Intensive Care Med (1993) 19:265–272

Intensive Care Medicine

Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients

D. Pittet[1], B. Thiévent[2], R.P. Wenzel[3], N. Li[4], G. Gurman[5] and P.M. Suter[2]

[1] Divisions of Infectious Diseases and [2] Surgical Intensive Care, Department of Internal Medicine and Department of Anesthesiology, University Hospital of Geneva, Geneva, Switzerland
[3] Division of General Medicine, Clinical Epidemiology and Health Services Research, and [4] Division of Biostatistics, University of Iowa College of Medicine, Iowa City, Iowa, USA
[5] General Intensive Care Unit, Division of Anesthesiology, Soroka Medical Center, Beer Sheva, Israel

Received: 11 June 1992; accepted: 5 February 1993

Abstract. *Objective:* To determine admission characteristics associated with the outcome of septicemia in critically ill patients and more specifically assess the prognostic value of pre-existing co-morbidities.
Design: 5 year-retrospective cohort study.
Setting: Surgical Intensive Care Unit (ICU-20 beds) in a 1600 bed-tertiary care center.
Patients: Among 5457 patients admitted to the ICU between 1984 and 1988, 176 (3.2%) met prospectively-defined criteria for blood culture-proven septicemia (8.77 per 1000 patient-days). Overall septicemic patients had a 5-fold increased risk of death compared to non-septicemic patients (relative risk 5.03, 95% confidence intervals 4.17–6.07, $p<0.0001$), and this estimate persisted after stratification according to age, sex, primary diagnosis and conditions of admission to the ICU (emergency/elective).
Results: Prognostic factors recorded on admission to ICU that were associated with mortality from septicemia among 173 patients were older age, higher admission Apache II score, gastrointestinal surgery, ultimately and rapidly fatal diseases and the number of co-morbidities in addition to the principal diagnosis (active smoking, alcohol abuse, non-cured malignancy, diabetes mellitus, splenectomy, recent antibiotic therapy, major surgery, or major cardiac event). In the multivariate analysis with logistic regression procedures, Apache II and co-morbidities were identified as the two independent predictors of mortality.
Conclusions: Pre-existing co-morbidities assessed at the admission to the ICU significantly improved the prediction of mortality from septicemia compared to Apache II score alone.

Key words: Septicemia – Co-morbidities – Prognostic factors – Multivariate analysis – Mortality – Critically ill

Infection is the main cause of multiple organ failure and a major cause of death in patients admitted to the intensive care unit (ICU) [1–3]. Currently septicemia is a leading cause of death in the United States [4], and ICUs, by design, are units where the most critical patients are managed. Moreover, together with bone marrow transplant units, ICUs are the hospital wards carrying the highest rates of nosocomial bloodstream infection [3, 5, 6]. We recently determined that the relative risk associated with the acquisition of nosocomial bloodstream infections was higher in surgical intensive care units than in other ICUs [6], extending previous observations [3, 7–9].

In 1962, McCabe and Jackson proposed stratifying patients according to underlying disease – fatal, ultimately fatal or non fatal – in order to estimate the prognosis of Gram-negative bacteremia [10]. Subsequent studies by Freid and colleagues [11] confirmed that the associated underlying disease was a major determinant of fatality in patients with Gram-negative bacteremia. Importantly, age stratification among the respective groups also suggested that older patients carry a significantly higher risk of death from the infection. Although McCabe's classification has been useful, it was not designed to assess patients admitted to the ICU. The Apache scoring system developed by Knaus and colleagues and commonly used in intensive care settings [12, 13], is based on a physiology score reflecting the degree of acute illness and the patient's preadmission health status. It is reliable and has been prospectively validated [12–16]. Apache II was used to stratify risk for decision making and for randomized clinical trials [17–19]. More recently, it was used to adjust for severity of underlying disease in trials designed to evaluate the role of new therapies for sepsis and Gram-negative bacteremia [20, 21].

Co-morbid conditions have been shown to predict the length of stay and the number of infectious and non-infectious complications independent of primary diagnosis both in general hospital as well as in medical ICU populations [22–24]. Importantly, only severe co-morbidities are accounted in the Apache II, since only severe organ dysfunctions are scored. In the present investigation on the prognosis of septicemia in critically ill patients, we studied the impact of pre-existing co-morbidities com-

monly recorded in the patients' past medical history and not objectively measured with the Apache II score.

Methods

Hospital setting

All patients admitted to the surgical intensive care unit (ICU) of the University Hospital of Geneva, Switzerland, between January 1, 1984 and December 31, 1988 were included in the study. This hospital is a 1600-bed tertiary health care center, admitting approximately 35000 patients annually for a mean length of stay of 10 days. The surgical ICU is a 20-bed referral unit admitting more than 1000 patients a year for a mean length of stay of 4.3 days.

Patient selection

The charts of all ICU patients with positive blood cultures were reviewed by two of the authors (B.T. and D.P.). Patients presenting with septicemia during their hospitalization in the ICU and those admitted for the treatment of septicemia or its complications such as septic shock or organ failure were included in the investigation. Only the first episode of septicemia in each patient was considered in this analysis.

