CHEST

Original Research

CRITICAL CARE

Mycobacterium tuberculosis Septic Shock

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Background: **Septic shock due to *Mycobacterium tuberculosis* (MTB) is an uncommon but well-recognized clinical syndrome. The objective of this study was to describe the unique clinical characteristics, epidemiologic risk factors, and covariates of survival of patients with MTB septic shock in comparison with other bacterial septic shock.**

Methods: **A retrospective nested cohort study was conducted of patients given a diagnosis of MTB septic shock derived from a trinational, 8,670-patient database of patients with septic shock between 1996 and 2007.**

Results: **In the database, 53 patients had been given a diagnosis of MTB shock compared with 5,419 with septic shock associated with isolation of more common bacterial pathogens. Patients with MTB and other bacterial septic shock had in-hospital mortality rates of 79.2% and 49.7%, respectively ($P < .0001$). Of the cases of MTB shock, all but five patients had recognized respiratory tract involvement. Fifty-five percent of patients (29 of 53) were documented (by direct culture or stain) as having disseminated extrapulmonary involvement. Inappropriate and appropriate initial empirical therapy was delivered in 28 patients (52.8%) and 25 patients (47.2%); survival was 7.1% and 36.0%, respectively ($P = .0114$). Ten patients (18.9%) did not receive anti-MTB therapy; all died. The median time to appropriate antimicrobial therapy for MTB septic shock was 31.0 h (interquartile range, 18.9-71.9 h). Only 11 patients received anti-MTB therapy within 24 h of documentation of hypotension; six of these (54.5%) survived. Only one of 21 patients (4.8%) who started anti-MTB therapy after 24 h survived ($P = .0003$ vs < 24 h). Survival differences between these time intervals are not significantly different from those seen with bacterial septic shock due to more common bacterial pathogens.**

Conclusions: **MTB septic shock behaves similarly to bacterial septic shock. As with bacterial septic shock, early appropriate antimicrobial therapy appears to improve mortality.**

CHEST 2013; 144(2):474–482

Abbreviations: AFB = acid-fast bacilli; APACHE = Acute Physiology and Chronic Health Evaluation; CATSS = Cooperative Antimicrobial Therapy of Septic Shock; IQR = interquartile range; MTB = *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB) infects nearly one-third of the world's population, resulting in 9.4 million new cases and nearly 1.7 million deaths each year[1]; 25% of these deaths occur among patients with HIV.[2] Although the incidence of TB in the United States and Canada (3.6 in 2010 and 4.7 in 2009 per 100,000 population, respectively) is low and continues to decrease annually, the proportions of infected foreign-born patients and patients in medically underserved populations are much higher.[3,4]

Untreated progressive TB is usually fatal, with death typically resulting from ARDS and various forms of miliary involvement of extrapulmonary organs. Little is known regarding the characteristics of the subset of infected patients who develop septic shock. To date, there have been approximately 25 cases of MTB septic shock reported sporadically in the literature. Our case series focused on identifying the unique clinical characteristics, epidemiologic risk factors, and covariates of mortality of patients with MTB septic shock in comparison with other bacterial septic shock.

Materials and Methods

Methods

A retrospective review was performed of adult patients (≥ 18 years of age) diagnosed with septic shock. A waived consent

protocol was approved by the Health Ethics Board of the University of Manitoba (H2003-087) and at each individual participating center. Consecutive adult patients with septic shock from 28 medical academic and community institutions interested in contributing to the study in Canada, the United States, and Saudi Arabia for periods between 1996 and 2007 were identified retrospectively using either internal ICU registries/databases (96% of cases) and/or *International Classification of Diseases, Ninth Revision* or *Tenth Revision* coding strategies (4% of cases). A breakdown of the geographic regions and the academic/community natures of the contributing institutions has been published previously.[5] 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.[6] As per that definition, case patients were required to have documented or suspected infection, persistent hypotension requiring therapy with vasopressors, and two of the following four elements: (1) a heart rate of $\geq$ 90 beats/min; (2) a respiratory rate of $\geq$ 20 breaths/min or Pco_2 of $\leq$ 32 mm Hg; (3) a core temperature of $\leq$ 36°C or $\geq$ 38°C; and (4) a WBC count of $\leq$ 4,000/μL, $\geq$ 12,000/μL, or $\geq$ 10% immature (bands) forms. Each institution contributed a minimum of 50 cases of septic shock. This data set comprised the most current iteration of the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database.

The diagnosis of MTB septic shock was based on appropriate clinical suspicion in combination with positive staining for acid-fast bacilli (AFB) and cultures from sputum, body fluids, and tissues, as well as the absence of another more plausible pathogen. All cases were confirmed by standard laboratory testing and/or polymerase chain reaction. Each potential MTB septic shock case was adjudicated to have MTB septic shock by the attending physician of record, the infectious diseases consultant, and the primary investigator. The decision was based, in part, on the pathogenicity, isolation site, and density of any bacterial or fungal copathogen. In 14 cases, patients with AFB positivity/MTB isolation were adjudicated to not have MTB septic shock based on the presence of more likely pathogens in the blood or other infection site. Those cases were not used in this analysis. Confirmed MTB septic shock cases were compared with culture-positive cases of bacterial septic shock in the database.

