale, Brest, France. [4]Médecine Intensive Réanimation, Centre Hospitalier Intercommunal Robert Ballanger, Aulnay Sous-Bois, France. [5]Médecine Intensive Réanimation CHU, Hôpital de Hautepierre, Strasbourg, France. [6]Médecine Intensive Réanimation CHU de Reims, Reims, France. [7]Medical ICU, Saint Louis Hospital, APHP, 1 Avenue Claude Vellefaux, Paris, France. [8]Medical Intensive Care Unit, Amiens University Hospital, Amiens, France. [9]Medical Intensive Care Unit, GHRMSA, Mulhouse, France. [10]Service de Médecine Intensive-Réanimation, AP-HP, Hôpital de Bicêtre, DMU CORREVE, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [11]Maladies Infectieuses Et Tropicales, Hospices Civils de Lyon, Lyon, France. [12]Médecine Intensive Réanimation, Centre Hospitalier Universitaire de Poitiers, Université de Poitiers, Poitiers, France. [13]Service de Médecine Intensive Réanimation Centre Hospitalier de Bethune, Bethune, France.

Received: 18 April 2023 Accepted: 11 June 2023
Published online: 04 July 2023

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