Intensive Care Med (2002) 28:108–121
DOI 10.1007/s00134-001-1143-z

ORIGINAL

Corinne Alberti
Christian Brun-Buisson
Hilmar Burchardi
Claudio Martin
Sergey Goodman
Antonio Artigas
Alberto Sicignano
Mark Palazzo
Rui Moreno
Ronan Boulmé
Eric Lepage
Jean Roger Le Gall

Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study

Received: 9 January 2001
Final revision received: 9 January 2001
Accepted: 6 September 2001
Published online: 4 December 2001

The authors for the European Sepsis Group Supported by an educational grant from Roche. Presented in part at the Congress of the European Society in Intensive Care Medicine in 1998 and at the Congress of the American Thoracic Society in 1999.

C. Alberti (✉)
Department of Biostatistics,
Saint-Louis Hospital, U444-INSERM,
1 Avenue Claude Vellefaux,
75475 Paris Cedex 10, France
e-mail: corinne.alberti@rdb.ap-hop-paris.fr

C. Alberti · J.R. Le Gall
Intensive Care Unit, Saint-Louis Hospital,
Paris 7 University,
1 Avenue Claude Vellefaux,
75475 Paris Cedex 10, France

C. Brun-Buisson
Intensive Care Unit,
Henri-Mondor Hospital, Créteil, France

H. Burchardi
Intensive Care Unit, Göttingen Hospital,
Göttingen, Germany

C. Martin
Critical Care–Trauma Centre,
London Health Sciences Centre,
London, Canada

S. Goodman
Intensive Care Unit,
Hadassah Hebrew University
Medical Center, Jerusalem, Israel

A. Artigas
Intensive Care Unit, Parc Taulli Hospital,
Sabadell Barcelona, Spain

A. Sicignano
Anestesia e Rianimazione,
Maggiore Hospital, Milan, Italy

M. Palazzo
Intensive Care Unit,
Charing Cross Hospital, London, UK

R. Moreno
Intensive Care Unit,
Santo Antonio dos Capuchos Hospital,
Lisbon, Portugal

R. Boulmé · E. Lepage
Medical Information Unit,
Henri-Mondor Hospital, Créteil, France

Abstract *Objectives:* To examine the incidence of infections and to describe them and their outcome in intensive care unit (ICU) patients. *Design and setting:* International prospective cohort study in which all patients admitted to the 28 participating units in eight countries between May 1997 and May 1998 were followed until hospital discharge. *Patients:* A total of 14,364 patients were admitted to the ICUs, 6011 of whom stayed less than 24 h and 8353 more than 24 h. *Results:* Overall 3034 infectious episodes were recorded at ICU admission (crude incidence: 21.1%). In ICU patients hospitalised longer than 24 h there were 1581 infectious episodes (crude incidence: 18.9%) including 713 (45%) in patients already infected at ICU admission. These rates varied between ICUs. Respiratory, digestive, urinary tracts, and primary bloodstream infections represented about 80% of all sites. Hospital-acquired and ICU-acquired infections were documented more frequently microbiologically than community-acquired infections (71% and 86%, respectively vs. 55%). About 28% of infections were associated with sepsis, 24% with severe sepsis and 30% with septic shock, and 18% were not classified. Crude hospital mortality rates ranged from 16.9% in non-infected patients to 53.6% in patients with hospital-acquired infections at the time of ICU admission and acquiring infection during the ICU stay. *Conclusions:* The crude incidence of ICU infections remains high, although the rate varies between ICUs and patient subsets, illustrating the added burden of nosocomial infections in the use of ICU resources.

Keywords Sepsis · Infection · Critical care · Incidences · Epidemiology · Mortality

Introduction

Sepsis is an important cause of admission in intensive care units (ICU) [1], probably due to the more severe illnesses of hospitalised patients and to the persistently high incidence of nosocomial infections. However, despite the availability of potent antibiotics and refined supportive care the mortality of septic patients remains high, with overall estimates of about 30% and increasing to 50% when associated with shock [2].

This high mortality has prompted intensive research into the development of new adjunctive therapies in the management of sepsis. Over the past decade a number of randomised, controlled clinical trials have been conducted to test the efficacy of agents modulating the host response to infection. Until the PROWESS study [3] these studies failed to show any benefit of the new therapies in terms of survival [4, 5, 6]. These disappointing results may be explained at least partially by the heterogeneity of patients included in such clinical trials, the heterogeneity in infections studied and the lack of better knowledge of the patho-physiological mechanisms of sepsis and acute inflammatory response [4, 7].

A panel of experts of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) produced a consensus statement on definitions for the septic syndromes in 1992 that has helped to characterise the various stages of the associated inflammatory response and to differentiate infectious from non-infectious processes [8]. These criteria have commonly been used to enrol patients in recent therapeutic trials and to describe patients in epidemiological studies. However, these broad definitions cannot provide accurate estimates of mortality in septic patient subsets, and estimates range from 30% to 60% [9]. In clinical trials the inclusion criteria are often restrictive and the differing definitions of sepsis make comparison of their results difficult [5, 7, 10, 11], while most epidemiological studies focus on only one particular aspect of infection, such as bacteraemia, nosocomial infection, ventilator-acquired pneumonia, or sepsis and related conditions. Hence the incidence, characteristics and outcome of unselected infected patients are poorly described, except in a few reports [12, 13]. Therefore there is a need for a better understanding of the epidemiology and outcome of sepsis and infection-related syndromes in the critically ill patients.

We conducted a large cohort study in 14,364 unselected consecutive adult patients admitted to 28 ICUs in Europe, Canada and Israel from May 1997 to May 1998. Before studying the relationship of infection characteristics to sepsis and related conditions, we review the incidence and epidemiology of infections in ICU patients and the outcome of infected patients.

Patients and methods

Eligibility criteria

This prospective multicentre cohort study was conducted over a 1-year period in 28 intensive care units (ICU) in six European countries, Canada and Israel. All adult patients (age ≥18 years) consecutively admitted in the participating ICUs between 1 May 1997 and 31 May 1998 were enrolled. Approximately 500 patients had been expected to be enrolled in each unit. Three ICUs with a yearly admission rate of 1,000 patients enrolled only one-half of their patients, randomly selected to avoid selection bias. If a patient was admitted more than once, only the data from the first admission were analysed, except when the delay between one ICU discharge and the next ICU admission was longer than 30 days.

Definitions and measurements

ICU

The ICUs were classified as surgical if surgical patients accounted for more than 75% of ICU admissions, as medical if the rate of admitted medical patients was more than 75%, and otherwise as mixed. None of the participating ICUs specialised in trauma.

Definitions of groups

The whole cohort was divided into two groups depending on the length of stay (LOS) in ICU: those staying 24 h or less (short-stay group) and those staying more than 24 h (long-stay group). In the former group, which was a large component of admissions in some ICUs (mainly used as recovery room), it was decided to collect only a minimal set of data. On these patients, information was collected only if they were infected at ICU admission, or died within the 24-h period. The two groups were analysed separately.

Data collection

Data were collected by a single trained data collector in each participating unit, using standardised forms and a specific database-oriented software derived from FoxPro (Microsoft Visual FoxPro 5.0 1995). Trained data collectors were either a physician (22 ICUs) or a research nurse (6 ICUs). They were responsible for the prospective and daily data collection both from interviewing the physician in charge of the patient and from reviewing daily medical charts. For all variables collected, precise definitions were provided in an operating manual.

