Survival Analysis of 314 Episodes of Sepsis in Medical Intensive Care Unit in University Hospital: Impact of Intensive Care Unit Performance and Antimicrobial Therapy

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> **Received:** March 1, 2006
> **Accepted:** March 26, 2006

> **Croat Med J. 2006;47:385-97**

Aim To evaluate epidemiology of sepsis in medical intensive care unit (ICU) in a university hospital, and the impact of ICU performance and appropriate empirical antibiotic therapy on survival of septic patients.

Methods Observational, partly prospective study conducted over 6 years assessed all patients meeting the criteria for sepsis at ICU admission at the Sisters of Mercy University Hospital. Clinical presentation of sepsis was defined according to 2001 International Sepsis Definitions Conference. Demographic data, admission category, source of infection, severity of sepsis, ICU or hospital stay and outcome, ICU performance, and appropriateness of empirical antibiotic therapy were analyzed.

Results The analysis included 314 of 5022 (6.3%) patients admitted to ICU during the study period. There were 176 (56.1%) ICU survivors. At the ICU admission, sepsis was present in 100 (31.8%), severe sepsis in 89 (28.6%), and septic shock in 125 (39.8%) patients with mortality rates 17%, 33.7%, 72.1%, respectively. During ICU treatment, 244 (77.7%) patients developed at least one organ dysfunction syndrome. Of 138 (43.9%) patients who met the criteria for septic shock, 107 (75.4) were non-survivors ($P<0.001$). Factors associated with in-ICU mortality were acquisition of sepsis at another department (odds ratio [OR] 0.06; 95% confidence interval [CI], 0.02-0.19), winter season (OR 0.42; 0.20-0.89), limited mobility (OR 0.28; 0.14-0.59), ICU length of stay (OR 0.82; 0.75-0.91), sepsis-related organ failure assessment (SOFA) score on day 1 (OR 0.80; 0.72-0.89), history of global heart failure (OR 0.33; 0.16-0.67), chronic obstructive pulmonary disease (COPD)-connected respiratory failure (OR 0.50; 0.27-0.93), septic shock present during ICU treatment (OR 0.03; 0.01-0.10), and negative blood culture at admission (OR 2.60; 0.81-6.23). Microbiological documentation of sepsis was obtained in 235 (74.8%) patients. Urinary tract infections were present in 168 (53.5%) patients, followed by skin or soft tissue infections in 58 (18.5%) and lower respiratory tract infections in 44 (14.0%) patients. Lower respiratory tract as focus of sepsis was connected with worse outcome ($P<0.001$). Empirical antibiotic treatment was considered adequate in 107 (60.8%) survivors and 42 (30.4%) non-survivors. Patients treated with adequate empirical antibiotic therapy had significantly higher survival time in hospital (log-rank, $P=0.001$).

Conclusion The mortality rate of sepsis was unacceptably high. The odds for poor outcome increased with acquisition of sepsis at another department, winter season, limited mobility, higher SOFA score on day 1, history of chronic global heart failure, COPD-connected respiratory failure, and septic shock present during ICU treatment, whereas longer ICU length of stay, positive blood culture, and adequate empirical antibiotic therapy were protective factors.

Sepsis is a systemic response of the host to infectious stimuli, which consists of clinical, hemodynamic, biochemical, and inflammatory components (1,2). When an organ system begins to fail because of sepsis, the condition is considered severe and is one of the leading causes of death in the critically ill, with the mortality rate of 28-55% (3). The death rates in some subgroups of patients with sepsis-induced organ failure have decreased, even though there is no specific therapy (2). The reduced mortality may be due to changes in the definition of sepsis, better detection and treatment of the underlying infection, or improved supportive care (4). Effective treatment of organ failure is essential because the average risk of death increases by 15-20% with failure of each additional organ (5). The host response is perhaps as important as the site of infection or the type of microorganism causing sepsis. The lung is the most common site of infection, followed by abdominal and urinary tract organs (6). Positive blood cultures are accepted as the evidence of serious infection, but they are positive in only 30% of patients (6). Antimicrobial drugs are necessary, but not sufficient for the treatment of sepsis. Around 10% of the patients do not receive prompt antibiotic therapy for causative pathogen, and their mortality rate is 10-15% higher than in those who receive immediate, appropriate antibiotic therapy (5). The adequacy of initial empirical antimicrobial treatment is crucial in terms of outcome, although early mortality rate is unaffected by the appropriate empirical antibiotic therapy (7). The application of proven medical and technological interventions in a standard therapeutical algorithm is important in everyday performance of intensive care unit (ICU) (8). Since epidemiology and surveillance data significantly differ between medical and surgical ICU patients (9), each ICU has to assess its own epidemiological data and establish critical pathways for the management and treatment of patients with sepsis (10).

Our aim was to evaluate the epidemiology of sepsis syndrome in the medical ICU at University Hospital and the impact of ICU performance and adequate empirical antibiotic therapy on the outcome in patients with sepsis.

Patients and methods

Patients

The study was conducted in an 11-bed medical ICU at Sisters of Mercy University Hospital, Zagreb, Croatia. The patients with sepsis treated at the ICU between January 1, 2000 and December 31, 2002, were retrospectively included, and those admitted between January 1, 2003 and December 31, 2005, were included prospectively. Of 5022 medical ICU patients admitted during study period, 368 had an initial diagnosis of sepsis and 150 had a diagnosis of fever with suspected sepsis at ICU admission. All patients were referred to the ICU from the emergency department. As the criteria for ICU admission were not standardized, the emergency department attending physician had to request the ICU admission on the basis of clinical condition of the patient. During the first 24 hours, 86 patients with inital diagnosis of sepsis and 118 patients with initial diagnosis of fever with suspected sepsis did not meet the criteria for sepsis (1,2) and thus were excluded from the study. The final sample consisted of 314 patients who met the criteria for sepsis. Median age of the analyzed patients was 71 years (range, 19-92).