Septicemia was defined as a clinical condition associated with one or more positive blood cultures for a commonly accepted pathogen or two or more positive blood cultures for less usual pathogens (coagulase negative *staphylococci* and *Candida spp*) *and* either signs of severe infection or evidence of systemic response to severe infection. Signs of severe infection required at least three of the following: 1) rectal or core temperature $>39\,^{\circ}C$ or $<36.5\,^{\circ}C$; 2) total leucocyte count $>12\times10^9$ or $<4\times10^9/l$; 3) more than 20% band forms on the differential count; 4) a known or strongly suspected source of infection with a positive bacterial culture for a pathogen; 5) gross pus in a closed space. Any of the following was accepted as evidence of systemic response to severe infection: unexplained systemic arterial hypotension, i.e. systolic blood pressure less than 90 mmHg for more than 2 h when hypovolemia has been ruled out; systemic vascular resistance of less than 800 dynes/s/cm^{-5}; unexplained metabolic acidosis i.e. base deficit >5 mmol/l, when other causes had been excluded, the intravascular volume estimated as being normal and arterial oxygenation adequate. In other words, in order to be considered as having septicemia, all patients must have bacteremia and at least meet the definition of sepsis recently proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [25].

Objective and design of the study

The objective of the study was to determine patients' characteristics and prognostic factors associated with the outcome of septicemia in critically ill patients at admission to the ICU. This investigation was a retrospective analysis of all ICU patients who met prospectively-defined criteria of septicemia over a 5 year period.

All study variables were available at admission to the ICU and included demographic data (age, sex, reason for admission to ICU, primary diagnosis); Apache II score [13], chronic organ insufficiencies, as defined in part C Apache II score by Knaus et al. [13]; McCabe-Jackson classification [10], and Injury Severity Score (ISS) for multiple trauma patients, calculated as proposed by Baker et al. [26], from the Abbreviated Injury Scale [27] at admission to ICU.

"Active Pre-existing Co-morbidities score" (APC), a currently unvalidated scoring system, accounts for co-morbidities not usually recorded in other severity of illness scores, including Apache II. Gross and colleagues [24] defined a co-morbidity as a pre-existing disease or condition in addition to the disease or condition designated as the principal diagnosis, and which is considered as an active problem. We elected to restrict the number of co-morbidities to nine conditions in an attempt to standardize this factor. APC simply sums up the number of active pre-existing co-morbidities at admission to the ICU among the nine following conditions: smoking habit (active smoking of ≥10 cigarettes/day with ≥10 UPY-unit pack years); alcoholism defined as a regular intake of more than 80 g of alcohol per day or one or more of the conditions described by Pine [28]; non-cured malignancy; diabetes mellitus requiring treatment; splenectomy before admission to ICU; major surgery[1] within 2 months prior to admission; previous antibiotic therapy within 2 months prior to admission and for at least 2 weeks; previous cardiogenic shock or cardiopulmonary resuscitation before admission to the ICU. These co-morbidities were defined in advance – predetermined – and recorded as categorical variables – present or absent – in the case report form.

A random sample of 43 charts (25%) was examined independently by two investigators to assess reproducibility in recording co-morbidities; observed agreement ranged 93–100% depending on the variable considered. Corresponding kappa coefficients – defined as (observed agreement-expected agreement)/(1-expected agreement) – ranged 0.83–1.00. Additional independent validation was performed by a research nurse unaware of the study question. Inter-observer reliability assessed by kappa coefficients which corrected expected agreement for chance was excellent (all kappa coefficients >0.80).

In-hospital mortality was the outcome measure in most of the analyses reported. However, when indicated in the text, we also conducted the analysis using life status at 21 days following the day of bacteremia as one outcome variable.

Statistical analysis

The strength of the association between the demographic/prognostic variables and the outcome (mortality) was determined using relative risks (RR) and their corresponding 95% confidence intervals (CI_{95}). For continuous variables, mean values have been compared using two sample *t*-tests for independent samples after correction for equality of variance (F-test). Differences in proportions were compared using the χ^2 test (or Fisher's exact test for expected cell frequencies less than 5). Yates correction has been used when applicable. As a result, variables predicting mortality in the univariate analysis have been identified. *P* values less than 0.05 were considered as statistically significant. All tests of significance were two-tailed.

Stepwise multiple logistic regression was used to estimate the independent effect of each prognostic variable on outcome after controlling for the other variables. Candidate variables tested for inclusion in the regression model were selected according to their significance levels in the univariate analysis or to their presumed clinical relevance. The significance level for entry into the model was set at 0.10. All statistical analyses were carried out using LOGIT procedure in the Statistical Analysis System (SAS) version 6.

Results

During the 5 year study, 5457 patients were admitted to the ICU. Emergency admissions ($n = 1190$) represented 22%. Of the patients 43% were cardiovascular post-operative patients, 18.3% post-operative gastrointestinal patients, 13.1% multiple trauma patients and 25.4% among other surgical diagnostic categories (neurosurgery, thoracic surgery, orthopedic, ENT, gynecology and obstetric, urology). There were 18 heart transplant and 17 hepatic transplant recipients.

