Antimicrobial Therapy for Life-threatening Infections: Speed is Life

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- Antimicrobial therapy
- Septic shock
- Early therapy
- Survival

This thing all things devours:
Birds, beasts, trees, flowers;
Gnaws iron, bites steel
Grinds hard stones to meal;
Slays king, ruins town,
And beats High Mountain down.

The answer to this riddle, from JRR Tolkien’s *The Hobbit* is time. In the context of acute illness, time is always a critical issue. Physicians routinely attempt to reverse or slow the temporal progression of illness to improve the lives of patients. Those of us who practice critical care have also tried to use time to our advantage. The trauma surgeons amongst us were the first to develop the concept of the golden hour that was critical to the survival of those with traumatic and hemorrhagic shock.1 This concept subsequently expanded to cardiogenic and obstructive shock with the use of thrombolytics for myocardial infarction2 and more recently, obstructive shock caused by massive pulmonary embolism.3

In recent decades, the importance of rapid initiation of appropriate antimicrobial therapy for life-threatening infection has become apparent. In the late 1970s and early 1980s, pediatricians, emergentologists, and infectious diseases physicians began to recognize the critical importance of rapid antimicrobial therapy for pediatric meningitis. This knowledge has translated into internationally accepted guidelines that mandate initiation of appropriate antimicrobial therapy as quickly as possible after
recognition of potential bacterial meningitis (preferably within an hour or less). During the 1990s, the importance of rapid initiation of appropriate antimicrobials for community-acquired pneumonia (CAP) became appreciated and was eventually integrated into Joint Commission on Accreditation of Health care Organizations (JHACO) guidelines. In the last decade, the critical importance of time to effective antimicrobial therapy in the context of bacteremia/candidemia and particularly septic shock has come to the forefront. International guidelines for sepsis and septic shock management have, throughout the decade, included a recommendation for rapid (<1 hour) initiation of antimicrobial therapy.

Nonetheless, there remains controversy about this issue in the broader context. Some of these concerns have to do with the retrospective methodology of studies that have yielded evidence of a relationship between outcome and antimicrobial delay. Much of the work supporting this relationship is confounded by other therapeutic factors. Biologic plausibility may also be an issue for mild disease. Fortunately, interventional studies that support the proposition that early initiation of appropriate antimicrobial therapy is the key factor in determining survival from severe infections have recently been published. This article describes the concept of early appropriate therapy, and reviews the evidence behind the early administration of antimicrobials as a key determinant in survival from septic shock, bacteremia/candidemia, pneumonia, and meningitis.

WHAT CONSTITUTES EARLY AND APPROPRIATE ANTIMICROBIAL THERAPY?

The concept of what constitutes early appropriate therapy is discussed further in another article in this issue. However, when describing appropriate therapy, many factors must be taken into account. Most of the current studies on appropriate therapy have defined this as the selection of an antimicrobial that has in vitro activity against the organism that was isolated from the index culture. Other studies have defined appropriate as consistent with current practice guidelines for the particular site of infection (ie, ventilator-acquired pneumonia [VAP]).

When defining appropriate therapy, the use of culture results should be the gold standard, as the antibiograms of organisms at different institutions or even on different wards within a given institution show great variability. This definition, although microbiologically sound, ignores the unique pharmacokinetics and pharmacodynamics of antimicrobials, particularly in the critically ill. Elements that may affect appropriateness include route of administration, dose and dosing schedule (ie, optimization of pharmacokinetic indices in view of alterations in absorption, volume of distribution, and drug elimination kinetics in the critically ill), penetration and cidality of the antimicrobial agent, and the use of combination therapy in some contexts (eg, Pseudomonas infection).

Clinicians assessing the extensive literature on the benefit of initiation of appropriate antimicrobial therapy for life-threatening infections should be aware that the term appropriate therapy intrinsically includes a time element. That provision of microbiologically inappropriate antimicrobials simply represents a marker of delayed delivery of appropriate therapy (assuming the patient lives long enough) should be obvious. When defined as the use of an antimicrobial without activity for the causative pathogen, inappropriate therapy is fundamentally equivalent to no therapy at all. Therefore, almost all studies that have favored appropriate rather than inappropriate initial antimicrobial therapy for serious infections can be interpreted to be favoring early rather than delayed antimicrobial therapy.
The rest of this article deals with the specific infections where data have shown that time to appropriate therapy is a key factor in survival. Limitations of the current literature are also highlighted.

ANIMAL DATA

Few experimental animal studies have examined the effect of delays of antimicrobial therapy on outcome in systemic infections such as sepsis. Knudsen and colleagues\(^\text{13}\) and Fridmodt-Moller and Thomsen\(^\text{14}\) have demonstrated a critical effect of timing of antimicrobial therapy relative to intraperitoneal inoculation of *S. pneumoniae* into mice. The degree of bacterial propagation and survival was shown to be highly dependent on antimicrobial timing with 100% mortality if penicillin was initiated at 24 hours after inoculation. Similarly, Greisman and colleagues\(^\text{15}\) have shown that sequential delays in aminoglycoside therapy after intraperitoneal or intravenous inoculation of enteric organisms (*Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*) results in progressive increases in mortality from 0% to 90% to 100%. Kumar and colleagues\(^\text{16}\) have examined the relationship between peritonitis induction using implantation of an *E coli*–containing fibrin/\(\alpha\)-cellulose clot encased in a gelatin capsule, the onset of hypotension, and outcome in mice. A critical inflection point with respect to survival occurred between 12 and 15 hours after sepsis induction, the point at which physiologically relevant hypotension was manifested. Antibiotic therapy before 12 hours yielded less than 15% mortality but after 15 hours there was more than 80% mortality. Heart rate diverged by 6 hours after sepsis induction, whereas cardiac output and stroke volume divergence did not occur until 18 to 24 hours after sepsis induction. Antibiotic administration 12 hours or longer after *E coli* capsule implant was associated with persistence of increased circulating lactate, tumor necrosis factor \(\alpha\) (TNF\(\alpha\)), and interleukin-6 levels.

