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Original Research

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Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

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Objective: **Our goal was to determine the impact of the initiation of inappropriate antimicrobial therapy on survival to hospital discharge of patients with septic shock.**

Methods: **The appropriateness of initial antimicrobial therapy, the clinical infection site, and relevant pathogens were retrospectively determined for 5,715 patients with septic shock in three countries.**

Results: **Therapy with appropriate antimicrobial agents was initiated in 80.1% of cases. Overall, the survival rate was 43.7%. There were marked differences in the distribution of comorbidities, clinical infections, and pathogens in patients who received appropriate and inappropriate initial antimicrobial therapy ($p < 0.0001$ for each). The survival rates after appropriate and inappropriate initial therapy were 52.0% and 10.3%, respectively (odds ratio [OR], 9.45; 95% CI, 7.74 to 11.54; $p < 0.0001$). Similar differences in survival were seen in all major epidemiologic, clinical, and organism subgroups. The decrease in survival with inappropriate initial therapy ranged from 2.3-fold for pneumococcal infection to 17.6-fold with primary bacteremia. After adjustment for acute physiology and chronic health evaluation II score, comorbidities, hospital site, and other potential risk factors, the inappropriateness of initial antimicrobial therapy remained most highly associated with risk of death (OR, 8.99; 95% CI, 6.60 to 12.23).**

Conclusions: **Inappropriate initial antimicrobial therapy for septic shock occurs in about 20% of patients and is associated with a fivefold reduction in survival. Efforts to increase the frequency of the appropriateness of initial antimicrobial therapy must be central to efforts to reduce the mortality of patients with septic shock.** ***(CHEST 2009; 136:1237–1248)***

Abbreviations: APACHE = acute physiology and chronic health evaluation; OR = odds ratio

With a mortality risk of 40 to 70%, septic shock is the most common cause of death in the modern ICU.[1,2] Research efforts in this area over the last 2 decades have focused primarily on the study of resuscitative modalities and experimental anti-inflammatory agents. However, several studies[3,4] have indicated that the effective use of antimicrobial agents is central to the optimization of outcome in life-threatening infections in critically ill patients. We have demonstrated in a large retrospective cohort study[3] that delay in the initiation of effective antimicrobial therapy following the onset of hypotension is the critical determinant of outcome in septic shock. The initiation of treatment with inappropriate antimicrobial agents (in relation to the subsequently demonstrated sensitivity of the pathogen) as the initial empiric therapy may be the single most common cause of prolonged delays in the introduction of effective therapy.

A large body of literature[4–27] has addressed the issue of inappropriate antimicrobial therapy in patients with bacteremia and other serious infections. Equivalent data on septic shock are very limited.[18,26] Accordingly, a retrospective multicenter study was undertaken to examine the relationship between the appropriateness of initial empiric antimicrobial therapy and survival in patients with septic shock and major clinical subgroups of patients with septic shock.

Materials and Methods

A retrospective review of adult patients (≥ 18 years of age) who had received a diagnosis of septic shock was performed. A waived consent protocol was approved by the health ethics boards of the University of Manitoba and at each individual participating center. Consecutive adult patients with septic shock from 22 medical institutions from Canada (17 sites), the United States (4 sites), and Saudi Arabia (1 site) were collected from discrete periods between 1996 and 2005. Each institution contributed a minimum of 100 cases. Potential cases were initially identified by using a combination of internal ICU registries/databases and/or *International Classification of Diseases, Ninth Revision, Clinical Modification*, coding strategies. Each potential case was screened to determine whether the case met the 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.[28] As per that definition, case patients were required to have documented or suspected infection, persistent hypotension requiring therapy with pressors, and two of the following four elements: (1) a heart rate of > 90 beats/min; (2) a respiratory rate of > 20 breaths/min or P_{CO_2} of < 32 mm Hg; (3) a core temperature of < 36°C or > 38°C; and (4) a WBC count of < 4,000/μL, >12,000/μL, or > 10% immature (bands) forms.

Data Elements and Definitions

Clinical infection definitions were adapted from previous recommendations or studies.[3,29,30] In order to qualify as potential pathogens causing shock, isolates from both the local site and/or blood cultures were required to have been obtained within 48 h of the onset of shock. The use of appropriate antimicrobial therapy (*ie*, with *in vitro* activity appropriate to isolated pathogenic organisms or, if a pathogenic organism was not isolated, appropriate for the underlying clinical syndrome) was determined for all cases. Questionable cases or data elements were reviewed by the principal investigator for adjudication.

Predetermined rules were created to assess the appropriateness of antimicrobial therapy (see Appendices 1 and 2). For culture-negative septic shock, appropriate therapy was deemed to be initiated when antimicrobial agents consistent with broadly accepted norms for empiric management of the typical pathogens for the clinical syndrome (in the context of host immune/health status, environmental factors, and local flora) were administered. At each participating institution, infectious diseases physicians/microbiologists were consulted to establish the requirement for appropriate empiric coverage in view of local community and nosocomial flora during the time period covered by data collection. Otherwise, appropriate empiric therapy of culture-negative infections leading to septic shock was defined by the recommendations enumerated in Table 1 of the "Clinical Approach to Initial Choice of Antimicrobial Therapy" in the *Sanford Guide to Antimicrobial Therapy* 2004 (34th ed),[31] which encompassed the official guidelines that were available for that edition. For unanticipated scenarios not covered by the predetermined rules, data were reviewed independently by two infectious disease/critical care medicine physicians who were 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.

Key definitions and data collection methods were enumerated in a previous publication.[3] Appropriate antimicrobial therapy was considered to have been initiated if an antimicrobial with *in vitro* activity appropriate for the isolated pathogen or pathogens (or in the case of culture-negative septic shock, an antimicrobial or antimicrobial agent concordant with accepted international norms for empiric therapy and modified to local flora) was either the first new antimicrobial agent with which therapy was started after the onset of recurrent or persistent hypotension or was initiated within 6 h of the administration of the first new antimicrobial agent. Otherwise, inappropriate therapy was considered to have been initiated.

