Intensive Care Med (2015) 41:1181–1196
DOI 10.1007/s00134-015-3853-7

Strategies to reduce curative antibiotic therapy in intensive care units (adult and paediatric)

Cédric Bretonnière
Marc Leone
Christophe Milési
Bernard Allaouchiche
Laurence Armand-Lefevre
Olivier Baldesi
Lila Bouadma
Dominique Decré
Samy Figueiredo
Rémy Gauzit
Benoît Guery
Nicolas Joram
Boris Jung
Sigismond Lasocki
Alain Lepape
Fabrice Lesage
Olivier Pajot
François Philippart
Bertrand Souweine
Pierre Tattevin
Jean-François Timsit
Renaud Vialet
Jean Ralph Zahar
Benoît Misset
Jean-Pierre Bedos

Received: 28 November 2014
Accepted: 28 April 2015
Published online: 3 June 2015

On the behalf of the French Intensive Care Society (Société de Réanimation de Langue Française, SRLF) and the French Society of Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation, SFAR).

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3853-7) contains supplementary material, which is available to authorized users.

C. Bretonnière
Réanimation Médicale Polyvalente, Pôle Hospitalo-Universitaire 3, CHU-Immeuble Jean Monnet, 44093 Nantes, France

M. Leone
Service d'anesthésie et de Réanimation, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, Aix Marseille Université, Marseille, France
e-mail: marc.leone@ap-hm.fr

C. Bretonnière
EA3826, Thérapeutiques Cliniques et Expérimentales des Infections, Université de Nantes, 44035 Nantes, France

C. Milési
Service de Réanimation Pédiatrique, Hôpital Arnaud de Villeneuve, 371 av doyen Giraud, 34296 Montpellier, France
e-mail: c-milesi@chu-montpellier.fr

B. Allaouchiche
Department of Intensive Care, Hôtel-Dieu Hospital, Lyon, France
e-mail: allaouch@univ-lyon1.fr

L. Armand-Lefevre
Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Bichat-Claude Bernard, Service de Bactériologie, 46 rue Henri Huchard, 75877 Paris Cedex 18, France
e-mail: laurence.armand-lefevre@bch.aphp.fr

O. Baldesi
Centre Hospitalier Intercommunal Aix-Pertuis, Aix En Provence, France
e-mail: obaldesi@ch-aix.fr

L. Bouadma · J.-F. Timsit
AP-HP, Hôpital Bichat, Réanimation Médicale et des Maladies Infectieuses, 75018 Paris, France

L. Bouadma
e-mail: lila.bouadma@bch.aphp.fr

J.-F. Timsit
e-mail: jean-francois.timsit@bch.aphp.fr

D. Decré
AP-HP, Microbiology, St-Antoine Hospital, Paris, France
e-mail: dominique.decre@upmc.fr

S. Figueiredo
Département Anesthésie-Réanimation, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, K.-Bicêtre, France
e-mail: samy.figueiredo@bct.aphp.fr

S. Figueiredo
Faculté de Médecine et, INSERM U914 Emerging Resistance to Antibiotics, Université Paris-Sud, Orsay, France

R. Gauzit
Infectious Disease and Intensive Care Unit, Cochin University Hospital, 75014 Paris, France
e-mail: remy.gauzit@htd.aphp.fr

B. Guery
Service de Gestion du Risque Infectieux, Vigilances et Infectiologie, Hôpital Huriez, 59045 Lille, France
e-mail: bguery@gmail.com

N. Joram
Réanimation Pédiatrique, Pôle Hospitalo-Universitaire 5, CHU Nantes-HME, 44093 Nantes, France
e-mail: nicolas.joram@chu-nantes.fr

B. Jung
Department of Critical Care Medicine and Anesthesiology, Saint Eloi Teaching Hospital, Montpellier, France
e-mail: borisjung@dbmail.com

B. Jung
Centre National de la Recherche Scientifique (CNRS 9214), Institut National de la Santé et de la Recherche Médicale (INSERM U-1046), Montpellier, France

S. Lasocki
University Montpellier, Montpellier, France
e-mail: silasocki@chu-angers.fr

A. Lepape
Intensive Care Unit, University Hospital Lyon-Sud, Pierre-Bénite, France
e-mail: alain.lepape@chu-lyon.fr

F. Lesage
Hôpital Necker-Enfants Malades Réanimation Pédiatrique, APHP, Hôpital Necker, 75015 Paris, France
e-mail: fabrice.lesage@nck.aphp.fr

O. Pajot
Intensive Care Unit, Victor Dupouy Hospital, 95100, Argenteuil, France
e-mail: olivier.pajot@ch-argenteuil.fr

F. Philippart
Medical Surgical ICU, Groupe Hospitalier Paris Saint Joseph, Paris, France
e-mail: fphilippart@gmail.com

B. Souweine
Medical Intensive Care Unit, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France
e-mail: bsouweine@chu-clermontferrand.fr

P. Tattevin
Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 35033 Rennes, France
e-mail: pierre.tattevin@chu-rennes.fr

J.-F. Timsit
UMR 1137, IAME Team 5, Decision Sciences in Infectious Diseases, Control and Care Inserm/Univ Paris Diderot, Sorbonne Paris Cité, 75018 Paris, France

R. Vialet
Department of Anesthesia and Intensive Care, Marseilles University Hospital System, 13915 Marseilles, France
e-mail: renaud.vialet@mail.ap-hm.fr

J. R. Zahar
Unité de Prévention et de Lutte Contre les Infections Nosocomiales, Université d'Angers, CHU Angers, 49000 Angers, France
e-mail: jrzahar@gmail.com

B. Misset
Service de Médecine Intensive et Réanimation, Centre de Recherche Clinique, Groupe Hospitalier Paris Saint Joseph, Paris, France
e-mail: bmisset@hpsj.fr

B. Misset
Université Paris Descartes, Paris, France

S. Lasocki
Département d'Anesthésie-Réanimation, CHU Angers, Angers, France

J.-P. Bedos
Réanimation, Hôpital André Mignot, Centre Hospitalier de Versailles, 78157 Le Chesnay, France
e-mail: JPBEDOS@ch-versailles.fr

Abstract Emerging resistance to antibiotics shows no signs of decline. At the same time, few new antibacterials are being discovered. There is a worldwide recognition regarding the danger of this situation. The urgency of the situation and the conviction that practices should change led the Société de Réanimation de Langue Française (SRLF) and the Société Française d'Anesthésie et de Réanimation (SFAR) to set up a panel of experts from various disciplines. These experts met for the first time at the end of 2012 and have since met regularly to issue the following 67 recommendations, according to the rigorous GRADE methodology. Five fields were explored: i) the link between the resistance of bacteria and the use of antibiotics in intensive care; ii) which microbiological data and how to use them to reduce antibiotic consumption; iii) how should antibiotic therapy be chosen to limit consumption of antibiotics; iv) how can antibiotic administration be optimized; v) review and duration of antibiotic treatments. In each institution, the appropriation of these recommendations should arouse multidisciplinary discussions resulting in better knowledge of local epidemiology, rate of antibiotic use, and finally protocols for improving the stewardship of antibiotics. These efforts should contribute to limit the emergence of resistant bacteria.

Keywords Antimicrobial stewardship · Epidemiology · Microbiological diagnostic techniques · Pharmacokinetics/pharmacodynamics · Therapeutic drug monitoring

Introduction

Emerging resistance to antibiotics shows no signs of decline [1]. At the same time, few new antibacterials are being discovered [2–4]. There is worldwide recognition of the danger of this situation [5–7].

Hospitalized patients are the first victims of the increasing resistance of bacteria. Those admitted to

intensive care units are particularly affected [8–10], often by species resistant to virtually all antibiotics [11–14].

The urgency of the situation and the conviction that practices should change (using new clinical data and technical advances) led the Société de Réanimation de Langue Française (SRLF) and the Société Française d'Anesthésie et de Réanimation (SFAR) to set up a panel of experts from various fields. This expert panel met for the first time at the end of 2012 and has since met regularly to issue the following recommendations, according to the rigorous methodology described below.

These recommendations are aimed at intensivists managing adult and paediatric patients. In the case of the latter, the literature is often poor. The section headings of the recommendations should therefore be taken as formulated for the care of adults. If they are valid also for children, this is specified.

Methodology

These recommendations were drawn up by an expert panel brought together by the SRLF and the SFAR. The various disciplines involved in the prescription of antibiotics in intensive care units (critical care, microbiology, infectious diseases, hospital hygiene, paediatrics) were represented.

