Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

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Objective: **To determine the prevalence and impact on mortality of delays in initiation of effective antimicrobial therapy from initial onset of recurrent/persistent hypotension of septic shock.**

Design: **A retrospective cohort study performed between July 1989 and June 2004.**

Setting: **Fourteen intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States.**

Patients: **Medical records of 2,731 adult patients with septic shock.**

Interventions: **None.**

Measurements and Main Results: **The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103–1.136, $p < .0001$). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12–2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Median time to effective antimicrobial therapy was 6 hrs (25–75th percentile, 2.0–15.0 hrs).**

Conclusions: **Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. Despite a progressive increase in mortality rate with increasing delays, only 50% of septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension. (Crit Care Med 2006; 34:1589–1596)**

KEY WORDS: sepsis; antimicrobial; timing; delay; outcome

Despite the fact that current international guidelines suggest initiation of antimicrobial therapy within an hour of presentation with severe sepsis and septic shock, no clinical studies exist to support this recommendation (1). In reality, initiation of antimicrobial therapy for infections causing critical illness often awaits thorough clinical evaluation, resuscitative measures, initial stabilization, and investigative efforts (2–6).

Relatively few studies have rigorously examined the effect of delays of antimicrobial therapy in critically ill, infected patients (7–17). To the extent that these studies have been done, the delay has most often been timed to admission to the intensive care unit (ICU) or the emergency room. No studies have examined treatment delays in relation to defined physiologic variables such as hypotension. We have recently demonstrated that the onset of hypotension is a critical

***See also p. 1819.**

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marker of increased mortality in a murine model of *Escherichia coli* peritonitis/septic shock (18). Based on these findings, a retrospective multiple-center study was undertaken to examine the relationship between the delay in initiation of effective antimicrobial therapy from initial onset of recurrent or persistent hypotension and survival in septic shock.

METHODS

A retrospective review of three patient cohorts of adult (≥18 yrs of age) septic shock was performed. The study was approved through the Health Ethics Board of the University of Manitoba and at each individual participating center. A waiver of the requirement for informed consent was obtained under the regulations of each participating site.

In the first cohort, all septic shock cases admitted to the adult ICUs (two medical, two general surgical, five mixed) of all hospitals (two tertiary, five community) in the province of Manitoba, Canada, from May 1999 to June 2004 were identified using a locally developed ICU database in which ICU admission and acquired diagnoses are prospectively encoded by the attending physician and confirmed by specially trained research nurses (19).

In a second, comprehensive cohort, all cases of septic shock occurring between June 1989 and April 1999 at a single adult academic tertiary care institution (one medical and one general surgical) in Winnipeg, Manitoba, were similarly identified using the same database.

In the final cohort, consecutive adult septic shock patients (approximately 150 each from July 1999 to June 2004) at three academic American institutions were identified using a combination of internal ICU registries and/or International Classification of Diseases Revision 9 coding strategies depending on the specific institutions coding practices.

Following initial identification, each potential case was screened to determine whether the case met specific criteria for septic shock as described by the 1991 Society of Critical Care Medicine/American College of Chest Physicians Consensus Statement on Sepsis Definitions (20). All included cases were required to have no other obvious cause of shock.

Data including choice of antimicrobials used and actual time of initial parenteral antimicrobial administration were retrospectively collected using a uniform data extraction template by several trained research nurses or research assistants with medical training (medical students, residents, fellows). All data extractors reviewed ≥100 charts.

Data Elements. Clinical infection definitions were adapted from previous recommendations (21, 22) as summarized in the Appendix. To qualify as potential pathogens causing shock, isolates from both local site and/or blood cultures were required to have been obtained within 48 hrs of onset of shock. The time of initiation of effective antimicrobial therapy (i.e., with *in vitro* activity appropriate to isolated pathogenic organisms or, if a pathogenic organism was not isolated, appropriate for the underlying clinical syndrome) following onset of recurrent or persistent hypotension was determined for all cases. Identification of recurrent/persistent hypotension as described subsequently was inclusive of ambulance, paramedic, or nursing home records. Questionable cases or data elements were reviewed by the principal investigator for adjudication.

