



INFECTION AND DRUG RESISTANCE VOLUME 11 - 1011 - OPEN ACCESS

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/didr20

Optimizing antimicrobial therapy in critically ill patients

Virginie Vitrat, Serge Hautefeuille, Cécile Janssen, David Bougon, Michel Sirodot & Leonardo Pagani

To cite this article: Virginie Vitrat, Serge Hautefeuille, Cécile Janssen, David Bougon, Michel Sirodot & Leonardo Pagani (2014) Optimizing antimicrobial therapy in critically ill patients, Infection and Drug Resistance, , 261-271, DOI: 10.2147/IDR.S44357

To link to this article: https://doi.org/10.2147/IDR.S44357

9 © 2014 Vitrat et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution - Non Commercial (unported, v3.0) License



Published online: 20 Oct 2014.

Submit your article to this journal





View related articles



View Crossmark data 🗹



Citing articles: 1 View citing articles 🕑

Open Access Full Text Article

REVIEW

Optimizing antimicrobial therapy in critically ill patients

Virginie Vitrat¹ Serge Hautefeuille² Cécile Janssen¹ David Bougon² Michel Sirodot² Leonardo Pagani^{1,3}

¹Antimicrobial Stewardship Program, Infectious Diseases Unit, ²Intensive Care Unit, Annecy-Genevois Hospital Center (CHANGE), Annecy, France; ³Infectious Diseases Unit, Bolzano Central Hospital, Bolzano, Italy

Correspondence: Leonardo Pagani Infectious Diseases Unit, Bolzano Central Hospital, Via L. Boehler 5, I-39100, Bolzano, Italy Tel +39 0471 908131 Fax +39 0471 908552 Email Ipagani.id@gmail.com

submit your manuscript | www.dovepress.com

http://dx.doi.org/10.2147/IDR.S44357

Abstract: Critically ill patients with infection in the intensive care unit (ICU) would certainly benefit from timely bacterial identification and effective antimicrobial treatment. Diagnostic techniques have clearly improved in the last years and allow earlier identification of bacterial strains in some cases, but these techniques are still quite expensive and not readily available in all institutions. Moreover, the ever increasing rates of resistance to antimicrobials, especially in Gram-negative pathogens, are threatening the outcome for such patients because of the lack of effective medical treatment; ICU physicians are therefore resorting to combination therapies to overcome resistance, with the direct consequence of promoting further resistance. A more appropriate use of available antimicrobials in the ICU should be pursued, and adjustments in doses and dosing through pharmacokinetics and pharmacodynamics have recently shown promising results in improving outcomes and reducing antimicrobial resistance. The aim of multidisciplinary antimicrobial stewardship programs is to improve antimicrobial prescription, and in this review we analyze the available experiences of such programs carried out in ICUs, with emphasis on results, challenges, and pitfalls. Any effective intervention aimed at improving antibiotic usage in ICUs must be brought about at the present time; otherwise, we will face the challenge of intractable infections in critically ill patients in the near future.

Keywords: ICU, antimicrobial therapies, antimicrobial stewardship, pharmacokinetics, pharmacodynamics, antimicrobial resistance, early diagnosis

Early diagnosis of infection: new tools

Effective antimicrobial administration within the first hour of documented hypotension is associated with increased survival in patients with septic shock,¹ whereas inappropriate empirical antimicrobial therapy has been associated with a five-fold reduction in survival.² Rapid and accurate identification of bacterial species in blood cultures is therefore warranted to improve the management of these patients.³

Bacterial identification is routinely based initially on simple tests like Gram staining, catalase and oxidase tests. Subsequent phenotypic tests complete the identification. Although some of these tests are performed within minutes, complete identification is routinely achieved within 24 to 48 hours, but it may take several days for fastidious organisms. Blood cultures, which are the gold standard for the diagnosis of bloodstream infections, still need 48 to 72 hours for a complete identification.

However, two newer methods may allow an earlier identification of pathogens in patients with severe sepsis: 1) the use of protein profiles obtained by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) that allows rapid and accurate identification of bacteria as well as fungi directly from

Infection and Drug Resistance 2014:7 261-271

© 2014 Vitrat et al. This work is published by Dove Medical Press Limited, and licensed under Creative Commons Attribution — Non Commercial (unported, v3.0) permission from Dove Medical Press Limited, provided the work is properly attributed. Permissions beyond the scope of the License are administered by Dove Medical Press Limited, Information on how to request permission may be found at: http://www.dovepress.com/permissions/pp colonies; and 2) molecular biology tools that enable rapid bacterial identification using real-time polymerase chain reaction (RT-PCR).

In this review, we will not discuss biomarkers for the diagnosis of invasive infection, as they have been extensively investigated and relevant reviews have already been published.^{4,5}

MALDI-TOF-MS

Mass spectrometry is an analytical technique that produces spectra of the masses of the atoms or molecules constituting a sample of material. The principle of mass spectrometry is to detect the mass:charge ratio of a bioanalyte, providing its own specific spectrum. This method is used to profile microorganism proteins from cell extracts and allows identification of bacteria, yeasts, and filamentous fungi. The procedure provides a unique mass spectral fingerprint of the microorganisms. In practice, bacterial cells are spread across the well of a conductive metallic plate called "target". Each specimen is then covered with an appropriate "matrix", which creates a mixture with the analyte molecules. The target is then placed in the MALDI-TOF-MS machine, and brief laser pulses hit the mixture. The small desorbed and ionized molecules are accelerated through an electrostatic field, and drift through a field-free tunnel until they reach the mass spectrometer detector. Molecules of different masses and charges will fly at different speeds ("time-of-flight"). The result is a spectral signature, with specific spikes. This signature is then searched for in a database for the identification of the microorganism.6

This method needs a minimal amount of labor compared with conventional methods,⁷ and different studies confirm the excellent results obtained by this technology.^{8–10}The time necessary for the identification in blood is less than 5 minutes,^{7,11} and this technique can be extended to other biological fluids such as cerebrospinal fluid¹² or urine.¹³

The most widespread application of MALDI-TOF-MS is bacterial identification from bacterial colonies, and one main interest is the identification of anaerobes and other fastidious organisms, which are poorly identified by current phenotypic methods. However, a major current limitation is failure to accurately identify *Streptococcus pneumoniae*. Erroneous identifications were also obtained for some strains of *Stenotrophomonas maltophilia*, *Propionibacterium acnes*, and *Shigella* spp.⁹ Moreover, when the infection is due to several bacterial species, only the most abundant germ detected by Gram staining is identified by MALDI-TOF-MS.¹¹ The difficulty in identifying polymicrobial cultures by this method

underscores the importance of continued reliance on Gram stain and subcultures for definitive identification.