Selection and organization of the expert panel

The selection of committee members was based on interest and expertise in specific aspects such as microbiology, infectious diseases, infection control, epidemiology etc. Executive committee members (CB, CM, ML and BM) were first chosen by the SRLF and the SFAR as was the expert panel coordinator (JPB). Then, the executive committee with the expert panel coordinator defined the questions or fields to be covered (Table 1). They designated the experts in charge of each question. The latter had to disclose any financial or non-financial/academic competing interest before participating in that group.

Table 1 Five fields explored by the 54 recommendations

1	There is a link between the resistance of bacteria and the use of antibiotics in intensive care
2	Which microbiological data and how to use them to reduce antibiotic consumption?
3	How should antibiotic therapy be chosen to limit consumption of antibiotics?
4	How can antibiotic administration be optimized?
5	Review and duration of antibiotic treatments

Grading of recommendations

The grading of recommendations assessment, development and evaluation (GRADE) system was used to convey the recommendations [15, 16].

A separate literature search was performed for each field. Experts worked with executive committee members to identify pertinent search terms that were included. The authors were asked to search a minimum of one general database (i.e. MEDLINE, EMBASE) and the Cochrane library. For each question, available evidence was summarized in the form of evidence tables. During all the recommendations process, these tables were shared online on a specific, dedicated server.

The authors were asked to follow the principles of the GRADE system to guide assessment of quality of evidence and to determine the strength of recommendations [15]. The GRADE system is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between benefits and risks. Burden and cost are then considered, leading to development and grading of each recommendation. Keeping the rating of quality of evidence and strength of recommendation explicitly separate constitutes a crucial feature of the GRADE approach.

This system classifies quality of evidence as high (grade A), moderate (grade B), low (grade C) or very low (grade D). Randomized trials begin as high-quality evidence but may be downgraded owing to factors such as study limitations, inconsistent results, and indirectness of evidence, imprecision or possible reporting bias (Table 2). Although well-done observational studies generally yield low quality of evidence, three factors may contribute to produce moderate or even high quality of evidence: large magnitude effect, plausible confounding, which would reduce a demonstrated effect, or dose–response gradient effect (Table 2).

The GRADE system classifies recommendations as strong (grade 1) or weak (grade 2). The factors influencing this determination are presented in Table 2. The assignment of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. The committee assessed whether the desirable effects of adherence would outweigh the undesirable effects. The strength of a recommendation reflects the group's degree of confidence in that assessment.[1]

[1]Thus, a strong recommendation in favour of an intervention reflects the panel's opinion that the desirable effects of adherence to a recommendation (beneficial health outcomes, lesser burden on staff and patients, and cost savings) will clearly outweigh the undesirable effects (harm to health, more burden on staff and patients, and greater costs). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were taken into account. A weak recommendation in favour of an intervention indicates the judgment that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these trade-offs either because some of the evidence is low quality (and thus uncertainty remains

Table 2 GRADE system (adapted from [16, 17])

Criteria for assigning grade of evidence[a]
Type of evidence
Randomised trial = high
Observational study = low
Any other evidence = very low
Decrease grade if
Serious or very serious limitation to study quality
Important inconsistency
Some or major uncertainty about directness
Imprecise or sparse data
High probability of reporting bias
Increase grade if
Strong evidence of association: significant relative risk of >2 (<0.5) based on consistent evidence from ≥2 observational studies, with no plausible confounders
Very strong evidence of association: significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity
Evidence of a dose response gradient
All plausible confounders would have reduced the effect
Factors that affect the strength of a recommendation[b]
Quality of evidence
Uncertainty about the balance between desirable and undesirable effects
Uncertainty or variability in values and preferences
Uncertainty about whether the intervention represents a wise use of resources

[a] Quality of evidence is classified as high (grade A), moderate (grade B), low (grade C), very low (grade D) or ungraded (UG)

[b] Recommendations are classified as strong (grade 1) or weak (grade 2)

A strong recommendation is worded as 'we recommend' or 'must be done, must not be done' and a weak recommendation as 'we suggest' or 'should probably be done, should probably not be done'. Throughout the document are a number of statements that either follow graded recommendations or are listed as stand-alone numbered statements followed by 'ungraded' in parentheses (UG). For our group, these recommendations were not conducive for the GRADE process. Committee members were familiar with the GRADE system. Rules were discussed concerning assessing the body of evidence and committee members were available for advice throughout the process.

Subgroups agreed electronically on draft proposals that were then discussed with all the experts. The results of the discussion were incorporated into the next version of recommendations and again discussed with the whole group. Draft recommendations were then mailed to the group for vote.

The aim was not necessarily to reach a single and convergent opinion for all proposals, but rather to highlight points of agreement and points of disagreement or indecision. Each recommendation was then scored by each expert on a scale ranging from 1 (incomplete agreement) to 9 (complete agreement). The collective scoring was established using a methodology derived from the RAND/UCLA appropriateness method [18]: after elimination of the extreme values (outliers), the median and confidence interval of the scores were calculated. The median defined agreement between the experts when it was between 7 and 9, disagreement between 1 and 3 and indecision between 4 and 6. The agreement, disagreement or indecision were 'strong' if the confidence intervals were within one of three ranges, namely 1–3, 4–6 or 7–9, and 'weak' if they were out of these ranges. In the absence of strong agreement, the recommendations were reformulated and again scored with a view to achieving a better consensus.

Two rounds of scoring were therefore performed and the 67 recommendations presented below.

Conflict of interest policy

Committee members' and experts' potential conflicts of interest have been examined at the beginning and at the end of the process. There was no industry input into recommendations development. Industry awareness or comments on these recommendations were not allowed. No member of the group received honoraria for any role during the process. Logistic support was provided by the SRLF and the SFAR.

Results

The different recommendations are presented below. For each field, the recommendations are listed with quality of evidence and strength in a dedicated table. The rationale is then summarized for each field but detailed argumentation and/or additional references can also be found as electronic supplementary material (ESM).

Q1: There is a link between the resistance of bacteria and the use of antibiotics in intensive care

Recommendations are presented in Table 3. There was a strong agreement in the group for the first two statements. Nevertheless, it was decided that the literature data did not allow grading of these items, so they appear as 'ungraded' (UG) in the table.

Rationale

Antibiotic selection pressure is an important determinant of the emergence and spread of resistance to antibiotics.

Footnote 1 continued
regarding the benefits and risks) or the benefits and downsides are closely balanced. A weak recommendation might also reflect uncertainty about whether the intervention represents a wise use of resources.

Table 3 Recommendations for field 1: link between resistance of bacteria and the use of antibiotics in intensive care

Recommendation	
Data on local and nationwide bacterial epidemiology must be used	UG
Scientific societies must communicate (through journals and/or websites) existing data on the epidemiology of bacterial infections acquired in intensive care units, gathered by surveillance networks	UG
We recommend using local epidemiological data (intensive care units, healthcare facilities) that specify the rate of bacterial species isolated by type of infection and the rate of resistance by species	1C
The antibiotic consumption calculated as defined daily dose (DDD) should be monitored for all intensive care units, globally and for specific antimicrobial drug classes (notably carbapenems and fluoroquinolones)	2D

Table 4 Recommendations for field 5: microbiological data: how to use them to reduce antibiotic consumption

Recommendation	
For rapid de-escalation and rational antibiotic use, we recommend collecting bacteriological samples, if possible before any antibiotic therapy	1C
In the patients with ventilator-associated pneumonia (VAP), before the antibiotic treatment onset, we recommend collecting respiratory samples for quantitative culture, in order to reduce exposure to antibiotics	1C
We recommend that the results of respiratory specimen Gram stain are communicated to the clinician without delay	1C
In the absence of signs of severe VAP, if direct examination is negative, we suggest not initiating empirical antibiotic treatment	2C
In the presence of signs of severe VAP, we suggest starting antibiotic treatment based on result of direct examination (or empirically if direct examination is negative)	2C
A first culture result should be available in the 24 h following sampling	UG
If the blood culture is positive, we recommend doing bacterial identification and antibiotic susceptibility testing directly using the blood culture bottle	1B
If the culture is positive, we suggest tailoring antibiotic treatment early after rapid bacterial identification by mass spectrometry	2C
In positive blood cultures with clustered Gram-positive cocci on direct examination, we recommend using rapid tests to detect the presence of *S. aureus* and to determine methicillin (oxacillin) susceptibility	1B
We recommend determining the minimum inhibitory concentrations, as recommended by the European Committee on antimicrobial susceptibility testing, and communicating them to clinicians	1B
After discussion between microbiologist and clinician, we suggest determining the minimum inhibitory concentration for specific infected sites and bacterial species	1C
In the patients with community-acquired pneumonia, if urinary pneumococcal antigen is positive in adults, we suggest stopping antibiotics, considering intracellular bacteria. If there is no urinary pneumococcal antigen, diagnosis of pneumococcal pneumonia should not be discarded	2B
If there is urinary *Legionella* antigen, we suggest stopping the prescribed β-lactam. When there is no urinary *Legionella* antigen, the diagnosis of Legionella pneumonia should not be discarded	2B

Moreover, it is one of the few factors (with hand hygiene) that can be influenced or modified through practice. In intensive care, studies are above all of uncontrolled before-and-after design, the main focus of which is not always bacterial resistance [19–21]. A systematic review by Kaki et al. [22] confirms this trend. The conclusion can be drawn that bacteriological ecology in intensive care is (partially) dependent on the antibiotic policy of a given unit.

