Sepsis Syndrome and Associated Sequelae in Patients at High Risk for Gram-Negative Sepsis

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We conducted a prospective surveillance study of 80 hospitals across the United States to determine the incidence of sepsis syndrome and its associated sequelae in hospitalized patients over age 18 years who were administered antibiotics for suspected or documented gram-negative infection. A sample of 1754 hospitalized patients were followed from onset of antimicrobial therapy to discharge or death. Mortality rates (MR) varied depending on the suspected source of sepsis syndrome. For patients in whom the syndrome was associated with community-acquired urinary tract infections, mortality was 20% (relative risk [RR] = 0.51, $p<0.05$), for those with trauma 20.6% (RR = 0.51, $p<0.05$), and patients with nosocomial respiratory tract infections 57.1% (RR = 1.66, $p<0.05$). More than two complications occurred in 65.2% of patients under age 60 years (MR 31%), 40.8% of those age 60–80 (MR 42%), and 35.6% of patients older than 80 years (MR 33.3%, $p>0.05$). Various patient populations had significant differences in both the incidence of the syndrome and its complications, and consequent mortality. Perhaps morbidity as well as mortality should be used as outcomes when testing the efficacy of innovative therapies for sepsis.

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In the United States it is estimated that 100,000–300,000 hospitalized patients develop septicemia each year, with an associated mortality rate of 20–50%.[1, 2] Sepsis is currently the most common cause of death in the intensive care unit.[3, 4] As the use of advanced life support systems increases, and the population ages and becomes more severely ill, we are faced with an ever growing number of individuals at risk for this devastating syndrome.

It is well recognized that the incidence of sepsis and its associated sequelae vary among patient populations. Those reported to be at high risk for sepsis include the elderly, and critically ill and/or immunosuppressed patients,[1, 3, 4–6] but comparative information in other high-risk populations is lacking. Identifying such patients is an important first step to enhancing our understanding of the evolution of this complex disease process. This information will assist in pinpointing population-specific risk factors for complications and mortality, allow refining of treatment algorithms,

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and aid in developing cost-effective strategies to lessen the financial burden of new therapies on the health care system.

Methods

Our overall goal was to develop a descriptive data base of the natural history of sepsis and complications resulting from suspected or documented gram-negative infections in selected high-risk patient populations.

Subjects and Design

This study was performed using the nationwide Drug Surveillance Network[7] of clinical pharmacists organized to conduct surveillance studies of hospitalized patients. Data were collected at 80 hospitals across the United States and Canada, 65% of which were affiliated with a medical school. The hospitals ranged in size from 48–941 beds [mean (SD) 391 (213) beds]. The mean (SD) bed size for medical school-affiliated hospitals was 480 (204), and for nonmedical school-affiliated hospitals 249 (149).

To identify patients with a high incidence of gram-negative sepsis, certain populations were targeted. Specifically, patients were enrolled in the study if antibiotic therapy was initiated for suspected or documented gram-negative infection and they had at least one of the following presumed sources of infection: documented intraabdominal infection (abscess, gangrenous or necrotic organs, peritonitis); suspected or documented gram-negative or mixed skin flora infections and systemic signs of infection such as fever (temperature > 38.3°C) and elevated white blood cell count (> 10,500/mm^3); cancer with an absolute neutrophil count less than 1000 cells/mm^3 and temperature above 38.3°C; multiple trauma expected to require intensive care unit (ICU) treatment for longer than 3 days; documented gram-negative bacteremia with or without an identifiable source; suspected or documented gram-negative urinary tract infection acquired in the community, hospital, or nursing home, and 65 years of age or greater; or suspected or documented gram-negative respiratory tract infection acquired in the hospital or nursing home, and 65 years of age or greater. Based on these inclusion criteria, patients were classified into the following populations: urinary tract infection acquired in the community, nursing home, or hospital; respiratory tract infection acquired in a nursing home or hospital; intraabdominal infection; skin infection; multiple trauma; febrile neutropenic cancer; and documented gram-negative bacteremia with or without an identifiable source of infection and mutually exclusive of other patient populations.

Patients were excluded from participation if they were less than 18 years of age or had one of the following: fungal, viral, or gram-positive infection as documented by culture without evidence of concurrent gram-negative infection; suspected or documented gram-positive skin infection, including cellulitis, wound infection, and fasciitis; organ transplantation during the current hospitalization; presence of human immunodeficiency virus; obstetric-gynecologic infection; or experimental therapy with antiendotoxin monoclonal antibodies. Patients with only one of the following were also excluded: uncomplicated diagnosis of cholecystitis, acute appendicitis, pancreatitis, or acute perforated peptic ulcer; diverticulitis without abscess or peritonitis; peritonitis associated with peritoneal dialysis; intravenous or intraarterial catheter-related infection; uncomplicated diagnosis of upper respiratory tract infection; or prostatitis. These exclusion criteria were developed as guidelines for patient selection, thus decreasing the variability of diagnostic criteria by the investigator. Patients classified as "do not resuscitate" at study entry were excluded.

