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Medical care related laboratory-confirmed bloodstream infections in paediatrics

Sepsi correlate alle cure microbiologicamente documentate in pediatria

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INTRODUCTION

Bloodstream infections (BSIs) continue to represent a significant source of morbidity and mortality in paediatric wards affecting primarily paediatric and neonatal intensive care units [1-3]. BSIs have been traditionally classified as healthcare-associated (HA) or community-acquired (CA). Nowadays complex medical services are increasingly provided in the community setting. So that BSIs occurring in community based patients may share many characteristics with HA infections such as associated comorbid diseases, increased risk for antimicrobial resistance and higher mortality [4-5]. The aim of this study is to investigate clinical and microbiological features and outcome of medical care related and laboratory-confirmed bloodstream infections (LCBIs) in children admitted to a paediatric hospital, or with history of a recent hospital admission or exposure to serious medical care in the outpatient setting.

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PATIENTS AND METHODS

A prospective observational study was performed between the 1st of June 2010 and the 31st of May 2011 at Regina Margherita Children's Hospital (Turin, Italy), a Paediatric referral teaching hospital comprehensive of medical and surgical wards and transplant divisions (solid organs and stem cells).
In order to identify all septic episodes, Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHS) surveillance definitions of LCBIs and central line-associated BSIs (CLABSIs) were integrated with additional criteria. All patients with clinical signs of sepsis (fever, tachycardia, hypotension, etc.), positive laboratory markers of infection (increase of inflammatory markers, such as white blood

cells count, C reactive protein, procalcitonin) and one or more of the following tests positive: blood culture for aerobic and anaerobic bacteria and fungi (BacT/ALERT, bioMérieux), multiplex real time Polymerase Chain Reaction (PCR) test on blood (LightCycler SeptiFast, Roche Diagnostics) and culture on intravascular device tip, were recruited [6-11]. Only LCBIs occurred in children with recent history of healthcare exposure were included in the analysis of the study. LCBIs were identified as healthcare-associated (HA) according to 1996-2008 CDC/NHSN definitions [7, 10]. As previously proposed, we defined as healthcare outpatient associated (HOA) LCBIs those septic episodes occurring at the time of hospital admission or within 48 hours upon admission in previously home-based patients with at least one of the following characteristics: (I) intravenous therapy, chemotherapy or haemodialysis in the 30 days before BSI onset; (II) Intensive Care Unit hospitalization lasting two or more days in the 90 days before BSI onset [4, 5].

All cases of positive microbiological tests not associated with clinical and/or serological signs of infection and not included in the previous criteria for LCBIs were considered sample contamination. Basing on data provided by antibiogram, the antibiotic treatment was defined as adequate when the microorganism isolated was sensitive to the antibiotic administered. If susceptibility testing was not available the antibiotic treatment was considered adequate when the pathogen isolated was theoretically sensitive to the antibiotic administered and an improvement of patient clinical conditions after treatment was observed.

Prematurity was defined as birth before 37 weeks of gestation age. Five patients aged >18 years old affected by chronic diseases followed by our centre beyond the adult age were included because our purpose was to describe characteristics of sepsis in the whole hospital population.

Incidence (ratio) of HA-LCBIs was expressed as the total number of septic episodes per 1,000 hospitalized patients. Incidence density (rate) was calculated as the total number of bloodstream infections per 1,000 inpatient days. Incidence of HOA-LCBIs was not calculated due to the impossibility of inferring the exact number of children at risk. The total number of admissions was the denominator used to calculate the CLABSI incidence since the study design did not provide a control group and data about CVC-days were not obtainable.

Risk of developing LCBI in males and females was evaluated by chi-square test with one degree of freedom. The two-tailed p value was considered statistically significant if <0.05.

RESULTS

A total of 140 episodes of LCBI occurred in 131 children over one-year of observation (5 children presented more than one episode of LCBI): 37 (26.4%) were classified as healthcare outpatient associated, 91 (65.0%) as healthcare associated and 12 (8.6%) as community-acquired. In this survey we only refer to the 128 episodes of medical care related LCBIs (healthcare outpatient associated plus healthcare associated LCBIs). In 195 cases the positivity of one or more microbiological test was considered as sample contamination. Coagulase-negative staphylococci (CoNS) (84.9%) were the most frequent pathogens identified in these cases.