A series of predetermined rules were created to assess effectiveness and timing of antimicrobial therapy (e.g., how to determine at what point shock has occurred; how to determine which antimicrobial should be considered critical for implementation of effective antimicrobial therapy in a mixed infection). Notable examples of these rules included that the numerically dominant fungal or Gram-negative isolate was generally considered to have the primary role for mixed flora intraabdominal infections. With semiquantitatively similar organism densities, the most resistant Gram-negative (or fungal organism if present) was considered to be the primary pathogen. Similar rules held for multiple lung isolates although in that case, enterococci were considered to be the primary etiological organism only in the absence of other, more plausible pathogens. In addition, *Candida* species isolated from lung were considered to be colonizers (unless also present at multiple other sites and/or the patient was immunosuppressed, in which case disseminated infection was diagnosed). *Staphylococcus epidermidis* was uniformly considered to be incapable of causing septic shock. Other coagulase-negative staphylococci were similarly considered to be unlikely to cause septic shock unless present as a sole isolate in multiple blood cultures in the absence of evidence of endovascular infection.

For culture-negative septic shock, effective therapy was deemed to be initiated when antimicrobials consistent with broadly accepted guidelines for empirical management of the typical pathogens for the clinical syndrome (in the context of host immune/health status, environmental factors, and local flora) were given. For the purposes of this study, effective (empirical) therapy of culture negative infections leading to septic shock was defined by the recommendations enumerated in Table 1 "Clinical approach to initial choice of antimicrobial therapy" in the Sanford Guide to Antimicrobial Therapy (34th Ed.) (23).

For unanticipated scenarios not covered by the predetermined rules, data were reviewed independently by two infectious disease/critical care medicine physicians blinded to outcome. Agreement allowed data entry. Discordant assessments were reviewed by a third similarly trained physician whose decision was determinative. A similar adjudication approach was used for other issues where clinical judgment was required.

Definitions. Hypotension was defined as a mean blood pressure of <65 mm Hg, a systolic blood pressure of <90 mm Hg, or a decrease in systolic pressure of 40 mm Hg from the patient's baseline consistent with Society of Critical Care Medicine/American College of Chest Physicians criteria for septic shock (20). An episode of hypotension was considered to represent the initial onset of septic shock when a) hypotension persisted from onset despite fluid (>2 L of saline or equivalent) ad-

Table 1. Chronic comorbidities of patients with septic shock

	%
Acquired immune deficiency syndrome (1993 CDC criteria)	1.4
Acute or chronic lymphoma	3.7
Acute or chronic leukemia/multiple myeloma	6.8
Metastatic solid cancer	9.1
Immunosuppressive chemotherapy or long-term steroid therapy (>10 mg prednisone equivalent daily)	15.4
Neutropenia (<500 cells/μL)	6.8
Liver failure (biopsy-proven cirrhosis, documented variceal hemorrhage or portal hypertension, hepatic ascites, or encephalopathy)	7.4
New York Heart Association class IV heart failure	4.8
COPD (medication or oxygen requiring)	9.0
Chronic renal failure (serum creatinine >1.5 upper limit of normal)	14.9
Chronic dialysis dependence	7.4
Diabetes mellitus (medication dependent)	16.1
Diabetes mellitus (insulin dependent)	8.3
Alcohol abuse	13.8
Elective surgery	15.1
Emergency surgery/trauma	6.7

CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease.

ministration (persistent hypotension); or b) hypotension was only transiently improved (hypotension resolution for <1 hr) with fluid resuscitation (recurrent hypotension). Hypotension that resolved in the absence of therapy or following administration of <2 L of normal saline (or equivalent) without subsequent clinical deterioration was not considered to represent initial onset of septic shock-related hypotension. Nosocomial infection-related septic shock was defined as septic shock caused by any infection developing >48 hrs after hospital admission. Cases not meeting this definition were considered to be septic shock associated with community-acquired infections. Documented infections were those in which a plausible microbial pathogen was identified from the clinical infection site or blood in the context of a compatible clinical syndrome or in which infection was supported by a definitive radiologic, surgical, or pathologic diagnosis (autopsy or biopsy). All other infections were considered to be suspected. Effective antimicrobial therapy was considered to have been initiated if antimicrobials with *in vitro* activity appropriate for the isolated pathogen or pathogens (or in the case of culture-negative septic shock, antimicrobial therapy matching accepted national guidelines modified to local flora) were received within 6 hrs of administration of the first new antimicrobial following onset of recurrent or persistent hypotension. Otherwise, ineffective therapy was considered to have been initiated.