MALDI-TOF-MS is a rapid and precise method for identification of bacteria, compared to conventional phenotypic techniques. It is expected to become a widely used technique in routine clinical laboratories for bacterial identification, replacing other phenotypic techniques.

RT-PCR

RT-PCR has been developed in order to rapidly detect pathogens.¹⁴ After a first step of extraction and purification of deoxyribonucleic acid (DNA), this method can detect several target pathogens. This promising technology is obviously of interest in order to quickly identify the pathogen of patients with severe sepsis or septic shock. RT-PCR combines amplification and detection of amplified products in a unique reaction. It is based on amplification of the 16S or 23S ribosomal ribonucleic acid gene, which is present in all bacteria. A positive detection is recorded if the fluorescent signal emitted by internal hybridization probes reaches the threshold; subsequently, a melting curve analysis proceeds to identify the species.¹⁴

This technique is the most promising for the routine diagnosis of bloodstream infections in clinical microbiology laboratories because it is based on amplification of the internal transcribed spacer. This non-coding region of the ribosomal DNA is localized among highly conserved genes, shows a high level of heterogeneity among bacterial genera and species, and allows a high level of identification using a limited pool of slightly degenerated primers.¹⁵

The obvious advantage of RT-PCR in the intensive care unit (ICU) is to obtain a result in whole blood quicker than conventional blood culture. This technology could give valuable information to the clinician in order to adapt antimicrobial therapy rapidly in the ICU.

However, RT-PCR technologies have a number of limitations which restrict their applicability. The sensitivity of universal RT-PCR is lower than that of many species-specific RT-PCRs. A major issue is the restricted panel of pathogens. In a meta-analysis conducted by Chang et al, who enrolled 34 studies with 6,012 patients with suspected sepsis, the tool showed a positive post-test probability of 80% but a negative post-test probability of 5% including bacteremia and fungi.¹⁶

Another issue is the work time required for RT-PCR in the real-life setting. Although results are obtained within 6 hours, the technique requires a level of expertise that is not usually available around the clock. The time to the final result in clinical settings may therefore be significantly longer.¹⁷ At this time, the delay in real-life settings makes the clinical usefulness of the RT-PCR test for rapid diagnosis questionable. Last, PCR detects DNA rather than living microorganisms. A positive RT-PCR signal in the presence of a negative blood culture can be challenging, making the results difficult to interpret.¹⁴

New technologies such as MALDI-TOF-MS and RT-PCR have appeared over the last 10 years. MALDI-TOF-MS is a reliable tool and has become a widely used technique in routine clinical laboratories. RT-PCR is a promising tool, considering the ability to detect and identify pathogens without any previous culture. Nevertheless, RT-PCR remains expensive, has a limited panel of pathogens for the moment, and should be used paired with conventional blood culture. Prospective studies are warranted in order to assess specifically the benefits and drawbacks of these tools in the clinical management of patients with infection in the ICU.

The global threat of multi-drug resistant Gram-negative pathogens

The ICU population is highly susceptible to colonization and infection by pathogens with reduced antimicrobial susceptibility or resistance. In addition, the host response to infection may be significantly impaired by acute illness, altered immune function or underlying co-morbidities. Given the high rates of infection-related morbidity and mortality in patients with septic shock, prompt antimicrobial therapy along with infection source control and supportive care are important determinants of the clinical outcome.

ICU physicians are challenged by the threats of multi-drug resistant (MDR) organisms or extensively or pan-drug resistant (XDR) strains, especially among Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii.¹⁸⁻²⁰ In some countries or geographical areas, the epidemic spread of such strains endangers the possibility of curing critically ill patients with infection.²¹ As a matter of fact, the increasing prevalence of MDR organisms within ICUs has caused physicians to broaden the spectrum of antimicrobials used, at least for empirical therapy, with the direct consequence of promoting the emergence of new resistance patterns.²² However, resistance mechanisms are not superimposable from a clinical point of view, and knowledge of them should prompt ICU physicians to streamline treatment as soon as possible, targeting the causative pathogen with an effective drug with the least selection pressure on the environment.

Surveillance of local epidemiology is obviously of paramount importance in ICUs to monitor resistance rates and adapt empirical treatment accordingly. The main mechanisms conferring resistance to β -lactams among *Enterobacteriaceae* are alteration of the penicillin-binding protein; increased active efflux; and reduced or absent expression of outer membrane receptor and β -lactamase enzymes. These enzymes have within their active site either a serine group (serine- β -lactamases) or metallic ions (Zn²⁺) (metallo- β -lactamases [MBLs]), and these active site inclusions are the most important mechanism of β -lactam resistance in *Enterobacteriaceae*.

Extended-spectrum β -lactamases

Extended-spectrum β -lactamases (ESBLs) are molecular class A enzymes, and are able to hydrolyze all the oxymino-cephalosporins (cefotaxime, ceftriaxone, cefuroxime, ceftazidime, and cefepime) and monobactams, but not carbapenems and cephamycins (cefoxitin and cefotetan). TEM, SHV, and CTX-M types, among others, belong to this class of hydrolyzing enzymes.^{23–25}

This kind of enzyme is inactivated by β -lactamase inhibitors such as clavulanic acid, tazobactam, or sulbactam (whilst kinds of high-level cephalosporinases [AmpC] are not). The major importance of ESBLs resides in their ability to efficiently spread among *Enterobacteriaceae* through different transmission mechanisms, with epidemic diffusion not only in nosocomial strains, but also in the community.²⁶

Strains harboring ESBLs are frequently resistant to several antimicrobial classes (fluoroquinolones and aminoglycosides). Amoxicillin/clavulanic acid, piperacillin/tazobactam, or carbapenems (mostly ertapenem) should be considered the treatment of choice according to the site of infection.²³

Cephalosporinases (AmpC)

AmpC cephalosporinases are enzymes hydrolyzing penicillins, cephalosporins, and cephamycins, whereas cefepime and cefpirome are resistant to hydrolysis. These enzymes may be chromosomal or transferable, constitutive or inducible.²⁷ One important risk is represented by the fact that empirical treatment with third-generation cephalosporins induces derepression of AmpC during therapy, especially in *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Morganella morganii, Proteus vulgaris*, and *Providencia* spp., and these strains may develop complete resistance to cephalosporins within 3–4 days of treatment as a consequence.²⁸ Overall, AmpC cephalosporinases are able to inactivate penicillins (except temocillin), third-generation cephalosporins and cephamycins; show variable activity on aztreonam; and are inhibited by cefepime²⁹ and cefpirome, by β -lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) and carbapenems. It has recently been shown that cefepime should be considered a drug of choice against pathogens carrying cephalosporinases, in order to limit the use of carbapenems and avoid consequent selection pressure.²⁹ Clinical relevance relies on the possible selection of constitutive mutants during therapy and the possibility of cross-resistance with other antimicrobial classes.