All patients with sepsis were treated by standard supportive treatment, fluid resuscitation, vasoactive drugs, medical and technological interventions for organ dysfunction or failure (11), and empirical antibiotic therapy according to the hospital practice guidelines.

Method

Sepsis definition. Sepsis, severe sepsis, and septic shock were defined according to the criteria of the American College of Chest Physicians

and the Society of Critical Care Medicine (1,2). Multiple organ dysfunction syndrome (MODS) was defined according to the criteria of Bulk (11). Patients in septic shock who met criteria for two or more organs failure before the start of ICU treatment were included in MODS group. Most patients had strong evidence of infection site, whereas patients with clinical criteria of sepsis but no evident source of infection were considered as having sepsis of unknown origin. Bacteremia was defined as positive blood culture to one or more microbial specimens. For common skin-dwelling bacteria, such as coagulase-negative staphylococci (SCN), two or more positive blood cultures were considered indicative. Nosocomial infection was defined as the infection that developed 48 hours after admission to any hospital department or to other hospitals, but before ICU admission. New sepsis was defined as sepsis that developed 48 hours after ICU admission in a patient with chills or body temperature ≥38°C or ≤36°C and positive blood culture. Documented sepsis was considered when a relevant microorganism was isolated from blood and suspected focus (pus, urine, sputum or quantitative tracheal aspirate in intubated patients). If a catheter was considered as the source of infection, it was removed and culture was performed. Polymicrobial infection was considered when more than one organism was detected in the sample. Fungal infection was diagnosed when a fungus was isolated in any sterile sample.

Empirical antibiotic therapy was considered adequate when at least one effective drug was included in the treatment and the dose and pattern of administration were in accordance with medical standards and in ICU survivors without microbiologically detected microorganism in bloodstream or focus. When the empirical antibiotic therapy had to be changed after microbiological detection of microorganism, it was considered inadequate, whereas in non-survivors without microbiologically detected microorganism in bloodstream or focus it was considered not evaluable.

Variables. The following variables were recorded: year of ICU treatment, patient age, sex, ICU and hospital length of stay, ICU and hospital outcome, season of the year when the treatment took place, type of infection (nosocomial or community acquired infection), suspected site of infection, patient mobility, emergency department length of stay, time of the day of ICU admission, physician in charge on ICU admission and during the first hours of treatment, chronic diseases (cardiovascular, pulmonary, cerebrovascular, liver, renal, malignancy, diabetes mellitus, and immunosuppression), clinical picture of sepsis (sepsis, severe sepsis, septic shock, or MODS) (1,2,11), development of organ dysfunction or failure and septic shock during treatment, development of new sepsis and pseudomembranous colitis during treatment, need for mechanical ventilation, hemodialysis and surgical intervention or percutaneous drainage as mandatory as part of the treatment of the infection, microbiologically documented infection in blood, urine and sputum/tracheal aspirate, microorganism isolated, and empirical antibiotic therapy. The severity of illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE II) score (12) on days 1 and 3 and mental status by Glasgow Coma Score (GCS) (13,14) on days 1 and 3. Failure of organs and severity of MODS (10) were evaluated by the Sepsis-related Organ Failure Assessment (SOFA) scale (15) on days 1 and 3. Organ dysfunction was defined by SOFA score 1 or 2, and organ failure by a SOFA score 3 or 4 (16).

Study design

Patients enrolled in the study were followed until ICU or hospital death or hospital discharge. Five investigators assessed the patients for the eligibility for inclusion in the study according to the described criteria, and collected data through out the study period. All data were revised by two senior investigators (DV, SM), if any problem was detected patient history was evaluated. During the

study period our unit did not participate in any trial designed to evaluate new therapies in sepsis.

Assays

All clinical and laboratory data were a part of the standard sepsis ICU management. Blood samples in standard ethylenediaminetetraacetic (EDTA)-K_3 containing tubes were used for hematological assays on Coulter-Counter S plus junior (Coulter Electronics Limited, Luton, UK), coagulation parameters were assessed by Quick method from blood samples in 3.8% sodium citrate tubes, 1:10 ratio, plasma was immediately separated by centrifugation (3000 G for 10 minutes) and analyzed automatically with Behring Coagulation Timer (Dade Behring, Marburg, Germany). Aspartat transaminase, alanin transaminase, serum bilirubin, albumin, urea, creatinine, and electrolytes were determined with commercially available kits on Olympus AU 600 and Olympus Fractoscan junior (Olympus Diagnostica GmbH, Hamburg, Germany). Blood was cultured by the method of bedside inoculation of blood culture bottles (FAN Aerobic and Anaerobic Culture Bottles, Organon Teknika Corp., Durham, the Netherlands). Microbiology analysis was preformed on a microbial detection system (Organon Bact-Alert, Organon Teknika Corp.).

Statistical analysis

Data were analyzed descriptively and results for continuous variables with normal distribution presented as means ±standard deviation (±SD) and those with non-normal distribution as medians with range. Homogeneity of variance was tested with Leven's test. For those variables where variances were not homogenous, differences between the groups were tested with Kruskal-Wallis test and compared with Mann-Whitney test with *post hoc* Bonferroni correction ($P<0.008$). Qualitative variables were presented as frequency tables, and differences were tested with χ^2 test by using Yates correction. The association between risk factors and death was first examined by means of univariate analysis. Multivariate analysis with logistic regression analysis was used to evaluate the independent contribution of the variables using a forward stepwise method. The odds ratio (OR) and the corresponding 95% confidence intervals (CI) were calculated. Differences in survival were analyzed with the Kaplan-Meier method, data on surviving patients were censored at the date of hospital discharge, and data for non-surviving patients were censored at the date of hospital death, the results were compared with the use of log-rank test. $P<0.05$ was considered statistically significant. Data analysis was performed with the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The number of septic patients in 2005 was significantly higher in comparison with previous study years (χ^2 test, $P<0.001$), when their number did not vary significantly (Table 1). There was no significant difference in the age of the patients among analyzed years (Kruskal-Wal-