To minimize sampling bias, two sampling strategies were used. In the first strategy, clinical pharmacists identified all patients in the hospital who met particular inclusion criteria (e.g., all febrile neutropenic patients with cancer, all those with multiple trauma) and enrolled them consecutively. In the alternative strategy, subjects were enrolled using the entire hospital patient population as a basis for recruitment. Because the latter would likely result in a large number of simultaneously eligible patients, each site selected one or more days per week for routine screening. On the preselected day(s), all eligible patients (e.g., those started on antibiotics for suspected gram-negative infection) were identified. The maximum number of patients to be enrolled on a screening day was determined before the start of data collection. To ensure that patients were systematically enrolled, the order of their entry was based on the last four digits of the hospital identification number in ascending order until the maximum number was achieved.

All data were recorded on a form specifically designed for the study. The form recorded patient demographics and comorbidities; antibiotic regimens; vital signs, hemodynamic monitoring,

Table 1. Definitions of Events

Event	Definition	
Sepsis syndrome	Temperature ≥ 38.3°C or ≤ 35.6°C, tachycardia ≥ 90 bpm, tachypnea ≥ 20 bpm, evidence of decreased organ perfusion as measured by one of the following: changes in mental status, PaO_2/FIO_2 < 280, elevated plasma lactate level, urinary output < 0.5 ml/kg[8]	
Complication	Definition	Resolution
Refractory shock	Systolic BP < 90 mm Hg or (in a hypertensive patient) ≥ 40-mm Hg decrease, neither responsive to i.v. fluids or vasopressors.	Systolic BP > 90 mm Hg or (in a hypertensive patient) ≥ 40-mm Hg increase, both without vasopressor support.
Adult respiratory distress syndrome	PaO_2/FIO_2 < 175 bilateral pulmonary infiltrates on chest film, and/or PCWP < 18 mm Hg.[8]	Clearing of bilateral lung infiltrates and PaO_2/FIO_2 > 175.
Acute renal failure	Serum creatinine increases to ≥ 176 µmol/L.	Serum creatinine returned to < 176 µmol/L or baseline in patients with preexisting renal insufficiency.
Acute renal failure without baseline data	Serum creatinine greater than normal (> 132 µmol/L) and BUN greater than normal (> 78.9 umol/L) with both rising for several days, or patients with new onset of dialysis.	Serum creatinine returned to < 132 µmol/L.
Disseminated intravascular coagulation	Elevated fibrin degradation products (FDP) titer > 1:40 or D-Dimers > 2.0 in conjunction with decrease > 25% of baseline in platelet count and either an elevated PT or PTT, or clinical evidence of bleeding.[8]	D-Dimers < 2.0, FDP < 1:40, PT or PTT returned to normal, and platelets increased by 25% over nadir and returned to normal.
Coagulopathy	Decrease > 25% of baseline in platelet count and either an elevated PT or PTT, or clinical evidence of bleeding.	PT or PTT returned to normal, and platelets increased by 25% over nadir and returned to normal.
Hepatobiliary dysfunction	Bilirubin > 34 µmol/L; alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, or alanine aminotransferase exceeded twice the upper limit of normal.[8]	Bilirubin < 34 µmol/L, and confirming enzyme abnormality resolved.
Central nervous system dysfunction	Glasgow Coma Scale < 15 or 1 point lower than a baseline GCS, physician judgment of change in mental status.	GCS returned to 15 or baseline.

PaO_2 = partial pressure of oxygen; FIO_2 = fractional concentration of inspired oxygen; PCWP = pulmonary capillary wedge pressure; BUN = blood urea nitrogen; PT = prothrombin time; PTT = partial thromboplastin time.
At the time this study was initiated the new definitions proposed by ACCP-SCCM were not published.

ventilation status, serum chemistries, hematology, blood transfusions, blood gases; microbiology with results of cultures and susceptibilities; concomitant drugs including vasopressors and fluids; and patient status at discharge. This information was recorded on a daily basis. In addition, the following information was obtained to document inadequate organ function or perfusion: alteration in mental status as measured by Glasgow Coma Score or clinician evaluation; hypoxemia with a partial pressure of oxygen (PaO_2) below 75 torr breathing room air in the absence of severe lung disease; increased plasma lactate concentration (> 2 mmol/L or above the upper limits for the laboratory); and oliguria (urine output < 30 ml/hr).

Renal failure, adult respiratory distress syndrome, disseminated intravascular coagulation, liver dysfunction, and central nervous system dysfunction were specifically targeted as potential complications associated with sepsis, and are reported as such. Refractory shock was not reported as a complication, but as a separate entity. Specific information was collected regarding the date of onset, severity, treatment modalities, duration, and outcome for each complication.

Clinical pharmacists evaluated each patient on a daily basis and made an assessment as to whether or not the patient had sepsis syndrome and its associated complications based on the clinical impressions of the medical team and objective clinical data. To minimize bias, the clinical pharmacists were provided standard definitions for sepsis and its complications (Table 1). When we started this protocol, sepsis syndrome was the definition in current use. However, enough data were collected to look at new definitions.[9]

On receipt at the research center, case report forms were reviewed for completeness and consistency. When necessary, participants were contacted to provide missing information or to clarify data entries or omissions. A toll-free telephone number was maintained to facilitate communication and resolve study questions. A 10% random sample of each institution's patient discharge summaries was collected and compared with the case report forms for quality assurance purposes. All patients were monitored from the time of initiation of antimicrobial therapy for the infectious episode until discharge or death, or for a minimum of 14 days.

