Best evidence in critical care medicine

Early antibiotics and survival from septic shock: it's about time

Article appraised

Kumar A, Roberts D, Wood KE, Light B, 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.

Structured abstract

Background: International guidelines recommend appropriate antimicrobial therapy within an hour of recognizing severe sepsis and septic shock.[1] Unfortunately, delays are common.[2,3] This study was undertaken to quantify the association between mortality and time to administration of effective antibiotics following hypotension in septic shock.

Question: What is the relationship between delay of effective antibiotics from the initial onset of hypotension and survival-to-hospital-discharge in adult patients with suspected or confirmed septic shock?

Design: A retrospective cohort review of the medical records of 2,731 adult patients with septic shock (and with no other obvious cause of shock), conducted between July 1989 and June 2004 and involving 14 intensive care units in Canada and the United States.

Patients: Hypotension was defined as a mean arterial pressure (MAP) < 65 mmHg, a systolic blood pressure (SBP) < 90 mmHg, or a fall in SBP of 40 mmHg from the patient's baseline. These criteria were consistent with the 1991 Society of Critical Care Medicine/American College of Chest Physicians Consensus Statement on Sepsis Definitions.[4] Time zero was determined to be either 1) the first episode of hypotension that persisted despite at least two litres of crystalloid resuscitation (so called "persistent hypotension"), or 2) hypotension that resolved for less than one hour following fluid resuscitation (so called "recurrent hypotension"). Hypotension that resolved without therapy or with less than two litres normal saline (or equivalent) did not qualify. Potential pathogens had to be isolated within 48 hr of the onset of shock. The effectiveness of antimicrobials was determined by an extensive list of predetermined rules that included broadly accepted guidelines for known and suspected infections.

Intervention: No intervention. Instead, medical charts were reviewed and the antimicrobial used, the time of initial administration, the source of infection, patient demographics and the APACHE II score were collected.

Primary endpoint: Survival to hospital-discharge.

Results: Of 2,731 patients with septic shock, 2,154 (79%) patients did not receive effective antimicrobial therapy until after the onset of hypotension. Amongst these 2,154, the in-hospital mortality rate was 56.2%. After the onset of hypotension, each hour of delay was associated with a mean decrease in survival of 7.6% (range 3.6–9.9%). Survival was 79.9% if antibiotics were administered in the first hour, and 42% by the sixth hour. The median time to effective antibiotics was six hours after onset of hypotension. Multivariate analysis showed that time to administration of effective antimicrobial therapy was the single strongest predictor of outcome. The delay from onset of persistent/recurrent hypotension to initiation of effective antibiotics accounted for 28.1% of variance in survival to discharge while APACHE II only explained 24.6% and the volume of fluid infused in the first hour accounted for < 2%. Subgroup analysis showed the relationship of survival and antibiotic-delay following hypotension held regardless of site of infection; whether gram-negative, gram-positive or fungal, whether bacteremia was present or not; or whether the infection was documented or suspected.

Conclusions: Effective antimicrobial therapy for adult patients with septic shock provided within the first hour of hypotension was associated with increased survival to hospital discharge. Only 50% of these patients received such therapy within the first six hours of documented hypotension.

Commentary

It seems intuitive that early antibiotics in septic shock would improve survival. However, while previous studies did suggest that delays might be associated with decreased survival,[2,3] the delays were often timed to admission to the intensive care unit or emergency room presentation, and not to antibiotic admission. Furthermore, no study has previously examined treatment delays in relation to physiologic variables such as the onset of hypotension. This alone makes this work of Kumar *et al.* important. However, what is most notable is that this publication highlights timing of antibiotics as the single strongest predictor of outcome in septic shock. The strong association persists even when therapeutic factors such as the rapidity of fluid resuscitation are included, or non-therapeutic variables - that are typically predictive of survival - such as APACHE II, number of admission organ failures, the site of infection, and neutropenia were examined. This relationship held whether the infection was documented or suspected; whether source control was required; the pathogen isolated or not; and whether bacteremia was present or absent.

Each hour of delay was associated, on average, with a remarkable 7.6% decrease in survival. For example, survival was 82.7% if effective therapy was initiated within 30 min of hypotension. Survival decreased to 70.5% just by delaying antibiotics until the second hour. Comparing treatment within one hour to treatment by six hours, survival decreased from an encouraging 79.9% to a disheartening 43.8%. With delays of nine to 12 hr, survival was only 25.4%. These findings alone are concerning. However, Kumar *et al.* also highlight how common antibiotics delays are: 79% did not receive antibiotics until the onset of hypotension, and of those patients only 14.5% received them within the first hour of hypotension. Only 32.5% received antibiotics by three hours, and only 51.4% by six hours. Even 12 hr after the onset of recurrent or sustained hypotension, 29.8% (i.e., more than one in four) had not received effective antimicrobials. Nineteen patients died without ever receiving antibiotics. Overall, the median time to antibiotic administration was six hours after hypotension. While this study may be criticized because it was neither prospective nor randomized, the primary outcome measure was objective and the sample size was large. Accordingly, these results may profoundly impact everyday acute-care delivery.