Carbapenemases

Carbapenem-resistant Enterobacteriaceae are increasingly prevalent in many parts of the world.^{30,31} It should be remarked that resistance to carbapenems is not always associated with the presence of carbapenemases; resistance to carbapenems, indeed, may be driven by two main mechanisms: 1) membrane impermeability and 2) carbapenemases. Impermeability yields to decreased susceptibility to carbapenems because of lack of porins in the outer membrane, leading to low-level resistance to carbapenems and higher minimum inhibitory concentration (MIC) only to ertapenem. Normally, MDR to other antimicrobial classes is atypical. Enterobacter cloacae is the primary carrier of this phenotype.³² True carbapenemases, on the other hand, may be either serine- β -lactamases or MBLs, showing low to high level of resistance that often translates also into MDR (aminoglycosides, fluoroquinolones), and may be detected in various strains of Enterobacteriaceae; they usually show a true increased MIC to imipenem (and ertapenem as well).

Most carbapenemase producers are almost completely resistant to β -lactam antibiotics, except those with OXA-48 alone, which remain susceptible to several cephalosporins.³³ Serine-carbapenemases belong to A or D molecular class; class As are inhibited by clavulanic acid and tazobactam, and therefore remain clinically susceptible to amoxicillin/clavulanic acid or piperacillin/tazobactam. Both may be chromosomal or plasmidic, or even inducible, and ertapenem is used to screen their presence, as it is the most sensitive carbapenem to these enzymes.³⁴ MBLs may be either chromosomal or plasmidic and are resistant to β -lactamase inhibitors, third- and fourthgeneration cephalosporins and display elevated MIC to carbapenems; however, MBLs remain susceptible to aztreonam: monobactams are therefore the first-line treatment in case of infection sustained by MBL-producers.34 Evidence of resistance to aztreonam implies that ESBLs or AmpCs are also present in the same strain.³⁵ All the main features of carbapenemases have been recently reviewed by Patel and Bonomo.36

Klebsiella pneumoniae carbapenemaseproducing Enterobacteriaceae

Since the beginning of 2000, *K. pneumoniae* carbapenemaseproducing (KPC) *Enterobacteriaceae* have been increasingly detected in several regions worldwide and in some of them, such as in Israel and in Greece, they have become endemic.^{37–39} Moreover, bla-KPC genes are easily transferable and are often linked with various non- β -lactam resistance determinants, further compromising the therapeutic alternatives for clinically significant infections. Clinical reports have already documented that hospital infections due to KPC are commonly associated with increasing therapeutic failure⁴⁰ and mortality.^{41,42}

KPC enzymes confer various levels of resistance to all β -lactams, including carbapenems. However, optimized carbapenem dosing has been shown to be effective in overcoming resistance to some extent.⁴³ Concomitant aminoglycoside resistance is extensive but variable, as is resistance for multiple classes. Susceptibility testing data suggest that treatment of infections caused by KPC requires the use of tigecycline or colistin as last-resort drugs, often associated with carbapenem, fosfomycin, or rifampin.^{40,44} The ever-changing scenario about KPC and potential XDRresistant Gram-negative pathogens, such as *A. baumannii* and *P. aeruginosa*, as well as their potential treatment options with different drug cocktails, will not herein be reviewed, as detailed reviews have been recently published.^{44–49}

The treatment in ICUs of acute infection from MDR germs and XDR germs needs a good understanding and knowledge of the local ecology. The prudent use of antibiotics, mainly those used as last-resort treatment, like carbapenems, is of utmost importance in order to prevent increasing pressure that may lead to the emergence of highly resistant strains. Furthermore, appropriate antimicrobial therapy must consider the significant pathophysiological changes associated with critical illness that may alter the pharmacokinetics (PK) (eg, increased volume of distribution [Vd], augmented clearance [CL]) and therefore dosing in this patient population (see the "Principles and practice of β-lactam pharmacokinetics/pharmacodynamics in ICUs" section). The development of new antibiotics effective against drug-resistant bacteria remains important, but optimized use of available ones based on local surveillance data and specific pharmacologic characteristics may allow improving clinical outcome and lessening selection pressure. However, any intervention in ICUs aimed at improving antimicrobial prescription practices should not leave aside infection control and prevention procedures, whose usefulness has been clearly established in containing the spread of antimicrobial resistance in such a critical setting.50

Principles and practice of β-lactam pharmacokinetics/ pharmacodynamics in ICUs

Although selecting the appropriate antimicrobial in terms of spectrum of activity is certainly the mainstay of antimicrobial therapy in critical ill patients, the choice of correct dose and dosing is also very important in ensuring clinical cure and microbiological eradication. β -lactam antibiotics are among the first-line therapies for critically ill patients, because of their large antimicrobial spectrum and low toxicity. β-lactams are time-dependent antimicrobials whose activity is mainly related to the duration of time the free drug level exceeds the pathogen MIC (T > MIC). A T > MIC of 100% of the dosage interval should be a theoretical target for β -lactams.^{51–53} For carbapenems, which have a longer post-antibiotic effect, a bactericidal effect is observed for a T > MIC of 40%. Further improvement in efficacy has been observed when concentrations four- to five-fold greater than the MIC are achieved for prolonged time periods during each dosing interval (100% T >4-5× MIC).54-56

T > MIC is dependent on drug half-life and serum concentration, which in turn depends on the dose delivered and its Vd. β -lactams are hydrophilic drugs with a low Vd, a low intracellular penetration, and predominant renal CL.⁵¹ In septic patients, Vd may be increased because of a capillary leak syndrome, hypoalbuminemia, and therapeutic procedures (fluid replacement, mechanical ventilation, extracorporeal circuits, surgical drains).^{57,58} Increased Vd reduces drug concentration, but might increase the half-life if the CL remains unchanged.⁵⁹ Hypoalbuminemia increases the unbound fraction of the drug and consequently its Vd and CL.^{60,61}

Renal CL of antibiotics depends on renal function. In septic patients without significant organ dysfunction, there is often an increased renal perfusion (massive fluid infusions, use of vasopressor agents) and consequently increased creatinine $CL(CL_{CR})$ and elimination of hydrophilic antibiotics. The incidence of augmented renal CL (ARC) is high and varies between 30% and 85% depending on the studied population and the cut-off used for its definition.62-65 In septic and trauma patients, ARC defined as a $CL_{CR} \ge 130 \text{ mL/min}/1.73 \text{ m}^2 \text{ was}$ observed in 57.7% of the patients with a higher prevalence in trauma (85.7%) than in septic patients (39.5%). Young $(\leq 50 \text{ years of age})$ trauma patients, without significant organ dysfunction (modified Sequential Organ Failure Assessment score ≤ 4) appear to be at greater risk of ARC. ARC appears to be an important predictor of subtherapeutic β -lactam concentrations. In the study by Udy et al,⁶⁴ CL_{CP} values $\geq 130 \text{ mL/min}/1.73 \text{ m}^2$ were associated with