All laboratory studies, patient care procedures, diagnostic procedures, and drug therapy decisions were performed according to the usual clinical practice at the participating institutions. On identification of an eligible patient, only information available in the medical record was collected, and no changes in patient care were required for the purposes of this survey. The only risk to patients was a breach of confidentiality, and safeguards were implemented to protect their identity. Clinical pharmacists were required to follow federal and institutional guidelines that govern participation in observational research.

Statistical Analysis

The primary end points for this analysis were the development of signs and symptoms of sepsis syndrome, development of refractory shock, specific complications including adult respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation, hepatobiliary dysfunction, central nervous system dysfunction, and mortality.

A data base was created using a dBase III plus (Borland International Inc., Scotts Valley, CA) application and was analyzed using the SAS (SAS Institute Inc., Cary, NC) statistical package. Double entry of data was performed to ensure accuracy. The incidences of sepsis syndrome, refractory shock, and complications were determined for the overall patient population and within each subpopulation. An interim analysis showed a high recruitment of patients with community-acquired urinary tract infections and skin infections, and a low incidence of sepsis syndrome; hence recruitment into these populations was terminated early. Therefore, the relative proportion of patients within each patient population should be interpreted cautiously.

Summary statistics of demographics were reported for all patients. χ^2 tests were used to determine differences in the incidence of end points among patient populations. The following demographics were compared between patients within a population with those of all other patients using the χ^2 test: gender, surgery during study enrollment, outpatient antibiotic use, source of infection, and type of organism. Student's *t* test was employed to compare the subpopulation with all other patients with regard to age, time from admission to sepsis, hospital duration, ICU stay, and number of comorbidities. Relative risk (RR) of mortality was calculated as the incidence rate among those patients in a specific population divided by the incidence rate in all other patient populations. Statistical significance was defined as p below 0.05.

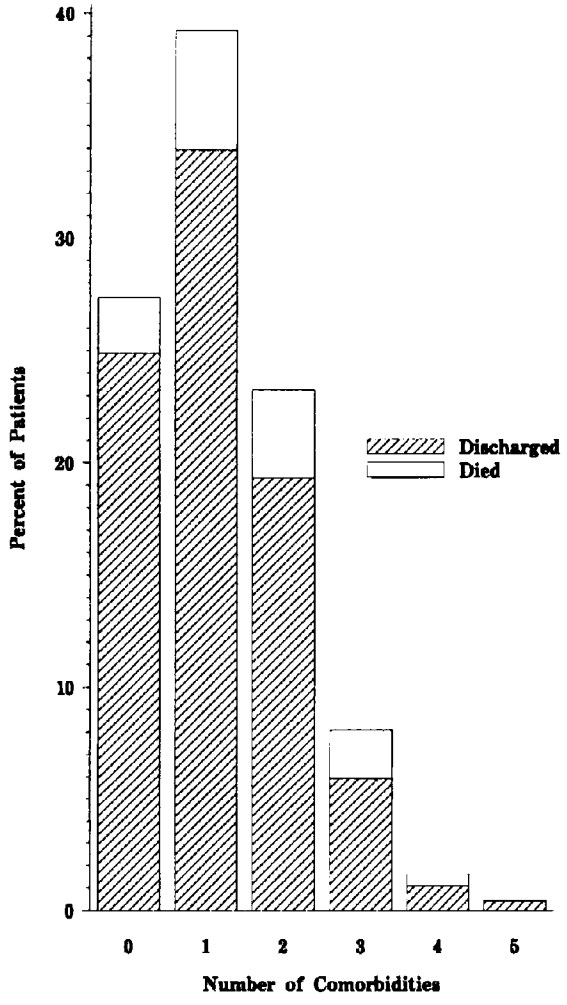

Figure 1. Number of comorbidities stratified by mortality. For all 1754 patients comorbidities included chronic obstructive pulmonary disease, congestive heart failure, stroke or cerebral hemorrhage, diabetes mellitus, hepatic disease, malignancy, renal disease, major burn, and history of alcoholism.

Table 2. Incidence of Complications

	All Patients (n = 1754) No. (%)	Patients With Sepsis Syndrome		
		All Patients (n = 457) No. (%)	With Refractory Shock (n = 216) No. (%)	Mortality No. (%)[a]
Refractory shock		216 (47.3)		116 (53.7)
Adult respiratory distress syndrome	85 (4.8)	82 (17.9)	57 (26.4)	39 (47.6)
Acute renal failure	75 (4.3)	65 (14.2)	47 (21.8)	39 (60.0)
Acute renal failure without baseline data	48 (2.7)	44 (9.6)	36 (16.7)	31 (70.5)
Disseminated intravascular coagulopathy	37 (2.1)	35 (7.7)	30 (13.9)	27 (77.1)
Coagulopathy	51 (2.9)	49 (10.7)	38 (17.6)	25 (51.0)
Hepatobiliary dysfunction	79 (4.5)	75 (16.4)	53 (24.5)	36 (48.0)
Central nervous system dysfunction	151 (8.6)	146 (31.9)	95 (44.0)	81 (55.5)

[a]Denominator = number of patients with sepsis syndrome in that complication category.