Statistical Analysis. The primary outcome variable was survival to hospital discharge inclusive of discharges to chronic health care facilities (nursing homes, etc.). The time to initiation of effective antimicrobial therapy relative to the first occurrence of recurrent or persistent hypotension was the primary independent variable. Data are expressed as mean ± SD unless otherwise indicated.

Logistic regression modeling was used to examine survival to hospital discharge as a function of time delay to effective antimicrobial administration using interval data. Sensitivity of this delay as a continuous variable was also examined by stratifying over specific subgroups. In addition, a multiple logistic regression model was used to examine the independent impact of a variety of clinical and therapeutic variables (including time to effective antimicrobial initiation) on survival to hospital discharge. These statistical analyses were performed using SAS 9.0. Nagelkerke R^2 tests to determine the contribution of specific variables to variance in outcome (survival to hospital discharge) were performed using SPSS 13.0.

RESULTS

In total, 2,731 cases were determined to fit the diagnostic criteria for septic shock. All cohorts were similar in terms of average Acute Physiology and Chronic Health Evaluation (APACHE) score (24), distribution of clinical infections, time to effective antimicrobial therapy following onset of hypotension, and outcome. Therefore, data were combined for analysis. Of the total number, 56 were moribund on admission based on predefined criteria (cardiac arrest or requirement for epinephrine in the field or immediately on arrival to the emergency room). All were included in this analysis.

Demographic and Descriptive Data. The average age of septic shock patients was 62.7 ± 16.4, with 54.3% males and 45.7% females. Average APACHE II score determined from the most abnormal results within 24 hrs of shock onset was 26.0 ± 8.6. Drotrecogin-alfa (activated) was used in 91 cases (outside of randomized trials), whereas low-dose steroid therapy was used in 657 cases. An indication for source control (either open surgical or percutaneous) existed in 1,068 cases.

Community-acquired infections accounted for 58.1% of cases of septic shock, whereas 41.9% of cases were deemed to represent nosocomial infection. Direct admissions from the emergency room accounted for 44.4% of the total. Table 1 describes the frequency of chronic comorbidities among septic shock patients. Table 2 lists the frequency of clinically defined infection sites. The respiratory system (almost entirely pneumonia) and gastrointestinal/intraabdominal sites together accounted for two thirds of all infections resulting in septic shock.

Documented infections were present in 77.9% of cases. The remaining 22.1% of cases represented suspected infections without either a plausible bacterial pathogen isolated or definitive radiologic, surgical, autopsy, or biopsy evidence of infection. A plausible microbial pathogen was identified in 70.0% of cases and isolated from the blood in 34.2%. Among the 1,546 patients in whom a plausible pathogen was identified, the breakdown of specific organisms is shown in Table 3.

Antimicrobial Therapy and Septic Shock Mortality. Overall mortality rate was 56.2%. Survival was similar whether the infection was documented or suspected; whether a plausible pathogen was identified or not; and whether bacteremia was present or absent. Of the total of 2,731 patients with septic shock, 19 did