Table 1. Proportion, age, and length of stay of patients with sepsis among all patients at the medical intensive care unit (ICU) in 2000-2005 period

	No. of patients		Variable (median, range)		
Year	total	with sepsis (%)	age (years)	ICU length of stay (days)	overall mortality rate (%)
2000	970	36 (3.7)	70.5 (22-92)	3 (1-22)	14.2
2001	928	36 (3.9)	70.5 (27-82)	5 (1-15)	13.1
2002	816	45 (5.5)	70 (19-92)	7 (1-36)	13.3
2003	734	56 (7.6)	70.5 (23-87)	6.5 (1-22)	17.9
2004	740	43 (5.8)	70 (31-87)	6 (1-35)	17.9
2005	834	98 (11.7)	72.5 (22-92)	6 (1-30)	20.3
Total	5022	314 (6.2)	71 (19-92)	6 (1-36)	17.4

lis, P=0.911) or in ICU length of stay (Kruskal-Wallis, P=0.526). There were 176 (56.1%) ICU survivors and 138 (43.9%) ICU non-survivors. Fifteen patients (4.7%) died either in the step-down unit or during hospital stay. Finally, there were 161 (51.3%) hospital survivors and 153 (48.7%) hospital non-survivors. During the first 24 hours of the ICU treatment, 35 deaths (11.1%) were recorded. Number of deaths in 2002 (15 patients, or 33.3%) was significantly lower than in other years (P=0.025).

Of 55 patients (17.5%) who underwent cardiopulmonary resuscitation during ICU treatment, 53 (16.8%) did not survive. Nosocomial origin of sepsis was found in 119 (37.8%) patients (Table 2). In-ICU mortality was associated with acquisition of sepsis at another department (OR, 0.06; 95% CI, 0.02-0.19), winter season (OR, 0.42; 0.20-0.89), limited mobility (OR, 0.28; 0.14-0.59), ICU length of stay (OR, 0.82; 0.75-0.91), and SOFA score on day 1 (OR, 0.80; 0.72-0.89).

There was no significant difference between survivors and non-survivors with respect to history of chronic diseases except for the presence of global heart failure (OR, 0.33; 0.16-0.67), and chronic obstructive pulmonary disease (COPD)-connected respiratory failure (OR, 0.50; 0.27-0.93; Table 3).

Hospital and ICU performance

More than half of the patients (51.6%) spent more than 3 hours in the emergency department and most were admitted to the ICU during the afternoon shift (Table 4). There was no difference in length of stay in emergency department between survivors and non-survivors. No difference in the outcome of patients admitted during the night shift was found (Table 4). Although more non-survivors were admitted to the ICU by a non-ICU physician (OR, 0.48; 95% CI,

Table 2. Characteristics of patients with sepsis admitted to medical intensive care unit (ICU) in 2000-2005 period and risk factors for in-ICU mortality

Characteristic*	No. (%) of patients		
	total (n = 314)	survivors (n = 176)	non-survivors (n = 138)
Age (years; median, range)	71 (19-92)	70 (22-90)	72.5 (19-92)
Sex:			
men	164 (52.2)	76 (46.3)	88 (53.6)
women	150 (47.8)	85 (56.6)	65 (43.3)
Acquisition of sepsis:			
home	195 (62.1)	112 (63.6)	83 (60.2)
nursing home	21 (6.7)	11 (6.3)	10 (7.2)
another department†	74 (23.6)	39 (22.2)	35 (25.4)
another hospital	24 (7.6)	14 (8.0)	10 (7.2)
Season:			
spring	68 (21.7)	45 (25.6)	23 (16.7)
summer	67 (21.3)	38 (21.6)	29 (21.0)
autumn	71 (22.6)	42 (23.9)	29 (21.0)
winter‡	108 (34.4)	51 (29.1)	57 (41.3)
Patient mobility:			
unlimited	114 (36.3)	86 (48.9)	28 (20.3)
limited†	200 (63.7)	90 (51.1)	110 (79.7)
Length of stay (days, median, range):†			
ICU	6 (1-36)	7 (1-36)	3 (1-35)
hospital	13 (1-107)	18 (3-107)	4 (1-77)
Scores (mean±SD):			
Day 1:			
GSC	10.84 ± 3.98	12.17 ± 3.40	9.15 ± 4.04
APACHE II	19.98 ± 7.86	17.32 ± 7.24	23.37 ± 7.32
SOFA†	5.82 ± 3.35	4.57 ± 3.09	7.42 ± 2.96
Day 3:	(n = 243)	(n = 164)	(n = 79)
APACHE II	15.72 ± 7.42	12.73 ± 5.88	21.91 ± 6.04
SOFA	4.95 ± 3.47	3.77 ± 2.99	7.41 ± 3.11

*Abbreviations: ICU – intensive care unit; GCS – Glasgow Coma Score; APACHE II – Acute Physiology and Chronic Health Evaluation score; SOFA – sepsis-related organ failure assessment score.
†Stepwise logistic analysis, P<0.001.
‡Stepwise logistic analysis, P = 0.022.

Table 3. History of chronic disease in patients with sepsis and logistic regression analysis of risk factors for mortality in intensive care unit

Characteristic	No. (%) of patients		
	total (n = 314)	survivors (n = 176)	non-survivors (n = 138)
History of chronic heart failure:			
absent	205 (65.3)	130 (73.9)	75 (54.3)
left-sided	11 (3.5)	5 (2.8)	6 (4.3)
right-sided	51 (16.2)	27 (15.3)	24 (17.4)
global*	47 (15.0)	14 (8.0)	33 (23.9)
History of chronic respiratory disease:			
absent	245 (78.0)	151 (85.8)	94 (68.1)
chronic obstructive pulmonary disease†	59 (18.8)	22 (12.5)	37 (26.8)
emphysema	3 (1.0)	1 (0.6)	2 (1.4)
pleural fibrosis and calcification	7 (2.2)	2 (1.1)	5 (3.6)
Cerebrovascular disease:			
absent	212 (67.5)	122 (69.3)	90 (65.2)
present	102 (32.5)	54 (30.7)	48 (34.8)
Malignancy:			
absent	266 (84.7)	154 (87.5)	112 (81.2)
present	48 (15.3)	22 (12.5)	26 (18.8)
Chronic kidney disease:			
absent	222 (70.7)	131 (74.4)	91 (65.9)
present	92 (29.3)	45 (25.6)	47 (34.1)
Diabetes mellitus:			
absent	174 (55.4)	94 (53.7)	80 (58.1)
present	140 (44.6)	82 (46.3)	58 (41.9)

*Stepwise logistic analysis, P<0.001.
†Stepwise logistic analysis, P = 0.028.