Results

Overall Patient Population

A total of 1754 patients were enrolled, of whom 889 (50.7%) were men. The mean (SD) age was 67 (18.4) years (range 18–110 yrs). The majority of patients (1188, 67.7%) were admitted from the community, 427 (24.3%) from a nursing home or long-term care facility, and 136 (7.8%) from another hospital. On admission, 12.8% of patients were admitted directly to an ICU, and another 26.9% were admitted to the ICU at some time later in their hospitalization. Of the 1754 patients, 74% were admitted to a medical service, 25% to a surgical service, and 1% unknown. Figure 1 shows comorbidities of all patients and their relationship to discharge or death. The patients who died had a mean (SD) of 1.5 (0.99) comorbidities, and those who were discharged had 1.1 (1.07) comorbidities, which was statistically significant ($p<0.0001$).

Overall, 389 (22.2%) had gram-negative bacteremia; 457 (26.1%) had sepsis syndrome, 216 (47.3%) of whom developed refractory shock. The mortality rates were 14.5%, 37.6%, and 53.7% for all patients, those with sepsis syndrome, and patients with refractory shock, respectively. The relative risk of death in patients with sepsis syndrome compared with patients without the syndrome was 5.97 ($p<0.0001$). The relative risk of death in patients with sepsis syndrome and refractory shock compared with patients with sepsis syndrome and no refractory shock was 2.3 ($p<0.0001$).

The incidence of complications was significantly greater in patients with sepsis syndrome who had refractory shock than in those without shock ($p<0.001$; Table 2). It ranged from a low of 7.7% for disseminated intravascular coagulation to a high of 31.9% for central nervous system dysfunction. Mortality was highest for patients with disseminated intravascular coagulation (77.1%). Of the 457 patients with sepsis syndrome, no complications developed in 37.4%, one complication in 34.1%, two in 16.2%, three in 8.7%, four in 1.8%, and five in 1.8%; their respective mortality rates were 15.8%, 43.0%, 55.4%, 65.0%, 50.0%, and 87.5%.

Sepsis syndrome developed in 120 (26.3%) of patients less than 60 years of age, 250 (54.7%) of those age 60–80 years, and 87 (19.0%) of patients older than 80 years. For these three age groups, 93.3%, 74.8%, and 52.9% were in the ICU ($p<0.001$). Patients with sepsis syndrome and less than 60 years of age were more likely to be in the ICU for more than 9 days than those in the other age groups, 53.6%, 33.7%, 21.7%, respectively, ($p<0.001$). Two or more complications occurred in 62.5% of patients with sepsis syndrome who were less than 60 years of age, 40.8% of those 60–80 years of age, and 35.6% of those older than 80 years. Mortality rates for the patients with sepsis syndrome in the three age groups were 31.0%, 42%, and 33.3%, respectively ($p>0.05$). In patients without sepsis syndrome, the rates were 1.3%, 7.4%, 9.2%, respectively ($p<0.001$).

Of the 389 patients with gram-negative bacteremia, the suspected sources of organisms were the urinary tract 41.4%, unknown 17.5%, intraabdominal 15.4%, several possible sources 10.8%, respiratory tract 10.0%, skin 2.8%, intravascular catheter 1.8%, and other sources 0.6%. The suspected sources of gram-negative bacteremia for the subset of 164 patients with sepsis syndrome were the urinary tract 37.6%, several possible sources 16.7%, intraabdominal 15.4%, respiratory tract 13.6%, unknown 13%,

intravascular catheter 1.9%, skin 1.2%, and other sources 0.6%. Patients with a lower respiratory tract infection and those with several possible sources of bacteremia were significantly more likely to develop sepsis syndrome than those with other sources. In contrast, patients who had a skin or an unknown source of bacteremia were significantly less likely to develop sepsis ($p<0.05$).

The specific gram-negative organisms cultured from blood were not significantly different in patients with and without sepsis syndrome ($p>0.05$; Figure 2). Patients with *Enterobacter* sp (*E. cloacae*, *E. aerogenes*, *E. agglomerans*) isolated from their blood had a high mortality rate (34.5%, RR = 2.00, $p<0.01$) as did those with *Pseudomonas* sp (*P. aeruginosa*, *P. cepacia*; 34.8%, RR = 2.13, $p<0.01$) compared with patients with other isolates. In contrast, patients with *Escherichia coli* had a mortality rate of 9.7% (RR = 0.40, $p<0.01$), which was significantly lower than that in patients with other gram-negative isolates. In the subset of patients with sepsis syndrome, with the exception of those with *E. coli*, who had a lower risk of death, the bacterial isolate did not influence mortality.

Table 3 shows the 10 most common isolates and their sources. *Staphylococcus* sp were isolated from 10.6% of blood cultures (MR 23.5%), *Staphylococcus aureus* from 3.6% (MR 30.7%), and *Candida albicans* from 0.6% (MR 66.7%). Overall, 20% of patients had no positive cultures (MR 9.1 %), 34% had one positive culture (MR 10.9%), 20.4% had two positive cultures (MR 15.7%), 11.5% had three positive cultures (MR 21.9%), 6.7% had four positive cultures (MR 16.1%), 4.7% had five positive cultures (MR 31.3%), 1.8% had six positive cultures (MR 19.4%), and 1% had seven or more positive cultures (MR 35.3%).

The mean (SD) duration of hospital stay for all patients was 18 (17.8) days. Mean (SD) overall antibiotic duration was 14.3 (11.2) days. As required for study enrollment, all patients received antibiotics; however, the agents administered varied greatly. Overall, patients received a total of 605 different combinations of antibiotic classes during the course of this study. The most commonly prescribed regimens for patients with sepsis syndrome were third-generation cephalosporins, penicillins, aminoglycosides plus a third-generation cephalosporin, aminoglycoside plus a penicillin, and imipenem. Specific evaluation of individual regimens and their impact on outcome will be the subjects of future reports.