Table 2. Clinical site infections

	No.	% Total
Lung	1016	37.2
Intraabdominal	801	29.3
Bowel perforation/peritonitis	226	8.3
Postoperative bowel perforation/anastomotic dehiscence	65	2.4
Spontaneous bacterial peritonitis	50	1.8
Other peritonitis	18	0.7
Intraabdominal abscess	44	1.6
Cholecystitis	40	1.5
Ascending cholangitis	43	1.6
Ischemic bowel/bowel infarction	166	6.1
Clostridium difficile enterocolitis/toxic megacolon	47	1.7
Genitourinary	293	10.7
Skin and soft tissue	197	7.2
Necrotizing soft tissue infections	74	2.7
Cellulitis	46	1.7
Operative wound infection	22	0.8
Soft tissue abscess	20	0.7
Decubitus ulcer	16	0.6
Diabetic lower extremity ulcer/cellulitis	13	0.5
Surgical site infection	31	1.1
Central nervous system infection (meningitis/abscess)	20	0.7
Intravascular catheter infection	100	3.7
Primary bloodstream infection (bacteremia without identifiable source)	120	4.4
Systemically disseminated infection (including yeast and tuberculosis)	58	2.1
Septic arthritis	21	0.8
Mediastinitis	15	0.5
Other	59	2.1

Table 3. Suspected primary microbiologic pathogens in septic shock

Pathogen	No. of Patients	% Total
Gram-negative organisms	930	47.9
Escherichia coli	435	22.4
Klebsiella species	131	6.7
Pseudomonas aeruginosa	115	5.9
Enterobacter species	80	4.1
Haemophilus influenzae	44	2.2
Proteus species	25	1.2
Acinetobacter species	21	1.1
Serratia species	20	1.0
Stenotrophomonas maltophila	16	0.8
Morganella morganii	14	0.7
Citrobacter species	13	0.7
Neisseria meningitidis	6	0.3
Burkholderia cepacia	3	0.2
Haemophilus parainfluenzae	3	0.2
Other Gram-negative bacilli	8	0.4
Gram-positive organisms	731	38.3
Staphylococcus aureus	302	15.6
Streptococcus pneumoniae	170	8.8
Streptococcus faecalis	77	4.0
Group A *Streptococcus* species	69	3.6
Other β-hemolytic streptococci	43	2.2
Viridans streptococci	37	1.9
Streptococcus faecium	29	1.5
Bacillus species	5	0.3
Corynebacterium jeijkeium	5	0.3
Staphylococcus lugdunensis	1	0.3
Yeast/fungi	160	8.2
Candida albicans	91	4.7
Candida glabrata	18	0.9
Aspergillus/Mucor species	14	0.7
Blastomyces species	10	0.5
Candida tropicalis	4	0.2
Candida parapsilosis	4	0.2
Candida krusei	3	0.2
Cryptococcus neoformans	1	0.1
Histoplasma species	1	0.1
Other unidentified yeast	13	0.6
Anaerobes	69	3.6
Clostridium difficile	46	2.4
Bacteroides fragilis	15	0.8
Other clostridia	8	0.4
Legionella species	8	0.4
Mycobacterium tuberculosis	11	0.6

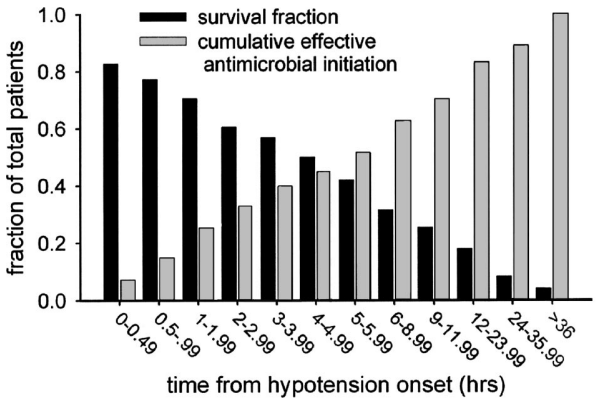

Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

not receive effective antimicrobials before death and 558 were on antimicrobial therapy that was either proven (defined pathogen) or adjudicated (undefined pathogen) effective for the infection thought to underlie septic shock before the onset of hypotension. Of the remaining 2,154 patients who received effective antimicrobials only after onset of hypotension, mortality rate was 58.0%.