Statistical Analysis

The primary outcome variable was survival to hospital discharge, including discharge to a chronic health-care facility. The actual (culture positive) or probable (culture negative) appropriateness of the initial antimicrobial regimen was the primary independent variable.

A χ^2 analysis was used to compare survival in subgroups of patients receiving appropriate vs inappropriate initial empiric therapy. A multivariable logistic regression model was used to examine the independent impact of a variety of clinical and therapeutic variables (including the appropriateness or inappropriateness of initial antimicrobial therapy) on survival to hospital discharge in all patients, in culture-positive patients and in blood culture-positive patients. These statistical analyses were performed using a statistical software package (Statistical Analysis Software, version 9.0; SAS Institute, Inc; Cary, NC). The data are expressed as the mean ± SD for normally distributed variables and median (interquartile range) for others.

The χ^2 tests were used to examine the distribution of comorbidities and clinical infection sites among those patients receiving

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*A complete list of participants is located in Appendix 3.
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appropriate or inappropriate initial therapy. Similarly, the Fisher exact test was used to examine distributions of organisms in the same groups.

Results

Demographic and Descriptive Data

In total, 5,715 cases were found to fit the diagnostic criteria for septic shock. The mean age of case patients with septic shock was 62.6 ± 16.3 years, with 56.3% male patients and 43.7% female patients. The mean acute physiology and chronic health evaluation (APACHE) II score[32] determined from the most abnormal results within 24 h of shock onset was 25.2 ± 9.7. Treatment with drotrecogin-alfa (activated)[33] was used in 124 cases (outside of randomized trials), while low-dose steroid therapy was utilized in 1,548 cases. An indication for source control (either open surgical or percutaneous) existed in 2,480 cases.

Community-acquired infections accounted for 55.0% of cases, while 45.0% of cases were deemed to be of nosocomial origin. Table 1 describes the frequency of chronic comorbidities among patients with septic shock. Table 2 lists the frequency of clinically defined infection sites.

Documented infections were present in 4,698 of the total of 5,715 cases (82.2%). The remaining 1,017 cases (17.8%) were suspected infections without either a plausible bacterial pathogen isolated, or definitive radiologic, surgical, autopsy, or biopsy evidence of infection. The survival rate in these groups was similar at 43.3% and 45.9%, respectively. A plausible primary microbial pathogen was identified in 4,056 cases (71.0%) and was isolated from the blood in 2,012 cases (35.2%). The breakdown of the specific organisms isolated is shown in Table 3.

Appropriateness of Initial Antimicrobial Therapy

Overall, the rate of survival to hospital discharge was 43.7%. Survival was similar whether the infection was documented or suspected, whether a plausible pathogen was identified, and whether bacteremia was present or absent.

Of the entire septic shock study population, 4.8% of patients did not receive therapy that was either proven (defined pathogen) or adjudicated (undefined pathogen) to be effective for the infection thought to underlie septic shock prior to death. The fraction of the total number of patients in whom septic shock developed after they had received apparently effective antimicrobial therapy was 21.8%. Among the remaining 73.4% of patients, the median time to the administration of effective antimicrobial therapy was 5.82 h (interquartile range, 2.2 to 14.3).

Table 1—*Chronic Comorbidities of Patients With Septic Shock (% of Patients With Comorbidity)*

Characteristics	Appropriate (n = 4,579)	Inappropriate (n = 1,136)	Total (n = 5,715)
AIDS (1993 CDC criteria)	2.0	3.2	2.2
Acute or chronic lymphoma	3.5	4.7	3.7
Acute or chronic leukemia/multiple myeloma	5.9	7.1	6.2
Metastatic solid cancer	8.3	10.8	8.8
Immunosuppressive chemotherapy or long-term steroid therapy (> 10 mg of prednisone equivalent daily)	15.0	19.8	15.9*
Major organ transplant	4.0	4.9	4.2
Neutropenia (< 500 cells/μL)	5.6	8.0	6.1
Liver failure (biopsy-proven cirrhosis, documented variceal hemorrhage or portal hypertension, hepatic ascites, or encephalopathy)	8.0	9.8	8.4
New York Heart Association class IV			
Heart failure	3.4	4.2	3.6
COPD (medication or oxygen requiring)	13.6	14.1	13.7*
Chronic renal failure (serum creatinine concentration > 1.5 the upper limit of normal)	14.6	21.6	16.0†
Long-term dialysis dependence	7.3	10.7	8.0*
Diabetes mellitus (medication dependent)	17.2	17.2	17.2
Diabetes mellitus (insulin dependent)	9.3	9.9	9.4
Systemic autoimmune disease	3.2	4.8	3.6
Organic brain syndrome	5.5	5.3	5.4
Substance abuse	13.2	12.2	13.0†
Elective surgery	16.1	17.2	16.3
Emergency surgery/trauma	7.7	8.6	7.8

CDC = Centers for Disease Control and Prevention.

*$p < 0.05$.

†$p < 0.01$ (χ^2 test); indicates that the distribution of the specified comorbidity in appropriate and inappropriate therapy groups varied significantly in comparison with overall distribution of comorbidities.