Patients' characteristics, morbidity and mortality from septicemia

A total of 176 patients (3.23 per 100) experienced 225 episodes of septicemia during the study period. Thus, the overall incidence of septicemia among ICU patients was

[1] Major surgery defines surgical procedures performed under general anesthesia and excludes arthroscopic procedures

Table 1. Patients' characteristics associated with septicemia in a surgical intensive care unit[a]

Characteristic	Septicemia	Total	Relative risk[b]	95% CI	*p* value[d]
No. of patients (%)					
Age (years)					
≥65	37 (3.1)	1198	1.00		
<65	139 (3.3)	4259	1.06	0.74–1.51	0.83
Sex					
Male	118 (3.0)	3937	1.00		
Female	58 (3.8)	1520	1.27	0.93–1.73	0.15
Type of admission to SICU					
Elective	25 (5.9)	4267	1.00		
Emergency	151 (13)	1190	21.7	14.3–32.9	<0.0001
Surgical diagnostic category					
Cardiovascular	26 (1.1)	2360	1.00		
Multiple trauma	50 (7.0)	717	6.33	3.97–10.10	<0.0001
Gastrointestinal	66 (6.6)	999	6.00	3.83–9.38	<0.0001
Others[c]	34 (2.5)	1381	2.23	1.35–3.71	0.0023
All patients	176 (3.2)	5457			

[a] Only the first episodes of septicemia were considered
[b] For surgical diagnostic categories, the relative risk for developing a septicemia has been expressed as a function of the cardiovascular category
[c] Neurosurgery, thoracic surgery, orthopedic, ENT, gynecology, urology, others
[d] Univariate analysis

8.77 episodes per 1000 patient-days. A total of 173/176 (98%) charts was available and analyzed. The three remaining patients were not included in the final analysis (Tables 3 and 4).

Characteristics of septicemic patients ($n = 176$) were compared with those of non-septicemic patients ($n = 5281$; Table 1). Age and sex did not correlate with a significant risk of septicemia in ICU patients. Patients seen after emergency admission had a 20-fold higher relative risk of septicemia than elective ICU patients (RR = 21.7, CI_{95} 14.3–32.9, $p < 0.0001$). Among the different surgical diagnostics, gastrointestinal and multiple trauma patients were the higher risk categories, with a 6-fold increased risk of developing a septicemia when compared with cardiovascular patients (RR = 6.00 and 6.33, respectively, $p < 0.0001$).

Importantly, the mean total length of ICU stay of septicemic patients was almost 4-fold longer than that of non-septicemic patients (17.6 days versus 4.3 days). The length of ICU stay after the first episode of septicemia averaged 11.8 days; thus the extra length of stay in the unit attributable to septicemia could be estimated at 7.5 days. Assuming average direct costs of $ 2000 per day in our ICU, the excess length of stay of septicemic patients

Table 2. Patients' characteristics associated with mortality in 5457 ICU patients[a]

Characteristics	With septicemia	Without septicemia	Relative risk[b]	95% CI	*p* value
No. of deaths/total no. of patients (%)					
Age (years)					
<65	47/139 (34)	308/4120 (7.5)	4.52	3.50–5.84	<0.0001
≥65	31/37 (84)	157/1161 (14)	6.20	5.06–7.59	<0.0001
Sex					
Male	54/118 (46)	321/3819 (8.4)	5.44	4.36–6.80	<0.0001
Female	24/58 (41)	144/1462 (9.8)	4.20	2.98–5.92	<0.0001
Type of admission to ICU					
Elective	10/25 (40)	113/4242 (2.7)	15.0	8.99–25.1	<0.0001
Emergency	68/151 (45)	352/1039 (34)	1.33	1.09–1.62	<0.001
Surgical diagnostic category					
Cardiovascular	11/26 (42)	57/2334 (2.4)	17.3	10.3–29.0	<0.0001
Gastrointestinal	35/66 (53)	96/933 (10)	5.15	3.83–6.93	<0.0001
Others[c]	31/84 (38)	312/2014 (8.8)	2.46	1.84–3.29	<0.0001
All patients	78/176 (44)	465/5281 (8.8)	5.03	4.17–6.07	<0.0001

[a] For the analysis of the outcome, the hospital mortality of the first episodes of septicemia was considered
[b] For each characteristic, the relative risk for dying has been expressed as a function of the group of patients who did not develop septicemia (RR = 1.00)
[c] Multiple trauma (717 patients), neurosurgery, thoracic surgery, orthopedic, ENT, gynecology, urology, others

Table 3. Risk factors associated with mortality of septicemia in 173 ICU patients – univariate analysis[a]

