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REVIEW

Optimizing antimicrobial therapy in critically ill patients

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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

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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 fluid[12] 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 (Zn^{2+}) (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 cefepime[29] 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 fourth-generation 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 carbapenemase-producing *Enterobacteriaceae*

Since the beginning of 2000, *K. pneumoniae* carbapenemase-producing (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 failure[40] 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 XDR-resistant 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} ≥130 mL/min/1.73 m^2 was observed in 57.7% of the patients with a higher prevalence in trauma (85.7%) than in septic patients (39.5%). Young (≤50 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_{CR} values ≥130 mL/min/1.73 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 al[66] 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_{CR}, β-lactam PK changes are not predicted by CL_{CR} 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 rate[68] 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 al[74] 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 al[77] 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× MIC attainment, Roberts et al[76] 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 al[86] reported that the serum ceftazidime concentration was <5× 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 al[91] 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 broad-spectrum 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 al[93] 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.

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 al[94] 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

Table 1 Summary of main studies on ASPs in ICUs

Authors	Study design	Strategy/procedure	Study results
Slain et al[92]	Pre-/post-intervention Observational study ICU	Multimodal ASP	– Reduction of intravenous ciprofloxacin use and ceftazidime – 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 *Clostridium difficile* or resistant *Enterobacteriaceae* – 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[96]	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 14- and 28-day mortality between the two groups. Interestingly, Garnacho-Montero et al[97] 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.

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