It is worth stressing the importance of using local epidemiological data on antibiotic resistance because there are major disparities between European countries and those of other continents, notably North America. The susceptibility rate for given species has to be determined locally. But the actual frequency of patients infected by these given bacteria is almost as important.

The DDD should be considered separately from individual description of treatments. DDDs recommended by the World Health Organisation (WHO) often differ substantially from the doses actually used in intensive care, particularly in the case of β-lactam antibiotics. They artificially increase the consumption of antibiotics attributed to intensive care. Like all aggregate data, they have to be reduced to a common denominator, usually the number of days of hospitalization, a value easy to record in intensive care. Despite these imperfections, the DDD is the most useful parameter because it can be easily and quickly recorded and because, to some extent, it enables comparisons between intensive care units [23].

Q2: Which microbiological data and how to use them to reduce antibiotic consumption?

Recommendations are presented in Table 4. For this field, to grade the strength of recommendations, the group has paid particular attention to the resource use.

Rationale

Sampling for diagnostic purposes must be done early, if possible before the onset of antibiotics administration. The quality of microbiological examinations depends on the information given to the laboratory, the choice and methods of sampling and the sample transport and storage conditions. Deep or invasive sampling is the most appropriate [24] and should enable de-escalation, which is facilitated if documentation is available [25, 26].

For patients with ventilator-associated pneumonia (VAP), three studies compared the invasive strategy with

quantitative cultures (bronchoalveolar lavage or protected specimen brush sampling) and the non-invasive strategy with qualitative or semi-quantitative cultures of tracheal aspirates. One study showed that invasive sampling reduced mortality and increased the number of days without antibiotic [27]. The second study showed that this practice reduced the duration of empirical antibiotic therapy, without increasing time on ventilation or morbidity and mortality [28]. The largest study did not confirm these results, but it did not use invasive sampling to guide antibiotic therapy [29]. The sensitivity of direct testing is closely associated with the quantity of bacteria present: between 10^3 and 10^5 bacteria/mL, 60 % of direct tests give positive findings. A meta-analysis indicated a negative predictive value of 91 % and a positive predictive value of 40 % for an approximately 30 % prevalence of VAP [30].

Depending on the study, automated systems for liquid samples provide bacterial identification and antibiotic susceptibility results in 3–6 and 7–13 h, respectively. However, this means that the results become available outside laboratory hours. Real-time transmission of the results to clinicians demands reorganization of human resources [31]. Mass spectrometry provides identification in a few minutes, with 84–94 % agreement with conventional techniques.

Bacterial identification and antibiotic susceptibility testing using liquid directly from positive blood culture bottles can reduce by 20 % the consumption of antibiotics [32]. Bacterial identification is possible directly by mass spectrometry (average time 30 min) with good agreement (80–98 %) as compared with conventional methods, particularly for Gram-negative bacilli [33]. The time gained (1.2–1.5 days) enables earlier adaptation of antibiotic therapy in 35 % of patients with bacteraemia (vs. 21 % if adaptation is only done on reading of the Gram staining results), plus a 5.5–11.3 % increase, depending on the study, in the proportion of patients correctly treated [33]. Earlier bacterial identification and antibiotic susceptibility results in the case of bacteraemia reduce hospital stay and costs [34].

Mass spectrometry can be used for bacterial identification in a few minutes, with 84–94 % agreement with conventional techniques. Bacterial identification enables adaptation of the antibiotic therapy even if the antibiotic susceptibility results are not yet known.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) specifies the antibiotic–bacteria pairs for which the minimum inhibitory concentration (MIC) should be reported. The MIC should probably also be determined for particular infected sites (endocarditis, bone infections etc.) and for potentially resistant bacterial species (e.g. *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter*, *Staphylococci* and glycopeptide antibiotics).

It is difficult to establish the impact of the use of urinary antigen tests [35–37]. In an interventional study, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* reduced the prescription of broad-spectrum antibiotics, but at the price of a greater risk of clinical relapse [36].

Q3: How should antibiotic therapy be chosen to limit consumption of antibiotics?

a)	What impact does colonization status have on the choice of initial antibiotictreatment?

Recommendations are presented in Table 5. The required constrained format has only a limited number of references. However, a more detailed argumentation with more numerous references can be found as ESM.

Rationale

To date, there is no randomized controlled study on reducing quantity or quality of antibiotic therapy using colonization data. Few teams perform surveillance cultures [38, 39], but caution is needed because the prescription of empirical antibiotic therapy guided by tests on endotracheal aspirates (colonization) is not necessarily better than the application of guidelines [40]. Also, such practices could lead to the prescription of excessive antibiotic therapy based on a result reflecting colonization status.

Table 5 Recommendations for field 3a: how to use colonization status?

Recommendation	
Routine antibiotic treatment must not be prescribed if a bacterium, whatever its type, is identified when determining colonization status, particularly in the case of endotracheal aspiration	UG
In the presence of signs of severe infection, we suggest considering colonization status when there are multidrug-resistant bacteria, whatever the sampling sites, in the choice of empirical antibiotic treatment for ventilator-associated pneumonia or nosocomial bacteraemia	2C

When involvement of multidrug-resistant bacteria in VAP is suspected, studies confirmed the value of taking into account the colonization status of different sites. Tracheal aspirates are more reliable than samples collected at other sites. One study suggests that colonization status was useful for predicting appropriate antibiotic therapy for bacteraemia caused by antibiotic-resistant Gram-negative bacteria.

b) When and how should use of carbapenems be reduced?

Recommendations are presented in Table 6.

Rationale

The use of carbapenems in intensive care is associated with the emergence of bacterial resistance [41, 42]. To preserve their efficacy, these molecules should be spared as much as possible [43].

Given the new EUCAST recommendations on MIC breakpoints (third-generation cephalosporin and aztreonam), based on pharmacokinetic-pharmacodynamic data, there are possible alternatives to carbapenems [44], including β-lactam/β-lactamase inhibitor combinations [45]. In all cases, these adaptations are made taking into account the site and the microbiological data (MIC).

c) When and how should use of quinolones be reduced?

Recommendations are presented in Table 7.

Rationale

Fluoroquinolones are widely used because of their undeniable clinical value, good oral bioavailability and favourable diffusion in tissues.

But their use is accompanied by numerous deleterious effects. The ecological consequences [46, 47] include the emergence of resistance to fluoroquinolones [21] by mutation of DNA gyrase or of topoisomerase, overexpression of efflux pumps or lack of permeability. Some of these mechanisms affect both Gram-negative bacilli and Gram-positive cocci. They also affect the resistance of other classes of antibiotics. The emergence of MRSA associated with fluoroquinolones use should therefore be noted [48]. There is also an impact on intestinal flora, with the emergence of highly virulent *Clostridium difficile* [49] or the emergence and spread of extended-spectrum β-lactamase-producing *Enterobacteriaceae* [50, 51].

Moreover, the toxicity and side effects of these antibiotics may be significant (tendinopathy, phototoxicity, hepatitis, QT prolongation), which led the European Medicines Agency (EMA) to issue warnings and restrictions for use.