Manuscript received May 22, 2012; revision accepted January 10, 2013.
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*A complete list of participants is located in e-Appendix 1.
Funding/Support: This study was supported by unrestricted research grants to Anand Kumar from Eli-Lilly and Company; Pfizer, Inc; Bayer; Astellas Pharma; Merck & Co, Inc; the Manitoba Health Research Council; the Health Sciences Centre (Winnipeg) Foundation; the Innovations and Opportunities Foundation (Winnipeg); and the Deacon Foundation (Winnipeg).
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DOI: 10.1378/chest.12-1286

Subsets of subject data from the CATSS database examined in this study have been used for several earlier publications[5,7] Data collection methods were described in those previous studies.[7,8] Data were collected by trained research nurses/medical students using a standardized and piloted data-extraction template. Variables collected included patient demographics, baseline comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score[9]/physiologic/laboratory parameters following onset of shock, and the need for hemodynamic or ventilatory support. The first use of any appropriate antimicrobial therapy was determined for all cases. Appropriate antimicrobial therapy was considered to have been initiated if an antimicrobial with proven or expected (for MTB and some specific bacterial [eg, Legionella species])[7] in vitro activity appropriate for the isolated pathogen or pathogens was either the first new antimicrobial started after onset of recurrent or persistent hypotension or was initiated within 6 h of administration (for bacterial isolates) of the first new antimicrobial. Otherwise, inappropriate therapy was considered to have been initiated. MTB cases were required to have had at least two standard antimicrobials (including rifampin and isoniazid) initiated to be considered appropriate. The site of infection, microbiologic culture results, and time to appropriate antimicrobial therapy from the first documentation of persistent/recurrent hypotension were also recorded.

A priori criteria were developed to determine uniformly the primary pathogen(s) and to assess the appropriateness of antimicrobial therapy across participating institutions, as described previously.[7] 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 for which clinical judgment was required.

Statistical Analysis

The primary outcome variable was survival to hospital discharge, including discharge to a chronic health care facility. χ^2 analysis was used to compare survival in subgroups of patients. χ^2 tests were used to examine the distribution of comorbidities and clinical infection sites among those receiving appropriate or inappropriate initial therapy. Similarly, the Fisher exact test was used to examine for smaller groups where appropriate. Student *t* tests were used for comparisons of continuous variables, including laboratory values. Data are expressed as mean ± SD for normally distributed variables and median (interquartile range [IQR]) for others.

Results

This iteration of the CATSS database contained 8,670 patients who met the criteria for septic shock. Of these, 5,419 represented cases of culture-positive bacterial septic shock. The remainder represented culture-negative septic shock (n = 2,651) or septic shock associated with other pathogens.

We describe the characteristics of the 53 patients with a specific diagnosis of septic shock from MTB in the database. Overall, 1.0% of culture-positive bacterial septic shock cases within the CATSS database were caused by MTB. The frequency of MTB septic shock cases (relative to all culture-positive septic shock) ranged from 0% at several North American sites to

3.3% in Saudi Arabia. The highest frequency in North American sites was 1.1% in Manitoba. The frequency of MTB septic shock relative to reported incidence of MTB cases in Manitoba averaged 1.8% for the decade from 1998 to 2007. The demographics and major sites of infection in comparison with bacterial septic shock are presented in Table 1. Notably, the average age of MTB septic shock cases was almost a decade lower than bacterial septic shock cases (54.8 ± 17.9 years vs 62.1 ± 16.2 years, $P < .0001$). The sex distribution was similar in both groups, with a modest preponderance of males (52.8% MTB vs 57.7% bacterial, $P = .4731$). APACHE II scores were similar in both groups (24.6 ± 7.3 MTB vs 25.6 ± 8.2 bacterial septic shock) with the one-point difference explainable by the difference in age distributions.

There were significant differences in mean BMI between patients with MTB and those with bacterial shock (22.2 kg/m² vs 27.3 kg/m²; $P = .003$; 95% CI, 1.66-8.53). Among patients with MTB septic shock with an evaluable BMI, no patient with a BMI ≤ 20 kg/m² (mean BMI, 17.3 kg/m²) survived. Mean BMI among survivors was 25.4 kg/m². Nonsurvivors with a lower BMI (< 20 kg/m²) died nearly 2 weeks earlier (17.8 days) than nonsurvivors with a BMI > 20 (36.3 days), although this difference was not statistically significant ($P = .2753$; 95% CI, −17.4 to 55.4).