Table 2—*Clinical Site Infections*

Sites	Appropriate, %	Inappropriate, %	Total, %
Lung	38.1	37.2	38.0
Pneumonia	37.2	36.5	37.1
Empyema	0.9	0.7	0.9
Intraabdominal	30.1	30.0	30.1
Bowel perforation/peritonitis	7.9	8.8	8.1
Postoperative bowel perforation/anastamotic dehiscence	2.4	3.1	2.5
Spontaneous bacterial peritonitis	2.2	2.9	2.4
Other peritonitis	0.6	0.7	0.6
Intraabdominal abscess	2.1	2.7	2.2
Cholecystitis	2.0	0.6	1.8†
Ascending cholangitis	2.3	1.8	2.2
Ischemic bowel/bowel infarction	5.7	5.5	5.7
C difficile entercolitis/toxic megacolon	1.6	2.3	1.7
Genitourinary	10.9	7.3	10.1†
Skin and soft tissue	8.1	4.6	7.4†
Necrotizing soft-tissue infections	3.5	1.6	3.1†
Cellulitis	1.7	0.7	1.5*
Operative wound infection	0.9	1.0	0.6
Soft-tissue abscess	0.9	0.4	0.8
Decubitus ulcer	0.4	0.4	0.4
Diabetic lower extremity ulcer/cellulitis	0.6	0.4	0.6
Surgical site infection	0.6	0.6	0.6
CNS infection (meningitis/abscess)	1.1	0.3	0.9*
Intravascular catheter infection	3.4	5.5	3.8†
Primary bloodstream infection (bacteremia without identifiable source)	4.3	6.9	4.8†
Systemically disseminated infection (including yeast and tuberculosis)	1.7	6.8	2.7†
Septic arthritis	0.9	0.4	0.8
Mediastinitis	0.7	0.9	0.8

*$p < 0.05$.
†$p < 0.01$ (χ^2 test); indicates that the distribution of the specified clinical infection in appropriate and inappropriate therapy groups varied significantly in comparison with overall distribution of the clinical infections.

Table 3—*Suspected Primary Microbiological Pathogens in Septic Shock*

Pathogens	Distribution Appropriate, % (n = 3,109)	Distribution Inappropriate, % (n = 947)	Distribution, % of Total (n = 4,056)
Gram-negative organisms	53.9	34.4	49.4†
Escherichia coli	24.6	11.1	21.4†
Klebsiella sp	8.7	4.2	7.7†
P aeruginosa	6.6	9.5	7.3†
Enterobacter sp	3.7	3.4	3.6
H influenzae	2.0	0.4	1.7†
Acinetobacter sp	1.4	1.5	1.4
Serratia sp	1.5	0.5	1.3*
Proteus sp	1.4	0.2	1.1†
Stenotrophomonas maltophila	0.6	1.7	0.8†
Citrobacter sp	0.9	0.5	0.8
N meningitidis	0.9	0.0	0.7†
Morganella morganii	0.5	0.6	0.5
Moraxella catarrhalis	0.2	0.0	0.1
Aeromonas hydrophila	0.1	0.0	0.1
Burkholderia cepacia	0.0	0.2	0.1
Haemophilus parainfluenzae	0.1	0.0	0.1
Other Gram-negative bacilli	0.6	0.1	0.6
Gram-positive organisms	33.9	31.8	33.4
S aureus	13.2	19.7	14.7†
S pneumoniae	8.6	1.8	7.0†
Streptococcus faecalis	2.8	4.4	3.2†
Group A Streptococcus sp	4.1	0.4	3.3†
Other β-hemolytic streptococci	2.2	0.4	1.8†
Viridans streptococci	1.9	0.6	1.6†
Streptococcus faecium	0.7	3.4	1.3†
Bacillus sp	0.1	0.4	0.2
Corynebacterium jeikeium	0.2	0.1	0.1
Other Gram-positive	0.1	0.1	0.1
Yeast/fungi	6.5	28.8	12.2†
C albicans	4.2	16.7	7.1†
Candida glabrata	0.9	5.4	2.0†
Aspergillus/Mucor sp	0.2	2.5	0.7†
Blastomyces sp	0.4	0.5	0.4
Candida tropicalis	0.5	1.1	0.6*
Candida parapsilosis	0.1	0.7	0.3†
Candida krusei	0.2	1.0	0.3†
Cryptococcus neoformans	0.0	0.2	0.1
Other unidentified yeast	0.4	1.2	0.6*
Anaerobes	4.3	2.1	3.9*
C difficile	2.0	0.2	2.0*
Bacteroides fragilis	0.9	0.1	0.7*
Other clostridia	0.6	0.1	0.5*
Legionella sp	0.3	0.1	0.2
Mycobacterium tuberculosis	0.7	1.5	0.9*

*$p < 0.05$.
†$p < 0.01$ (χ^2 test); indicates that the distribution of the specified pathogen in appropriate and inappropriate therapy groups varied significantly in comparison with overall distribution of pathogens.

Appropriate empiric antimicrobial therapy was initiated in 80.1% of all cases of septic shock. There was substantial variation between subgroups in the fraction of patients in whom appropriate empiric therapy had been initiated (Table 4, Fig 1). There were also significant variations in the appropriateness of initial antimicrobial therapy between groups of clinical infections and organisms (Fig 1). Urinary tract infection (84.8%) and skin and soft-tissue infection (86.9%) appeared to have signifi-

Table 4—*Differences in Antimicrobial Appropriateness in Major Subgroups*

Characteristics	Cases, No. (% Total Cases)	Appropriate Initial Therapy, %	OR (95% CI)/p Value
Documented	4,698 (82.2)	78.3	
Suspected	1,017 (17.8)	88.6	0.4728 (0.3856–0.5799)/< 0.0001
Culture positive	4,056 (71.0)	76.7	
Culture negative	1,659 (29.0)	88.6	0.4233 (0.3578–0.5007)/< 0.0001
Blood culture positive	2,012 (35.2)	76.3	
Blood culture negative	2,044 (35.8)	77.0	0.9609 (0.8308–1.1114)/NS
Community-acquired infection	3,142 (55.0)	81.2	
Nosocomial infection	2,573 (45.0)	71.6	1.7159 (1.5159–1.9423)/< 0.0001

NS = not significant.

cantly better initial antimicrobial coverage than pneumonia (75.5%) or intraabdominal infection (75.8%; $p < 0.0001$). Catheter-associated infection (69.8%) and primary bloodstream infection (68.6%) appeared to have initial coverage that was inferior to that for the other major clinical syndromes ($p < 0.0001$). Similarly, major differences in the appropriateness of initial antimicrobial coverage existed depending on whether the isolated organism was a Gram-positive organism (77.8% initially appropriate antimicrobial therapy), Gram-negative organism (83.7%), anaerobic organism (84.6%), or fungal organism (43.6%; $p < 0.0001$ vs other groups) [Fig 1]. Variations in the appropriateness of initial antimicrobial coverage with different microbial species also occurred ($p < 0.0001$) [Fig 1]. Initial antimicrobial coverage was highest with Streptococcus species, followed by Gram-negative organisms, *Staphylococcus aureus*, enterococci, and fungi ($p < 0.0001$).