 β -lactam trough concentrations less than MIC in 82% and less than 4× MIC in 72% of cases, and multivariate modeling confirmed CL_{CR} as a significant covariate for predicting low trough concentrations. Carlier et al⁶⁶ also found that ARC was associated with a higher risk of not attaining PK/ pharmacodynamics (PD) targets even when administering β -lactams through extended infusion. In the study by Casu et al,⁶⁷ the proportion of patients with insufficient β -lactam concentrations progressively increased with the increasing of CL_{CR} , reaching >50% when CL_{CR} exceeded 120 mL/ min. If β -lactam PK is significantly correlated with CL_{CP} , β -lactam PK changes are not predicted by CL_{CP} changes, and dosing adjustment could not be reliably adapted to changes in renal function alone. Moreover, in the critically ill patient there is no readily available method to measure accurately the glomerular filtration rate⁶⁸ and the derived estimates of glomerular filtration (Modification of Diet in Renal Disease and Cockcroft-Gault formulae) significantly underestimate the measured CL_{CR} in patients with ARC.⁶⁹ Renal replacement therapies (RRTs) are very efficient in removing hydrophilic antibiotics, especially those with low protein binding. The amount of antibiotic eliminated will depend on the type and dose of RRT delivered, blood flow rate, filter material, and surface area.^{70–72} As the loading dose mainly depends on the Vd and is unaffected by RRT, an increase of the initial dose may be required in critically ill patients.73 Trotman et al74 formulated recommendations for antibiotic dosing in critically ill patients receiving continuous RRT (CRRT) with an ultrafiltration rate of 1 L/h or a dialysate flow rate of 1 L/h and no residual renal function.75 In the study of Roberts et al,⁷⁶ 30.6% of patients receiving CRRT (dialysis flow rate of 1,000 mL/h and ultrafiltration rate of 2,000 mL/h) achieved target concentrations, 19.4% required a dose increase, and 50% a dose decrease. With empirical dosing, Roberts et al⁷⁷ reported a significant variability in β-lactam trough concentrations in patients receiving CRRT, with no correlation with the efflux flow rate (25 or 40 mL/kg/h). The lower therapeutic target (100% T > MIC) was achieved in 100% of patients, but the higher target (100% T >4× MIC) was achieved only in 76% of patients for meropenem and 86% for piperacillin.

Antimicrobial target concentration attainment in the infected tissue is also an important determinant of clinical outcome. The plasma concentration of unbound antibiotic is predictive of interstitial tissue fluid concentration,⁵² but in critically ill patients, distribution of antibiotics in tissue may be substantially impaired, and a discrepancy between plasma and interstitial fluid level may occur.⁷⁸ In septic shock

patients, piperacillin concentrations in the interstitium of soft tissues (skeletal muscle, subcutaneous fat tissue), as evaluated by microdialysis, have been found five- to ten-fold lower than free plasma concentrations, and several-fold lower than in a control group of healthy volunteers.⁷⁹ The tissue penetration of cefpirome is also significantly impaired in septic patients compared with that in healthy subjects.⁸⁰

β-lactams should be more effective when delivered by continuous infusion after a loading dose to reach a steady state more rapidly, or by extended infusion if the drug is unstable once reconstituted at room temperature.^{81,82} A recent study confirms that continuous administration of β-lactams in severe sepsis produces higher plasma and interstitial fluid antibiotic concentration than intermittent administration, with significant improvement in clinical cure.⁸³ The available evidence from mainly nonrandomized studies suggests also that extended or continuous infusion of carbapenem or piperacillin/tazobactam is associated with lower mortality (relative risk, 0.59; 95% confidence interval, 0.41–0.83), and this difference in mortality was higher in patients with pneumonia (relative risk, 0.50; 95% confidence interval, 0.26–0.96).⁸⁴

As mentioned above, PK properties of β-lactams in ICU patients may be profoundly altered due to the dynamic and unpredictable pathophysiological changes that occur in severe sepsis.⁸⁵ Therapeutic drug monitoring (TDM) may be useful to improve β -lactam dosing, as any assumptions about drug concentrations are unreliable, and dose-effect relationships are rather unpredictable in this setting. Targeting a 100% T $>4-5\times$ MIC attainment, Roberts et al⁷⁶ reported that dose adjustment was required in 175 (74.2%) of the ICU patients, 50.4% requiring dose increase after the first TDM, and 23.7% required dose decrease. In 92 ICU patients, Aubert et al⁸⁶ reported that the serum ceftazidime concentration was $<5\times$ MIC of the targeted pathogen in 15.7% of patients, and with a target of 40±10 mg/L (P. aeruginosa breakpoint MIC of 8 mg/L), the serum level was insufficient in 36.9% and excessive in 27.2% of patients. These studies support both the need for adjusting dosing and the major role of TDM in tailoring antimicrobial therapy in critically ill patients whenever possible. However, the positive impact of β -lactam TDM on clinical outcome remains to be assessed in randomized controlled clinical trials.

Usefulness and pitfalls of antimicrobial stewardship programs in ICUs

Antimicrobial stewardship programs (ASPs) are multidisciplinary programs whose primary aim is to optimize antibiotic use (improve clinical outcomes; minimize the untoward effects of antimicrobial use, and selection of resistant pathogens; and reduce ICU length of stay and costs). As detailed in the antimicrobial stewardship guidelines from the Infectious Diseases Society of America,⁸⁷ ASPs usually include several strategies: educational programs, implementation of guidelines, prospective audit and feedback, antibiotics formulary restriction (preauthorization), computer-assisted decision and prescription, PK/PD optimization, de-escalation, shortened antibiotic treatment, prevention of patient-to-patient transfer of resistant microorganisms, and intravenous-to-oral conversion. We will briefly review the main available studies on ASPs in ICUs, with their strategy and endpoints, and discuss pitfalls.

