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Original Paper

Bloodstream Infections in Children with Cancer: a Multicentre Surveillance Study of the Italian Association of Paediatric Haematology and Oncology

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A one-year prospective, multicentre surveillance study on aetiology, main clinical features and outcome of bloodstream infections in children with cancer was conducted in 18 paediatric haematology centres belonging to the Italian Association for Paediatric Haematology and Oncology. A total of 191 bloodstream infections were reported during the study period. Of them, 123 (64%) occurred in neutropenic and 68 (36%) in non-neutropenic patients. Gram-positive cocci caused 45% (85/191) of the episodes, gram-negative rods 41% (78/191), and fungi 9% (18/191). The remaining 5% (10/191) of the episodes were poly-microbial infections. A total of 204 pathogens were isolated (46% gram-positive cocci; 44% gram-negative rods; and 10% fungi). The aetiologic distribution was similar among neutropenic and non-neutropenic patients. A correlation between the infection and the presence of an indwelling central venous catheter was found in 20% (23/114) of the episodes among neutropenic patients and in 55% (23/62) among non-neutropenic patients. Gram-negative micro-organisms were isolated in an unusually high proportion of catheter-related infections (48%). The overall mortality rate from any cause within 30 days from the first positive blood culture was 11%, and was higher among patients who were neutropenic at the onset of the infection than among those who were not neutropenic (15 versus 4%, $P = 0.03$). In addition, the mortality was significantly higher in recipients of bone marrow transplantation than in patients with acute leukaemia or solid tumour (21, 11 and 6%,

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respectively) and was also higher in fungaemias and poly-microbial infections (22 and 30%) than in single gram-positive and gram-negative bacteraemias (11 and 6%).

Key words: bacteraemia, fungaemia, cancer infections
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INTRODUCTION

BLOODSTREAM INFECTIONS represent an important complication in patients receiving chemotherapy for neoplastic diseases. Morbidity and mortality remain high, as well as the potential impact of these complications on the projected dose-intensity of antineoplastic chemotherapy [1, 2]. Epidemiological data about bloodstream infections in cancer patients are rarely generated by *ad hoc* surveillance studies [3–5] but are usually extrapolated from studies of empirical antibiotic therapy of febrile neutropenia [6–10]. However, the patient population included in these studies is selected according to inclusion and exclusion criteria and is consequently inadequate to describe the actual epidemiological situation in the general patient population. In addition, little information is available in non-neutropenic patients and in paediatric populations.

With the aim of performing a prospective evaluation of aetiology, main clinical features and outcome of bloodstream infections in paediatric cancer patients, we conducted a 1-year surveillance study of these infections in patients followed at centres belonging to the Italian Association of Paediatric Haematology and Oncology (Associazione Italiana Ematologia ed Oncologia Pediatrica), an association which performs clinical studies (and shares treatment protocols) for several paediatric neoplastic diseases [11–13]. All consecutive patients with a neoplastic disease and a documented bloodstream infection observed from 1 January to 31 December 1995 were enrolled in the study.

PATIENTS AND METHODS

All participating institutions were required to nominate a local reference investigator, who was responsible for reporting to the Data Centre all cases of microbiologically documented bloodstream infection observed at each participating institution every month during the study period. Within 2 months from the first positive blood culture, a final clinical report based on inpatient and outpatient hospital records and laboratory data had to be completed for each episode and sent to the Data Centre. Demographic information included initials, sex and age. Patient history information included the type of underlying disease and whether or not the episode was following a procedure of bone marrow transplantation (BMT) (performed within the preceding 365 days). Information about the bloodstream infection itself included presence and type of central venous catheter, total white cell and granulocyte count, and presence of fever, shock and signs of localised infection at the time of the first positive blood culture. Microbiological information included the number of positive blood cultures, the type of the isolated pathogen and its antibiotic susceptibility pattern (sensitivity to penicillin and oxacillin/methicillin for gram-positive bacteria; sensitivity to ceftazidime, ceftriaxone, imipenem, amikacin and ciprofloxacin for gram-negative rods). Outcome information included survival status at day 30 from diagnosis and day of death (if applicable). All clinical report forms were centralised and computerised at the Immunocompromised Host Disease Unit of the National Institute for Cancer Research in Genoa, where a first review was performed for major discrepancies and for missing data by the study data manager. All forms were then reviewed by the study co-ordinators for eligibility and adherence to definitions. Episodes were classified according to the underlying neoplasm and those developing in patients who had undergone BMT were classified as 'post BMT' episodes, regardless of the underlying disease.

