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CONFERENCE REPORTS AND EXPERT PANEL

Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance

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Abstract

Antimicrobial resistance (AMR) is a clear and present danger to patients in any intensive care unit (ICU) around the world. Whereas AMR may affect any patient in the hospital, patients in the ICU are particularly at risk of acquiring AMR infections due to the intensity of the treatment, use of invasive devices, increased risk of transmission and exposure to antibiotics. AMR is present in every ICU, although prevalence is geographically different and AMR pathogens encountered are variable. Intensive care and infectious disease specialists from the European Society of Intensive Care Medicine, European Society of Microbiology and Infectious Diseases and World Alliance Against Antimicrobial Resistance, united in the ANTARCTICA (Antimicrobial Resistance in Critical Care) coalition, call for increased awareness and action among health care professionals to reduce AMR development in critically ill patients, to improve treatment of AMR infections and to coordinate scientific research in this high-risk patient population. Close collaboration with other specialties, and combining these and other interventions in antibiotic stewardship programmes should be a priority in every ICU. Considerate antibiotic use and adopting strict infection control practices to halt AMR remains a responsibility shared by all healthcare workers, from physicians to maintenance personnel, from nurses to physiotherapists, from consultants to medical students. Together, we can reduce AMR in our ICUs and continue to treat our patients effectively.

Keywords: Antibiotic, Resistance, Stewardship, Infection

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Introduction

Antimicrobial resistance (AMR) has emerged as one of the most important determinants of outcome in patients with serious infections, along with the virulence of the culprit pathogen and the concomitant comorbidities [1]. A recent report estimates that by 2050 10 million people will die all over the world every year due to AMR unless a global response to the problem is mounted [2, 3]. The impact of such a response has particular relevance in settings with a high prevalence of multi-drug resistance (MDR), since it may affect choices for empirically selected regimens, facilitate de-escalation of unnecessary antimicrobials and support infection control decisions. To address these issues, the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the World Alliance Against Antimicrobial Resistance (WAAAR), organized a round table on MDR prior to the 2016 LIVES meeting held in Milan. During a full-day meeting, experts from both societies reviewed the challenges of MDR in the intensive care unit (ICU), identified knowledge gaps, and discussed threats and solutions for the future. This manuscript serves as a report of this Round Table meeting in which we summarize the discussions, list priorities in the management of infection with MDR pathogens, identify areas that urgently require more research, and make recommendations that can be implemented today.

The extent of AMR in the ICU

The most urgent and serious threats for the ICU include Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBLs), derepressed AmpC and/or carbapenemases [commonly referred to as carbapenem-resistant Enterobacteraceae (CRE)], carbapenem-resistant *Acinetobacter baumannii*, MDR-*Pseudomonas aeruginosa* and methicillin resistant *Staphylococcus aureus* (MRSA) [4]. There are important regional differences in prevalence of most AMR patterns including ESBL at various levels (Table 1). Within Europe, southern Europe seems to be a particular hotspot for many of these pathogens but overall, the prevalence is increasing in hospitals and even more so in the ICU. Aggregated data of the incidence of infections caused by AMR pathogens and resistance trends in the ICU are limited at European level, with most reports providing data of local patterns and trends for short periods of time only. Additionally, the focus has frequently been on the reporting of outbreaks and colonization, without consideration of different infection foci. Surveillance networks do provide important information when it comes to overall trends, and it is assumed that these also reflect the situation in the ICU.

There are different mechanisms involved in MDR spread which make risk stratification a challenging issue. Risk factors include mainly exposure to antibiotics (in the previous 90 days), duration of hospitalization, use of invasive devices, immunosuppression and the colonization pressure in the hospital (defined as the proportion of patients colonized with a particular microorganism in a unit of the hospital) and the community [5]. Also, the impact of travel and migration from areas with high AMR prevalence to countries with low prevalence could be significant. It should be acknowledged that risk factors may be different for different microorganisms. Comorbidity is also increasingly identified as a risk factor for MDR infection [6]. Whereas most analyses have focused on identifying risk factors for MDR in healthcare associated infections, MDR bacteria are also increasingly recognized as the cause of community acquired infections,