This study pointed out the potential importance of rapidity of effective antimicrobial therapy on risk of death once hypotension is present. In healthy animals, only a modest increase in mortality occurs with delayed therapy before the hypotension of early septic shock. However, once such hypotension is present, mortality risk increases rapidly and death eventually becomes inevitable irrespective of any intervention, a process of irreversible shock that had previously been described only for hemorrhagic shock.\(^\text{17,18}\) These data suggest that sustained hypotension in septic shock is associated with irreversible injury leading to inevitable deterioration and death many hours after the initial injury. This study provides a biologic rationale for a linkage between delays in initiation of effective antimicrobial therapy and outcome of septic shock in humans.

HUMAN STUDIES

**Inflammatory Markers and Organ Failure**

Several studies have examined the role of delays in initiation of effective antimicrobial therapy and persistence of inflammatory markers and/or development of organ failure. Calbo and colleagues\(^\text{19}\) showed that patients with pneumococcal pneumonia with a longer time of evolution presented with higher levels of proinflammatory cytokines (TNF\(\alpha\)) and a higher expression of acute phase proteins (including C-reactive protein and fibrinogen). This study parallels the finding in the mouse study by Kumar and colleagues\(^\text{16}\) with respect to persistence of increased TNF\(\alpha\) in untreated sepsis.

Bagshaw and colleagues\(^\text{20}\) have also demonstrated in a multivariate analysis of more than 4500 patients with septic shock that delays in initiation of appropriate antimicrobial therapy are associated with increased risk and severity of renal injury.
Similarly, Iscimen and colleagues\textsuperscript{21} have shown using multivariate analysis that the risk of acute lung injury in patients with septic shock is positively related to increasing delays in initiation of appropriate antimicrobial therapy. Garnacho-Montero and colleagues\textsuperscript{22} have demonstrated a relationship between antimicrobial delay and increase in the Sequential Organ Failure Assessment (SOFA) score in patients with sepsis. Thus, any finding of increased mortality with delays in initiation of antimicrobial therapy for serious infections in humans is supported by congruent inflammatory injury and organ dysfunction data.

Mortality Studies

Sepsis and septic shock

The most life-threatening infectious disease that intensivists confront is septic shock. With a mortality of 30\% to 40\%, the early recognition and treatment of this disease is key to improving survival. If early antimicrobial therapy has an effect on mortality, this is the disease where the largest effect should be realized. Numerous studies have looked at time to antimicrobial therapy in septic shock, and virtually all have found a reduction in mortality when antimicrobials were given in a timely fashion.

Kumar and colleagues have provided the most direct data on the question of the specific effect of early appropriate antimicrobial therapy on survival in septic shock. Parallel to our earlier experimental mouse study, we retrospectively looked at the duration of hypotension before initiation of effective antimicrobial therapy in 2731 adult patients with septic shock.\textsuperscript{6} The delay to initial administration of effective antimicrobial therapy was shown to be the single strongest predictor of survival.

Initiation of effective antimicrobial therapy within the first hour after onset of septic shock–related hypotension was associated with 79.9\% survival to hospital discharge (\textbf{Fig. 1}). For every additional hour to effective antimicrobial initiation in the first 6 hours

\textbf{Fig. 1.} Cumulative initiation of effective antimicrobial therapy and survival in septic shock. In a large retrospective study of septic shock, Kumar and colleagues demonstrated that median time to effective/appropriate antimicrobial therapy was 6 hours and that for every hour delay more than the first 6 hours, the projected mortality increased by 7.6%/h. X axis represents time (hours) after first documentation of septic shock–associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge and the gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point. (\textit{From} Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96; with permission.)
after onset of hypotension, survival dropped an average of 7.6%. With effective antimicrobial initiation between the first and second hour after onset of hypotension, survival had already dropped to 70.5%. With effective antimicrobial therapy delay of 5 to 6 hours after hypotension onset, survival was just 42.0% and 25.4% by 9 to 12 hours. The adjusted odds ratio of death was already significantly increased by the second hour after onset of hypotension and the ratio continued to climb with longer delays (Fig. 2).

Substantial delays before initiation of effective therapy have been shown in several studies of serious infections.\(^5,23–25\) In septic shock, the median time to delivery of effective antimicrobial therapy after initial onset of recurrent/persistent hypotension was 6 hours.\(^6\) Only 14.5% of all patients who had not received effective antimicrobials before shock received them within the first hour of documentation of onset of recurrent or persistent hypotension (see Fig. 1). Only 51.4% had received them by 6 hours after onset of hypotension. Even 12 hours after the first occurrence of recurrent or sustained hypotension, 29.8% of patients had not received effective antimicrobial therapy. The effect was sustained across a broad group of organisms including gram-negatives, gram-positives, and Candida species.

After adjustment for various comorbidities (including the number of presenting organ failures), therapeutic variables (use of mechanical ventilation, drotrecogin-alpha and low-dose steroids) and severity of illness (APACHE II score [Acute Physiology and Chronic Health Evaluation]), the delay in initiation of antimicrobial therapy remained the strongest correlate of outcome. Although often referred to as linear, a graphic representation of the relationship between antimicrobial delay relative to onset of hypotension and outcome in human septic shock suggests a logarithmic decay of survival probability (Fig. 3).

The strong relationship between delays in antimicrobial therapy and outcome in septic shock (and less so, sepsis) have been confirmed by several other groups. In these studies, time to effective antimicrobial therapy has been assessed in the context of rapidity of vasopressor initiation,\(^26\) polymorphisms of inflammatory genes,\(^22\) or time

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**Fig. 2.** Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% CI. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension onset). The risk of death continues to increase up to more than 36 hours after hypotension onset. (From Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96; with permission.)
to qualification for early goal-directed therapy. Benefit has even been shown in patients with cancer with septic shock, a group with exceptionally high mortality (>65%). In a study on candidemic septic shock, multivariate analysis demonstrated that a delay in antimicrobial administration of greater than 15 hours after initial positive blood cultures resulted in a significant increase in mortality.

