Review

Bench-to-bedside review: Antimicrobial utilization strategies aimed at preventing the emergence of bacterial resistance in the intensive care unit

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Abstract

Antimicrobial resistance has emerged as one of the most important issues complicating the management of critically ill patients with infection. This is largely due to the increasing presence of pathogenic microorganisms with resistance to existing antimicrobial agents resulting in the administration of inappropriate treatment. Effective strategies for the prevention of antimicrobial resistance within intensive care units are available and should be aggressively implemented. The importance of preventing antimicrobial resistance is magnified by the limited availability of new antimicrobial drug classes for the foreseeable future.

Introduction

Antimicrobial resistance has emerged as an important variable influencing patient mortality and overall resource utilization in the intensive care unit (ICU) setting [1-3]. ICUs worldwide are faced with increasingly rapid emergence and spread of antibiotic-resistant bacteria. Both antibiotic-resistant Gram-negative bacilli and Gram-positive bacteria are reported as important causes of hospital-acquired infections [4-12]. In many circumstances, particularly with methicillin-resistant *Staphylococcus aureus*, with vancomycin-resistant *Enterococcus faecium*, and with Gram-negative bacteria producing extended spectrum beta-lactamases with resistance to multiple other antibiotics, few antimicrobial agents remain for effective treatment [13-19]. ICUs are an important area for the emergence of antimicrobial resistance due to the frequent use of broad-spectrum antibiotics, due to the crowding of patients with high levels of disease acuity within relatively small specialized areas, due to reductions in nursing staff and other support staff because of economic pressures that increase the likelihood of person-to-person transmission of microorganisms, and due to the presence of more chronically and acutely ill patients who require prolonged hospitalization and often harbor antibiotic-resistant bacteria [2,20,21].

Many strategies have been advocated to prevent the emergence of antibiotic resistance in the ICU setting [22]. These strategies also have application outside ICUs and in non-bacterial pathogens. It is important to note that these interventions attempt to balance the somewhat competing goals of providing appropriate antimicrobial treatment to critically ill patients while avoiding the unnecessary administration of antibiotics. This review will describe antimicrobial utilization strategies aimed at preventing the emergence of resistance in the ICU setting.

Why does antimicrobial resistance develop?

Antimicrobial use drives the emergence of resistance. Strategies aimed at limiting or modifying the administration of antimicrobial agents therefore have the greatest likelihood of preventing resistance to these agents [21]. A number of investigators have demonstrated a close association between the prior use of antibiotics and the emergence of subsequent antibiotic resistance both in Gram-negative bacteria and in Gram-positive bacteria [23-34]. Other factors promoting antimicrobial resistance include prolonged hospitalization, the presence of invasive devices such as endotracheal tubes and intravascular catheters (possibly due to the formation of biofilms on the surfaces of these devices), residence in long-term treatment facilities, and inadequate infection control practices [21]. The prolonged administration of antimicrobial regimens, however, especially with a single or predominant antibiotic or drug class, appears to be the most important factor promoting the emergence of antibiotic resistance that is potentially amenable to intervention [31,35,36].

Implications of increasing bacterial antibiotic resistance

Previous investigations have shown that antimicrobial regimens lacking activity against identified microorganisms

ICU = intensive care unit.

causing serious infections (e.g. hospital-acquired pneumonia, bloodstream infections) are associated with greater hospital mortality [37-46]. The same finding has more recently been demonstrated for patients with severe sepsis [47-50]. Unfortunately, changing antimicrobial therapy to an appropriate regimen after susceptibility data become available has not been demonstrated to improve clinical outcomes [39,43,45].

These studies suggest that clinicians should strive to administer appropriate initial antimicrobial treatment to patients with serious infections, especially those infected with potentially high-risk antibiotic-resistant pathogens (*Pseudomonas aeruginosa*, *Acinetobacter* species, methicillin-resistant *S. aureus*), in order to minimize the risk of mortality. In addition to selecting an appropriate initial antimicrobial regimen, optimal dosing, interval of drug administration, and duration of treatment are required for antimicrobial efficacy, limiting toxicity, and to prevent the emergence of bacterial resistance [21].

Antimicrobial resistance prevention strategies

The following section describes the most common employed antimicrobial modification strategies aimed at limiting antibiotic resistance. This is provided to place antimicrobial cycling in the proper context of these other interventions. It is assumed that whenever antibiotics are prescribed they will be used in doses and administered at time intervals aimed at optimizing their pharmacokinetic/pharmacodynamic properties [21].

Formal protocols and guidelines

Antibiotic practice guidelines or protocols have emerged as a potentially effective means of both avoiding unnecessary antibiotic administration and increasing the effectiveness of prescribed antibiotics. Automated antimicrobial utilization guidelines have been successfully employed to identify and minimize the occurrence of adverse drug effects due to antibiotic administration and to improve antibiotic selection [51,52]. Their use has also been associated with stable antibiotic susceptibility patterns for both Gram-positive and Gram-negative bacteria, possibly as a result of promoting antimicrobial heterogeneity and specific endpoints for antibiotic discontinuation [53,54].