In all patients from the long-stay group and in infected patients from the short-stay the following information was recorded. It comprised demographic characteristics (age, sex), admission category (medical, scheduled surgery, unscheduled surgery, or trauma), and origin (emergency, operating or recovery rooms, wards, or another ICU from the same hospital, or transferred from another hospital). The presence of underlying disease [metastatic cancer, haematological malignancy, acquired immunodeficiency syndrome (AIDS)] was recorded using SAPS II definitions [14], as well as other comorbidities such as cirrhosis, chronic heart failure, chronic pulmonary failure using Acute Physiology and Chronic Health Evaluation II definitions [16], non-metastatic cancer, chronic obstructive pulmonary disease, alcoholism (regular intake of more than 80 g of alcohol per day for at least 6 months), diabetes mellitus (need of daily injection of insulin prior to ICU admission), chronic renal failure (need of chronic renal support or history of chronic renal insufficiency with a serum creatinine level over 300–400 µmol/l), human immunodeficiency virus (HIV) status

(without complications defining AIDS), bone marrow transplantation (autologous or homologous infusion), drug addiction (with intravenous drugs as opiates and derivatives for at least 6 months prior to admission). Immuno-compromised state was defined by either administration in the 6 months prior to ICU admission of steroid treatment (at least 0.3 mg/kg prednisolone), radiation therapy, chemotherapy, or as severe malnutrition, congenital immunohumoral or cellular immune deficiency state.

For the calculation of SAPS II and LOD scores, laboratory and clinical data not measured were assigned the value score of zero. To determine neurological status patients receiving sedative drugs were assigned the Glasgow Coma Score measured or estimated before sedation.

All patients were screened for infection at ICU admission and every day during the ICU stay. Infection was defined on the basis of clinical history, clinical symptoms, physical examination and laboratory findings suggesting the presence of infection (a known or strongly suspected source of infection with positive bacterial culture for a pathogen or presence of gross pus in a closed space) that justified administration of anti-infective therapy (excluding antimicrobial prophylaxis). Infection was characterised as follows: microbiologically or clinically documented, community-, hospital- or ICU-acquired, anatomical site(s) involved, aetiological microorganism(s), presence of bacteraemia and grade of sepsis. Definitions of infection were those from the Centres for Diseases Control [17].

The source of infection was defined as follows:

- Microbiologically documented infection: confirmed by positive cultures of blood or body fluid from a site of suspected infection.
- Clinically documented infection: presence of gross purulence or an abscess (anatomical and/or by imagery and/or histological evidence), which may not be microbiologically documented if the culture remains sterile due to antibiotic therapy.
- Community-acquired infection: infection present on admission to hospital or developing within 48 h of admission.
- Hospital-acquired infection: infection not present on admission to hospital and developing 48 h or more after admission or secondary to a medical/surgical intervention.
- ICU-acquired infection: infection not present on admission to ICU and developing 48 h or more after ICU admission or secondary to a medical/surgical intervention in the ICU.

Categorisation of infection as clinically documented infection was based either on real time interviews of clinicians in charge of the patient if the data collector was a nurse or from the personal experience of the data collector if he was physician himself; a diagnosis of microbiologically documented infection was based on the same clinical information complemented by microbiology laboratory results. When a patient experienced more than one episode of ICU-acquired infection, only the first episode was utilised in the analysis.

Sepsis and sepsis-related conditions were diagnosed according to the criteria proposed by the ACCP/SCCM [8]:

- Systemic inflammatory response syndrome (SIRS): more than one criterion of the following: temperature >38°C or <36°C, tachycardia (heart rate >90 beats per min), tachypnoea [manifested by a raised respiratory rate (>20 breaths per min) or hyperventilation ($PaCO_2$<32 mmHg) or mechanical ventilation, altered white blood cell count (>12,000 per mm^3, <4000 per mm^3).
- Sepsis: systemic inflammatory response to infection.
- Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion abnormality or sepsis-induced hypotension in the absence of any obvious explanation other than sepsis (hypotension: systolic blood pressure <90 mmHg or a drop in systolic blood pressure of >40 mmHg from baseline; metabolic acidosis: elevated plasma lactate or unexplained metabolic acidosis with pH <7.3 or base excess ≥–5 mEq/l; arterial hypoxaemia: $PaO_2 \leq 70$ mmHg or $PaO_2/FIO_2 \leq 280$; oliguria: <30 ml/h for 3 h or 700 ml/24 h; coagulopathy: increase ≥20% in prothrombin time or drop in platelet count by 50% or to $<100\times10^9$/l; encephalopathy: Glasgow Coma Score <13).
- Septic shock: sepsis-induced hypotension persisting despite adequate fluid resuscitation along with the presence of hypoperfusion abnormalities or organ dysfunction (patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction but would be considered to have septic shock).

Finally, outcomes at ICU and hospital discharge were recorded.

In non-infected patients from the short-stay group only minimal data were recorded: demographic data, admission category, date of ICU discharge and outcome.

Data evaluation and quality control

Quality control of data was performed as follows. First, the responsibility for data collection was in the hands of a trained data collector in each participating unit, using standardised forms and a computer program. Training in data collection was organised at the operating centre (Paris) and in each participating country. Secondly, reliability checks were developed into the computer programs based on ranges for physiological and biological data and logical checks. Thirdly, quality control of data was performed at the mid-point of the study by an external auditor, who reviewed 15 main variables from 15 ICU admissions randomly selected in each unit. The auditor blindly measured all these variables; then the inter-rater reproducibility of the 15 variables was studied using Cohen's κ statistic for the 11 categorical variables (admission categories, SAPS II comorbidity, presence of infection, microbiologically or clinically documented, community-, hospital- or ICU-acquired, infection sites, ICU and hospital vital status) and intraclass correlation coefficient for the four continuous variables (SAPS II, age, ICU and hospital LOS).

In addition, a ''hotline'' was available at the operating centre for any requests, questions or problems with protocol, forms, operating manual and software. At the end of the study, missing data and inconsistencies were resolved by e-mails addressed to each data collector and by data management work.

Statistical analysis

Comparisons with baseline characteristics used the χ^2 test for categorical data and the Wilcoxon or Kruskal-Wallis tests for continuous data. Results are expressed as numerical values and percentages with 95% confidence interval (95%CI) for categorical variables, and as median and 5th–95th percentiles for continuous variables. Survival curves from ICU admission were computed using the Kaplan-Meier method and were compared using the log-rank test. All statistical tests were two-tailed. Confidence intervals are presented with a type I risk error of 5%. Statistical analysis was performed using SAS 6.12 (SAS, Cary, N.C., USA) and S-plus 2000 (MathSoft, Seattle, Wash., USA) software packages for PC computer.

Results

Characteristics of participating units

There were five ICUs each in Italy, France and Spain, four in Canada, three units each in Germany and Portugal, two in the UK, and one in Israel (Table 1, see Ap-

Table 1 Characteristics of intensive care units of the study

	Length of study (months)	No. of included ICU admissions	Patients with ICU LOS more than 24 h						
			n	Surgical		Infected at admission		ICU-acquired infection	
				n	%	*n*	%	*n*	%
Canada									
Unit 1	7.5	1206	550	251	45.6	99	18.0	96	17.5
Unit 2	10	648	402	174	43.3	131	32.6	70	17.4
Unit 3	12	1525	711	399	56.1	135	19.0	90	12.7
Unit 4	10	690	524	172	32.8	8	1.5	159	30.3
France									
Unit 1	12	501	361	26	7.2	223	61.8	51	14.1
Unit 2	12	372	247	79	32.0	149	60.3	56	22.7
Unit 3	12	500	381	84	22.0	159	41.7	99	26.0
Unit 4[a]	12	473	301	30	10.0	164	54.5	74	24.6
Unit 5[a]	12	342	179	18	10.1	104	58.1	36	20.1
Germany									
Unit 1	9	1599	617	496	80.4	81	13.1	47	7.6
Unit 2	12	300	82	9	11.0	14	17.1	4	4.9
Unit 3	12	881	403	363	90.1	105	26.1	67	16.6
Israel									
Unit 1	12	516	346	210	60.7	118	34.1	61	17.6
Italy									
Unit 1	12	232	162	99	61.1	70	43.2	46	28.4
Unit 2	9	278	134	54	40.3	57	42.5	30	22.4
Unit 3	9	359	243	143	58.8	30	12.3	27	11.1
Unit 4	12	325	183	118	64.5	50	27.3	22	12.0
Unit 5	12	349	237	129	54.4	93	39.2	74	31.2
Portugal									
Unit 1	7	272	200	46	23.0	99	49.5	38	19.0
Unit 2	12	192	119	33	27.7	68	57.1	37	31.1
Unit 3	12	264	195	39	20.0	124	63.6	47	24.1
Spain									
Unit 1	9	339	263	16	6.1	48	18.3	6	2.3
Unit 2	12	227	199	71	35.7	131	65.8	46	23.1
Unit 3	12	349	284	137	48.2	110	38.7	78	27.5
Unit 4[a]	12	492	370	144	38.9	52	14.1	40	10.8
Unit 5	9	386	203	44	21.7	43	21.2	21	10.3
UK									
Unit 1	12	248	184	119	64.3	123	66.5	91	49.2
Unit 2	11	499	273	125	45.8	108	39.6	68	24.9

[a] Only one-half of ICU admissions were included in the study; percentages are based on the available data

pendix). Twenty-five (89%) units were from teaching hospitals. The median number of beds per hospital was 632 (5th–95th percentiles: 450–1,660) and that per ICU was 14 (6–28). There were 2 (7.1%) surgical units, 8 (28.6%) medical units and 18 (64.3%) mixed units.