Over the first 6 hrs after the onset of recurrent or persistent hypotension, each hour of delay in initiation of effective antimicrobial therapy was associated with mean decrease in survival of 7.6% (range 3.6–9.9%; Fig. 1). Survival was 82.7% if effective antimicrobials were administered within 30 mins of initial evidence of hypotension, 77.2% in the second half hour (79.9% aggregate in the first hour), and 42.0% in the sixth hour. The median time to implementation of effective antimicrobial therapy following the first onset of recurrent/persistent hypotension was 6 hrs (25–75% interval, 2.0–15.0 hrs; Fig. 1). Average times were 13.51 ± 0.45 (SE) hrs.

On univariate analysis, the delay from initial recurrent or persistent hypotension to administration of effective antimicrobial therapy was a critical determinant of survival to ICU and hospital discharge (each $p < .0001$ by log rank analysis). By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (adjusted odds ratio 1.67; 95% confidence interval, 1.12 −2.48; Fig. 2). The odds ratio of death continued to climb with progressive delays to a maximum value of 92.54 (95% confidence interval, 44.92–190.53) with delays >36 hrs after onset of hypotension (Fig. 2). When delay to initiation of effective antimicrobial therapy was assessed as a continuous variable, the adjusted odds ratio was 1.119 (per hour delay) (95% confidence interval 1.103–1.136, $p < .0001$); that is, every hour delay was associated with an approximately 12% decreased probability of survival compared with the previous hour over the entire observation period (Fig. 3).

In multivariate analysis with other management variables including effectiveness of initial antimicrobial therapy, choice and magnitude of early fluid resuscitation, single vs. multiple drug class antimicrobial therapy, and choice and rapidity of initiation of initial vasopressor/inotropic support, time to effective anti-

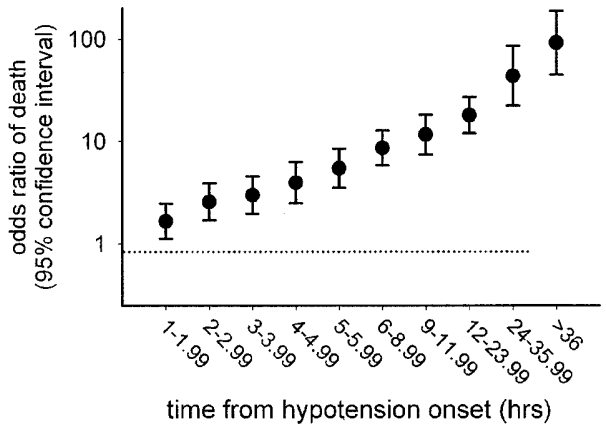

Figure 2. Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% confidence interval. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension). The risk of death continues to climb, though, to >36 hrs after hypotension onset.