Antimicrobial guidelines have also been employed to reduce the overall use of antibiotics and to limit the use of inappropriate antimicrobial treatment, both of which could impact upon the development of antibiotic resistance [40,55,56]. One way in which these guidelines limit the unnecessary use of antimicrobial agents is by recommending that therapy be modified when initial empiric broad-spectrum antibiotics are prescribed and the culture results reveal that more narrow-spectrum antibiotics can be employed [56].

Hospital formulary restrictions

Restricted use of specific antibiotics or antibiotic classes from the hospital formulary has been employed as a strategy to reduce the occurrence of antibiotic resistance and antimicrobial costs [21]. Such an approach has been shown to achieve reductions in pharmacy expenses and in adverse drug reactions from the restricted drugs [57]. Restricted use of specific antibiotics has generally been applied to those drugs with a broad spectrum of action (e.g. carbapenems), rapid emergence of antibiotic resistance (e.g. cephalosporins), and readily identified toxicity (e.g. aminoglycosides). To date it has been difficult to demonstrate that restricted hospital formularies are effective in curbing the overall emergence of antibiotic resistance among bacterial species. This may be due in large part to methodologic problems. However, their use has been successful in specific outbreaks of infection with antibiotic-resistant bacteria, particularly in conjunction with infection control practices and antibiotic educational activities [31,58,59]. It is important to note that this type of intervention will only be successfully implemented if such outbreaks are recognized by monitoring patient surveillance cultures and clinical cultures.

Use of narrow-spectrum antibiotics

Another proposed strategy to curtail the development of antimicrobial resistance, in addition to the judicious overall use of antibiotics, is to use drugs with a narrow antimicrobial spectrum. Several investigations suggest that infections such as community-acquired pneumonia can usually be successfully treated with narrow-spectrum antibiotic agents, especially if the infections are not life-threatening [60,61]. Similarly, the avoidance of broad-spectrum antibiotics (e.g. cephalosporins) and the reintroduction of narrow-spectrum agents (penicillin, trimethoprim, gentamicin) along with infection control practices have been successful in reducing the occurrence of *Clostridium difficile* infections [62]. Unfortunately, ICU patients often have already received prior antimicrobial treatment, making it more probable that they will be infected with an antibiotic-resistant pathogen [34]. Initial empiric treatment with broad-spectrum agents is therefore often necessary in order to avoid inappropriate treatment until culture results become available [41,42].

Combination antibiotic therapy

The use of combination antimicrobial therapy has been proposed as a strategy to reduce the emergence of bacterial resistance, as has been employed for *Mycobacterium tuberculosis* [63]. Unfortunately, no convincing data exist to validate this hypothesis for nosocomial infections. Several recent meta-analyses recommend the use of monotherapy with a beta-lactam antibiotic for the definitive treatment of neutropenic fever and severe sepsis, once antimicrobial susceptibilities are known [64,65]. Additionally, there is no definitive evidence that the emergence of antibiotic resistance is reduced by the use of combination antimicrobial therapy. However, empiric combination therapy directed against high-risk pathogens such as *P. aeruginosa* should be encouraged until the results of antimicrobial susceptibility become available. Such an approach to empiric treatment

can increase the likelihood of providing appropriate initial antimicrobial therapy with improved outcomes [46,66].

Shorter courses of antibiotic treatment

Prolonged administration of antibiotics in ICU patients has been shown to be an important risk factor for the emergence of colonization and infection with antibiotic-resistant bacteria [36,40]. Recent attempts have therefore been made to reduce the duration of antibiotic treatment for specific bacterial infections. Several clinical trials have found that 7–8 days of antibiotic treatment is acceptable for most non-bacteremic patients with ventilator-associated pneumonia [35,40,56]. Similarly, shorter courses of antibiotic treatment have been successfully employed in patients at low-risk for ventilator-associated pneumonia [67], in patients with pyelonephritis [68], and in patients with community-acquired pneumonia [69].

Antibiotic heterogeneity

The concept of antibiotic heterogeneity has been suggested as a potential strategy for reducing the emergence of antimicrobial resistance [70]. In theory, a class of antibiotics or a specific antibiotic drug is withdrawn from use for a defined time period and reintroduced at a later point in time in an attempt to limit bacterial resistance to the cycled antimicrobial agents. This offers the potential for antibiotic classes to be used that possess greater overall activity against the predominant ICU pathogens, resulting in more effective treatment of nosocomial infections. Antibiotic cycling is one method of achieving antimicrobial heterogeneity. Other methods include mixing of antibiotic classes, scheduled changes of antibiotic classes, and the rotation of antibiotics.