Several studies have demonstrated that ASPs consistently reduce antimicrobial use. Global reduction in antimicrobial consumption ranged from 22% to 36%.88-90 Ng et al91 showed that antibiotic restriction could reduce consumption of restricted antibiotic (by 47.2%) but interestingly, it also decreases consumption of non-restricted antibiotics (by 7.9%). This is an important point, as reduction in antibiotic prescription is correlated to reduction in antimicrobial resistance. Accordingly, Carling et al,⁸⁸ in a 7-year study, evaluated the impact of an interventional multidisciplinary ASPs on vancomycin-resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus, and Clostridium difficile through minimization of third-generation cephalosporin use. They showed a 22% decrease (P < 0.0001) of intravenous broadspectrum antibiotics use and a significant decrease in nosocomial infections caused by C. difficile (P=0.002) or resistant Enterobacteriaceae (P=0.02). However, prevalence of VRE and S. aureus did not change significantly. Another pitfall of antibiotic restriction is that resistance decrease is often transitory, even with multimodal ASPs, as described by Slain et al.92 They indeed evaluated the impact of a multimodal ASP on P. aeruginosa resistance and showed a decrease between a pre-2004 and post-2007 ASP period concerning intravenous ciprofloxacin and ceftazidime use, correlated with a significant decrease in ciprofloxacin-resistant P. aeruginosa prevalence. Unfortunately, in this study, the ciprofloxacin resistant rate increased to 47.6% in 2010, and it seems difficult to maintain prolonged low bacterial resistance rate.

ASP could also impact not only on quantity but also on quality of antimicrobial prescription and justification of antimicrobial regimen choice. Katsios et al⁹³ evaluated the antimicrobial treatment of positive clinically relevant culture in a mixed ICU over 2 months before and after ASP implementation. In the post-ASP period, they showed a significant increase in the treatment of sterile site cultures (64% pre-ASP versus [vs] 83% post-ASP, P=0.01), and a reduction in the treatment of non-sterile site cultures (which may represent colonization or contamination) (71% pre-ASP vs 46% post-ASP, P=0.0002). They also showed that ASPs improved documentation of antimicrobial use in the medical record (26% pre-ASP vs 71% post-ASP, P<0.0001). Moreover, strategies employed in this study did not use formulary restriction, and did preserve prescriber autonomy.

Table	I Summai	y of main	studies	on ASPs	in ICUs
-------	----------	-----------	---------	---------	---------

Other authors showed that antimicrobial restriction (formulary restriction with prior authorization) not only decreased bacterial resistance, but also improved patient outcome (length of stay), especially considering ICU patients. Gentry et al⁹⁴ developed a stewardship program which used the core strategy of formulary restriction with prior authorization (combined with protocol development and one-on-one education of physicians). Comparing pre- and post-ASP periods, they showed a significantly decreased length of stay, down

Authors	Study design	Strategy/procedure	Study results
Slain et al ⁹²	Pre-/post-intervention	Multimodal ASP	- Reduction of intravenous ciprofloxacin use and ceftazidime
	Observational study ICU		- Transitory decrease in Pseudomonas aeruginosa resistance
Carling et al ⁸⁸	Pre-/post-intervention (7 yrs) Observational study All units	Multimodal ASP	 Significant decrease of parenteral broad-spectrum antibiotics Decrease in nosocomial infections by <i>Clostridium difficile</i> or resistant <i>Enterobacteriaceae</i> No impact on VRE and MRSA prevalence
Katsios et al ⁹³	Pre-/post-intervention Observational study ICU 269 patients	Multimodal ASP	 Microbiologically-targeted therapy (treatment of positive sterile sites > non-sterile sites) Reduction in cost and DDDs
Rimawi et al ¹⁰²	Pre-/post-intervention Observational study ICU 246 patients	Education, prescription review	 Significant reduction in extended-spectrum antibiotics, carbapenem, vancomycin, metronidazole Better adherence to guidelines Reduction in mechanical ventilation days, length of stay, and costs Reduction in mortality
Kim et al%	Open-label randomized Monocentric ICU 109 patients	De-escalation in VAP	 No statistical difference in length of stay, 14-day and 28-day mortality Multivariate analysis: emergence of MRSA was significantly higher in de-escalation group vs non de-escalation group
Garnacho- Montero et al ⁹⁷	Prospective observational study in ICU 628 patients	De-escalation	– Reduction in hospital mortality and 90-day mortality
Ng et al ⁹¹	Pre-/post-intervention Observational study All units	Antibiotic restriction	 Decrease in restricted and non-restricted antibiotic consumption
Gentry et al ⁹⁴	Pre-/post-intervention Observational study ICU	Antibiotic restriction	 Reduced length of stay No difference in mortality rate
Rahal et al ⁹⁵	Pre-/post-intervention Observational study ICU All units sub-study	Antibiotic restriction	 Significant decrease in resistant Klebsiella spp. Increase in imipenem use and incidence of imipenem- resistant P. aeruginosa
Jain et al ¹⁰³	Pre-/post-intervention 196 ICUs 2 million patients	Barrier precautions	- Decrease in infections caused by MRSA and other pathogens
Huskins et al ¹⁰⁴	18 ICUs 9,000 patients	Barrier precautions	 No effect on colonization or infection rates
Huang et al ¹⁰⁵	All units 501 patients	Multimodal ASP combined with MALDI-TOF-MS	 Improved time to effective and optimal antibiotic therapy Decreased mortality, length of stay in ICU, and recurrent bacteremia

Note: Study results in bold type represent the only studies showing a decrease in mortality as the major outcome indicator.

Abbreviations: ASP, antimicrobial stewardship program; ICU, intensive care unit; yrs, years; VAP, ventilator-associated pneumonia; MALDI-TOF-MS, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; VRE, vancomycin-resistant enterococci; MRSA, methicillin-resistant *Staphylococcus aureus*; DDDs, defined daily doses; vs, versus.

from 13.2±15.3 to 10.8±12.7 days (P < 0.0001), especially in the subgroup of ICU patients (from 15.0±14.4 days to 12.8±16.7 days, P=0.0004). Readmission rate within 30 days and mortality were not significantly affected. However, in the study by Rahal et al,⁹⁵ even though the restriction of cephalosporin use was associated with significant decrease in the development of resistant *Klebsiella* spp., imipenem/ cilastatin use increased 141% during the study period and was accompanied by a 69% increase in the incidence of imipenem-resistant *P. aeruginosa*, as confirmed also by Tam et al.²² Moreover, antibiotic restriction strategies with preauthorization require availability of personnel to approve the use of the antimicrobial, which could lead to delayed treatment administration in critically ill patients with potential unintended consequences.

Only one randomized study (open-label monocentric study) evaluated the impact of broad-spectrum antibiotic followed with de-escalation vs no de-escalation.⁹⁶ There was neither statistical difference in length of stay, nor in 14and 28-day mortality between the two groups. Interestingly, Garnacho-Montero et al⁹⁷ prospectively evaluated the impact on in-hospital mortality and 90-day mortality of de-escalation therapy in patients admitted to the ICU with severe sepsis or septic shock. De-escalation was applied in 219 patients (34.9%). De-escalation therapy was also a protective factor for 90-day mortality, even after a strict adjustment for confounding variables including baseline characteristics and severity of illness on the day of culture results.