Table 4. Hospital and intensive care unit (ICU) performance and risk factors for in-ICU mortality

Characteristic	No. (%) of patients* total (n = 314)	survivors (n = 176)	non-survivors (n = 138)
Time spent in emergency department (hours):			
≤1	69 (22.0)	32 (18.2)	37 (26.8)
>1, ≤2	46 (14.6)	25 (14.2)	21 (15.2)
>2, ≤3	37 (11.8)	22 (12.5)	15 (10.9)
>3	162 (51.6)	97 (55.1)	65 (47.1)
Time of ICU admission:			
08 AM-04 PM	119 (37.9)	65 (36.9)	54 (39.1)
04 PM-12 PM	153 (48.7)	84 (47.7)	69 (50.0)
00 AM-08 AM	42 (13.4)	27 (15.3)	15 (10.9)
Physician in charge:			
ICU staff	152 (48.4)	92 (52.3)	60 (43.5)
non-ICU staff	162 (51.6.)	84 (47.7)	78 (56.5)

*Stepwise logistic analysis showed no significant differences.

0.26-0.87), there was no significant association between survival and admission by ICU or non-ICU staff. The severity of illness scores (GCS and APACHE II) and sepsis related organ dysfunction/failure score (SOFA) obtained on the arrival to the ICU showed that patients spent more than 3 hours in ED regardless of the presence of septic shock or impaired consciousness and/or organ dysfunction/failure syndrome (Table 5).

Table 5. Analysis of severity of Glasgow Coma Score (GCS), Acute Physiology and Chronic Health Evaluation score (APACHE II), and sepsis-related organ failure assessment (SOFA) score on day 1 with respect to the length of stay in emergency department

Score (day 1)	Median (range) emergency department length of stay (h) ≤1 (n=69)	>1, ≤2 (n=46)	>2, ≤3 (n=37)	>3 (n=162)	*P**
GCS	13 (3-15)	10.5 (3-15)	12 (3-15)	12 (3-15)	0.167
APACHE II	20 (3-43)	19 (0-36)	19 (1-30)	21 (0-38)	0.122
SOFA	6 (0-13)	5.5 (0-15)	6 (0-11)	6 (0-13)	0.974

*Kruskal-Wallis test.

Clinical presentation

At the ICU admission, clinical picture of sepsis was present in 100 (31.8%) patients, severe sepsis in 89 (28.6%), and septic shock in 125 (39.8%) patients. In the septic shock group, 39 patients (12.4%) met criteria for two or more organs dysfunction/failure syndrome on the ICU admission (MODS group). Mortality rate for sepsis was 17.0%, severe sepsis 33.7%, septic shock 72.1% and MODS 74.4%. Until the ICU discharge or ICU death, 244 (77.7%) patients developed signs of at least one organ dysfunction (three organs, 68 (21.7%); two organs, 52 (16.6%); four organs, 50 (15.9%); and a maximum of seven organs, 1 (0.3%) patient). The most frequent dysfunction was septic encephalopathy, followed by hemodynamic instability, respiratory failure, renal failure, and disseminated intravascular coagulation (DIC). Thirteen patients with severe sepsis developed septic shock during the ICU treatment; at the end, out of 138 (43.9%) patients who met criteria for septic shock at some point of the ICU treatment there were 107 (75.4) non-survivors (Table 6). Septic shock present during ICU treatment (OR, 0.03; 0.01-0.10) and negative blood culture at admission (OR, 2.60; 0.81-6.23) were associated with a significant increase in risk of death. During the ICU treatment, 26 (8.3%) patients developed new sepsis, with no difference between survivors and non-survivors (OR, 0.87; 0.16-4.77). Patients with sepsis, severe sepsis, septic shock, and MODS significantly differed in the severity of illness scores (GCS and APACHE II) and

Table 6. Septic shock, new sepsis during treatment at intensive care unit (ICU), microbiological cultures in specimens obtained on admission, and risk factors for in-ICU mortality

Characteristic	No. (%) of patients total (n = 314)	survivors (n = 176)	non-survivors (n = 138)
Septic shock present during ICU treatment:			
yes*	138 (43.9)	17 (19.3)	107 (75.4)
no	176 (56.1)	142 (80.7)	34 (24.6)
Development of new sepsis during ICU treatment:			
yes	26 (8.3)	17 (9.7)	9 (6.5)
no	288 (91.7)	159 (90.3)	129 (93.5)
Blood culture on admission:			
none	24 (7.6)	4 (2.3)	20 (14.5)
positive	154 (49.0)	107 (60.8)	47 (34.1)
negative†	136 (43.3.)	65 (36.9)	71 (51.4)
Urine culture on admission:			
none	23 (7.3)	3 (1.7)	20 (13,9)
positive	157 (50.0)	99 (56.3)	58 (42.3)
negative	134 (42.7)	74 (42.0)	60 (43.8)
Smear/tracheal aspirate at admission:			
none	209 (66.6)	120 (68.0)	90 (65.2)
positive	30 (9.6)	13 (7.4)	17 (12.3)
negative	74 (23.6)	43 (24.6)	31 (22.5)

*Stepwise logistic analysis, $P<0.001$.
†Stepwise logistic analysis, $P=0.049$.