Risk factor	Non-survivors	Survivors	Relative risk[b]	95% CI	*p* value
No. of patients (%)					
Age (years)	53.7 ± 18.4	47.2 ± 7.5	–	–	0.02
< 65	46 (33)	92	1.00		
≥ 65	29 (83)	6	6.32	2.76 – 14.5	< 0.0001
Sex					
Male	53 (45)	64	1.00		
Female	22 (39)	34	0.87	0.59 – 1.27	0.56
Type of admission					
Elective	10 (40)	15	1.00		
Emergency	65 (44)	83	1.10	0.66 – 1.83	0.71
Surgery[c]					
No	14 (41)	20	1.00		
Yes	61 (44)	78	1.07	0.68 – 1.66	0.77
Diagnosis					
Multiple trauma	18 (36)	32	1.00		
Cardiovascular[d]	11 (42)	15	1.18	0.66 – 2.10	0.79
Gastrointestinal[e]	33 (52)	31	1.43	0.92 – 2.22	0.01
Others[f]	13 (39)	20	1.09	0.62 – 1.92	0.75
McCabe-Jackson					
Non fatal	50 (38)	83	1.00		
Ultimately fatal	19 (61)	12	1.64	1.14 – 2.33	0.02
Rapidly fatal	6 (67)	3	1.78	1.06 – 2.94	0.15
Chronic organ insufficiencies[g]					
Liver	6 (75)	2	2.37	0.69 – 7.78	0.078
Cardiovascular	0	0	–	–	–
Respiratory	1	1	1.13	0.28 – 4.56	1.0
Renal	3 (100)	0	4.60	0.34 – 61.8	0.08
Immuno-compromised	9 (69)	4	1.91	0.83 – 4.36	0.078
Active preexisting comorbidities[h]					
Smoker	27 (49)	28	1.16	0.86 – 1.57	0.29
Alcohol abuse	21 (57)	16	1.39	0.94 – 2.06	0.095
Malignancy	12 (71)	5	2.02	0.96 – 4.28	0.033
Diabetes mellitus	5 (46)	6	1.04	0.59 – 1.81	1.0
Splenectomy	5 (36)	9	0.87	0.57 – 1.31	0.54
Major surgery	55 (49)	58	1.31	0.97 – 2.19	0.076
Antibiotic therapy	19 (64)	11	1.65	1.01 – 2.70	0.026
Cardiac arrest	12 (71)	5	2.02	0.96 – 4.28	0.033
Shock	21 (64)	12	1.69	1.05 – 2.70	0.015
Number of comorbidities					
– APC score –	2.4 ± 1.7	1.5 ± 1.5	–	–	0.0005
≤ 2	40 (34)	77	1.00		
> 2	35 (63)	21	1.83	1.32 – 2.53	0.0008
ISS score[i]	33.6 ± 14	27.8 ± 10	–	–	0.65
Apache II score[j]	22.0 ± 8	15.8 ± 7	–	–	< 0.0001
< 20	29 (30)	68	1.00		
≥ 20	46 (61)	30	2.02	1.42 – 2.89	< 0.0001

[a] For the analysis of the outcome, the in-hospital mortality of the first episodes of septicemia was considered. Plus-minus values are means ± SD

[b] For diagnosis, the relative risk (RR) has been expressed as a function of the multiple trauma patient's group, and for chronic organ insufficiencies and active pre-existing co-morbidities (APC), the relative risk has been expressed as a function of the patient's group without the risk factor considered

[c] Surgical procedures before admission to ICU: digestive (80 patients), cardiovascular (22), orthopedic (11), neurosurgery (13), thoracic surgery (5), others (5)

[d] Coronary (14), vascular (4), valvular (8)

[e] Pancreatitis (18), peritonitis (22), liver surgery (7), others (14)

[f] Orthopedic surgery (5), neurosurgery (7), thoracic surgery (8), ENT surgery (1), gynecology (5), urology (2), burned (2), others (3)

[g] As defined by Knaus et al. in Apache II score

[h] Not included in the Apache II score (see Methods for definitions)

[i] As defined by Baker et al. [26]

[j] Calculated at admission to ICU

in the ICU represented overall extra costs of at least $ 500000 per year.

The relative risk of death for ICU septicemic patients was compared to that of non-septicemic patients (Table 2). Whereas the overall mortality rate of non-septicemic was 8.8/100, that of septicemic patients was 44.3/100. Thus, septicemic patients had a 5-fold increased risk of dying when compared with non-septicemic patients (RR = 5.03, CI_{95} 4.17 – 6.07, $p < 0.0001$). Importantly, this estimate persisted when ICU patients were stratified according to age, sex, type of admission to ICU (elective versus emergency) and primary diagnosis. Septicemia most significantly affected the prognosis of patients admitted after elective surgery (RR = 15.0, CI_{95} 8.99 – 25.1, $p < 0.0001$), particularly cardiovascular surgery (RR = 17.3, CI_{95} 10.3 – 29.0, $p < 0.0001$).

Prognostic factors of septicemia in ICU patients

Among 176 patients with septicemia, 78 died; the crude hospital mortality rate of ICU septicemic patients was thus 44.3 per 100 (Table 2). A total of 125 infections were nosocomial (71%) and mortality rates were similar among community- and hospital-acquired infections (42% versus 44%, respectively). The average length of stay from admission to the day of septicemia was not significantly different between patients who died and those who survived septicemia (mean 6.5 and 5.0 days, respectively, $p = 0.28$) and median lengths of stay were similar (3 days for both groups).

We analyzed the prognostic factors associated with mortality among 173 septicemic patients (Table 3). Patients 65 years and older had a significantly higher risk of death than patients under 65 ($p < 0.0001$). On the other hand, sex, type of admission, surgery and primary diagnosis, with the exception of conditions following gastrointestinal surgery, were not associated with a significantly higher risk of death. Diseases classified as rapidly or ultimately fatal according to McCabe and Jackson were associated with higher risk of death from septicemia ($p = 0.02$).

Chronic organ insufficiencies, as defined by Knaus and colleagues (Apache II score, part C), have also been considered separately (Table 3). Although the death rates of immunocompromised patients and those with chronic liver and renal insufficiencies were high, their relative risk of death did not reach statistical significance in our population. None of the chronic organ insufficiencies was associated with a statistically significant increase in the risk of death from septicemia.

