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Empiric antibiotics in the critically ill patient: Panacea or poison?

BY MARY-ANNE AARTS, MD, AND JOHN MARSHALL, MD

Empiric antibiotic therapy – the administration of antibiotics before a microbiological diagnosis of infection is established – is a widely used but unproven practice in contemporary intensive care units (ICUs). The perceived need for preemptive antibiotic therapy stems from factors unique to infection in the critically ill. Nosocomial infection is common,¹ occurring in up to one-third of all patients admitted to the ICU. The diagnosis is challenging²⁻⁵ since clinical manifestations are non-specific,^{6,7} culture data are unreliable because of concomitant antibiotic use,⁸ and the differentiation of colonization from invasive infection is notoriously difficult.^{9,10} Infecting organisms are commonly resistant to first-line antibiotics.¹¹ ICU-acquired infections develop in the sickest patients, for whom maximal therapeutic intervention is the norm, and clinicians are often reluctant to stop therapy even when cultures are negative.^{12,13} On the other hand, indiscriminate use of broad-spectrum coverage is associated with the emergence of multiresistant organisms, an increased rate of super-infections in exposed patients, and substantial cost for the healthcare system.¹⁴⁻¹⁷ Individual clinicians vary in their approach to the indications for empiric therapy and attitudes, though divergent, are strongly held. Although the benefits of antibiotics as specific anti-infective therapy for community-acquired infection are well-accepted, those of empiric broad-spectrum coverage for suspected nosocomial infection in the ICU are not. In addition, available research does not permit firm conclusions about whether such empiric therapy helps, harms, or yields no net benefit. Potentially, a practice of restrictive antibiotic therapy that delays the institution of antibiotics until infection is documented microbiologically and encourages the use of narrow-spectrum therapy will prove to be as efficacious as empiric broad-spectrum therapy for critically ill patients with suspected nosocomial infection. This restrictive strategy may reduce the attendant costs of unnecessary treatment and reduce the risks of antibiotic exposure to patients.

Antibiotic resistance is a significant public health concern

The introduction of effective antimicrobial agents in the mid-20th century is recognized as one of the great accomplishments of modern scientific medicine. Infections that were previously lethal due to microorganisms such as *Streptococci* or the tubercle bacillus yielded to therapy and less serious, but more common infections, such as tonsillitis, otitis media, and urinary tract infections could be quickly cured. The use of prophylactic antibiotics led to a significant reduction in the morbidity of surgery, while documentation of an infectious etiology for peptic ulcer disease has virtually eliminated the need for surgical management of this common disorder.



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Although antibiotics have revolutionized the treatment of individual patients, their impact on public health is less clear. An analysis of the consequences of antibiotic use in hospitalized patients revealed that rates and mortality of infection were unchanged when data from the 1930s were compared with those from the 1950s. However, the bacterial flora of these infections had been significantly altered: endogenous organisms replaced exogenous species as the most common infecting pathogens.¹⁸ Data from the Centers for Disease Control (CDC) show that although there was a 10-fold reduction in infectious disease mortality over the first half of the 20th century (largely through advances in public health measures), mortality rates remained constant during the second half of the century.¹⁹

The widespread introduction of antibiotics has had a profound effect on microbial ecology, promoting the spread of antibiotic resistance and potentially threatening the very utility of antibiotics in treating infection. Vancomycin resistance, for example, has been detected in strains of *S aureus*, raising the fear that future treatment of Staphylococcal infections may be ineffectual. The rapid spread of antibiotic resistance has been a cause for significant concern and has prompted editorial comment on the need to reduce the unnecessary use of these agents. The ICU is not only a significant consumer of antibiotic agents, but is also a reservoir of resistant organisms. It is, therefore, an attractive venue for the evaluation of strategies to limit unnecessary antibiotic use.