Considering both paediatric and neonatal wards, there were 14,342 hospital admissions, with a HA-LCBIs incidence (ratio) of 13.6/1,000 patients and an incidence density (rate) of 1.4/1,000 inpatient days. Forty-seven episodes have occurred in newborns (median age at diagnosis 0.03 years; IQR (InterQuartile Range) 0.01-0.06 years) while 81 episodes have been recorded in infants (median age at diagnosis 9.1 years; IQR 3.3-15.4 years). Median weight at diagnosis was 1.7 kg (IQR 0.9-3.0 kg) and 23.8 kg (IQR 14.2-64.0 kg) respectively in newborns and infants. Twenty-one episodes (16.4%) of LCBIs occurred in very low birth weight babies (birth weight <1.5 kg). Risk of developing LCBI was higher in males (p=0.011), who presented a total of 85 (66.4%) LCBI, while only 43 (33.6%) LCBI were observed in females. The 86.7% of episodes regarded patients with serious underlying medical conditions (prematurity 26.1%, cancer 39.1%, hematopoietic stem cell transplantation 7.8%, malformative syndromes 7.8%, dialysis 6.1%, solid organ transplantation 3.5%, immunosuppression 2.6%, other 7.0%).

Oncology and stem cell transplant divisions, neonatal intensive care unit, neonatal wards and nephrology division counted respectively the 40.6%, 26.6%, 7.0%, and 6.3% of episodes (Table 1).

Table 1 - Incidence of medical care related laboratory-confirmed bloodstream infection (LCBI) by specialty.

	HOA-LCBI[a]	*HA-LCBI*[b]	*Total*	*Incidence of HA-LCBI*[b]	
Ward	*No. patients*	*No. patients*	*No. patients (%)*	*(for 1,000 admissions)*	*(for 1,000 inpatients days)*
Neonatology unit	0	9	9 (7.0)	1.2	0.3
Neonatal intensive care unit	1	33	34 (26.6)	91.7	3.4
Oncology and stem cell transplant center	27	25	52 (40.6)	30.7	3.6
Infectious diseases unit	1	3	4 (3.1)	6.9	0.8
Cardiac surgery unit	0	4	4 (3.1)	24.5	1.6
Neurosurgery unit	0	1	1 (0.8)	3.1	0.4
Gastroenterology unit	0	2	2 (1.6)	9.8	1.5
Pneumology unit	0	3	3 (2.3)	12.0	1.0
Emergence department	0	2	2 (1.6)	2.3	0.4
Orthopedic unit	0	1	1 (0.8)	2.7	0.8
Pediatric intensive care unit	0	1	1 (0.8)	26.3	0.9
Neonatal surgery	0	4	4 (3.1)	61.5	1.8
General pediatrics	2	1	3 (2.3)	3.5	0.5
Nephrology unit	6	2	8 (6.3)	9.5	0.8
Total	37	91	128(100.0)	13.6	1.4

[a]HOA-LCBI: healthcare outpatient associated laboratory confirmed bloodstream infection. [b]HA-LCBI: healthcare associated laboratory confirmed bloodstream infection

A total of 107 episodes (83.6%) of HA and HOA LCBIs occurred in children with central venous catheter (CVC), but only 62 (48.4%) episodes were CLABSI. Sources of infections in the remaining cases were throat and upper airways (12.5%), lung (10.2%), gastrointestinal tract (7.8%), urinary tract (3.1%), ears (0.8%), other (9.4%), unknown (7.8%). Positive blood culture alone was the main test to diagnose LCBIs (79.7%). A second positive blood culture was required if the microorganism identified was a common commensal (such as *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., CoNS, *Streptococcus viridans*, *Aerococcus* spp., *Micrococcus* spp.). Other cultural and molecular tests performed were: PCR detection of pathogen DNA on blood (1.6%), positive blood culture and PCR detection of pathogen DNA on blood (3.1%), positive blood and removed CVC tip cultures (12.5%), PCR detection of pathogen DNA on blood and positive removed CVC tip culture (0.8%), PCR detection of pathogen DNA on blood and positive blood and removed CVC tip cultures (1.6%), positive coagglutination test on cerebrospinal fluid and positive blood/cerebrospinal fluid cultures (0.8%).