Table 6 Recommendations for field 3b: how to use carbapenems

Recommendation	
We recommend not using carbapenem as empirical antimicrobial treatment when community-acquired bacterial infection is suspected	1B
Carbapenem should, however, be considered in patients with a combination of: A known history of colonization/infection by extended-spectrum β-lactamase-producing *Enterobacteriaceae* or by ceftazidime-resistant *P. aeruginosa*, determined within the last 3 months, whatever the sampling site, and Severe sepsis or septic shock	2D
In terms of empirical antimicrobial treatment, if a hospital-acquired severe bacterial infection is suspected, we recommend not prescribing carbapenem solely on the basis of the nosocomial nature of the infection, but rather considering the presence of at least two of the following criteria: Previous treatment with a third-generation cephalosporin, fluoroquinolones (including a single dose) or a piperacillin–tazobactam combination in the last 3 months, Carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* or of ceftazidime-resistant *P. aeruginosa*, determined within the last 3 months, whatever the sampling site, Hospitalization during the last 12 months, Patient living in a nursing facility or in a long-term care facility for elderly and carrying an indwelling catheter and/or a gastrostomy tube, Ongoing epidemic episode of multidrug-resistant bacteria in the healthcare institution for which the only treatment option is carbapenem	1C
After documenting the bacterial infection, an alternative to carbapenems should be found, according to the infected site and after microbiologist and clinician interactions	UG

Table 7 Recommendations for field 3c: how to use fluoroquinolones

Recommendation	
In septic shock, in combination with β-lactam antibiotic, we recommend preferring aminoglycosides to fluoroquinolones	UG
We recommend not prescribing fluoroquinolones when other antibiotics could be used	UG
Fluoroquinolones can, however, be used in the following indications: Proven severe Legionnaires' disease, Infections of bone and of the diabetic foot after antibiotic susceptibility testing, Prostatitis after antibiotic susceptibility testing	2C
We recommend not prescribing fluoroquinolones repeatedly in the same patient (take into account prescriptions of fluoroquinolones within the last 6 months, whatever the indication)	1B
We recommend not prescribing fluoroquinolones as empirical monotherapy in severe nosocomial infections	1B
We recommend not prescribing fluoroquinolones for strains of *Enterobacteriaceae* that have acquired resistance to nalidixic acid and/or pipemidic acid	1B

d) When and how should use of antibiotics for methicillin (oxacillin)-resistant *Staphylococcus aureus* and coagulase-negative staphylococci be reduced?

Recommendations are presented in Table 8. As in previous sections, the reader can refer to the ESM for a wider list of included studies.

Rationale

Although some studies in the USA reported that up to 12 % of MRSA infections are community-acquired, this resistance is much less frequent in Europe.

It is important to consider possible MRSA for treating severe infections in patients with MRSA discharged from hospital within the last year. Carriage of multidrug-resistant bacteria is increased in hospital-acquired infections. Antibiotic therapy within the last 6 months approximately doubles the risk of multidrug-resistant bacteria [52]. This risk is 12 % for MRSA in chronic haemodialysis patients [53] and 8.6–22 % in long-stay hospital patients [54, 55]. Half of patients are still MRSA carriers at 1 year. The estimated median time to MRSA clearance after hospital discharge is 8.5 months, and may be longer if the patients are still receiving care and antibiotic therapy [56].

The proportion of MRSA among *S. aureus* is in constant decline and reached 25.5 % in 2012 in the French REA-RAISIN database, but the epidemiology varies greatly from one centre to another.

For CoNS, most international recommendations specify that only episodes with more than one positive blood culture should be taken into account. In a retrospective review, CoNS was found to be responsible for only four of 369 episodes of VAP in 1955 patients ventilated for more than 48 h [57]. Review of the diagnosis of VAP associated with CoNS and the search for an alternative diagnosis should therefore be routine.

Fowler et al. [58] in a subgroup analysis showed that a daptomycin dosage of 6 mg/kg/day was not inferior to standard therapy in the treatment of bacteraemia and right-sided endocarditis. In a single-centre nonrandomized study comparing daptomycin with vancomycin (median residual concentration 17.6 mg/L) in the treatment of MRSA bacteraemia with a vancomycin MIC >1 mg/L, there were fewer failures (20 vs. 48 %) and fewer deaths at 30 days (3.5 vs. 12.9 %) with daptomycin [59]. Despite the inherent limitations due to the nature of this study, these findings suggest that daptomycin should be used in this indication. High-dose daptomycin can be used to limit the emergence of resistant mutants even if the modalities of administration are not yet formally established.

A randomized study of 448 cases of nosocomial pneumonia [60] showed that the activity of linezolid was equivalent to that of vancomycin administered discontinuously. The clinical response in per protocol analysis was even better with linezolid (57.6 vs. 46.6 %; $p = 0.042$). However, the vancomycin plasma concentrations obtained were below those recommended. In addition, caution is required in drawing conclusions because of imbalances between the two groups.

The probability of survival in MRSA bacteraemia is greater if the vancomycin concentration over time divided by the vancomycin MIC for the bacterium is high (AUC_{24h}/MIC ratio > 400). This target is very difficult to attain for vancomycin MICs above 1 mg/L [61]. However, the causal relation between high AUC/MIC and survival is not demonstrated.

Table 8 Recommendations for field 3d: how to use antibiotics for MRSA or MRCoNS

Recommendation	
Empirical treatment	
We recommend not using antibiotics for MRSA (or MRCoNS) in the empirical antimicrobial treatment of community-acquired infections	1B
We recommend considering the possibility of MRSA in severe healthcare-associated infections for patients on chronic haemodialysis, with chronic wounds, with an indwelling catheter, or those who reside in long-term care facilities	1A
We recommend using local epidemiology of the institution to choose to use (or to avoid) antibiotic treatment for MRSA (or MRCoNS) for the empirical antimicrobial treatment of nosocomial infections in the intensive care unit	1C
Documented treatment	
We recommend not initiating treatment only because of positive blood culture with CoNS (whether or not methicillin-resistant)	1B
In adults and children (except for the neonatal period), we recommend changing central and arterial lines if several blood cultures are positive for MRCoNS	1B
In adults and children (except for the neonatal period), if several blood cultures are positive for MRCoNS, we recommend initiating treatment, considering the following disease severity, immunosuppression and antibacterial resistance pattern	1B
Except for patients with immunosuppression, we recommend not considering MRCoNS in ventilator-associated pneumonia and not using antibiotic treatment for MRCoNS	1A
We suggest using high-dose daptomycin to treat endocarditis or bacteraemia due to MRSA with vancomycin minimal inhibitory concentration (MIC) ≥1 mg/L	2B
We recommend using linezolid in patients with ventilator-associated pneumonia due to MRSA	1A
In patients with MRSA infection, we recommend to determine vancomycin MIC	1B
If there is no clinical improvement after 3 days, for an MRSA infection with MIC >1 mg/L, an alternative to vancomycin must be used	1C
Depending on the infected site, an anti-MRSA combination should probably be discussed	UG

MRSA methicillin-resistant *Staphylococcus aureus, MRCoNS* methicillin-resistant coagulase-negative staphylococci

Q4: How can antibiotic administration be optimized?

a) When is there a formal indication for antibiotic treatment?

Recommendations are presented in Table 9.

Rationale

The authors of the Surviving Sepsis Campaign conclude that effective antibiotic therapy must be administered within 1 h of recognition of septic shock [62].

Several studies suggest that no more than 4 h should elapse between the admission and the first dose of antibiotic. However, a meta-analysis comparing early versus delayed antibiotics did not confirm this result [63]. The only prospective study included in this analysis even showed that early antibiotic administration did not shorten time to clinical stability [64]. In another literature analysis of the level of proof supporting a short time to first antibiotic dose in community-acquired pneumonia, the authors emphasized that reduction in the time between admission and the first dose was associated with antibiotic misuse, without mortality data sufficiently solid to counterbalance this risk.

On the basis of various studies, the 2009 French guidelines stipulated 3 h (ideally 1 h) as the time between admission and administration of the first antibiotic dose [65].

Although the medical literature does not provide evidence, it seems that 'good practice' is to recommend optimization of the time to first antibiotic dose in the frail patients, such as those with post-splenectomy fever, neutropenic fever, and bacterial necrotizing dermatitis.

Table 9 Recommendations for field 4a: when is there a formal indication for antibiotics?

Recommendation	
We recommend starting empirical antibiotic therapy within 1 h after recognition of septic shock	1B
In patients with suspected severe community-acquired pneumonia, before any antibiotic therapy, we suggest considering other diagnoses within the first 4 h after admission, thus avoiding unnecessary prescription	2B
In bacterial meningitis, we recommend to administer antibiotics within the 3 h after hospital admission, and ideally within 1 h	1B
The time to first antibiotic dose should probably be minimized in frail patients (asplenic or neutropenic patients) or in life-threatening infections (bacterial necrotizing cellulitis, purpura fulminans, septic shock etc.)	UG

b) When should therapeutic drug monitoring (TDM) of antimicrobials be performed?

Recommendations are presented in Table 10. As in previous sections, additional text and references are available online as ESM.

