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The intensive care unit as a research laboratory: Developing strategies to prevent antimicrobial resistance

Marin H. Kollef
Washington University School of Medicine in St. Louis

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The Intensive Care Unit as a Research Laboratory: Developing Strategies to Prevent Antimicrobial Resistance

MARIN H. KOLLEF

ABSTRACT

***Objective*: To assemble the available clinical data on the prevention of antimicrobial resistance in the intensive care unit (ICU) setting.**

***Data Source*: A MEDLINE database search and references from identified articles were employed to obtain the literature relating to the prevention of antimicrobial resistance in the ICU.**

***Conclusions*: The ICU presents a unique environment for the conduct of clinical research. The closed physical space with centralized patient management and efficient data recovery allows important clinical questions to be evaluated in a timely manner. Antimicrobial resistance has emerged as an important determinant of mortality for patients in the ICU. Additionally, there is currently a limited pipeline of new agents for the treatment of emerging bacteria with new resistance genes that pose an increasing threat to the ICU patient. Effective strategies for the prevention of antimicrobial resistance within ICUs are available and should be implemented aggressively. These strategies can be divided into non-pharmacologic infection-control strategies (e.g., routine hand hygiene, infection-specific prevention protocols) and antibiotic management strategies (e.g., shorter courses of appropriate antibiotics, narrowing of the antimicrobial spectrum on the basis of culture results). Additional studies conducted in ICUs are needed urgently to identify the optimal approaches for the management of antibiotics in order to balance the need for efficacy with the ability to minimize resistance.**

ANTIMICROBIAL RESISTANCE HAS EMERGED as an important issue influencing patient mortality and overall resource utilization in the intensive care unit (ICU) setting [1–3]. Intensive care units worldwide are faced with increasingly rapid emergence and spread of antibiotic-resistant bacteria. Both gram-negative and gram-positive bacteria resistant to antibiotics are reported as important causes of hospital-acquired infections [4–12]. In many circumstances, particularly with methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, and gram-negative bacteria producing extended-spectrum beta-lactamase (ESBL) enzymes with resistance to multiple other antibiotics, few agents remain for effective treatment [13–20].

Intensive care units are an important area for the emergence of antimicrobial resistance be-

Pulmonary and Critical Care Division, Washington University School of Medicine, Barnes Jewish Hospital, St. Louis, Missouri.

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cause of the frequent use of broad-spectrum antibiotics, the crowding of patients with high levels of disease acuity within relatively small specialized areas, reductions in nursing and other support staff because of economic pressures (increasing the likelihood of person-to-person transmission of microorganisms), and the presence of more chronically and acutely ill patients who require prolonged hospitalization and often harbor antibiotic-resistant bacteria [2,21,22]. Therefore, it makes sense to employ the ICU as a model for the conduct of clinical research aimed at curbing or at least minimizing this problem. Many of the strategies described below have been developed in the ICU setting but also are applicable in other areas of the hospital. In general, these interventions simply attempt to balance the somewhat-competing goals of providing appropriate antimicrobial treatment to critically ill patients while avoiding the unnecessary administration of antibiotics. It is this balance that needs to drive future clinical research in the area of resistance. The strategies described in this review adhere to the Centers for Disease Control and Prevention 12-step program for the prevention of antimicrobial resistance (http://www.cdc.gov/drugresistance/healthcare). One of the key elements in this strategy is to consult experts in the field of antimicrobial resistance (e.g., infectious disease experts, infection control practitioners, microbiologists) when designing interventions aimed at minimizing the emergence of antimicrobial resistance.

ANTIBIOTIC EXPOSURE IS THE MAIN RISK FACTOR FOR ANTIMICROBIAL RESISTANCE

A number of investigators have demonstrated a close association between the use of antibiotics and the emergence of subsequent antibiotic resistance in both gram-negative and gram-positive bacteria [23–33]. Therefore, strategies aimed at limiting or modifying the administration of antimicrobial agents have the greatest likelihood of preventing resistance to these agents. Other factors promoting antimicrobial resistance include prolonged hospitalization; the presence of invasive devices such as endotracheal tubes and intravascular catheters, possibly because of the formation of biofilms on their surfaces; residence in long-term treatment facilities; and inadequate infection control practices [22]. The emergence of new strains of existing pathogens within the community has created additional stressors favoring the entry of resistant microorganisms into the ICU. This has been demonstrated most recently by the identification and spread of community-associated methicillin-resistant *S. aureus* (CA-MRSA) [34,35]. However, prolonged regimens of antimicrobial agents appear to be the most important factor promoting the emergence of antibiotic resistance, one that is potentially amenable to intervention [36,37].