Gram positive and Gram negative bacteria were isolated in the 62.3% and 30.4% of the episodes, respectively; fungi were responsible for the remaining 7.2% (Table 2). Concerning the distribution of antimicrobial resistance among Gram positive bacteria, methicillin-resistant was observed in 9.5% of *Staphylococcus aureus* (MRSA) and in 78.4% of coagulase-negative staphylococci (CoNS). *Pseudomonas aeruginosa* was isolated in 7 children: in 5 cases it was a drug-susceptible strain, while in 2 cases drug susceptibility was not available because the bacteria was identified by PCR test only.

Empirical antibiotic therapy administered at onset of symptoms was adequate in 105 cases (82.0%). In the remaining cases, appropriate antibiotic treatment was administered within 24 hours in 8 cases (6.3%), within 48 hours in 2 cases (1.6%), within 72 hours or more in 12 cases (9.4%). One patient never received an adequate antibiotic treatment because he died for an end-stage haematological cancer 24 hours after sample collection for microbiological tests. Five patients died because of LCBIs, corresponding to an overall mortality rate of 3.9%: 3 of them were children affected by end-stage cancer and two were premature newborns of extremely low birth weight. *Escherichia coli* (2 cases), *P. aeruginosa* (1 case), *Streptococcus agalactiae* (1 case) and *Enterococcus faecium* (1 case) were the responsible pathogens isolated.

Among all episodes of LCBIs, we identified 62

Table 2 - Pathogens isolated from children affected by medical care related laboratory-confirmed bloodstream infections (LCBIs).

	No. pathogens isolated (%)		
Pathogens	*HOA-LCBI*[a]	*HA-LCBI*[b]	*Medical care related LCBIs*
Gram positive	19 (47.5)	67 (68.4)	86 (62.3)
Staphylococcus aureus	10 (25.0)	11 (11.2)	21 (15.2)
Coagulase-negative staphylococci	6 (15.0)	31 (31.6)	37 (26.8)
Streptococcus agalactiae	0 (0.0)	5 (5.1)	5 (3.6)
Streptococcus pneumoniae	0 (0.0)	1 (1.0)	1 (0.7)
Other streptococci	1 (2.5)	6 (6.1)	7 (5.1)
Enterococcus faecium	1 (2.5)	4 (4.1)	5 (3.6)
Enterococcus faecalis	0 (0.0)	5 (5.1)	5 (3.6)
Other	1 (2.5)	4 (4.1)	5 (3.6)
Gram negative	21 (52.5)	21 (21.4)	42 (30.4)
Escherichia coli	4 (10.0)	8 (8.2)	12 (8.7)
Klebsiella spp.	3 (7.5)	4 (4.1)	7 (5.1)
Enterobacter cloacae	2 (5.0)	1 (1.0)	3 (2.2)
Acinetobacter spp.	3 (7.5)	0 (0.0)	3 (2.2)
Pseudomonas aeruginosa	2 (5.0)	5 (5.1)	7 (5.1)
Sphingomonas paucimobilis	0 (0.0)	1 (1.0)	1 (0.7)
Haemophilus influenzae type b	0 (0.0)	1 (1.0)	1 (0.7)
Other	7 (17.5)	1 (1.0)	8 (5.8)
Fungi	0 (0.0)	10 (10.2)	10 (7.2)
Candida albicans	0 (0.0)	4 (4.1)	4 (2.9)
other *Candida* spp	0 (0.0)	6 (6.1)	6 (4.3)
Total*	40 (100.0)	98 (100.0)	138 (100.0)

