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CLINICAL THERAPEUTICS

Shock and Early Death in Hematologic Patients with Febrile Neutropenia

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ABSTRACT Empirical antibiotic therapy with a beta-lactam is the standard of care in febrile neutropenia (FN) and is given to prevent early death. The addition of vancomycin is recommended in certain circumstances, but the quality of evidence is low, reflecting the lack of clinical data. In order to characterize the epidemiology of early death and shock in FN, we reviewed all episodes of FN from 2003 to 2017 at University Hospital, Federal University of Rio de Janeiro, and looked at factors associated with shock at first fever and early death (within 3 days from first fever) by univariate and multivariate analyses. Among 1,305 episodes of FN, shock occurred in 42 episodes (3.2%) and early death in 15 (1.1%). Predictors of shock were bacteremia due to *Escherichia coli* (odds ratio [OR], 8.47; 95% confidence interval [95% CI], 4.08 to 17.55; $P < 0.001$), *Enterobacter* sp. (OR, 7.53; 95% CI, 1.60 to 35.33; $P = 0.01$), and *Acinetobacter* sp. (OR, 6.95; 95% CI, 1.49 to 32.36; $P = 0.01$). Factors associated with early death were non-Hodgkin's lymphoma (OR, 3.57; 95% CI, 1.18 to 10.73; $P = 0.02$), pneumonia (OR, 21.36; 95% CI, 5.72 to 79.72; $P < 0.001$), shock (OR, 11.64: 95% CI, 2.77 to 48.86; $P = 0.01$), and bacteremia due to *Klebsiella pneumoniae* (OR, 5.91; 95% CI, 1.11 to 31.47; $P = 0.03$). Adequate empirical antibiotic therapy was protective (OR, 0.23; 95% CI, 0.07 to 0.81; $P = 0.02$). Shock or early death was not associated with Gram-positive bacteremia; catheter-related, skin, or soft tissue infection; or inadequate Gram-positive coverage. These data challenge guideline recommendations for the empirical use of vancomycin at first fever in neutropenic patients.

KEYWORDS antibiotic, death, empiric therapy, febrile neutropenia, neutropenia, shock

The immediate initiation of empirical antibiotic therapy in febrile neutropenic patients is the standard of care and aims to prevent early death (1, 2). Over the past 40 years, various antibiotic regimens have been used in febrile neutropenia, reflecting changes in the epidemiology of bacterial infections and the introduction of new antimicrobials and strategies (3, 4). Anti-Gram-negative coverage has evolved from a combination of antibiotics (usually a beta-lactam plus an aminoglycoside) to monotherapy, after the availability of broad-spectrum antibiotics, such as cefepime, piperacillin-tazobactam, and carbapenems (5, 6).

In alignment with epidemiologic changes showing an increase in infection by Gram-positive organisms, anti-Gram-positive antibiotics (usually vancomycin) have been incorporated in the empirical regimen (7–9). However, a meta-analysis of randomized trials comparing regimens with or without vancomycin failed to show an advantage of vancomycin in the initial empirical regimen (10, 11). Indeed, practical guidelines for the management of febrile neutropenia do not recommend its routine use in the empirical antibiotic regimen, except in certain circumstances, such as suspected catheter-related infection, skin and soft tissue infection, pneumonia, or

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TABLE 1 Characteristics of 1,305 episodes of febrile neutropenia in 826 patients

Characteristic	*n* (%)
Underlying disease	
Acute myeloid leukemia	323 (24.8)
Multiple myeloma	298 (22.8)
Non-Hodgkin's lymphoma	232 (17.8)
Acute lymphoid leukemia	177 (13.6)
Hodgkin's lymphoma	138 (10.6)
Other[a]	137 (10.4)
Hematopoietic cell transplantation	504 (38.6)
Autologous	413 (31.6)
Allogeneic	90 (6.9)
Outpatient at onset of fever	333 (25.5)
Central venous catheter	761 (58.3)
Antifungal prophylaxis	448 (34.3)
Fluconazole	401 (30.7)
Other[b]	47 (3.6)
Quinolone prophylaxis	585 (44.9)
Empiric antibiotic therapy in the first fever	
Monotherapy	1,155 (88.5)
Cefepime-based	1,096 (84.0)
Carbapenem-based	135 (10.3)
Use of vancomycin	54 (4.1)
Positive blood culture on day 1 of fever	364 (27.4)
Gram positive	156/364 (42.8)
Gram negative	198/364 (54.4)
Fungi	5/364 (1.4)
Polymicrobial	5/364 (1.4)
Shock	42 (3.2)
Early death	15 (1.1)