Empiric antibiotic use for suspected ICU-acquired infection is common, but unproven

The goal of empiric antibiotic therapy is to provide effective therapy prior to the availability of the results of culture and radiological investigations. The expectation is that early treatment of infection will result in improved patient survival.¹⁰ Empiric therapy is commonly employed in patients with suspected ICU-acquired infection. Infection is difficult to diagnose in the ICU even when culture data are available because fever, leukocytosis, and hemodynamic instability can be the result, not only of infection, but also of such common noninfectious triggers as tissue ischemia, iatrogenic insult, drug toxicity, and multiple organ failure.²⁰

An American study found that empiric therapy was initiated for suspected infection in 1557/3708 (42%) of consecutive ICU patients and ward patients diagnosed as having sepsis, severe sepsis, or septic shock on the basis of clinical findings. Interestingly, only 41% of these patients had an infection documented by a positive culture result.⁷ Similar antibiotic prescribing

practice patterns have been observed in Australian and New Zealand ICUs. In a multicentre study of patients receiving antibiotics, suspected infection was the second most common indication for prescribing antibiotics after surgical prophylaxis.²¹ Of 183 patients who received empiric therapy, only 46 (25.1%) were found to have confirmed infection. At the University of Toronto, we recently completed a multicentre international study of 529 ICU patients with suspected infection to evaluate a novel assay for endotoxin. The diagnosis of infection was established by CDC criteria and through a detailed retrospective review by a clinical evaluation committee of clinicians with expertise in infection in the critically ill. Only 26% of patients met CDC criteria for infection and only 17% were adjudicated as being infected by the committee. On the other hand, 80% of these patients were prescribed antibiotics, and this percentage did not change over the 7 days of the study [Marshall et al, unpublished].

Choice of empiric antibiotic agents

Even when culture results become available, empiric therapy is frequently found to be inadequate. In 4 studies reviewed by Kollef,²² rates of inadequate empiric therapy for suspected ventilator-associated pneumonia (VAP) ranged from 27% to 73% because of the prevalence of resistant Gram-negative bacteria (*Pseudomonas aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae* and *Enterobacter* species) or methicillin-resistant *Staphylococcus aureus* (MRSA). In a study of 530 patients with clinically diagnosed VAP, 214 empiric antibiotic regimens were later modified because of isolation of an organism not covered by the empiric regimen (62.1%), lack of clinical response (36%), or the development of resistance (6.6%).²³ Alternatively, when culture results are negative or inconclusive, empiric antibiotics are rarely discontinued.^{12,13,24,25} Failure to stop empiric therapy may reflect a fear of missing occult infection or the perception that clinical improvement implies a therapeutic response, while a worsening clinical course implies a new infection.^{9,10}

Widespread empiric administration of broad-spectrum agents does not appear to have reduced the prevalence of nosocomial infection. A European point prevalence study – the EPIC study – found the prevalence of nosocomial infections in ICU patients to be 21%.¹ Although case-controlled studies suggest that these infections are associated with an increased risk of morbidity and mortality,^{1,14,26,27} when patients are matched by severity of illness and degree of multiple organ dysfunction, nosocomial infection is no longer independently associated with mortality.²⁸⁻³⁰ It is unclear, therefore, whether mortality is attributable to infection or alterna-

tively, whether the development of nosocomial infection is a marker of illness severity and an increased risk of death.

The risks of broad-spectrum empiric antibiotics for suspected ICU-acquired infections

The effects of indiscriminate antibiotic use are well-recognized and the ICU has been identified as a particularly important site for the emergence of bacterial resistance.³¹ The Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) guidelines for the prevention of antimicrobial resistance note that antimicrobial resistance is more common in nosocomial than in community-acquired bacterial strains. Areas within the hospital with the highest use of antibiotics also have the highest rates of resistance. Changes in antimicrobial usage are paralleled by changes in the prevalence of resistance and patients who have been infected with resistant strains are more likely than controls to have received previous antibiotics.¹⁷

