Antibiotic stewardship in the intensive care unit

Charles-Edouard Luyt*, Nicolas Bréchot, Jean-Louis Trouillet and Jean Chastre

Abstract

The rapid emergence and dissemination of antimicrobial-resistant microorganisms in ICUs worldwide constitute a problem of crisis dimensions. The root causes of this problem are multifactorial, but the core issues are clear. The emergence of antibiotic resistance is highly correlated with selective pressure resulting from inappropriate use of these drugs. Appropriate antibiotic stewardship in ICUs includes not only rapid identification and optimal treatment of bacterial infections in these critically ill patients, based on pharmacokinetic-pharmacodynamic characteristics, but also improving our ability to avoid administering unnecessary broad-spectrum antibiotics, shortening the duration of their administration, and reducing the numbers of patients receiving undue antibiotic therapy. Either we will be able to implement such a policy or we and our patients will face an uncontrollable surge of very difficult-to-treat pathogens.

Introduction

Optimal antibiotic use is crucial in the critical care setting, especially in an era of rising antibiotic resistance and lack of new antimicrobial development [1-3]. Study results indicate that 30% to 60% of antibiotics prescribed in ICUs are unnecessary, inappropriate, or suboptimal [4-7]. Over-prescribing and misprescribing antibiotics are undoubtedly contributing to the growing challenges posed by antibiotic-resistant bacteria, and epidemiological studies have clearly demonstrated direct relationships between antibiotic consumption and the emergence and dissemination of resistant strains in hospitals and ICUs [7-20]. As defined by the Society of Healthcare Epidemiology of America and Infectious Diseases Society of America (IDSA) Joint Committee on the Prevention of Antimicrobial Resistance in hospitals, ‘stewardship of antimicrobials is an apt descriptor of related activities that help optimize antimicrobial therapy, ensuring the best clinical outcome for the patient while lowering the risk of subsequent development of antimicrobial resistance’ [14]. Thus, in-ICU antibiotic stewardship encompasses rapid identification of patients with bacterial infections, better empirical treatment selection, using pharmacokinetic-pharmacodynamic (PK-PD) characteristics to optimize antibiotic dosing and administration modalities, de-escalation once culture results become available, shortening therapy duration, and reducing the numbers of patients treated unnecessarily.

Unfortunately, improving in-ICU antibiotic use is particularly difficult for three main reasons: infection severity often precludes withdrawing or postponing antibiotics, the complex decision-making process frequently involves doctors with limited expertise, and it is difficult to ensure disease-long continuity of care by the same medical team 24 hours a day, 7 days a week. Here, we review how in-ICU antibiotic therapy could possibly be optimized and rationalized.

Rapid identification of intensive care unit patients with bacterial infections

Most published observational data suggest that the time to appropriate antibiotic administration is a major outcome determinant for ICU patients with severe bacterial infections. Indeed, each hour of delay in administering effective antibiotics for septic shock is associated with measurably increased mortality [6,21-25]. Thus, as strongly recommended by all guidelines [26-29], obtaining biological specimens should not postpone timely antibiotic administration to patients with severe sepsis or septic shock.

However, owing to methodological concerns, the harmful effects of inadequate therapy are not accepted by all [30-36]. Because in-ICU signs and symptoms of infection due to non-infectious causes are common, rushing to prescribe antibiotics may mean that many uninfected patients receive unnecessary treatment. In a quasi-experimental, before-and-after, observational cohort study of patients...
admitted to the University of Virginia surgical ICU, Hranjec and colleagues [32] postulated that delaying antibiotics for hemodynamically stable patients with suspected infections (35% pneumonia) until they were objectively documented would not worsen mortality. Notably, that conservative approach was associated with lower all-cause mortality, more initially appropriate therapy, and shorter mean treatment duration than the aggressive strategy. Thus, for clinically stable patients, that strategy might achieve better antibiotic use without impacting prognosis. Obtaining specimens for appropriate cultures before antibiotic administration is essential to confirm infection, identify responsible pathogens, and enable therapy de-escalation in response to susceptibility profiles.

The inaccuracy of conventional approaches to diagnose hospital-acquired infections (HAIs) and the impossibility of those strategies to avoid antibiotic overprescription led some investigators to hypothesize that using biological markers - for example, C-reactive protein, soluble-triggering receptor expressed on myeloid cells-1, or procalcitonin (PCT) - might better identify true bacterial infections and facilitate therapeutic decisions. However, although PCT is a good marker of community-acquired infections (CAIs), it does not seem to be for HAIs [37,38,43-47]. Indeed, blood PCT concentrations can rise in various non-septic conditions: major trauma, surgery, acute respiratory distress syndrome, multiorgan failure, post-transplantation rejection, cardiogenic shock, severe burns, heat stroke, and so on. Thus, high PCT concentrations the day sepsis is suspected are non-contributory because increases that are attributable to a prior non-infectious condition or active infection cannot be distinguished [39,42,43]. Moreover, PCT can remain low in some microbiologically proven bacterial infections, either because the infection remains contained in a tissue compartment that can synthesize PCT locally without systemic release, thereby explaining the low serum level despite true infection, or because of a 24- to 48-hour lag time in infection onset to peak PCT release. Thus, intensivists are rightly reluctant to rely exclusively on biological markers when severe infection is suspected [37,38,43-47].

Selection of initial antibiotic therapy

Owing to the emergence of multiresistant Gram-negative bacilli (GNB) (for example, Pseudomonas aeruginosa, extended-spectrum β-lactamase-producing Enterobacteriaceae, and carbapenemase-producing Klebsiella pneumoniae) and the increasing role of Gram-positive bacteria (like methicillin-resistant Staphylococcus aureus, or MRSA), empirical broad-spectrum antibiotics are justified for most ICU patients with clinically suspected HAIs [25-27,48]. Regimen choice should be based on local antimicrobial susceptibility patterns and anticipated side effects while considering the antibiotics received within the preceding 2 weeks and striving whenever possible not to use the same classes [49-51]. Having current and frequently updated knowledge of local bacteriological epidemiology increases the likelihood of prescribing appropriate initial antibiotics. Whether surveillance cultures could further improve empirical treatment selection for ICU patients with suspected hospital-acquired pneumonia (HAP) is still debated but certainly should be weighed when difficult-to-treat microorganisms abound, making initial choices particularly risky [52,53]. Observational study results confirmed that initial regimens combining a broad-spectrum β-lactam and an aminoglycoside increased the proportion of appropriately treated patients compared with monotherapy or a combination of β-lactam and fluoroquinolone [54,55]. Only patients with mildly or moderately severe, early-onset infections and no specific risk factors (for example, prolonged hospitalization, immunosuppression, or recent prolonged antibiotics or a combination of these) can receive a relatively narrow-spectrum drug, like a non-pseudomonal third-generation cephalosporin.

