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Conservative initiation of antimicrobial treatment in ICU patients with suspected ICU-acquired infection: more haste less speed

Tjasa Hranjec and **Robert G. Sawyer**
University of Virginia, Charlottesville, Virginia, USA

Abstract

Purpose of review—To review the recent literature supporting the idea that in some patients suspected of having a new ICU-acquired infection, antibiotics can be withheld until evidence to confirm diagnosis is obtained.

Recent findings—Recent publications demonstrate that in community-acquired pneumonia, severe sepsis presenting to the emergency room, and suspected ICU-acquired infection, the time to antibiotic therapy does not necessarily seem to be a key determinant of outcome.

Summary—In the ICU, patients without septic shock but suspected of having an ICU-acquired infection may be able to have antibiotics withheld until infection is confirmed using a combination of laboratory, radiologic, and microbiological data.

Keywords

antibiotic delay; empiric antibiotic therapy; ICU-acquired infection; sepsis

Introduction

Timely and adequate administration of antibiotic therapy has become an important determinant of survival in critically ill populations with ICU-acquired infections. Excessive and injudicious use of antimicrobials has, however, led to an increase in microbial resistance, changes in the endemic flora, and infection rates with potential for significant harm to the patients. Ideally, a balance between the spread of antimicrobial resistance caused by the overuse of these agents and the timely diagnosis of infection, followed by appropriate administration of antibiotics, should be achieved.

The Dilemma

The uncertainty attached to the early diagnosis of infection in critically ill patients is well known, resulting from two limiting circumstances. First, patients can exhibit the signs and symptoms of infection (systemic inflammatory response or SIRS) because of noninfectious causes (pancreatitis, burns, venous thrombosis, acid aspiration, transfusions, noninfectious ischemia, etc.). Second, to a greater extent, the diagnosis of infection still depends upon the growth of pathogens from culture, a process that generally takes at least 48h, resulting in a period of time in which the diagnosis remains unclear. Basing the initiation of antimicrobial therapy on the signs and symptoms in critically ill patients with or without infections is woefully imprecise, in which even experienced intensivists have a difficult time correctly

Correspondence to Tjasa Hranjec, 1382 Queenscroft, Keswick, VA 22947, USA. Tel: +1 434 987 3201; tjasa.hranjec@gmail.com.

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identifying those who are infected and who might benefit from early empiric therapy. Additionally, many other infections are hard to identify, presenting with few if any of the usual criteria used for making a definitive diagnosis, for example, the elderly patient with a severe infection who does not mount a fever or leukocytosis.

Several official guidelines have supported a more aggressive approach to antibiotic initiation, as earlier treatment with appropriate antibiotics appears to have a very real impact on the ultimate survival of the patient, based on previous retrospective, observational studies. Utilization of aggressive and early broad initial empiric therapy would not be problematic except for the known risk for the induction of resistance, potential for morbidity given selection for other infectious agents like *Clostridium difficile*, and known toxicities of antibiotics.

Attempts to delay antibiotics until the diagnosis of infection is more certain, even in patients with more severe infections, have recently challenged the most current antimicrobial prescribing practices. The purpose of this review is to provide the most up-to-date research on the topic of timing of antibiotic administration, in which a more conservative approach and the consequential decreased antibiotic use seems to be feasible.

Demonstrating The Safety of Waiting For A More Accurate Diagnosis of Infection

A recent Cochrane review by Spurling *et al*.[1▪] examined the effects of delayed antibiotic prescription on acute respiratory tract infections in the outpatient setting. Delay in prescription, which was defined as providing the prescription by advising the patient to delay their use in the hope of symptom resolution, was compared to either no prescription or immediate antibiotic acquisition and consumption. Ten randomized studies with a total of 3157 participants were identified. The use of the delayed strategy was associated with a 32% decrease in antibiotics without significantly affecting the patient's outcomes, especially for pulmonary infections. Interestingly, delayed antibiotic therapy was associated with significantly lower patient satisfaction compared with immediate antibiotic administration (87 versus 92%), highlighting the fact that patient education in this area continues to be of paramount importance. This delay in antibiotic use appears to be a well tolerated strategy that can potentially reduce the collateral damage caused by antibiotic overuse.

Hranjec *et al*. [2▪▪] described the effects of delayed antibiotic administration in a critically ill population suspected of having an infection. This study was performed in a before-after format, in which an aggressive antibiotic use policy was employed for the first year (antibiotics were given as soon as an infection was suspected for any reason) and a more conservative approach was used in the second year (antibiotics were delayed until objective evidence of infection guided by Centers for Disease Control and Prevention criteria was obtained). Patients with septic shock, requiring vasoactive agents, were excluded. A total of 101 ICU-acquired infections were treated using the aggressive protocol and 100 using the conservative protocol. The most common infections were of the lungs and the abdomen, and the conservative protocol was associated with a delay in therapy of about 1 day. Even though the study originally intended to show equivalence between the two approaches, use of the conservative method was actually associated with an almost 50% lower mortality, even after adjusting for multiple other risk factors including age, sex, diagnosis, site of infection, and severity of illness (APACHE II score). Additional benefits for conservative therapy included a higher rate of appropriate initial antibiotic therapy (74 versus 62%, P=0.01) and shorter mean duration of treatment (12.5 versus 17.7 days, P=0.008). Interestingly, microbial resistance was not decreased despite less antibiotic use in the conservative group, though there were trends toward fewer fungal and C. *difficile* infections.