Definitions

The bloodstream infection episode was the unit of analysis in this study and all following data refer to episodes and not to patients. A bloodstream infection was defined as the isolation of a bacterial or fungal pathogen from at least one blood culture, in the presence of clinical signs of infection, including at least one of the following conditions: fever ($> 38^{\circ}C$), a systolic blood pressure < 60 mmHg, or signs of localised infection (inflammation) in a major organ/system. As previously defined [14], for coagulase-negative staphylococci, corynebacteria other than *Corynebacterium jeikeium*, and other common skin contaminants, at least two sets of positive blood cultures (at least one bottle for each set) were required, unless the same pathogen was concomitantly isolated from another site of infection. All bloodstream infections were then subclassified as single-agent or poly-microbial infections. Polymicrobial infections were those episodes in which two or more pathogens were isolated in a single blood culture or in at least two separate blood cultures obtained 24 h apart. As previously described [15], catheter-related bloodstream infections were defined as those infections in which at least one of the following conditions was met: (1) fever ($> 38^{\circ}C$) with chills and rigors within 1 h after catheter flushing or manipulation; (2) isolation of a pathogen from a blood culture drawn through the catheter, but not from another blood culture drawn from a peripheral vein at the same time; (3) isolation of the same pathogen from the catheter tip and from blood; (4) isolation of the same organism both from blood and from purulent material draining from the catheter exit site or from the subcutaneous (s.c.) tunnel. Fever was defined as an axillary temperature $> 38^{\circ}C$. Neutropenia was defined as an absolute granulocyte count $< 1000/\mu L$. Shock was defined as the development of hypotension (systolic blood pressure lower than 70 mmHg in infants and 90 mmHg in all other cases), in the presence of at least one of the following conditions: cutaneous hypoperfusion, tachicardia, polypnoea, cyanosis, mental status changes, or oliguria (< 0.5 ml/kg/h urinary output).

Statistical methods

Comparison between categorical variables was performed by means of a Chi-square test for heterogeneity or a Fisher's

exact test (when applicable), whilst the *t*-test for independent data was applied for comparisons between continuous variables. For continuous variables, the median values and range are reported. The standard *P* value of 0.05 was considered the threshold for statistical significance. All tests were two-sided.

RESULTS

During the study period, 191 bloodstream infections, in 156 patients, were reported by 18 paediatric haematology and oncology centres in Italy. Median and mean age, respectively, were 6.6 (range 0.2–24.7) and 7.9 years (95% CI 7.1–8.7). 84 patients were males and 72 were females. The median number of episodes by participating centre was 7 (range 1–41) with 3 centres reporting more than 16 episodes.

Clinical characteristics

Of 191 episodes, 123 (64%) occurred in the presence and 68 (36%) in the absence of neutropenia. In neutropenic episodes, the median duration of the preceding neutropenia was 6 days (range 0–138). In these cases the median absolute white blood cell count at the time of diagnosis was 250/μL (range 0–12800) and the median absolute granulocyte count was 18/μL (range 0–960). Among the episodes occurring in the absence of neutropenia, the median white blood cell count was 5320/μL (range 1550–22000) and the median absolute granulocyte count was 3945/μL (range 1073–21000). There was a statistically significant difference ($P < 0.001$) in the proportion of infectious episodes developing during granulocytopenia according to the underlying disease. Among acute leukaemia, 84% (68/81) of the episodes were correlated with granulocytopenia, versus only 47% (32/68) and 55% (23/42) in solid tumours and BMT, respectively. Among BMT cases, bloodstream infections in the absence of neutropenia developed after a median of 63 days (range 8–493) from transplantation. One patient was included in the post-transplant group despite the fact that his infection developed more than 365 days after the initial transplant (493 days). This episode was still considered a post-transplant episode because the patient had received two additional bone marrow infusions, due to lack of engraftment.