[a]HOA-LCBI: healthcare outpatient associated laboratory confirmed bloodstream infection. [b]HA-LCBI: healthcare associated laboratory confirmed bloodstream infection. *10 LCBI were polymicrobial.

cases of CLABSI, representing the 48.4% of LCBIs: 23 (37.1%) of them were HOA and 39 (62.9%) HA. Thirty-two (51.6%) cases affected long-term tunneled CVCs and 30 (48.4%) non tunneled CVCs. The incidence (ratio) of HA-CLABSI was 1.9/1,000 patients for tunneled CVC and 3.9/1,000 for non-tunneled ones, while incidence density (rate) was 0.2/1,000 and 0.4/1,000 inpatient days respectively. No significant seasonal variability was observed in the incidence of CLABSI. CoNS (39.7%) and *S. aureus* (14.7%) were the pathogens most frequently isolated. Intravascular device was removed in the 40.6% of CLABSIs related to tunneled catheter and in the 90.0% of non-tunneled catheters. All CLABSI episodes had a good outcome.

Forty seven neonatal sepsis were observed, representing the 36.7% of all cases: 46 (97.9%) were classified as HA and only one (2.1%) as HOA. Excluding all healthy infants discharged from the neonatal wards and 9 episodes of LCBI occurred outside the wards, the incidence (ratio) of neonatal HA-LCBIs was 102.8/1,000 admissions and the incidence density (rate) was 3.8/1,000 inpatient days. With reference to risk condition, prematurity was observed in the 59.6% of the neonatal LCBI. CoNS (35.4%), *S. aureus* (12.5%) and *S. agalactiae* (10.4%) were the predominant pathogens responsible for LCBIs. Mortality rate was 4.3%.

Fungal infections represented 7.8% of LCBIs cases (10 episodes recorded): 7 were CLABSIs while all the others occurred in immunocompromised patients. All the episodes of fungal LCBI recovered after appropriate antifungal treatment and CVC removal.

DISCUSSION

Medical care related LCBIs represent a significant health problem in the paediatric setting due to the high mortality and morbidity rates reported, especially among newborns and children with

chronic comorbidities. In recent years some Authors proposed a sub-classification of community onset BSIs into proper community-acquired and healthcare outpatient associated infection as a consequence of the increased opportunities of providing complex medical services also in the community setting [4, 5]. Since HA and HOA LCBIs occur in patients with specific characteristics (underlying diseases, predisposing conditions, medical exposure), and share epidemiological features, causative pathogens and mortality rates, they have been analyzed altogether. Few monocentric studies investigated LCBIs considering both general and specialized wards and intensive care units in a paediatric hospital, giving a general overview of the phenomenon in children. Many authors have evaluated subcategories of children, as those admitted to high risk single departments (paediatric or neonatal intensive care units, oncology or cardiac surgery services) or have focused on LCBIs caused by specific pathogens, such as *S. agalactiae, Streptococcus pneumoniae*, and *S. aureus*. Instead, our purpose was an accurate and comprehensive epidemiological description of LCBIs clinical and microbiological features possibly related to significant exposure to relevant medical care.

Incidence (ratio) of LCBIs observed in our survey (13.6/1,000 patients) was slightly higher than that reported in literature [12-14]. In addition to different definitions of LCBI used, this difference could be explained by several factors. First of all, the inclusion in the present survey of high risk wards, such as paediatric and neonatal intensive care units, solid organs and stem cells transplantation units and cardiac and neurosurgery services: indeed, neonatal wards and neonatal intensive care units accounted for 33.6% of all LCBIs. Secondly, also highly probable LCBI episodes supported by positive molecular tests other than blood culture were included in this survey for a complete overview of the disease [15]. Finally, study population included some patients aged >18 years, because paediatric patients suffering from chronic diseases are generally followed at our centre beyond the adult age.