Quality control

The percentage of missing data per item at ICU admission ranged from 0.2% to 3%. Regarding the ACCP/SCCM criteria in infected patients, the rate of missing values was 5.6% at ICU admission and reached 11.4% during ICU stay. Data on hospital outcome were not available in five units. Reproducibility was studied on a random sample of 335 ICU admissions. Overall, median κ statistics among the 11 categorical variables was 0.81 (range 0.54–1.0) and median intra-class correlation coefficient of the four continuous variables was 0.75 (range 0.70–0.98). The values were of 0.80 for presence of infection at ICU admission, 0.70 for presence of ICU-acquired infection, 0.70 for community-acquired

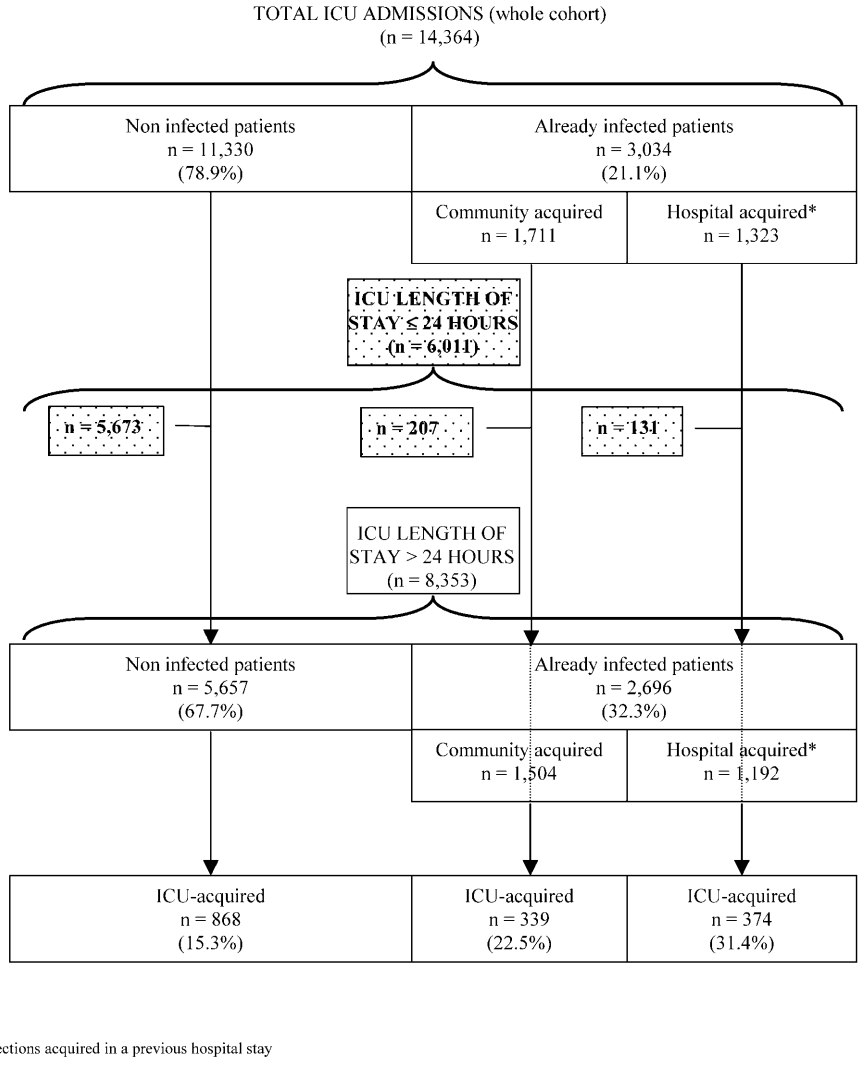

Fig. 1 Flow diagram of enrolled patients

versus hospital-acquired, 0.71 for microbiologically documented versus clinically documented. For sites of infection, agreement ranged from 0.73 (urinary tract) to 0.93 (neurological site). The κ value was 0.54 for the metastatic cancer variable, which had little effect on global results.

Characteristics of ICU admissions

The median number of admissions in the participating ICUs was 365 (229–1,413). Of all 14,364 patients admitted, 8,353 (58.2%) had an ICU length of stay >24 h (Fig. 1) and constituted the long-stay group. Their median age was 64 (27–83) years, and median SAPS II and LOD on ICU admission were 34 (13–67) and 4 (0–11), respectively (Table 2). The remaining 6,011 (41.8%) patients had a short (≤24 h) ICU stay (Fig. 1). Two-thirds of these patients (*n*=3,807) were surgical patients. Of these 6,011 patients, only 338 (5.6%) were infected at ICU admission and constituted the analysed short-stay group (Fig. 1); their median age was 62 years (26–82), median SAPS II 50 (12–105) and median LOD 7 (0–18).

Infection

A total of 3034 infectious episodes were recorded at ICU admission (338 in the short-stay group and 2696 in the long-stay group) and 1581 during ICU stay. About one-half of ICU-acquired infections occurred in patients previously infected at ICU admission (Fig. 1). Of the 4277 episodes of infection recorded in the long-stay group, 3946 (92.3%) could be classified into one of the categories of the ACCP/SCCM classification. Results are presented in Table 3. The severity of infectious episode did not markedly depend on the source or site of infection or on its microbiological documentation. However, abdominal infections were more likely to be associated with septic shock (46% vs. 28.4% in the remainders,

Table 2 Long-stay group: ICU admission (either community- or hospital-acquired) infection incidences according to main baseline characteristics of patients; percentage calculation are based on the total data available per item and are given by rows