With respect to invasive Candida infections, Hsu and colleagues have recently also shown that administration of an echinocandin within 72 hours of initial positive culture is associated with a higher response rate, improved time to clinical stability, and decreased length of stay (LOS). Similarly, Hood and colleagues have shown that early initiation (<4 hours after presentation) of antimicrobial therapy for about 24,000 cases of complicated urinary tract infections requiring hospital admission (most of whom likely had sepsis) was associated with decreased hospital LOS.

Using the 2008 Surviving Sepsis guidelines recommendations as a guide, many hospitals have implemented a bundled approach to the treatment of septic shock. Several studies have shown an improvement in outcome of sepsis/septic shock when such bundles are used. However, Barochia and colleagues have shown that the only consistent element of therapy that bundle implementation affected in studies to date was time to antimicrobial and appropriateness of initial antimicrobial therapy.

Efforts have been made to specifically delineate the role of each individual part of the bundle on the overall reduction in mortality. In a prospective study of 316 patients with severe sepsis/septic shock in Brazil, the individual parts of the Surviving Sepsis bundle were evaluated to determine their role in mortality reduction. The administration of antimicrobials within 120 minutes of the diagnosis and the collection of blood cultures were the only interventions that seemed to affect mortality (odds ratio [OR] for early antimicrobials = 0.44, 95% confidence interval [CI] 0.23–0.87, P<.009). In this study, appropriate early antimicrobials were delivered to patients 71.7% of the time.

Similar data were generated in a study from Finland in which the effect of different bundle elements including central mixed venous oxygen saturation was assessed in multivariate analysis in 92 patients with septic shock presenting from the community. About one-third of patients achieved 4 or more of the bundle elements. Among the bundle elements, only administration of antimicrobials within 3 hours of admission

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**Fig. 3.** The running average of the fraction of 250 patients with septic shock surviving to hospital discharge from fast to slowest antimicrobial initiation time after documentation of hypotension \((n = 5715)\). Decay of survival probability seems to represent a logarithmic function. Approximately 90% of survivors of septic shock received appropriate antimicrobial therapy within 12 hours of documentation of hypotension.
was associated with improved outcome, even when APACHE II score was added to the model. In another prospective observational study from Spain, 2796 patients with severe sepsis/septic shock were evaluated for the role of each of the bundle elements in the Surviving Sepsis campaign on mortality.\textsuperscript{43} Again, early antimicrobials were 1 of only 2 interventions that significantly reduced mortality, the other being the administration of drotrecogin-alpha in the case of multiorgan failure from sepsis. In this study, 85% of patients received an antimicrobial within 6 hours of the diagnosis of sepsis.

Gurnani and colleagues\textsuperscript{44} examined the outcomes of 118 patients in a single center after the implementation of a sepsis bundle. Bundle implementation (with associated improvements in antimicrobial delay and early fluid resuscitation volumes) was associated with decreased pressor days, ventilator days, and intensive care unit (ICU) LOS as well as 28-day (but not in-hospital) mortality. The time interval from documentation of shock to empiric antimicrobial therapy (less than or more than 4.5 hours), but not fluid variables, was independently associated with outcome.

Several studies have failed to find a significant association between antimicrobial timing and mortality in sepsis or septic shock. One prospective Spanish study (comparing 396 patients after bundle intervention with 84 historical controls) found that the only individual intervention associated with a reduced mortality in regression analysis was the achievement of a central mixed venous oxygen saturation of 70% or more.\textsuperscript{37} However, in this study, there was no significant improvement in either the administration of broad-spectrum antimicrobials or central mixed venous oxygen saturation in the intervention group and the historical controls (49% vs 57.3% for antimicrobial administration, $P = .168$). Compliance with the antimicrobial delivery aspect of the bundle was significantly lower than in other studies that have reported a benefit. It is possible that the lack of a beneficial effect of antimicrobials in this study was not seen because of the lack of improvement in this part of the bundle, and the low rate of appropriate antimicrobials overall. In addition, the analysis suggested an unusually strong degree of covariation among bundle elements rendering statistical differentiation of the effect of individual bundle elements difficult.

A similar negative result for early antimicrobial administration was seen in a Portuguese community-acquired sepsis bundle study involving more than 4000 patients.\textsuperscript{34} In this study, only collection of blood cultures was associated with improved outcome. In another study of 182 patients with surgical sepsis, only the use of activated protein C was associated with improved outcome.\textsuperscript{45} A major problem with all these studies may be the difficulty of defining the baseline point from the point of view of timing of therapies. However, in all these studies, mortality at least trended in favor of earlier antimicrobial therapy.

Given the ethical challenges in study design, just 1 randomized study of early antimicrobial initiation in septic shock has been documented in the literature.\textsuperscript{46} In this Australian study, 198 patients with septic shock requiring transport in a rural environment were randomized to broad-spectrum prehospital antimicrobials or standard care (antimicrobials on arrival at hospital). All patients received standard fluid resuscitation in the field. The (3.4 ± 2.6)-hour relative delay to initial antimicrobial administration after emergency department admission in the control group was significantly greater than in patients receiving prehospital antimicrobials ($P = .02$). The 28-day mortality was significantly reduced to 42.4% in the intervention group compared with 56.7% in the control group ($P = .049$, OR = 0.56; 95% CI = 0.32–1.00). Length of hospital stay was similarly reduced in patients randomized to prehospital antimicrobial therapy.

In most of the studies looking at time and appropriateness of antimicrobial therapy, anywhere from 20% to 40% of patients received inappropriate treatment. It is
therefore critically important to consider how to improve on the institution of broad-spectrum antimicrobial therapy based on the presumed source of sepsis, antibiogram at the particular institution (or even within the ICU), and risk factors for resistant organisms. The current weight of evidence supports the early institution of appropriate antimicrobial therapy in patients with septic shock and perhaps less strongly, sepsis. Obstacles to delivering optimal antimicrobial therapy including delayed diagnosis of a serious infection and poor selection of antimicrobials must be overcome to reduce mortality.