For ICU patients admitted with health care-associated or community-onset infections or CAIs, more restraints for antimicrobial therapy selection are certainly possible. For example, it is increasingly recognized that applying current criteria for health care-associated pneumonia - hospitalization for at least 2 days during the preceding 90 days, residence in a nursing home or extended-care facility, home intravenous (antibiotics or chemotherapy) therapy, and chronic dialysis or home wound care (or both) during the preceding 30 days - as indications for broad-spectrum antibiotics may lead to overtreatment of many patients with pneumonia [>56-62]. To address this conceptual limitation, investigators developed multiple risk-assessment models that refine those criteria [61,63,64]. Available data suggest that the incidence of pathogens resistant to the usual in-patient IDSA-American Thoracic Society guideline-recommended antibiotic regimen (that is, a non-pseudomonal cephalosporin and a macrolide) is usually not significantly increased unless two or more risk factors are present, with prior antibiotic use or hospitalization and poor functional status being more important predictors of resistant bacteria than nursing-home residence alone [61]. Using such an algorithm could lead to fewer pneumonia patients unnecessarily receiving broad-spectrum antibiotics.

Within the past decade, the way clinical microbiology laboratories identify microorganisms was revolutionized, leaving behind slow traditional methods based on phenotype characteristics (for example, growth on defined media, colony morphology, Gram staining, and biochemical reactions) incurring significant diagnosis delay, in exchange for new diagnostic techniques (real-time multiplex polymerase chain reaction and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) [65,66].
The latter, making possible rapid pathogen identification and their antimicrobial resistance patterns (at least for certain organisms), could undoubtedly promote earlier therapy appropriateness and de-escalation [67]. Multiple instrument platforms, marketed by well-established manufacturers, are beginning to displace or complement (or both) automated conventional phenotyping tools, providing accurate microbial identification from blood cultures within 1 to 2 hours. Nevertheless, it is unlikely that any of those new diagnostic methods will completely replace phenotyping for antibiotic susceptibility testing in the near future.

Pending the complete development of those above-mentioned techniques, Bouza and colleagues [68] described simple microbiology laboratory-accessible, rapid, antimicrobial susceptibility E-tests directly on samples (lower respiratory tract or other biological specimens) to improve early appropriate in-ICU antimicrobial choices. In a prospective randomized study of 250 patients with microbiologically confirmed ventilator-associated pneumonia (VAP), the authors showed that reporting rapid E-test-obtained antibiotic susceptibility of responsible microorganisms to the treating physicians (mean ± standard deviation: 1.4 ± 0.75 days post-sampling versus 4.2 days with standard methods) was associated with fewer days of fever and antibiotics until VAP-episode resolution, less antibiotic consumption, less Clostridium difficile-associated diarrhea, lower antimicrobial costs, and fewer days on mechanical ventilation (MV) [68].

**Pharmacokinetic-pharmacodynamic-optimized antimicrobial therapy**

Reported findings demonstrated the need to individually adjust the antibiotic target doses and administration modalities to treat severe bacterial infection to each patient’s PK and putative or documented pathogens’ susceptibilities, as assessed by their minimal inhibitory concentrations (MICs) [69-73]. Most investigators distinguish antimicrobials by their killing mechanism: concentration-dependent (for example, aminoglycosides and fluoroquinolones) or time-dependent (for example, β-lactams and carbapenem). The most important PK-PD parameters are peak concentration/MIC >8-10 and 24-hour area under the concentration curve (AUC)/MIC >100-125 for aminoglycosides and fluoroquinolones. For β-lactams and carbapenem, the blood concentration should be maintained for >90-100% of the between-dose interval above MIC, at least in the case of severe infection [74,75]. However, it should be acknowledged that the exact target for PK-PD-optimized therapy remains elusive. Some antibiotics, such as fluoroquinolones and glycopeptides, are more complex and exhibit both concentration- and time-dependent kill characteristics where the best predictor of efficacy is the AUC/MIC. Others, such as carbapenems, have a marked post-antibiotic effect (that is, lead to a prolonged suppression of bacterial growth even with antibiotic concentrations below the MIC) [76,77].

ICU patients’ altered PK secondary to increased volume of distribution and decreased elimination can result in insufficient serum aminoglycosides or β-lactam concentrations (or both) when standard doses are administered, emphasizing the need to carefully monitor peak and trough antibiotic levels when treating resistant pathogens, respectively [5,78,79]. Antibiotic doses for ICU patients derived from other patient groups are likely to be suboptimal because of significant antibiotic PK changes, particularly volume of distribution and clearance. Organ support techniques, including renal replacement therapy and extracorporeal membrane oxygenation, increase PK variability (Figure 1) [80-82]. In a recent prospective study

---

**Figure 1** Pathophysiological changes commonly observed in critically ill patients and their effects on drug concentrations. Reproduced with permission from Elsevier Limited [75]. ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy.
conducted at 64 hospitals worldwide, 20% and 40% of 248 ICU patients receiving β-lactams for infection did not achieve free antibiotic concentrations above their pathogens’ MICs during 50% and 100% (50% and 100% fT>MIC, respectively) of the dosing interval (Figure 2) [5]. Frequently, higher than usually recommended antibiotic doses or continuous or extended infusions (or a combination of these) are needed [5,70,71,73,79,83-85]. Interestingly, use of prolonged infusion appeared to be associated with a significant reduction in mortality and improvement in clinical success when compared with intermittent boluses in a recent meta-analysis of 29 studies (18 randomized controlled trials and 11 observational studies) with a total of 2,206 patients [85].

Development of a priori dosing algorithms based on MIC, creatinine clearance and weight, and the clinician-specified AUC target might improve management of these patients, obtaining more precise antibiotic use than current guidelines [73,79,83,84,86]. Ultimately, adjusting antibiotic doses based on pathogen MICs and daily free antibiotic blood concentrations may reach optimized PK-PD targets in most ICU patients. A therapeutic drug-monitoring strategy, compared with traditional dosing methods, might not only reduce clinical failure rates in ICU patients but also prevent adverse events due to too high (toxic) antibiotic levels [87,88].