The reasons why these outcomes were not predicted by the previous retrospective studies are not clear, but may be related to the large number of treated infections that required mechanical intervention as well as antibiotics (e.g., drainage or debridement) and the fact that whereas in retrospective studies the time to initiation of therapy was probably a marker of time to recognition of infection, in the Hranjec study only antibiotics were delayed, whereas other therapies (resuscitation, etc.) were promptly started.

Defining The Patient In Whom Antibiotics May Be Withheld

Early initiation of appropriate antibiotics has been considered to have a pivotal role in determining the length and severity of illness in the management of patients arriving to the emergency room with possible community-acquired pneumonia. Sucov *et al.* [3] pointed out the discrepancy in the published data with the Joint Commission/Centers for Medicare and Medicaid (CMS) recommending an initial allowable 4-h time delay to the initiation of antibiotics in patients with pneumonia, increased to 6 h in 2008, and then a completely removed delay in the latest consensus guidelines created by the Infectious Society of America and the American Thoracic society. A total of 444 consecutive patients admitted with pneumonia through the emergency room were studied. The majority of patients received antibiotics within 4 h of presentation; yet, these patients had a higher rate of complications, including admission to an intensive care unit, intubation, or death (27versus 3%), similar to previous publications. Nonetheless, these findings do not suggest that holding antibiotics is necessarily beneficial. Instead, as a significantly higher severity of illness was found in the patients receiving antibiotics in less than 4 h, a reasonable conclusion is that the physicians caring for these patients could accurately identify patients who could have their antibiotics delayed safely while waiting for a greater degree of diagnostic certainty to occur.

The surviving sepsis campaign (SSC) international consensus guidelines recommended initiation of broad-spectrum antibiotics within the first hour of recognizing severe sepsis and septic shock. Several studies reported difficulties in achieving these goals in routine clinical practice. Consequently, Puskarich *et al.* [4] aimed to evaluate the effects of timing of antibiotics as a determinant of in-hospital mortality versus strict early resuscitation protocols in the emergency rooms of three academic medical centers. A total of 291 patients were followed after enrollment in a study of lactate clearance versus central venous oxygen saturation as resuscitation endpoints in patients presenting with severe infection and managed with an aggressive resuscitation protocol. Pneumonias and urinary tract infections were the most common infections, and the overall mortality was 19%. Despite studying several hourly cut-off points, there was no relationship between time from triage to antibiotics and mortality. We agree with the authors' conclusions that '…when all other parts of early resuscitation are sufficiently refined, the importance of timeliness of antibiotics appears to recede'. These data highlight the fact that the management of sepsis is not limited to antibiotic use, and that retrospective studies in this area do not generally report the delays in other forms of therapy that almost certainly accompany delays in the initiation of antibiotics.

The Promise of Improved Diagnostics

Identification of the causative infectious pathogens is crucial for the optimal treatment management of critically ill patients with administration of early, appropriate antibiotics resulting in the most favorable outcomes. Conventional species identification is, however, very time-consuming, often lasting for more than 48 h after blood culture becomes positive in patients with sepsis. True advances in the management of the critically ill patient suspected of having a new infection, therefore, will depend on improved technology that

will allow for more rapid identification of pathogens and their sensitivities, particularly in the ICU where resistance is common. Vlek *et al.* [5▪] developed and reported on the novel and exciting matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF) technique that allows for correct identification of species in 66–87% of bacterial isolates after positive blood cultures are obtained. The authors compared 89 patients with bloodstream infection treated using MALDI-TOF to 164 treated using standard microbiological methods. MALDI-TOF resulted in a 28.8-h reduction in the median time to species identification, from 45.2 to 16.4 h, and appeared to be particularly accurate for Gram-negative monomicrobial isolates, species that are of great importance in the current war on resistance. This translated to the availability of data within 10 h in 23.6% of patients after MALDI-TOF method application, with 75.3% of patients treated appropriately within 24 h compared to 64% with the standard species identification methods (P=0.01). No differences in morbidity or mortality were reported, though with a larger sample size, such an intervention would be hoped to improve multiple outcomes.

Discussion

Appropriate timing of antibiotics requires a thoughtful consideration of the complex interplay between starting antimicrobials immediately in response to the patient's nonspecific signs and symptoms – knowing that many uninfected patients would be needlessly treated – versus withholding antibiotics until infection is confirmed through objective data – understanding that some patients may have potential harmful delays in treatment. Timing of treatment initiation, especially in patients who are critically ill, is one of the most difficult tasks set before clinicians.