**Bacteremia/fungemia**

In one of the first studies to suggest that a delay in delivery of timely antimicrobials to patients with bacteremia adversely affected outcome, Bodey and colleagues\(^47\) retrospectively reviewed 410 cases of *Pseudomonas* bacteremia in 1985. They discovered that a delay in appropriate antimicrobials of 1 to 2 days resulted in a decrease in the cure rate from 74% to 46%. However, this study did not address mortality. Similar, but more recent work showed that patients \((n = 100)\) who were bacteremic with *Pseudomonas* and received their antimicrobials more than 52 hours after the blood culture was drawn had more than double the mortality of patients who received their antimicrobials before this time period \((44 \text{ vs } 19\%, \ P = .008)\).\(^48\) In a multivariate analysis, delayed therapy was independently associated with a 4.1-fold increase in 30-day mortality \((95\% \text{ CI } 1.2–13.9, \ P = .03)\).

Kang and colleagues\(^49\) also demonstrated increased mortality with delays of more than 24 hours from the time blood cultures were drawn in 136 patients with *Pseudomonas* bacteremia. A trend toward progressive mortality with increasing delays was also seen. Notably, 85% of the patients had septic shock. Significant subsets of patients in all 3 studies had delays in delivery of more than 1 to 2 days. Similar data have been developed for multidrug resistant *Klebsiella* bloodstream infection where a delay of more than 72 hours to appropriate antibiotic therapy was associated with an increased mortality risk in adjusted analysis.\(^50\)

At first glance, these lengthy times to appropriate therapy for *Pseudomonas* and other gram-negative bacteremia seem disturbing, considering the disease has a mortality of 18% to 61%.\(^48,49\) However, it is not surprising that these delays occur, as *Pseudomonas* and other gram-negatives found in the ICU are often resistant to several antimicrobials. So, unless clinicians are specifically suspicious of *Pseudomonas* or another resistant gram-negative, therapy may often be initially inappropriate and will not be altered to an active agent until the results of cultures and sensitivity are available, usually after several days.

Typical risk factors for *Pseudomonas* infection, including immunocompromised state, need for hemodialysis, ICU admission, and residence in a nursing home should alert the clinician to begin treatment with antipseudomonal therapy.\(^51,52\) Similar delays in treatment are seen with *Staphylococcus aureus* bacteremia. This organism can be methicillin resistant in more than 50% of cases. Unless clinicians are suspicious that a patient is at risk for methicillin-resistant *Staphylococcus aureus*, inappropriate therapy may be initially prescribed pending preliminary sensitivity results. Lodise and colleagues\(^53\) looked at the effect of antimicrobial delay on mortality in *Staphylococcus aureus* bacteremia. Using regression analysis, they determined that the break point for mortality increase in *Staphylococcus aureus* bacteremia was 44.75 hours, similar to that seen with *Pseudomonas* bacteremia. In this study, delayed antimicrobial therapy for *Staphylococcus aureus* was found to confer a 3.8-fold increase in hospital mortality. Other studies have yielded similar results with *Staphylococcus aureus* bacteremia.\(^54\) Bacteremic pneumococcal pneumonia has also been shown to be
sensitive to delays in appropriate antimicrobial therapy. Garnacho-Montero and colleagues\(^5\) showed that a delay of more than 4 hours from admission to start of adequate antimicrobial treatment (adjusted hazard ratio [aHR] 2.62, 95% CI 1.06–6.45; \(P = .037\)) and severe sepsis or septic shock (aHR 5.06, 95% CI 1.63–15.71; \(P = .005\)) were independently associated with in-hospital mortality.

Candidemia is another infection where substantial delays in initiation of appropriate antimicrobial therapy may occur. Fernandez and colleagues\(^6\) showed a median delay of 43.3 and 98.1 hours in the initiation of appropriate antimicrobial therapy for *Candida albicans* and *Candida glabrata* infections respectively (from the time the index culture was drawn). Such delays are often related to the lack of recognition of the possibility of a *Candida* infection (which precludes appropriate empiric therapy initiation) and prolonged turnaround time for the culture results from the microbiology laboratory given the slow growth rate of the organism.\(^5\) The effect of this delay in initiation of antifungal therapy on mortality has been studied extensively in the last few years.

Blot and colleagues\(^5\) had shown as early as 2002 that a delay of antifungal therapy of more than 48 hours after the index blood culture was associated with an increased mortality of 78% from 44%. Later, Morrell and colleagues\(^5\) demonstrated that in a multivariate regression analysis only APACHE II score and administration of antifungal therapy greater than 12 hours after blood cultures were drawn was associated with an increase in mortality of patients with *Candida* bloodstream infections (CBSI) (Fig. 4). The risk of death was nearly doubled when therapy for CBSI was delayed for greater than 12 hours. The specific antifungal agents used were not defined, and approximately 25% of patients had septic shock. Garey and colleagues\(^7\) have also examined this issue in 230 patients with candidemia treated with fluconazole from 4 American medical centers. They found that hospital mortality was significantly linked to delay in fluconazole initiation (after the first positive blood culture). In regression analysis, this delay and APACHE II score were independently associated with outcome.

There have been studies of bacteremia that have failed to show decreased survival with increased delays in appropriate antimicrobial therapy. Lin and colleagues\(^6\) examined more than 1500 episodes of monomicrobial bacteremia. They found that

**Fig. 4.** Hospital mortality of candidemic patients in relation to delay in initiating antifungal therapy after index positive blood culture. Mortality risk climbs with increasing delays. (From Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005;49:3640–5; with permission.)
in the presence of neutropenia (absolute neutrophil count <100 cells/μL), a delay in effective antimicrobial therapy beyond 24 hours after draw of a positive blood culture was associated with an increased risk of death. In their adjusted analysis, neutropenia and a delay in antimicrobials were associated with an adjusted OR of risk of death of 18 (95% CI 2.84–114.5, \( P < .01 \)). However, a delay-dependent mortality risk was not seen in non-neutropenic patients. Only 9.5% of patients in this study had septic shock. Similarly, Carona and colleagues\(^6\) have also suggested a lack of relationship between delays of antimicrobial therapy and outcome in bacteremic ICU cases (of whom more than one-third had septic shock).