A double-blind randomized trial comparing 7 days of doripenem three times a day (4-hour infusion of 1 gram) with 10 days of imipenem-cilastin (1-hour infusion of 1 gram) for GNB VAP was prematurely stopped after random assignment of 274 patients because of inferior efficacy and higher day-28 all-cause mortality in the subgroup of doripenem-treated, P. aeruginosa-infected patients [89]. Despite longer doripenem infusions to optimize targeted antibiotic concentrations above the pathogens’ MICs during the 8-hour interval, this protocol performed more poorly, clearly documenting the risk associated with a so-called PK-PD-optimized antibiotic strategy when blood concentrations cannot be monitored and adjusted to stay above the responsible pathogens’ MICs. Perhaps the treatment duration or concentrations (or both) were sub-therapeutic for patients with elevated creatinine clearance, clearly documenting the risk associated with a so-called PK-PD-optimized antibiotic strategy when blood concentrations cannot be monitored and adjusted to stay above the MIC of the responsible pathogens [90].

For patients on MV, aerosolized antibiotics delivered via an efficient system, synchronized with inspiration, achieved airway drug concentrations 100- to 300-fold higher than the MICs of most bacteria, including multidrug-resistant pathogens [91-95]. Those levels, without systemic toxicity,
might eradicate proximal airway pathogens in patients on MV and lower the pressure for selection of new resistant organisms, as shown in a recent, double-blind, placebo-controlled study of 42 ICU patients who required prolonged MV and who were colonized or infected (or both) with potentially difficult-to-treat pathogens (for example, MRSA and non-fermenting GNB) [96]. However, larger clinical trials must confirm those findings before that strategy can be recommended, in light of its potentially deleterious impact on the local epidemiology when used for all ICU patients over prolonged periods [97-99].

**Antimicrobial therapy de-escalation**

The need to ensure that ICU patients with true bacterial infections receive prompt and appropriate antibiotics can lead to many more patients receiving antimicrobials than necessary, because of non-specific clinical signs of infection. This is particularly true for HAP/VAP, which represents the first in-ICU indication for starting antibiotics. Thus, regardless of the diagnostic strategy used for suspected HAP/VAP, serial clinical and microbiological evaluations are highly relevant to re-assess therapy after 48 to 72 hours and to stop it if infection is unlikely [48,100]. To accomplish that goal, each ICU should design its own diagnostic decision-tree strategy to manage patients with clinically suspected HAP/VAP to identify those with a low probability of infection, whose therapy can be discontinued when infection appears improbable [27,48]. At least, antibiotics should be withdrawn when the following three criteria are fulfilled on day 3: (a) the clinical diagnosis of pneumonia is unlikely - no definite infiltrates seen on repeat chest radiography and only one of the following three findings is present: temperature greater than 38.3°C, leukocytosis (greater than 12,000/mm³) or the following three findings is present: temperature greater than 38.3°C, leukocytosis (greater than 12,000/mm³) or leukopenia (less than 4,000/mm³), or purulent tracheobronchial secretions - or an alternative non-infectious diagnosis is confirmed; (b) non-significant tracheobronchial aspirate culture results; and (c) no severe sepsis or shock [101]. Direct examination of distal pulmonary samples collected by bronchoalveolar lavage with or without a bronchoscope and quantitative culture results have consistently yielded fewer microorganisms growing above the diagnostic threshold than qualitative tracheal aspirate cultures [48,102]. Pertinently, when therapeutic decisions were based on those results, compared with the clinical approach, fewer patients received antibiotics that were of a potentially narrower spectrum, thereby limiting the emergence and dissemination of drug-resistant strains and minimizing antibiotic-related toxicity [103]. For many ICU patients with infections (including late-onset infections), therapy can be de-escalated, once respiratory tract, blood, or other specimen culture results become available, if no resistant organism (for example, *P. aeruginosa, Acinetobacter spp.,* or MRSA) is recovered or because the isolated pathogen is sensitive to a narrower-spectrum antibiotic than that prescribed empirically [26,27,48]. For example, if MRSA is not found, vancomycin and linezolid should be stopped unless the patient is allergic to β-lactams or has developed an infection with Gram-positive bacteria susceptible only to them. Very-broad-spectrum agents (like carbapenems, piperacillin-tazobactam, and cefepime) should also be restricted to patients whose infectious pathogens are susceptible only to them. Because fluoroquinolones have been associated with the emergence of resistant strains, their in-ICU use probably should be discouraged [104,105]. Antifungals should never be prescribed for *Candida* isolated from respiratory secretions alone [106]. However, clinicians should know that, when third-generation cephalosporins are chosen to treat infections caused by *Enterobacteriaceae* with inducible β-lactamase (*Enterobacter, Citrobacter, Morganella morganii,* indole-positive Proteus, or *Serratia* spp.), the emergence of resistant variants may lead to treatment failure. Unfortunately, study results showed that de-escalation, though not associated with any adverse outcomes, was not consistently applied in many ICUs [107-111].

The two most commonly cited reasons to prescribe combined antibiotics for the entire treatment duration are to achieve synergy and to prevent the emergence of resistant strains. However, antibiotic synergy has been shown to be valuable only *in vitro* and in patients with neutropenia, bacteremia, or a greater than 25% probability of death [25,112-122]. Randomized controlled trial results on combined therapy showed its benefit to be inconsistent or null, even when they were pooled in meta-analyses or when analysis was restricted to *P. aeruginosa*-infected patients [113,121,123,124]. Importantly, such regimens did not prevent the emergence of antimicrobial resistance during therapy and were associated with significantly more nephrotoxicity [121]. Those observations were confirmed in a randomized, open-label trial on 600 patients meeting criteria for severe sepsis or septic shock: combined mero- penem and moxifloxacin versus meropenem alone did not achieve less organ failure or better survival or any secondary endpoints [113]. Based on those data, most patients’ therapy could be safely switched to monotherapy after 3 to 5 days, provided that the initial therapy was appropriate, the clinical course evolved favorably, and microbiological data did not indicate difficult-to-treat microorganisms, with high *in vitro* MICs, as can be observed for some non-fermenting GNB.

**Shortening treatment duration**

Although shortening the duration of antibiotic administration for ICU patients may represent the most powerful strategy to reduce antibiotic impact on resistance emergence, most guidelines still recommend relatively prolonged or imprecise durations [26,28,125,126]. Efforts
to shorten the duration for bacterial infections are justified by study results on the natural history of therapeutic responses. Most patients who had CAIs or HAIs, including VAP, and who received appropriate antimicrobial therapy had good clinical responses within the first 6 days [127-129]. Prolonged therapy facilitates colonization with antibiotic-resistant bacteria, which may precede recurrent infectious episodes.