Fever without signs of a localised infection represented the initial clinical presentation of the bloodstream infection in 71% (136/191) of the episodes. When a localised infection was present, the most frequent site was the oral cavity (21 cases), followed by skin and soft tissues (19 cases—4 non-neutropenic) and the lower (6 cases—2 non-neutropenic) and upper (4 cases—2 non-neutropenic) respiratory tracts. There were also 5 genito-urinary infections (2 non-neutropenic). Septic shock was found to complicate bacteraemic episodes in 15 cases (8%)—the majority of these cases occurred during neutropenia (13/15; 87%).

Isolated pathogens and antibiotic susceptibility

In the present study, pathogens isolated in blood culture were not centralised at a reference laboratory, and both identification and susceptibility tests were performed at the local hospital laboratory. Of the 191 episodes, 85 (45%) were due to gram-positive cocci, 78 (41%) to gram-negative rods and 18 (9%) to fungal organisms. In addition, there were 10 poly-microbial infections (5%). The overall number of isolated pathogens was 204. Of these, 93 (46%) were gram-positive cocci, 90 (44%) gram-negative rods and 21 (10%) fungal organisms. As shown in Table 1, there was no statistically significant difference in the distribution of gram-positive, gram-negative, and fungal isolates ($P = 0.54$), according to the presence or absence of neutropenia at presentation. Coagulase-negative *staphylococci* were the most frequently isolated pathogens (43/204; 21%), followed by *Pseudomonass sp* (28/204; 14%) and bacteria of the KES group (*Klebsiella-Enterobacter-Serratia*) (22/204; 11%). Viridans streptococci and *Escherichia coli* accounted for 20/204 pathogens each (10%). The other isolated pathogens were *Staphylococcus aureus* (19/204; 9%), *Candida sp.* (18/204; 9%) and enterococci (4/204; 2%). Gram-negative rods represented the most frequently isolated pathogens in cases of septic shock. Indeed, out of 15 cases of septic shock, 3 were due to *E. coli*, 6 to *Pseudomonas* and 1 each to *Klebsiella*, viridans *streptococci*, *S. aureus*, coagulase-negative *Staphylococcus* and *Candida*. The remaining case was observed in the setting of a poly-microbial infection (*E. faecium* and *P. aeruginosa*). *Pseudomonas* bacteraemias were much more likely to be complicated with septic shock than all other bacteraemias.

Resistance to oxacillin was tested in 49 of 62 staphylococcal strains (33 coagulase-negative staphylococci and 16 *S. aureus*): 35% of coagulase-negative staphylococci and 6% of *S. aureus* isolates were oxacillin resistant. Resistance to penicillin was tested in 19/20 viridans streptococci, of which, 8 (42%) were resistant. The proportion of gram-negative rods that were resistant to amikacin and ceftazidime, amikacin and ceftriaxone, and to the carbapenems was similar. 5/58 (9%) strains tested were resistant to both amikacin and ceftriaxone, 10/78 (13%) to both amikacin and ceftazidime, and 11/59 (19%) to the carbapenems ($P = 0.276$). *In vitro* resistance to fluoroquinolones was detected in 12/80 gram-negative rods (15%). Interestingly, 5 of these came from the only centre in which quinolone prophylaxis was used routinely.