Categories more vulnerable to LCBIs were oncologic children (40.6%) and newborns (36.7%). Among the latter, prematurity and very low birth weight were the conditions more often associated with LCBIs and CoNS were the main responsible pathogens in newborns, as observed elsewhere [16-18]. Few episodes occurred in intensive care unit and cardiac surgery service, probably as a result of particular effort into prevention programs and education of medical and nursing staff (protocols for hand-washing, CVC management, use of antimicrobial-coated CVC) together with a proper administration of antibiotic therapy.

Similarly to other surveys, CoNS, *S. aureus*, and streptococci were the most frequent responsible pathogens for LCBIs, while the principal causative agents among Gram negative bacteria were *E. coli*, *Klebsiella* spp., and *P. aeruginosa* [18-20]. Considering HOA and HA LCBIs separately, Gram negatives were responsible for the majority of episodes (52.5 %) in the first category, while Gram positives were prevalent among HA-LCBIs (the 68.4% of cases). As a matter of fact, HOA-LCBIs usually occur in chronic patients more susceptible to Gram negative infections while the majority of HA-LBSIs affect newborns or children with an indwelling CVC, in which CoNS are frequently isolated. *Candida* spp were less represented than in other studies (7.2% vs 9.3%). No deaths for candidemia occurred during the observation period, despite the high mortality rate due to *Candida* spp reported in literature, probably as a consequence of the extensive use of antifungal prophylaxis with fluconazole in high risk children [18, 21-23]. LCBIs caused by MRSA, oxacillin-resistant CoNS and Multi-Drug Resistant (MDR) *P. aeruginosa* were less frequent than in other studies [14, 18-20, 24-26]. This may be explained by a low prevalence of resistant pathogens in paediatric population compared to the overall national rates including mostly adults. Children present naturally low risk of infections caused by antibiotic-resistant microorganisms compared with adults, but no data about antibiotic-resistance primarily in children is actually available for a proper comparison [24].

Overall mortality rate was lower than data reported in literature [13, 18, 20]. All deaths involved critically ill children with serious underlying diseases, as prematurity and end-stage cancer, who had received a prompt and appropriate antibiotic treatment. The cause of death has been assigned to infection and not to other causes because a rapid deterioration of the general condition of the children was observed concomitantly to the development of the infectious disease, which precipitated already severely compromised clinical conditions.

To calculate CLABSI incidence, the total number of admissions was the denominator used since no control group was provided for by the study design. Consequently, it was not possible to compare our results with other surveys that used CVC-days as denominator [27-30]. CLABSI mainly occurred in newborns, patients with cancer or children who had undergone solid organ or stem cells transplantation, major surgery or dialysis. In the present survey, CVC was removed only in the 40.6% of CLABSI involving tunnelled CVC. In some cases a salvage effort with lock-therapy was made when removal was deemed unfeasible due to concomitant conditions (thrombocytopenia, unstable critical conditions, difficult venous access in children with absolute needs such as dialysis or intravenous therapy) [31]. In other cases CVC was removed after multiple episodes of CLABSI involving the same CVC. In spite of the relatively low rate of CVC removal, all CLABSI recovered after appropriate systemic and local (lock) antimicrobial therapy.

In conclusion, we observed encouraging and reassuring results in terms of epidemiology, clinical management and outcome of paediatric LCBIs, although sepsis continues to represent a significant source of morbidity and mortality in newborns and oncologic children, so that a particular care should be encouraged in the management of these high risk categories. A prompt and appropriate antimicrobial treatment is associated with positive outcome and reduced mortality in most cases. Despite guidelines for prevention of intravascular catheter-related infections strongly recommend CVC removal in case of BSIs, clinical practice often rules out the possibility of immediate removal because of critical and unstable conditions of the patient [32].

A limit of this survey is that it was performed in a single centre. As medical care related LCBIs represent an important cause of morbidity and death in children, further multicentre studies with prolonged surveillance time are needed to improve the knowledge on clinical and microbiological features of LCBIs, to optimize prevention procedures and to reduce the impact of these infections in children.

Keywords: HAIs, laboratory-confirmed BSIs, paediatric BSIs, sepsis.