Table 1 Overview of antibacterial resistance across the globe

Range of resistance (%) for the main resistant bacteria worldwide (clinical isolates)						
	African region	**Americas region**	**Eastern Mediterranean region**	**European region**	**Southeast Asia region**	**Western Pacific region**
Escherichia coli resistant to third generation cephalosporins	2–70	0–48	22–63	3–82	16–68	0–77
Escherichia coli: resistance to fluoroquinolones	14–71	8–58	21–62	8–48	32–64	3–96
Klebsiella pneumoniae: resistance to carbapenems	0–4	0–11	0–54	0–68	0–55	0–8
MRSA	12–80	21–90	10–53	0.3–60	2–81	4–84

Antimicrobial resistance: global report on surveillance. World Health Organization 2014

MRSA methicillin-resistant *Staphylococcus aureus*

with ESBL-producing bacteria as the most common MDR pathogens. In these patients, again comorbidity, but also age, nursing home residency, previous hospitalization, recent antibiotic consumption and chronic renal failure have been identified as relevant risk factors [7].

Current treatment options in MDR infections

At this moment, antibiotics are still key to treating MDR infections, and inadequate therapy (spectrum of activity, adequacy of dose and tissue penetration when needed) is a modifiable risk factor that has an important impact on patient outcome, especially in patients with septic shock. Combination therapy and high doses to maximize the antibiotics pharmacokinetic/pharmacodynamic (PK/PD) properties are usually recommended for MDR infection, particularly in the empirical phase [4]; once pathogen susceptibility characteristics are known, regimens can be directed based on these results. To expedite this process, rapid diagnosis in routine clinical microbiology laboratories is also needed. New technologies beyond molecular approaches that are being used to this end, include amongst others, mass spectrometry, flow cytometry and real-time microscopy [8]. One major issue in the spread in the community and hospital of MDR Gram-negative bacteria, is the overuse of carbapenems for empirical therapy. It should be known that the rate of infection due to ESBL-producing bacteria in carriers was around 16% in a recent report from France [9]. Recently there has been a reappraisal of old compounds and a number of new drugs have come to the market that will be important in the treatment of selected MDR pathogens [10]. Colistin and fosfomycin are old antibiotics and have been used in the past for years; their optimal use for MDR is still to be fully elucidated. New drugs include ceftolozane/tazobactam, ceftazidime/avibactam (as well as other combinations with avibactam such as ceftaroline and aztreonam), carbapenems combined with new beta-lactamase inhibitors, cefiderocol, plazomicin and eravacycline (Table 2); several more are in the process of development (Table S1). Until now most of these new drugs have only been tested in complicated urinary tract infections (UTIs) and intra-abdominal infections (IAIs), skin and soft tissue infection, and limited data for the ICU patients is presently available. Studies specifically targeting more resistant pathogens such as XDR pathogens or CRE are limited as well. However, studies investigating nosocomial pneumonia are now underway and will provide evidence about the use of these new agents in respiratory infections in the critically ill. Ceftazidime/avibactam has been found to be non-inferior to meropenem in patients with nosocomial pneumonia (data on clinicaltrials.gov). Unfortunately, with the exception of cefiderocol, no drug has a spectrum that covers all of the current MDR pathogens, which makes empirical therapy an ongoing challenge. Data from randomized controlled trials (RCTs) in ICU patients are needed for all these new drugs as some recently introduced antibiotics have failed in non-inferiority studies in ICU patients.

PK/PD optimized therapy is one of the newer approaches in the improved use of our currently available antibiotics, but also important in the development of new antibiotics [11, 12]. Current dosing strategies consider pathogen susceptibility (i.e. minimum inhibitory concentration, MIC) and PK to be normal but this approach is challenged in critically ill patients with MDR infections, where integrating the PK and PD to optimize the administration of the antibiotic is necessary. Relevant strategies may include the use of a loading dose, higher doses and optimized infusion strategies such as prolonged infusion of beta-lactam antibiotics. One limitation in this strategy is the assessment of pathogen susceptibility, namely the role of the MIC value, which remains the preferred measure of susceptibility. Furthermore, drug concentrations are not available in the first hours [13].

Accuracy and early availability of susceptibility is currently problematic. Manipulating antibiotic dosing and administration to achieve target PK/PD indices is the goal of a PK/PD optimized approach, and this may be relevant for clinical cure, as well as for preventing resistance development. For many drugs that are crucial in the treatment of MDR infections, there is a lack of solid PK and PD data that can generate robust dosing advice (e.g. fosfomycin, temocillin, mecillinam, among others). In order to even further optimize therapy, individualized dosing using therapeutic drug monitoring (TDM) and dose adaptation may be the solution [12].