In most patients with MTB septic shock, overt clinical signs of infection were present at the time of presentation; mean temperature was 37.6 (±1.83)°C, with 56% of patients presenting with temperatures > 38° and 16% with temperatures < 36°; mean heart rate

Table 1—*Demographic Characteristics of Patients With MTB or Bacterial Septic Shock*

Demographics	MTB All	Bacterial All	*P* Value (95% CI)	MTB Survivors	MTB Nonsurvivors	*P* Value (95% CI)
Total	53 (1)	5,419 (99)	…	11	42	…
Age, y	54.8 ± 17.9	62.1 ± 16.2	.009 (3.02 to 11.7)	50.9 ± 14.4	55.8 ± 18.7	.423 (−7.3 to 17.1)
Sex						
Male	28 (53.0)	3,128 (58.0)	.487	5 (45.0)	23 (55.0)	1.0
Female	25 (47.0)	2,291 (42.0)	…	6 (54.0)	19 (45.0)	…
BMI, kg/m²	22.2 ± 4.1	27.3 ± 7.6	.003 (1.66 to 8.53)	25.4 ± 2.8	20.9 ± 4.0	.074 (−0.45 to 8.6)
Temp, °C	37.6 ± 1.8	37.6 ± 1.7	1.0 (−0.47 to 0.47)	37.1 ± 2.9	37.7 ± 1.5	.363 (−1.9 to 0.71)
APACHE II	24.6 ± 7.3	25.6 ± 8.2	.267 (−1.0 to 3.6)	20 ± 3.9	25.9 ± 7.5	.016 (1.15 to 10.6)
WBC, cells/uL	10.4 ± 6.7	16.2 ± 13.9	.003 (1.95 to 9.84)	9.0 ± 6.3	10.8 ± 6.9	.459 (−6.06 to 3.06)
Creatinine, μmol/L	152.2 ± 122.3[a]	204.3 ± 162.3[b]	.0338 (3.8 to 100.3)	80.5 ± 45.1[c]	176.1 ± 130.8[d]	.0227 (14.0 to 177)
Albumin, g/dL	1.76 ± 0.24[e]	2.25 ± 0.71[f]	.0131 (0.10 to 0.87)	1.70 ± 0.10[g]	1.78 ± 0.27[h]	−0.5314 (−0.18 to 0.34)
No. organ failure day 1	3.8	3.7	1.0	2.8	4.1	1.0
Major comorbid illness						
Diabetes	10 (18.8)	1,481 (27.3)	.214	1 (9.0)	9 (21.4)	.670
ETOH/substance abuse	16 (30.2)	2,216 (40.8)	.124	4 (36.0)	12 (28.5)	.716
COPD	5 (9.4)	2,347 (43.3)	< .0001	2 (18.1)	3 (7.1)	.274
ESRD	2 (3.7)	558 (10.2)	.167	0 (0)	2 (4.7)	1.0
Liver failure	8 (15.1)	414 (7.6)	.062	1 (9.0)	7 (16.6)	1.0
Immunosuppression[i]	20 (37.7)	2,235 (41.2)	.675	2 (18.1)	18 (42.8)	.175
HIV/AIDS	8 (15.1)	156 (2.8)	.0003	1 (9.0)	7 (16.6)	1.0
Sites of infection[j]						
Respiratory	49 (92.4)	2,143 (39.5)	< .0001	11 (100)	38 (90.4)	.568
Genitourinary	8 (15.1)	729 (13.4)	.686	3 (27.2)	5 (11.9)	.340
Intraabdominal	4 (7.5)	1,292 (23.8)	.003	1 (9.0)	3 (7.1)	1.0
CNS	2 (3.7)	62 (1.1)	.023	0 (0)	2 (4.7)	1.0
Soft tissue	3 (5.6)	532 (9.8)	.482	0 (0)	3 (7.1)	1.0
Cardiac/pericardial	2 (3.7)	76 (1.4)	.174	2 (18.1)	0 (0)	.040
Bacteremia	7 (13.2)	2,562 (47.3)	< .0001	0 (0)	7 (16.6)	.059
No respiratory involvement	5 (9.4)	3,276 (60.5)	< .0001	0 (0)	5 (11.9)	.571

Data are presented as No. (%) or mean ± SD. APACHE = Acute Physiology and Chronic Health Evaluation; ESRD = end-stage renal disease; ETOH = alcohol; MTB = *Mycobacterium tuberculosis*.

[a]n = 44.

[b]n = 4,244.

[c]n = 11.

[d]n = 33.

[e]n = 13.

[f]n = 1,103.

[g]n = 5.

[h]n = 15.

[i]Immunosuppression includes diagnosis of AIDS, organ transplant, leukemia/lymphoma, metastatic malignancy, and neutropenia.