An important aspect of the decision to initiate antibiotics for suspected infection is the role of the clinician in deciding which patients appear healthy enough to wait for more clinical, laboratory, and microbiological data to return prior to initiating antibiotics. Clearly, not all potentially infected patients are similar, and unfortunately the usual objective measures of illness (fever, leukocytosis, etc.) are not able to differentiate infected from un-infected patients. Recent publications concerning the treatment of upper respiratory infections, including community-acquired pneumonia, demonstrate that in select populations withholding antibiotics until further data are available is not associated with worse outcomes. A logical possibility is that clinicians are able to differentiate patients who are adequately healthy to have antibiotics safely delayed until clinical symptoms worsened, as in the case of Spurling *et al.* [1▪] or where antibiotic administration in the emergency department can be safely delayed for more than 4 h, ostensibly to await the results of further testing, as in the case of Sucov *et al.* [3]. Thus, although some patients may benefit from the rapid administration of antimicrobials, for example, those with severe septic shock, the less sick may benefit from a wait-and-see approach.

The recent research by Puskarich *et al.* [4] demonstrated that the importance of antibiotic timing might be lessened through adequate patient resuscitation. In other words, there appeared to be no association between the timing of antibiotics and hospital mortality when patients with severe sepsis received aggressive resuscitation, permitting the delay of antibiotic treatment. Similarly, Hranjec *et al.* [2▪▪] tested the idea of intentional antibiotic delay in patients suspected of having, but not confirmed to have an ICU-acquired infection. Aggressive initiation of antibiotics was associated with a worse, rather than a better, outcome. The unexpected and somewhat controversial results from these two publications are difficult to explain, but the key to success may lie within the resuscitation protocols. All patients in the Puskarich *et al.* [4] study were treated with a well defined resuscitation protocol in the emergency room, whereas in the study by Hranjec *et al.* [2▪▪], patients suspected of having an ICU-acquired infection were treated with active resuscitation and the

withholding of antibiotics did not mean withholding the overall treatment. Consequently, in these settings, the importance of timing of antibiotics appears to have decreased.

Initiation of appropriate antibiotics plays an important role in both individual patient treatment and the prevention of development of drug resistance. Ultimately, better diagnostic techniques are needed to rapidly diagnose an infection and determine the most appropriate antimicrobial therapy. The results reported by Vlek *et al.* [5▪] represent the possibility that molecular techniques will allow the clinician of the future to rapidly determine not only who is (or is not) infected, but also exactly which narrow-spectrum antimicrobial will be most effective.

Conclusion

The pressure to commence treatment in patients suspected of having an ICU-acquired infection is tremendous. Retrospective studies have shown that any delay in treatment could mean increased patient mortality and morbidity. Yet, an approach promoting profligate antimicrobial administration will certainly damage both uninfected patients and patients who subsequently acquire infections caused by resistant pathogens. Recent studies appear to support the concept that in the setting of careful patient selection and appropriate non antibiotic infection therapy including resuscitation, withholding antibiotics while awaiting further evidence of infection may not be harmful. Further studies are needed to more accurately define in which populations this wait-and-see approach can be safely used.

Acknowledgments

None.

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 517).

1▪. Spurling GK, Del Mar CB, Dooley L, et al. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev 2013. 4:CD004417. The authors report that clinical outcomes between delayed and immediate administration of antibiotics in acute respiratory tract infections are equivalent in the outpatient setting, allowing for overall lower antibiotic utilization.

2▪▪. Hranjec T, Rosenberger LH, Swenson BL, et al. 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. The authors published a 50% decrease in mortality when antimicrobial administration is delayed until objective evidence of infection is obtained in surgical patients with ICU-acquired infections. [PubMed: 22951600]

3. Sucov A, Valente J, Reinert SE, et al. Time to first antibiotics for pneumonia is not associated with in-hospital mortality. J Emerg Med. 2013; 45:1–7. [PubMed: 23485266]

4. Puskarich MA, Trzeciak S, Shapiro SE, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med. 2011; 39:2066–2071. [PubMed: 21572327]

5▪. Vlek AL, Bonten MJ, Boel CH. Direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry improves appropriateness of antibiotic treatment of bacteremia. PLoS One. 2012; 7:e32589. The authors describe a new technique for identification of microbial species allowing for earlier adequate/appropriate antimicrobial treatment. [PubMed: 22438880]

Key Points

- The time to antibiotic therapy does not necessarily seem to be a key determinant of outcomes in patients with community-acquired pneumonia, severe sepsis, or ICU-acquired infections when appropriate therapies (resuscitation, etc.) are promptly started.
- The most important aspect of antibiotic initiation for suspected infection is the role of the clinician in deciding which patients appear healthy enough to wait for additional data prior to initiating antimicrobials.
- True advances in the management of the critically ill patients suspected of having a new infection will depend on improved diagnostic techniques that will allow for more rapid identification of pathogens and their antibiotic sensitivities.