	Total of long-stay admissions (*n*=8353)	Community-acquired (*n*=1504)	Hospital-acquired (*n*=1192)	Total infected patients at admission (*n*=2696)
Age (years)	64 (27–83)	61 (24–83)	64 (31–82)	63 (27–83)
Sex male	5149 (61.6%)	939 (62.6%)	777 (65.3%)	1716 (63.6%)
Origin				
Emergency room, public place, or consultation	2330	640 (27.5%)	68 (2.9%)	708 (30.4%)
Wards	2086	318 (15.2%)	579 (27.8%)	897 (43.0%)
Operating, recovery rooms	2323	178 (7.7%)	223 (9.6%)	401 (17.3%)
Other ICU	228	25 (11.0%)	76 (33.3%)	101 (44.3%)
Transferred from another hospital	1267	338 (26.7%)	243 (19.2%)	581 (45.9%)
Admission categories				
Medical	4407	1154 (26.2%)	654 (14.8%)	1808 (41.0%)
Surgical scheduled	1915	53 (2.8%)	178 (9.3%)	231 (12.1%)
Surgical emergency	1244	226 (18.2%)	299 (24.0%)	525 (42.2%)
Trauma	751	67 (8.9%)	60 (8.0%)	127 (16.9%)
Comorbidities				
No comorbidity	3844	642 (16.7%)	389 (10.1%)	1031 (26.8%)
At least one comorbidity	4509	862 (19.1%)	803 (17.8%)	1665 (36.9%)
Chronic obstructive pulmonary disease	1225	304 (24.8%)	210 (17.1%)	514 (42.0%)
Non-metastatic cancer	996	98 (9.8%)	165 (16.6%)	263 (26.4%)
Diabetes mellitus	977	168 (17.2%)	170 (17.4%)	338 (34.6%)
Alcoholism	735	216 (29.4%)	146 (19.9%)	362 (49.3%)
Chronic heart failure	688	129 (18.8%)	121 (17.6%)	250 (36.3%)
Immuno-compromised state	597	137 (22.9%)	192 (32.2%)	329 (55.1%)
Chronic renal failure	566	118 (20.8%)	143 (25.3%)	261 (46.1%)
Cirrhosis	431	87 (20.2%)	84 (19.5%)	171 (39.7%)
Metastatic cancer	396	54 (13.6%)	81 (20.5%)	135 (34.1%)
Chronic pulmonary failure	372	95 (25.5%)	55 (14.8%)	150 (40.3%)
Haematological malignancy	361	93 (25.8%)	131 (36.3%)	224 (62.0%)
Drug addiction	170	69 (40.6%)	41 (24.1%)	110 (64.7%)
AIDS or HIV positive	155	85 (54.8%)	34 (21.9%)	119 (76.8%)
Bone marrow transplantation	83	22 (26.5%)	37 (44.6%)	59 (71.1%)
LOS before ICU entry	2 (1–30)	1 (1–12)	10 (1–59)	2 (1–38)
SAPS II at ICU admission	34 (13–67)	40 (17–74)	43 (21–76)	42 (18–75)
LOD at ICU admission	4 (0–11)	5 (1–12)	6 (1–12)	6 (1–12)

p=0.001), as well as bloodstream infections (41.2% vs. 18.8%, *p*=0.001), and *Candida* or fungal infections (38.9% vs. 31.8%, *p*=0.003). In the short-stay group septic shock represented 55.8% of infections, severe sepsis 8.6%, sepsis 24.7%, and infection without SIRS 10.9%.

Infections at ICU admission

The overall incidence of infection at ICU admission in the entire cohort was 21.1% (95%CI 20.4–21.8), with similar incidences of community-acquired infections (11.9%; 95%CI 11.4–12.4) and hospital-acquired infections (9.2%; 95%CI 8.7–9.7; Fig. 1).

Long-stay group

The incidence of infection recorded at ICU admission was 32.3% overall (95%CI 31.3%–33.3%; Fig. 1), and ranged from 1.5% to 66.5% across the ICUs (median 39%). The incidence was 18.2% (95%CI 15.9%–20.6%) in surgical units, 29.3% (95%CI 28.1%–30.5%) in mixed units, and 47.7% (95%CI 45.4%–49.9%) in medical units. Likewise, the incidence of infection was higher in medical (41.0%) and emergency surgical patients (42.2%) than in trauma (16.9%) and scheduled surgical patients (12.1%). The severity of illness of infected patients, measured either by the median SAPS II or LOD at admission, was significantly higher (42 and 6, respectively) than that of non-infected patients (median SAPS II 31, 5th–95th percentiles 13–63, *p*=0.001; median LOD 4, 5th–95th percentiles, 0–10, *p*=0.001).

Table 3 Long-stay group: incidence of sepsis and sepsis-related conditions according to infection characteristics; percentages are calculated for rows

	Total (*n*=3946) *n*	Infection without SIRS (*n*=707, 17.9%)		Sepsis (*n*=1115, 28.3%)		Severe sepsis (*n*=944, 23.9%)		Septic shock (*n*=1180, 29.9%)	
		n	%	*n*	%	*n*	%	*n*	%
Source of infection									
Community-acquired	1432	287	20.0	453	31.6	301	21.0	391	27.3
Hospital-acquired	1114	177	15.9	291	26.1	272	24.4	374	33.6
ICU-acquired	1400	243	17.4	371	26.5	371	26.5	415	29.6
Main sites									
Respiratory	2438	478	19.6	702	28.8	621	25.5	637	26.1
Digestive	533	57	10.7	143	26.8	88	16.5	245	46.0
Primary bacteraemia	489	57	11.7	114	23.3	131	26.8	187	38.2
Urinary tract	433	87	20.1	107	24.7	108	24.9	131	30.3
Multi-sites	531	69	13.0	125	23.5	157	29.6	180	33.9
Microbiologically documented	2804	456	16.3	735	26.2	728	26.0	885	31.6
Clinically documented	1142	251	22.0	380	33.3	216	18.9	295	25.8
Bloodstream infection	774	66	8.5	173	22.4	216	27.9	319	41.2
No bloodstream infection	3172	641	20.2	942	29.7	728	23.0	861	27.1
Main microbiology									
Gram-positive cocci	1525	232	15.2	367	24.1	428	28.1	498	32.7
Gram-negative bacilli	1890	304	16.1	539	28.5	460	24.3	587	31.1
Candida, fungi	411	78	19.0	84	20.4	89	21.7	160	38.9
Polymicrobial	968	156	16.1	249	25.7	249	25.7	314	32.4

Table 2 reports the incidence rates of infection at ICU admission (community- and hospital-acquired) according to the main baseline characteristics of patients in the long-stay group. These rates differed significantly depending on the origin of patients, with higher incidence recorded in patients transferred from another ICU (44.3%), from the wards (43.0%) or from another hospital (45.9%), than in patients newly admitted to the hospital (30.4%) or admitted from the operating/recovery rooms (17.3%).

Community-acquired infections accounted for 55.8% and hospital-acquired infections for 44.2% of infections recorded on ICU admission, and their respective incidence rates were 18.0% (95%CI 17.2–18.8) and 14.3% (95%CI 13.5–15.0). At least one comorbidity was reported in 4509 patients (54.0%). Cancer (either metastatic or not; 16.7%), chronic obstructive pulmonary disease (15%) and diabetes mellitus (11.7%) were the comorbidities most often recorded. Infection on ICU admission was associated with the presence of pre-existing disease, with a 36.9% incidence in patients with at least one comorbidity, and a 26.8% incidence in patients with no comorbidity (p=0.001). The incidence of infection ranged from 26.4% (in patients with non-metastatic cancer) to 76.8% (in patients with AIDS or HIV positive).

The characteristics of infections are displayed in Table 4. Respiratory tract infection (mainly pneumonia) was the most common site for both community- and hospital-acquired infections, followed by digestive tract sites (mainly peritonitis), and urinary tract infection in community-acquired infections or primary bloodstream infection in hospital-acquired ones. These four major sites accounted for more than 80% of all sources of infection. Multiple sites were involved in 10% of community-acquired infections and 16.7% of hospital-acquired infections.

A microbiological documentation was available for 70.6% of hospital-acquired infections but only 54.8% of community-acquired infections recorded on admission. In these two groups bacteraemia occurred in 33.3% and 29.2% of microbiologically documented infections, respectively. The major isolated micro-organisms are listed in Table 5, and shown according to sites involved in Fig. 2. Polymicrobial infections were recorded in 41.5% of hospital-acquired infections and 28.6% of community-acquired infections. Gram-positive cocci accounted for 39.1% and 35.7% of community- and hospital-acquired isolates, respectively, whereas Gram-negative bacilli represented 35.3% and 47.9% of community- and hospital-acquired isolates, respectively.