Rationale

Critically ill patients (severe sepsis/septic shock, fluid challenges and vasopressors, haemorrhagic shock, burns, fever and neutropenia, acute kidney failure, continuous renal replacement therapy, morbid obesity, children) have major pathophysiological changes [66, 67]. These changes result in unpredictable between- and within-individual pharmacokinetic variability, in particular for hydrophilic antibiotics (aminoglycosides, vancomycin, β-lactam antibiotics) [68, 69]. Plasma and infected site antibiotic concentrations may be subtherapeutic, leading to clinical failure and development of bacterial resistance. Conversely, kidney and/or liver failure may result in toxic concentrations [70]. In children, this variability is increased by large age-related differences in volume of distribution, metabolism and elimination.

Pharmacokinetic/pharmacodynamic approaches show the value, in terms of clinical efficacy, toxicity and prevention of resistant mutants, of measuring the peak plasma concentration of aminoglycosides, which are hydrophilic antibiotics with concentration-dependent activity and a narrow therapeutic index [69].

Table 10 Recommendations for field 4b: when is antibacterial dosing needed?

Recommendation	
Given large unpredictable pharmacokinetic variability, we recommend therapeutic drug monitoring (TDM) of antibiotics in intensive care unit adults and paediatric patients	1B
In all intensive care unit patients, we suggest measuring the peak plasma concentration of aminoglycosides 30 min after the first dose (administered in 30-min infusion). If the concentration is below the target the next dose should be increased	2C
We suggest measuring the residual concentration of aminoglycosides in order to avoid toxicity associated with cumulative administrations, especially in patients with renal failure	2C
In adults and children, we recommend determining the steady-state vancomycin concentration in the case of continuous infusion after a loading dose, or the residual concentration in the case of discontinuous administrations	1B
For assessing efficacy and toxicity, we suggest determining residual concentrations of broad-spectrum β-lactam antibiotics, in discontinuous and prolonged administration, or of the steady-state concentration in continuous infusion	2C

The bactericidal activity of vancomycin is AUC_{24h}/MIC-dependent. AUC_{24h} cannot be monitored routinely, but it correlates with residual concentration, which should therefore be measured. In discontinuous administration, the residual concentration must be determined before administration of the fourth dose. The target for residual concentration or steady-state concentration in continuous infusion is around 20 mg/L. It can be higher for the treatment of specific infected sites (central nervous system, cardiac vegetations or bone).

c) Should certain methods be used to optimize antibiotic administration (route of administration [intravenous, local], dosage)?

Recommendations are presented in Table 11.

Rationale

For β-lactam antibiotics, the percentage time above the MIC, which varies according to the antibiotic (50–60 % for penicillins, 60–70 % for cephalosporins) [71] and the bacterium, is the best pharmacodynamic predictor of therapeutic efficacy. There is a clear and compelling rationale suggesting that the bactericidal activity of β-lactam antibiotics increases when the plasma concentrations increase to 4–6 times the MIC. However, few published data correlated achievement of these targets and the microbiological or clinical outcome of the patients [72]. In intensive care unit patients, Mohr et al. [73] suggested that a percentage time above the MIC of 100 % was associated with a C_{min}/MIC ratio above 5 as a pharmacodynamic target for β-lactam antibiotics. Li et al. [74] confirmed this target, showing that this ratio is predictive of clinical success in the treatment of lower respiratory tract infection.

Pharmacokinetic studies and modelling data agree: the administration of β-lactam antibiotics by continuous or prolonged (3 or 4 h) intravenous infusion increases the time spent above the MIC between two administered doses. Several studies suggested that prolonged infusion (3 or 4 h) of β-lactam antibiotics (cefepime, piperacillin–tazobactam, carbapenems) was associated with mortality reduction. Lastly, in a meta-analysis, Falagas et al. [75] showed 10.8 % mortality in patients treated by prolonged infusion of carbapenems or piperacillin–tazobactam, compared with 16.8 % in patients treated by intermittent perfusion ($p = 0.03$).

Several studies on ICU patients showed that continuous infusion of piperacillin–tazobactam, meropenem, ticarcillin–clavulanate, or ceftazidime produced plasma concentrations above the MIC more frequently than intermittent infusion. On the other hand, evaluations, including meta-analyses, of the clinical benefit of continuous intravenous infusion of β-lactam antibiotics did not show the previously mentioned theoretical pharmacokinetic advantage of this mode of administration. Failure to demonstrate the greater efficacy of continuous infusion may stem from methodological considerations, instability of the antibiotics, particularly penems, an inoculum effect or concentrations that are too low at the site of the infection.

Recent in vitro and clinical studies show that an AUC_{24h}/MIC ratio greater than 400 is predictive of the clinical efficacy of vancomycin treatment of pneumonia and MRSA bacteraemia. Clinical studies directly comparing continuous and intermittent intravenous infusion of vancomycin are contradictory [76]. However, continuous infusion does achieve target plasma concentrations more rapidly and limits the number of blood assays as well as the cost of treatment. In a Monte Carlo simulation study, in patients with severe sepsis, a loading dose of 35 mg/kg seems necessary to quickly reach a concentration of approximately 20 mg/L, followed by continuous infusion of 35 mg/kg to maintain this target concentration [77].

In vitro and animal studies showed that the development of bacterial resistance is affected by antibiotic concentrations. Some pharmacodynamic variables (AUC/MIC, peak/MIC, AUC/mutant prevention concentration,

Table 11 Recommendations for field 4c: how to administer antibiotics

Recommendation	
For intensive care patients with severe infections, we suggest maintaining the plasma concentrations of β-lactam antibiotics above MIC for at least 70 % of the time in order to increase success rate	2C
We suggest achieving a higher target (C_{min}/MIC >4–6)	2C
In intensive care unit patients, we recommend administering β-lactam antibiotics (cefepime, piperacillin–tazobactam, meropenem and doripenem) by intravenous infusion for 3 or 4 h to treat severe infections, especially if the identified bacteria have high MICs	1B
We suggest administering by continuous infusion antibiotics such as carbapenems (meropenem and doripenem), ceftazidime and piperacillin–tazobactam for the treatment of severe infections when there is a risk of pharmacodynamic failure (deep infection sites, major pharmacokinetic changes, high MIC)	2C
We recommend administering vancomycin by continuous infusion, after administration of a loading dose, to reach early target plasma concentrations, which are determinant for its efficacy	1B
We suggest using prolonged or continuous infusion of antibiotics to prevent the emergence of bacterial resistance, particularly with regard to certain strains (*S. aureus*, *P. aeruginosa*, *Enterobacteriaceae*)	UG

time above the mutant prevention concentration) have been correlated with the emergence of resistant strains of *Enterobacteriaceae*. However, the theoretical advantages of continuous administration of antibiotics have not been confirmed by clinical studies of high level of evidence [78].

d) Antibiotic combinations: indications and duration

Recommendations

Very few studies offer direct, consistent arguments which allow one to assess the balance between the benefits and risks of using antibiotic combinations. Thus, the group issued ungraded statements. These are presented in Table 12.

Rationale

Monotherapy might be sufficient for VAP on two conditions: time to onset from intubation of less than 7 days and the patient has received no previous recent antibiotic therapy. Length of hospital stay before intubation should also be considered. This 'monotherapy' approach should probably be extended to all hospital-acquired pneumonia without risk factors for multidrug-resistant bacteria.

Despite a low level of evidence, empirical treatment with a combination of antibiotics is usually recommended in the most critically ill (septic shock) or frail (blood cancer) patients, especially as they are at risk of infection by multidrug-resistant bacteria [62, 79]. However, even in frail patients, there should be a collective understanding of the fundamental importance of rational use of these combinations of antibiotics in order to avoid the emergence of multidrug-resistant bacteria [80].

Table 12 Recommendations for field 4c: antibiotic combinations

Recommendation	
If there are no risk factors for multidrug-resistant bacteria, we suggest using empirical monotherapy to treat hospital-acquired pneumonia	UG
We suggest using empirical combination treatment for patients with shock, neutropenia or suspected infection by multidrug-resistant bacteria	UG

Q5: Review and duration of antibiotic treatments

Recommendations are presented in Table 13.

Rationale

Few studies evaluated strategies for shortening the length of antibiotic treatments in intensive care units. Several strategies have been used: empirical reduction of treatment duration [81], short course of empirical antibiotic therapy [82] and daily assay of procalcitonin [83].