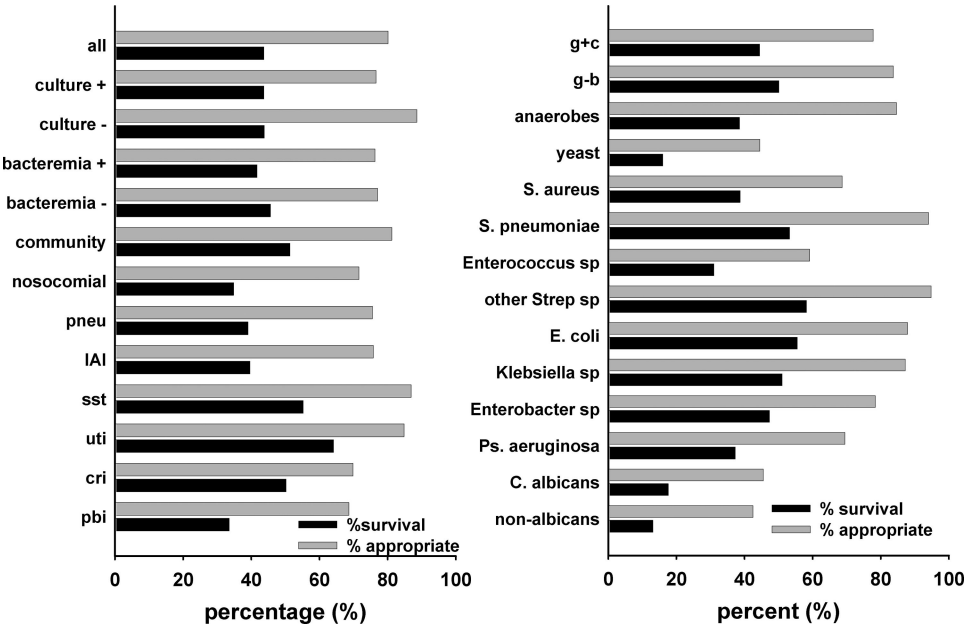

FIGURE 1. Appropriateness of antimicrobial therapy and survival in septic shock subgroups. Culture + = culture-positive infections; culture − = culture-negative infections; bacteremia + = bacteremic infections; bacteremia − = nonbacteremic infections; community = community-acquired infections; nosocomial = nosocomial infections; pneu = all infections of the respiratory tract including pneumonia and empyema; IAI = all intraabdominal infections, including, for example, peritonitis, cholangitis, cholecystitis, intraabdominal abscess, and ischemic bowel, but excluding infections of the abdominal wall; sst = skin and soft tissue infections including fascial or skeletal muscle excluding surgical wound infections; UTI = all infections of the urinary tract including pyelonephritis (with or without obstruction) and perinephric abcesses, but exclusive of infections of the reproductive tract; cri = catheter-related infections including central venous, dialysis, pulmonary artery, and arterial catheters; pbi = primary bloodstream infections; g+c = infections caused by Gram-positive cocci; g−b = infections caused by Gram-negative bacilli; yeast = Candida and other yeast infections excluding blastomycosis and filamentous fungi such as Aspergillus; sp = species; Strep = Streptococcus.

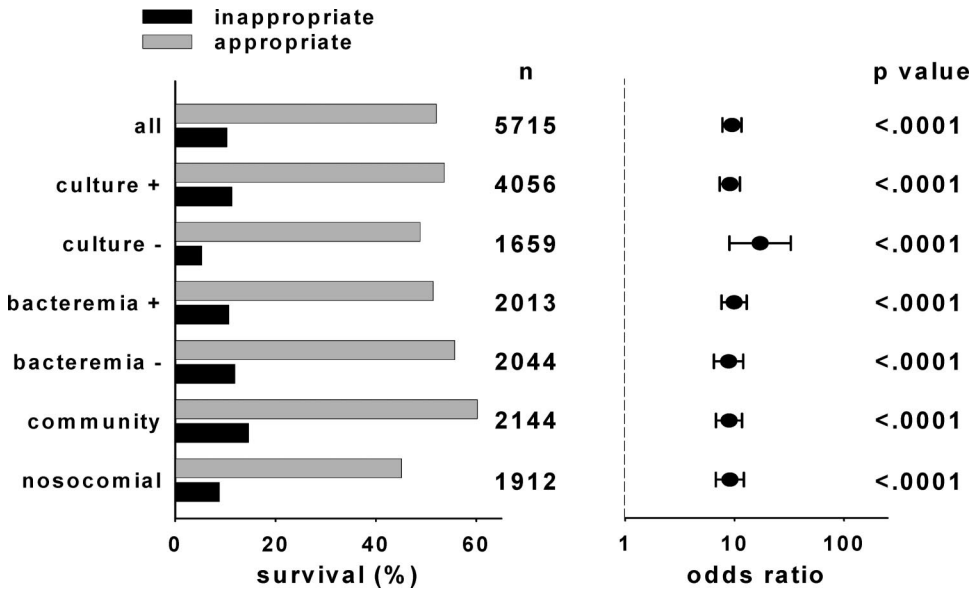

FIGURE 2. Impact of antimicrobial appropriateness on survival in major epidemiologic subgroups. See the legend of Figure 1 for abbreviations not used in the text.