Subset Analysis

Patient populations varied widely in a number of

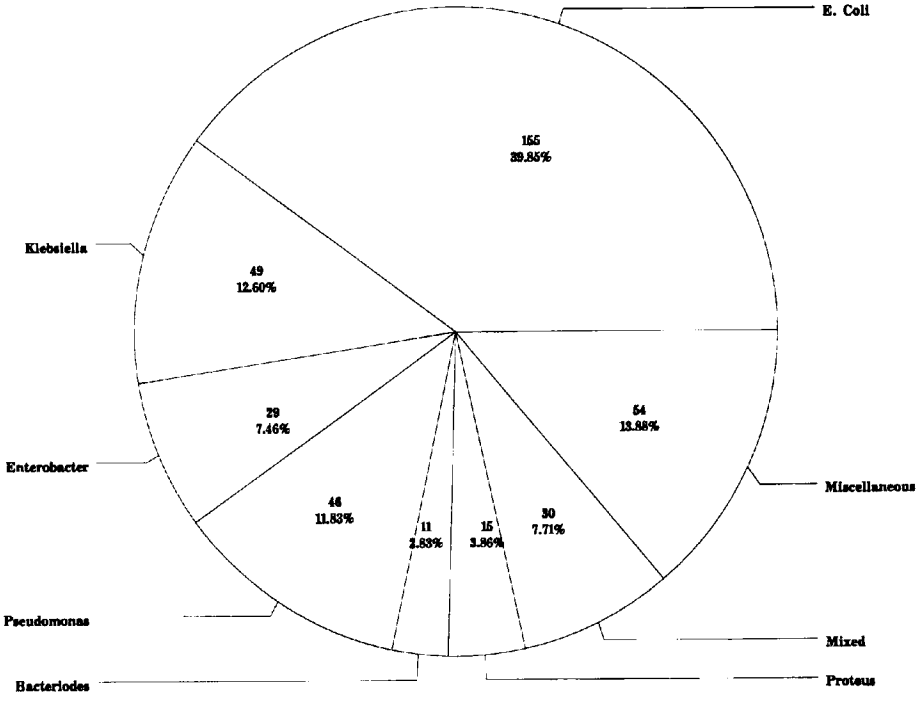

Figure 2. Frequency of gram-negative blood isolates (n=389). Miscellaneous = a gram-negative blood isolate not listed above; mixed = more than one gram-negative organism isolated.

Table 3. Organisms Stratified by Site of Culture

Organism	Blood No. (%)	Urine No. (%)	Sputum No. (%)	Wound No. (%)	Other No. (%)	All No. (%)
Escherichia coli	185 (17.1)	257 (25.2)	26 (5.3)	15 (19.7)	130 (21.0)	613 (34.9)
Pseudomonas aeruginosa	54 (5.0)	87 (8.5)	112 (22.9)	14 (18.4)	100 (16.1)	367 (20.9)
Staphylococcus sp	115 (10.6)	28 (2.7)	38 (7.8)	14 (18.4)	98 (15.8)	293 (16.7)
Enterococcus sp	25 (2.3)	105 (10.3)	31 (6.3)	11 (14.5)	79 (12.7)	252 (14.4)
Klebsiella pneumoniae	67 (6.2)	74 (7.3)	45 (9.2)	5 (6.6)	56 (9.0)	248 (14.1)
Staphylococcus aureus	39 (3.6)	8 (0.8)	72 (14.7)	13 (17.1)	82 (13.2)	214 (12.2)
Enterobacter cloacae	24 (2.2)	20 (2.0)	42 (8.6)	3 (3.9)	83 (13.4)	172 (9.8)
Gram-negative sp	38 (3.5)	33 (3.2)	33 (6.7)	3 (3.9)	33 (5.3)	140 (8.0)
Proteus mirabilis	22 (2.0)	56 (5.5)	13 (2.7)	10 (13.2)	25 (4.0)	127 (7.2)
Candida albicans	6 (0.6)	40 (3.9)	27 (5.5)	3 (3.9)	27 (4.4)	104 (5.9)

Denominators for percentages are total number of patients with a culture for that site: blood = 1081, urine = 1020, sputum = 490, wound = 76, other = 620, all = 1754.

demographic variables (Table 4). Most patients (74%) were admitted to the medical service, except for trauma patients who were all admitted to the surgical service. Sixty percent of patients with intraabdominal infection were also admitted to the surgical service. The mean (SD) age of patients, excluding the populations restricted to ages greater than 65 (community-acquired urinary tract infection, nursing home-acquired urinary tract and respiratory tract infections, nosocomial urinary tract and respiratory tract infections), was 54.8 (18.8) years. In this group, 53.3% were women, whereas of all patients less than 50 years of age, 58.2% were men. Also, the time to onset of sepsis was significantly different in the patient populations. Of the 152 patients admitted to the hospital with sepsis already, 48% had nursing home-acquired infections. Patients with community-acquired urinary tract infections had the shortest antibiotic treatment and hospital stay, and were most likely to be discharged taking antibiotics, 47% versus 26.4% of all other populations ($p<0.001$). Other significant events that have been reported to affect a patient's risk of sepsis, as well as mortality, are ICU stay and performance of surgical procedures.