ANTIBIOTIC RESISTANCE AS A DETERMINANT OF HOSPITAL MORTALITY AND HIGHER HEALTH CARE COSTS

Antimicrobial regimens lacking activity against identified microorganisms causing serious infections (i.e., inappropriate antimicrobial therapy) are associated with greater hospital mortality [38–47]. More recently, the same finding has been demonstrated for patients with severe sepsis [48–51]. Unfortunately, changing antimicrobial therapy to an appropriate regimen after susceptibility data become available does not improve clinical outcomes [40,44,46]. These studies suggest that escalating resistance has led to greater overall hospital mortality, in part through the administration of less effective antimicrobial agents. The recent Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines for the treatment of ventilator-associated pneumonia (VAP) emphasize the importance of inappropriate antimicrobial therapy as a determinant of hospital mortality [52]. These guidelines also stress the importance of maintaining local, frequently updated antibiograms within individual hospitals and ICUs to ensure the appropriateness of antibiotic coverage and the use of proper drug doses to optimize the tissue concentrations of antibiotics.

In addition to increased hospital mortality, antimicrobial resistance is associated with excess costs. Most of this cost is associated with the acquisition of nosocomial infections, many of which are potentially caused by antibiotic-resistant bacteria [33,53]. However, resistance may actually confer added morbidity and costs as well. For example, MRSA infections are associated with worse clinical outcomes than those attributable to methicillin-sensitive *S. aureus* (MSSA). Cosgrove et al., in a meta-analysis of 30 investigations focusing on bacteremia, concluded that MRSA bacteremia independently increased the risk of death [54]. Similarly, Blot et al. observed that the mortality difference attributable to MRSA relative to MSSA was approximately 25% [55].

All of these efforts have been limited by lack of information about two key confounders: Severity of illness and administration of inappropriate antibiotic therapy. Generally, subjects who develop infections with MRSA are more severely ill, both at admission and at the time of diagnosis, than subjects infected with MSSA. Patients with VAP caused by MRSA also tend to have been hospitalized longer than similar persons with MSSA infection. Most careful investigators have attempted to control for confounding by severity. We recently conducted a retrospective analysis of a large cohort of subjects with bronchoscopically confirmed VAP caused by *S. aureus*, which suggested that MRSA infection has important effects on ICU length of stay and healthcare costs [56]. That is, independent of major contributors to ICU length of stay, such as severity of illness, duration of mechanical ventilation, and administration of appropriate antibiotic therapy, MRSA increased the ICU hospitalization by nearly 50%. Correcting for outliers and for those who consume substantial resources by restricting the analysis to ICU-free days confirmed the disproportionate impact of MRSA on ICU bed use. Assuming conservatively that the cost per day of ICU care equals $2,000 in the U.S., one can compute that each case of MRSA VAP amplified hospital costs by at least $10,000 to $15,000. Therefore, there is an economic motive, along with a clinical efficacy motive, for attempting to minimize the emergence of antibiotic resistance.

WHAT STRATEGIES PREVENT ANTIMICROBIAL RESISTANCE?

Infection control strategies

In general, strategies aimed at the prevention of nosocomial infections caused by antibiotic-resistant bacteria should be employed routinely in all ICUs (Table 1). These interventions can be separated into two broad categories: Specific interventions aimed at the primary prevention of nosocomial infections (e.g., catheter-associated bacteremia, VAP) and the use of infection control practices to prevent horizontal transmission of antibiotic-resistant bacteria.