Overall, there were significant variations in the distribution of patients who had received appropriate vs inappropriate initial empiric antimicrobial therapy when stratified by comorbidities (Table 1), clinical infection syndromes (Table 2), and pathogens (Table 3) [each $p < 0.0001$]. In some cases, even when such variations did not appear to exist in larger groups (*eg*, Gram-positive infection), they were nonetheless present in the distribution of individual organisms within that group (Table 3).

Impact of Administration of Inappropriate Initial Antimicrobial Therapy

Survival to hospital discharge with appropriate and inappropriate initial therapy was 52.0% and 10.3%, respectively (odds ratio [OR], 9.45; 95% CI, 7.74 to 11.54; $p < 0.0001$), an approximately fivefold decrease. Similar differences in survival were seen in all major epidemiologic, clinical, and organism subgroups (Figs 2–5). The decrease in survival with inappropriate initial therapy ranged from 2.3-fold for pneumococcal infection (Fig 5) to 17.6-fold with primary bloodstream infection-associated septic shock (Fig 3).

A multivariable logistic regression analysis was performed with other factors that might be potentially associated with outcome. Variables encompassed in the model included age, sex, hospital admission APACHE II score, the presence of major comorbid illnesses (AIDS; lymphoma; leukemia; metastatic malignancy; neutropenia; immunosuppression including chemotherapy, major organ transplant, clinically significant liver cirrhosis or failure; heart failure; severe chronic obstructive lung disease; chronic renal failure; end-stage renal disease with long-term dialysis; medication-dependent diabetes mellitus; recent history of elective or emergency surgery or major trauma; substance abuse; systemic autoimmune disease; organic brain syndrome; and major neuromuscular disorder), infection acquisition site (community or nosocomial), hospital, clinical infection site, the presence of a surgical/source

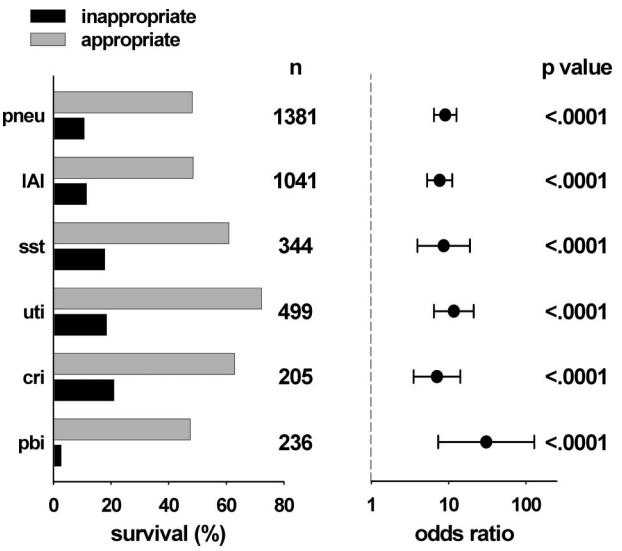

FIGURE 3. Impact of antimicrobial appropriateness on survival in clinical infection subgroups. See the legend of Figure 1 for abbreviations not used in the text.

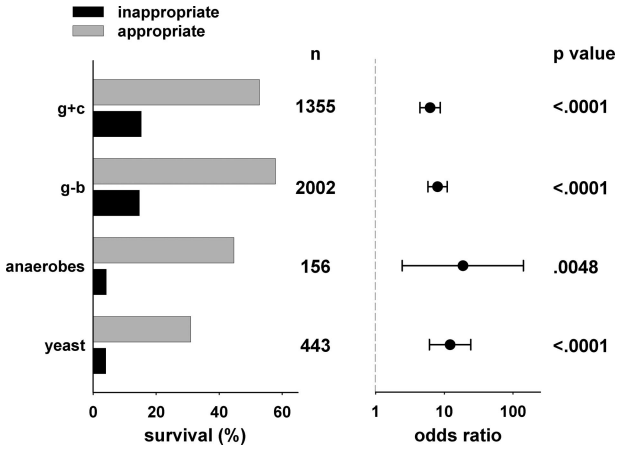

FIGURE 4. Impact of antimicrobial appropriateness on survival in major organism categories subgroups. See the legend of Figure 1 for abbreviations not used in the text.

control-requiring infection, magnitude of early fluid resuscitation, and choice and rapidity of initiation of initial vasopressor/inotropic support. After adjustment for all variables, the appropriateness of the initial antimicrobial therapy remained most strongly associated with outcome (OR, 8.99; 95% CI, 6.60 to 12.23; $p < 0.0001$) among all the risk factors assessed (Table 5). Similar results were obtained when the analysis was restricted to culture-positive cases (OR, 6.95; 95% CI, 3.11 to 15.52; $p < 0.0001$) and blood culture-positive cases (OR, 7.19; 95% CI, 4.90 to 10.55; $p < 0.0001$) [Table 5].

DISCUSSION

These data suggest that the provision of inappropriate initial empiric antimicrobial therapy has a very substantial adverse effect on survival in patients with septic shock and that this effect is present across all major clinical subgroups. Further, the study confirms that the occurrence of the initiation of organism-inappropriate empiric therapy is surprisingly common.

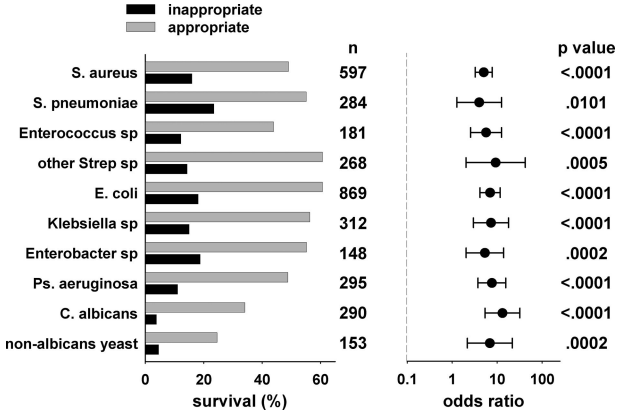

FIGURE 5. Impact of antimicrobial appropriateness on survival in specific organisms. See the legend of Figure 1 for abbreviation not used in the text.