[j]Nonrespiratory sites include involvement of respiratory tract unless specified.

was 120 (± 32.5) beats/min; respiratory rate was markedly elevated for the most part (mean value, 31[± 11.6]/min) even though P_{CO_2} was not decreased on average (38.1[± 13.0] mm Hg). The WBC count of cases with MTB septic shock was within the normal range (10.4 ± 6.7 cells/μL) and was significantly lower than the mean WBC count of cases with bacterial septic shock (16.2 ± 13.9 cell/μL) ($P = .003$). Mean albumin levels were 1.76 (± 0.20) g/dL. Mean creatinine in survivors and nonsurvivors (80.4 ± 45.1 μmol/L vs 176.1 ± 130.7 μmol/L; $P = .0227$; 95% CI, 14.0-177) at the onset of shock appeared to separate out the two groups more effectively than any other individual laboratory test (Table 1). Random cortisol levels were collected sporadically (16 patients) with no significant difference between survivors of MTB and nonsurvivors (mean value, 876 (± 507) μg/dL). Only one patient had values < 150 μg/dL. Sixteen additional patients were treated with low-dose corticosteroids. Hyponatremia has been considered an indicator of the syndrome of inappropriate antidiuretic hormone secretion or adrenal insufficiency in patients with disseminated TB.[10,11] Mean sodium levels in our cohort were 137 (± 10.6) mg/dL, with only six patients (one survivor) considered hyponatremic (sodium levels < 130 mg/dL) at onset of shock.

Almost all patients with MTB septic shock (48 of 53; 90.1%) had primary respiratory disease with isolation from the respiratory tract. Of the five others, two had isolation from the urinary tract, one from both the urinary and the gastrointestinal tract, one from soft tissues, and one from blood only. In addition, extrapulmonary disease was seen in association with respiratory disease in about 25 of 48 patients (52%) by direct culture or stain at an extrapulmonary site (urinary, 11; intraabdominal, six; cerebrospinal fluid two; soft tissue, two; other, nine [not mutually exclusive]). In total, 29 of 53 patients (55%) had extrapulmonary (disseminated) infection. Among those patients without primary respiratory involvement, three had mycobacteremia, one with genitourinary TB and another with gastrointestinal TB. Primary respiratory involvement was far less common (39.5%) in the bacterial septic shock group ($P < .0001$) (Table 1). Among patients with presumed TB-associated septic shock, other bacterial organisms were isolated in the lung (six patients) and/or at other anatomic sites (four patients).

A chest radiograph or radiologist's report of the same was available for 34 patients. Only four films demonstrated a miliary pattern. In one case of a nonpulmonary focus, the chest radiograph was clear of any acute process. In all the remaining 29 cases, multilobar consolidation, frequently diffuse, occasionally with associated nodularity (n = 6) or cavitation (n = 6), was noted at shock presentation. As a consequence of the frequency of diffuse lobar consolidation at that time, an upper-lobe predilection (n = 15) was not consistently apparent. Review of available films from before shock onset (days/weeks) when available yielded this upper-lobe focus in two additional patients with diffuse infiltrates at presentation.

Patient Outcomes

The 53 patients with MTB septic shock and the 5,419 patients with other bacterial septic shock exhibited a hospital mortality of 79.2% and 49.7%, respectively ($P < .0001$) (Table 2). Among nonsurvivors of MTB septic shock, about one-half died in the first 15 days after the onset of shock, compared with about one-third of patients with bacterial septic shock ($P = .052$) (Table 2). Similarly, among cases of MTB septic shock, approximately three-quarters had succumbed by 90 days after shock but < 50% of patients with bacterial septic shock died within the same time frame ($P < .0001$).

APACHE II scores underestimated the probability of mortality for cases with MTB septic shock.[9] Patients with a mean score of 19 in our series had a 70% mortality, rather than 25%; mean scores of 24 in our series had associated mortality of 80% vs a predicted 40% to 50%.[9] This reduced survival was notable when compared with bacterial septic shock. For each quartile of APACHE II scores for MTB septic shock, the equivalent division of bacterial septic shock cases showed a consistently and substantially higher hospital survival ($P < .0001$) (Fig 1).

Survivors of MTB septic shock exhibited triple the length of time to extubation than did their counterparts with bacterial shock (12 days vs 4 days; $P = .0018$; 95% CI, 3.23-14.1). Median hospital stay among survivors of MTB was twice that of patients with bacterial shock (48 days vs 23 days; $P = .0330$; 95% CI, 1.97-48.0). Nonsurvivors experienced median hospital stays of 10.5 days (MTB) and 8 days (bacterial) ($P = .7344$; 95% CI, −12.5 to 16.3) Twenty-eight percent of patients with MTB survived to leave the ICU; however, only 20% survived their hospital stay. Of four patients who survived the ICU but died in hospital, two received anti-TB treatment and had longer hospital stays (50 and 92 days) when compared with the other two, who did not receive anti-TB therapy and had shorter hospital stays (4 and 7.9 days).