Short-stay group

The incidence of infection recorded at ICU admission in this subset of patients was 5.6% (95%CI, 5.0%–6.2%;

Table 4 Long-stay group: infection characteristics, sepsis syndromes and sites

	Community-acquired (*n*=1504)		Hospital-acquired (*n*=1192)		ICU-acquired (*n*=1581)	
	n	%	*n*	%	*n*	%
Sepsis and related conditions[a]						
Infection without SIRS	287	20.0	177	15.9	243	17.4
Sepsis	453	31.6	291	26.1	371	26.5
Severe sepsis	301	21.0	272	24.4	371	26.6
Septic shock	391	27.3	374	33.6	415	29.6
Sites						
Number of multi-site infections[a]	151	10.0	199	16.7	212	13.4
Total number of sites	1680		1422		1821	
Respiratory[b]	976	58.1	648	45.6	1004	155.1
Pneumonia[b]	739	44.0	531	37.3	759	41.7
Digestive[b]	192	11.4	268	18.8	104	5.7
Peritonitis[b]	102	6.1	198	13.9	51	2.8
Urinary tract[b]	121	7.2	116	8.2	230	12.6
Primary bloodstream infections[b]	97	5.8	160	11.3	279	15.3
Skin and soft tissue[b]	73	4.3	93	6.5	89	4.9
Neurological[b]	73	4.3	18	1.3	13	0.7
Meningo-encephalitis[b]	62	3.7	13	0.9	11	0.6
Miscellaneous[b]	123	7.3	84	5.9	72	4.0
Unknown[b]	25	1.5	35	2.5	30	1.6

[a] Percentages by number of infections
[b] Percentages by number of infected sites

Table 5 Long-stay group: infection characteristics, microbiology

	Community-acquired (*n*=1504)		Hospital-acquired (*n*=1192)		ICU-acquired (*n*=1581)	
	n	%	*n*	%	*n*	%
Number of microbiologically documented infections[a]	824	54.8	841	70.6	1356	85.8
Number of bloodstream infections[b]	241	29.2	280	33.3	309	22.8
Polymicrobial infections[b]	236	28.6	349	41.5	459	33.8
Total number of micro-organisms	1147		1347		1985	
Staphylococcus aureus[c]	134	11.7	185	13.7	295	14.9
Other Gram-positive cocci[c]	315	27.5	296	22.0	447	22.5
Total Gram-positive cocci[c]	449	39.1	481	35.7	742	37.4
Haemophilus, Moraxella[c]	71	6.2	39	2.9	67	3.4
Escherichia coli, Proteus[c]	154	13.4	150	11.1	210	10.6
Enterobacteraceae[c]	80	7.0	178	13.2	263	13.2
Aerobic Gram-negative bacilli[c]	81	7.1	251	18.6	381	19.2
Other Gram-negative bacilli[c]	19	1.7	27	2.0	56	2.8
Total gram-negative bacilli[c]	405	35.3	645	47.9	977	49.2
Anaerobes[c]	37	3.2	35	2.6	31	1.6
Mycobacteria, viruses, parasites[c]	104	9.1	25	1.9	11	0.6
Candida, fungi[c]	103	9.0	140	10.4	192	9.7
Intra-cellular micro-organisms[c]	25	2.2	8	(0.6)	2	(0.1)
Miscellaneous[c]	24	2.1	13	1.0	30	1.5

[a] Percentages by number of infections
[b] Percentages by number of microbiologically documented infections
[c] Percentages by number of isolates

Fig. 1). Community-acquired infections accounted for 61.2% and hospital-acquired infections for 38.8% of infections. The major infected sites were the respiratory (*n*=166/377, 44%) and digestive tract (*n*=76/377, 20%) and primary bloodstream infections (*n*=35/377, 9.3%). Infection was microbiologically documented in 46.1% (*n*=156), and bacteraemia occurred in 41% of such episodes (*n*=64/156). Gram-positive cocci represented 38% (*n*=81/212) of isolates and Gram-negative bacilli 47.2% (100/212).

ICU-acquired infection

Of the 8353 patients in the long-stay group 1581 (crude incidence: 18.9%; 95%CI 18.1–19.8) developed at least one ICU-acquired infection (Fig. 1). The crude incidence of ICU-acquired infection ranged from 2.3% to 49.2% across ICUs, and varied from 11.2% (95%CI 9.2–13.1) in surgical units, 18.1% (95%CI 16.4–19.8) in medical units, and up to 20.7% (95%CI 19.6–21.8) in mixed

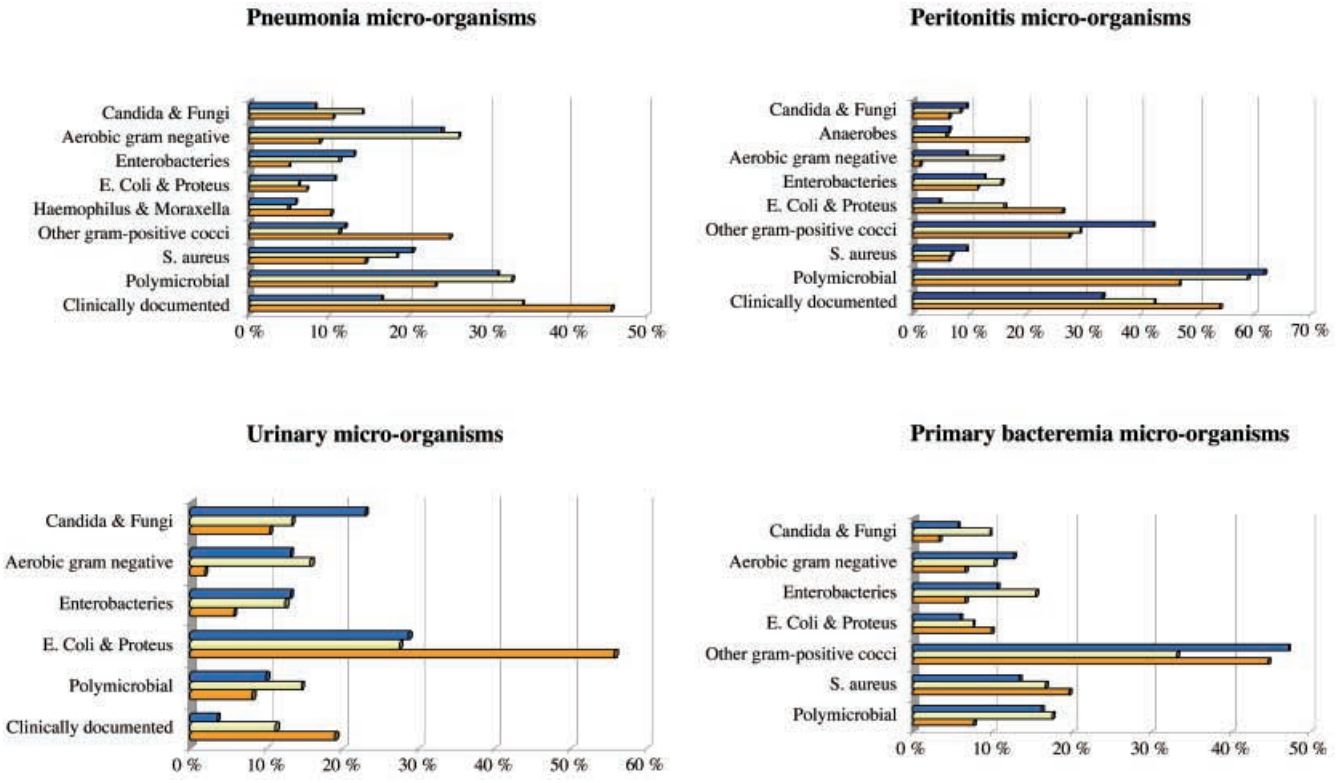

Fig. 2 Description of micro-organisms according to infected site and source of infection. *Orange* community-acquired; *yellow* hospital-acquired; *blue* ICU-acquired. Percentages are calculated as in Table 4

units. ICU-acquired infection occurred in 868 of the 5567 non-infected patients on ICU admission (crude incidence: 15.3%; 95%CI 14.4–16.3), and in 713 (crude incidence: 26.4%; 95%CI 24.8–28.1) of the 2696 patients infected on admission (Fig. 1). In the latter group the incidence of ICU-acquired infection was higher in patients with hospital-acquired infection on admission (31.4%; 95%CI 28.7–34.0) than in patients with community-acquired infection (22.5%; 95%CI 20.4–24.7; p=0.001).

The characteristics of ICU-acquired infections are displayed in Table 4 (only the first episode is shown). The three main sources of infection were the respiratory tract (pneumonia in 75.6% of cases), primary bloodstream infection and urinary tract infections, which altogether represented 83% of all reported sites; multiple sources were involved in 13.4% of infections. Of the 1581 ICU-acquired infections 85.8% were microbiologically documented (Table 5). Bloodstream infection occurred in 22.8% of microbiologically documented infections. The micro-organisms recovered from ICU-acquired infections are displayed for the major sites described above (Fig. 2). Polymicrobial infection occurred in 33.8% of infections. Gram-positive cocci represented 37.4% of isolates and Gram-negative bacilli 49.2%.

