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Aetiology and prognosis of bacteraemia in Italy

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SUMMARY

A prospective multi-centre study was conducted to assess the microbiological pattern and prognostic factors of bacteraemia and their impact on clinical outcome. All patients admitted to 41 Italian hospitals over 2 months, from whom one or more clinically significant organisms were isolated from blood culture, were studied according to a standardized protocol and case definition. A total of 156 episodes of bacteraemia were identified in 20 601 patients. There were 3·9 episodes of nosocomially acquired bacteraemia and 3·7 episodes of community-acquired bacteraemia per 1000 admissions. The most frequent pathogens isolated were Gram-negative bacteria (44·9%) but Gram-positive species accounted for 40·4% of episodes. Fungal infections due to *Candida* spp. were found in 3·8% of episodes, and multiple pathogens were recovered from 9·6% of episodes. The clinical response to bacteraemia was classified as sepsis in 90 episodes (57·7%), severe sepsis in 21 (13·5%) and septic shock in 26 (16·7%); 19 episodes (12·2%) showed no clinical response. The total in-hospital mortality was 25·0%. By multivariate logistic regression, the variables which independently predicted mortality were increasing age, the presence of septic shock, infection with Gram-positive bacteria or fungi and nosocomial acquisition.

INTRODUCTION

Recent surveillance studies on bacteraemia suggest a trend towards an increasing incidence as well as a shift in the aetiology of this condition. This is probably related to changes in the underlying diseases of susceptible populations, as well as more aggressive and invasive medical practice and the presence of virulent and difficult-to-treat micro-organisms [1, 2]. Despite the availability of broad-spectrum antibiotics and improved therapy, bloodstream infections are still associated with a high morbidity and mortality among hospitalized patients, particularly those with compromised host defences [3, 4].

The relationships between bacteraemia and sepsis are well described [5–10], but there is an evident lack of data from Italy [11]. The reported total mortality rates for bacteraemia range from 18 to 60% [4, 12, 13], and these rates are higher for nosocomially acquired infections than those associated with community-acquired infections [13, 14]. The identification of independent risk factors for mortality in populations

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with bacteraemia may, therefore, be of value for the development of design and analysis of clinical trials [15].

To this end we conducted a prospective multi-centre study to assess microbiological patterns and prognostic factors of bacteraemia in patients and their impact on clinical outcome.

MATERIALS AND METHODS

Study design

Prospective multi-centre study

The following case definitions were used. Systemic Inflammatory Response Syndrome (SIRS) and sepsis were defined according to ACCP/SCCM criteria [16]. Primary and secondary bacteraemia and sites of infections were defined according to CDC criteria [17]. Bacteraemia was considered to be clinically significant when one or more micro-organisms were isolated from blood culture with two or more signs of SIRS, or, in the absence of signs of SIRS, when the same organism(s) was also isolated from another culture from the same patient. A new episode of bacteraemia was recorded if the initial pathogen had previously been eradicated from the bloodstream or if an interval of at least 1 month had elapsed without signs of infection since the primary episode. Polymicrobial bacteraemia was defined as the isolation of different species in one or more blood cultures with clinical evidence of the same primary septic focus. An infection was deemed to be nosocomial if it was not present at hospital admission and developed 48 h or more after hospital admission. The total mortality rate included all deaths that occurred during the hospital stay, independent of the underlying cause, among patients with bacteraemia. Bacteraemia was identified as the cause of death if the patient died within 7 days of the last positive blood culture and when there was no other obvious explanation for the death.

Study population

A prospective multi-centre study was carried out for all patients admitted to 101 care units of 41 different Italian hospitals, between October and December 1997, for whom one or more clinically significant species was isolated from blood culture. Patients with HIV and those under 14 years of age were excluded. Patients were followed up until discharge or death in hospital.

The following data were recorded for each episode of bacteraemia: clinical outcome, cause of death, admission date, date of discharge, age at hospitalization, sex, hospital ward, date of collection of blood samples for culture, the result of blood culture, presence of SIRS or sepsis at time of blood culture request, site of infection, origin of infection (hospital or community), surgical and diagnostic procedures performed and invasive devices (bladder catheter, intravenous or arterial catheter, tracheal cannula) positioned within 72 h prior to onset of infection; antibiotic treatment started within 48 h following the first blood-culture collection.