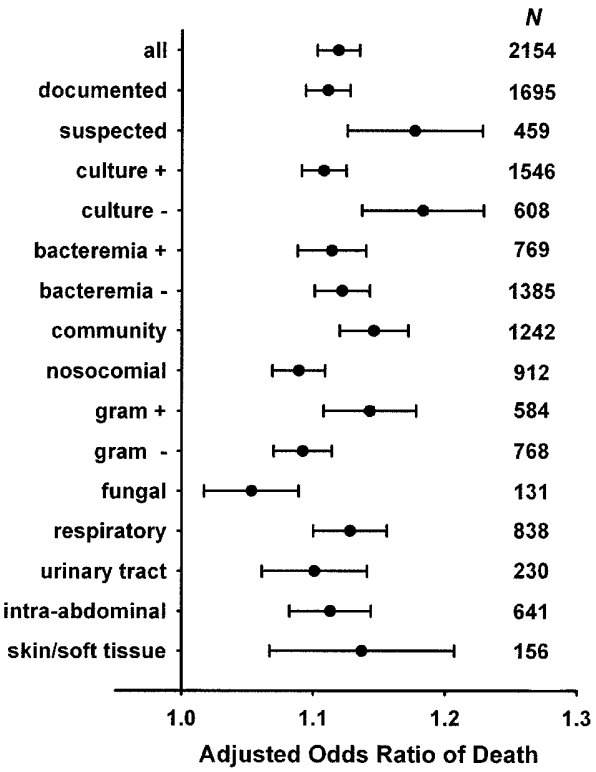

Figure 3. Relationship of antimicrobial delay to hospital mortality in major subgroups expressed as adjusted odds ratio of death per hour delay. *Bars* represent 95% confidence intervals. All major subgroups demonstrate a highly significant increase in mortality risk with increasing delays in administration of effective antimicrobial therapy following onset of sepsis-associated hypotension. For the overall group, mortality risk increases approximately 12% every hour relative to the risk in the previous hour. $p < .0001$ for all subgroups. *Culture +*, culture-positive infections; *culture −*, culture-negative infections; *bacteremia +*, bacteremic infections; *bacteremia −*, nonbacteremic infections; *community*, community-acquired infections; *nosocomial*, nosocomial infections; *gram +*, infections caused by Gram stain positive cocci; *gram −*, infections caused by Gram-negative bacilli; *fungal*, fungal infections; *respiratory*, all infections of the respiratory tract including pneumonia and empyema; *urinary tract*, all infections of the urinary tract including pyelonephritis (with or without obstruction) and perinephric abscesses but exclusive of infections of the reproductive tract; *intra-abdominal*, all infections localized to the intraabdominal space including peritonitis, cholangitis, cholecystitis, intraabdominal abscess, ischemic bowel, etc.; *skin/soft tissue,* soft tissue infections of skin, fascia, or skeletal muscle excluding surgical wound infections.

microbial therapy was most strongly associated with outcome ($p < .0001$). This strong association persisted even when nontherapeutic variables predictive of outcome including admission APACHE II score, number of admission organ failures, and clinical infection site were added to the model.

The delay from onset of persistent/recurrent hypotension to initiation of effective antimicrobial therapy accounted for 28.1% of the variance in outcome (survival to hospital discharge) in patients with septic shock. In comparison, APACHE II score at ICU admission could explain only 24.6% of the variance. Notably, the volume of fluids infused in the first hour of hypotension (the only one of several fluid resuscitation-associated variables tested in the model to reach significance; $p = .038$ in the multivariate model) accounted for <2% of the variance in outcome.

Subgroup analysis demonstrated that the relationship between hospital survival and duration of time between onset of recurrent/persistent hypotension and effective antimicrobial administration held whether the infection was clinically suspected or documented, culture positive or negative, bacteremic or nonbacteremic, community acquired or nosocomial, or Gram-positive, Gram-negative, or fungal (Fig. 3). The relationship also held in all major clinical infections including those involving the respiratory, urinary, gastrointestinal/peritoneal and skin/soft tissue sites (Fig. 3). The effect also held for additional subgroups including those with neutropenia or requiring source control efforts.

The 558 patients who received effective antimicrobial therapy before onset of hypotension (and were therefore not included in the primary analysis) and the 2,154 who received such therapy after onset of hypotension were comparable except for a higher proportion of patients requiring source control (44.8% vs. 37.9% of the total respectively). Survival in this subgroup was slightly higher than the overall group at 52.2%.

DISCUSSION

These data suggest that the delay in initiation of effective antimicrobial therapy following the onset of hypotension is a critical therapeutic variable associated with septic shock mortality. Initiation of effective antimicrobial therapy within the first hour following onset of septic shock-related hypotension was associated with

79.9% survival to hospital discharge (Fig. 1). For every additional hour to effective antimicrobial initiation in the first 6 hrs after hypotension onset, survival dropped an average of 7.6%. With effective antimicrobial initiation between the first and second hour after hypotension onset, survival had already dropped to 70.5%. With effective antimicrobial therapy delay to 5–6 hrs after hypotension onset, survival was just 42.0% and by 9–12 hrs 25.4%. The adjusted odds ratio of death was already significantly increased by the second hour after hypotension onset, and the ratio continued to climb with longer delays (Fig. 2).