The degree to which the administration of inappropriate initial empiric therapy adversely affected survival in the study group was startling. Overall, survival dropped fivefold from 52.0% to 10.3% (OR, 9.45; 95% CI, 7.74 to 11.54; $p < 0.0001$) with inappropriate initial therapy (Fig 2). Even after adjustment for multiple other putative risk factors, the association of poor outcome with the initiation of inappropriate therapy remained singularly powerful for the overall data set (OR, 8.99; 95% CI, 6.60 to 12.23; $p < 0.0001$) but also for the culture-positive subgroups (OR, 6.95; 95% CI, 3.11 to 15.52; $p < 0.0001$) and blood culture-positive subgroups (OR, 7.19; 95% CI, 4.89 to 10.55; $p < 0.0001$) [Table 5].

Similar associations between mortality and inappropriate initial antimicrobial therapy were shown for every major clinical subgroup. Patients with and without documented bacteremia had comparable reductions in survival depending on whether they received appropriate or inappropriate initial antimicrobial therapy (4.8-fold and 4.7-fold decrease in survival percentage, respectively) [Fig 2]. The relative reduction in survival percentage for appropriate vs inappropriate initial empiric therapy was significantly greater in culture-negative cases than in culture-positive cases (9.2-fold vs 4.7-fold difference in survival, respectively) [Fig 2]. This may be a consequence of the fact that appropriateness must be adjudicated without knowledge of antimicrobial isolate sensitivity for culture-negative cases (*ie*, we are assessing concordance with international recommendations or guidelines for antimicrobial therapy of these conditions). This may lead to a bias, overestimating the fraction of patients receiving appropriate therapy and underestimating those receiving initial inappropriate therapy.

As noted, nosocomial infection–associated septic shock had a significantly higher overall mortality risk than community-acquired infection-associated septic shock (Fig 1). However, the relative decrease in the fraction of survivors in those patients receiving appropriate vs inappropriate initial therapy in the two groups was similar (5.1-fold vs 4.1-fold, respectively). All major clinical infections (pneumonia, intraabdominal infections, urinary tract infections, skin and soft-tissue infections, catheter-associated infections, and primary bloodstream infections without an overt clinical focus) demonstrated a similar benefit of appropriate therapy over inappropriate initial empiric therapy. The relative decrease in the fraction of survivors in

Table 5—*Adjusted OR of Death for Selected Elements of Multivariable Regression Analysis*