The optimal duration of antibiotic treatment of MDR infections has not been established, but prolonged therapy is not advisable. Short-course treatment of VAP was associated with more antibiotic-free days and no difference regarding mortality/relapses although a strong trend for fewer relapses due to non-fermentative Gram-negative bacilli was observed in long-course treatment [14], which was not confirmed in other studies. Procalcitonin guided antibiotic therapy algorithms could help in reducing the duration of antimicrobial administration without having a negative impact on survival [15, 16].

The importance of infection control

Infection control is a critical element in the overall management of MDR infections [17], and infection control measures can either focus on specific pathogens or target all patients. Minimizing transmission of MDR pathogens is the goal in infection control strategies—with emphasis on hand hygiene, isolation measures, surveillance including specific screening for MDR and XDR pathogens,

Table 2 The most important antibacterial agents recently approved or in late-phase drug development

Drug class	Drug name	Development phase	Potential indications
Cephalosporin	Cefiderocol	Phase 3	Bloodstream infections (BSI), hospital acquired pneumonia (HAP), Complicated urinary tract infection (cUTI), ventilator associated pneumonia (VAP)
Novel cephalosporin + β-lactamase inhibitor	Ceftolozane + tazobactam	Approved 2015	Complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection), hospital-acquired bacterial pneumonia/ventilator associated pneumonia
	Ceftazidime + avibactam	Approved 2015	Complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection), hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
	Cefepime + tazobactam	Phase 3	Complicated urinary tract infections including acute pyelonephritis. Cefepime-resistant *Enterobacteriaceae*
Carbapenem + novel β-lactamase inhibitor	Meropenem/vaborbactam	Approved 2017	Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, febrile neutropenia
	Imipenem/cilastatin + relebactam	Phase 3	Complicated urinary tract infections, acute pyelonephritis, complicated intra-abdominal infections
Monobactam + novel β-lactamase inhibitor	Aztreonam + avibactam	Phase 3	MDR pathogens
Aminoglycoside	Plazomicin	Finished phase 3	Bloodstream infections and nosocomial pneumonia caused by carbapenem-resistant Enterobacteriaceae
Fluoroquinolones	Delafloxacin	Approved 2017	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, uncomplicated gonorrhea
Oxazolidinone	Tedizolid	Approved 2014	Acute bacterial skin and skin structure infections, hospital acquired bacterial pneumonia/ventilator associated bacterial pneumonia
	Cadazolid (quinolonyl-oxalidinone)	Phase 3	*Clostridium difficile*-associated diarrhea
Lipoglycopeptide	Oritavancin	Approved 2014	Acute bacterial skin and skin structure infections
	Dalbavancin	Approved 2014	Acute bacterial skin and skin structure infections
Lipopeptide	Surotomycin	Phase 3	*Clostridium difficile*-associated diarrhea
Macrolide	Solithromycin	Phase 3	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea
Tetracycline	Omadacycline	Finished phase 3	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections
	Eravacycline	Finished phase 3	Complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired bacterial pneumonia

and environmental measures. However, interventions required may be different according to the pathogen involved. The MOSAR study showed that the effect of the impact of hand hygiene and chlorhexidine plus screening and isolation had an effect on MRSA, but not on other pathogens [18]. The risk of environmental contamination is species specific and is of particular concern with MRSA, VRE, *Klebsiella, Pseudomonas* and *Acinetobacter*

species. The role of antibiotics though should not be underestimated. In a universal approach, the overall goal is to improve antibiotic use, hand hygiene and environmental cleaning to reduce the global risk of acquiring Gram-positive MDR pathogens. Acquisition and carriage are most evidently countered by hand hygiene and environmental cleaning; in case MDR patterns persist and get amplified, restoring the gut microbiome and the colonization resistance that it provides may represent an attractive target. At all times, antibiotic therapy should be kept as short as possible.