In summary, the discovery of bacteremia or candidemia in an acutely ill patient is always of major concern to the clinician. Delayed antimicrobial therapy results in an increase in mortality, however the adverse effect of antimicrobial delays is more limited than for septic shock and longer periods are required to manifest an adverse effect. Nonetheless, rapid initiation of appropriate empiric therapy in patients suspected of bacteremia or candidemia is clearly warranted.

**Pneumonia**

Timely administration of antimicrobials has been recognized as a key element in the survival of patients with CAP. The time to antimicrobial delivery for patients presenting to the emergency department (ED) with pneumonia is a quality measure for Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Current JCAHO recommendations are that patients receive antimicrobials within 6 hours of presentation to hospital with evidence of CAP.\(^6\) This suggestion was based on retrospective cohort analyses by Meehan and colleagues\(^5\) and Houck and colleagues.\(^2\)

In the first key paper on this subject, Meehan and colleagues\(^5\) used the Medicare quality indicator system, a data collection system that tracks the care of hospitalized Medicare patients, to look at 14,069 patients older than 65 years presenting to the emergency room with pneumonia. The study found that antimicrobial administration within 8 hours of presenting to hospital was associated with a lower 30-day mortality (OR = 0.85, 95% CI 0.75–0.96). The odds ratio of death, however, increased gradually with longer delays (Fig. 5). The study was not designed to answer the question of whether or not the antimicrobials prescribed were appropriate.

Houck and colleagues,\(^2\) using a similar approach, queried the Center for Medicare and Medicaid services database to look at time to antimicrobial administration in

![Fig. 5](image-url)

*Fig. 5.* Distribution of antimicrobial delays (A) and odds ratios of 30-day survival (B) in patients more than age 65 years presenting to the ER with community-acquired pneumonia. Approximately 25% of patients did not receive antimicrobial therapy after 8 hours in the ER; mortality in this group was significantly increased. (From Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA 1997;278:2080–4; with permission.)
13,771 hospitalized patients older than 65 years of age with CAP. Again, the database was not able to make the determination of appropriate therapy, but there was a reduction of in-hospital mortality of patients who received antimicrobials within 4 hours of emergency room (ER) admission (6.8% vs 7.4%, adjusted OR = 0.85, 95% CI 0.74–0.98). After adjustment for admission severity of illness, decreased 30-day mortality was found for elderly patients with CAP in whom antibiotics were administered within 4 hours (or within 2 hour for immunocompromised patients) in a large pre- and post-intervention study by Kahn and colleagues.

Battleman and colleagues used a slightly different approach by randomly selecting 100 patients with CAP from each of 7 institutions. In logistic regression, each of 3 primary quality parameters was shown to be associated with reduced length of hospital stay: (1) initial antimicrobial treatment in the ED (OR = 0.31; 95% CI 0.19–0.48); (2) appropriate antimicrobial selection (OR = 0.55; 95% CI 0.35–0.88); and (3) antimicrobial door-to-needle time (OR = 1.75 per 8 hours; 95% CI 1.34–2.29).

Other studies have confirmed these findings for general CAP, bacteremic pneumococcal CAP, Legionella pneumonia, ICU pneumonia, and ventilator-acquired pneumonia. In addition, several studies that have assessed the effect of CAP guidelines (that include recommendations on rapid antimicrobial administration) have noted an improvement in mortality with implementation. However, none of these studies specifically examined the role of improvements in time to antimicrobials in relation to outcome.

Not all studies confirm the existence of antimicrobial delay–dependent adverse effects. In a recent article by Cheng and colleagues, the time to antimicrobial administration was not associated with survival. This study was much smaller than those previously mentioned (501 patients), and the median time to antimicrobial administration was only 2.7 hours. Ninety-one percent of patients received antimicrobials within the JCAHO proscribed 8 hours. This was in contrast to the studies Meehan and colleagues and Houck and colleagues where antimicrobial administration was within 8 hours 75.5% and 85.8% of the time, respectively. The criticisms of the study by Cheng and colleagues were that median time to antimicrobial administration was already low, and most patients received antimicrobials within the appropriate time frame. Furthermore, patients who were at the greatest risk of death (pneumonia severity index of IV or V) received their antimicrobials earlier than those who were less ill. These factors confound the time/mortality association.

At least 2 other studies have similarly failed to demonstrate evidence of a benefit of early antimicrobial therapy in CAP. In the study of more than 1000 patients with CAP in 38 American medical centers by Dedier and colleagues, achievement of process-of-care markers including time to antimicrobials of less than 8 hours was not associated with outcome (time to clinical stability, LOS, and inpatient mortality). However, there seemed to be marked confounding in the study with more severely ill patients consistently receiving earlier antimicrobial therapy. With respect to the study by Silber and colleagues, the patient population assessed was limited to those with mild to moderate CAP. Based on the studies of septic shock discussed earlier, the benefit of early antimicrobial therapy seems to be greatest in the most severely ill and may be lacking in those with only modest disease.

The assessment of oxygenation status in these patients also plays a role in their survival. Blot and colleagues looked at the delay in oxygen assessment in patients with pneumonia and found that a delay of greater than 1 hour was associated with a longer median time to antimicrobial administration (6 vs 3 hours). If this oxygen assessment was delayed even further (to >3 hours), the result was an increased risk of death (OR = 2.24, 95% CI 1.17–4.30). The lack of recognition of severity of illness
(based on an oxygenation defect) in these patients with CAP probably results in the delay in antimicrobials. Patients with an atypical presentation of their pneumonia (ie, afebrile, or not hypoxic), or with an altered mental state were at higher risk of not receiving their antimicrobials in a timely fashion.65

**Meningitis**

Acute bacterial meningitis is an infectious disease emergency with mortality and morbidity of 25% and 60%, respectively.76,77 The data for the early administration of antimicrobials in bacterial meningitis are at least as extensive as with CAP, and are no less compelling. But as with pneumonia, the data are not entirely definitive because no prospective randomized studies have been performed and likely never will be.