Hand hygiene and protective barriers

Hand hygiene is still the most important and effective measure to prevent horizontal transmission of antibiotic-resistant nosocomial pathogens [57,58]. Unfortunately, greater patient workloads and decreased staffing have contributed to poor compliance with handwashing and other routine infection control measures, especially in the ICU [59]. Alternative hand hygiene methods using alcohol solutions have been developed that are effective, do not require sinks, can be performed more rapidly than traditional handwashing using soap solutions in order to improve compliance, and are more effective at reducing bacterial colony counts on the hands (60,61). The use of gowns and gloves also reduces horizontal transmission of antibiotic-resistant bacterial pathogens [62,63]. Therefore, appropriate hand disinfection and barrier precautions should be employed to reduce transmission of antibiotic-resistant bacteria in the ICU [64]. The importance of employing routine barrier precautions has been amplified with the emergence of antibiotic-resistant strains of *Clostridium difficile* that possess added virulence attributable both to antibiotic resistance and to the elaboration of a binary toxin [64–66].

The use of hand hygiene, universal gloving, and strict contact precautions appears to be most important in patients colonized or at high risk for colonization with antibiotic-resistant bacteria [67]. Additionally, the use of surveil-

Table 1. Strategies to Prevent Resistance in the ICU

P: Prophylactic administration of antibiotics should be discouraged unless clinically indicated in high-risk patients.

R: Routine appropriate (i.e., active against the identified pathogen) and adequate (e.g., optimal dosing, duration of therapy) treatment of infections.

E: Encourage avoidance of unnecessary use of antimicrobial agents (e.g., empiric antibiotics in the absence of clinical and microbiologic data supporting the presence of infection).

V: Ventilator-associated pneumonia and other specific infection prevention and treatment protocols should be establisned for the local ICU.

E: Employ antiseptic techniques for all invasive procedures.

N: Noncompliance with local infection prevention and antibiotic treatment protocols should not be tolerated.

T: Try always to de-escalate to more narrow-spectrum antibiotic regimens on the basis of culture results and antimicrobial susceptibility data.

R: Restricted formulary control for specific antimicrobial agents or drug classes if there are outbreaks of antibiotic-resistant bacteria.

E: Evade antimicrobial homogeneity. Promote appropriate use of multiple drug classes (e.g., avoid highly restricted antibiotic formularies; consider use of antimicrobial mixing).

S: Strict isolation precautions for patients at high risk for (e.g., patients transferred from long-term care facilities) or found to have infection/colonization with clinically important antibiotic-resistant bacteria.

I: Infectious disease consultation for difficult-to-manage antibiotic-resistant infections and infection control problems.

S: Systematic disinfection of commonly used instruments, devices, patient care materials, and rooms between uses.

T: Teach infection control procedures and optimal antibiotic utilization practices to all staff participating in the care of ICU patients.

A: Active culture surveillance programs to identify patients infected/colonized with clinically important antibiotic-resistant bacteria.

N: Narrow-spectrum antibiotics should be used when appropriate on the basis of microbiology data.

C: Cease appropriate antibiotics for bacterial infections 24 to 48 hours after achieving an appropriate clinical response.

E: Embrace locally developed antibiotic guidelines and protocols aimed at balancing antimicrobial efficacy and preventing the emergence of resistance.

lance cultures to identify patients colonized with antibiotic-resistant bacteria, allowing them to be placed in isolation in an efficient manner, may help to reduce the spread of resistant bacteria [63,68]. Nevertheless, controversy exists over the optimal use of strict isolation precautions typically employing sterile gloves, gowns, and more aggressive surveillance practices to prevent the spread of resistant microbes [69,70]. One potential concern about these techniques is that they may pose a safety issue if health care workers have less contact with critically ill patients [71]. However, the threat and consequences of horizontal cross-infection with antibiotic-resistant bacteria probably outweigh the potential risks of isolation practices in the ICU setting.

Surveillance to detect antimicrobial resistance

Antimicrobial surveillance appears to be a reasonable strategy for detecting the presence of antibiotic-resistant organisms. This may allow the application of both appropriate contact precautions and the prescription of appropriate antimicrobial treatment. Michel et al. recently evaluated twice-weekly quantitative surveillance cultures of endotracheal aspirates in all intubated patients who were receiving mechanical ventilation to assist in the choice