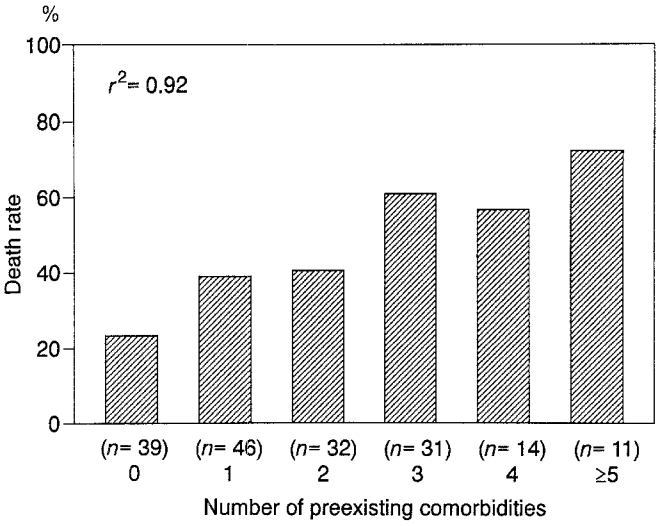

Fig. 1. Death rates from septicemia according to the number of co-morbidities in 173 ICU patients. Patients are stratified according to the number of pre-existing co-morbidities recorded on admission to the ICU (co-morbidities are defined in the methods section). Death rates have been calculated from hospital mortality. A close correlation between number of co-morbidities and fatality rates was observed ($r^2 = 0.92$)

Among co-morbidities recorded at admission to ICU, non-cured malignancy, previous antibiotic therapy, previous cardiopulmonary resuscitation and cardiogenic shock were associated with a significantly higher risk of death from septicemia. In contrast, smoking status, alcohol abuse, diabetes mellitus, previous splenectomy or major surgery did not reach statistical significance. In order to account for pre-existing comorbidities in the overall prognosis of septicemia, we measured the total sum of all to record as an "active pre-existing co-morbidities' score" (APC). The mean APC scores were higher in non-survivors than in survivors (2.4 ± 1.7 vs. 1.5 ± 1.5), and the difference was highly statistically significant ($p = 0.0005$). ICU septicemic patients with more than two pre-existing co-morbidities showed a significantly higher risk of death (RR = 1.83, CI_{95} 1.32–2.53, $p = 0.0008$).

Figure 1 relates the mortality rates among the 173 septicemic patients stratified according to the number of pre-existing co-morbidities recorded at admission to ICU. The number of co-morbidities showed a highly significant correlation with hospital mortality by simple linear regression analysis ($r^2 = 0.92$).

Admission ISS and Apache II scores were used to assess the severity of underlying disease. ISS of multiple trauma patients, averaged 27.8 ± 10 in survivors ($n = 32$) and 33.6 ± 14 in nonsurvivors ($n = 18$, $p = 0.65$, Table 3). Thus, ISS did not predict higher death rate from septicemia in multiple trauma patients. In contrast, mean Apache II scores recorded at admission to the ICU significantly differed between the populations of patients who survived septicemia and those who did not (15.8 ± 7 vs. 22.0 ± 8, $p < 0.0001$). The patients with an Apache II score ≥ 20 had a two-fold higher risk of death than those who scored less than 20 (RR = 2.02, CI_{95} 1.42–2.89, $p < 0.0001$).

Independent predictors of mortality

A model predicting mortality from septicemia in ICU patients was derived using stepwise logistic regression procedures. Variables entered into the model were age, sex, type of admission, high risk surgical diagnostic category (defined as gastrointestinal surgery versus cardiovascular, multiple trauma and other diagnostics), ultimately and rapidly fatal diseases, Active Pre-existing Co-morbidities' and Apache II scores. The two single independent predictors of mortality from septicemia identified by this analysis were the admission Apache II score ($\chi^2 = 17.08$, $p < 0.0001$) and the Active Pre-existing Co-morbidities' score ($\chi^2 = 7.32$, $p = 0.0068$, Table 4). The calculated odds ratios for dying from septicemia were 1.10 (CI_{95} 1.05–1.15) per point in the admission Apache II score and 1.16 (CI_{95} 1.04–1.28) per pre-existing co-morbidity present at the admission to the ICU. The logistic equation derived from the regression model (Table 4) provided the probability for death from septicemia in ICU patients.

Since it might be expected that co-morbidities may affect long term more than short term survival, we also performed the analysis using life status at 21 days as the outcome variable. Of the 173 septicemic patients 56 (32%) died in this time period. Interestingly, both Apache II ($\chi^2 = 15.44$, $p = 0.0001$) and pre-existing co-morbidities ($\chi^2 = 7.01$, $p = 0.0081$) were selected as independent predictors of mortality within the first 21 days after septicemia by the logistic regression procedure.

Apache II reflects both acute imbalance in physiologic parameters and chronic organ disturbances. We thus performed a subsequent logistic procedure without considering variables collected in part A of the Apache II scoring system [13]. In a separate analysis, we thus considered only the chronic organ insufficiencies accounted in Apache II (part C of the scoring system, see also Table 3) together with the other variables. By logistic regres-

Table 4. Independent factors predicting mortality from septicemia in patients at the time of admission to ICU (stepwise logistic regression model)

	Parameter estimate	s.e.	Odds ratio	CI_{95}	p value
Intercept	−3.5055	0.7028			
Apache II	0.0976	0.0236	1.10	1.05–1.15	<0.0001
Pre-existing co-morbidities	0.1457	0.0538	1.16	1.04–1.28	0.0068