[a]Other underlying diseases include chronic myeloid leukemia ($n = 52$), myelodysplasia ($n = 36$), aplastic anemia ($n = 24$), chronic lymphocytic leukemia ($n = 14$), hairy cell leukemia ($n = 4$), amyloidosis ($n = 4$), and polycythemia vera ($n = 3$).
[b]Other antifungal prophylaxis include voriconazole ($n = 26$), posaconazole ($n = 14$), itraconazole ($n = 6$), and micafungin ($n = 1$).

hemodynamic instability (12, 13). However, the level of evidence of these recommendations is weak (BIII; i.e., moderate strength of recommendation, based on the opinion of experts), reflecting the lack of clinical data supporting these recommendations.

The main objective of empirical antibiotic therapy in febrile neutropenic patients is to prevent early death, a complication that occurs mostly in the setting of Gram-negative bacteremia (14–16). In this study, we evaluated the frequency and epidemiology of early death and shock in febrile neutropenic patients. Specifically, we investigated the association between these outcomes and documentation of infection by Gram-positive and Gram-negative bacteria and/or the prompt use of adequate anti-Gram-positive antibiotics.

RESULTS

During the 15-year period, we recorded 1,305 episodes of febrile neutropenia occurring in 826 patients. The median age of the 826 patients was 45 years (range, 6 to 83) and 59% were males. As shown in Table 1, the main underlying diseases among the 1,305 episodes of febrile neutropenia were acute myeloid leukemia (27.4%), multiple myeloma (22.8%), and non-Hodgkin's lymphoma (17.8%). The episode of febrile neutropenia occurred in the context of hematopoietic cell transplantation (HCT) in 38.6% (mostly autologous) of patients. Quinolone prophylaxis was given in 44.9% of the episodes. Upon fever, most patients received monotherapy (88.5%) with cefepime (84.0%).

TABLE 2 Comparison of the characteristics of episodes of febrile neutropenia with and without shock

Variable[a]	Shock (*n* [%])		*P* value
	Yes (*n* = 42)	No (*n* = 1,263)	
Underlying disease			
Acute myeloid leukemia	8 (19.0)	349 (27.6)	0.22
Multiple myeloma	9 (21.4)	289 (22.9)	0.82
Non-Hodgkin's lymphoma	9 (21.4)	223 (17.7)	0.53
Acute lymphoid leukemia	6 (14.3)	171 (13.5)	0.89
Hodgkin's lymphoma	7 (16.7)	131 (10.4)	0.19
Autologous HCT	9 (21.4)	404 (32.0)	0.15
Allogeneic HCT	2 (4.8)	88 (7.0)	1.00
Quinolone prophylaxis	18 (42.9)	568 (45.0)	0.79
Fluconazole prophylaxis	10 (23.8)	390 (30.9)	0.33
Positive blood culture	27 (64.3)	337 (26.7)	<0.001
Gram negative	20 (46.7)	178 (14.1)	<0.001
Escherichia coli	12 (28.6)	64 (5.1)	<0.001
Klebsiella pneumoniae	2 (4.8)	34 (2.7)	0.32
Pseudomonas aeruginosa	1 (2.4)	27 (2.1)	0.60
Acinetobacter sp.	2 (4.8)	13 (1.0)	0.08
Enterobacter sp.	2 (4.8)	12 (1.0)	0.07
Gram positive	5 (11.9)	151 (12.0)	0.99
CONS	2 (4.8)	85 (6.7)	1,00
Viridans streptococci	1 (2.4)	30 (2.4)	1.00
Staphylococcus aureus	1 (2.4)	19 (1.5)	0.48
Polymicrobial	1 (2.4)	4 (0.3)	0.15
Yeast	1 (2.4)	4 (0.3)	0.15
Adequate empirical antibiotic	39 (92.9)	1151 (91.1)	1.00
Gram-negative coverage	41 (97.6)	1224 (96.9)	1.00
Gram-positive coverage	41 (97.6)	1192 (94.4)	0.73

[a]HCT, hematopoietic cell transplantation; CONS, coagulase-negative streptococci.