SUMMARY

The aim of this survey was to describe the incidence, epidemiology, microbiology, risk factors and outcome of medical care related laboratory-confirmed bloodstream infections (LCBIs) observed during a twelve-month prospective study in a Paediatric Teaching Hospital in Turin, Italy. Inclusion criteria were clinical signs of sepsis and positivity of one or more of the following tests: blood culture, polymerase chain reaction for bacterial and fungal DNA on blood, and culture on intravascular device tips. In all, 140 episodes of sepsis were documented in 131 children: 37 (26.4%) were healthcare outpatient-associated, 91 (65.0%) healthcare-associated and 12 (8.6%) community-acquired. The overall incidence of healthcare-associated LCBIs was 13.6/1,000 hospitalized patients and incidence density 1.4/1,000 inpatient days. The overall mortality was 3.9%. Forty-seven (36.7%) episodes involved newborns and 107 (83.6%) episodes were observed in children with an indwelling central venous catheter. Coagulase-negative staphylococci (26.8%), *Staphylococcus aureus* (15.2%), *Escherichia coli* (8.7%) and *Candida* spp. (7.2%) were responsible for the majority of cases. 9.5% of *S. aureus* isolates were methicillin-resistant and 6.5% of Gram negatives were extended-spectrum beta-lactamase-producing. Incidence and epidemiology of medical care related LCBIs were similar to the existing literature data. LCBIs caused by antibiotic-resistant microorganisms were fewer and mortality rate was lower. Most of the LCBIs recorded involved newborns and oncological children.

RIASSUNTO

*L'obiettivo di questo studio è la descrizione dell'incidenza, dell'epidemiologia, della microbiologia, dei fattori di rischio e dell'*outcome *delle sepsi correlate alle cure e microbiologicamente documentate (LCBIs) che si sono verificate presso l'Ospedale Infantile Regina Margherita di Torino nel corso di un anno di osservazione. Si tratta di uno studio prospettico nel quale sono stati arruolati tutti i pazienti che presentavano segni clinici e laboratoristici suggestivi per sepsi e la positività di almeno uno tra i seguenti esami: emocoltura,* Polymerase Chain Reaction *per la ricerca di DNA microbico e fungino su sangue, esame colturale sulla punta di cateteri venosi intravascolari asportati. Durante il periodo di osservazione sono stati documentati 140 episodi settici in 131 bambini: 37 (26.4%) sono stati classificati come sepsi correlate all'assistenza medica poiché sviluppatesi in soggetti affetti da patologia cronica, ma non ricoverati in ospedale al momento dell'insorgenza dei sintomi, 91 (65.0%) come sepsi correlate alle cure propriamente dette e 12 (8.6%) come sepsi comunitarie, quindi escluse dallo studio. L'incidenza di sepsi correlate alle cure è stata di 13.6/1,000 pazienti ricoverati e di 1.4/1,000 giorni di ricovero, mentre la mortalità è stata del 3.9%. 47 (36.7%) episodi hanno coinvolto la popolazione neonatale e 107 (83.6%) eventi settici si sono verificati in pazienti portatori di catetere venoso centrale. I microrganismi isolati più frequentemente sono stati gli stafilococchi coagulasi negativi (26.8%), lo* Staphylococcus aureus *(15.2%), l'*Escherichia coli *(8.7%) e la* Candida *spp. (7.2%). Tra gli isolati di* Staphylococcus aureus*, il 9.5% era rappresentato da isolati meticillino-resistenti (MRSA) e il 6.5% dei Gram negativi identificati era in grado di produrre beta-lattamasi ad ampio spettro (ESBL). L'epidemiologia e l'incidenza delle sepsi correlate alle cure registrate in questo studio sono paragonabili ai valori riportati dalla letteratura, mentre il numero di episodi causati da microrganismi antibiotico-resistenti, così come il tasso di mortalità, si sono dimostrati più bassi. La maggior parte degli episodi registrati ha coinvolto prevalentemente la popolazione neonatale e i bambini affetti da patologia oncologica, come riportato anche nei pochi studi analoghi disponibili in letteratura.*

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