Variables entered into the model have been cited in the text
Parameter estimates as well as calculated odds ratios for Apache II score and pre-existing co-morbidities correspond to values for one unit of these variables, one point in the Apache II and one co-morbidity listed in the method section, respectively
The logistic equation derived from this model which allows to determine the probability of dying from septicemia while in the ICU is the following:

$$\text{Prob}\,(1/1-\text{P}) = -3.5055 + 0.0976 \times \text{Apache II} + 0.1457 \times \text{APC}$$

where Apache II score is the score defined by Knaus and colleagues [13] and APC score is the active pre-existing co-morbidities' score which gives the number of co-morbidities recorded at admission to the ICU (see Methods)

sion, the three independent predictors for septicemia mortality were age ($\chi^2 = 4.46$; $p = 0.034$), chronic organ insufficiencies ($\chi^2 = 9.06$, $p = 0.002$) and pre-existing co-morbidities ($\chi^2 = 11.51$, $p < 0.001$). When chronic organ insufficiencies were analyzed separately, only immunocompromised state reached statistical significance ($\chi^2 = 4.40$, $p = 0.036$). Thus, in the absence of the physiological disturbances expressed by the acute points (part A) of the Apache II score, the number of pre-existing co-morbidities was the strongest independent predictor of mortality from septicemia in our population.

Figure 2 illustrates the predicted impact of pre-existing co-morbidities on the mortality predicted by the Apache II score only, based on the model generated in our study. As shown, there is a considerable overlap between mortality rates predicted by Apache II scores when the co-morbidities are considered.

Discussion

In the present study the number of pre-existing co-morbidities before admission to the ICU showed a positive correlation with mortality from septicemia, constituting an independent predictor of fatality. Weinstein and colleagues previously showed the influence of pre-disposing factors, in particular cirrhosis, neoplasms and combinations of co-morbid or coexistent conditions on the overall outcome of bacteremia of fungemia [29], extending previous observations suggesting that underlying disease severity may affect the prognosis of bacteremia, in particular due to Gram-negative organisms [10, 11, 30, 31]. In our series, co-morbidities influence the outcome of septicemic ICU patients independently to Apache II score. Importantly, the co-morbidities selected proved to be more powerful indicators of mortality than chronic organ insufficiencies recorded in the Apache II score. As expected in the latter analysis which was performed after removing Apache II score from the logistic regression procedure, age, usually weighted in the Apache II score, was an additional independent predictor of fatality.

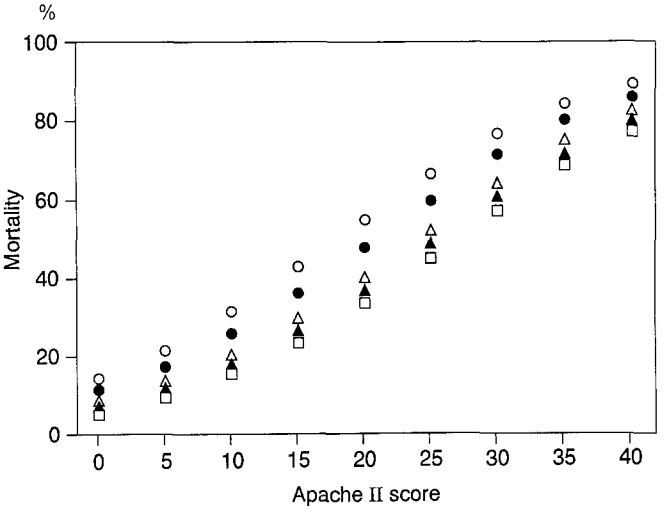

Fig. 2. Impact of pre-existing co-morbidities on the mortality predicted by Apache II score. Predicted death rates (*vertical axis*) have been calculated using the logistic equation derived from the model described in Table 4, taking into account Apache II scores on admission to the ICU (*horizontal axis*) in patients without (□) or with 1 (▲), 2 (△), 4 (●), or 6 (○) pre-existing co-morbidities (defined in the methods section). The figure illustrates the influence of pre-existing co-morbidities on mortality rates predicted by Apache II scores

Our study demonstrates that the risk of septicemia is 20-fold higher following emergency than following elective admission. In addition, patients who carried the highest risk of septicemia were those admitted after surgery of the digestive tract or after multiple trauma.

Septicemia is associated with high morbidity and mortality in ICU. Overall, the mortality of septicemic ICU patients proved to be 5-fold higher than that of non-septicemic patients over the 5 years of the study, and this figure persisted even when possible confounders were considered such as age, sex, type of admission, and primary diagnosis. Considering only the excess length of stay in the ICU, the estimated extra ICU costs attributed to septicemia approximated $ 500000 per year at our institution. Importantly, this estimate does not include indirect costs and is not adjusted for additional confounding factors. Appropriate measurements require specifically designed studies [23].

The crude hospital mortality was 44% in patients with septicemia. Higher mortality rates (50%) were reported among ICU patients with Gram-negative septic shock [32]; in the later study, only 6% of deaths were attributed to the underlying disease. In our series, 38 patients (22%) died in the first week after the diagnosis. Importantly, 19/75 (25%) of the patients who died were still alive 21 days after the day the first positive blood culture was drawn, suggesting that a substantial part of the crude mortality was attributable to the underlying disease or to the intricate complications from both primary infection and co-morbidities. Roberts and colleagues reported the results of the analysis of 1242 episodes of bacteremia over a 3-year period (1984–1987) at the Vancouver General Hospital [33]. Their data demonstrated that the influence of bacteremia on patient survival extended well beyond seven days, up to at least 30 days for most infections.

Although useful in many studies [10, 11, 21, 30–32], categorizing patient's underlying disease according to McCabe and Jackson was not selected as an independent predictor for mortality from septicemia in our population. This classification system was neither designed nor validated for use in ICU patients, and there is no study comparing it to Apache II or another prognostic index in patients with septicemia. Although our study findings need further confirmation, accounting for co-morbidities was a stronger predictor of mortality from septicemia than the McCabe and Jackson categorization in this series.