Data analysis

Data from patients' forms were entered in an Epi-Info database [18] and imported and analysed using STATA 5 (Stata Corporation, College Station, TX, USA). The incidence of bacteraemia was calculated as the ratio of the observed number of nosocomial episodes and the number of ward admissions during the study period. Associations of categorical variables with mortality were assessed by odds ratios (OR) and their 95% confidence intervals (95% CI). Multivariate analyses were by logistic regression [15, 19], which introduced further adjustment for multi-level clustering of observation groups such as hospital ward or site of infection. This analysis specifies that the observations are independent across groups but not necessarily within groups. Variables were selected for the final models if they were significantly associated with mortality at $P<0{\cdot}1$. In the final model, only variables that contributed significantly ($P<0{\cdot}05$) were retained.

Microbiology

At least one set of two bottles was collected per febrile episode. Different blood-culture systems were used by the participating laboratories, most of them using either the BacT/Alert (bioMérieux, Marcy l'Etoile, France) or the BACTEC (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) automated systems. Bacterial isolates were identified according to standard laboratory practice by biochemical tests and/or commercial identification systems.

RESULTS

The total number of admissions among participating hospitals during the study period was 20 601 and one

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Table 1. *Incidence rates of bacteraemia by wards*

Wards (no. admitted patients)	No. (rate per 1000 admissions)		
	Hospital-acquired	Community-acquired	Total
Surgery (10 901)	6 (0·6)	4 (0·4)	10 (1·0)
Medicine (7099)	28 (3·9)	58 (8·2)	86 (12·1)
Oncology and Haematology (383)	15 (39·2)	5 (13·1)	20 (52·3)
Intensive care (2218)	31 (14·0)	9 (4·1)	40 (18·1)
Total (20 601)	80 (3·9)	76 (3·7)	156 (7·6)

Table 2. *Most frequent significant micro-organisms isolated from blood, by primary site of infection*

Micro-organism	Total no. (%)	No. of episodes					
		Blood-stream	Lower respiratory tract	Gastro-intestinal tract	Urinary tract	Other sites	Multiple sites
Gram-positive	63 (40·4)						
S. aureus	23 (14·7)	12	5	1	—	5	—
Enterococcus spp.	12 (7·7)	8	2	—	—	2	—
Coagulase-negative staphylococci	8 (5·1)	5	2	—	—	—	1
S. pneumoniae	8 (5·1)	2	6	—	—	—	—
Other species	12 (7·7)	3	1	2	1	5	—
Gram-negative	68 (43·5)						
E. coli	36 (23·1)	14	4	2	13	3	—
K. pneumoniae	7 (4·5)	6	—	—	1	—	—
Other enterobacteriaceae	5 (3·2)	3	—	1	1	—	—
P. aeruginosa	8 (5·1)	6	1	1	—	—	—
S. maltophilia	6 (3·8)	4	1	—	—	1	—
Other species	6 (3·8)	5	—	—	—	1	—
Anaerobes	2 (1·3)	1	—	1	—	—	—
Fungi	8 (5·1)						
Candida spp.	6 (3·8)	2	1	2	—	—	1
Other species	2 (1·3)	1	1	—	—	—	—
Polymicrobial	15 (9·6)	8	4	1	—	1	1
Total	156 (100)	80	28	11	16	18	3

or more blood cultures were performed in 735 patients (3·6%). There were 156 episodes of bacteraemia identified, giving an infection rate of 7·6 episodes/1000 admissions. No patient had more than one episode. Eighty episodes (3·9/1000) were determined to be hospital acquired, and 76 (3·7/1000) community acquired. The incidence rates of bacteraemia by wards are shown in Table 1.

Most hospital-acquired cases were associated with haematological/oncology patients and the rate for community infections in this patient group was three-fold less than hospital-acquired cases. Cancer patients constituted half of all cases and 21·2% of patients who were examined for bacteraemia proved to have positive blood cultures. Eighty episodes (51·8%) were classified as primary, and 76 (48·2%) as secondary bacteraemia. The most frequent site in secondary bacteraemia was the lower respiratory tract (Table 2).