Characteristics	All Septic Shock Patients (n = 5,715)		Culture-Positive Septic Shock Patients (n = 4,056)		Blood Culture-Positive Septic Shock Patients (n = 2,012)	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yr	1.02 (1.01–1.03)	< 0.0001	1.02 (1.01–1.03)	< 0.0001	1.02 (1.01–1.03)	< 0.0001
Sex, female	0.82 (0.71–0.94)	0.0051	0.75 (0.63–0.89)	0.0012	0.75 (0.58–0.98)	0.0343
Nosocomial infection	1.73 (1.47–2.02)	< 0.0001	1.81 (1.49–2.20)	< 0.0001	2.04 (1.51–2.76)	< 0.0001
APACHE II[32] score, unit	1.11 (1.09–1.12)	< 0.0001	1.11 (1.10–1.13)	< 0.0001	1.13 (1.11–1.15)	< 0.0001
No. day 1 organ failures	1.21 (1.15–1.27)	< 0.0001	1.18 (1.11–1.26)	< 0.0001	1.21 (1.10–1.21)	< 0.0001
Comorbidities						
AIDS	2.62 (1.63–4.21)	< 0.0001	2.26 (1.27–4.03)	< 0.0001	2.50 (1.15–5.44)	< 0.0001
Lymphoma	2.04 (1.34–3.10)	0.0009	1.77 (1.07–2.94)	0.0271	1.61 (0.81–3.19)	0.1758
Leukemia	1.32 (0.92–1.90)	0.1320	1.15 (0.73–1.82)	0.5535	0.84 (0.46–1.54)	0.5737
Metastatic malignancy	1.80 (1.41–2.31)	< 0.0001	2.01 (1.47–2.75)	< 0.0001	1.56 (0.97–2.52)	0.0694
Chemotherapy	1.17 (0.90–1.51)	0.2362	1.38 (1.01–1.89)	0.0433	1.71 (1.07–2.73)	0.0244
Solid organ transplant	0.89 (0.60–1.31)	0.5408	0.71 (0.44–1.16)	0.1725	0.49 (0.25–0.96)	0.0377
Neutropenia (< 500/μL)	1.56 (1.05–2.32)	0.0290	1.46 (0.89–2.39)	0.1367	1.42 (0.76–2.66)	0.2622
Liver cirrhosis/failure	3.32 (2.48–4.44)	< 0.0001	3.81 (2.67–5.40)	< 0.0001	2.98 (1.79–4.97)	< 0.0001
Severe COPD	1.29 (1.02–1.64)	0.0340	1.37 (1.01–1.86)	0.0436	1.33 (0.77–2.32)	0.3083
Chronic renal failure (> ×1.5 normal range)	1.06 (0.84–1.34)	0.6502	1.14 (0.82–1.58)	0.4523	0.89 (0.54–1.47)	0.6559
ESRD (on dialysis)	1.29 (0.93–1.81)	0.1292	1.45 (0.94–2.21)	0.0908	1.97 (1.05–3.70)	0.0349
Diabetes mellitus, insulin-dependent	0.98 (0.76–1.25)	0.8542	1.01 (0.75–1.35)	0.9605	0.99 (0.64–1.41)	0.9642
Elective surgery	0.75 (0.61–0.91)	0.0044	0.82 (0.65–1.04)	0.1047	0.95 (0.64–1.41)	0.8139
Post-trauma/surgery	1.22 (0.94–1.58)	0.1419	1.38 (1.00–1.90)	0.0468	1.63 (0.96–2.79)	0.0721
Substance abuse	0.92 (0.74–1.15)	0.4673	0.93 (0.72–1.21)	0.6053	1.05 (0.71–1.56)	0.8101
Dementia/organic brain syndrome	0.96 (0.71–1.29)	0.7755	0.98 (0.66–1.46)	0.9293	1.58 (0.80–3.12)	0.1837
Neuromuscular disorder	1.36 (0.46–4.07)	0.4673	2.36 (0.44–4.25)	0.5938	2.47 (0.33–18.62)	0.3809
Clinical infection*						
Pneumonia	0.75 (0.57–0.99)	0.0420	0.90 (0.64–1.26)	0.5298	0.72 (0.43–1.21)	0.2164
UTI	0.33 (0.24–0.45)	< 0.0001	0.37 (0.25–0.53)	< 0.0001	0.23 (0.13–0.39)	< 0.0001
Primary BSI	0.63 (0.40–0.98)	0.0419	0.55 (0.33–0.92)	0.0229	0.49 (0.26–0.92)	0.0270
CR BSI	0.36 (0.24–0.53)	< 0.0001	0.33 (0.21–0.51)	< 0.0001	0.28 (0.16–0.47)	< 0.0001
Skin and soft–tissue infection	0.76 (0.57–1.01)	0.0551	0.93 (0.66–1.31)	0.6838	0.79 (0.45–1.40)	0.4164
Other infection	1.17 (0.84–1.63)	0.3490	0.95 (0.65–1.39)	0.7842	0.78 (0.46–1.33)	0.3601
Source control-requiring infection	0.90 (0.70–1.15)	0.4022	0.82 (0.62–1.09)	0.1727	0.86 (0.57–1.28)	0.4517
Inappropriate therapy	8.99 (6.60–12.23)	< 0.0001	6.95 (3.11–15.52)	< 0.0001	7.19 (4.89–10.55)	< 0.0001
1st h fluid resuscitation, L	0.82 (0.73–0.91)	0.0002	0.80 (0.70–0.92)	0.0012	0.84 (0.68–1.02)	0.0791
Pressor choice†						
Norepinephrine	0.96 (0.81–1.15)	0.6727	0.97 (0.82–11.8)	0.6988	0.99 (0.83–1.20)	0.7752
Phenylephrine	0.98 (0.74–1.23)	0.7730	1.01 (0.77–1.29)	0.7905	0.97 (0.70–1.27)	0.8891
Epinephrine	1.44 (0.37–5.61)	0.6017	1.35 (0.27–6.22)	0.6722	1.42 (0.26–6.51)	0.7204
Dobutamine	0.79 (0.35–1.75)	0.5628	0.82 (0.34–1.81)	0.6112	0.80 (0.28–1.96)	0.7311
aPC use	0.50 (0.35–0.71)	< 0.0001	0.44 (0.28–0.69)	0.0004	0.37 (0.19–0.71)	0.0030
Microorganism characteristics						
Gram negative‡			0.84 (0.67–1.02)	0.0812	0.60 (0.44–0.82)	0.0016
Fungal‡			3.30 (2.27–4.80)	< 0.0001	3.30 (1.94–5.62)	< 0.0001
Culture positive§	0.86 (0.71–1.03)	0.0841				
Blood culture positive‖			1.10 (0.91–1.34)	0.3214		

ESRD = end-stage renal disease; UTI = urinary tract infection; BSI = bloodstream infection; CR = catheter-related; aPC = activated protein C (drotrecogin-alfa activated); organ failures defined as per Bernard et al.[33]

*Reference group = intraabdominal infections.

†Reference group = dopamine-receiving patients.

‡Reference group = Gram-positive pathogen.

§Reference group = culture negative.

‖Reference group = primary site culture positive/blood culture negative.

these groups with inappropriate initial empiric therapy ranged from 3.4 to 4.5. The only exception was primary bloodstream infections without an obvious clinical source. In that subgroup (mostly neutropenic, Candida, and *S aureus* septic shock), appropriate therapy was associated with 17.6-fold better survival than inappropriate initial therapy (47.5% vs 2.7%, respectively).

Patients with septic shock associated with Gram-positive cocci and Gram-negative bacilli infection

had relatively similar survival and survival fraction changes with inappropriate initial empiric therapy (52.8% and 15.3%, respectively; Gram-positive cocci, 57.9% and 14.7%, respectively; Gram-negative bacilli infection, 3.5-fold and 3.9-fold decrease, respectively). Patients with both anaerobic and yeast infections had substantially greater differences in outcome depending on whether the initial therapy had been appropriate (decrease in the fraction of survivors of 10.6-fold and 7.8-fold, respectively). With regard to specific organisms, *Streptococcus pneumoniae* demonstrated the smallest fractional change in survival when inappropriate initial empiric therapy was given (55.1% appropriate vs 23.5% inappropriate, 2.3-fold change). At the other end, septic shock caused by *Candida albicans* demonstrated a 24.6% survival rate with initial appropriate therapy, but only a 4.6% survival rate without it (ninefold decrease).