Many retrospective studies have shown a relationship between delays in antimicrobial therapy and outcome of bacterial meningitis. However, others have failed to demonstrate such a relationship. The positive studies are notable for indexing delays to clinical/physiologic markers such as altered level of consciousness (LOC) and other clinical manifestations (similar to the indexing to hypotension in Kumar and colleagues6,16 study of septic shock). This approach seems to yield the most consistently positive results.

For example, Lepur and Barsic78 examined 268 adult patients with community-acquired bacterial meningitis in Croatia. Among patients with a poor clinical outcome, the start of appropriate antimicrobial treatment in relation to the onset of first symptoms and particularly to the onset of consciousness disturbance was significantly delayed \( (P = .018 \text{ and } P < .001, \text{ respectively}) \) compared with the favorable group. Earlier adequate antimicrobial treatment related to the onset of overt altered LOC was independently associated with favorable outcome \( (OR = 11.19; 95\% \text{ CI } 4.37–32.57; P < .001) \). This effect was incremental with longer delays associated with worse outcome. No relationship was found between time from hospital presentation to antimicrobial administration and outcome. Another notable element of this study is the long durations of time involved. Mean time to antimicrobial administration from hospital arrival was \( 1.21 \pm 0.9 \) SD days.

Aronin and colleagues79 have similarly found an association between antimicrobial delays and outcome when the patient’s condition had progressed to the highest stage of clinical severity. Many investigators have demonstrated that severity of neurologic presentation and/or time of antimicrobial administration is closely linked to outcome.77,80,81

Others have focused on door-to-needle time. Miner and colleagues82 retrospectively looked at their database of 171 cases of bacterial meningitis. Of the patients who presented to the hospital with meningitis, 76% of them received their antimicrobials in the ED, with a mean time to administration of \( 68 \pm 13 \) minutes. The remaining 24% of patients received their antimicrobials after being admitted to the hospital, with a median time to antimicrobials of \( 6 \pm 9 \) hours. The mortality of the patients who received their antimicrobials earlier in the ED was 7.9%, whereas the group who received their antimicrobials as inpatients had a mortality of 29% \( (P = .003) \).

Similarly, Auburtin and colleagues83 sought to prospectively identify factors associated with mortality and morbidity in adults admitted to ICUs with pneumococcal meningitis. Among 156 patients, 3 variables were independently associated with 3-month mortality: Simplified Acute Physiology Score II \( (OR = 1.12; 95\% \text{ CI } 1.072–1.153; P = .002) \); isolation of a nonsusceptible strain \( (OR = 6.83; 95\% \text{ CI } 2.94–20.8; P < .0001) \), and an interval of more than 3 hours between hospital admission and administration of antimicrobials \( (OR = 14.12; 95\% \text{ CI } 3.93–50.9; P < .0001) \).
In the most recent study, Koster-Rasmussen and colleagues\textsuperscript{84} studied all 186 patients presenting with bacterial meningitis in eastern Denmark in a 2-year period. Delay of antibiotic therapy (door-to-needle time) was independently associated with unfavorable outcome (OR = 1.09/h, CI 1.01–1.19) among the 125 adult cases (Fig. 6). In the group of 109 adults receiving adequate antibiotic therapy within 12 hours, the association between antibiotic delay and unfavorable outcome was an astonishing 30% per hour delay (OR = 1.30/h, CI 1.080–1.57). Although the median time to appropriate antimicrobial therapy among adults was 2 hours, almost 20% were delayed beyond 12 hours. Mortality outcomes paralleled unfavorable results.

In another study by Proulx and colleagues\textsuperscript{25}, a delay in antimicrobial administration of greater than 6 hours (door-to-needle time) among 123 cases of adult bacterial meningitis was associated with an 8.4 times increased risk of death (95% CI 1.7–40.9) in regression analysis. This effect of treatment delay on mortality was incremental. Increasing the length of time to antimicrobial administration increased the risk of death, with a delay of greater than 8 to 10 hours resulting in mortality of 75%.

Two other interesting findings from this study deserve mention. First, the failure to administer antimicrobials before transfer from another institution was associated with a 21.8-fold increase in the risk of death. This study took place at a referral facility, and the need for diagnostic computed tomography (CT) scanning of the head was the most common reason for transfer. The time delay in transferring the patients engendered the antimicrobial delay. The other surprising finding from the study was the diagnostic sequence for meningitis. In this relatively recent study (2005), less than 40% of physicians used a decision pathway that involved the administration of antimicrobials before other interventions such as diagnostic lumbar puncture (LP) or CT scan of the head. Twenty-two percent of physicians in the study performed a CT scan, and then an LP before administering antimicrobials. In studies of the CT findings in bacterial meningitis, less than 2.7% to 5% of patients showed evidence of significant mass effect; almost all of these patients exhibited clinical findings of the abnormality.\textsuperscript{85,86} Concerns about precipitating transtentorial herniation with an LP, although valid, are still not an excuse to delay antimicrobial administration.

Several other studies have demonstrated that antimicrobial delays in acute bacterial meningitis are associated with poor outcomes, particularly for meningococcal

![Fig. 6. Rate of hospital mortality and unfavorable outcome according to the treatment delay in time interval in acute bacterial meningitis. (Data from Koster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect 2008;57:449–54.)](image-url)
meningitis; studies have suggested that administration of drug by family practitioners in the community may improve outcomes.\textsuperscript{76,87–91} Others have questioned these results.\textsuperscript{77,92,93}

Some clinicians argue that delivery of antimicrobials before a diagnostic LP results in sterilization of the cerebrospinal fluid (CSF) and thus the inability to identify a causative organism. Although this is potentially the case, antimicrobials do not alter the CSF biochemistry and cytology sufficiently to alter the diagnostic yield. Furthermore, a causative diagnosis may be made from the CSF Gram stain or antigen tests. The minimization of door-to-needle time in this deadly disease should take precedence over all other diagnostic tests, based on these studies.