The leading pathogens among cases of monomicrobial bacteraemia were, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* which

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Table 3. *Type of systemic response and mortality by micro-organism isolated from blood*

Micro-organism	No. (%) of episodes					
	Total	SIRS absent	Sepsis	Severe sepsis	Septic shock	Crude mortality
Gram-positive	63 (100)	8 (12·7)	35 (55·6)	11 (17·5)	9 (14·3)	19 (30·2)
S. aureus	23	3	11	5	4	13 (56·5)
Enterococcus spp.	12	2	8	1	1	5 (41·7)
Coagulase-negative staphylococci	8	1	5	1	1	1 (12·5)
S. pneumoniae	8	—	6	2	—	—
Other species	12	2	5	2	3	4 (33·3)
Gram-negative	68 (100)	11 (15·7)	47 (76·1)	5 (7·1)	7 (10·0)	6 (8·6)
E. coli	36	6	23	4	3	3 (8·3)
K. pneumoniae	7	1	5	—	1	—
Other enterobacteriaceae	5	1	3	1	—	1 (20·0)
P. aeruginosa	8	1	5	—	2	1 (12·5)
S. maltophilia	6	1	5	—	—	
Other species	6	1	4	—	1	1 (16·7)
Anaerobes	2 (100)	—	2 (100)	—	—	—
Fungi	8 (100)	—	8 (34·8)	5 (21·7)	10 (43·5)	9 (39·1)
Candida spp.	6	—	1	2	3	4 (66·7)
Other species	2	—	—	—	2	1 (50·0)
Polymicrobial	15 (100)	—	7 (46·7)	3 (20·0)	5 (33·3)	4 (26·7)
Total	156 (100)	19 (12·2)	90 (57·7)	21 (13·5)	26 (16·7)	39 (25·0)

together accounted for 32·6% of cases. Gram-positive micro-organisms were identified in 40·4% of episodes, and *Staphylococcus aureus* accounted for one-third of the isolates. Anaerobes were isolated in only two cases. Fungal infection due to *Candida* spp. represented 3·8% of episodes, and polymicrobial episodes 9·6% (Table 2).

The distribution of systemic response and crude mortality according to major groups of micro-organisms involved in bacteraemia is presented in Table 3. A septic response to bacteraemia was observed in 90 episodes (57·7%), with severe sepsis in 21 (13·5%) and septic shock in 26 (16·7%); 19 episodes (12·2%) showed no sign of systemic response. Thirty-nine of the patients with bacteraemia died during hospitalization, 29 of causes related to bacteraemia, representing a total in-hospital mortality of 25·0% and a cause-related mortality of 18·6%.

In the univariate analysis (Table 4), the variables associated with a high total mortality rate were: age, source of bacteraemia, aetiological agent, presence of an intravascular catheter, presence of an urinary catheter and nosocomial origin of the infection. Similar results were obtained for cause-related mortality (data not shown). Empirical antibiotic treatment was initiated within 48 h of performance of the blood culture for 67·3% of patients and the mortality rate for this group was 22·9% compared to 29·4% for those patients who did not receive antibiotics in the same interval. Although a slightly increased total and cause-related mortality rate for patients with bacteraemia who had a delay in receiving antibiotic treatment was observed, this was not statistically significant ($P=0·376$). Bacteraemia due to *E. coli* or coagulase-negative staphylococci (CNS) was associated with a lower risk of total and cause-related death, whereas *S. aureus* and fungi were associated with an increased risk of total and cause-related death.

By multivariate logistic regression (Table 5), the variables that independently predicted total mortality were increasing age, presence of septic shock, Gram-positive bacteraemia or fungal infection. Results were similar for cause-related mortality and this did not vary significantly when adjustment was made for clusters (hospital ward or site of primary infection).