Critical care units, by design, serve patients with severe underlying diseases that compromise host defenses. Each patient must be assessed individually to determine how the underlying processes affect the defense mechanisms. The Apache II score has been prospectively validated and provides reliable estimates of patient outcomes; it accurately predicted mortality despite important differences in therapeutic modalities [13–15, 18, 19,

34] and may allow outcome comparisons among ICUs from different hospitals [16]. In the study by Knaus et al. [13] hospital mortality correlated with Apache II scores ≥ 10 in patients with septic shock. There were only 6 patients with Apache II < 10 in their study. In our study, admission Apache II was the strongest independent predictor of mortality from septicemia. The mortality rates of patients with Apache II in the 0–9, 10–19, 20–29, and ≥ 30 ranges were 23%, 33%, 54%, and 83%, respectively. These figures correspond closely to those observed by Knaus et al. in patients with septic shock (33%, 26%, 55%, and 80%, respectively) [13].

Reviewing the hospital stay of 2647 surgical patients, Munoz and colleagues clearly demonstrated a relationship between the number of co-morbidities and increased morbidities, hospital costs, and mortality [22]. In particular, they observed that ICU utilization increased with the number of diagnoses, with 47% of patients with over 5 diagnoses treated in the ICU. Furthermore, even after stratification by surgical Diagnostic-Related Groups (DRG), patients with more co-morbidities had a higher mortality.

Gross and colleagues quantified the number of co-morbidities in 148 patients admitted to a combined medical ICU-coronary care unit who stayed in the unit at least three days and found that this index was directly correlated with increased length of ICU stay and the development of infectious and non-infectious complications [24]. In their study, the length of ICU stay increased by 0.72 days for each additional co-morbidity. Similarly, pre-existing co-morbidities showed a significant relationship with the subsequent development of complications. The authors did not report death rates.

The data presented here strongly suggest the need to record and score co-existing conditions that may affect the overall prognosis of patients admitted to critical care units. Accounting for co-morbidities improved predictions available from the Apache II alone. Apache II recorded at the onset of septicemia – i.e. the day of bacteremia – takes into account changes in physiology that occur between admission to the ICU and the time of sepsis; we recently suggested that onset-of-sepsis Apache II could be a better predictor of mortality from septicemia than admission Apache II score [35]. In this series, accounting for co-morbidities improves mortality predictions available from onset-of-sepsis Apache II similar to the way it improves mortality predictions from admission Apache II. Apache III is presently under investigation and is available [36, 37]. It does include co-morbidities and more chronic health measures and disease categorizations than Apache II. It remains to be seen if Apache III predicts mortality from septicemia better than Apache II.

Although pre-determined, the choice of nine pre-existing co-morbidities in this study was somewhat arbitrary; it was based mainly on clinical judgement. Not all co-morbidities were univariately associated with higher mortality from septicemia in this study, and additional co-morbid conditions may affect the prognosis. The reason behind using a co-morbidity score was to standardize the way co-morbidities were recorded; our intention was not to propose a new scoring system. We hope to promote new investigations to validate and refine our study findings.

We recognize that our study constitutes an exploratory analysis that needs independent replications and cross validation among other institutions before definitive conclusions could be drawn. Although our study design does not allow generalization to all critical care units, we hypothesize that accounting for co-morbidities may improve Apache II outcome prediction in medical ICU population as well as it does in our surgical population. Medical patients frequently present with numerous underlying conditions which may have an impact on prognosis. Case fatality rates for critically ill patients with cancer or respiratory failure have been shown to be extremely high [38, 39]. It is also tempting to speculate that in instances where clinical judgement has been shown to predict outcome more appropriately than the Apache II score in medical ICU patients [40, 41], accounting for co-morbidities could improve the performance of the Apache II score.

References

1. Meakins JL, Marshall JC (1986) The gastrointestinal tract: the "motor" of MOF. Arch Surg 121:197–201
2. Manship L, McMillin RD, Brown JJ (1984) The influence of sepsis and multiorgan failure on mortality in the surgical intensive care unit. Am Surg 50:94–101
3. Pittet D, Herwaldt LA, Massanari RM (1992) The intensive care unit. In: Brachman PS, Bennett JV (eds) Hospital infections, Little, Brown and Company, Boston, MA, pp 405–439k
4. Monthly vital Statistics Report (1992) National Center of Health Statistics 40:February 1992
5. Donowitz LG, Wenzel RP, Hoyt JW (1982) High risk of hospital-acquired infection in the ICU patient. Crit Care Med 10:355–357
6. Pittet D, Omahen J, Tarara D, Wenzel RP (1991) Current risk factors for nosocomial bloodstream infection in a tertiary health care center. 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1991, Chicago, A800
7. Daschner FD, Frey P, Wolff G, Baumann PC, Suter PM (1982) Nosocomial infections in intensive care wards: a multicenter prospective study. Intensive Care Med 8:5–9
8. Craven DE, Kunches LM, Lichtenberg DA (1988) Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch Intern Med 148:1161–1168
9. Chandrasekar PH, Kruse JA, Matthews MF (1986) Nosocomial infection among patients in different types of intensive care units at a city hospital. Crit Care Med 14:508–510
10. McCabe WR, Jackson GG (1962) Gram-negative bacteremia. II. Clinical, laboratory, and therapeutic observations. Arch Intern Med 110:856–864
11. Freid MA, Vosti KL (1968) The importance of underlying disease in patients with gram-negative bacteremia. Arch Intern Med 121:418–423
12. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE (1981) Apache – acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 9:591–597
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) Apache II: a severity of disease classification system. Crit Care Med 13:818–829
14. Knaus WA, Draper EA, Wagner DP (1982) Evaluating outcome from intensive care: a preliminary multihospital comparison. Crit Care Med 10:491–495
15. Knaus WA, Le Gall JR, Wagner DP (1982) A comparison of intensive care in the USA and France. Lancet II:642–645