Though it might be assumed that the initiation of appropriate antimicrobial therapy should have a beneficial effect on outcome, there are a surprising number of studies[24,27,34–43] that have failed to demonstrate such an effect. Apart from insufficient sample size, there are plausible scientific rationales to support the possibility that initial empiric antimicrobial therapy might not significantly impact survival in patients with sepsis and other severe infections. For example, *in vitro* sensitivity testing of pathogenic microbial isolates may not reflect clinical efficacy, as has been suggested in some studies of pneumococcal infection.[37] Sepsis may represent a manifestation of an inflammatory/coagulation cascade that advances independent of the initial infectious trigger.[44,45] If so, then the syndrome may be expected to progress independently of the control of the underlying infection through the initiation of appropriate antimicrobial therapy. This may suggest that the most critically ill patients with shock could fail to demonstrate sensitivity to the beneficial effects of appropriate antimicrobial therapy, as has been noted by Rello et al[46] in their study of nosocomial bacteremia.

The primary weakness of the study is that it was observational in nature. All such studies are susceptible to several forms of bias, most notably selection bias. The large study population obviates this problem to some extent in that the key observation is replicated consistently across all subgroups. As in any observational study, outcomes may also be influenced by unmeasured quality elements. For example, institutions with a high degree of antimicrobial appropriateness may also have other quality-of-care advantages, resulting in a fallacious link between a high degree of initial antimicrobial appropriateness and survival. Against this possibility is that the survival advantage held even when the patient's institution was added to the multivariate analysis. The inclusion of patients with culture-negative septic shock can be criticized. Their inclusion leads to a requirement for a relative judgment as to the appropriateness of the initial empiric therapy (*ie*, concordance with international recommendations for empiric therapy) in these patients. However, the use of a predefined algorithm for the assessment of appropriateness should minimize the problem of subjective judgment. The fact that the association of survival with appropriate therapy for the subgroups of culture-positive and blood culture-positive cases substantially parallels the response for the entire group (inclusive of the culture-negative cases) suggests a relatively consistent assessment of the appropriateness therapy between the groups. Notably, exclusion of the subgroup could itself be criticized as not being representative of clinical reality.

We have demonstrated that the time to the initiation of effective antimicrobial therapy is the critical determinant of outcome in patients with septic shock.[3] The choice of an appropriate empiric antimicrobial agent is one of the key elements in effecting the rapid initiation of effective antimicrobial therapy. This study supports other investigations emphasizing that the selection of an initial antimicrobial regimen with coverage against the inciting isolated or presumed pathogens is required for the best possible survival from septic shock.[26] The empiric selection of antimicrobial agents must be a central element in any efforts to address the suboptimal management of this condition.

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Author contributions: Study design: Dr. Anand Kumar. Data collection: members of the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Data analysis and interpretation: Drs. Anand Kumar and Chateau. Manuscript development: Drs. Anand Kumar, Ellis, Arabi, Roberts, Light, Parrillo, Dodek, Wood, Aseem Kumar, Ahsan, and Simon, and Ms. Peters. Dr. Anand Kumar had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix 1

Rules To Assign Clinical Significance to Microbial Isolates

1. Clinically significant isolates from either local site and/or blood cultures were required to have been obtained within 48 h of the onset of shock.
2. The following were considered to represent clinically significant isolates:
   a. A blood culture positive for any pathogen other than coagulase-negative staphylococci or other skin contaminants;
   b. Any growth from a normally sterile site (*eg*, gall bladder, bronchial lavage, peritoneal, pleural fluid, or operative tissue specimen) apart from coagulase-negative staphylococci and other skin contaminants;
   c. Growth of a pathogen in a sputum sample from a patient with respiratory signs and symptoms, or a new infiltrate seen on chest radiography, with no other likely source of infection;
   d. Growth of a pathogen in a urine sample ($> 10^8$ organisms per liter) with either local clinical symptoms or in the absence of a more plausible clinical infection site;
   e. Growth from a deep biopsy specimen or a deep aspirate of a finding in soft tissue or skin;
   f. Concurrent congruent positive semi-quantitative catheter colonization (> 15 colonies) with blood culture or clinical evidence of site infection; and
   g. A positive direct measurement of *Legionella pneumophila* antigen in the urine; or *S pneumoniae*, *Neisseria meningitides*, or *Haemophilus influenzae* in the sputum.
3. Candida lung isolates were considered to be colonizers unless also isolated from multiple other normally sterile sites in which case disseminated infection was diagnosed. Enterococci were considered to be clinically significant only in the absence of other more plausible pathogens.
4. *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.

Appendix 2

Designation of Appropriateness of Antimicrobial Therapy

1. The following were considered appropriate therapy even in the absence of specific sensitivity testing: (a) group A, B, and G Streptococcus treated with all β-lactams; (b) all Gram-positive bacteria except enterococci treated with vancomycin; (c) anaerobes treated with metronidazole, β-lactam inhibitor combinations, and carbapenems; and (d) organisms treated with β-lactamase inhibitor combinations if treated with the β-lactam alone.
2. The following were considered inappropriate therapy even in absence of specific sensitivity testing: (a) Enterococci treated with all cephalosporins and trimethoprim/sulfamethoxazole; (b) *Enterococcus faecalis* sensitive to quinupristin-dalfopristin; and (c) any bacteria treated with monotherapy with aminoglycoside at standard dosing every 8 h.
3. Legionella species were considered appropriately treated with macrolides or quinolones.
4. Treatment with oral or IV metronidazole or oral vancomycin along with broad-spectrum antienteric antimicrobial therapy was considered to be a requirement for appropriate antimicrobial therapy of septic shock caused by *Clostridium difficile* entercolitis.
5. Clindamycin, macrolides, and third-generation cephalosporins were not considered appropriate for the treatment of *S aureus* infection irrespective of listed sensitivity.
6. Cefotaxime and ceftriaxone were not considered appropriate therapy for *Pseudomonas aeruginosa* infection irrespective of listed sensitivity.
7. In cases where multiple isolates were found at a local site, appropriate therapy was considered to have been delivered if the densest pathogen was covered. If multiple pathogens were isolated at a similar density, all pathogens were required to have been covered.
8. For multiple simultaneous blood isolates, appropriate therapy had to cover all pathogens.

Appendix 3

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Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

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