of antibiotic when VAP was suspected [72]. In 34 of 41 cases (83%), pre-VAP endotracheal aspirate cultures identified the same pathogens with similar antibiotic susceptibility patterns as cultures of bronchoalveolar lavage (BAL) fluid obtained when VAP was suspected, and the antibiotic selected on the basis of the results of endotracheal aspirate cultures was appropriate in 38 patients (95%). In contrast, had the original ATS Guidelines [73] or those of Trouillet et al. [33] been followed, the empiric antibiotic treatment would have been appropriate in only 68% and 83% of the patients, respectively. The main reason for the inappropriate coverage using the published guidelines was the failure to treat highly resistant pathogens. In addition to the better coverage, antibiotic selection on the basis of pre-VAP endotracheal aspirate cultures reduced the unnecessary use of some antibiotics, such as the β-lactam agents, compared with strategies based on the original ATS and Trouillet guidelines [33,73]. The results of this study suggest that twice-weekly quantitative surveillance cultures of endotracheal aspirates will assist in the early prescription of appropriate antibiotic treatments for patients who develop VAP. This strategy may improve clinical outcomes, reduce antibiotic resistance within ICUs, and lower hospitalization costs.

Infection-specific protocols and guidelines

Several focused clinical efforts have demonstrated the potential for practice guidelines or protocols promoting sound clinical practices to reduce the rates of VAP [74–79]. Similarly, prevention programs have reduced the occurrence of nosocomial bacteremia by achieving higher rates of compliance with basic prevention practices [80–84]. These protocols and guidelines apply well-accepted practices for infection-specific prevention (e.g., use of sterile gowns/masks/gloves and full drapes during catheter insertion to prevent catheter-associated bacteremia; drainage of ventilator circuit condensate) that are promoted in mandatory education programs. The success of such interventions depends on the degree to which they are accepted by the local ICU community and overall compliance with their implementation [85,86].

Reducing ICU length of stay

The duration of ICU stay and of mechanical ventilation are important risk factors for the development of infections caused by antibiotic-resistant bacteria [33,87]. Therefore, efforts aimed at reducing the duration of hospitalization or exposure to high-risk environments such as the ICU could also reduce the occurrence of infections or colonization attributable to antibiotic-resistant pathogens. Noninvasive mechanical ventilation is one accepted approach to minimizing the duration of hospitalization secondary to respiratory failure; its use has been associated with a lower risk of nosocomial infection [88–90].

Avoidance of the biofilm burden

Biofilms form on surfaces such as endotracheal tubes or urinary catheters when they are encountered by bacteria that settle on them and upregulate genes involved in matrix production [91]. The colonies of bacteria forming the biofilm and detaching from it are under the control of chemical signals of the same type that regulate quorum sensing, and these regulatory molecules guide the formation of the slime-enclosed microcolonies and water channels that make up the biofilm. Certain bacteria, such as *Pseudomonas* species, appear to be more capable of forming biofilms [92]. Biofilms appear to promote the emergence of antibiotic resistance by limiting the access of antibiotics to the bacteria and by inducing the production of chemicals promoting antibiotic resistance [93]. Currently, biofilm prevention technology has been applied only to urinary catheters and central venous catheters.

In general, invasive devices such as central venous catheters should be removed as soon as clinically indicated, as they promote the emergence of infections with antibiotic-resistant bacteria. However, for individuals who cannot be managed without these devices, antimicrobial-coated intravascular and urinary catheters have been associated with reductions in nosocomial infection rates [94–96]. Interestingly, a

recent in vitro study found that subinhibitory concentrations of aminoglycoside antibiotics induce biofilm formation by *Pseudomonas aeruginosa* and *Escherichia coli* [97]. In *P. aeruginosa*, a gene, designated "aminoglycoside response regulator" (*arr*), is essential for this induction and contributes to biofilm-specific aminoglycoside resistance. Therefore, it appears that the degree of antibiotic penetration into a tissue compartment such as the lung can determine whether antibiotic resistance emerges. This finding has been the impetus for the evaluation of aerosolized aminoglycosides as an adjunct for the treatment of gram-negative bacterial pneumonia.

Vaccines

Vaccines for the prevention of antibiotic-resistant bacterial infections are not currently available for clinical use in the ICU setting. However, conjugate vaccine-induced antibodies to *S. aureus* have been demonstrated to reduce blood-stream infection with this pathogen among patients requiring chronic hemodialysis [98]. Investigation of this vaccine among potential ICU patient populations is ongoing [99]. More importantly, the threat of pandemic avian influenza not only carries the risk of a large proportion of the population succumbing to this disease but the threat of greater antibiotic resistance secondary to the likely widespread empiric use of antibiotics during the flu outbreak. This risk has resulted in international efforts to develop a vaccine against this important threat [100].