Patients spending the most time [mean (SD) days] in the ICU before the development of sepsis syndrome were those with trauma [11.0 (9.1) days] and those with nosocomial respiratory tract infections [10.5 (9.4) days], significantly longer than for the other subsets ($p<0.01$). Those undergoing the most surgical procedures before the development of sepsis syndrome were patients with trauma (82.5%, RR = 2.59, $p<0.001$), intraabdominal infections (73.1%, RR = 2.35, $p<0.001$), skin infections (53.1%, RR = 1.51, $p<0.001$), and nosocomial respiratory tract infections (52.1%, RR = 1.5, $p<0.001$).

Table 5 gives the incidence of sepsis syndrome, bacteremia, refractory shock, and complications (excluding refractory shock) in each patient population. The incidence of gram-negative bacteremia ranged from a low of 2.5% in patients with a nursing home-acquired respiratory tract infection to a high of 27.3% in those with a community-acquired urinary tract infection. The incidence of sepsis ranged from a low of 13.2% in patients with community-acquired urinary tract infections to a high of 39.4% in those with trauma and 40.6% in patients with gram-negative bacteremia mutually exclusive of other patient populations.

The gram-negative isolates cultured from blood varied somewhat among the populations. *Escherichia coli* was the most frequently isolated in patients with community-acquired urinary tract infections (62.9%), nursing home-acquired urinary tract infections (57.5%), nursing home-acquired respiratory tract infections (50.0%), intraabdominal infections (36.6%), and gram-negative bacteremia (41.2%). *Pseudomonas* sp were isolated most frequently in patients with nosocomial respiratory tract infections (38.5%) and febrile patients with cancer (29.0%). Trauma patients were most likely to have *Enterobacter* sp isolated (33.3%), and patients with nosocomial urinary tract infections had a combination of gram-negative isolates (25%). Skin infections were most often attributable to a single gram-negative isolate (35.7%).

The overall mortality rate ranged from 5.3% in patients with community-acquired urinary tract infections to 31.4% in patients with nosocomial respiratory tract infections. Patients with community-acquired urinary tract infections were at a reduced risk of mortality (RR = 0.33,

Table 4. Patient Demographics Stratified by High-Risk Populations

Patient Population	No. of Patients	Age (yrs) Mean (SD)	Men No. (%)	Admitted to Medical School-Affiliated Hospital Mean (SD)	Onset of Sepsis from Admission (days) Mean (SD)	Hospital Duration (days) Mean (SD)	Number of Comorbidities[a] Mean (SD)	Overall RR of Morality[b]
Neutropenic cancer	232	59.0 (16.4)[d]	115 (49.6)	171 (73.7)	10.2 (15.3)	15.7 (15.1)[d]	1.3 (0.6)	0.95
Community-acquired UTI[c]	227	76.0 (7.5)[d]	106 (46.7)	106 (46.7)[d]	1.3 (2.10)[d]	10.6 (7.6)[d]	1.3 (1.0)	0.33[d]
Nursing home-acquired UTI[c]	210	81.4 (8.5)[d]	78 (37.1)[d]	122 (58.1)	0.6 (3.0)[d]	11.8 (8.8)[d]	1.2 (1.0)	0.73
Nursing home-acquired RTI[c]	243	80.9 (8.1)[d]	103 (42.4)	158 (65.0)	1.2 (2.8)[d]	12.3 (8.9)[d]	1.4 (1.1)[d]	0.80
Nosocomial UTI[c]	134	76.5 (7.0)[d]	61 (45.5)	84 (62.7)	20.3 (17.7)[d]	28.6 (21.1)[d]	1.5 (1.1)[d]	1.68
Nosocomial RTI[c]	188	75.2 (7.2)[d]	116 (61.7)[d]	133 (71.1)	12.4 (22.8)	30.7 (30.1)[d]	1.4 (1.06)[d]	2.52[d]
Skin	128	61.5 (18.9)[d]	77 (60.6)	85 (66.4)	6.9 (10.3)	21.4 (18.8)	1.3 (1.07)	0.69
Trauma	160	40.6 (18.3)[d]	110 (68.8)	142 (88.8)[d]	6.6 (13.2)	31.6 (21.1)[d]	0.4 (0.6)[d]	0.76
Intraabdominal infection	223	59.8 (17.8)[d]	120 (53.8)	147 (65.9)	8.6 (19.8)	21.7 (23.2)	1.0 (1.1)	1.25
Gram-negative bacteremia	165	58.4 (18)[d]	78 (47.3)	106 (64.2)	9.2(13.7)	19.1 (19.5)	1.2 (1.0)	1.24
Overall	1754	67 (18.4)	889 (50.7)	1150 (65.6)	7.4 (14.6)	18 (17.9)	1.2 (1.0)	

RR = relative risk; UTI = urinary tract infection; RTI = respiratory tract infection.
[a]Comorbidities include chronic obstructive pulmonary disease, congestive heart failure, stroke or cerebral hemorrhage, diabetes mellitus, hepatic disease, malignancy, renal disease, major burn, and history of alcoholism.
[b]Overall mortality compared with the entire population.
[c]Patients were restricted to those over age 65 years.
[d]$p<0.001$, comparisons made with overall population.