Table 7. Glasgow Coma Score (GCS), Acute Physiology and Chronic Health Evaluation score (APACHE II), and Sepsis-related Organ Dysfunction or Failure score (SOFA) with respect to clinical presentation of sepsis

	Score (median, range)*					
Scale	sepsis (n=100)	severe sepsis (n=89)	septic shock (n=86)	multiple organ dysfunction syndrome (MODS) (n=39)	multiple comparisons	P†
Day 1:						
GCS	14 (3-15)	13 (3-15)	9 (3-15)	11 (3-15)	sepsis/septic shock	<0.001
					sepsis/MODS	<0.001
					severe sepsis/septic shock	0.001
APACHE II	15.5 (0-37)	20 (3-34)	24 (0-38)	26 (4-43)	sepsis/severe sepsis	0.001
					sepsis/septic shock	<0.001
					sepsis/MODS	<0.001
					severe sepsis/septic shock	<0.001
					severe sepsis/MODS	0.003
SOFA	4 (0-13)	5 (0-12)	7 (0-15)	9 (1-14)	sepsis/severe sepsis	0.001
					sepsis/septic shock	<0.001
					sepsis/MODS	<0.001
					severe sepsis/septic shock	<0.001
					severe sepsis/MODS	<0.001
					septic shock/MODS	0.003
Day 3:	(n=90)	(n=75)	(n=51)	(n=27)		
APACHE II	11 (2-27)	15 (1-32)	21 (9-32)	18 (8-33)		
SOFA	2 (0-9)	4 (0-15)	7 (1-15)	9 (1-14)	sepsis/MODS	0.002

*Kruskal-Wallis test, $P<0.001$ for all.
†*post hoc* Bonferroni correction for Mann-Whitney test ($P<0.008$).

SOFA score recorded on day 1 (n = 314) and day 3 (n = 243) (Table 7).

Of 314 septic patients, 61 (19.4%) needed mechanical ventilation support that lasted 2 days on average (range, 1-6), and 26 (8.3%) patients were on hemodialysis for 3 days on average (range, 1-22). Forty-one patients (13.1%) needed surgical intervention during sepsis treatment and only 13 (4.1%) developed MRSA pseudo-membranous colitis as a complication of the treatment.

Sepsis documentation

Microbiological documentation of sepsis was obtained in 235 (74.8%) patients; bloodstream infection alone was documented in 62 (19.8%) patients, urinary tract infection in 65 (20.7%) patients, and respiratory tract as the only source of infection in 16 (5.1%) as focus of sepsis. Eighty-six (27.4%) patients presented with documented infection in bloodstream and focus, and 6 (1.9%) patients presented with documented sepsis of two different focuses. Positive blood culture rate obtained on admission was 49%.

The site of infection was determined by clinical presentation and/or positive focus cultures. Urinary tract infections were the most common, followed by skin/soft tissue, lower respiratory tract, and gallbladder/bile ducts infections (Table 8). Lower respiratory tract as focus of sepsis was associated with worse outcome (χ^2 test, $P<0.001$). Most patients had community acquired primary sepsis (Table 8). According to

Table 8. Site of infection and source of admission analysis in septic patients treated in medical intensive care unit (ICU) in 2000-2005 period

	No. (%) of patients			
Characteristic	total (n = 314)	survivors (n = 176)	non-survivors (n = 138)	P*
Occurrence of infection:				
unknown	2 (0.6)	2 (1.1)	–	
upper respiratory tract	5 (1.6)	2 (1.1)	3 (2.2)	
lower respiratory tract	44 (14.0)	15 (8.5)	29 (21.0)	0.001
urinary tract	168 (53.5)	100 (56.8)	68 (49.3)	0.186
gallbladder and bile ducts	17 (5.4)	12 (6.8)	5 (3.6)	0.226
gastro-intestinal tract	6 (1.9)	3 (1.7)	3 (2.2)	
wound/drainage	10 (3.2)	6 (3.4)	4 (2.9)	
foreign body	2 (0.6)	1 (0.6)	1 (0.7)	
central venous catheter	2 (0.6)	2 (1.1)	–	
skin/soft tissue	58 (18.5)	33 (18.8)	25 (18.1)	0.889
Source of admission:				
home	227 (72.3)	122 (69.3)	105 (76.1)	0.183
department of medicine	31 (9.9)	18 (10.2)	13 (9.4)	
department of surgery	18 (5.7)	10 (5.7)	8 (5.8)	
department of urology	7 (2.2)	4 (2.3)	3 (2.2)	
department of gynecology	4 (1.3)	2 (1.1)	2 (1.4)	
department of dermatology	3 (1.0)	3 (1.7)	–	
department of rehabilitation	6 (1.9)	5 (2.8)	1 (0.7)	
other ICU	2 (0.6)	2 (1.1)	–	
other hospital	16 (5.1)	10 (5.7)	6 (4.3)	

*χ^2 test.

Table 9. Microorganisms isolated in different site of infection and bloodstream in patients with sepsis obtained on admission to intensive care unit