ANTIBIOTIC MANAGEMENT STRATEGIES

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 (Fig. 1). Automated antimicrobial utilization guidelines have been successful in identifying and minimizing the occurrence of adverse effects secondary to antibiotic administration and to better antibiotic selection [101,102]. Their use has also been associated with stable antibiotic susceptibility patterns for both gram-positive and gram-negative bacteria, possibly as a result of pro-

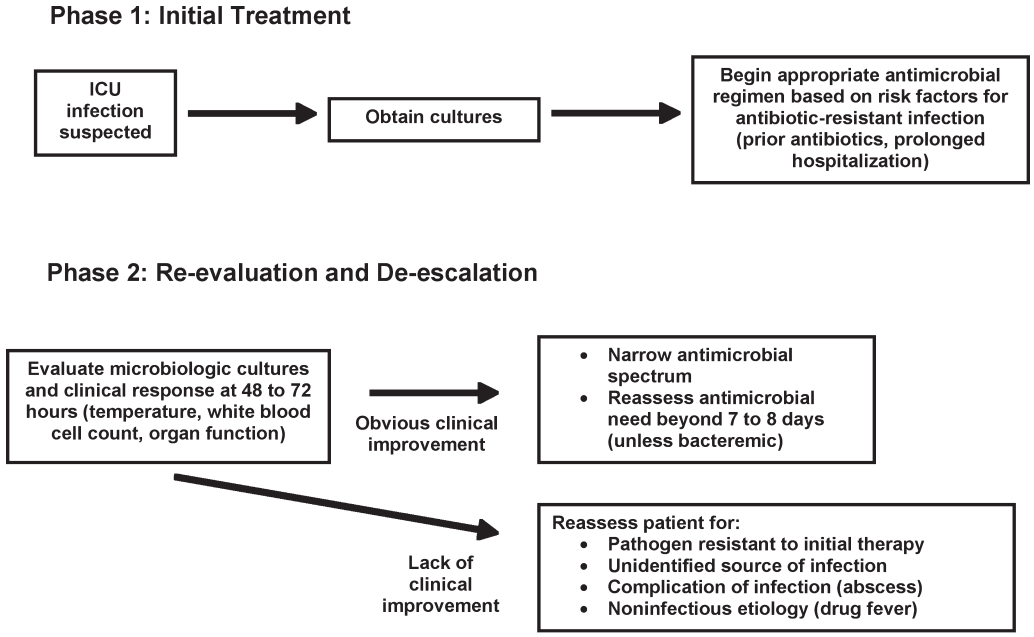

FIG. 1. Antimicrobial treatment algorithm aimed at providing appropriate initial treatment to patients while monitoring clinical response along with microbiologic data to facilitate antimicrobial de-escalation (e.g., more narrow-spectrum regimen, shortest course of therapy according to individual patient clinical response).

moting antimicrobial heterogeneity and specific endpoints for antibiotic discontinuation [103,104]. Automated and nonautomated 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 the development of antibiotic resistance [41,105,106]. One way these guidelines limit the unnecessary use of antimicrobial agents is by recommending that initial prescriptions for empiric broad-spectrum antibiotics be modified when the culture results reveal that narrow-spectrum antibiotics can be employed instead [106]. This practice is described as "antimicrobial de-escalation." Unfortunately, clinicians appear to be reluctant to de-escalate despite the emerging evidence in favor of this concept [107].

Hospital formulary restrictions

Restricted use of specific antibiotics or antibiotic classes from the hospital formulary has been employed to reduce the occurrence of antibiotic resistance as well as drug acquisition costs [22]. Although such an approach can achieve reductions in pharmacy expenses and adverse reactions attributable to the restricted drugs [108], not all experiences have been successful; indeed, some have been associated with higher overall antibiotic costs [109]. Restricted use of specific antibiotics has generally been applied to those 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. This may be secondary 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 [30,110,111]. It is important to note that implementation of this type of intervention will be successful only if such outbreaks are recognized. This requires a systematic approach to patient surveillance for the detection of potentially antibiotic-resistant bacteria and a microbiology laboratory that can detect the presence of resistance. The latter is not always a simple matter, especially for the detection of gram-negative bacteria possessing ESBL enzymes [30,31].