Studies showed that the duration of antibiotic therapy is reduced by following recommendations to interrupt antibiotic therapy when procalcitonin plasma concentrations decrease by 80–90 % from the initial value or below a threshold, most often 0.5 ng/mL [84]. Some of these studies included patients with all types of infections in intensive care units, but most focused on lower respiratory tract infections. Lastly, it should be noted that immunocompromised patients (neutropenia, blood

Table 13 Recommendations for field 5: reassessment of antibiotic treatments

Recommendation	
We recommend reassessing antibiotic treatment in all intensive care unit patients at 48–72 h and de-escalated in light of the clinical conditions and microbiological data	1C
With respect to calcitonin:	
We suggest using procalcitonin to guide the interruption of antibiotic therapy in intensive care unit patients, especially those with lower respiratory tract infections. When plasma procalcitonin concentration is below 0.5 ng/mL or has decreased by over 80 % from the peak value, antibiotic treatment can be stopped	2B
Regarding reassessment, we recommend implementing local recommendations in order to reduce antibiotic exposure	1B
We suggest assaying procalcitonin every 48–72 h after day 3, to reduce the length of antibiotic therapy	2B
When the initial antibiotic treatment is adequate for non-immunosuppressed patients with ventilator-associated pneumonia, we suggest limiting the total duration of treatment to 8 days, irrespective of the causative organisms	2B
Outside particular clinical situations, we recommend limiting treatment of a community-acquired infection to 5–7 days	1B
Apart from *S. aureus* bacteraemia, we recommend limiting treatment of catheter-associated bacteraemia to 5–7 days if the blood cultures become negative in the first 3 days of treatment, if the catheter has been removed and in the absence of secondary infected sites	1B
We recommend organizing, in each intensive care unit, a regular (e.g. at least weekly) multidisciplinary staff meeting in order to improve the quality of antibiotic treatment and the rate of de-escalation and to limit the antibiotic use	1B
We recommend implementing antibiotic treatment protocols in order to improve the patient outcomes and to limit the emergence of resistance	1C

disease, organ transplantation, receiving immunosuppressive treatment) were excluded from these studies.

Four randomized controlled studies compared two fixed treatment durations in non-immunocompromised adult patients with VAP. A fifth study, in neonatology, concerned bacteraemia. Other studies compared strategies using antibiotic therapy duration guided by clinical progression, biomarker kinetics or the use of antibiotic therapy protocols.

In VAP identified by microbiological criteria, 8-day compared with 15-day antibiotic therapy did not reduce 28-day survival, including when the causative organism was a non-fermenting Gram-negative bacillus (23 vs. 30 %, respectively). Relapse rate did not differ between the two strategies, except in the case of non-fermenting Gram-negative bacilli: 21/64 (32.8 %) in the 8-day group versus 12/63 (19 %) in the 15-day group [81].

In non-immunocompromised patients without criteria of severe disease who have an uncomplicated community-acquired respiratory, intra-abdominal, or urinary infection of satisfactory clinical progression in the first 5 days, 5- to 7-day antibiotic therapy does not involve a greater risk of treatment failure than longer antibiotic therapy, including in patients with bacteraemia [85]. Apart from a *S. aureus* bacteraemia, or from a complicated bacteraemia, treatment should probably be limited to 5–7 days for a catheter-related bacteraemia if blood cultures become negative in the first 3 days of treatment and if the catheter has been removed [86, 87].

The advantages of a specialized consultation (infectious diseases physicians) with the intensive care unit team are still open to debate. Five nonrandomized, single-centre, before-and-after studies examining this question have evaluated the consumption of antibiotics, the appropriateness of the antibiotics prescribed compared with the recommendations, the increasing cost of antibiotics and in some cases mortality [88].

There are no intensive care units studies that specifically assess the impact of antibiotic therapy protocols on resistance. There are only six studies (five of which are prospective before-and-after studies; no randomized studies) of low level of evidence. They suggest that the use of protocols improves the outcomes of patients and limits the emergence of resistance to antibiotics.

Discussion

These guidelines are aimed at reducing the spread of multidrug-resistant pathogens related to the overuse of antibiotics in intensive care units. The multidisciplinary expert panel selected 67 relevant recommendations that should support the decision to improve antibiotic stewardship at the bedside. These guidelines should facilitate the intensivist decisions for avoiding unnecessary antibiotic initiation, using narrow-spectrum antibiotics if possible, and interrupting early antibiotics. In contrast, patients requiring antibiotics should receive an adequate, early and efficient treatment. This strategy should minimize the development of resistance and offset the lack of new molecules. As experts, our role now is to convey these guidelines in each institution.

The first strength of these guidelines is the multidisciplinary nature of the expert panel group. Thus, adult intensivists, infectious disease specialists, epidemiologists and microbiologists discussed together throughout the elaboration process. Paediatric intensivists have also participated to produce recommendations for the specific paediatric population. The second strength is the adhesion to a meticulous process of methodology. The literature analysis, the elaboration of summaries of evidence and then the determination of the strength of the recommendations followed the GRADE methodology (see "Methodology" section).

However, one can discuss several limitations. Detractors can note a lack of details, making it difficult to transfer these guidelines in their routine practice. For instance, we did not detail the rules for adapting the antibiotic dosages in patients with renal failure. The readers are invited to refer back to recent papers [67–69]. De-escalation in real-life practice remains unclear, probably reflecting the lack of strong agreement between experts [9, 25, 26, 89–93]. Several aspects of our practice were not reported in the guidelines. The role of historical molecules (fosfomycin, minocycline etc.) could have been expanded [4]. The experts, probably as a result of their routine practice, did not consider entirely these old antibiotics. Aerosolizing of antibiotics was not developed, whereas there is a substantial amount of data on such a strategy [94–96]. However, in routine, aerosol antibiotics remain a relatively rare practice. We probably did not stress enough the need to avoid most prophylactic antibiotics. That was a weakness of the guidelines. One should nevertheless note that strategies based on the use of selective digestive decontamination resulted in a large decrease of antibiotic use [97]. The goal of our group was not to be exhaustive but to produce a few recommendations that were eligible in routine practice. Finally, a few recommendations may seem provocative for the readers. For example, the duration of treatment for pseudomonal infections might be questionable [98]. Our goal was consistently to encourage the reduction of antibiotic use, and we analysed the literature in this single way. In the ESM, the readers will find the argumentation based on our data assessment.

We reported above the guidelines as stated by the expert panel group. According to our methodology, we cannot change the content and meaning of each recommendation. We acknowledge that some recommendations are a matter of debate.

To date, the challenge is to diffuse, improve knowledge and implement these guidelines. In each institution, their appropriation should stimulate multidisciplinary discussions resulting in better knowledge of local epidemiology, rate of antibiotic use and finally protocols for improving the stewardship of antibiotics.

We hope these efforts will contribute to limit the emergence of resistant bacteria, and we are committed to assess their impact on this issue.

Conflicts of interest The process for reporting conflicts of interest (COI) of the organizing committee members and of the experts is described in the "Methodology" section. Finally, during the manuscript writing final process, authors were again asked to declare whether they have or not any COI to disclose. Experts and organizing committee members indicate that they have no COI in particular that they have no financial relationship with the organization that sponsored the research.

Appendix

Recommendations by an expert panel from the French Intensive Care Society (Société de Réanimation de Langue Française, SRLF) and the French Society of Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation, SFAR), with the participation of the French Group for Paediatric Intensive Care and Emergencies (Groupe Francophone de Réanimation et Urgences Pédiatriques, GFRUP), the French Microbiology Society (Société Française de Microbiologie, SFM), the French Infectious Diseases Society (Société de Pathologie Infectieuse de Langue Française, SPILF), and the French Society for Hospital Hygiene (Société Française d'Hygiène Hospitalière, SF2H).

Expert panel coordinator: J-P. Bedos (Versaille).

Expert panel: Bernard Allaouchiche (Lyon), Laurence Armand-Lefèvre (Paris), Olivier Baldesi (Aix), Lila Bouadma (Paris), Dominique Decré (Paris), Samy Figueiredo (Le Kremlin-Bicêtre), Rémy Gauzit (Paris), Benoit Guery (Lille), Nicolas Joram (Nantes), Boris Jung (Montpellier), Sigismond Lasocki (Angers), Alain Lepape (Lyon), Fabrice Lesage (Paris), Olivier Pajot (Argenteuil), François Philippart (Paris), Bertrand Souweine (Clermont-Ferrand), Pierre Tattevin (Rennes), Jean-François Timsit (Paris), Jean Ralph Zahar (Angers).

Executive committee: C. Bretonnière (Nantes), C. Milesi (Montpellier), M. Leone (Marseille), B. Misset (Paris).