Pathogen	No. (%) episodes of sepsis			
	bloodstream infection (n = 154)	urinary tract infection (n = 157)	respiratory tract infection (n = 32)	total (n = 343)
Gram-negative organisms:				
Escherichia coli	44 (28.6)	61 (38.8)	2 (6.3)	107 (31.2)
Pseudomonas aeruginosa	4 (2.7)	26 (16.6)	3 (9.4)	33 (9.6)
Proteus mirabilis	7 (4.5)	20 (12.7)	–	27 (7.9)
Klebsiella pneumoniae	7 (4.5)	10 (6.3)	3 (9.4)	20 (5.8)
Serratia marcenscens	3 (1.9)	3 (1.9)	1 (3.1)	7 (2.1)
Acinetobacter species	2 (1.3)	4 (2.4)		6 (1.7)
Salmonella enteritidis	4 (2.7)	–	–	4 (1.2)
Hemophylus influenzae	–	–	1 (3.1)	1 (0.3)
other enterobacteriaceae*	3 (1.9)	12 (7.7)	–	15 (4.4)
Gram positive organisms:†				
MSSA	19 (12.3)	3 (1.9)	2 (6.3)	24 (7.0)
SCN	18 (11.7)	–	–	18 (5.3)
MRSA	9 (5.8)	1 (0.6)	4 (12.5)	14 (4.1)
Streptococcus pneumoniae	13 (8.4)	1 (0.6)	7 (21.9)	20 (5.8)
Enterococcus	3 (1.9)	4 (2.4)	1 (3.1)	8 (2.3)
Streptococcus pyogenes	4 (2.7)	–	1 (3.1)	5 (1.4)
Streptococcus agalactiae	3 (1.9)	1 (0.6)	–	4 (1.2)
Clostridium species	1 (0.6)	–	–	1 (0.3)
Polymicrobial infection	10 (6.6)	5 (3.1)	2 (6.2)	17 (4.9)
Fungi:				
Candida species	–	7 (4.4)	5 (15.6)	12 (3.5)
Total	154 (100.0)	157 (100.0)	32 (100.0)	343 (100.0)

*Other enterobacteriaceae: *Enterobacter* species, *Klebsiella oxytoca*, *Klebsiella* species, *Morganella morgani*, *Providencia rettgeri*, and *Providentia* species.
†Abbreviations: MSSA – methicillin-sensitive *Staphylococcus aureus*; MRSA – methicillin-resistant *Staphylococcus aureus*; SCN – staphylococcus coagulase negative.

the causative agent, Gram-negative sepsis was the most frequent, followed by Gram-positive and polymicrobial sepsis (Table 9). *Escherichia coli* was the most frequently isolated organism irrespective of the severity and clinical presentation of sepsis (Table 10).

Antimicrobial therapy

Empirical antimicrobial therapy was initiated in all patients chosen by the attending ICU physician following current Hospital recommendations. In 79 (25.1%) patients with no microbiological documentation of sepsis, antimicrobial therapy was empirical until hospital discharge or death. The therapy was changed during the ICU stay in 34 of 79 (10.8%) patients on the basis of clinical judgment of ICU physicians. In 235 (74.8%) patients with microbiologically documented sepsis the antibiotic treatment pattern was changed by attending ICU physician according to the in vitro testing for antibiotic sensitivity, patient's organ functions, and history of allergy on antibiotics. We were able to evaluate the appropriateness of treatment in 266 patients (48 non survivors with no microbiologically documented sepsis were considered not evaluable, and 31 survivors with no microbiological documentation of sepsis were considered as patients with adequate empirical antibiotic treatment). Empirical antibiotic treatment was considered adequate in 107 (60.8%) survivors and 42 (30.4%) non-survivors, and inadequate in 69 (39.2%) survivor and 96 (69.6%) non-survivors (Table 11). The survival of patients with adequate empirical antibiotic therapy compared to those with inadequate empirical antibiotic therapy or not evaluable treatment was significantly higher (Figure 1).

Discussion

The mortality rate of sepsis in most centers remains unacceptably high (17). Similar to other life threatening conditions, the speed and appropriateness of therapy administered in the initial hours after the onset of disease influence outcome (18). In the early 1990s, door-to-drug time of more than 60 minutes decreased to approximately 30-35 minutes on average in patients

Table 10. Most frequently isolated microorganisms in bloodstream documented infection in relation to clinical presentation of sepsis obtained on admission to intensive care unit

	No. (%) episodes of sepsis (n = 314)			
Pathogen	sepsis (n = 100)	severe sepsis (n = 89)	septic shock (n = 86)	multiple organ dysfunction syndrome (n = 39)
Documented bloodstream infection	48 (48.0)	43 (48.3)	41 (47.6)	22 (56.4)
Gram-negative organisms:				
Escherichia coli	12 (12.0)	12 (13.5)	13 (15.1)	7 (17.9)
Pseudomonas aeruginosa	–	1 (1.1)	1 (1.1)	2 (5.1)
Proteus mirabilis	4 (4.0)	–	3 (3.9)	–
Klebsiella pneumoniae	3 (3.0)	2 (2.2)	–	2 (5.1)
Serratia marcenscens	–	2 (2.2)	–	1 (2.6)
Acinetobacter species	–	2 (2.2)	–	–
Salmonella enteritidis	1 (1.0)	1 (1.1)	2 (2.3)	–
Other enterobacteriaceae*	–	1 (1.1)	2 (2.3)	–
Gram positive organisms:†				
MSSA	9 (9.0)	5 (5.6)	3 (3.9)	2 (5.1)
SCN	7 (7.0)	2 (2.2)	6 (7.0)	3 (7.7)
MRSA	2 (2.0)	4 (4.4)	3 (3.5)	–
Streptococcus pneumoniae	5 (5.0)	2 (2.2)	4 (4.7)	2 (5.1)
Enterococcus	1 (1.0)	2 (2.2)	–	–
Streptococcus pyogenes	2 (2.0)	1 (1.1)	1 (1.1)	1 (2.6)
Streptococcus agalactiae	–	1 (1.1)	–	1 (2.6)
Clostridium species	–	–	1 (1.1)	–
Polymicrobial infection	2 (2.0)	5 (5.6)	2 (2.3)	2 (5.1)

*Other enterobacteriaceae: *Enterobacter* species, *Klebsiella oxytoca*, *Klebsiella* species, *Morganella morgani*, *Providencia rettgeri*, *Providentia* species.
†Abbreviations: MSSA – methicillin sensitive *Staphylococcus aureus*; MRSA – methicillin resistant *Staphylococcus aureus*; SCN – staphylococcus coagulase negative.

with acute myocardial infarction (18). Critical pathways, such as door-to-drug time, are needed as standardized protocols for optimizing and streamlining patient care, because many patients do not receive evidence-based therapies (9). Although we implemented a critical pathway in managing patient with sepsis in emergency department in Sisters of Mercy University Hospital, an effort to reduce the time needed to perform all the various steps from the time a patient arrives in the emergency department to the time she or he arrives to the ICU, we did not record parallel improvement in the ICU mortality. The overriding goal of critical pathways is to optimize care by improving the use of appropriate treatments and on facilitating patient triage to the appropriate level of care, avoiding both under- and overutilization. Decreasing the use of inappropriate procedures can improve the quality of care while making that care more cost-efficient (10).