16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1986) An evaluation of outcome from intensive care in major medical centers. Ann Intern Med 104:410–418
17. Bohnen JMA, Mustard RA, Oxholm SE, Schouten BD (1988) Apache II score and abdominal sepsis. Arch Surg 133:225–229
18. Dellinger EP, Wertz MJ, Meakins JL, Solomkin JS, Allo MD, Howard RJ, Simmons RL (1985) Surgical infection stratification system for intra-abdominal infection. Arch Surg 120:21–29
19. Meakins JL, Solomkin JS, Allo MD, Dellinger EP, Howard RJ, Simmons RL (1984) A proposed classification of intra-abdominal infections. Arch Surg 119:1372–76
20. Ziegler EJ, Fisher CJ, Sprung CL, Straube RC, Sadoff JC, Foulke GE, Wortel CH, Fink MP, Dellinger RP, Teng NNH, Allen IE, Berger HJ, Knatterud GL, LoBuglio AF, Smith CR (1991) Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. N Engl J Med 324:429–436
21. Greenman RL, Schein RMH, Martin MA, Wenzel RP, MacIntyre NR, Emmanuel G, Chmel H, Kohler RB, McCarthy M, Plouffe J, Russell A (1991) A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 266:1097–1102
22. Munoz E, Sterman H, Cohen J, Goldstein J, Margolis IB, Wise L (1988) Financial risk, hospital cost, complications, and comorbidities in surgical noncomplication- and noncomorbidity-stratified diagnostic related groups. Ann Surg 207:305–309
23. Haley RW (1991) Measuring the costs of nosocomial infections: methods for estimating economic burden on the hospital. Am J Med 91(3B):32–38
24. Gross PA, DeMauro PJ, Van Antwerpen C, Wallenstein S, Chiang S (1988) Number of comorbidities as a predictor of nosocomial infection acquisition. Infect Control Hosp Epidemiol 9:497–500
25. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failures and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874
26. Baker SP, O'Neill B, Haddon W, Long WB (1974) The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 14:187–196
27. Greenspan L, McLellan BA, Greig H (1985) Abbreviated injury scale and injury severity score: a scoring chart. J Trauma 25:60–67
28. Pine RW, Wertz MJ, Lennard ES, Dellinger EP, Carrico CJ, Minshew BH (1983) Determinants of organ malfunction or death in patients with intra-abdominal sepsis. Arch Surg 118:242–249
29. Weinstein MP, Murphy JR, Reller LB, and Lichtenstein KA (1983) The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults: II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis 5:54–70
30. Kreger BE, Craven DE, Carling PC, and McCabe WR (1980) Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. Am J Med 68:332–343
31. Bryan CS, Reynolds KL, and Brenner ER (1983) Analysis of 1186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. Rev Infect Dis 5:629–638
32. Calandra T, Glauser MP, Schellekens J, Verhoef J and the Swiss-Dutch J5 Immunoglobulin Study Group (1988) Treatment of gram-negative septic shock with human IgG antibody to Escherichia coli J5: a prospective, double-blind, randomized trial. J Infect Dis 158:312–319
33. Roberts FJ, Geere IW, and Coldman A (1991) A three-year study of positive blood cultures, with emphasis on prognosis. Rev Infect Dis 13:34–46
34. Knaus WA, Wagner DP, Draper EA (1989) The value of measuring severity of disease in clinical research on acutely ill patients. J Chron Dis 37:455–461
35. Pittet D, Thiévent B, Wenzel RP, Li N, Suter PM (1992) Onset-of-sepsis Apache II is a better predictor of mortality from septicemia than admission Apache II score. 32st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), October 1992, Anaheim, CA, A7
36. Knaus WA, Wagner DP, Draper EA et al (1991) The Apache III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636
37. Knaus WA, Wagner DP, Lynn J (1991) Short-term mortality predictions for critically ill hospitalized adults: science and ethics. Science 254:389–394
38. Davis H, Lefrak SS, Miller D, Malt S (1980) Prolonged mechanically-assisted ventilation: an analysis of outcome and charges. JAMA 243:43–45
39. Hauser JH, Tabak J, Baier H (1982) Survival of patients with cancer in a medical critical care unit. Arch Intern Med 142:527–529
40. Kruse JA, Thill-Baharozian MC, Carlson RW (1988) Comparison of clinical trial assessment with Apache-II for predicting mortality risk in patients admitted to a medical intensive care unit. JAMA 260:1739–1742
41. Brannen AL, Godfrey LJ, Groetter WE (1989) Prediction of outcome from critical illness. A comparison of clinical judgment with a prediction rule. Arch Intern Med 149:1083–1086

D. Pittet, M.D., M.S.
Division of Infectious Diseases
Department of Internal Medicine
University Hospital of Geneva
CH-1211 Geneva-14
Switzerland