Results of a multicenter, randomized controlled trial on 401 patients with microbiologically proven VAP showed that their clinical outcomes were similar to those of patients receiving appropriate empirical therapy for 8 or 15 days [130]. Relapse rates for short-duration therapy tended to be higher when P. aeruginosa or Acinetobacter spp. was the causative agent, but clinical outcomes were indistinguishable. Those observations were confirmed by trials that evaluated an antibiotic discontinuation policy for patients with other infections [111,131-138].

Many clinicians remain reluctant to prescribe fewer days of antibiotics for patients with severe HAIs and prefer tailoring antibiotic duration to the ensuing clinical course or using serial biomarker (for example, PCT) determinations (or both). The rationale for using the latter to customize treatment duration relies on evidence that the inflammatory response is often proportional to infection severity. When the response is absent or mild, antibiotics might logically be discontinued earlier. Thus, adapting treatment duration to PCT kinetics seems reasonable and was demonstrated to be useful in several randomized trials, including seven in the ICU, targeting patients with acute respiratory infections [37,41,139-143]. The largest of those studies was the PRORATA trial that included 621 ICU patients; 67% of these patients were on MV, 50% had CAIs, and 50% had HAIs, and half of them had septic shock [37]; patients in the PCT group had significantly more (mean ± standard deviation) days without antibiotics than controls (14.3 ± 9.1 versus 11.6 ± 8.2; absolute difference 2.7 days; 95% confidence interval 1.4 to 4.1; P < 0.0001), and this lower antibiotic consumption was not associated with poorer outcomes. Furthermore, regardless of infection site and the infectious agent, results were consistent (Figure 3).

In summary, shortening the treatment duration for ICU patients with infections is possible and not detrimental for most of them. Indeed, the diversity of patients enrolled in those trials and the consistency of the findings suggest that the conclusions may be applicable to most critically ill patients who develop infections, including severe sepsis or septic shock, with the possible exception of those who are immunosuppressed, those who are infected with multi-tiresistant microorganisms or whose course deteriorates despite treatment, or those whose initial regimen was inappropriate for the responsible pathogens. That strategy should help contain health-care costs and limit in-ICU emergence of bacterial resistance.

Implementing a structured antibiotic stewardship program

Optimizing in-ICU antimicrobial therapy is difficult. No single measure alone can succeed, emphasizing the need to devise a structured antibiotic stewardship program. Unfortunately, the exact set of key interventions essential to this multifaceted and multidisciplinary ‘care bundle’ remains unknown, as do the factors contributing to its success [1,3,109,144-146]. The interventions should be packaged so that compliance is readily assessable and achievable, which usually means that each bundle includes no more than five to eight interventions. Table 1 provides an example of antibiotic stewardship for patients with VAP. Successful implementation requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health-care workers. Several studies using quasi-experimental designs confirmed the usefulness of such a strategy to optimize in-ICU antibiotic stewardship, but not all designs proved to be effective [111,147,148]. As the results of a recent study [149] showed, simply having a reference checklist, without a robust implementation-and-adherence strategy, is unlikely to improve patient outcomes [149,150].

Computerized decision-support programs linked to electronic patient records can facilitate the dissemination of information to physicians for immediate use in therapeutic decision making and improving quality of care [151-154]. Partially or non-automated protocols, often instigated by hospital-based quality-improvement teams, also had demonstrated efficacy [154-157]. A prospective intervention of having an infectious disease specialist interact regularly with the medical ICU team was conducted to assess guideline compliance and antibiotic and health-care costs; it achieved significantly reduced use of extended-spectrum penicillins, carbapenems, vancomycin, and metronidazole [157]. Specifically, the intervention group had a significantly lower rate of treatments not corresponding to guidelines, with fewer MV days, shorter stays, and lower in-hospital mortality. Moreover, $89,944 was saved for early antibiotic discontinuation alone [157].

Conclusions

The high antibiotic resistance observed in ICU patients who develop infections limits treatment options and justifies using regimens combining several broad-spectrum antibiotics, even when the presumed infection probability is low, because initial inappropriate therapy has been linked to poor prognoses. More than its economic impact, this ‘spiraling empirical’ practice increasingly leads to undue antibiotic administration to many ICU patients without true infections, paradoxically causing the emergence of more antibiotic-resistant microorganisms causing infections that, in turn, are associated with heightened mortality and morbidity. Therefore, antibiotic therapy for ICU
patients with infections should be viewed as a two-stage process: the first involves administering broad-spectrum antibiotics to avoid inappropriate treatment of true bacterial infections, and the second focuses on trying to achieve the first without antibiotic overuse or abuse. In general, the first goal can be accomplished by rapidly identifying patients with infection and starting empirical therapy likely to treat the institution’s most common etiological agents. This strategy requires that initial antibiotic choices be guided by local antibiotic resistance patterns and laboratory test results (including Gram staining), rapidly yielding identities of likely responsible pathogens. The second aim involves stopping therapy when the probability of infection is low, focusing and narrowing treatment once the microorganism is known, switching to monotherapy after day 3 whenever possible, and shortening treatment to 7 to 8 days for most patients, based on the clinical response and bacteriology findings. Therefore, every effort...

Table 1 A personal care bundle for optimizing antimicrobial treatment for intensive care unit patients with ventilator-associated pneumonia

| Antibiotic stewardship items                                      | Rationale                                                                                                                                       |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Step 1: Obtain bronchoalveolar specimens for Gram staining and   | Every effort should be made to obtain reliable specimens from the specific infection site for direct microscope examination and cultures in order to enable de-escalation. |
| cultures before introducing new antibiotics.                     |                                                                                                                                                  |
| Step 2: Start antibiotics less than 2 hours after bronchoalveolar| Time to appropriate antimicrobial administration is a major outcome determinant for intensive care unit patients with severe bacterial infections.             |
| lavage.                                                           |                                                                                                                                                  |
| Step 3: Start therapy using broad-spectrum antibiotics unless    | Owing to the emergence of multiresistant GNB (for example, *Pseudomonas aeruginosa* and ESBL-producing GNB), empirical broad-spectrum antibiotics are justified for most patients with clinically suspected VAP. |
| no risk factors for resistant pathogens are present.             |                                                                                                                                                  |
| Step 4: Stop therapy on day 3 if infection becomes unlikely.     | Antibiotics can be discontinued very early when VAP diagnosis becomes highly unlikely based on negative cultures and clinical course and the elimination of an extrapulmonary infection. |
| Step 5: Use pharmacokinetic-pharmacodynamic data to optimize     | Clinical and bacteriological outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic-pharmacodynamic properties of the selected agents. |
| treatment.                                                       |                                                                                                                                                  |
| Step 6: Streamline antibiotic therapy by using narrower-spectrum  | For many patients with VAP, including those with late-onset infections, therapy can be narrowed once respiratory tract and blood culture results become available, either because an anticipated bacterium (for example, *P. aeruginosa*, *Acinetobacter* spp., or methicillin-resistant Staphylococcus aureus) was not recovered or because the isolated pathogen is sensitive to a narrower-spectrum antibiotic than that used initially. |
| antibiotics once the etiological agent is identified.            |                                                                                                                                                  |
| Step 7: Switch to monotherapy on days 3 to 5.                    | Using a two-antibiotic regimen for more than 3 to 5 days has no clinical benefits, provided that initial therapy was appropriate, the clinical course evolves favorably, and microbiological data exclude difficult-to-treat microorganisms. |
| Step 8: Shorten the treatment duration based on procalcitonin    | Shorter antibiotic administration for patients with VAP has achieved good outcomes with less antibiotic consumption. Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede recurrent VAP episodes. |
| kinetics.                                                        |                                                                                                                                                  |