Blood cultures collected at the first day of fever were positive in 364 episodes (27.9%), including 198 (15.2%) for Gram-negative and 156 (12.0%) for Gram-positive bacteria. Five episodes were polymicrobial and five grew yeast. The most frequent organisms were *Escherichia coli* ($n = 76$), *Klebsiella pneumoniae* ($n = 36$), and *Pseudomonas aeruginosa* ($n = 28$) among Gram-negative bacteria and coagulase-negative staphylococci ($n = 87$), viridans streptococci ($n = 31$), and *Staphylococcus aureus* ($n = 20$) among Gram-positive bacteria. Bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) was observed in seven episodes (35% of *S. aureus* bacteremia, 1.9% of episodes with bacteremia, and 0.5% of all episodes of febrile neutropenia). Among the seven patients with bacteremia by MRSA, six did not receive vancomycin in the initial empirical antibiotic regimen; none developed shock or died by day 4 or at the end the episode of febrile neutropenia.

Shock on the first day of the febrile episode occurred in 42 episodes (3.2%). Table 2 compares the characteristics of febrile episodes with and without shock. There was a significant association between shock and positive blood culture, specifically *E. coli* bacteremia (28.6% in patients with shock versus 5.1% in patients without shock, $P < 0.001$). In addition, episodes with shock were more likely to have bacteremia due to *Acinetobacter* sp. and *Enterobacter* sp., with *P* values of 0.08 and 0.07, respectively. Of note, we did not observe any association between Gram-positive bacteremia and shock. Early death occurred in 3 of 42 patients with shock (7.1%) versus 12 in 1,263 without shock (1.0%, $P = 0.01$). By multivariate analysis (Table 3), variables associated with shock at onset of fever were bacteremia due to *E. coli* (odds ratio [OR], 8.47; 95% confidence interval [95% CI], 4.08 to 17.55; $P < 0.001$), bacteremia due to *Enterobacter* sp. (OR, 7.53; 95% CI, 1.60 to 35.33; $P = 0.01$), and bacteremia due to *Acinetobacter* sp. (OR, 6.95; 95% CI, 1.49 to 32.36; $P = 0.01$).

The mortality rate by day 30 of febrile neutropenia was 8.3%. Early death occurred

TABLE 3 Multivariate analysis of factors associated with shock and early death among 1,305 episodes of febrile neutropenia[a]

Variable	OR	95% CI	*P* value
Shock			
Bacteremia due to *Escherichia coli*	8.47	4.08–17.55	<0.001
Bacteremia due to *Enterobacter* sp.	7.53	1.60–35.33	0.01
Bacteremia due to *Acinetobacter* sp.	6.95	1.49–32.36	0.01
Early death			
Non-Hodgkin's lymphoma	3.57	1.18–10.73	0.02
Pneumonia	21.36	5.72–79.72	<0.001
Shock	11.64	2.77–48.86	0.01
Bacteremia due to *Klebsiella pneumoniae*	5.91	1.11–31.47	0.03
Adequate empirical antibiotic therapy	0.23	0.07–0.81	0.02

[a]OR, odds ratio; 95% CI, 95% confidence interval.

in 15 patients (1.1%). As shown in Table 4, early death was significantly more frequent in patients with non-Hodgkin's lymphoma (40.0% versus 17.5%, $P = 0.04$), pneumonia (26.7% versus 3.3%, $P = 0.001$), shock (20.0% versus 3.0%, $P = 0.01$), positive blood culture for Gram-negative bacteria (40.0% versus 14.9%, $P = 0.02$), and bacteremia due to *Pseudomonas aeruginosa* (13.3% versus 2.0%, $P = 0.04$). Neither skin or soft tissue

TABLE 4 Univariate analysis of factors associated with early death among 1,305 episodes of febrile neutropenia