Gruson and colleagues performed one of the first cycling studies in an ICU setting [71]. Their program consisted of restricting the use of ceftazidime and ciprofloxacin along with cycling other antibiotics directed against Gram-negative bacteria. Antibiotic consumption and resistance profiles were monitored on a monthly basis to help determine the antibiotics to be used during each subsequent time cycle. The occurrence of ventilator-associated pneumonia significantly decreased during the 2-year intervention period compared with the 2-year control period when cycling and restriction of quinolones and cephalosporins were not applied. The reduction in ventilator-associated pneumonia was primarily attributable to a decreased incidence of infection with antibiotic-resistant Gram-negative bacteria. Indeed, it appeared that part of the explanation for these findings was the greater administration of effective antibiotic regimens during the cycling periods, as also demonstrated in previous investigations [72,73].

The results of Gruson and colleagues were confirmed by Raymond and colleagues, who conducted a 2-year before–after study in a surgical ICU [74]. Specific antibiotic rotation schedules were developed for pneumonia and for intra-abdominal infections, respectively. Outcome analysis revealed significant reductions in the incidence of Gram-positive bacterial infections, of antibiotic-resistant Gram-negative bacterial infections, and of mortality associated with infection. This same group of investigators subsequently demonstrated that this strategy of antibiotic rotation in the ICU setting was associated with a reduction in infection-related morbidity (hospital-acquired and antibiotic-resistant hospital-acquired infection rates) on non-ICU wards to which patients were transferred [75]. Unfortunately, these earlier studies of antibiotic rotation suffered from methodological limitations, including lack of concurrent control groups and changes in infection control practices during the cycling interventions.

van Loon and colleagues cycled two different antibiotic classes (fluoroquinolone and beta-lactam) in a surgical ICU during four 4-month cycling periods, obtaining respiratory aspirates and rectal swab cultures [76]. In all, 388 patients were evaluated along with 2520 cultures. There was good adherence to the antibiotic protocol, but overall antibiotic use increased by 24%. Acquisition of resistant bacteria was highest during use of levofloxacin and piperacillin/tazobactam. The potential for selection of antibiotic-resistant Gram-negative bacteria during periods of homogeneous exposure increased from cefpirome to piperacillin/tazobactam to levofloxacin.

Warren and colleagues similarly cycled four classes of antibiotics with Gram-negative activity over 3-month to 4-month intervals for 24 months, following a 5-month baseline period of uncontrolled-antibiotic use [77]. Acquisition of resistance was evaluated using cultures of *Enterobacteriaceae* and *P. aeruginosa* obtained from rectal swabs on admission, weekly in the ICU, and at discharge. Among study patients who were not already cultured with a resistant organism, the rate of acquisition of enteric colonization with a bacteria resistant to any of the target drugs remained stable during the cycling period – *P. aeruginosa*: relative rate, 0.96; 95% confidence interval, 0.47–2.16; and *Enterobacteriaceae*: relative rate, 1.57; 95% confidence interval, 0.80–3.34. However, the proportion of *P. aeruginosa* resistant to the target drugs increased hospital-wide during the cycling period but decreased in the ICU undergoing antimicrobial cycling [77].

Optimizing pharmacokinetic/pharmacodynamic principles

Antibiotic concentrations that are sublethal can promote the emergence of resistant pathogens. Optimization of antibiotic regimens on the basis of pharmacokinetic/pharmacodynamic principles could play a role in the reduction of antibiotic resistance.

The duration of time that the serum drug concentration remains above the minimum inhibitory concentration of the

antibiotic enhances the bacterial eradication with beta-lactams, carbapenems, monbactams, glycopeptides, and oxazolidinones. Frequent dosing, prolonged infusion times, or continuous infusions can increase the duration of time that the serum drug concentration remains above the minimum inhibitory concentration of the antibiotic, and can improve clinical and microbiological cure rates [78-81].

In order to maximize the bactericidal effects of aminoglycosides, clinicians must optimize the maximum drug concentration to minimum inhibitory concentration ratio. A maximum drug concentration to minimum inhibitory concentration ratio ≥ 10:1 using once-daily aminoglycoside dosing (5–7 mg/kg) has been associated with preventing the emergence of resistant organisms [82-84].

The 24-h area under the antibiotic concentration curve to minimum inhibitory concentration ratio is correlated with fluoroquinolone efficacy and prevention of resistance development. A 24-h area under the antibiotic concentration curve to minimum inhibitory concentration ratio value >100 has been associated with a significant reduction in the risk of resistance development while on therapy [85,86].

Summary

Clinicians working in the ICU setting should routinely employ antibiotic strategies aimed at limiting the emergence of resistance [21]. These strategies should focus on providing appropriate antibiotics to patients with infection, based on culture data and antimicrobial susceptibility testing, while using optimal dosing of antibiotics for the shortest duration of use that is clinically acceptable.

Competing interests

The author(s) declare that they have no competing interests.

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