ESBL, extended-spectrum β-lactamase; GNB, Gram-negative bacilli; VAP, ventilator-associated pneumonia.
should be made to obtain reliable specimens from the specific suspected infection site in each patient for direct microscope examination and cultures in order to de-escalate antibiotics.

Key messages

- The rapid in-ICU emergence and dissemination of multidrug-resistant microorganisms worldwide constitute a problem of crisis dimensions that is linked directly to inappropriate antimicrobial use.
- Appropriate antibiotic stewardship is a two-stage process.
- Stage I includes rapidly identifying patients with infection, starting an empirical regimen likely to treat the institution’s most common etiological agents, and optimizing bacterial killing by adjusting antibiotic doses and administration modalities based on PK-PD characteristics.
- Stage II involves stopping therapy in patients unlikely to have infections, focusing and narrowing treatment once the responsible pathogen is known, switching to monotherapy after day 3 whenever possible, and shortening antibiotic administration to 7 to 8 days for most patients, based on the therapeutic response and microbiology data.
- Any antibiotic stewardship program should be implemented in a structured manner and requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health-care workers.

Note

This article is part of a series on Antibiotic resistance in the ICU, edited by Steven Opal. Other articles in this series can be found at http://ccforum.com/series/antibioticresistance.

Abbreviations

AUC: Area under the concentration curve; CAI: Community-acquired infection; GNB: Gram-negative bacilli; HAI: Hospital-acquired infection; HAP: Hospital-acquired pneumonia; IDSA: Infectious Diseases Society of America; MIC: Minimal inhibitory concentration; MRSA: Methicillin-resistant Staphylococcus aureus; MV: Mechanical ventilation; PCT: Procalcitonin; PK-PD: Pharmacokinetic-pharmacodynamic; VAP: Ventilator-associated pneumonia.

Competing interests

C-EL has received lecture honoraria from or served on the advisory board of Thermo Fisher Brahms (Hennigsdorf, Germany), MSD (Whitehouse Station, NJ, USA), bioMérieux (Caponne, France), and Bayer (Leverkusen, Germany). JC has received lecture honoraria from or served on the advisory board of Astellas Pharma (Tokyo, Japan), Bayer/Nektar (San Francisco, CA, USA), Cubist (Lexington, MA, USA), Janssen-Cilag (Cisy-les-Mauilineaux, France), Pfizer (New York, NY, USA), and Sanofi Pasteur/Kalibios (Lyon, France). The other authors declare that they have no competing interests.

Published online: 13 August 2014

References

1. Arnold HM, Micek ST, Shuperky LP, Kollef MH. Antibiotic stewardship in the intensive care unit. Semin Respir Crit Care Med 2011, 32:215–227.
2. Laxminarayan R, Dye A, Wattal C, Wieringa J, Drobniewski F, Ali R, Hors井, Tsang KY, Harkins J,Were CF, Breda J. Antimicrobial resistance - the need for global solutions. Lancet Infect Dis 2013, 13:1057–1098.
3. Leutner KD, Doern GV. Antimicrobial stewardship programs. J Clin Microbiol 2013, 51:3916–3920.
4. Bergmans DC, Bonten MJ, Goulard CA, van Tiel FH, van der Geest S, de Leeuw PN, Stobberingh EE. Indications for antibiotic use in ICU patients: a one-year prospective surveillance. J Antimicrob Chemother 1997, 39:527–535.
5. Roberts JA, Paul SK, Akova M, Basseti M, De Waee JF, Dimopoulos G, Kaukonen KM, KoulentJ D, Martin C, Montaner P, Rello J, Rhodes A, Starr T, Wailis SC, Lipman J. DALL: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014, 58:1072–1083.
6. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. Crit Care 2001, 5:189–195.
7. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001, 134:298–314.
8. McGowan JE. Antimicrobial resistance in hospital organisms and its relative antibiotic use. Rev Infect Dis 1983, 5:1093–1048.
9. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals, a challenge to hospital leadership. JAMA 1996, 275:234–240.
10. Lipatch M, Bergstrom CT, Levin BR. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. Proc Natl Acad Sci U S A 2000, 97:1938–1943.
11. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005, 18:538–566.
12. Paterson DL. The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. Clin Infect Dis 2006, 42:590–595.
13. Rice LB. The maxwell fdlland lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. Clin Infect Dis 2008, 46:491–496.
14. Shlaes DM, Gerding DN, John JF Jr, Craig WA, Borin Daley AL, Ducan RA, Eckman MR, Farrow WE, Greene WH, Lorian V, Levy S, McGowan JE Jr, Paul SM, Ruskin J, Tenover FC, Watanakunakorn C. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America joint committee on the prevention of antimicrobial resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis 1997, 25:584–599.
15. Sievert DM, Rick's P, Edwards JR, Schneider A, Patel J, Srivinavan A, Kallen A, Limbago B, Fridkin S. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2009–2010. Infect Control Hosp Epidemiol 2013, 34:1–14.
16. Thomas JK, Forrest A, Bhavnani SM, Hyatt JM, Cheng A, Ballow CH, Schentag JJ. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. Antimicrob Agents Chemother 1998, 42:521–527.
17. Zillich AJ, Sutherland JM, Wilson SJ, Diekema D, Ernst EJ, Vaughn TE, Doebbeling BN. Antibiotic use control measures to prevent and control antimicrobial resistance in US hospitals. Infect Control Hosp Epidemiol 2006, 27:1088–1095.
18. Armand-Lefevre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppe E, Luyt et al. Critical Care 2014, 18:480.
19. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet 2007, 369:483–490.
20. Landman D, Quale JM, Mayorga D, Aveded A, Vanga R, Ravishankar J, Flores C, Brocks S. Citywide clonal outbreak of multiresistant...
21. Kollef MH: Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000, 31:513–518.