Removal of the degree of systemic response from the model, revealed that the remaining variables such as increasing age, Gram-positive bacteraemia or fungal infection, nosocomial acquisition, and the

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Table 4. *Univariate analysis of factors influencing total mortality in 156 patients with bacteraemia*

Variables	No. of patients	No. of deaths	% of deaths	OR	(95% CI)	*P* value
Age (years)						
14–50	42	4	9·5	1		
51–70	53	14	26·4	3·4	(1·03–11·3)	0·045
>70	61	21	34·4	5·0	(1·6–15·9)	0·007
Sex (female/male)	62/94	12/27	19·3/28·7	1·7	(0·8–3·8)	0·188
Speciality						
Surgery	10	3	30·0	1		
Medicine	86	16	18·6	0·5	(0·1–2·3)	0·398
Oncology–Haematology	20	5	25·0	0·8	(0·1–4·2)	0·771
ICU	40	15	37·5	1·4	(0·3–6·3)	0·659
Source						
Primary bloodstream infections	80	18	22·5	1		
Lower respiratory tract	28	12	42·9	2·6	(1·0–6·4)	0·042
Gastrointestinal tract	11	6	54·5	4·1	(1·1–15·1)	0·032
Urinary tract	16	—	—	—	—	—
Other sites	18	3	16·7	0·7	(0·2–2·6)	0·587
Multiple sites	3	—	—	—	—	—
Aetiology						
Gram-negative	68	7	10·3	1		
Gram-positive	63	23	36·5	5·0	(2·0–12·8)	0·001
Anaerobic organism	2	—	—	—	—	—
Fungi	8	5	62·5	14·5	(2·8–74·2)	0·001
Polymicrobial	15	4	26·7	3·2	(0·8–12·7)	0·103
Antibiotics started within 48 h (no/yes)	51/105	15/24	29·4/22·9	0·7	(0·3–1·5)	0·376
Central catheter IV or arterial (no/yes)	89/67	16/23	18·0/34·3	2·4	(1·1–5·0)	0·021
Bladder catheter (no/yes)	112/44	22/17	19·6/38·6	2·6	(1·2–5·5)	0·015
Intubation (no/yes)	127/29	29/10	22·8/34·5	1·8	(0·7–4·2)	0·195
Previous surgery (no/yes)	125/31	30/9	24·0/29·0	1·3	(0·5–3·1)	0·563
Origin						
Community-acquired	76	10	13·2	1		
Hospital-acquired	80	29	36·2	3·8	(1·7–8·4)	0·001
Systemic response						
Not SIRS	19	2	10·5	1		
Sepsis	90	12	13·3	1·3	(0·3–6·6)	0·716
Severe sepsis	21	7	33·3	4·2	(0·8–23·8)	0·100
Septic shock	26	18	69·2	19·1	(3·5–103·2)	0·001

gastrointestinal tract as source of infection were significantly associated with an increased risk of death (data not shown).

DISCUSSION

We studied a sample of unselected adults across a variety of hospitals in the country, including both university and community hospitals and found the incidence of bacteraemia was consistent with recent hospital-wide surveys [2, 4, 5, 11]. A difficulty often met when performing studies on bacteraemia is that blood cultures themselves have neither a 100% sensitivity nor specificity for this type of infection. First, not every patient with an infection has a blood culture taken and secondly, some patients with negative blood cultures undoubtedly have bacteraemias that are undetected [19]. The low rate of patients with blood culture performed and the high ratio of patients with positive blood culture (21·1%) observed here may reflect a lesser use in Italy of blood cultures which would normally be carried out on people with a high suspicion of bacteraemia.

The high incidence of aerobic Gram-positive cocci (40·4%) among isolates corroborates the findings of recent studies [1, 20], and appears to be related to the

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Table 5. *Multivariate analysis of factors influencing total and cause-related mortality in 156 patients with bacteraemia*