Twenty-eight of 53 patients (53%) were considered to have disseminated TB rather than pneumonia alone. Seven patients had bacteremia, all of whom died. We observed a substantially higher frequency of HIV/AIDS among patients with MTB shock when compared with their counterparts with bacterial shock (15% vs 2.8%, $P = .0003$) (Table 1). Immunocompromised patients (20 immunosuppressed and eight with liver failure; one with both) had the lowest overall

Table 2—*Survival Characteristics of Patients With MTB and Bacterial Septic Shock*

Characteristic	MTB Shock	Bacterial Shock	*P* Value (95% CI)	MTB Shock Survivors	MTB Shock Nonsurvivors	*P* Value (95% CI)
Hospital mortality	42 (79.2)	2,696 (49.7)	< .0001	…	…	…
ICU mortality	38 (71.7)	2,030 (37.5)	< .0001	…	…	…
Day 15	25 (47.2)	1,878 (34.6)	.052	…	…	…
Day 30	35 (66.0)	2,311 (42.6)	< .0001	…	…	…
Day 90	40 (75.4)	2,633 (48.5)	< .0001	…	…	…
Preshock hospital length of stay, d	2 (1-18.0)	1 (0.0-4.0)	.781 (−4.53 to 6.03)	2 (1.0-18.0)	2.5 (0.1-9.0)	.590 (−5.65 to 9.83)
Hospital stay, d	48 (20.5-69.5)	23 (13.0-46.0)	.655 (−7.13 to 11.3)	48 (20.5-69.5)	10.5 (5.0-22.0)	.0003 (15.4 to 47.7)
Hemodynamics, mean ± SD						
MAP, mm Hg	59 ± 21.2	58 ± 17.8	.684 (−8.62 to 5.66)	63 ± 3.2	61 ± 23.2	.694 (−19.7 to 29.1)
Cardiac index, L/min/m^2	4.0 ± 1.6	3.9 ± 1.6	.674 (−.85 to .55)	4.1 ± 0.6	3.4 ± 1.7	.866 (−1.92 to 2.26)
PCWP, mm Hg	19 ± 7.5	18 ± 6.3	.56 (−3.8 to 2.06)	15 ± 7.1	14 ± 7.7	.469 (−16.4 to 7.9)
Time to extubation in survivors, d	12 (5.5-19.0)	4 (0.0-8.0)	.002 (1.52 to 6.55)	12 (5.5-19.0)	2 (0.0-9.5)	.017 (1.63 to 15.8)
Time to vasopressor discontinuation in survivors, median d	3 (1.5-5.0)	2 (1.0-4.0)	< .0001 (1.19 to 3.16)	3 (1.5-5.0)	5.5 (2.0-8.3)	.098 (−7.58 to 0.66)
Steroids[a]	16 (30.1)	1,439 (26.5)	.656	1 (9.0)	15 (35.7)	.375
aPC	1 (1.8)	269 (4.9)	.520	0 (0)	1 (2.3)	1.0
Source control required	5 (9.4)	2,206 (40.7)	.0004	2 (18.1)	3 (7.1)	.275
Cause of death						
Shock	27 (64.3)	1,607 (59.6)	.540	…	…	…
Multiorgan failure	15 (35.7)	910 (33.8)	.790	…	…	…
Other	0 (0)	179 (6.6)	.017	…	…	…

Data are given as No. (%) or median (IQR) unless otherwise indicated. aPC = activated protein C (drotrecogin-α [activated]); IQR = interquartile range; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure.

[a]Hydrocortisone or methylprednisone. See Table 1 legend for expansion of other abbreviations.

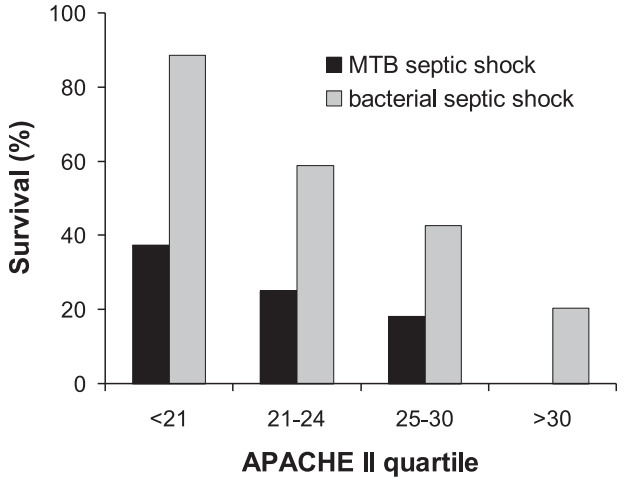

FIGURE 1. Relationship between APACHE II score[9] and survival in MTB and bacterial septic shock. APACHE = Acute Physiology and Chronic Health Evaluation; MTB = *Mycobacterium tuberculosis*.