Outcomes

Long-stay group

Five units had more than 50% missing data for hospital mortality and were excluded from further analyses. ICU mortality rates did not differ after exclusion of these five ICUs (Table 6). Crude overall ICU and hospital mortality rate were 20.4% (95%CI 19.5–21.2) and 26.6% (95%CI 25.6–27.6). Median hospital survival was 84 days (71–105) in non-infected patients, 69 (58–86) in patients with community-acquired infection at admission and 38 (33–47) in patients with hospital-acquired infection at admission (Fig. 3). Crude ICU- and hospital-mortality rates ranged, respectively, from 12.1% and 16.9% in non-infected patients to 43.9% and 53.6% in patients with hospital-acquired infection at ICU admission and further developing ICU-acquired infection (Table 6). These rates were significantly higher in patients having nosocomial infection (either at ICU admission or during ICU stay) than in non-infected patients and in patients having community-acquired infection and no ICU-acquired infection.

Median ICU LOS was 6 days (3–34) and median hospital LOS 16 days (3–69) in the overall cohort. ICU LOS could be divided into three groups: a first group of non-infected patients (median 4 days), a second group including patients with community-acquired and hospital-acquired infection on ICU admission and no ICU-acquired infection (median stay 7 days), and a third

Table 6 Long-stay group: ICU procedures and outcomes according to infected status. ICU and hospital mortality are presented as percentage by column (95% confidence intervals). For patients with infection on ICU admission and ICU-acquired infection, ACCP criteria were evaluated in the first 24 h of the first infection

	Not infected at ICU admission		Infected at ICU admission			
	No ICU-acquired infection (*n*=4789)	ICU-acquired infection (*n*=868)	Community		Hospital	
			No ICU-acquired infection (*n*=1165)	ICU-acquired infection (*n*=339)	No ICU-acquired infection (*n*=818)	ICU-acquired infection (*n*=374)
SAPS II at ICU admission	30 (12–62)	40 (19–70)	38 (15–70)	45 (24–78)	43 (20–75)	44 (23–79)
Whole population						
ICU mortality (38.9–48.9) (%; 95%CI)	12.1 (11.2–13.0)	32.1 (29.0–35.2)	22.1 (19.7–24.5)	38.4 (33.2–43.6)	35.7 (32.4–39.0)	43.9
ICU LOS (days; 5th–95th)	4 (3–13)	16 (5–56)	7 (3–24)	24 (7–73)	7 (3–23)	20 (7–67)
After excluding five units[a]						
ICU mortality (38.3–48.9) (%; 95%CI)	11.5 (10.5–12.5)	31.9 (28.2–35.6)	22.1 (19.6–24.6)	38.9 (33.4–44.4)	35.6 (32.1–39.1)	43.6
ICU LOS (days; 5th–95th)	4 (3–14)	18 (6–60)	7 (3–24)	23 (7–75)	7 (3–22)	21 (7–68)
Hospital mortality (48.2–59.0) (%; 95%CI)	16.9 (15.7–18.1)	39.6 (35.7–43.5)	27.8 (25.1–30.5)	46.3 (40.6–52.0)	45.7 (42.1–49.3)	53.6
Hospital LOS (days; 5th–95th)	14 (3–51)	30 (8–99)	16 (3–58)	30 (8–101)	15 (3–73)	30 (7–114)
According to ACCP classification						
No SIRS (%; 95%CI)						
ICU mortality (26.5–59.3)		23.6 (16.1–31.1)	15.9 (10.7–21.1)	36.8 (21.5–52.2)	22.4 (14.8–30.0)	42.9
Hospital mortality (32.0–65.1)		30.9 (22.7–39.1)	20.6 (14.9–26.4)	44.7 (28.9–60.5)	29.3 (21.0–37.6)	48.6
Sepsis (%; 95%CI)	–					
ICU mortality (26.3–48.7)	–	17.3 (11.5–23.0)	13.2 (9.6–16.8)	32.3 (20.6–43.9)	16.2 (10.7–21.7)	37.5
Hospital mortality (38.5–61.5)	–	26.8 (20.1–33.5)	17.0 (13.0–21.0)	38.7 (26.6–50.8)	28.3 (21.6–35.0)	50.0
Severe sepsis (%; 95%CI)	–					
ICU mortality (37.7–60.9)	–	33.6 (25.7–41.4)	19.6 (14.2–25.1)	40.3 (28.6–52.0)	35.3 (28.1–42.5)	49.3
Hospital mortality (44.8–67.9)	–	40.7 (32.6–48.9)	25.5 (19.5–31.5)	47.8 (35.8–59.7)	46.5 (39.0–54.0)	56.3
Septic shock (%; 95%CI)	–					
ICU mortality (37.6–54.3)	–	57.4 (48.8–65.9)	41.9 (35.8–48.1)	38.8 (29.9–47.7)	58.3 (51.6–64.9)	46.0
Hospital mortality (47.2–63.8)	–	62.8 (54.4–71.1)	50.0 (43.8–56.2)	45.7 (36.6–54.8)	66.8 (60.5–73.2)	55.5

[a] No hospital outcome measures

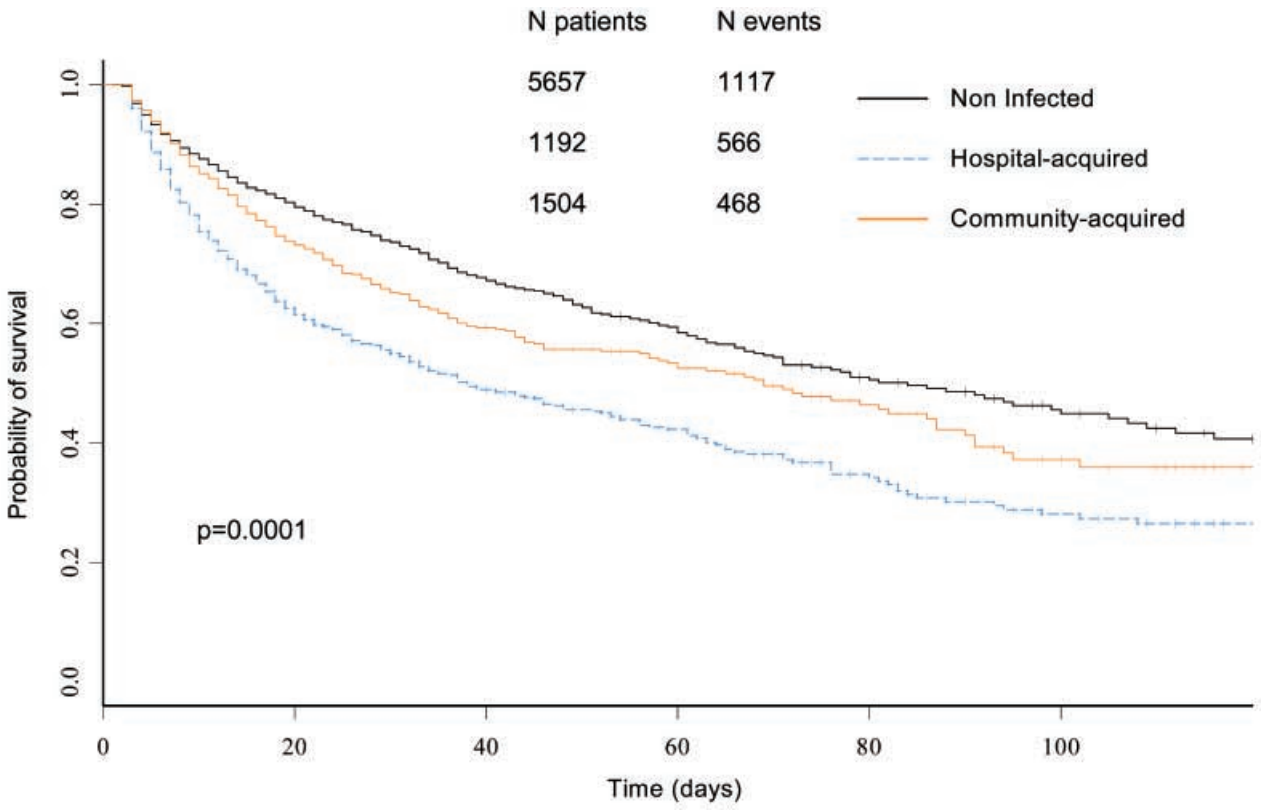

Fig. 3 Survival according to infected status at ICU admission. *N patients* Number of patients in each category at ICU admission; *N events* number of death in each category

group including patients developing ICU-acquired infection whatever their infected status at ICU admission (median stays 18, 21, 23 days). Similarly, hospital LOS only varied according to the occurrence of ICU-acquired infection, irrespective of the infection status on ICU admission, with a median stay of 14–16 days in patients not developing ICU-acquired infection, and of 30 days in patients developing such infection (Table 6).