	Death (*n* [%])		
Variable[a]	Yes (*n* = 15)	No (*n* = 1,293)	*P* value
Underlying disease			
Acute myeloid leukemia	5 (33.3)	318 (24.6)	0.43
Multiple myeloma	2 (13.3)	296 (22.9)	0.54
Non-Hodgkin's lymphoma	6 (40.0)	226 (17.5)	0.04
Acute lymphoid leukemia	2 (13.3)	175 (13.6)	0.54
Hodgkin's lymphoma	0 (0.0)	138 (10.7)	0.39
Autologous HCT	3 (20)	410 (31.8)	0.41
Allogeneic HCT	1 (6.7)	89 (6.9)	1.00
Quinolone prophylaxis	7 (46.7)	579 (44.9)	0.90
Fluconazole prophylaxis	3 (20)	397 (30.8)	0.57
Clinical manifestation of infection			
Skin or soft tissue infection	2 (13.3)	114 (8.8)	0.64
Pneumonia	4 (26.7)	42 (3.3)	0.001
Catheter-related infection	0	57 (4.4)	1.00
Abdominal	1 (6.7)	172 (13.2)	0.71
Neurologic	1 (6.7)	7 (0.5)	0.09
Shock	3 (20.0)	39 (3.0)	0.01
Positive blood culture	8 (53.3)	356 (27.6)	0.04
Gram negative	6 (40.0)	192 (14.9)	0.02
Escherichia coli	1 (6.7)	75 (5.8)	0.59
Klebsiella pneumoniae	2 (13.3)	34 (2.6)	0.06
Pseudomonas aeruginosa	2 (13.3)	26 (2.0)	0.04
Acinetobacter sp.	1 (6.7)	14 (1.1)	0.16
Enterobacter sp.	0	14 (1.1)	1.00
Gram positive	1 (6.7)	155 (12.0)	1.00
CONS	1 (6.7)	86 (6.7)	1.00
Viridans streptococci	0	31 (2.4)	1.00
Staphylococcus aureus	0	20 (1.6)	1.00
Polymicrobial	0	5 (0.4)	1.00
Yeast	1 (6.7)	4 (0.3)	0.06
Adequate empirical antibiotic	11 (73.3)	1,179 (91.4)	0.03
Gram negative	13 (86.7)	1,252 (97.1)	0.07
Gram positive	14 (93.3)	1,219 (94.5)	0.57

[a]HCT, hematopoietic cell transplantation; CONS, coagulase-negative streptococci.

infection nor bacteremia due to Gram-positive organisms was associated with early death. Patients receiving adequate empirical antibiotic therapy (especially for Gram-negative coverage) were less likely to die within 3 days from the onset of fever ($P = 0.03$). These variables plus neurologic symptoms ($P = 0.09$), bacteremia due to *Klebsiella pneumoniae* ($P = 0.06$), and fungemia ($P = 0.06$) were entered in the multivariate analysis. Predictors of early death by multivariate analysis (Table 3) were non-Hodgkin's lymphoma (OR, 3.57; 95% CI, 1.18 to 10.73; $P = 0.02$), pneumonia (OR, 21.36; 95% CI, 5.72 to 79.72; $P < 0.001$), shock (OR, 11.64; 95% CI, 2.77 to 48.86; $P = 0.01$), and bacteremia due to *Klebsiella pneumoniae* (OR, 5.91; 95% CI, 1.11 to 31.47; $P = 0.03$). Adequate empirical antibiotic therapy was protective (OR, 0.23; 95% CI, 0.07 to 0.81; $P = 0.02$).

We did the same analysis excluding the 87 episodes of febrile neutropenia with bacteremia due to coagulase-negative staphylococci. Univariate and multivariate analyses of factors associated with shock and early death did not change at all. The rate of shock among episodes with or without Gram-positive bacteremia was 7.5% and 5.6%, respectively ($P = 0.49$), and none of the 69 episodes of febrile neutropenia with Gram-positive bacteremia resulted in early death.

DISCUSSION

Our study yielded the following important findings: (1) shock and early death have low incidence in febrile neutropenic patients; (2) early death was more frequent in patients presenting with shock at the onset of febrile neutropenia; (3) bacteremia due to Gram-negative organisms was associated in shock and early death; (4) adequate empirical coverage (especially against Gram-negative bacteria) was associated with a lower chance of early death; and (5) we did not find any association between shock or early death and bacteremia due to Gram-positive organisms, catheter-related infection, skin or soft tissue infection, or inadequate Gram-positive coverage. The results did not change after excluding episodes with bacteremia due to coagulase-negative staphylococci.