In the last 5 years, newly proven medical and technological interventions are being applied, such as recombinant human activated protein C (19), tight glucose control with insulin (20), steroid administration to the patients with relative adrenal insufficiency and septic shock (21), and

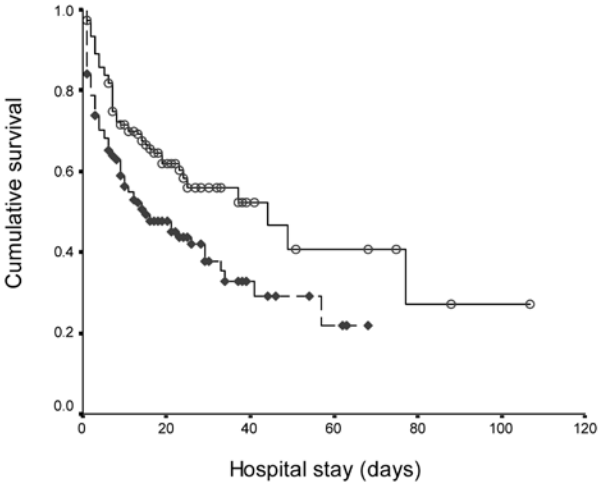

Figure 1. Kaplan-Meier survival curve for hospital stay in patients with adequate (full line) and either inadequate or not evaluable empirical antibiotic therapy (dashed line). Log-rank, $P = 0.001$. Open circles and closed diamonds – number of deaths.

low tidal volume ventilation for acute respiratory distress syndrome (22). Adequate antibiotic use reduced mortality rate by 43.4% in patients with septic shock, by 23.1% in those with severe sepsis, and by 19.8% in those with sepsis (7), which are higher than those reported in studies using extremely expensive therapies (19,20).

Our study recorded constant increase in the number of patients with sepsis, particularly in

Table 11. Mortality rate of patients in intensive care unit for various sites of infection depending on the adequacy of empirical antibiotic therapy

Empirical antibiotic therapy per infection site	No. (%) of patients		
	total (n = 314)	survivors (n = 176)	non-survivors (n = 138)
Urinary tract:	168 (53.5)	100 (56.8)	68 (49.3)
adequate	85 (50.6)	60 (60.0)	25 (36.7)
inadequate	61 (36.3)	40 (40.0)	21 (30.9)
not evaluable	22 (13.1)	–	22 (32.4)
Skin/soft tissue:	58 (18.5)	33 (56.9)	25 (43.1)
adequate	24 (41.3)	20 (60.6)	4 (16.0)
inadequate	24 (41.3)	13 (39.4)	11 (44.0)
not evaluable	10 (17.4)	–	10 (40.0)
Lower respiratory tract:	44 (14.0)	15 (34)	29 (66.0)
adequate	19 (43.1)	8 (53.3)	11 (37.9)
inadequate	14 (31.8)	7 (46.6)	7 (24.1)
not evaluable	11 (25.1)	–	11 (38.0)
Gallbladder and bile ducts:	17 (5.4)	12 (70.5)	5 (29.5)
adequate	10 (58.8)	10 (83.3)	–
inadequate	6 (35.3)	2 (16.7)	4 (80.0)
not evaluable	1 (5.9)	–	1 (20.0)
Upper respiratory tract:	5 (1.6)	2 (40.0)	3 (60.0)
adequate	1 ((20.0)	1 (50.0)	–
inadequate	4 (80.0)	1 (50.0)	3 (100.0)
not evaluable	–	–	–
Others:*	20 (6.3)	12 (60.0)	8 (40.0)
adequate	8 (40.0)	5 (41.6)	3 (37.5)
inadequate	8 (40.0)	7 (58.4)	1 (12.5)
not evaluable	4 (20.0)	–	4 (50)
Unknown:	2 (0.6)	2 (100.0)	–
adequate	2 (100.0)	2 (100.0)	–
inadequate	–	–	–
not evaluable	–	–	–

*Others include wound/drainage (n=10), gastrointestinal tract (n=6), foreign body (n=2), and central venous catheter (n=2).

2005, which was primarily attributable to hospital reorganization (closure of respiratory ICU), but also a result of the implementation of critical pathway for detecting and managing patients with sepsis with increased awareness and sensitivity for the diagnosis, continuous educational efforts for ICU staff and non-ICU staff physicians, better detection (microbiological and clinical) and treatment of the underlying infection, and improved supportive care. The incidence of sepsis among medical ICU patients in our study was lower than that reported by French (23) and Spanish (7) authors in mixed type ICU. It was related to the increasing number of elderly and immunocompromised patients. Large proportion of patients with sepsis in our study were men, those aged around 70 years, and those with reduced mobility, which is in accordance with other reports (7,23). Although the chances of developing sepsis differ for men and women by age, the likelihood of dying from sepsis is the same for men and women (24), which is consistent with our findings.

Survivors in our study had better severity of illness (GCS and APACHE II) and SOFA scores in comparison with non-survivors. However, we did not record any difference with respect to emergency department length of stay, where over half of our patients spent more than 3 hours. Time spent in emergency department was the same for patients with low and high probability of death, without adequate resuscitation therapy. On the other hand, there was no difference between management of patients and early mortality rate with respect to ICU or non-ICU physician in charge. This fact proves that with firm ICU organization, implementation of critical pathways, and education of senior residents (non-ICU physicians) quality of care was on the same level (25) as even the vast majority of patients were admitted to the ICU during afternoon and night without difference in outcome. A significant improvement in care of medical ICU patients with sepsis is related to the implementation of dedicated ICU staff specialist of intensive care medicine supervisors to residents and fellows. These observations are consistent with the results of other studies, which demonstrated that changes in physician staffing patterns favorably influenced the care of critically ill patients (26).