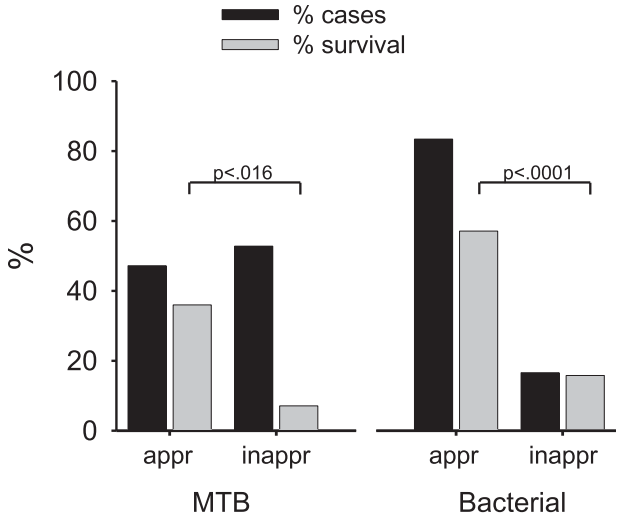

FIGURE 2. Relationship between empirical antimicrobial appropriateness and survival in MTB and bacterial septic shock. appr = appropriate empirical therapy; inappr = inappropriate empirical therapy. See Figure 1 legend for expansion of other abbreviation.

survival of 7.4% (two survivors from 27 cases). Among those with AIDS, one of eight patients survived. Alcohol was the single most common comorbidity observed in the series (16 of 53, seven of whom had liver failure). Alcohol/substance abusers overall had a 25% survival rate.

Inappropriate and appropriate initial empirical therapy was delivered in 28 cases (52.8%) and 25 cases (47.2%) of MTB septic shock, respectively; survival was 7.1% and 36.0%, respectively ($P = .016$) (Fig 2). For bacterial septic shock, inappropriate and appropriate initial therapy was delivered in 16.6% and 83.4% of cases; survival was 15.8% and 57.1%, respectively ($P < .0001$) (Fig 2). The frequency of inappropriate initial empirical therapy was substantially higher in cases of MTB than in cases of bacterial septic shock ($P < .0001$). Initiation of appropriate antimicrobials following the onset of hypotension among survivors (MTB, 81.8%; bacterial shock, 94.7%) was markedly higher than among nonsurvivors (MTB, 38.1%; bacterial shock, 71.8%; $P = .0418$) (Fig 2). In 10 cases of MTB (18.9%) and 217 cases of bacterial septic shock (4.0%) ($P < .0001$), no appropriate therapy was initiated during the hospitalization ($P < .0001$). Survival in these groups was 0% and 4.2%, respectively (P = NS). In 11 patients, anti-MTB therapy was initiated before the onset of septic shock (median, 24 h; range, 2.3-125 h); survival in this group was 36% (four of 11 patients).

The median time to appropriate antimicrobial therapy for MTB septic shock was 31.0 h (IQR, 18.9-71.9 h) compared with 4.8 h (IQR, 1.8-11.5 h) for bacterial septic shock ($P < .0001$). The median time to appropriate antimicrobial therapy among survivors and nonsurvivors of MTB shock was 10.2 h (IQR, 6.9-17.3 h) and 35.2 h (IQR, 26-78 h), respectively ($P = .0164$)

Only 11 patients received anti-MTB therapy within 24 h of documentation of hypotension; six (54.5%) of these survived (Fig 3). Only one of 21 patients (4.8%) who started anti-MTB therapy after 24 h survived ($P = .0003$ vs < 24 h) (Fig 3). Survival differences between these time intervals are not significantly different from those seen with bacterial septic shock due to standard pathogens (Fig 3).

Twenty-one patients had pulmonary artery catheter measurements within the first 24 h of shock onset. The mean cardiac index (4.0 [± 1.6] L/min/m^2) and pulmonary capillary wedge pressure (19 [± 7.5] mm Hg) indicate that, for the most part, filling pressures and

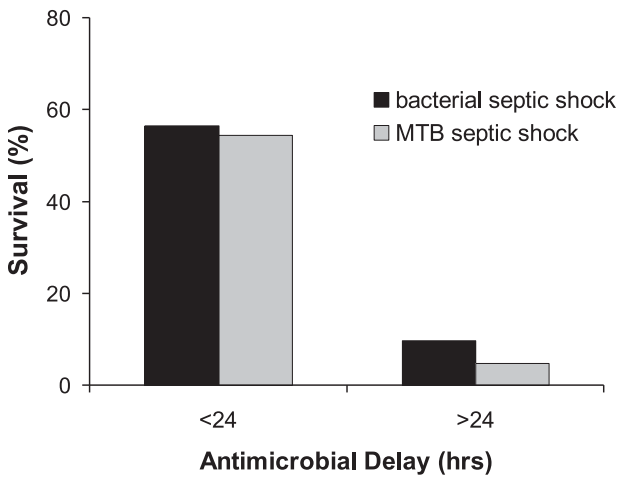

FIGURE 3. Relationship between antimicrobial delay and survival in MTB and bacterial septic shock. No. survivors/No. total for each group: < 24 h MTB shock, 6/11; < 24 h bacterial shock, 1,992/3,527; > 24 h MTB shock, 1/24; > 24 h bacterial shock, 47/478. See Figure 1 legend for expansion of abbreviation.

forward flow were adequate following fluid resuscitation and hemodynamic support.