While the routine use of vancomycin at first fever in neutropenic patients is not supported by randomized trials (17, 18), meta-analyses (10, 19), and guideline recommendations (12, 20), its use in certain circumstances, such as hemodynamic instability or skin, soft tissue, or catheter-related infection, is recommended by guidelines despite the absence of clinical data (12, 13, 20). Despite these recommendations, we have been very restrictive with the empirical use of vancomycin. Indeed, empirical vancomycin at the onset of fever was given in only 4.1% of episodes.

In the present study, we evaluated 1,305 episodes of febrile neutropenia occurring in a 15-year period at a single center and analyzed early death, the outcome that is intended to be prevented with empirical antibiotic therapy. None of the clinical circumstances in which the guidelines recommend the empirical use of vancomycin at first fever was associated with early death, even by univariate analysis, with the exception of shock. We then analyzed predictors of shock because if this outcome was associated with infection by Gram-positive bacteria, the empirical use of vancomycin would be justifiable in this situation. However, neither infection by Gram-positive bacteria nor catheter-related, skin, or soft tissue infection was associated with shock. Instead, Gram-negative bacterial infection was the main factor associated with both shock and early death.

In our study, shock was observed in 3.2% of the 1,305 episodes of febrile neutropenia. This incidence is similar to that reported in two studies, namely, 3.4% among 87 patients with acute myeloid leukemia or undergoing autologous HCT (21) and 3.8% among 576 febrile neutropenic adult patients with cancer (~60% with hematologic malignancies) (22). In contrast, three studies reported higher incidence, including 5.5% among 307 episodes of febrile neutropenia in 169 patients with cancer (83.5% with hematologic malignancies) (23), 12% among 414 episodes of febrile neutropenia in 264 children (24), and 13.4% among 164 febrile neutropenic patients with hematologic malignancies (25).

Factors associated with shock at the onset of fever in neutropenic patients were evaluated in two studies. Older age, progressive underlying disease, longer duration of fever before admission, and microbiologic documentation of infection were associated with shock by univariate analysis in one study (22), and polymicrobial bacteremia was the only risk factor by multivariate analysis in the other study (23). In our study, Gram-negative bacteremia caused by *Escherichia coli*, *Enterobacter* sp., or *Acinetobacter* sp. was associated with shock. Recently, infection by multidrug-resistant (MDR) Gram-negative bacteria has been described as a risk factor for shock (26). We did not find this association probably because the incidence of MDR Gram-negative bacteria in our unit is low (data not shown). Furthermore, inadequate empirical antibiotic coverage was not associated with shock, suggesting that infection by MDR Gram-negative bacteria was not a major driver for the association between Gram-negative bacteremia and shock.

In the present study, pneumonia was associated with early death by multivariate analysis. Pneumonia occurring at first fever in neutropenic patients is usually caused by bacteria (27). Gram-negative organisms (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*) are the leading agents recovered in blood cultures of neutropenic patients presenting with pneumonia (28, 29). A retrospective study evaluating pneumonia at any time during treatment of 801 patients with acute leukemia reported 79 cases with microbiologic documentation. *Staphylococcus aureus* was recovered in 11 cases, of which 6 were MRSA (30). The empirical use of vancomycin in neutropenic patients presenting with pneumonia should be considered depending on the local epidemiology and the characteristics of patients. The results of a baseline nasal swab may help to decide since a negative screening for MRSA has a high negative predictive value ($>$95%) for MRSA pneumonia (31).

Another variable associated with early death was non-Hodgkin's lymphoma. While we do not have a solid explanation for this observation, we must acknowledge that chemotherapeutic regimens given for the first-line treatment of non-Hodgkin's lymphomas are not associated with significant neutropenia and do not result in febrile neutropenia. Patients with non-Hodgkin's lymphoma who died within the first 3 days of febrile neutropenia were in relapse and had poor performance status (data not shown).

The management of febrile neutropenia has been challenged recently by the emergence of MDR Gram-negative bacteremia, with mortality rates as high as 71% (32). Most of the high mortality rate is attributed to inadequate empirical antibiotic coverage at the onset of fever. Our study provides data suggesting that this is not the case with Gram-positive bacteria; although our six patients with bacteremia caused by MRSA did not receive vancomycin at the onset of fever, none developed shock or died. Furthermore, inadequate Gram-positive coverage was not associated with early death.