Antibiotics alter patterns of microbial colonization of the respiratory and gastrointestinal tracts and are thought to play a pivotal role in the selection of opportunistic species. For instance, the most important risk factors for colonization with antibiotic-resistant enterococci and MRSA include treatment with more than 3 antibiotics, empiric use of antibiotics, and the use of third-generation cephalosporins.³²⁻³³ Previous antibiotic use is also a significant risk factor for the development of superinfections with such organisms as *Clostridium difficile* or *Candida*, and for infection with multi-resistant organisms.^{15,34-36} Trouillet and colleagues, in a retrospective cohort study of patients with VAP, found that prior antibiotic use (OR = 13.5) and prior use of broad-spectrum antibiotics (OR = 4.1) were associated with the development of subsequent VAP caused by resistant bacteria, (including MRSA, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*).¹⁵ This finding was replicated by Rello who found that rates of *Pseudomonas* infection were higher in patients who had previously received antibiotics and that these patients had a higher risk of death as compared to those who had not received previous antibiotics.¹⁴

The costs of broad-spectrum empiric antibiotics for suspected ICU-acquired infection

Antibiotic costs comprise a significant component of ICU operating budgets. In our ICU at the University Health Network in Toronto, with approximately 750 admissions per year, the annual drug acquisition cost for antimicrobial agents is approximately \$500,000. Based on a 4-month pharmacy audit, empiric antibiotics account for at least one-fifth of this sum. If this figure is

representative of antibiotic spending for the 80,000 patients admitted to ICUs across Canada, empiric antibiotic therapy in the ICU alone costs more than 10.5 million dollars per year. Costs associated with drug delivery, monitoring of levels, and managing adverse reactions are unknown.

The case for broad-spectrum empiric antibiotic therapy

No randomized controlled trials comparing broad-spectrum empiric therapy to delayed infection-directed therapy have ever been conducted. A systematic review of the literature revealed that support for a policy of liberal empiric antibiotic use in critically ill patients derives from cohort studies comparing patients who received adequate initial antimicrobial therapy with patients for whom the initial choice of antibiotics was deemed inadequate.³⁷⁻³⁹ Each of these studies considered antimicrobial therapy to be inadequate when an organism was subsequently isolated that was not sensitive to the initial antibiotic regimen, either because the therapy was inappropriate for the class of organism identified or the identified pathogen was resistant to the agents administered. For example, Kollef and colleagues reported a prospective cohort study of 2000 ICU patients, 655 of whom were thought to be infected. They found that patients whose initial therapy had been “inadequate” had a significantly higher mortality rate than those who had received “adequate therapy” (42% versus 17.7%).³⁷ However, patients in this study who had received inadequate therapy also had a higher rate of infection with resistant organisms and were more likely to have acquired their infection while in the ICU.

Thus, factors other than antibiotic selection may have confounded the increased mortality risk. In a similar study of Argentinean patients with ventilator-associated pneumonia, Luna and colleagues reported that patients whose empiric antibiotic regimen had been inadequate had a mortality of 90%, compared to 38% for patients whose initial empiric regimen had been considered adequate. Intriguingly, however, patients who received no antibiotics at all had an intermediate mortality of 60%, a value that was not significantly different from that of patients receiving adequate antibiotics in this small study.⁴⁰ Moreover, none of these cohort studies provided information on the outcomes of patients who received empiric antibiotic therapy, but in whom no pathogen was ever identified.

The evidence for more restrictive antimicrobial regimens

Other work suggests that reduction in the use of empiric antibiotics, through the more stringent criteria for the diagnosis of infection or the use of invasive

diagnostic techniques (such as bronchoscopy), may result in increased survival.^{41,42} Singh, in an unblinded controlled trial, randomly assigned 81 patients with a low suspicion of VAP to either standard therapy (as decided by the attending ICU physician) or a restrictive antibiotic regimen.⁴¹ Patients in the restrictive arm received ciprofloxacin for 48 hours, to be discontinued if cultures were negative. Patients in the restrictive arm received fewer antibiotics, developed significantly fewer super-infections, and showed a trend toward increased survival. Unfortunately, this study was discontinued early because participating physicians perceived it to be unethical for some patients to be denied the benefits of the restrictive regime. Fagon et al randomized 413 patients with suspected VAP to either an invasive diagnostic regime with bronchoscopy or a clinical regime, with the use of endotracheal aspirate specimens for culture.⁴² Patients undergoing bronchoscopy received fewer empiric antibiotics, and had antibiotics discontinued more frequently when culture results were available. Their survival at 14 days was significantly better (84% versus 75%).