In addition, Table 6 reports mortality according to ACCP/SCCM criteria at first episode of infection. In each sepsis category ICU and hospital mortality varied between infected states, confirming heterogeneity in terms of severity among this classification.

Short-stay group

In the entire group of short-stay patients, crude ICU mortality was 13.5% (95%CI 12.6–14.3) and in infected patients 55.3% (95%CI 50.0–60.6). In this latter group, crude hospital mortality was 61.7% (56.3–67.1) and median hospital LOS 2 (1–35) days.

Discussion

Despite the efforts at standardisation brought by the new ACCP/SCCM classification, categorisation of ICU patients into sepsis categories results in heterogeneous populations, which reflects the fact that sepsis represents a clinical syndrome and not a disease. Since the ACCP/SCCM expert panel proposal of classification of patients with infection into three subgroups of increasing severity and mortality risk [8] several epidemiological studies and clinical trials using this classification have been published [3, 5, 6, 12, 18, 19, 20]. As pointed out above, using this classification as an entry criterion in clinical trials is deceptive. Indeed, clinical trials have included highly selected patients and the global epidemiology of infection encountered in the ICU can hardly be accurately derived from these studies. Epidemiological studies have focused on the different degrees of physiological response attributable to infection [12, 18, 19, 21, 22] or on specific aspects of infection [23, 24, 25, 26, 27, 28, 29]. Thus it is difficult to pool studies and compare them due to heterogeneity of definitions and of data reported regarding, for example, the different severity scores used [30]. Finally, the usefulness of the sepsis classification has been challenged, because it requires microbiological documentation of infection, which is available only in retrospect, and because some patients with definite infection do not fulfil criteria for any of the sepsis categories [31].

This is illustrated by our study. First, only about 80% of clinically documented infections were classified in sepsis categories, of which about one-half had manifestations of either severe sepsis or septic shock. Second, one-fifth of infections did not fulfil criteria for any sepsis category (Table 3). Therefore, in addition to sepsis categorisation, it appears important to focus epidemiological studies on infection itself for a better understanding of the associated conditions, risks and outcomes of septic patients. The present study attempts to increase our knowledge and understanding of sepsis and infection, based on a large cohort study involving a substantial number of ICUs in various countries.

The principal goal of this study was to determine the incidence and characteristics of infection in ICU patients, contrasting the "infection approach" with the "sepsis approach". We observed a large cohort of patients using standardised definitions and involving a substantial effort to standardise data collection (including specific software and forms, operating manual providing definitions, training sessions of dedicated data collector in each unit, and external quality control). A clearcut distinction was made to distinguish three groups of ICU infections: (a) community-acquired infections, (b) hospital-acquired infections, i.e. infections occurring in a patient hospitalised (or institutionalised) before being transferred to the ICU, and (c) ICU-acquired infections. Our study shows that about one-fifth (21.1%) of all patients had infection on ICU admission, reaching one-third (32.3%) of patients in the long-stay group. In this long-stay group the crude incidence of ICU-acquired infections was 18.9%, but varied with infection status at ICU admission. It was 1.5 times higher (26.4%) in patients infected on admission than in non-infected patients (15.3%). In other words, about one-half of ICU-acquired infections occurred in patients infected previous to ICU admission.

These high figures point out that infection remains a major problem in ICUs, although the incidence varied between ICUs according to unit type or case-mix. The inflammatory response to infection was present in almost 80% of patients, but obviously it results in a mixture of patients with different infectious problems (Table 3). The hierarchy of primary sources of infection differed with the origin of infection (community- or hospital-acquired) and the time of infection (at admission or during ICU stay) but lung, abdomen, urinary tract and bloodstream infections accounted for 85% of reported sites, including in the short-stay group. These data suggest that in clinical trials these major sources could be targeted to reduce the heterogeneity of patients enrolled. Of the infected patients 30% had no microbiological documentation, a rate increasing to 46.1% in the short-stay group. While 85.8% of ICU-acquired infections were microbiologically documented, only 54.8% community-acquired infection had such documentation.

These differences are likely due to a different context. Indeed, many community-acquired infections cannot be microbiologically documented because of antimicrobial therapy prior to ICU admission and sampling, whereas microbiological samples are likely to be obtained during the ICU course. Conversely, a clinical diagnosis of infection may be easier to ascertain in the former than in the latter case, in the absence of interference of previous events occurring during the ICU stay. The ACCP/SCCM sepsis definitions exclude non-documented infections, which results in eliminating nearly one-half of patients with community-acquired infection, a major problem for evaluation of new therapeutic approaches. The microbiological findings are similar to those presented elsewhere. Overall, Gram-negative bacilli predominated (45% of reported isolates), followed by Gram-positive cocci (37% of isolates), while *Candida* spp. and fungi accounted for 10% of isolates. Again, the causal micro-organisms differed with the origin and source of infection (Fig. 2). However, while the percentage of Gram-positive cocci, *Candida* spp. and fungi was very similar in the different categories of infection, patients with nosocomial infections had a higher incidence of infections caused by Gram-negative bacilli (48–49% vs. 35%) due to a higher frequency of various other pathogens in community-acquired infections. Given the epidemiological nature of the study focus on the description of infections, data on central lines, urinary catheters, pathogen resistance, and antibiotic therapy were not collected. Indeed, the objective of the study was to describe and estimate rates of infections in the ICU and to focus on differences in ICUs in patients characteristics (Table 2), and in infections (Tables 4, 5; Fig. 2).

A further aim of our study was to examine outcome in infected patients. The origin of infection, and especially ICU-acquired infection, appeared markedly to affect ICU and hospital outcomes (Table 6). The rates (Table 6) were similar to those previously reported in the literature [28]. However, the impact of ICU-acquired infections on hospital mortality differed depending on the infected status at ICU admission. The difference in hospital mortality was higher in the non-infected group (22.7%) than in the community-infected group (18.5%) and the hospital-infected group (7.9%). This indicates that mortality in the latter groups is probably related to the primary disease.

The poorer outcome of nosocomially infected patients may in part be due to the higher rates of multiple sources and polymicrobial infections since these factors have been found to be independent factors of mortality [12]. Infection adds a substantial burden to ICU care in terms of LOS (Table 6). Specifically, patients infected on ICU admission and secondarily acquiring infection during the ICU stay define a high-risk population for mortality and resource use.

Nevertheless, many other factors contribute to various outcomes, including differences between patients in severity of illness, comorbidities, origin and sources of infection, but also probably "conventional management" such as choices of antimicrobial agents, type and timing of nutrition support, transfusion triggers, ventilation and cardiac

support strategies. These latter factors mostly reflect country and cultural differences and result in ICU variability. In this study there were 28 participating ICUs in eight countries. The number of ICUs by country was too small to be representative of the country. The units were selected on a volunteer-basis, mostly from teaching hospitals, and they differed in terms of the hospital sizes (from 200 to more then 3000 beds) and ICU size (from 5 to 30 beds). The differences between units are also illustrated by differences in the proportion of short stays (from 12.3% to 73%) and of surgical patients admitted (from 5.6% to 95%). However, such differences could only contribute to differences in infection and mortality rates between ICUs. It is likely that both patients and ICU characteristics contributed to heterogeneity. In a recent editorial Nasraway [11] advocated the reduction of heterogeneity before initiating further experimental studies since heterogeneity results in low signal/noise ratio. The study of potential sources of heterogeneity between ICUs will require further analyses.