$p<0.001$), whereas those with nosocomial urinary tract infections (RR = 1.68, $p=0.003$) and nosocomial respiratory tract infections (RR = 2.52, $p<0.001$) were at a significantly increased risk of mortality.

As one would expect, mortality rates generally increase as one develops sepsis, shock, and complications. The mortality rate for patients with sepsis syndrome and refractory shock ranged from a low of 33.3% in trauma patients (RR = 0.58, $p=0.016$) to a high of 73.9% in febrile patients with cancer (RR = 1.44, $p=0.004$) and 71% in those with nosocomial respiratory tract infections (RR = 1.40, $p=0.037$; Table 6). The types of complications, other than refractory shock, among patient groups was similar.

Discussion

This prospective surveillance study clearly demonstrates that the incidence of sepsis syndrome and associated morbidity and mortality varies depending on the population. The incidence of sepsis syndrome was 26.1%, as expected, somewhat lower than that reported in sepsis clinical trials.[10–12] The difference in incidence can readily be explained by differences in study design as well as the seriousness of patients' conditions. Other clinical trials conducted at large centers attempted to enroll patients who met stringent criteria that were designed to identify sepsis.[10, 11] In contrast, our study, in which 35% of hospitals were not affiliated with medical schools, was designed to monitor patients in whom antibiotics were initiated for suspected or documented gram-negative infection and who were at high risk for sepsis. Although other trials were designed to target patients who were septic, it is important to note that their incidence of sepsis was not 100%.[10–12] In one, for example, the number of patients reported with gram-negative sepsis was only 68%, suggesting that the criteria in and of themselves are not predictive of gram-negative sepsis.[10] Our prospective design allows for the calculation of incidence rates and the absolute difference in rates among groups (attributable

Table 5. Incidence of Specific Clinical Events Stratified by Risk Group (N = 1754)

Patient Population[a]	All Patients No. (%)[b]	Bacteremia No. (%)[c]	Sepsis Syndrome No. (%)[c]	Sepsis Syndrome and Bacteremia No. (%)[d]	Refractory Shock No. (%)[d]	Complication other than Refractory Shock No. (%)[d]
Neutropenic cancer	232 (13.2)	31 (13.4)	43 (18.5)[e]	15 (34.9)	23 (53.9)	30 (69.8)
Community-acquired UTI	227 (12.9)	62 (27.3)	30 (13.2)[e]	17 (56.7)	8 (26.7)[e]	16 (53.3)
Nursing home-acquired UTI	210 (12.0)	40 (19.0)	62 (29.5)	24 (38.7)	16 (25.8)[e]	27 (43.6)[e]
Nursing home-acquired RTI	243 (13.9)	6 (2.5)	57 (23.5)	5 (8.8)	20 (35.1)	26 (45.6)[e]
Nosocomial UTI	134 (7.6)	12 (9.0)	31 (23.1)	4 (12.9)	13 (41.9)	17 (54.8)
Nosocomial RTI	188 (10.7)	13 (6.9)	63 (33.5)[e]	8 (12.7)	31 (49.2)	42 (66.7)
Skin	128 (7.3)	14 (10.9)	31 (24.2)	8 (25.8)	13 (41.9)	18 (58.1)
Trauma	160 (9.1)	21 (13.1)	63 (39.4)[e]	9 (14.3)	30 (47.6)	47 (74.6)[e]
Abdominal	223 (12.7)	41 (18.4)	66 (29.6)	18 (27.3)	43 (65.2)[e]	52 (78.8)[e]
Gram-negative bacteremia	165 (9.4)		67 (40.6)[e]	67	41 (61.2)[e]	44 (65.7)
Overall	1754 (100)	389 (22.2)	457 (26.1)	164 (35.9)	216 (47.3)	286 (62.6)

[a]Risk groups are not mutually exclusive except for the gram-negative bacteremia patient population, which includes only those who did not fit criteria for other populations listed.
[b]Denominator = 1754.
[c]Denominator = total number of patients in the population.
[d]Denominator = total number of patients in the population with sepsis syndrome.
[e]$p<0.05$.

risks), as well as relative risks.[13] Thus, the results are more appropriate to use when developing treatment strategies for broadly defined patient populations.

Despite differences reported in the incidence of sepsis, the overall 28-day mortality in this study was 37.6%, and is strikingly similar to the 42% in several clinical trials.[10–12] Similarly, the published incidence of shock in patients with sepsis syndrome, 40%,[14] is close to that in our study, 47.7%. The similarity in sepsis-associated morbidity and mortality between this study and other clinical trials suggests that misclassification bias was minimal and that our numbers are representative of the outcomes due to this disease process. Mortality rates clearly change depending on the definition of sepsis. Applying the new definitions using the patients in this data base, 94% had systemic inflammatory response syndrome with a mortality rate of 15.2%, and (39.2%) had severe sepsis with a mortality rate of 28.2%.[9].

The incidence of gram-negative bacteremia in patients with sepsis syndrome in this study (35.9%) was virtually identical to that observed by others (37%)[11] and clearly demonstrates that positive blood cultures develop in a minority of patients. Of importance, 225 (57.8%) patients had positive blood cultures but did not have signs and symptoms of sepsis. Similar to previous studies, these data underscore the limitation in using the results of blood cultures as the sole criterion for sepsis syndrome. Approximately one-third of patients with the syndrome will have positive blood cultures, and over half of the patients with positive blood cultures do not have sepsis syndrome.