Proposed strategy for reducing the use of broad-spectrum antibiotics

Withholding antibiotic therapy until culture results are available may be a reasonable approach to avoid the unnecessary administration of antibiotics in the ICU. Previous observational studies have found that a delay in the initiation of antibiotic therapy does not alter outcomes. Pelletier and colleagues found that the time from fever onset to initiation of antibiotic therapy (0-12 hours, 12-24 hours, >24 hours) was not associated with an adverse outcome in a cohort of surgical patients with nosocomial infections stratified by APACHE II score.⁴³ In the study by Kollef of patients with both community-acquired and nosocomial infections, there was no significant difference in mortality between patients who received empiric therapy and those who did not, although the size of the latter group was small.³⁷ And finally, in a prospective study of 72 patients with microbiologically-confirmed VAP, a delay in starting antibiotics pending bronchoscopic culture results did not influence outcome.⁴⁴ The observational designs of these studies do not allow us to infer a cause-and-effect relationship as there may have been unmeasured differences between patients who did and those who did not receive empiric therapy.

Although there are significant risks, toxicity, and costs associated with empiric antibiotic use and little rigorous evidence of benefit, no randomized controlled trials comparing empiric antibiotics to delayed, infection-directed, narrow-spectrum therapy have been conducted. Clearly, there is no incentive for pharmaceutical companies to undertake studies that might reduce the market for antimicrobial agents. Equally potent, however, is the fear by some clinicians that such a study may be ethically difficult since it would deny patients of the potential benefits of antibiotics. However, there is clear-cut evidence of equipoise in the community of clinicians who most commonly treat these patients. At the University of Toronto, we undertook a scenario-based survey of 113 surgical infectious disease specialists, the majority of whom were Americans with an academic practice, and found that 62% of respondents agreed that overuse of antibiotics is a significant problem in their own ICU.⁴⁵ Approaches to the use of empiric antibiotics were evaluated using 3 scenarios describing hypothetical patients with new fever and leukocytosis, in whom physical exam and clinical investigations did not reveal an obvious source of infection. There was considerable variability in the approaches. For example, in a stable trauma patient, 59.3% of physicians were “very unlikely” or “unlikely” to add empiric antibiotics, while 32.7% were “very likely” or “likely” to add antibiotics. With evidence of increasing clinical deterioration, significantly more physicians would prescribe empiric antibiotics, however, even in the face of hypotension or worsening multiple organ failure, 30% were still “very unlikely” or “unlikely” to add empiric therapy. Significantly, few respondents voiced neutral opinions, although their approaches were variable. Depending on the scenario, respondents who would administer empiric therapy recommended 19 to 26 different antibiotic regimens. Physicians have strong, but divergent opinions regarding empiric antibiotics.

Based on these preliminary observations, a follow-up questionnaire was given to physicians who responded to our initial survey. Of 49 physicians who responded a second time, 96% thought that the utility of empiric therapy for ICU-acquired infections was an important issue that needed to be critically evaluated, but only 78% would be willing to enroll patients into a controlled clinical trial. Of the 10 physicians who offered a reason for not enrolling patients; 4 thought that

morbidity in the placebo arm would be greater than in the antibiotic arm; 4 thought morbidity in the antibiotic arm would be greater than in the placebo arm due to the emergence of resistant pathogens and superinfections, while 2 felt that the optimal approach was already known. Clearly, there is sufficient clinical equipoise with respect to our therapeutic decisions to justify a controlled study to address these questions.

Conclusions

Antibiotic overuse is a serious problem that contributes to the growing prevalence of resistant organisms in critical care units and an increased risk of superinfections in individual patients. Clinicians are divided on the merits of empiric therapy as there are no data from randomized controlled trials to guide treatment decisions. Given the potential risks associated with unrestrained antibiotic use on the one hand, and the risks of inadequate or delayed treatment of nosocomial infection on the other, the effectiveness and safety of delayed narrow-spectrum antibiotic therapy directed by culture results merits formal and rigorous evaluation.

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