As a matter of fact, no randomized controlled trials or well-done observational studies have assessed the clinical impact of de-escalation strategy in critically ill patients with severe sepsis or septic shock until recently. Indeed, observational studies that assessed de-escalation in episodes of hospital-acquired severe sepsis show that this strategy was accomplished in only 50% of the cases,⁹⁸ even in microbiologically confirmed episodes (bacteremia) where de-escalation occurred in 39% to 81% of cases.⁹⁹ All the relevant studies concerning ASPs in the ICU are summarized in Table 1.

To limit the spread of antimicrobial resistance, practitioners should be aware of prevention of patient-to-patient transfer of resistant microorganisms. Indeed, it has been shown that 31% of cases of imipenem-resistant *P. aeruginosa* acquisition among patients in medical and surgical ICUs were due to patient-to-patient transfer of organisms, whereas only 19% of the cases were thought to be due to acquisition from the endogenous flora.¹⁰⁰ The combination of a comprehensive infection control strategy and an effective ASP may lead to the prevention of emergence and transmission of resistant pathogens. Hand hygiene promotion, barrier precautions, and environmental decontamination should be the cornerstones of this strategy.

To summarize, ASPs should promote the optimal use of antimicrobial therapy, leading to the best clinical outcome for patients. The relative paucity of outcome data demonstrating the benefits of antimicrobial stewardship is likely due to its infancy: according to George and Morris,¹⁰¹ ASPs today are where infection control programs were roughly 30 years ago. ASPs should be multidisciplinary, taking advantage of expertise from intensivists, infectious disease specialists, microbiologists, and pharmacists, and new tools, such as PK/PD-driven dosing, should be the next step of ASPs in the ICU.

Conclusion

Optimizing antimicrobial therapy in critically ill patients with suspected or proven infections remains a challenge. Joint efforts by different professionals should concur to this aim. Ever-improving diagnostic techniques must be paralleled by the consciousness that any antimicrobial prescription today will impact on further prescriptions tomorrow, and that the extraordinary progress of ICU medicine should not be frustrated by the impossibility of treating infections in critically ill patients.

Disclosure

The authors report no conflicts of interest in this work.

References

- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6): 1589–1596.
- Kumar A, Ellis P, Arabi Y, et al; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*. 2009;136(5):1237–1248.
- Trenholme GM, Kaplan RL, Karakusis PH, et al. Clinical impact of rapid identification and susceptibility testing of bacterial blood culture isolates. *J Clin Microbiol.* 1989;27(6):1342–1345.
- 4. Dupuy AM, Philippart F, Péan Y, et al; Maurice Rapin Institute Biomarkers Group. Role of biomarkers in the management of antibiotic therapy: an expert panel review: I – currently available biomarkers for clinical use in acute infections. *Ann Intensive Care*. 2013;3(1):22.
- Quenot JP, Luyt CE, Roche N, et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy. *Ann Intensive Care*. 2013;3(1):21.
- Emonet S, Shah HN, Cherkaoui A, Schrenzel J. Application and use of various mass spectrometry methods in clinical microbiology. *Clin Microbiol Infect*. 2010;16(11):1604–1613.
- La Scola B, Raoult D. Direct identification of bacteria in positive blood culture bottles by matrix-assisted laser desorption ionisation time-offlight mass spectrometry. *PloS One*. 2009;4(11):e8041.

- Neville SA, Lecordier A, Ziochos H, et al. Utility of matrix-assisted laser desorption ionization-time of flight mass spectrometry following introduction for routine laboratory bacterial identification. J Clin Microbiol. 2011;49(8):2980–2984.
- Seng P, Drancourt M, Gouriet F, et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *Clin Infect Dis.* 2009;49(4):543–551.
- Blondiaux N, Gaillot O, Courcol R-J. [MALDI-TOF mass spectrometry to identify clinical bacterial isolates: evaluation in a teaching hospital in Lille]. *Pathol Biol (Paris)*. 2010;58(1):55–57. French.
- Ferroni A, Suarez S, Beretti JL, et al. Real-time identification of bacteria and Candida species in positive blood culture broths by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol.* 2010;48(5):1542–1548.
- Nyvang Hartmeyer G, Kvistholm Jensen A, Böcher S, et al. Mass spectrometry: pneumococcal meningitis verified and *Brucella* species identified in less than half an hour. *Scand J Infect Dis.* 2010;42(9):716–718.
- Ferreira L, Sánchez-Juanes F, González-Avila M, et al. Direct identification of urinary tract pathogens from urine samples by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol.* 2010;48(6):2110–2115.
- 14. Chang SS, Hsieh WH, Liu TS, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis a systemic review and meta-analysis. *PLoS One.* 2013;8(5):e62323.
- Mancini N, Carletti S, Ghidoli N, Cichero P, Burioni R, Clementi M. The era of molecular and other non-culture-based methods in diagnosis of sepsis. *Clin Microbiol Rev.* 2010;23(1):235–251.
- Chang SS, Hsieh WH, Liu TS, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis – a systemic review and meta-analysis. *PloS One*. 2013;8(5):e62323.
- Dierkes C, Ehrenstein B, Siebig S, Linde HJ, Reischl U, Salzberger B. Clinical impact of a commercially available multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis. *BMC Infect Dis.* 2009;9:126.
- Hirsch EB, Tam VH. Impact of multidrug-resistant *Pseudomonas* aeruginosa infection on patient outcomes. *Expert Rev Pharmacoecon Outcomes Res.* 2010;10(4):441–451.
- Zarrilli R, Pournaras S, Giannouli M, Tsakris A. Global evolution of multidrug-resistant Acinetobacter baumannii clonal lineages. *Int J Antimicrob Agents*. 2013;41(1):11–19.
- 20. Falagas ME, Maraki S, Karageorgopoulos DE, Kastoris AC, Mavromanolakis E, Samonis G. Antimicrobial susceptibility of multidrugresistant (MDR) and extensively drug-resistant (XDR) Enterobacteriaceae isolates to fosfomycin. *Int J Antimicrob Agents*. 2010;35(3):240–243.
- 21. Kontopidou F, Giamarellou H, Katerelos P, et al; Group for the Study of KPC-producing *Klebsiella pneumoniae* infections in intensive care units. Infections caused by carbapenem-resistant *Klebsiella pneumoniae* among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options. *Clin Microbiol Infect*. 2014;20(2):O117–O123.
- Tam VH, Hirsch EB, Lasco TM, Gentry LO, Palmer HR. Correlation of hospital carbapenem consumption and resistance trends in selected gramnegative bacteria. *Ann Pharmacother*. 2012;46(7–8):1120–1122.
- Livermore DM. Defining an extended-spectrum beta-lactamase. Clin Microbiol Infect. 2008;14(Suppl 1):3–10.
- Livermore DM, Canton R, Gniadkowski M, et al. CTX-M: changing the face of ESBLs in Europe. JAntimicrob Chemother. 2007;59(2):165–174.
- Rossolini GM, D'Andrea MM, Mugnaioli C. The spread of CTX-M-type extended-spectrum beta-lactamases. *Clin Microbiol Infect*. 2008;14(Suppl 1):33–41.
- Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol Rev.* 2005;18(4):657–686.
- Babic M, Hujer AM, Bonomo RA. What's new in antibiotic resistance? Focus on beta-lactamases. *Drug Resist Updat*. 2006;9(3):142–156.
- Hanson ND. AmpC beta-lactamases: what do we need to know for the future? JAntimicrob Chemother. 2003;52(1):2–4.