The cause of death among patients with MTB was attributed to persistent septic shock in approximately two-thirds of cases, with the majority of the remainder being due to sepsis-associated multiple organ failure (Table 2), values similar to those found in cases of bacterial septic shock. Neither patient with evidence of pericardial involvement exhibited evidence of obstructive shock due to cardiac tamponade.

Discussion

MTB infection is the leading cause of death in the developing world. However, the estimated incidence and case fatality rates due to TB in the United States, Canada, and Saudi Arabia (3.6, 4.7, and 32-64 per 100,000 and 0.2, 0.2, and 0.9 per 100,000 population, respectively) are considerably lower than for many other regions in the world.[2,12]

This comparative study of the characteristics of bacterial and MTB septic shock makes several novel observations. First and foremost, our data demonstrate that the probability of survival in patients with MTB septic shock is extremely poor. Further, the data suggest that delayed initiation of appropriate antimicrobial therapy likely due to impaired recognition of disease plays a substantial role in this high mortality.

In cases of severe bacterial septic shock, microbially appropriate empirical antimicrobial therapy appears to improve mortality.[7] Compared with bacterial septic shock, a substantially larger fraction of patients with MTB septic shock received inappropriate initial antimicrobial therapy, which was associated with a significantly worse clinical outcome, including decreased ICU and hospital survival (Fig 2, Table 2). Further, the fraction of patients who did not receive appropriate therapy before death was substantially higher in patients with MTB septic shock, indicative of delayed clinical suspicion. Our data suggest that recognition of a potential MTB cause prior to or early after the onset of hypotension and the development of organ system dysfunction is perhaps the most effective strategy to prevent death in MTB septic shock.

Delays in the initiation of appropriate empirical antimicrobial therapy have been shown to be associated with marked increases in mortality risk with severe infections, particularly septic shock.[8] Notably, this study shows that the mortality rate of MTB and other confirmed bacterial septic shock is very similar when mortality risk is stratified by delay to appropriate antimicrobial therapy (Fig 3). Mortality rates for therapy delayed by more or less than 24 h from the initial documented hypotension is similar in MTB and other bacterial septic shock, despite the significantly higher overall MTB septic shock mortality (Fig 3).

The consequences of the greater delays to initiation of appropriate antimicrobial therapy can be appreciated in the comparison of APACHE II-stratified mortality for MTB and other bacterial shock (Fig 1). MTB septic shock mortality appears to be much higher than APACHE II scores would predict and higher than mortality in the comparable bacterial septic shock groups. The disparity between the APACHE II score and observed mortality is likely because greater antimicrobial delays have an adverse impact on mortality that is independent of the presenting severity of illness.[8] This possibility is supported by observations that the mean duration from MTB infection symptom onset to the beginning of anti-TB treatment is often greater than a month and is an independent predictor of mortality.[13,14]

Comorbid illness and socioeconomic factors are also important risk factors in both the acquisition and mortality risk of active MTB. When compared with bacterial septic shock, diabetes, alcoholism, and immunosuppression (including HIV/AIDS, organ transplant, leukemia/lymphoma, metastatic malignancy, and neutropenia) appeared to be associated with poorer outcomes among patients with MTB septic shock. A nonsignificant trend toward higher mortality among patients with MTB shock and HIV/AIDS than compared with their counterparts with bacterial shock was also found ($P = .0846$). Several studies have described the increased incidence of TB infection among patients with HIV/AIDS with corresponding mortality rates of approximately 20% in the United States. This is lower than our observed morality of 75% in this particular subset of patients with MTB septic shock.[15,16]

Our findings relating to low BMI among patients with active TB appear concordant with studies in HIV-positive populations and patients in developing countries.[17] An Asian epidemiologic study of > 1 million patients with TB found that the risk of death from respiratory causes among people with a BMI ≤ 20.0 kg/m^2 was two to 4.5 times greater than for those with a BMI > 22.6 kg/m^2; these results are similar to our finding that no patient with MTB shock and a BMI ≤ 20 kg/m^2 survived, and all survivors of MTB shock had a BMI > 22.6 kg/m^2.[18]

Unfortunately, none of the risk factors or characteristics of MTB septic shock are sufficiently specific to allow early definitive differentiation from other causes of septic shock in the absence of staining for AFB. The vast majority of cases exhibited an abnormal chest radiograph pattern at presentation, usually involving a diffuse multilobar consolidation. Cavitation, nodularity of infiltrates, or a miliary pattern was seen in only a minority of cases. An upper-lobe predilection

of infiltrates/consolidation was seen in about one-half of the cases. Significant differences in epidemiologic characteristics and laboratory findings existed but were not sufficiently specific to allow consistent differentiation. As a consequence, early therapy of MTB shock should be predicated on an appreciation of local epidemiologic risk factors and/or the presence of suspicious features on the chest radiograph that trigger staining for AFB.