SRLF reference and evaluation commission: Cédric Bretonnière, Karim Chaoui, Aurélie Cravoisy, Michel Djibré, Laurence Donetti, Laurent Dupic, Fabienne Fieux, Dominique Hurel, Virginie Lemiale, Olivier Lesieur, Martine Lesny, Pascal Meyer, Christophe Milési, Benoit Misset, Mehran Monchi, David Orlikowski, David Osman, Jean-Pierre Quenot, Daniel Da Silva, Lilia Soufir, Thierry Van Der Linden, Isabelle Verheyde.

References

1. So A, Furlong M, Heddini A (2010) Globalisation and antibiotic resistance. BMJ 341:c5116
2. Bassetti M, Merelli M, Temperoni C, Astilean A (2013) New antibiotics for bad bugs: where are we? Ann Clin Microbiol Antimicrob 12:22
3. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 48:1–12
4. Corona A, Colombo R (2013) Towards the end of the antibiotic era: let's save the ancient soldier Colistin! Intensive Care Med 39:1660–1661
5. WHO (2014) Antimicrobial resistance: global report on surveillance. World Health Organization, Geneva, p 256
6. Carlet J (2012) World Alliance Against Antibiotic Resistance (WAAR): safeguarding antibiotics. Intensive Care Med 38:1723–1724
7. Paiva JA (2013) Adding risk factors for potentially resistant pathogens, increasing antibiotic pressure and risk creating the untreatable bacteria: time to change direction. Intensive Care Med 39:779–781
8. Damas P, Canivet JL, Ledoux D, Monchi M, Melin P, Nys M, De Mol P (2006) Selection of resistance during sequential use of preferential antibiotic classes. Intensive Care Med 32:67–74
9. Timsit JF, Harbarth S, Carlet J (2014) De-escalation as a potential way of reducing antibiotic use and antimicrobial resistance in ICU. Intensive Care Med 40:1580–1582
10. Visscher S, Schurink CA, Melsen WG, Lucas PJ, Bonten MJ (2008) Effects of systemic antibiotic therapy on bacterial persistence in the respiratory tract of mechanically ventilated patients. Intensive Care Med 34:692–699
11. Brusselaers N, Vogelaers D, Blot S (2011) The rising problem of antimicrobial resistance in the intensive care unit. Ann Intensive Care 1:47
12. Michalopoulos AS, Falagas ME (2011) Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care 1:30
13. Hanberger H, Arman D, Gill H, Jindrak V, Kalenic S, Kurcz A, Licker M, Naaber P, Scicluna EA, Vanis V, Walther SM (2009) Surveillance of microbial resistance in European intensive care units: a first report from the Care-ICU programme for improved infection control. Intensive Care Med 35:91–100
14. Bassetti M, De Waele JJ, Eggimann P, Garnacho-Montero J, Kahlmeter G, Menichetti F, Nicolau DP, Paiva JA, Tumbarello M, Welte T, Wilcox M, Zahar JR, Poulakou G (2015) Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. Intensive Care Med 41:776–795

15. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S (2004) Grading quality of evidence and strength of recommendations. BMJ 328:1490
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ (2008) Grade: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ Clin Res 336:924–926
17. GRADE Working Group (2004) Grading quality of evidence and strength of recommendations. BMJ 328:1490
18. Fitch K, Bernstein S, Aguilar M, Burnand B et al (2001) The RAND/UCLA appropriateness method user's manual. RAND, Santa Monica
19. DiazGranados CA (2012) Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. Am J Infect Control 40:526–529
20. Kim JW, Chung J, Choi SH, Jang HJ, Hong SB, Lim CM, Koh Y (2012) Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Critical Care 16:R28
21. Nijssen S, Fluit A, van de Vijver D, Top J, Willems R, Bonten MJ (2010) Effects of reducing beta-lactam antibiotic pressure on intestinal colonization of antibiotic-resistant gram-negative bacteria. Intensive Care Med 36:512–519
22. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N (2011) Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 66:1223–1230
23. Kuster SP, Ruef C, Ledergerber B, Hintermann A, Deplazes C, Neuber L, Weber R (2008) Quantitative antibiotic use in hospitals: comparison of measurements, literature review, and recommendations for a standard of reporting. Infection 36:549–559
24. Giantsou E, Liratzopoulos N, Efraimidou E, Panopoulou M, Alepopoulou E, Kartali-Ktenidou S, Manolas K (2007) De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. Intensive Care Med 33:1533–1540
25. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernandez-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Marquez-Vacaro JA (2014) De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 40:32–40
26. Mokart D, Slehofer G, Lambert J, Sannini A, Chow-Chine L, Brun JP, Berger P, Duran S, Faucher M, Blache JL, Saillard C, Vey N, Leone M (2014) De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. Intensive Care Med 40:41–49
27. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med 132:621–630
28. Swanson JM, Wood GC, Croce MA, Mueller EW, Boucher BA, Fabian TC (2008) Utility of preliminary bronchoalveolar lavage results in suspected ventilator-associated pneumonia. J Trauma 65:1271–1277
29. Canadian Critical Care Trials Group (2006) A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619–2630
30. O'Horo JC, Thompson D, Safdar N (2012) Is the gram stain useful in the microbiologic diagnosis of VAP? A meta-analysis. Clin Infect Dis 55:551–561
31. Galar A, Yuste JR, Espinosa M, Guillen-Grima F, Hernaez-Crespo S, Leiva J (2012) Clinical and economic impact of rapid reporting of bacterial identification and antimicrobial susceptibility results of the most frequently processed specimen types. Eur J Clin Microbiol Infect Dis 31:2445–2452
32. Kerremans JJ, Verboom P, Stijnen T, Hakkaart-van Roijen L, Goessens W, Verbrugh HA, Vos MC (2008) Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. J Antimicrob Chemother 61:428–435
33. Vlek AL, Bonten MJ, Boel CH (2012) Direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry improves appropriateness of antibiotic treatment of bacteremia. PLoS One 7:e32589
34. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Land GA, Peterson LE, Musser JM (2013) Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Arch Pathol Lab Med 137:1247–1254
35. Lasocki S, Scanvic A, Le Turdu F, Restoux A, Mentec H, Bleichner G, Sollet JP (2006) Evaluation of the Binax NOW *Streptococcus pneumoniae* urinary antigen assay in intensive care patients hospitalized for pneumonia. Intensive Care Med 32:1766–1772
36. Falguera M, Ruiz-Gonzalez A, Schoenenberger JA, Touzon C, Gazquez I, Galindo C, Porcel JM (2010) Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. Thorax 65:101–106
37. Matta M, Kerneis S, Day N, Lescat M, Hoi AB, Varon E, Gutmann L, Mainardi JL (2010) Do clinicians consider the results of the BinaxNOW Streptococcus pneumoniae urinary antigen test when adapting antibiotic regimens for pneumonia patients? Clin Microbiol Infect 16:1389–1393
38. Depuydt P, Benoit D, Vogelaers D, Decruyenaere J, Vandijck D, Claeys G, Verschraegen G, Blot S (2008) Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. Intensive Care Med 34:675–682
39. Jung B, Sebbane M, Chanques G, Courouble P, Verzilli D, Perrigault PF, Jean-Pierre H, Eledjam JJ, Jaber S (2009) Previous endotracheal aspirate allows guiding the initial treatment of ventilator-associated pneumonia. Intensive Care Med 35:101–107
40. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC (2010) Ventilator-associated pneumonia: role of colonizers and value of routine endotracheal aspirate cultures. Int J Infect Dis 14:e723–e729
41. Armand-Lefevre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppe E, Bronchard R, Lepeule R, Lucet JC, El Mniai A, Wolff M, Montravers P, Plesiat P, Andremont A (2013) Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother 57:1488–1495