The study also demonstrates the existence of substantial delays in delivery of effective antimicrobials in patients with septic shock. Among those patients who were not already on effective therapy, the median time to delivery of effective antimicrobial therapy following initial onset of recurrent/persistent hypotension was 6 hrs. 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 (Fig. 1). Only 32.5% had received them by 3 hrs after hypotension onset and 51.4% by 6 hrs postonset. Even 12 hrs after the first occurrence of recurrent or sustained hypotension, 29.8% of patients had not received effective antimicrobial therapy.

These findings are novel although not unexpected. A single previous study examined outcome of septic shock in the context of delays in antimicrobial therapy relative to ICU admission (16). Larche and colleagues (16) found that a delay of >2 hrs was associated with increased mortality in a cohort of 88 critically ill cancer patients with septic shock. Several other investigators have shown that delayed antimicrobial therapy is associated with increased mortality in community-acquired pneumonia (7–9, 17), nosocomial pneumonia (11, 12), and bacterial meningitis (10, 13). Similar increases in mortality with increasing delays in initiation of effective antimicrobial therapy have also been documented with *Pseudomonas aeruginosa* (14) and *Staphylococcus aureus* (15) bacteremia. Meehan et al. (9) showed that delays in initial antimicrobial administration >8 hrs after admission to the emergency room for community-acquired pneumonia were associated with increased mortality rate in a large cohort of Medicare patients. Houck et al. (17) pushed this boundary lower by demonstrating increased mortality rate in Medicare patients with community-acquired pneumonia who were treated with antimicrobials >4 hrs following ICU admission.

This study substantially extends previous investigations. Use of a large cohort of septic shock patients with a high overall mortality rate (56.2%) allows the demonstration of the progressive increase in hospital mortality associated with delay in administration of effective antimicrobial therapy. Delay intervals as short as an hour following onset of septic shock-related hypotension significantly increased hospital mortality rate. In addition, the large number of cases allows the demonstration that this mortality effect applies to major patient subgroups irrespective of the isolation of pathogenic bacteria, presence of bacteremia, clinical infection site, and epidemiologic (nosocomial vs. community-acquired)/etiological considerations (Fig. 3).

The adverse effect of delays of effective antimicrobial initiation on survival is robust in two regards. First, the relationship held in all major subgroups including culture-negative and nonbacteremic patient groups, as indicated in Figure 3. This implies that the processes underlying septic shock are similar across these groups and emphasizes the importance of early initiation of appropriately selected empirical therapy in all subgroups including culture-negative and nonbacteremic cases. Second, the relationship between antimicrobial delay and mortality holds even in multivariate analysis with other therapeutic variables and prognosis predictors such as APACHE score.

It is very unlikely that other covariant factors are responsible for the close association between mortality and time to initiation of effective antimicrobial therapy. Given the relationship between aggressive fluid resuscitation and improved septic shock survival demonstrated by Rivers et al. (25), a link between rapidity of fluid resuscitation and initiation of antimicrobial therapy is possible. Similarly, patients with greater severity of illness might have antimicrobial therapy delayed in order to accommodate resuscitative measures or investigative modalities resulting in a spurious relationship between mortality and antimicrobial initiation delay. Against these possibilities, the time from septic shock related-hypotension to effective antimicrobial initiation continues to be the variable most strongly associated with mortality even when rapidity of fluid resuscitation and APACHE II score are factored into the multivariate analysis.

The finding of a rapid upward inflection in mortality following onset of hypotension is consistent with experimental and clinical data from other shock states. Several experimental animal investigations have suggested a limited window of opportunity for therapy of the underlying injury once shock is present. The classic example of this is Wiggers' (26) hemorrhagic shock model in which resuscitation of animals invariably fails if initiated more than a few hours after the initial insult. We have recently demonstrated a similar rapid inflection in mortality following onset of hypotension in an experimental murine model of *E. coli* peritonitis/septic shock (18). In the clinical context, a "golden hour" has been described for therapy of hypovolemic shock due to trauma (27), cardiogenic shock due to myocardial infarction (28), and, most recently, obstructive shock due to massive pulmonary embolus (29). In serious human infections, rapidity of antimicrobial therapy following presentation has been understood to be a critical determinant of outcome for specific conditions including community-acquired pneumonia (7, 9, 14, 17), ventilator-associated pneumonia (11), meningitis (10, 13), bacteremia (14, 15), and septic shock (16). No human studies, however, have directly examined the relationship between hemodynamic responses to infection and outcome. Although early aggressive resuscitation of septic shock has been advocated (25, 30), administration of antimicrobials has often awaited hemodynamic stabilization in clinical practice. Our data strongly suggest that, as with other forms of shock, a "golden hour" during which effective antimicrobial therapy can optimize outcome exists for septic shock.