To the best of our knowledge, no other studies have similarly examined mortality risk factors in a large group of cases of MTB septic shock. Earlier small studies have suggested extremely high mortality rates from MTB septic shock. Chiu and colleagues[19] described 11 non-HIV-infected patients with MTB bacteremia at a university medical center in Taiwan, a country where TB is endemic with a reported incidence of 64 per 100,000 population and estimated case fatality rates of between 8% and 23%. Six of these 11 patients developed septic shock; five of the six died. Among a retrospective cohort of nearly 100 patients hospitalized with pulmonary TB, one-quarter of patients either presented with or developed septic shock within 48 h of ICU admission and experienced a 60% mortality.[14]

The primary strength of this study is the size of the MTB septic shock cohort. Despite the fact that only 1% of all patients with culture-positive septic shock had MTB septic shock, the large size of this database allowed us to collect >50 cases, by far the largest published cohort of cases of MTB septic shock. The size of this cohort allowed us to examine an array of epidemiologic and treatment factors associated with clinical outcome.

However, certain limitations are inherent in this study (database) design. First, the major weakness is that our study is retrospective and thus susceptible to several forms of bias with respect to the reported associations. In addition, there are limitations in the collection of data from any database. For example, although all patients included in our MTB shock data set were culture confirmed, drug resistance was not defined in the cohort. This limitation may have had a direct impact on our estimates as to what would have been ultimately considered appropriate or inappropriate drug therapy. We defined the appropriateness of anti-MTB therapy as the initiation of at least two active drugs (minimum of isoniazid and rifampin) given the data that this regimen should be sufficient for drug susceptible infections.[20] Our best assumption is that the isolates were drug susceptible; the most recent estimates of multidrug resistance in Canada and the United States, 0.9% and 1.3%, respectively, are much lower than those in other parts of the world.[3,4] However, reports from Saudi Arabia assess the frequency of multi-drug-resistant TB in the late 1990s as being 0.7% to as high as 25% in certain parts of the country; the most recent estimate is 4.5%.[21,22] Our approach seems reasonable because all patients in our dataset had been given a diagnosis of with active TB at the time of hospitalization and, thus, susceptibility data would not have been available to physicians at the onset of septic shock.

Similarly, because of the retrospective nature of this study, cortisol levels were not available for all patients. There is an increased incidence of adrenal insufficiency in patients with severe MTB infection. Although only a single patient among the 16 was assessed with a low random cortisol level, it is possible that there were more among the remainder. This could have caused shock in some patients. We can also not entirely rule out the possibility that some cases of adjudicated MTB septic shock were caused by bacterial shock where the bacterial pathogen was suppressed because of the concurrent antibacterial therapy used in many cases. Further, as a consequence of the intrinsic limitation of a retrospective database study, we are unable to comment on the cause of inappropriate initial therapy and delays in initiation of anti-MTB therapy. All patients eventually had AFB stain or MTB culture positivity in order to be included in this analysis. However, many had delayed and initially inappropriate therapy; whether this was because of absent or negative initial AFB smears is not known. This is particularly important in the approximately 20% of patients (five disseminated disease and five pneumonia) who did not receive appropriate anti-MTB therapy, of whom none survived. Another limitation, given the modest number of total patients, is that a cluster analysis between sites was not performed, which may have identified differences in practice patterns affecting both the timing and appropriateness of anti-MTB therapy.

Conclusions

In summary, we conducted a multicenter observational study on the epidemiologic and treatment factors associated with outcome in MTB septic shock. Our key observation demonstrates that much of the increased mortality of MTB compared with bacterial septic shock is attributable to the marked treatment delays seen with anti-MTB therapy. This study suggests that early recognition of active disease and early appropriate therapy prior to or at the onset of hypotension can potentially limit the high mortality observed with MTB septic shock. Early treatment can best be facilitated by a high index of suspicion based on population, locale, and individual patient risk factors and the presence of suspicious radiologic findings supplemented by rapid AFB staining of sputum, tissue, and/or body fluids.

Acknowledgments

Author contributions: Dr Anand Kumar had access to all data and analysis and takes primary responsibility for the integrity of the study.
Dr Kethireddy: contributed to the data analysis and drafting of the manuscript.
Dr Light: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Mirzanejad: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Maki: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Arabi: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Lapinsky: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Simon: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Aseem Kumar: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Parrillo: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.
Dr Anand Kumar: contributed to the conceptualization, design, and development of the septic shock database; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision and final approval of the version to be published.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Anand Kumar has received pharmaceutical grant money from Hoffmann-La Roche, Inc; GlaxoSmithKline; Astellas Pharma; and Pfizer, Inc. Drs Kethireddy, Light, Mirzanejad, Maki, Arabi, Lapinsky, Simon, Aseem Kumar, and Parrillo have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.
Additional information: The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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