- Tamma PD, Girdwood SCT, Gopaul R, et al. The use of cefepime for treating AmpC β-lactamase-producing Enterobacteriaceae. *Clin Infect Dis.* 2013;57(6):781–788.
- 30. Brink AJ, Coetzee J, Corcoran C, et al. Emergence of OXA-48 and OXA-181 carbapenemases among Enterobacteriaceae in South Africa and evidence of in vivo selection of colistin resistance as a consequence of selective decontamination of the gastrointestinal tract. *J Clin Microbiol*. 2013;51(1):369–372.
- Hirsch EB, Chang KT, Lasco TM, Caeiro JP, Tam VH. Emergence of KPC-producing *Klebsiella pneumoniae* in Texas. *Diagn Microbiol Infect Dis.* 2011;69(2):234–235.
- 32. Cornaglia G, Akova M, Amicosante G, et al; ESCMID Study Group for Antimicrobial Resistance Surveillance (ESGARS). Metallobeta-lactamases as emerging resistance determinants in Gram-negative pathogens: open issues. Int J Antimicrob Agents. 2007;29(4):380–388.
- Walther-Rasmussen J, Høiby N. OXA-type carbapenemases. JAntimicrob Chemother. 2006;57(3):373–383.
- Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev.* 2007;20(3):440–458.
- Walther-Rasmussen J, Høiby N. Class A carbapenemases. JAntimicrob Chemother. 2007;60(3):470–482.
- Patel G, Bonomo RA. "Stormy waters ahead": global emergence of carbapenemases. *Front Microbiol.* 2013;4:48.
- Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers in Enterobacteriaceae worldwide. *Clin Microbiol Infect*. Epub June 14, 2014.
- Hidalgo-Grass C, Warburg G, Temper V, et al. KPC-9, a novel carbapenemase from clinical specimens in Israel. *Antimicrob Agents Chemother*. 2012;56(11):6057–6059.
- Pournaras S, Protonotariou E, Voulgari E, et al. Clonal spread of KPC-2 carbapenemase-producing *Klebsiella pneumoniae* strains in Greece. *J Antimicrob Chemother*. 2009;64(2):348–352.
- 40. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin Infect Dis.* 2012;55(7):943–950.
- Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerg Infect Dis.* 2014;20(7):1170–1175.
- 42. Papadimitriou-Olivgeris M, Marangos M, Christofidou M, et al. Risk factors for infection and predictors of mortality among patients with KPC-producing *Klebsiella pneumoniae* bloodstream infections in the intensive care unit. *Scand J Infect Dis.* 2014;46(9):642–648.
- 43. Ho VP, Jenkins SG, Afaneh CI, Turbendian HK, Nicolau DP, Barie PS. Use of meropenem by continuous infusion to treat a patient with a Bla(kpc-2)-positive *Klebsiella pneumoniae* blood stream infection. *Surg Infect (Larchmt)*. 2011;12(4):325–327.
- Petrosillo N, Giannella M, Lewis R, Viale P. Treatment of carbapenemresistant *Klebsiella pneumoniae*: the state of the art. *Expert Rev Anti Infect Ther.* 2013;11(2):159–177.
- 45. Levy Hara G, Gould I, Endimiani A, et al. Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: recommendations from an International Working Group. *J Chemother*. 2013;25(3):129–140.
- 46. Djahmi N, Dunyach-Remy C, Pantel A, Dekhil M, Sotto A, Lavigne JP. Epidemiology of carbapenemase-producing Enterobacteriaceae and *Acinetobacter baumannii* in Mediterranean countries. *BioMed Res Int.* 2014;2014:305784.
- Stock I. [Infectious diseases caused by carbapenemase-producing Enterobacteriaceae – a particular challenge for antibacterial therapy]. *Med Monatsschr Pharm.* 2014;37(5):162–172. German.
- Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis.* 2013;13(9):785–796.
- Paul M, Carmeli Y, Durante-Mangoni E, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. *JAntimicrob Chemother*. 2014;69(9):2305–2309.

- Landelle C, Marimuthu K, Harbarth S. Infection control measures to decrease the burden of antimicrobial resistance in the critical care setting. *Curr Opin Crit Care*. 2014;20(5):499–506.
- Turnidge JD. The pharmacodynamics of beta-lactams. *Clin Infect Dis*. 1998;27(1):10–22.
- Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26(1): 1–10.
- McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents*. 2008;31(4):345–351.
- Mouton JW, Vinks AA. Continuous infusion of beta-lactams. *Curr Opin Crit Care*. 2007;13(5):598–606.
- Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. *Antimicrob Agents Chemother*. 1994;38(5): 931–936.
- 56. Roosendaal R, Bakker-Woudenberg IA, van den Berghe-van Raffe M, Vink-van den Berg JC, Michel MF. Impact of the duration of infection on the activity of ceftazidime, gentamicin and ciprofloxacin in *Klebsiella pneumoniae* pneumonia and septicemia in leukopenic rats. *Eur J Clin Microbiol Infect Dis.* 1991;10(12):1019–1025.
- Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients. *Clin Pharmacokinet*. 2005;44(10):1009–1034.
- Roberts JA, Joynt GM, Choi GYS, Gomersall CD, Lipman J. How to optimise antimicrobial prescriptions in the intensive care unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. *Int J Antimicrob Agents*. 2012;39(3):187–192.
- Mehrotra R, De Gaudio R, Palazzo M. Antibiotic pharmacokinetic and pharmacodynamic considerations in critical illness. *Intensive Care Med*. 2004;30(12):2145–2156.
- Roberts JA, Pea F, Lipman J. The clinical relevance of plasma protein binding changes. *Clin Pharmacokinet*. 2013;52(1):1–8.
- Ulldemolins M, Rello J. The relevance of drug volume of distribution in antibiotic dosing. *Curr Pharm Biotechnol*. 2011;12(12):1996–2001.
- Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*. 2010;49(1):1–16.
- Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. *Crit Care*. 2013; 17(1):R35.
- 64. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest.* 2012;142(1):30–39.
- Carlier M, De Waele JJ. Identifying patients at risk for augmented renal clearance in the ICU – limitations and challenges. *Crit Care*. 2013;17(2):130.
- 66. Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/ tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Crit Care*. 2013;17(3):R84.
- Casu GS, Hites M, Jacobs F, et al. Can changes in renal function predict variations in β-lactam concentrations in septic patients? *Int J Antimicrob Agents*. 2013;42(5):422–428.
- Molitoris BA. Measuring glomerular filtration rate in the intensive care unit: no substitutes please. *Crit Care*. 2013;17(5):181.
- Baptista JP, Udy AA, Sousa E, et al. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. *Crit Care.* 2011;15(3):R139.
- Eyler RF, Mueller BA; Medscape. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat Rev Nephrol.* 2011;7(4):226–235.
- Fissell WH. Antimicrobial dosing in acute renal replacement. Adv Chronic Kidney Dis. 2013;20(1):85–93.