The incidence of sepsis syndrome and its sequelae varied widely across the different populations in this data base. Elderly patients with nosocomial respiratory tract infections had the highest risk for death, 57.1% (RR = 1.66, $p<0.05$). Other groups identified nosocomial pneumonia as the leading infectious cause of death as well as the leading cause of nosocomial-associated mortality.[15, 16] Conversely, patients with community-acquired urinary tract infections and sepsis syndrome had the lowest risk for death, 20% (RR = 0.51, $p<0.05$), confirming a recent report that patients with urinary tract infections have significantly lower mortality than those with the syndrome due to other causes.[17]

Although the mortality rate for patients with trauma was relatively low, 20%, the incidence of

Table 6. Mortality Rates for Clinical Events Stratified by Patient Population

	Mortality			
	Sepsis Syndrome		Sepsis Syndrome and Refractory Shock	
Patient Population	No. (%)[a]	RR[b]	No. (%)[a]	RR[b]
Neutropenic cancer	24 (55.8)	1.56[c]	17 (73.9)	1.44[c]
Community UTI	6 (20)	0.51[c]	4 (50)	0.93
Nursing home UTI	15 (24.2)	0.61[c]	7 (43.8)	0.80
Nursing home RTI	17 (29.8)	0.77	9 (45.0)	0.82
Nosocomial UTI	15 (51.6)	1.4	7 (53.8)	1.0
Nosocomial RTI	36 (57.1)	1.66[c]	22 (71.0)	1.40[c]
Skin	11 (35.5)	0.94	7 (53.8)	1.0
Trauma	13 (20.6)	0.51[c]	10 (33.3)	0.58[c]
Abdominal	30 (45.5)	1.25	28 (65.1)	1.28
Gram-negative bacteremia	23 (34.3)	0.90	17 (41.5)	0.73
Overall	172 (37.6)		116 (53.7)	

[a]Denominator = number of patients in the population.
[b]RR = Relative risk computed as incidence in patient population/incidence in all other populations.
[c]$p<0.05$.

sepsis syndrome was high, 39.4% (RR = 1.59, $p<0.05$). This indicates that the incidence of sepsis syndrome does not parallel mortality. The low rate of mortality in trauma patients may be explained by the fact that these patients were younger (mean age 40 yrs) and had fewer (< 10%) comorbidities than other populations. In addition, they were monitored aggressively in specialized university hospital trauma centers.

Overall, the marked disparity in the incidence of sepsis syndrome versus mortality rate raises several issues. The first is to identify patients who should be targeted to receive therapies specific for sepsis syndrome. The second is to establish the appropriate end point for patient monitoring of outcomes. Given the fact that the elderly have fewer complications and shorter ICU stays, one would expect their mortality to be lower, however, the rate is similar across age groups. This may suggest that morbidity might be an alternative end point to mortality in clinical trials of agents that prevent or modulate the systemic inflammatory response. Elderly patients with sepsis syndrome did not use more medical resources, as measured by length of ICU stay and complication rates. Most resources went to younger patients age 18–59 years, 50% of whom were in the ICU more than 9 days. Thus, perhaps innovative therapies would be wisely administered in this group potentially to reduce ICU stay and costs of treating complications.

As mentioned, our study differed from previous clinical trials in a number of important aspects. First, overall 47.8% of patients with sepsis syndrome were women, compared with 34.5% and 41.5% in other trials.[10, 12] The preponderance of men in those trials may have been attributed to the exclusion of women of childbearing age. On further analysis, however, only 41% of the patients in our study were women under 50 years of age, which would support the fact that men are predominantly at risk for sepsis.[18,19] Second, severely neutropenic patients were excluded from other trials,[20] and therefore the results should not be extrapolated to the general population of patients with sepsis syndrome. Third, our study shows that large numbers of patients are in fact at low risk for developing the syndrome and its sequelae; therefore they may not be candidates for any innovative therapies of the kind given in the clinical trials.

Our study did have some limitations. Sepsis syndrome was used as an end point, and mortality rate varies depending on the definition of sepsis. This also makes it difficult to compare results of this surveillance study with those of clinical trials due to different criteria for sepsis. Because our study required that subjects have suspected or documented gram-negative infection and have initiated antibiotic coverage at study entry, the patient populations were clearly skewed toward those with gram-negative infections. Finally, because of economic and time constraints, we focused on a sample of patients at high risk of developing sepsis.

The impressive variability in the incidence of sepsis syndrome and its associated sequelae among different populations strongly suggests that sepsis treatment goals and algorithms have to be based in part on the targeted population, and that clinical trials must stratify patients among the various risk

populations. Theoretically, treatment approaches as well as efficacy may be quite different across patient risk groups. For example, our results suggest that patients with community-acquired urinary tract infections, because of their low incidence of complications and mortality, may require short-term supportive care outside the ICU, and may be discharged early taking oral antibiotics, thus conserving hospital resources for high-risk patients. These data also have implications for researchers designing clinical trials. Because elderly patients with community-acquired urinary tract infections are at such low risk, perhaps they should not be included in clinical trials of new agents designed to modulate the various inflammatory mediators responsible for the pathogenesis of sepsis. In addition, the rate of complications should be applied in conjunction with mortality when testing the efficacy of innovative treatment agents for the pathogenesis of sepsis syndrome.

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