Initiation of antibiotics to septic patients often occurs after initial investigations, resuscitation and stabilization. Kumar *et al.* argue that this approach is not acceptable. Experience has shown that in the midst of a busy resuscitation it is often difficult to remember the need for antibiotic or source control. Intensive care physicians are more accustomed to focusing initially on prioritizing central venous and arterial cannulation, vasopressors, and fluid management. These interventions are vitally important, but not at the expense of delaying antibiotics. Antibiotics should be viewed as being complementary to other time-dependent forms of acute therapy. Optimal resuscitation has always required concomitant rather than sequential treatment, and this should begin by thinking of antibiotics as acute life-saving agents. Those involved in acute resuscitation should be confirming that antibiotic administration is expedited, just as they are concerned that blood pressure has been quickly normalized. This represents a new paradigm. The profound effect of treatment delays also has significant implications for patients presenting outside of major centres, or where transport times are prolonged.

This publication has also renewed the call for protocolized sepsis orders, and should emphasize the importance of timely dispensing of antibiotics from pharmacy. A recent audit of practices in our institution demonstrated that all first doses must be ordered STAT. This avoids the possibility of a nurse waiting to give an antibiotic at pre-scheduled administration times (for example at 0600 hr, 1200 hr, etc.). One area of uncertainty is the extent to which the use of broad spectrum antibiotics will increase, and what effect this might have on drug resistance. In the meantime, the principles of daily reassessment, ensuring adequate source control (e.g., drainage or debridement), changing to narrower-spectrum antibiotics as patients improve, and tracking local antibiotic susceptibility patterns should be standard care for these patients.

Recently, Angus *et al.* showed that the incidence, cost and mortality of severe sepsis and septic shock is comparable to that of acute coronary syndromes (ACS).[5] Unfortunately, few would claim that sepsis has received similar attention. The comparison with ACS is useful: it highlights the need for increased funding in sepsis research, and parallels lessons already learned from ACS. For example, in sepsis, just as with ACS, the importance of "door-to-needle times" should be recognized, along with the need to educate the public and medical profession. In ACS the "chain-of-survival" has been summarized as: 1) early access; 2) early cardiopulmonary resuscitation; 3) early defibrillation; and 4) early advanced care.[6] It is not unreasonable to similarly describe sepsis care as requiring: 1) early recognition;[1] 2) early goal directed therapy;[7] 3) early antibiotics; and 4) early advanced care.[8] There needs

to be seamless transition-of-care from the emergency to the operating room to the intensive care unit. This starts by understanding the seriousness of the disease, and that opportunities exist to do better.

It is useful to emphasize that patients do not die of "pneumonia" or "peritonitis" *per-se*, but rather from multi-system organ failure (MSOF) if the disease progresses. Microcirculatory cascades promote inflammation and microthrombi which can lead to organ failure remote from the site of initial infection.[8] The idea that genetic and biochemical responses influence survival is further supported by provocative work which showed a stronger familiar link between sepsis and death, than exists for coronary disease.[9] Researchers are therefore attempting to unravel the heterogeneous biochemical and cellular responses to severe infection. This may lead to molecular therapies in addition to antibiotics. It may also eventually lead to therapies based on genetic make-up and phenotypic expression, as opposed to antibiotics which are based on site of infection and presumptive pathogen. Regardless, the best current treatments for MSOF are merely supportive. As such, the best way to manage MSOF is to focus on its prevention.

Recognition is the vital first-step towards decreasing delays. Unfortunately, recognition can be challenging. Clinicians typically rely upon crude abnormalities in the macrocirculation such as altered temperature, increased respiratory rate, increased heart rate, or altered white count. These signs are known as the systemic inflammatory response syndrome (SIRS) criteria.[4] Systemic inflammatory response syndrome is of course very non-specific, but should provide the first warning to look for infection. In addition, an elevated lactate level offers a clue as to microcirculatory supply/demand imbalance that in turn suggests an infection is serious. This is the second warning sign. Anuria, hypotension, acute respiratory respiratory distress syndrome and coagulopathies are even later signs. Waiting until compensatory mechanisms have been exhausted greatly increases the likelihood of MSOF with its attendant pronounced mortality. This is why early treatment saves lives and why late treatment is unacceptable.

One must be cautious if assuming that mortality is high only when sepsis is accompanied by hypotension. Recent work by Rivers *et al.* has shown that so-called "normotensive severe sepsis" or "cryptic-shock" (diagnosed by the presence of SIRS plus microcirculatory compromise - manifested by a lactate > 4 $mmol \cdot L^{-1}$; but with a MAP > 100 mmHg) is associated with a 40% mortality.[7] Hypotension is usually preceded by hypoperfusion. This is especially true in sepsis, and especially true in young patients who posses strong compensatory mechanisms and may not become hypotensive until late in their clinical presentation. Hypoperfusion is not innocuous, but rather stimulates the aforementioned microcirculatory cascades. Equally, it has been argued that mortality from cryptic shock is high because these patients may be comparatively ignored when compared to those with low blood pressure. Less urgent medical attention may include marked delays in antibiotic administration.

The study of Kumar *et al.* included both surgical and medical patients, those with community-acquired and nosocomial-infections, patients with documented and suspected infections, bacteremic and non-bacteremic patients with a range of APACHE II scores (26.0 ± 8.6), and those who did and did not receive sepsis adjuncts such as Drotrecogin-alfa and low-dose steroids. Strong evidence suggests that early and effective antimicrobials have a profound association with survival. The clinical implications for the care of septic patients are significant. It remains to be seen how quickly the intensive care community responds.

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