- Jamal JA, Economou CJ, Lipman J, Roberts JA. Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation. *Curr Opin Crit Care*. 2012;18(5):460–471.
- Bouman CS. Antimicrobial dosing strategies in critically ill patients with acute kidney injury and high-dose continuous veno-venous hemofiltration. *Curr Opin Crit Care*. 2008;14(6):654–659.
- Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis.* 2005;41(8):1159–1166.
- 75. Seyler L, Cotton F, Taccone FS, et al. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. *Crit Care*. 2011;15(3):R137.
- Roberts JA, Ulldemolins M, Roberts MS, et al. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. *Int J Antimicrob Agents*. 2010;36(4):332–339.
- 77. Roberts DM, Roberts JA, Roberts MS, et al; RENAL Replacement Therapy Study Investigators. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med.* 2012;40(5): 1523–1528.
- Müller M, dela Peña A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. *Antimicrob Agents Chemother*. 2004;48(5):1441–1453.
- Joukhadar C, Frossard M, Mayer BX, et al. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. *Crit Care Med.* 2001;29(2):385–391.
- Sauermann R, Delle-Karth G, Marsik C, et al. Pharmacokinetics and pharmacodynamics of cefpirome in subcutaneous adipose tissue of septic patients. *Antimicrob Agents Chemother*. 2005;49(2): 650–655.
- Van Herendael B, Jeurissen A, Tulkens PM, et al. Continuous infusion of antibiotics in the critically ill: the new holy grail for beta-lactams and vancomycin? *Ann Intensive Care*. 2012;2(1):22.
- Abdul-Aziz MH, Dulhunty JM, Bellomo R, Lipman J, Roberts JA. Continuous beta-lactam infusion in critically ill patients: the clinical evidence. *Ann Intensive Care*. 2012;2(1):37.
- Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis.* 2013;56(2):236–244.
- 84. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. 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.* 2013;56(2):272–282.
- Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. *Crit Care*. 2011;15(5):R206.
- Aubert G, Carricajo A, Coudrot M, Guyomarc'h S, Auboyer C, Zeni F. Prospective determination of serum ceftazidime concentrations in intensive care units. *Ther Drug Monit.* 2010;32(4):517–519.
- Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159–177.
- Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol.* 2003;24(9):699–706.
- LaRocco A Jr. Concurrent antibiotic review programs a role for infectious diseases specialists at small community hospitals. *Clin Infect Dis.* 2003;37(5):742–743.
- Rüttimann S, Keck B, Hartmeier C, Maetzel A, Bucher HC. Long-term antibiotic cost savings from a comprehensive intervention program in a medical department of a university-affiliated teaching hospital. *Clin Infect Dis.* 2004;38(3):348–356.
- Ng CK, Wu TC, Chan WM, et al. Clinical and economic impact of an antibiotics stewardship programme in a regional hospital in Hong Kong. *Qual Saf Health Care*. 2008;17(5):387–392.

- 92. Slain D, Sarwari AR, Petros KO, et al. Impact of a multimodal antimicrobial stewardship program on *Pseudomonas aeruginosa* susceptibility and antimicrobial use in the intensive care unit setting. *Crit Care Res Pract*. 2011;2011:416426.
- Katsios CM, Burry L, Nelson S, et al. An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial prescribing in critically ill patients. *Crit Care*. 2012;16:R216.
- Gentry CA, Greenfield RA, Slater LN, Wack M, Huycke MM. Outcomes of an antimicrobial control program in a teaching hospital. *Am J Health Syst Pharm*. 2000;57(3):268–274.
- Rahal JJ, Urban C, Horn D, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. *JAMA*. 1998;280(14):1233–1237.
- 96. Kim JW, Chung J, Choi SH, et al. 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. *Crit Care*. 2012;16(1):R28.
- Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med.* 2014;40(1):32–40.
- Gomes Silva BN, Andriolo RB, Atallah AN, Salomão R. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock [review]. *Cochrane Database Syst Rev.* 2010;12:CD007934.

- Shime N, Satake S, Fujita N. De-escalation of antimicrobials in the treatment of bacteraemia due to antibiotic-sensitive pathogens in immunocompetent patients. *Infection*. 2011;39(4):319–325.
- 100. Johnson JK, Smith G, Lee MS, et al. The role of patient-to-patient transmission in the acquisition of imipenem-resistant *Pseudomonas aeruginosa* colonization in the intensive care unit. *J Infect Dis*. 2009;200(6):900–905.
- 101. George P, Morris AM. Pro/con debate: should antimicrobial stewardship programs be adopted universally in the intensive care unit? *Crit Care*. 2010;14(1):205.
- 102. Rimawi RH, Mazer MA, Siraj DS, Gooch M, Cook PP. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Crit Care Med.* 2013;41(9):2099–2107.
- Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med.* 2011;364(15):1419–1430.
- 104. Huskins WC, Huckabee CM, O'Grady NP, et al; STAR*ICU Trial Investigators. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med.* 2011;364(15):1407–1418.
- 105. Huang AM, Newton D, Kunapuli A, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization timeof-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis.* 2013;57(9):1237–1245.

Infection and Drug Resistance

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed openaccess journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peerreview system, which is all easy to use. Visit http://www.dovepress.com/ testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/infection-and-drug-resistance-journal

Dovepress