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 have suggested that infections such as community-acquired pneumonia can usually be treated successfully with narrow-spectrum agents, especially if the infections are not life threatening [112, 113]. Similarly, avoidance of broad-spectrum antibiotics (e.g., cephalosporins) and reintroduction of narrow-spectrum agents (e.g., penicillin, trimethoprim, gentamicin) along with infection control practices have reduced the occurrence of *C. difficile* infections [114]. Unfortunately, ICU patients often have already received antimicrobial treatment, making it more likely that they will be infected with an antibiotic-resistant pathogen [33]. Additionally, pathogens in the community have changed with the advent of more antibiotic-resistant bacteria such as MRSA and the increasing presence of risk factors for health care-acquired infections [115]. Therefore, initial empiric treatment with broad-spectrum agents is often necessary for ICU patients to avoid inappropriate treatment until culture results become available [42,43].

Quantitative cultures and assessment of infection risk

Pneumonia is the most common hospital-acquired infection among mechanically ventilated patients [3,116]. Unfortunately, establishing a definite diagnosis is difficult because of the nonspecific signs and symptoms associated with this infection. This, in turn, has resulted in largely empiric treatment for VAP. A recent meta-analysis of four randomized trials demonstrated that quantitative bacterial cultures of material obtained from the lower respiratory tract may facilitate de-escalation of empiric broad-spectrum antibiotics and reduce drug-

specific days of treatment [117]. Another recent study found that patients with a clinical suspicion of VAP and culture-negative BAL results for a major pathogen could safely have antimicrobial therapy discontinued within 72 h [118]. Interestingly, the mean modified clinical pulmonary infection score of these patients was approximately six, suggesting that this quantitative clinical assessment of the risk for VAP could have been employed to discontinue antibiotics [119].

Combination antibiotic therapy

Several recent meta-analyses recommend the use of monotherapy with a beta-lactam antibiotic as opposed to combination therapy including an aminoglycoside for the definitive treatment of neutropenic fever and severe sepsis once antimicrobial susceptibilities are known [120,121]. Additionally, there is no definitive evidence that the emergence of antibiotic resistance is reduced by 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 testing become available. Such an approach to empiric treatment can increase the likelihood of providing appropriate initial antimicrobial therapy with improved outcomes [47]. Patients at high risk for infection with potentially antibiotic-resistant bacteria usually can be identified by the presence of factors such as prior antibiotic exposure and longer hospitalization preceding the onset of nosocomial infection [33].

Antibiotic cycling and scheduled antibiotic changes

The concept of antibiotic class cycling has been suggested as a strategy for reducing the emergence of antimicrobial resistance [122]. In theory, a class of antibiotics or a specific antibiotic drug is withdrawn from use for a defined time and reintroduced later in an attempt to limit bacterial resistance to the cycled antimicrobial agents. This offers the potential for antibiotic classes that possess greater overall activity against the predominant ICU pathogens to be used, resulting in more effective treatment of nosocomial infections. Unfortunately, mathematical modeling suggests that the use of antibiotic cycling will be inferior to mixing of antibiotics as a strategy to reduce the emergence of resistance [123]. Nevertheless, several earlier studies of antimicrobial cycling have found beneficial outcomes in terms of antibiotic resistance, with benefits extending outside the ICU setting [124–127]. Because of methodological limitations, including the introduction of uncontrolled changes in infection control and the lack of appropriate control groups, interpretation of these studies has been difficult.

Two recent studies attempted to minimize the influences of confounding effects in order to evaluate the role of antimicrobial cycling on resistance. Warren et al., employing scheduled surveillance cultures, demonstrated that antimicrobial cycling did not influence the emergence of resistance in an ICU adhering to the principles of antimicrobial de-escalation [128]. Similarly, van Loon et al., who evaluated the impact of antibiotic cycling using rectal and respiratory surveillance cultures and DNA fingerprinting [129], found that overall antibiotic use increased by 24%, with acquisition of resistant bacteria being highest with levofloxacin and pipercillin/tazobactam exposure. Although antimicrobial heterogeneity or mixing seems to be a logical policy, simple cycling of antibiotics combined with prolonged treatment seems only to promote further antibiotic resistance [130].