42. Routsi C, Pratikaki M, Platsouka E, Sotiropoulou C, Papas V, Pitsiolis T, Tsakris A, Nanas S, Roussos C (2013) Risk factors for carbapenem-resistant Gram-negative bacteremia in intensive care unit patients. Intensive Care Med 39:1253–1261
43. Razazi K, Derde LP, Verachten M, Legrand P, Lesprit P, Brun-Buisson C (2012) Clinical impact and risk factors for colonization with extended-spectrum beta-lactamase-producing bacteria in the intensive care unit. Intensive Care Med 38:1769–1778
44. Andes D, Craig WA (2005) Treatment of infections with ESBL-producing organisms: pharmacokinetic and pharmacodynamic considerations. Clin Microbiol Infect 11(Suppl 6):10–17
45. Nguyen HM, Shier KL, Graber CJ (2014) Determining a clinical framework for use of cefepime and beta-lactam/beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum-beta-lactamase-producing *Enterobacteriaceae*. J Antimicrob Chemother 69:871–880
46. Aubert G, Carricajo A, Vautrin AC, Guyomarc'h S, Fonsale N, Page D, Brunel P, Rusch P, Zeni F (2005) Impact of restricting fluoroquinolone prescription on bacterial resistance in an intensive care unit. J Hosp Infect 59:83–89
47. Nseir S, Di Pompeo C, Soubrier S, Delour P, Lenci H, Roussel-Delvallez M, Onimus T, Saulnier F, Mathieu D, Durocher A (2005) First-generation fluoroquinolone use and subsequent emergence of multiple drug-resistant bacteria in the intensive care unit. Crit Care Med 33:283–289
48. Charbonneau P, Parienti JJ, Thibon P, Ramakers M, Daubin C, du Cheyron D, Lebouvier G, Le Coutour X, Leclercq R (2006) Fluoroquinolone use and methicillin-resistant Staphylococcus aureus isolation rates in hospitalized patients: a quasi experimental study. Clin Infect Dis 42:778–784
49. Goorhuis A, Bakker D, Corver J, Debast SB, Harmanus C, Notermans DW, Bergwerff AA, Dekker FW, Kuijper EJ (2008) Emergence of Clostridium difficile infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis 47:1162–1170
50. Drieux L, Brossier F, Duquesnoy O, Aubry A, Robert J, Sougakoff W, Lecso-Bornet M, Jarlier V (2009) Increase in hospital-acquired bloodstream infections caused by extended spectrum beta-lactamase-producing *Escherichia coli* in a large French teaching hospital. Euro J Clin Microbiol Infect Dis 28:491–498
51. Ortega M, Marco F, Soriano A, Almela M, Martinez JA, Munoz A, Mensa J (2009) Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother 63:568–574
52. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD (2010) Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 340:c2096
53. Berman SJ, Johnson EW, Nakatsu C, Alkan M, Chen R, LeDuc J (2004) Burden of infection in patients with end-stage renal disease requiring long-term dialysis. Clin Infect Dis 39:1747–1753
54. El Solh AA, Pietrantoni C, Bhat A, Bhora M, Berbary E (2004) Indicators of potentially drug-resistant bacteria in severe nursing home-acquired pneumonia. Clin Infect Dis 39:474–480
55. Polverino E, Dambrava P, Cilloniz C, Balasso V, Marcos MA, Esquinas C, Mensa J, Ewig S, Torres A (2010) Nursing home-acquired pneumonia: a 10 year single-centre experience. Thorax 65:354–359
56. Scanvic A, Denic L, Gaillon S, Giry P, Andremont A, Lucet JC (2001) Duration of colonization by methicillin-resistant *Staphylococcus aureus* after hospital discharge and risk factors for prolonged carriage. Clin Infect Dis 32:1393–1398
57. Lambotte O, Timsit JF, Garrouste-Orgeas M, Misset B, Benali A, Carlet J (2002) The significance of distal bronchial samples with commensals in ventilator-associated pneumonia: colonizer or pathogen? Chest 122:1389–1399
58. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, Levine DP, Chambers HF, Tally FP, Vigliani GA, Cabell CH, Link AS, DeMeyer I, Filler SG, Zervos M, Cook P, Parsonnet J, Bernstein JM, Price CS, Forrest GN, Fatkenheuer G, Gareca M, Rehm SJ, Brodt HR, Tice A, Cosgrove SE (2006) Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 355:653–665
59. Murray KP, Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, Rybak MJ (2013) Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration > 1 mg/L: a matched cohort study. Clin Infect Dis 56:1562–1569
60. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, McGee WT, Reisman A, Chastre J (2012) Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis 54:621–629
61. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP (2011) Vancomycin: we can not get there from here. Clin Infect Dis 52:969–974
62. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
63. Yu KT, Wyer PC (2008) Evidence-based emergency medicine/critically appraised topic. Evidence behind the 4-h rule for initiation of antibiotic therapy in community-acquired pneumonia. Ann Emerg Med 51:651–662
64. Silber SH, Garrett C, Singh R, Sweeney A, Rosenberg C, Parachiv D, Okafo T (2003) Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. Chest 124:1798–1804
65. SPILF (2009) 17th Consensus conference. Consensus conference on bacterial meningitis. Short text. Med Mal Infect 39:175–186
66. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA (2012) Does beta-lactam pharmacokinetic variability in critically Ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2:35
67. Pletz MW, Lipman J (2013) Clinical measures for increased creatinine clearances and suboptimal antibiotic dosing. Intensive Care Med 39:1322–1324
68. Povoa P, Spriet I, Zahar JR (2014) Antibiotic dosing in the critically ill: asking the same questions but expecting different answers. Intensive Care Med 40:1780–1782
69. Udy AA, Roberts JA, Lipman J (2013) Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 39:2070–2082

70. Chatellier D, Jourdain M, Mangalaboyi J, Ader F, Chopin C, Derambure P, Fourrier F (2002) Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. Intensive Care Med 28:214–217
71. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10; quiz 11–12
72. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58:1072–1083
73. Mohr JF, Wanger A, Rex JH (2004) Pharmacokinetic/pharmacodynamic modeling can help guide targeted antimicrobial therapy for nosocomial gram-negative infections in critically ill patients. Diagn Microbiol Infect Dis 48:125–130
74. Li C, Du X, Kuti JL, Nicolau DP (2007) Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 51:1725–1730
75. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ (2013) Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis 56:272–282
76. Spapen HD, Janssen van Doorn K, Diltoer M, Verbrugghe W, Jacobs R, Dobbeleir N, Honore PM, Jorens PG (2011) Retrospective evaluation of possible renal toxicity associated with continuous infusion of vancomycin in critically ill patients. Ann Intensive Care 1:26
77. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55:2704–2709
78. Abdul-Aziz MH, Dulhunty JM, Bellomo R, Lipman J, Roberts JA (2012) Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care 2:37
79. Legrand M, Max A, Schlemmer B, Azoulay E, Gachot B (2011) The strategy of antibiotic use in critically ill neutropenic patients. Ann Intensive Care 1:22
80. Gyssens IC, Kern WV, Livermore DM (2013) The role of antibiotic stewardship in limiting antibacterial resistance among hematology patients. Haematologica 98:1821–1825
81. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S (2003) Comparison of 8 versus 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598
82. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511
83. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 375:463–474
84. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G (2012) An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Med 38:940–949
85. Havey TC, Fowler RA, Daneman N (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care 15:R267
86. Chong YP, Moon SM, Bang KM, Park HJ, Park SY, Kim MN, Park KH, Kim SH, Lee SO, Choi SH, Jeong JY, Woo JH, Kim YS (2013) Treatment duration for uncomplicated *Staphylococcus aureus* bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother 57:1150–1156
87. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Torok ME, Walker S, Wertheim HF, Wilson P, Llewelyn MJ (2011) Clinical management of *Staphylococcus aureus* bacteraemia. Lancet Infect Dis 11:208–222
88. Rimawi RH, Mazer MA, Siraj DS, Gooch M, Cook PP (2013) Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. Crit Care Med 41:2099–2107
89. De Waele JJ, Bassetti M, Martin-Loeches I (2014) Impact of de-escalation on ICU patients' prognosis. Intensive Care Med 40:1583–1585
90. Kapoor G, Saigal S (2014) De-escalation in severe sepsis: still an important part of our armamentarium against antimicrobial resistance. Intensive Care Med 40:1618
91. Leone M, Bechis C, Baumstarck K (2014) De-escalation in severe sepsis: still an important part of our armamentarium against antimicrobial resistance, of course! Intensive Care Med 40:1619
92. Silva BN, Andriolo RB, Atallah AN, Salomao R (2013) De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. Cochrane Database Syst Rev 3:CD007934
93. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanese J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bezulier K, Antonini F, Textoris J, Martin C (2014) De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med 40:1399–1408
94. Kofteridis DP, Alexopoulou C, Valachis A, Maraki S, Dimopoulou D, Georgopoulos D, Samonis G (2010) Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. Clin Infect dis 51:1238–1244
95. Nair GB, Niederman MS (2015) Ventilator-associated pneumonia: present understanding and ongoing debates. Intensive Care Med 41:34–48
96. Palmer LB, Smaldone GC (2014) Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med 189:1225–1233
97. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH, Su DCSG (2013) Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis 13:328–341
98. Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, Cirillo I, Kimko H, Redman R (2012) A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care 16:R218