MDR spreading outside of the hospital

MDR is evolving to an endemic problem in many countries. Furthermore, MDR is spreading to commensal species due to mobile genetic elements, which can then become a huge reservoir of MDR, a large proportion of which may be difficult to identify—the hidden reservoir. Prolonged antibiotic exposure is an important contributor to the development of AMR, and historically antibiotic use in the ICU has been high. It is important to understand the elements contributing to this high antibiotic consumption including an often all too low threshold to initiate antibiotic therapy; unfortunately, the threat of AMR further increases the use of antimicrobials (Fig. 1). A major question remains whether different antibiotic classes have a different risk of selecting and promoting AMR, with data suggesting that there is a higher risk of ESBL isolation in patients exposed to fluoroquinolones and third and fourth generation cephalosporins [19]; also the effect of carbapenems and carbapenem-sparing agents needs to be elucidated. Antibiotic de-escalation (defined as reducing the number of antimicrobial drugs or narrowing the spectrum of antibiotic therapy) in the ICU has been demonstrated to be safe although it is only applied in 20–50% of ICU patients; the impact on MDR development remains unclear. Finally, selective decontamination of the digestive tract (SDD) may affect the incidence of ESBL but many questions still remain. Ongoing multinational studies including countries with high rates of MDR will elucidate the role of SDD in different settings. The role of the microbiome in MDR acquisition is interesting but largely unexplored [20].

Solutions to this problem

Although antibiotics are currently the mainstay of the treatment of infections, many new strategies are under development. These approaches include drugs with different mechanisms of action, and may target specific resistance mechanisms such as efflux pumps, inhibit the actions of LPS, or target bacteria directly such as phage therapy or CRISPR/Cas9 genome editing technology (Table 3). Although most of them are in the development phase, these offer new opportunities for effective treatment of bacterial infections.

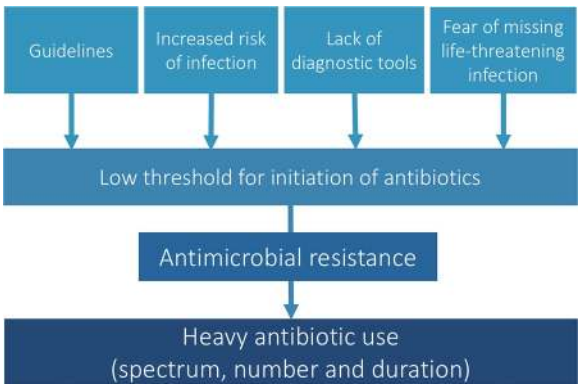

Fig. 1 Elements contributing to high antibiotic consumption in the critically ill patient

Given the complexity of AMR and the involvement of several areas in the society, we strongly plea for a concerted approach to combat the problem. For a long time, it was taken for granted that AMR would not become a problem because science would always be one step ahead. Today it is clear that action is urgently required and multiple aspects need to be covered. Clinicians and patients need to be aware of AMR, the factors contributing to AMR, as well as limited treatment options with the current antimicrobial armamentarium. Microbiological labs need to understand the need for a rapid and correct identification of pathogens and their susceptibility. Antimicrobial stewardship programs, an integrated approach where all stakeholders involved in the management of patients with infections collaborate to improve outcome of patients and decrease AMR are crucial, and should be mandatory in every hospital and supported by governmental health agencies. A continued commitment of pharmaceutical industry to develop new antibiotics, and make them available for all will be necessary, and this should be encouraged by governments. Scientific societies play an important role to support all of the above efforts and provide clinical guidance for their members; just as antibiotic stewardship programs unite specialities around the topic of AMR, a collaboration across different specialities is desirable. Finally, politicians and policy makers could greatly impact the problem of AMR by enforcing the appropriate use of any antibiotic in any part of the society (including primary care, veterinary medicine and agriculture), imposing the instalment of antimicrobial stewardship programs with clear mandates in acute care hospitals, promoting the development of new antibiotics as well as non-antibiotic strategies to treat infections, and supporting research activities that

Table 3 Antimicrobial treatment alternatives with their mechanisms of action. (Modified from Bassetti et al. [3])

Treatment	Mechanism of action
Antimicrobial peptides (AMP)	Mainly cellular membrane damage
Phage therapy	Use of lytic phages to kill bacteria
Eligobiotics	System injected by a phage
Phage endolysins	Use of a phage endolysin instead of the whole phage
Anti-virulence factors	Adjuvants or adjunct therapies to complement the use of antibiotics
Phytochemicals	Multiple actions
Metallo-antibiotic	Increased spectrum of conventional antibiotic action
Efflux pump inhibitor	Molecules to inhibit the active protein pump in the bacterial cell
Lipo-polysaccharide (LPS) inhibitors	Inhibitor of an enzyme important in LPS pathway

improve our understanding of the development and spread of AMR, the optimal treatment of MDR infections and correct antibiotic use.