Most patients with meningitis present to clinicians who have limited experience in diagnosing and treating this disease. The prototypical clinical presentation of fever, altered LOC, and nuchal rigidity is not always present, making the diagnosis challenging. Clinicians should have a low threshold of instituting antimicrobials in patients who are at risk of this disease, even before the results of CSF analysis are available.

\textbf{Limitations of Human Data}

The question of whether delays in antimicrobial therapy for acute life-threatening infection including meningitis, pneumonia, bacteremia, invasive candidiasis, sepsis, and septic shock have a significant effect on outcome is a critical one. Given the difficulties in developing an ethical trial design, prospective randomized data may be almost impossible to generate. As a consequence, an answer has to be inferred from appropriate experimental animal models, retrospective or prospective cohort analyses, and before-after interventions. However, these approaches have significant limitations, which may explain some of the divergent results seen in studies.

First, confounding is a major issue. Patients who present with a more obvious or more severe presentation may receive earlier assessment and antimicrobial therapy. These patients may also have more intact or robust immune systems which could explain the better outcomes in this group. Alternately, it is possible that less ill patients with a higher probability of survival may receive faster antimicrobials because their clinical condition is more easily and rapidly assessed. Divergent results in different trials could be accounted for, in part, by variations in the nonrandom distribution of patients to early or delayed therapy. For example, some studies have shown that sicker patients often get earlier therapy, whereas those with atypical presentations are significantly delayed.\textsuperscript{65,94,95} Confounding seems inconsistent between studies making comparisons difficult.

Second, variations in study results may occur as a consequence of the quality of the data collected. Administrative database studies\textsuperscript{5,23} necessarily use data that have not been assessed for the individual patient. Such databases are known to have high error/miscoding rates relative to study designs in which data are collected by trained abstractors. In addition, these studies can necessarily only examine standard data collection elements such as when the first dose of antimicrobial was given (irrespective of whether it was appropriate or not). This can be a substantial issue because 20% to 40% of initial antimicrobials may be inappropriate in some circumstances.\textsuperscript{96,97}

A third cause of inconsistency in results can be the use of different points for indexing of when antimicrobials are started. This is an obvious issue with administrative databases because, typically, only the arrival time to hospital and time of antimicrobial dispensing from the pharmacy are recorded routinely. The study by Leper and Barusic\textsuperscript{78} was notable in demonstrating a significant relationship between the onset of altered LOC and antimicrobial administration. This study failed to demonstrate a relationship between ER admission time and antimicrobial administration with respect to
clinical outcome of patients with bacterial meningitis. The studies reviewed in this article suggest that outcomes may be more closely linked to the time between occurrence of important pathophysiologic responses (hypotension for septic shock, altered LOC for meningitis) and antimicrobial administration than administrative events (hospital or ER admission) and antimicrobial administration.

Fourth, the studies examined within each clinical syndrome indicate substantial variations in the degree and pace of illness. The studies of meningitis and bacteremia/sepsis/septic shock seem to suggest that the ability to show a statistical relationship between antimicrobial delays and outcome may be substantially contingent on the degree of illness being studied. Radetsky and colleagues have suggested that any connection between a delay in the treatment of bacterial meningitis and outcome depends on the presenting clinical pattern. With an early presentation and modest clinical illness, relatively short delays (even on the order of days) may not substantially affect survival or be associated with severe sequelae. On the other hand, late presentations with fulminant illness may show no substantial response to any antimicrobial therapy. Only clinically overt presentations where a risk of irreversible injury is imminent may demonstrate sensitivity to delays in administration of antimicrobial therapy. A similar phenomenon may exist with bacteremia/sepsis/septic shock. Bacteremia or candidemia without sepsis-induced organ failure is a relatively mild disease with a low mortality risk (compared with septic shock with the same organisms). In such situations, relatively short delays in antimicrobial therapy are unlikely to yield evidence of adverse outcomes. Accordingly, the studies that do show an effect of antimicrobial delays show break points in the range of days rather than hours. In contrast, several studies show that hours (or less) make a difference with septic shock. For this reason, mild to moderate CAP should not be expected to demonstrate evidence of sensitivity to modest variations in antimicrobial delays.

As a statistical issue, the intrastudy range of values of antimicrobial delivery delays may be an important source of variation in study results. If the range of delays is similar (whether very short or very long), then it would not be possible in logistic regression to show any effect of such delays. The studies by Lepur and Barsic on meningitis and by Kumar and colleagues on septic shock showed a very broad range of delays from minutes to days. In contrast, some other studies showed very short antimicrobial delays, which may make it much harder to demonstrate an effect without extremely large datasets.

With respect to non-necrotizing pneumonia without septic shock and bacteremia/fungemia, it is not clear that a solid pathophysiologic rationale to support sensitivity of mortality to antimicrobial delay exists. The authors believe that to exhibit such sensitivity, the condition under study must pose a risk of irreversible and irreplaceable organ injury. Septic shock and meningitis fit that criteria, the former because multiple, simultaneous organ failure can rarely be reversed even with maximal support. However, non-necrotizing pneumonia, bacteremia, and sepsis without shock do not. One possibility to be considered is that it is the subset of patients with septic shock or who develop septic shock that drive antimicrobial delay sensitivity in these groups.