Antimicrobial decolonization strategies

The prophylactic administration of parenteral antibiotics reduces the occurrence of nosocomial infections in specific high-risk patient populations requiring intensive care [131,132]. Similarly, topical antibiotic administration (i.e., selective digestive decontamination), with or without concomitant parenteral antibiotics, is also effective at reducing nosocomial infections [133–135]. However, the routine use of selective digestive decontamination has been associated with the emergence of antimicrobial resistance [136,137]. Additionally, the results of recent negative trials for VAP prevention employing iseganan and chlorhexidine, an antimicrobial peptide and antiseptic, respectively, to decontaminate the oropharynx in mechanically ventilated patients sheds doubt on the overall

utility of this practice [138,139]. According to these studies, antimicrobial and non-antimicrobial agents should be considered for oral decontamination only in appropriate high-risk ICU patients or to assist in the containment of outbreaks of infections with multi-drug-resistant bacteria in conjunction with established infection control practices [140].

Shorter courses of antibiotic treatment

Prolonged administration of antibiotics to ICU patients is an important risk factor for the emergence of colonization and infection with antibiotic-resistant bacteria [33,37,130]. Therefore, recent attempts have been made to reduce the duration of antibiotic treatment for specific bacterial infections. Several clinical trials have found that seven or eight days of antibiotic treatment is acceptable for most non-bacteremic patients with VAP [36,41,106]. Similarly, shorter courses of antibiotic treatment have been successful in patients at low risk for VAP [106,118,119], with pyelonephritis [141], and with community-acquired pneumonia [142]. In general, the shorter-course regimens have been associated with significantly lower risks of emergence of antimicrobial resistance than the more traditional durations of 14 to 21 days. In the future, more specific markers for the presence of bacterial infection (e.g., sTREM1) may allow shorter courses of empiric antibiotic administration in patients without identified bacterial infection [143,144]. Several recently published guidelines for the antibiotic management of nosocomial pneumonia and severe sepsis recommend the discontinuation of empiric antibiotic therapy after 48–72 h if cultures are negative or the signs of infection have resolved [52,145].

Optimizing pharmacokinetic/pharmocodynamic (PK/PD) principles

Sublethal antibiotic concentrations can promote the emergence of resistant pathogens. Optimization of antibiotic regimens on the basis of pharmacokinetic and pharmacodynamic (PK/PD) principles thus could play a role in the reduction of antibiotic resistance. The time the serum drug concentration remains above the minimum inhibitory concentration (MIC) of the antibiotic ($T > MIC$) enhances bacterial eradication by beta-lactams, carbapenems, monobactams, glycopeptides, and oxazolidinones. Frequent dosing, prolonged infusion times, or continuous infusions can increase the $T > MIC$ and improve clinical and microbiological cure rates [146–150]. In order to maximize the bactericidal effects of aminoglycosides, clinicians must optimize the maximum drug concentration (C_{max}):MIC ratio. A C_{max}:MIC ratio of $\geq$10:1 using once-daily aminoglycoside dosing (5–7 mg/kg) has prevented the emergence of resistant organisms, improved the clinical response to treatment, and avoided toxicity [151–153]. The 24-hour area under the antibiotic concentration curve:MIC ratio (AUIC) is correlated with fluoroquinolone efficacy and prevention of resistance development. An AUIC value >100 has been associated with a significant reduction in the risk of resistance development during therapy [154–155].

CONCLUSION

The ICU should be considered a laboratory for the conduct of important outcomes research. Because of the importance of antimicrobial resistance as a determinant of outcome for critically ill patients, this is a logical location for the investigation of this important clinical problem. Although a lack of federal funding and resources may stand in the way of such research, its importance requires a dedicated group of investigators willing to devote time and career development to this area. Therefore, long-term efforts are required to identify and develop new and dependable sources of funding to enhance this scientific agenda, as well as other important areas of ICU outcomes research.

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Address reprint requests to:
Dr. Marin H. Kollef
Pulmonary and Critical Care Division
Washington University School of Medicine
Barnes Jewish Hospital
Campus Box 8052
660 South Euclid Avenue
St. Louis, MO 63110

E-mail: mkollef@im.wustl.edu