Recommendations from the ANTARCTICA coalition

Based on the discussions at the 2016 ESICM/ESCMID Round Table on MDR, we specialists of infectious diseases, pharmacy and critical care, united in the ANTARCTICA (Antimicrobial Resistance in Critical Care) coalition, have identified priorities for improved MDR management in different domains (risk stratification, diagnosis, therapy and prevention) (Fig. 2), and recommend to urgently increase awareness among all healthcare workers in the ICU, investigate AMR in critically ill patients, as well as develop guidance for managing these patients (Table 4). We realize, however, that it may take time to realise these goals, whereas the problem of AMR requires our attention today. Here, we propose a number of immediately actionable interventions to combat AMR in the ICU (Fig. 3). These are simple, low-cost tools that should be adopted by the whole team, and can be implemented universally.

Conclusion

In conclusion, AMR is a severe and urgent public healthcare threat that requires global and multi-sectoral collaboration. We are not doing nearly enough to combat this imminent and dire danger. The world urgently needs new drugs to replace the antibiotics that are losing effectiveness, but we need to work on alternative strategies to reverse this trend and to provide a means to treat these pathogens. Although some promising antibiotics currently in phase 2 and 3 of development will soon be licensed and utilized in ICU, the continuous development of an alternative generation of compounds is extremely important. At the same moment, these newly developed antibiotics should be used prudently as development of resistance may be imminent once they are widely used for the indications they have been approved

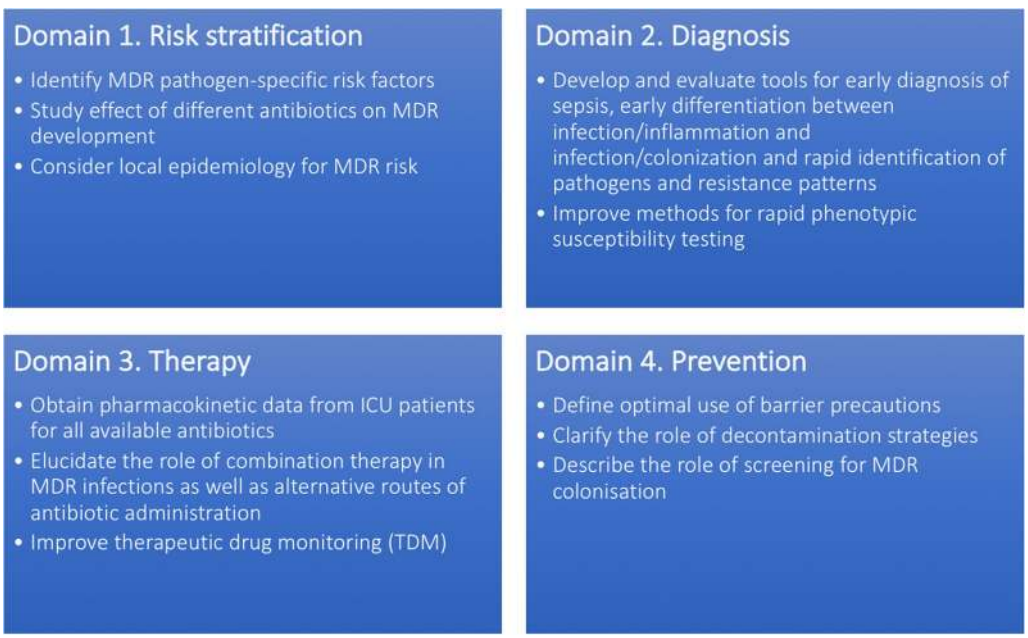

Fig. 2 Priorities in different domains for improved MDR management in the ICU

Table 4 Recommendations from the ESICM/ESCMID MDR round table panel

1.	To increase awareness among ICU health care workers, committing to making AMR a priority in guideline development and research activities
2.	To document the prevalence of Gram-negative AMR infection and colonization from a global perspective
3.	To develop guidance for clinical use on specific topics including antibiotic dosing in the ICU including the use of TDM, optimization of empirical treatment, the role of combination therapy for XDR/PDR pathogens, as well as de-escalation, duration of antibiotic therapy, barrier precautions and infection prevention
4.	To collect data on treatment and outcome of XDR/PDR infections including *Acinetobacter* spp., CRE and MDR *P. aeruginosa*
5.	To facilitate joint educational events on AMR
6.	To assemble a consortium for collaborative research on AMR in the ICU