22. Kollef MH, Zimmerman G, Word S, Fraser VJ: Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999, 115:462–474.

23. Kumar A: Early antimicrobial therapy in severe sepsis and septic shock. Curr Infec Dis Rep 2010, 12:336–344.

24. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Talberg L, Gurka D, Cheang M: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006, 34:1589–1596.

25. Kumar A, Zarchanis R, Light B, Parrillo J, Maik D, Simon D, Laporta D, Lapinsky S, Ellis P, Mirzanejad Y, Martinka G, Keenan S, Wood G, Araby Y, Feinstein D, Dodek P, Mavroyannis D, Leduc C: Early combination antibiotic therapy yields improved survival compared with monootherapy in septic shock: a propensity-matched analysis. Crit Care Med 2010, 38:1773–1785.

26. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jhaeschke R, Osborn TM, Munnell TE, Townsend SR, Reinhart K, Kaspell RM, Angus DC, Beilman GS, Machado FR, Rubinfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med 2004, 32:852–953.

27. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005, 171:388–416.

28. Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E, Cleverley J, Dilworth P, Fry C, Gascoigne AD, Knox A, Nathwani D, Spencer R, Wilcox M: Guidelines for the management of ventilator-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2008, 625–34.

29. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D: Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment. J Crit Care 2008, 23:138–147.

30. Amaral AC, Holder MW: Timing of antimicrobial therapy after identification of ventilator-associated condition is not associated with mortality in patients with ventilator-associated pneumonia: a cohort study. PLoS One 2014, 9(7):e97575.

31. Bloos F, Thomas-Ruddell D, Ruddell H, Engel C, Schwarzkopf D, Marshall JC, Harbach S, Simon P, Rissler R, Dei K, Wel M, Tousaint S, Schadler D, Woyland A, Ragaller M, Schwarzkopf K, Eich K, Kuhnke H, Hoyer H, Hartog C, Kaisers U, Reinhart K: Impact of compliance with infection management guidelines on outcomes in patients with severe sepsis: a prospective observational multi-center study. Crit Care 2014, 18:R42.

32. Hranjec T, Rosenberger LH, Swenson B, Metzger R, Fehl TR, Polittano AD, Riccio LM, Popovsky KA, Sawyer RG: Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet Infect Dis 2012, 12:774–780.

33. Pines JM, Isserman JA, Hinify PB: The measurement of time to first antibiotic dose for pneumonia in the emergency department: a white paper and position statement prepared for the American Academy of Emergency Medicine. J Emerg Med 2009, 37:335–340.

34. Quattromani E, Powell ES, Khare RK, Cheema N, Sausa K, Periyanayagam U, Pirotte MJ, Feinjans J, Mark Courtney D: Hospital-reported data on the pneumonia quality measure ‘Time to first antibiotic dose’ are not associated with inpatient mortality: results of a nationwide cross-sectional analysis. J Emerg Med 2011, 40:406–403.

35. Weller JA, Huxton M, McCue JD: Antibiotic timing and errors in diagnosing pneumonia. Arch Intern Med 2008, 168:351–356.

36. Yahav D, Lebovici L, Goldberg E, Bishara J, Paul M: Time to first antibiotic dose for patients hospitalised with community-acquired pneumonia. Int J Antimicrob Agents 2013, 41:410–413.

37. Boxrud D, Luyt CE, Tubach F, Caccio A, Alvarez A, Schwebel C, Chongten F, Lasocki S, Veber B, Dehour M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M: Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (prorata trial): a multicentre randomised controlled trial. Lancet 2010, 375:463–474.

38. Layos N, Lambermont B, Canivet JL, Morimoto P, Preiser JC, Garwec C, Ledoux D, Friauf P, Frits S, Grot JB, Wiesen P, Mears C, Massion P, Leonard P, Nys M, Lancelotti L, Chapelle JP, Dumas P: Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. Crit Care Med 2012, 40:2304–2309.

39. Luyt CE, Combes A, Trouillet JL, Chastre J: Value of the serum procalcitonin level to guide antimicrobial therapy for patients with ventilator-associated pneumonia. Semin Repor Crit Care Med 2011, 32:181–187.

40. Schuetz P, Muller B, Chastre J, Mota I, Manenti M, Merker C: Procalcitonin for guidance of antibiotic therapy. Expert Rev Anti Infect Ther 2010, 8:575–587.

41. Schuetz P, Muller B, Chastre J, Mota I, Manenti M, Merker C: Procalcitonin for guidance of antibiotic therapy. Expert Rev Anti Infect Ther 2010, 8:575–587.
54. Martinez JA, Cobos-Trigueros N, Soriano A, Almela M, Ortega M, Marco F, Pitart C, Sterzik H, Lopez I, Mensa J: Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteraemia due to gram-negative microorganisms. *Antimicrob Agents Chemother* 2010, 54:3590–3596.

55. Macedo ST, Welch EC, Khan J, Perez M, Doherty JA, Reichly RM, Kollef MH: Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother* 2010, 54:1742–1748.

56. Chalmers JD, Taylor JK, Singanayagam A, Fleming GB, Brambilla AM, Seghal S, Tania P, Mantero M, Basi F: Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012, 54:70–77.

57. Cardoso T, Ribeiro O, Araqao IC, Costa-Pereira A, Sarmento AE: Additional risk factors for infection by multidrug-resistant pathogens in healthcare-associated infection: a large cohort study. * BMC Infect Dis* 2012, 12:757.

58. Jeong BH, Koh WJ, Yoo H, Um SW, Suh GY, Chung MP, Kim H, Kwon OJ, Jon K: Performances of prognostic scoring systems in patients with healthcare-associated pneumonia requiring hospitalization. *Clin Microbiol Infect* 2011, 17:1659–1665.

59. Aliberti S, Di Pasquale M, Zanaboni AM, Cosentini R, Brambilla AM, Seghal S, Tania P, Mantero M, Basi F: Validation of a scoring tool to predict drug-resistant pathogens in healthcare-associated pneumonia. *Clin Infect Dis* 2013, 56:625–632.

60. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, Goto Y, Fukui Y, Ogasawara T, Nomura F, Saka H, Yamamoto M, Taniguchi H, Suzuki R, Saito K: Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2013, 188:985–995.