Table 1. *Pathogens isolated in neutropenic and non-neutropenic episodes*

	Neutropenia		
Pathogens	Yes (%)	No (%)	Total
Gram-positive bacteria	61 (66)	32 (34)	93 (100)
viridans streptococci	18	2	20
Streptococcus pyogenes	1	–	1
Staphylococcus aureus	8	11	19
coagulase-negative-staphylococci	27	16	43
Enterococci	3	1	4
Actinomyces sp.	1	–	1
Other	3	2	5
Gram-negative bacteria	54 (60)	36 (40)	90 (100)
Escherichia coli	17	3	20
Pseudomonas sp.	18	10	28
KES group	11	11	22
Other	8	12	20
Fungi	15 (71)	6 (29)	21 (100)
Candida albicans	5	3	8
Non albicans *Candida*	7	3	10
Fusarium sp.	2	–	2
Saccharomyces cerevisiae	1	–	1

Overall *P* value = 0.54. KES, *Klebsiella*, *Enterobacter*, *Serratia*.

Table 2. Pathogens isolated in catheter-related and catheter-unrelated episodes

	Catheter-related	
Pathogens	Yes (%)	No (%)
Gram-positive bacteria	23 (38)	70 (49)
Gram-negative bacteria	29 (48)	61 (42)
Fungi	8 (13)	13 (9)
Total	60 (100)	144 (100)

Overall P value = 0.35.

Correlation with central venous catheters

Of 191 bloodstream infections, 176 (92%) occurred in patients fitted with a central venous catheter. Most (166/176, 94%) were partially implanted catheters of the Hickman-Broviac type. Of 176 episodes, 114 occurred in the presence and 62 in the absence of neutropenia. The proportion of catheter-related infections was 20% (23/114) among neutropenic episodes versus 55% (34/62) among non-neutropenic episodes ($P < 0.001$). There was no difference in the proportion of catheter-related infections according to the type of underlying disease. As shown in Table 2, gram-positive, gram-negative and fungal organisms were equally distributed in catheter-related and catheter-unrelated infections, although, gram-negative rods were isolated in an unexpected high proportion of catheter-related infections (48%).

Mortality

The overall 30-day mortality rate from any cause was 11% (death was the outcome in 21/191 episodes) and it was significantly higher ($P = 0.03$) in neutropenic (18/123, 15%) than in non-neutropenic episodes (3/68, 4%). Mortality was also significantly higher ($P < 0.001$) amongst episodes in BMT patients (9/43, 21%) than among episodes in solid tumour (4/67, 6%) and acute leukaemia (9/81, 11%). It was also significantly higher ($P = 0.05$) in fungaemias (4/18, 22%) and in poly-microbial infections (3/10, 30%) than in gram-positive (9/85, 11%) and gram-negative (5/78, 6%) infections. Although the difference was not statistically significant, the mortality rate associated with primary episodes (16 deaths among 156 primary episodes, 10%) appeared to be somewhat lower than the mortality rate associated with secondary episodes (5 deaths among 35 secondary episodes, 14%). 5 deaths, all in neutropenic episodes, occurred within 4 days from the first positive blood culture: 3 within the first 24 h (1, *E. coli*; 1, *Pseudomonas sp*; and 1, *C. septicum*), 1 after 3 days (*E. faecalis* and *P. aeruginosa*) and 1 after 4 days (*S. mitis*).

DISCUSSION

Most of the information about the epidemiology of infection in cancer patients is extrapolated from the results of randomised clinical trials of empirical antibiotic therapy of febrile neutropenia, i.e. from studies that were not specifically designed with epidemiological purposes. These studies included, by definition, only a subset of the population of cancer patients with infection, i.e., those patients that were eligible for enrolment in the trial according to predetermined inclusion and exclusion criteria. For example, in most studies of empirical therapy of febrile neutropenia, for methodological reasons, patients cannot be enrolled more than once and, therefore, second or third episodes in the same patients are missed. In addition, trials of empirical antibiotic therapy are usually conducted in neutropenic patients, and nothing is known about infections in non-neutropenic patients.

With the aim of collecting information about the clinical and aetiological pattern of infection in children with cancer, we conducted a nationwide multicentre surveillance study of bloodstream infections in this patient population.