Our study shares the limitations of retrospective studies. In addition, we did not analyze time from first fever to start of antibiotics, a variable that is associated with death in febrile neutropenia (33). Even considering that our institution follows strict recommendations for starting empirical antibiotic as soon as possible, we could not evaluate the effect of this important variable as a risk factor for early death. In addition, due to the retrospective nature of the study, we restricted the definition for shock and did not include other sepsis syndromes. Despite these limitations, our findings have important implications. Considering that neither shock nor early death was associated with skin, soft tissue, catheter-related, or other Gram-positive infections, clinicians could wait for a documentation of methicillin-resistant infection before starting vancomycin in febrile neutropenic patients, especially if the incidence of MRSA is low in the unit/hospital. On the other hand, given the strong association between Gram-negative bacterial infection and shock and early death, careful attention to local trends in Gram-negative resistance should be given in order to maximize Gram-negative coverage at first fever in neutropenic patients, especially with the emergence of MDR Gram-negative infection.

In conclusion, early death is a rare event in febrile neutropenia in a scenario of appropriate empirical Gram-negative coverage and is associated mostly with Gram-negative infection. None of the clinical circumstances in which the guidelines recom-

mend the empirical use of vancomycin at first fever was associated with early death. These data challenge the guideline recommendations for the empirical use of vancomycin at first fever in neutropenic patients.

MATERIALS AND METHODS

This is a retrospective study conducted at Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Brazil, a tertiary care hospital with ~400 beds, including a hematology unit with 16 beds (8 with high-efficiency particulate air filter). The study was approved by the institution's ethical committee (study 077-16).

In order to evaluate the frequency and epidemiology of shock and early death in febrile neutropenic patients, we reviewed all consecutive episodes of febrile neutropenia occurring in a 15-year period (2003 to 2017) in patients with hematologic malignancies receiving chemotherapy or undergoing hematopoietic cell transplantation (HCT). All data had been collected prospectively, using a standardized case report form, with the help of a dictionary of terms containing all definitions of the variables collected.

The standards of care of neutropenic patients did not differ substantially over the 15-year period, except for the use of quinolone prophylaxis, no prophylaxis until 2006, and ciprofloxacin to patients with expected duration of neutropenia for >7 days from 2007 on. At the onset of fever, blood cultures were obtained and the patients were immediately started on intravenous cefepime, unless a previous episode of febrile neutropenia documented a cefepime-resistant Gram-negative organism. In this case, an appropriate antibiotic (usually carbapenem) was started. Regarding the empirical use of vancomycin, we have been very restrictive since the frequency of infection by MRSA and of penicillin-resistant viridans streptococci is low in our institution.

We analyzed demographics (age and gender), underlying disease, type of HCT, presence of a central venous catheter, antibiotic and antifungal prophylaxis, clinical manifestations and microbiologic documentation of infection at the onset of fever, adequate empirical antibiotic therapy, shock occurring at onset of the episode of febrile neutropenia, and early death.

Neutropenia was defined as an absolute neutrophil count of <500/mm^3, and fever was defined as an axillary temperature of >38°C. Shock was defined as hypotension despite adequate fluid resuscitation, requiring vasoactive drugs (34). Early death was defined as death within 3 days from the onset of fever. Polymicrobial bacteremia was defined if more than one pathogen was isolated from one or more blood cultures taken at the onset of fever. Catheter-related infection was defined in the presence of signs of infection at the exit site, tunnel, or port or in case of fever and rigors after manipulation of the catheter. The empirical antibiotic regimen was considered inadequate in all episodes with bacteremia in which the organism was resistant to the antibiotic regimen given. In all other episodes (including those without microbiologic documentation), the antibiotic regimen was considered adequate. The febrile episodes were classified as fever of unknown origin, bacteremia, microbiologically documented infection without bacteremia, or clinically documented infection, as previously defined (35).

In order to evaluate predictors of shock and early death, we compared the characteristics of patients with and without these features. Categorical variables were compared using the chi-square or Fisher exact tests as appropriate, and continuous variables were compared using the Mann-Whitney U test. Variables with P values of <0.10 by univariate analysis were entered in a multivariate logistic regression analysis. P values of <0.05 were considered statistically significant. All analyses were performed using SPSS 21.0 for Windows (IBM, Inc.).

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