In conclusion, our epidemiological findings emphasise the high incidence of infection both at admission and during the ICU stay, although varying among ICUs and patient subsets. They illustrate the added burden of nosocomial infections in the use of ICU resources as reflected by ICU and hospital LOS. This argues that identifying infections overall is important, not just sepsis and sepsis-related conditions, a classification which eliminated about one-fifth of infections.

Acknowledgements We gratefully thank Dr. Geneviève Ruault for the initiation of the project, Viviane Teboul for her efficacious management, Dr. Sylvie Chevret for her helpful reviewing of the manuscript and all the participating members of the study (see "Appendix").

Appendix: Study participants

European Consortium for Intensive Care Data: H. Burchardi, MD, Göttingen, Chairman

Paris-Coordinating centre: J.R. Le Gall, MD, Director; E. Lepage, MD, PhD, Biostatistician, C. Alberti, MD; Biostatistician; Ronan Boulmé, Database manager; Viviane Teboul, Administrative secretary

Scientific committee: C. Brun Buisson, MD, Créteil; P. Loirat, MD, Suresnes; P. Metnitz, MD, Vienna; B. Misset, MD, Paris; R. Moreno, MD, Lisbon; M. Palazzo, MD, London; M. Smithies, MD, Cardiff

Participating units: Canada: C. Martin, MD, Country Coordinator, L. MacCarthy, Victoria Campus, London; H. Fuller, MD, S. Spisak, Saint Joseph's Hospital, Hamilton; J. Granton, MD, D. Foster, Toronto Hospital, Toronto; S. Magder, MD, D. Jones, Royal Victoria Hospital, Montreal. France: C. Brun Buisson, MD, Country Coordinator, E. Girou, Pharm D, Henri Mondor Hospital, Créteil; J. Carlet, MD, L. Montuclard, MD, Saint Joseph Hospital, Paris; J.F. Dhainaut, MD, S. Bouam, MD, Cochin Hospital, Paris; J.R. Le Gall, MD, S. Bouam, MD, Saint Louis Hospital, Paris; F. Saulnier, MD, S. Beague, Albert Calmette Hospital, Lille. Germany: H. Burchardi, MD, Country Coordinator, O. Thomas, MD, Göttingen Hospital, Göttingen; H. Reith, MD, U. Mittelkötter, MD, Chirurgische Universitätsklinik, Würzburg; K. Werdan, MD, N. Kühn, Klinikum Kröllwitz, Halle. Israel: C. Sprung, MD, S. Goodman, MD, Hadassah Hebrew University Medical Center, Jerusalem. Italy: M. Langer, MD, Country Coordinator, A. Sicignano, MD, Maggiore Hospital, Milan; R. Fumagalli, MD, C. Carozzi, San Gerardo Tintori Hospital, Monza; A. Gasparetto, MD, M. Antonelli, MD, Policlinico Umberto Ier, Rome; D. Guidici, MD, E. Casaletti, San Raffaele Hospital, Milan; S. Vesconi, MD, G. Fontana, Desio Hospital, Desio. Portugal: R. Moreno, MD, Country Coordinator, E. Pereira, MD, Santo Antonio dos Capuchos Hospital, Lisbon; J. Sá, MD, Unidade de Urgencia Medica, S. José Hospital, Lisbon; E. Silva, MD, M.J. Serra, MD, Desterro Hospital, Lisbon. Spain: A. Artigas, MD, Country Coordinator, A.R. Ochagavia, MD, Parc Taulli Hospital, Sabadell Barcelona; J.L. Boveda, MD, Valle Hebron Hospital, Barcelona; A. Esteban de la Torres, MD, D. Alia, De Getafe Hospital, Madrid; C. Leon Gil, MD, M.A. Sanchez, De Valme Hospital, Seville; F. Solsona, MD, R. Martinez, Del Mare Hospital, Barcelona. United Kingdom: M. Palazzo, MD, Country Coordinator, M. Templeton, Charing Cross Hospital, London; M. Smithies, MD, T. Jones, University Hospital of Wales, Cardiff

References

1. Bone R (1997) Important new findings in sepsis. JAMA 278:249
2. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP (1990) Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 113:227–242
3. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Fisher CJJ (2001) Recombinant human protein C worldwide evaluation in severe sepsis (PROWESS) study group. N Engl J Med 344:759–762
4. Abraham E (1999) Why immunomodulatory therapies have not worked in sepsis. Intensive Care Med 25:556–566
5. Natanson C, Esposito C, Banks S, Magnuson W (1998) The sirens' songs of confirmatory sepsis trials: selection bias and sampling error. Crit Care Med 26:1927–1931
6. Zeni F, Freeman B, Natanson C (1997) Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit Care Med 25:1095–1100

7. Eidelman L, Sprung C (1994) Why have new effective therapies for sepsis not been developed? Crit Care Med 22:1330–1334
8. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874
9. Knaus WA, Sun X, Nystrom O, Wagner DP (1992) Evaluation of definitions for sepsis. Chest 101:1656–1662
10. Astiz M, Rackow E (1998) Septic shock. Lancet 351:1501–1505
11. Nasraway SJ (1999) Sepsis research: we must change course. Crit Care Med 27:427–430
12. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B (1995) Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 274:968–974
13. Ponce de Leon-Rosales SP, Molinar-Ramos F, Dominguez-Cherit G, Rangel-Frausto MS, Vazquez-Ramos VG (2000) Prevalence of infections in intensive care units in Mexico: a multicenter study. Crit Care Med 28:1316–1321
14. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
15. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D (1996) The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 276:802–810
16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
17. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections 1988. Am J Infect Control 16:128–140
18. Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, Parsonnet J, Panzer R, Orav EJ, Snydman D (1997) Epidemiology of sepsis syndrome in 8 academic medical centers. Academic Medical Center Consortium Sepsis Project Working Group. JAMA 278:234–240
19. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP (1995) The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 273:117–123
20. Marshall JC (2000) Clinical trials of mediator-directed therapy in sepsis: what have we learned? Intensive Care Med 26:S75–S83
21. Friedman G, Silva E, Vincent JL (1998) Has the mortality of septic shock changed with time. Crit Care Med 26:2078–2086
22. Salvo I, de Cian W, Musicco M, Langer M, Piadena R, Wolfler A, Montani C, Magni E (1995) The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. Intensive Care Med 21:S244–S249
23. Cook D (2000) Ventilator associated pneumonia: perspectives on the burden of illness. Intensive Care Med 26:S31–S37
24. Hanberger H, Garcia-Rodriguez JA, Gobernado M, Goossens H, Nilsson LE, Struelens MJ (1999) Antibiotic susceptibility among aerobic gram-negative bacilli in intensive care units in 5 European countries. French and Portuguese ICU Study Groups. JAMA 281:67–71
25. Legras A, Malvy D, Quinioux AI, Villers D, Bouachour G, Robert R, Thomas R (1998) Nosocomial infections: prospective survey of incidence in five French intensive care units. Intensive Care Med 24:1040–1046
26. Pittet D, Thievent B, Wenzel RP, Li N, Auckenthaler R, Suter PM (1996) Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients. Am J Respir Crit Care Med 153:684–693
27. Richards MJ, Edwards JR, Culver DH, Gaynes RP (1999) Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 27:887–892
28. Vincent J-L, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin M-H, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. JAMA 274:639–644
29. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, Singer DE (1998) Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 279:1452–1457
30. Cohen NH (1998) Reduced mortality from septic shock-lessons for the future. Crit Care Med 26:1956–1958
31. Brun-Buisson C (2000) The epidemiology of the systemic inflammatory response. Intensive Care Med 26:S64–S74