Traditionally, bloodstream infections in cancer patients are mainly thought to be complications of neutropenia [16]. Therefore, when this study was planned, only a small number of bacteraemias in non-neutropenic patients was expected. Surprisingly, 36% of the observed episodes (68/191) developed in the absence of granulocytopenia. This means that the conventional wisdom that bacterial infections are uncommon in cancer patients outside neutropenia is not completely true.

According to our definitions, 34/68 (50%) infections in non-neutropenic patients were correlated with an infected central catheter, versus only 23/114 (20%) among neutropenic patients. This confirms the relevant role played by central catheters in causing infection in non-granulocytopenic patients [17, 18]. In another 12 episodes (18%), the infection was associated with the presence of a clinically detectable source of infection (skin and soft tissues in 4, and 2 each for upper respiratory tracts, lungs, genito-urinary tract and oral cavity) while in the remaining 22 episodes (32%) no source of infection was identified.

As is widely known, the pattern of infective pathogens has changed significantly over time in many cancer centres in the world. Gram-positive bacteria, which were prevalent in the 1950s and early 1960s, have again become the most common infecting pathogens. This has been confirmed by the results of the eight therapeutic trials performed by the IATCG-EORTC in the last 22 years in febrile and neutropenic patients [1, 19, 20]. Currently, in IATCG-EORTC trials, gram-positive micro-organisms are isolated in approximately 15% of febrile episodes and cause approximately 60% of documented bacteraemias, whilst fungal organisms account for no more than 2% of all bloodstream infections [10]. Our study shows that the actual epidemiological situation might be slightly different. Although the relative distribution of gram-positive, gram-negative and fungal infections was not always the same in all participating centres, in general gram-positive and gram-negative bacteria were almost equally represented as the cause of bloodstream infection both in neutropenic and in non-neutropenic patients, and fungaemias accounted for 10% of the cases.

The present study also shows that the traditional wisdom that catheter-related infections are mainly due to gram-positive cocci is not completely true. Indeed, in recent years, an increasing role played by gram-negative bacteria in causing catheter-related infections has been reported by several investigators, including ourselves, in different patient populations [15, 21]. In the present study, gram-negative bacteria were involved in 48% of catheter-related infections and a large proportion of the isolated strains belonged to the group of bacteria that are usually associated with infusate contamination (*Klebsiella*, *Enterobacter*, *Citrobacter*, *Achromobacter*, *Serratia*, *Pseudomonas* non-*aeruginosa*) [22]. The high proportion of catheter-related gram-negative infections might result from inappropriate practices in the use of central catheters performed by non professional staff [23]. Indeed, the importance of a proper catheter management in the

prevention of catheter-related infections has been underlined in several reports [17, 21, 23, 24].

A recent comparison of outcomes of febrile episodes during neutropenia between children and adults enrolled in the therapeutic studies performed by the IATCG of the EORTC showed a 7% overall crude mortality rate in children [25], thus somewhat lower than the 11% mortality rate that we found in the present study. This suggests that outcome data stemming from randomised therapeutic trials of empirical therapy might underestimate the true infection mortality rate in the population of cancer patients.

In recent years there has been major concern about the increasing rate of antibiotic resistance among nosocomial pathogens [26]. In the paediatric centres participating in the study, no major problem of antibiotic resistance was detected. For example, oxacillin-resistance was detected in 35% of coagulase-negative staphylococci, but in only 6% of *S. aureus* isolates. When looking at the proportion of gram-negative isolates that were resistant both to ceftriaxone and amikacin, ceftazidime and amikacin and to a carbapenem, (i.e. three regimens commonly used in empirical therapy of febrile neutropenia), it appeared that none individually was active *in vitro* against 100% of the pathogens. The conclusion is that therapeutic adjustments are likely to be necessary with any kind of protocol and that strict clinical and microbiological surveillance remains the standard of care in cancer patients with infection.

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