61. Shorr AF, Zilberberg MD, Reichley R, Kan J, Hoban A, Hoffman J, Micek ST, Kollef MH: Continuous versus intermittent antibiotic therapy is associated with improved antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy. *Clin Pharmacokinet* 2007, 46:997–1038.

62. Roberts DM, Roberts JA, Mossi S, Liu X, Nair P, Cole L, Lipman J, Bellomo R: Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med* 2012, 40:1523–1528.

63. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL: Antimicrobial dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Ther* 2005, 27:1–18.

64. Lodise TP, Drusano GL: Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. *Clin Infect Dis* 2011, 53:393–401.

65. Shirazi A, Goto Y, Fukui Y, Iwaki M, Okumura J, Yamaguchi I, Yagi T, Tanikawa Y, Sugino Y, Shiodo J, Ogasawara T, Nomura F, Saka H, Yamamoto M, Taniguchi H, Suzuki R, Saito K, Hikawa M, Kasegawa Y: Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2013, 188:985–995.

66. Jon K: Validation of a scoring tool to predict drug-resistant pathogens in hospitalized patients with pneumonia. *Int J Tuberc Lung Dis* 2013, 17:704–709.

67. Shorr AF, Zilberberg MD, Reichley R, Kan J, Hoban A, Hoffman J, Micek ST, Kollef MH: Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012, 54:193–198.

68. Clark AE, Gaffney D, Korda A, Valk MCM: Matrix-assisted laser desorption ionization-time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. *Clin Microbiol Rev* 2013, 26:547–603.

69. Hrabak J, Chudackova E, Walkova R: Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry for detection of antibiotic resistance mechanisms: from research to routine diagnosis. *Clin Microbiol Rev* 2013, 26:103–114.

70. Clerc O, Prodhom G, Vogne C, Birzzi A, Calandra T, Greub G: Impact of matrix-assisted laser desorption ionization-time of flight mass spectrometry on the clinical management of patients with gram-negative bacteraemia: a prospective observational study. *Clin Infect Dis* 2013, 56:1101–1107.

71. Bouza E, Torres MV, Radice C, Cenecado E, de Diego R, Sanchez-Carrillo C, Munoz P: Direct E-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. *Clin Infect Dis* 2007, 44:382–387.

72. Arnold HM, Hollands JM, Skruply LP, Smith JR, Jaung PH, Hampton NB, McCormick S, Reichly RM, Hoban A, Hoffmann J, Micek ST, Kollef MH: Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study. *Ann Pharmacother* 2013, 47:170–180.

73. Dunilhtry JM, Roberts JA, Davis B, Webb SA, Bellomo R, Gomersall C, Shirwalder C, Eastwood GM, Myburgh J, Paterson DL, Lipman J: Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013, 56:236–244.

74. Shiu J, Wang E, Tejani AM, Waddell M: Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. *Cochrane Database Syst Rev* 2013, 3:CD008481.
mechanically ventilated patients with gram-negative pneumonia. 96. Palmer LB, Smaldone GC, Chen JJ, Baram D, Duan T, Monteforte M, Varela M, Temponi AK, O’Riordan T, Daroowalla F, Richman P: Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. 97. Crit Care Med 2006; 34:2008–2013. 98. Luyt CLE, Combes A, Nieszczewska A, Trouillet JL, Chastre J: Aerosolized antibiotics to treat ventilator-associated pneumonia. 99. Crit Compr Infect Dis 2009, 22:154–158. 100. Luyt CLE, Eldon MA, Stass H, Gribben D, Corkery K, Chastre J: Pharmacokinetics and tolerability of amikacin administered as bay41-6551 aerosol in mechanically ventilated patients with gram-negative pneumonia and acute renal failure. 101. J Aerosol Med Pulm Drug Deliv 2011, 24:183–190. 102. Palmer LB, Smaldone GC: Reduction of bacterial resistance with inhaled antibiotics in the ICU. 103. Am J Respir Crit Care Med 2014, 189:1225–1233. 104. Stevens RM, Teres D, Skillman JJ, Feingold DS: Pneumonia in an intensive care unit. A 30-month experience. 105. Arch Intern Med 1974, 134:106–111. 106. Buelow E, Gonzalez TB, Versluis D, Oostdijk EA, Ogilvie LA, van Mork M, Oosterink E, van Pasel MW, Smidt H, D’Andrea MM, de Been M, James BV, Willems PJ, Bonten MJ, van Schaiw W: Effects of selective digestive decontamination (SDD) on the gut resistome. 107. J Antimicrob Chemother 2014, [Epub ahead of print]. 108. Oostdijk EA, Smits L, de Smet AM, Levente-n van Hall MA, Kesechiou J, Bonten MJ: Colistin resistance in gram-negative bacteria during conventional antimicrobial therapy. 109. Am J Respir Crit Care Med 2008, 178:231–242. 110. Singh N, Rogers P, Atwood CW, Wager MM, Yu VL: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. 111. Am J Respir Crit Care Med 2000, 162:505–511. 112. Torres A, Ewig S: Diagnosing ventilator-associated pneumonia. 113. N Engl J Med 2004, 350:433–435. 114. Baselski VS, Wunderink RG: Bronchoscopic diagnosis of pneumonia. 115. Clin Microbiol Rev 1994, 7:533–558. 116. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski L, Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N: De-escalation therapy in ventilator-associated pneumonia. 117. Crit Care Med 2006, 33:663–666. 118. Singh N, Rogers P, Atwood CW, Wager MM, Yu VL: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. 119. Am J Respir Crit Care Med 2000, 162:505–511. 120. Torres A, Ewig S: Diagnosing ventilator-associated pneumonia. 121. N Engl J Med 2004, 350:433–435. 122. Baselski VS, Wunderink RG: Bronchoscopic diagnosis of pneumonia. 123. Clin Microbiol Rev 1994, 7:533–558. 124. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski L, Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N: De-escalation therapy in ventilator-associated pneumonia. 125. Crit Care Med 2006, 33:663–666. 126. Singh N, Rogers P, Atwood CW, Wager MM, Yu VL: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. 127. Am J Respir Crit Care Med 2000, 162:505–511. 128. Torres A, Ewig S: Diagnosing ventilator-associated pneumonia. 129. N Engl J Med 2004, 350:433–435. 130. Baselski VS, Wunderink RG: Bronchoscopic diagnosis of pneumonia. 131. Clin Microbiol Rev 1994, 7:533–558. 132. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski L, Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N: De-escalation therapy in ventilator-associated pneumonia. 123. Marcus R, Paul M, Elphick H, Leibovici L: Early use of monotherapy with beta-lactam and aminoglycoside combination therapy for sepsis and septic shock is contingent only on the risk of death: a meta-analysis of individual patient data. 134. Crit Care Med 2010, 38:1651–1664. 135. Heyland DK, Dodek P, Muscedere J, Day A, Cook D: Randomized trial of combination versus monotherapy for the empiric treatment of ventilator-associated pneumonia. 136. Crit Care Med 2008, 36:374–7. 137. Kumar A, Safdar N, Kethireddy S, Chateau D: A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. 138. Crit Care Med 2010, 38:1651–1664. 139. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L: Combination antibiotic therapy on mortality in pseudomonas aeruginosa bloodstream infections: a post hoc analysis of a prospective cohort. 140. Clin Infect Dis 2013, 57:208–216. 141. Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Ormquist A, Schaberg T, Torres A, van der Heijden G, Verheij T: Guidelines for the management of adult lower respiratory tract infections. 142. Eur Respir J 2005, 26:1368–1380. 143. Solomkin JS, Mazzucli JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O’Neill PJ, Chow AW, Dellingler EP, Echepamti SR, Gorbach S, Hilfiker M, May AK, Nethers AB, Sawyer RG, Bartlett JS: Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection society and the Infectious Diseases Society of America. 144. Clin Infect Dis 2010, 50:133–164.
127. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J: Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. *Crit Care Med* 2007, 35:146–154.

128. Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ: Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2001, 163:1371–1375.

129. Luna CM, Blanzaco D, Niederman MS, Matarucco B, Baredes NC, Desmery P, Paliza F, Menga G, Ros F, Apezteguia C. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 2003, 31:676–682.

130. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jussaud D, Asfar P, Perin D, Feix F, Aubas S. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003, 290:2588–2598.

131. Miczek ST, Ward S, Fraser VJ, Kollef MH: A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest* 2004, 125:1791–1799.

132. Hedrick TL, McElwee NT, Smith RL, Evans HL, Pruitt TL, Sawyer RG: Duration of antibiotic therapy for ventilator-associated pneumonia caused by non-fermentative gram-negative bacilli. *Surg Infect (Larchmt)* 2007, 8:S58–S59.

133. Capelli G, Mockly H, Charpentier C, Annane D, Blasco G, Desmettre T, Hedrick TL, McElearney ST, Smith RL, Evans HL, Pruett TL, Sawyer RG: Early-onset ventilator-associated pneumonia in adults randomized clinical trial: comparison of 8 versus 15 days of antibiotic treatment. *PloS One* 2012, 7:e41290.

134. Dimopoulous G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, Matthaiou DK: Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. *Chest* 2013, 144:1759–1767.

135. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev* 2011, 10, CD007577.

136. Elakim-Raz N, Yahav D, Paul M, Leibovici L: Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection - 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2013, 68:2183–2191.

137. Havey TC, Fowler RA, Daneman N: Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care Med* 2011, 15:R267.

138. Kyniakidou KG, Rafailidis P, Matthaiou DK, Athanasiou S, Falagas ME: Short-versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized controlled trials. *Clin Ther* 2008, 30:1859–1868.

139. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008, 177:498–505.

140. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Luyt CE, Chastre J, Tubach F, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tam M, Bhatnagar N, Bucher HC, Mueller B: Procalcitoin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis* 2012, 55:651–662.

141. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A: Procalcitoin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2010, 38:2229–2241.

142. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulous G. An ESICM systematic review and meta-analysis of procalcitoin-guided antibiotic therapy algorithms in adult critically ill patients. *Intensive Care Med* 2012, 38:940–949.

143. Prino A, Wacker C, Brunnhof FM, Schlattmann P: Procalcitoin-guided therapy in intensive care unit patients with severe sepsis and septic shock - a systematic review and meta-analysis. *Crit Care* 2013, 17:R291.

144. Cotta MO, Roberts JA, Tabah A, Lipman J, Vogelaers D, Blot S: Antimicrobial stewardship of beta-lactams in intensive care units. *Expert Rev Anti Infect Ther* 2014, 12:581–595.

145. Deliti TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeret M, Hooton TM: 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, 44:159–177.

146. Lawrence KL, Kollef MH: Antimicrobial stewardship in the intensive care unit: advances and obstacles, *Am J Respir Crit Care Med* 2009, 179:434–438.

147. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartman G, Holmes A, Ramsay C, Taylor E, Wilcox M, Wiften P. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2005, 4:CD003543.

148. Gomez Silva BN, Andriolo RB, Attalah AN, Salomao R: De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev* 2010, 12:CD007934.

149. Weiss CH, DiBardino D, Rho J, Sung N, Collebard B, Wunderink RG: A clinical trial comparing physician prompting with an unprompted automated electronic checklist to reduce empirical antibiotic utilization. *Crit Care Med* 2013, 41:2563–2569.

150. Weiss CH, Moazed F, McEvoy CA, Singer BD, Salefie R, Amara LA, Kwasny M, Watts CM, Persell SD, Baker DW, Szaajzer J, Wunderink RG: Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. *Am J Respir Crit Care Med* 2011, 184:680–686.

151. Pestonri SL, Claissen DC, Evans RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes. *Ann Intern Med* 1996, 124:884–890.

152. Belletti D, Zacker C, Mullins CD. Perspectives on electronic medical records adoption: electronic medical records (EMR) in outcomes research. *Patient Relat Outcome Meas* 2010, 1:29–37.

153. Kular N, Goff DA, Schulz LT, Fox BC, Rose WE. The ‘Epic’ challenge of optimizing antimicrobial stewardship: the role of electronic medical records and technology. *Clin Infect Dis* 2013, 57:1005–1013.

154. Leibovici L, Gitelman V, Yehezkelli Y, Poznanski O, Milo G, Paul M, Ein-Dor P: Improving empirical antibiotic treatment: prospective, nonintervention testing of a decision support system. *J Intern Med* 1997, 242:395–400.

155. Bailey TC, Ritchie DJ, McMullin ST, Kohn M, Rechley RM, Casabar E, Shannon W, Dunagan WC. A randomized, prospective evaluation of an Interventional program to discontinue intravenous antibiotics at two tertiary care teaching institutions. *Pharmacotherapy* 1997, 17:277–281.

156. Ibrahim EH, Ward S, Sherman G, Schaff R, Fraser VI, Kollef MH: Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001, 29:109–1115.

157. Ramawi RH, Mazer MA, Sinj DS, Gooch M, Cook P. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Crit Care Med* 2013, 41:2099–2107.

Cite this article as: Luyt et al: Antibiotic stewardship in the intensive care unit. *Critical Care* 2014, 18:480.