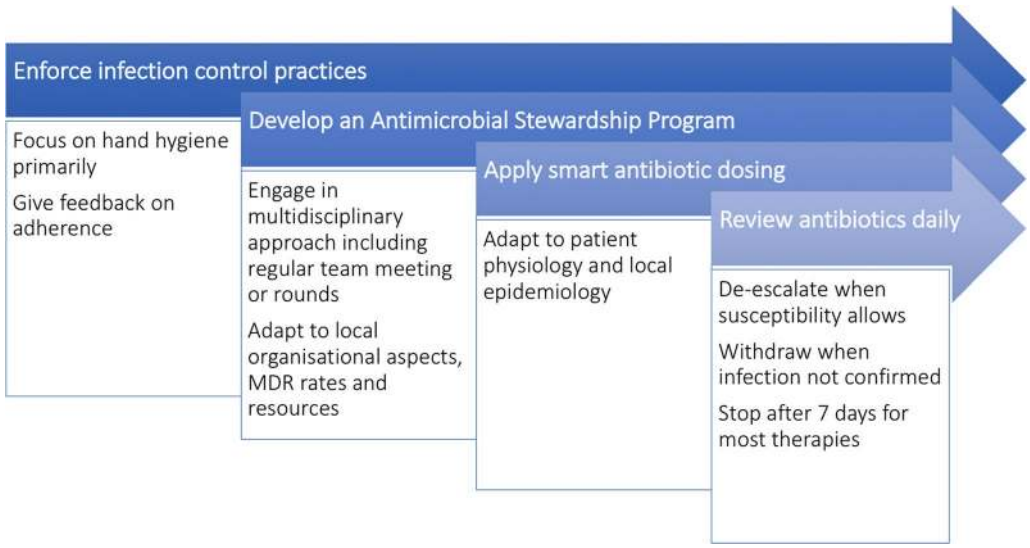

Fig. 3 Simple, immediately actionable interventions to tackle AMR in the ICU

instead of perfectly adequate "old" agents. Similarly, strategies that assist in early identification of MDR pathogens and targeted antibiotic use are urgently needed, in conjunction with ongoing efforts to avoid the spread of MDR in the ICU and beyond. To achieve these goals, an increased awareness of this menace among critical care health care workers is pivotal, with a heightened sense of urgency when it comes to tackling this problem in all its dimensions at the bedside. All considered, under these conditions—and only then—we believe that adequate treatment options for infections due to MDR microorganisms will remain available in the short term for most patients, and we are convinced that we will be able to better protect the critically ill from AMR in the future.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
Jan De Waele has consulted for Bayer Healthcare, Merck, and Pfizer. Murat Akova had received grants to support institutional research projects from Pfizer and MSD, and has participated accredited educational activities by Pfizer and Astellas. Massimo Antonelli received research grants from Orion, Toray, Pfizer and MSD, and received fees from GE, Maquet, Nihon Koden, Intersurgical and Orion for participation to International Boards. Rafael Canton has participated in educational programs sponsored by Angelini, AstraZeneca, Pfizer and MSD, and in research activities funded by AstraZeneca and MSD. Jean Carlet has participated in advisory boards with Beckton Dikinson, and has been a consultant for Cooper Alliance. George Dimopoulos has been a consultant for Bayer Healthcare, Merck, and Pfizer and Glenmark. José Garnacho-Montero has served as speaker for MSD, Astellas and has received research support from Astellas. Jozef Kesecioglu has received honorarium from Xenios AG. Jeff Lipman has consulted for Bayer and MSD. Mervyn Mer has participated in educational activities funded by MSD, Pfizer, Gilead, AstraZeneca, Sun Pharma. Jason Roberts has consulted for Astellas, bioMerieux and Bayer and has received investigator-initiated grant funding from MSD, Cardeas Pharma and The Medicines Company. Jesus Rodriguez-Bano has participated in research projects from AstraZeneca and InfectoPharm, and participated in accredited educational activities funded by Merck. Jean-Francois Timsit has participated in scientific boards of Bayer, Merck, Gilead, Paratek, Maat Pharma; the University Hospital of Jean-Francois Timsit received research grants from Merck, 3 M and Astellas and participated in advisory boards for 3 M, Merck, Gilead, Pfizer, Paratek, Bayer,. Jean-Ralph Zahar has consulted for Merck and Pfizer. The other authors state that they have no conflicts of interest. Matteo Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Gilead, Menarini, MSD, Pfizer, The Medicine Company, Tetraphase and Vifor.

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