Analysis of the ICU outcome according to the clinical presentation of sepsis showed mortality rate for sepsis and severe sepsis similar to other studies (27,28). Factors that contributed to these outcome data remain speculative. This high mortality found in our study is related to the high frequency of severe systemic response present in the studied population. In the group of non-survivors, there was a large proportion of patients ≥80 years old with history of different chronic diseases (chronic global heart and chronic obstructive pulmonary disease-connected respiratory failure were associated to worse outcome) who received

limited proportion of treatment partly because of financial constraints. These constraints influence a variety of services including cost of first choice drugs, nursing, respiratory therapy (especially mechanical ventilation), radiology diagnostic procedures, possibility of surgical intervention, and available beds in ICU. These data are also associated to the disturbing increase of the cost of non-survivors length of the ICU stay and the level of care compared with that of survivors.

Previous studies estimates of the incidence of septic shock during sepsis treatment vary from 23% to 50% (9). Our results showed that incidence of organ dysfunction or failure syndrome during the time course of sepsis treatment was not connected only to the first hours of the treatment. The reported incidence of organ failure varies according to the definition of failure and the patient population; however, when we used consensus definitions (1,2), a common pattern of frequency was observed. Lung dysfunction occurs often and early and persists, whereas shock, which also occurs early, resolves rapidly or becomes fatal. Serious abnormalities of liver function, coagulation, and central nervous system function tend to occur hours to days after the onset of sepsis and persist for some time. In addition to the number of organ failures, the severity of each failure affects the prognosis (29). While sepsis may represent precursor state to development of severe sepsis and septic shock with organ dysfunction or failure syndrome, patients should receive optimal treatment in ICU-s, and techniques are needed for developing scores for predicting which patient will progress to clinical presentation of sepsis with poor outcome. Valles et al (30) found three variables that were independently associated with an increase risk of death: APACHE II score at ICU admission ≥15, development of septic shock, and adequacy of empirical antibiotic treatment. Our data ruled out SOFA score on day 1, negative blood culture obtained at ICU admission, development of septic shock during ICU treatment, and inadequate empirical antibiotic therapy as variables associated with increase risk of mortality rate.

In or study, the main source of sepsis were urinary tract infections, followed by skin/soft tissue infections, lower respiratory tract infection and gallbladder/bile ducts infections. These four sources represented almost 91% of the episodes reported. Previously published studies (7,9,30,31) found that from the early 1990s, the most common source of sepsis were lower respiratory tract infections, intraabdominal, and urinary tract infections ,compared with reports from the 1970s and 1980s when Gram-negative microorganisms from genitourinary tract and intraabdominal infections were the leading causes of sepsis. The results of the analysis of the microbiological characteristics of the sepsis in our study differ from those previously reported (7,9,26,30). In our study, *Escherichia coli* was the leading pathogen in infections with confirmed bloodstream infection as well as focal infections. Other Gram-negative microorganisms are responsible for majority of sepsis documented in focus, while Gram-positive microorganisms are main pathogens in bloodstream infections. The incidence may be different from other countries where patients with higher degrees of severity of illness may be admitted to the ICU. Important observation is that 6.6% documented bloodstream infections are polymicrobial. Sites of occult infection, rare or antibiotic resistant organisms, and polymicrobial infections make it impossible to ensure prompt, complete empirical coverage in all cases. A common approach is to initiate broad spectrum antibiotic treatment when the pathogen is uncertain and then narrow the therapy as microbiologic sensitivity data become available. Indiscriminate use of broad-spectrum antibiotics has led to the development of resistant strains. While some studies have found that nosocomial sepsis secondary to intra-abdominal focus of infection was associated with a higher mortality (9), which was consistent with our data, Valle et al (30) found that either origin of sepsis or

microorganism were not associated with poor prognosis in community acquired sepsis documented microbiologically in bloodstream. Wong et al (32) reported that in the group of patients with sepsis and APACHE II score ≥15 mortality rate of patients with urinary sepsis and septic shock was 11.5% compared with 36.2% when the septic shock was derived from other sources. The present study found that lower respiratory tract infection as focus of sepsis was associated to worse outcome.

Recently, Guarnacho et al (7) found that the risk of in-hospital mortality was eight times greater in medical patients receiving inappropriate antimicrobial therapy within the first 24 hours and that choosing appropriate antibiotic did not influence early mortality rate. It depended rather on history of chronic diseases, severity of illness at admission, and development of organ dysfunction or failure syndrome. Regarding the high mortality rate in cases without microbiologically documented sepsis, the worse outcome of this episodes perhaps reflects an undiagnosed source of infection that might result in less aggressive approach and selection of appropriate empirical antibiotic.

The strengths of our study include the use of a national database that contained information over 6-year period, time interval appropriate for demographics, comorbidities, trends in pathogen microorganisms, and emerging new therapies. Our sample size was large enough to ensure that infrequent, but important, variables were not missed. Limitation of the study was that it was only partly prospective.

In conclusion, the clinical and demographic profile of patients with sepsis in our study shows that sepsis syndrome occurs most commonly among vulnerable patients, such as elderly and patients with multiple comorbidities. Our results confirmed that ICU management and performance with fully trained specialists and residents in intensive care medicine who are able to perform early and aggressive resuscitation of patients with sepsis and promptly administer appropriate empirical antimicrobial treatment is life saving. On the other hand, severity of illness of this group of patients was underestimated in the emergency department, which resulted in poor early resuscitation treatment and time delay in ICU admission that might be fatal in such cases. Knowledge of the epidemiology of sepsis is increasingly important as new and extremely expensive treatment modalities become available for this condition. Rational plan for treating patients with sepsis is that each ICU should develop critical pathways according to hospital resources, both technological and human, estimate expected number of cases, the setting in which these cases are likely to occur, and the patients who are likely to benefit from optimal therapeutical modalities.

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