Antimicrobial Delays

Health care professionals do not intentionally delay administration of antimicrobials in patients recognized to have life-threatening infection. The occurrence of delays is a consequence of difficulties in the prompt assessment of these patients and deficiencies in recognizing them as being at high risk of death and increased LOS with a delay in antimicrobial administration. Barriers to timely antimicrobial administration are consistently present across all serious infections.
Identified barriers to timely administration of antimicrobials for CAP have been described in the literature. These barriers include a lack of education of physicians, a lack of appreciation of the severity of pneumonia in the elderly, and increased work intensity in busy EDs. A major cause of delays is transfer of the patient to wards before antimicrobials are given. Atypical presentations with a lack of fever and toxicity or an altered mental state can also prevent prompt recognition and treatment. Similarly, atypical nonclassic meningitis presentations without fever and severely altered mental status may not be recognized, engendering significant delays. Provision of diagnostic procedures (CT and LP) and administrative delays related to transfer to general wards or other facilities are also associated with significant delays. Staffing issues relative to patient demand can also clearly play a significant role. With respect to sepsis, septic shock, and bacteremia, a similar list of potential causes (and recommended solutions) for delay can be generated (Box 1).

**Box 1**

**Causes of delay of effective antimicrobial therapy and a potential approach to reduce them**

<table>
<thead>
<tr>
<th>Causes of delays in administration of antimicrobials in severe infection and septic shock</th>
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<tbody>
<tr>
<td>1. Failure to recognize infection in a timely way</td>
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<tr>
<td>2. Failure to recognize that hypotension represents septic shock</td>
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<tr>
<td>3. Effect of inappropriate antimicrobial initiation (delays administration of appropriate antimicrobials)</td>
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<tr>
<td>4. Failure to appreciate risk of resistant organisms in certain scenarios (eg, immunocompromised versus immunosuppressed; antecedent antimicrobial use) leading to inappropriate initial antimicrobials</td>
</tr>
<tr>
<td>5. Wait for blood cultures from intravenous technicians before giving antibiotic</td>
</tr>
<tr>
<td>6. Requirement for 2 nurses to check for potential drug sensitivity before dosing of antimicrobials</td>
</tr>
<tr>
<td>7. Transfer from ER before ordered antibiotics given</td>
</tr>
<tr>
<td>8. Failure to use stat orders</td>
</tr>
<tr>
<td>9. Failure to recognize that administration of inappropriate antimicrobials is equivalent to absent antimicrobial therapy when responding to clinical failure (ie, should not delay appropriate antimicrobials because inappropriate drugs recently given)</td>
</tr>
<tr>
<td>10. No specified order with multiple drug regimens so that key drug (usually most expensive and hardest to access) may be given last</td>
</tr>
<tr>
<td>11. Administrative/logistic delays (nursing/pharmacy/ward clerk)</td>
</tr>
</tbody>
</table>

**Potential approaches to minimize delays in initiation of empiric antimicrobial therapy**

| 1. The presence of hypotension in a patient with known or suspected infection should be considered to be septic shock in the absence of a definitive alternate explanation |
| 2. No transfer from ER before ordered antibiotics given |
| 3. All initial orders for any intravenous antibiotic automatically stat |
| 4. Syndrome-based, algorithm-driven guidelines similar to meningitis and neutropenic sepsis with designated broad-spectrum antimicrobial regimen at each center |
| 5. Antimicrobial order to include sequence and time limit (eg, within 30 minutes of order) |
| 6. First intravenous dose of most broad-spectrum agents (ie, β-lactam/carbapenems) push by physician |
| 7. Health care worker and support staff education; a team approach |
Available data suggest that it is not difficult to reduce antimicrobial delivery delays especially when delays are substantial to begin with. Natsch and colleagues developed a program of guidelines and education to facilitate timely antibiotic administration in the ER. The program consisted of guidelines on handling patients with serious infections and on ordering immediate treatment, guidelines on obtaining culture samples, lectures to medical and nursing staff, improvement of availability of antibiotics in the ED, and removal of financial restraints on stocking and ordering of antibiotics. The investigators were able to decrease median door-to-needle time from 5.0 hours to 3.2 hours ($P = .04$). Similarly, Rollins and colleagues reduced average time to antimicrobial therapy from 6.8 to 3.6 hours at 1 institution within 6 months of the introduction of an ER preadmission procedure, an antibiotic treatment protocol, and a sputum collection protocol.

Even when door-to-needle times are low, appropriate strategies can reduce delays even further. Tuijn and colleagues were able to take approximately 30 minutes off a 3-hour time primarily by emphasizing the need to administer antimicrobials in the ER before patients were transferred to the wards. Our own data show that much greater delays occur on inpatient wards than the ER.

Vogtlander and colleagues have shown that although the time from writing the order to antimicrobial administration was 2.7 hours, this time could be reduced by 1 hour ($P = .003$) with simple administrative maneuvers and staff training.

The most reliable approach to decreasing the time to antimicrobial administration for acute life-threatening infections is to take a systems-based approach in which all members of the health care team are stakeholders in this process. This allows for the early recognition of serious infectious disease and the rapid institution of therapy. This involves nurses to perform a rapid and focused assessment of these patients, physicians to accurately diagnose the disease, and a pharmacy and transport system that delivers the appropriate antimicrobials to the patients in as short a time as possible. When this systems-based approach is undertaken, improvements in the time to antimicrobial administration can be realized. Such improvements should translate into a significant cost benefit particularly for high-risk patients.

**SUMMARY**

For decades, health care workers faced the challenge of how to adequately treat life-threatening infections. To a great extent, the primary focus on improving outcomes has centered on improvement in resuscitation, deployment of antimicrobials of increasing potency, and development of novel adjunctive therapies. However, a critical appraisal of available studies conclusively shows that the early recognition of life-threatening infection and rapid initiation of appropriate antimicrobial therapy is the critical element in reducing mortality. The challenge that hospitals now face is how best to implement systems to facilitate this goal. The processes to accomplish this goal has already been demonstrated in various aspects of medical care including provision of rapid surgical therapy after trauma and rapid interventions to open blocked coronary arteries in acute myocardial infarction. The fundamental requirement is the involvement all members of the health care team, including physicians, nurses, and pharmacists.

An important slogan used in the training of health care workers with respect to revascularization of arteries in acute myocardial infarction and obstructive stroke has been “Time is tissue.” If that is so, then an appropriate rule for life-threatening infections, particularly septic shock is “Speed is life.”
REFERENCES