Current international guidelines recommend initiation of empirical antimicrobial therapy within 1 hr of presentation with severe sepsis or septic shock (1). Until now, no clinical studies have existed to support this position. This study demonstrates that substantial delays in administration of effective antimicrobial therapy of septic shock exist even though rapid initiation of such therapy is closely associated with survival to hospital discharge. Mortality rate is significantly increased if effective antimicrobial therapy is delayed by even 1 hr following onset of septic shock-related hypotension. These data strongly support current international guidelines and suggest that empirical, broad-spectrum antimicrobial

administration should be considered an intrinsic component of initial resuscitation of septic shock.

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Appendix is on the next page.

APPENDIX A. Diagnostic criteria for site-specific infection

Site	Type	Diagnostic Criteria
Blood	Bacteremia	• Pathogen (other than coagulase-negative staphylococci) identified in one single culture
Pulmonary	Pneumonia	• Chest radiograph showing new or progressive infiltrate • In association with demonstration of a predominate organism on Gram stain obtained from sputum (with <10 squamous epithelial cells or bronchoalveolar lavage) or transthoracic needle biopsy
	Empyema, lung abscess	• Organism seen from aspirate or surgical tissue • Or, abscess cavity seen radiologically
Genitourinary	Urinary tract infection	• Presence of no more than two organisms at a concentration of $\geq 10^8$ organisms/L of urine
	Infection of kidneys	• Organism isolated from culture of fluid from affected site • Abscess seen on direct surgical or histopathologic examination
Surgical wound	Incisional wound infection	• Occurs within 30 days of surgery • Purulent drainage from site • Organism isolated from a wound closed primarily
	Deep infection	• Occurs within 30 days of surgery • Purulent drainage from drain site • Abscess seen during surgery or on histopathologic examination
Cardiovascular	Arterial, venous Endocarditis Pericarditis Mediastinitis	• Pathogen isolated from culture of arteries, veins, valves, blood • Evidence of infection from surgical or histopathologic examination
Sinus cavities	Sinusitis	• Organism isolated from culture of purulent material from sinus cavity
Intraabdominal	Includes gallbladder bile ducts, liver, pancreas, peritoneum	• Organism isolated from specimen of abdominal fluid from surgical intervention or percutaneous drainage
	Any intraabdominal space	• Abscess or other evidence of intraabdominal infection seen during surgery or histopathologic examination • Transmural ischemia/necrosis of a hollow viscus seen intraoperatively
Soft tissue	Skin infection/cellulitis	• Pathogenic organism isolated from blood or infected site in context of compatible clinical signs and symptoms
	Necrotizing fasciitis	• Organism isolated from culture of blood, tissue or abscess blood (with supportive clinical findings), or other evidence of infection seen on surgery or histopathologic examination
Bone and joint	Osteomyelitis	• Organism cultured from bone • Evidence of osteomyelitis seen during surgery or by histopathologic examination
	Septic joint	• Organism isolated from synovial fluid • Evidence of joint or bursa infection seen during surgery or histopathologic examination
Central nervous system	Intracranial infection	• Organism isolated from culture of brain tissue or dura • Abscess or evidence of intracranial infection seen during surgery or by histopathologic examination
	Meningitis	• Organism isolated from culture of cerebrospinal fluid
Implant-related infection	Intravascular catheter-related infection	• 15 or more colonies on semi-quantitative catheter culture with concurrent bacteremia with identical organism • Overt tunnel site infection with exit site erythema, tenderness, and expressed pus
	Prosthesis/implant-related infection	• Isolation of a pathogenic organism from a purulent aspirate or biopsy from implant site