	Total mortality			Cause-related mortality		
Variable	OR	(95% CI)	*P* value	OR	(95% CI)	*P* value
Age (years)						
14–50	1			1		
51–70	3·2	(0·8–13·6)	0·109	2·6	(0·5–13·5)	0·255
>70	6·5	(1·6–27·3)	0·010	5·9	(1·1–30·5)	0·034
Aetiology						
Gram-negative	1			1		
Gram-positive	6·2	(2·0–19·7)	0·002	7·6	(1·8–32·2)	0·006
Anaerobic organisms	n.a.	No deaths		n.a.	No deaths	
Fungi	4·2	(0·6–32·1)	0·166	3·7	(0·4–31·3)	0·227
Polymicrobial	1·5	(0·3–8·6)	0·670	2·8	(0·4–19·4)	0·291
Origin						
Community-acquired	1			1		
Hospital-acquired	4·0	(1·4–11·0)	0·008	4·7	(1·4–15·8)	0·013
Systemic response						
SIRS absent	1			n.a.	No deaths	
Sepsis	1·6	(0·3–9·1)	0·582	1		
Severe sepsis	3·1	(0·5–21·1)	0·241	1·7	(0·5–5·8)	0·379
Septic shock	24·1	(3·4–172·5)	0·002	16·1	(4·4–59·5)	0·000

multiple antibiotic treatments given to treat or prevent Gram-negative infections, especially in intensive care units, which results in the selection of Gram-positive bacteria. Another reason for the increased isolation of Gram-positive cocci is attributable to the high number of patients with intravascular catheters, for whom CNS are a common cause of bacteraemia. Although CNS have been frequently considered as contaminants in the past, recent studies have shown that even a single blood culture that was positive for these organisms was frequently associated with clinically relevant episodes of bloodstream infections [1, 21, 22].

An association between more severe systemic response and Gram-negative infection has been generally reported [4, 9]. However, we failed to find any significant difference in the incidence of severe sepsis in this patient group. This unexpected result may be explained by the fact that a high number of episodes of Gram-negative bacteraemia originated from urinary-tract infections, of which only two cases were accompanied by severe sepsis or septic shock without fatalities. Our figure of a 25% in-hospital mortality rate is in line with the most recent reports, and the degree of severity of the systemic manifestation of infection correlated with increasing crude mortality [4, 6, 13].

Multivariate analysis showed that the species of micro-organisms involved played an important role in the prognosis. In contrast to Vallés [4] and Weinstein [1], but consistent with other authors [5, 14] we observed a higher mortality rate associated with Gram-positive micro-organisms and fungi compared to Gram-negative bacteraemia, and this was associated with the different sources of bacteraemia, as suggested by other authors [4]. Again, this may be linked to the number of Gram-negative bacteraemias complicating urinary-tract infections. Moreover, Gram-positive mortality was mostly associated with bacteraemia caused by *S. aureus* and *Enterococcus* spp. which are among the most common agents of sepsis in the compromised host [7]. Although the impact of the antimicrobial susceptibility profile of the isolates was not addressed in this study, these findings may also be related to the spread of resistance to antimicrobial agents in Gram-positive cocci recorded worldwide, for which therapeutic options are more limited than for most infections due to Gram-negative bacilli.

The small, and not statistically significant, difference in mortality between those who did and those who did not receive antibiotic treatment within 48 h may reflect a lack of statistical power in the study to detect such a difference. Nevertheless, the influence of

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an inappropriate empirical antibiotic treatment cannot be excluded since the criteria for antibiotic prescription were not reviewed.

In comparison with other studies [4, 23], we found a lower rate of mortality for patients with polymicrobial bacteraemia. Rello et al. [24] attributed a similar finding to the fact that the main source of polymicrobial bacteraemia was intravascular catheters (54·5%), and several studies have shown that mortality tends to be lower in patients who developed bacteraemia from this source [4, 5, 13]. Indeed, in this study a vascular catheter was present in 73% of patients with polymicrobial bacteraemia. However, it is noteworthy that a significant association between mortality and source of infection was evident only when the severity of systemic response to infection was excluded from the multivariate analysis. Several studies have shown that mortality associated with secondary bloodstream infections was higher than with primary bacteraemia, suggesting that more appropriate management of primary sources of infection may be the most effective way to prevent the development of secondary bloodstream infections [1, 5, 14]. We found that bloodstream infections arising from the lower respiratory and gastrointestinal tracts were associated with a higher risk of death, and, in spite of the small number of episodes, a urinary-tract source was associated with a reduced mortality rate.

In summary, this study in Italian patients has confirmed that the outcome of bacteraemia is influenced by age, severity of systemic inflammatory response and aetiological agent. It also supports the findings from other countries that Gram-positive infections are increasingly associated with hospital mortality.

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