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Original articles

Community-acquired bloodstream infections among paediatric patients admitted to an Italian tertiary referral centre: a prospective survey

Sepsi comunitarie in una popolazione di pazienti pediatrici afferente a un centro di terzo livello: studio prospettico

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INTRODUCTION

Community-acquired bloodstream infections (CA-BSIs) are still considered a significant cause of morbidity and mortality in paediatric age, with *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* remaining the main pathogens responsible across Europe, although national immunization campaigns have reduced their global incidence [1]. Moreover, the emergence of previously secondary serotypes and bacteria, together with antibiotic-resistant strains, requires continuous surveillance. Epidemiological studies are needed both to guide vaccine strategies and to optimize empiric antibiotic treatment [2-4]. Here we describe the epidemiological features of CA-BSIs observed in paediatric patients admitted to a single referral hospital on a one-year prospective survey.

PATIENTS AND METHODS

Regina Margherita Children's Hospital is the tertiary referral paediatric teaching centre of Piedmont, a region in the North-West of Italy. Between June 1st 2010 and May 31st 2011, we prospectively collected cases of laboratory-confirmed CA-BSIs (CA-LBSIs), selected on the basis of bacteria isolation from common sterile fluids (blood, cerebrospinal fluid) collected on arrival in the Emergency Department (ED). We included patients of all ages and recovered both in general and specialized wards. Clinical data recorded included demographic information and previous vaccinations, underlying diseases and risk factors, clinical conditions from admission to discharge, including haematological parameters, empiric and targeted antimicrobial therapy, and final outcome. A case of CA-BSI is labelled by the presence of symptoms and signs of sepsis upon hospital admission, or their appearance within 48 hours from hospitalization. CDC criteria were used to correctly define CA-BSI cases as laboratory-confirmed [5]. Patients admitted to the ED within 48 hours of the appearance of symptoms and signs of acute meningitis were also included if there was clinical evidence of bacteraemia proved by one or more of the following criteria:

1) a distant infective focus (e.g. pneumonia);
2) presence of haemorrhagic diathesis;
3) septic shock [6].

All blood samples underwent aerobic and anaerobic culture (BacT/ALERT PF and FN

bottles, bioMérieux), while cerebrospinal fluid was examined through a co-agglutination test, polymerase chain reaction (PCR) tests and culture. Adjunctive microbiological tests (LightCycler SeptiFast test M(GRADE) Roche Diagnostics, pharyngeal swab, urinary pneumococcal antigen, etc.) were performed at the discretion of the patient's care provider. Study data were managed using Excel 2007 (Microsoft Corp., Redmond, WA-USA). The total number of ED accesses and the whole amount of hospitalizations during the study period were used to calculate incidence rates; incidence rates were expressed as the number of CA-LBSIs per 1,000 admissions.

RESULTS

Twelve episodes of CA-LBSIs were documented during the study period (Table 1). Mean age at diagnosis was 5.2±5.9 years (median age 1.7 years, range 0.3-16.6). Seven cases (58.3%) involved children <2 years, and 8 episodes regarded male patients (66.7%). Four patients (33.3%) presented underlying chronic conditions or risk factors for infective processes at diagnosis: three children had congenital abnormalities (tetralogy of Fallot, aortic coarctation, Saethre-Chotzen syndrome) and one was affected by type 1 diabetes mellitus. None of them was hospitalized in the previous two months before CA-LBSI onset. Incidence rates were 0.39/1,000 ED admissions, and 2.9/1,000 hospitalizations concerning all departments of Regina Margherita Children's Hospital.

We found six episodes of CA-LBSIs by Gram positive bacteria (4 by *Streptococcus pneumoniae*, 1 by *Streptococcus pyogenes*, 1 by methicillin-susceptible *Staphylococcus aureus* - MSSA), and six cases by Gram negative bacteria (3 by *Escherichia coli*, 2 by *Haemophilus influenzae* with one serotype b, 1 by *Neisseria meningitidis* group B). Types of positive tests *per pathogen* are summarized in Table 2. Of the four cases of CA-LBSIs caused by *Streptococcus pneumoniae,* one child was fully vaccinated with heptavalent pneumococcal conjugate vaccine (PCV-7). Moreover, two patients with CA-LBSI caused by *Haemophilus influenzae* failed to complete the relative vaccine schedule (Table 1). The serotypes responsible could not be identified in our hospital. The first infective focus was found in the lung (4 cases), in the upper respiratory tract (3 children), in the urinary tracts (2 children), and in the gastrointestinal tract, middle

Table 1 - Epidemiological features of CA-LBSI cases.

Patient	*Age*	*Risk factor*	*Vaccinations (PCV-7, Hib, MenC)*	*Isolated pathogen*
# 1	9.95	No	PCV-7, Hib, MenC	*E. coli*
# 2	6.31	Saethre-Chotzen syndrome	PCV-7, Hib, MenC	*S. pneumoniae*
# 3	14.76	No	No	*N. meningitidis* group B
# 4	0.48	No	No	*E. coli*
# 5	16.59	Type 1 Diabetes mellitus	No	*E. coli*
# 6	0.51	Aortic coarctation	Incomplete schedule for Hib	*H. influenzae* type b
#7	1.28	Tetralogy of Fallot	PCV-7, Hib, MenC	*S. aureus*
# 8	1.58	No	Hib, Men C	*S. pneumoniae*
# 9	0.35	No	Incomplete schedule for Hib and PCV-7	*H. influenzae*
# 10	0.3	No	No	*S. pneumoniae*
#11	8.45	No	Hib	*S. pyogenes*
# 12	1.81	No	Hib	*S. pneumoniae*

Table 2 - Primary infective focus and positive tests per pathogen.

					Cerebrospinal fluid			
Patient	*Isolated pathogen*	*Primary infective focus*	*Blood culture*	*Septifast*	*Culture*	*Co-agglutination*	*PCR*	*Urinary pneumococcal antigen*
# 1	*E. coli*	Gastrointestinal tract	POS	n.d	n.d	n.d	n.d	n.d
# 2	*S. pneumoniae*	Lung	NEG	n.d	POS	NEG	n.d.	NEG
# 3	*N. meningitidis* group B	Upper respiratory tract	NEG	n.d	n.d	POS	POS	n.d
# 4	*E. coli*	Urinary tract	POS	n.d	POS	n.d	n.d	n.d
# 5	*E. coli*	Urinary tract	POS	n.d	n.d	n.d	n.d	n.d
# 6	*H. influenzae* type b	Median ear	NEG	n.d	NEG	POS	n.d	n.d
#7	*S. aureus*	Upper respiratory tract	POS	n.d	n.d	n.d	n.d	n.d
# 8	*S. pneumoniae*	Lung	NEG	POS	n.d	n.d	n.d	POS
# 9	*H. influenzae*	Lung	POS	n.d	n.d	n.d	n.d	n.d
# 10	*S. pneumoniae*	Upper respiratory tract	NEG	n.d	POS	POS	n.d	n.d
#11	*S. pyogenes*	Peri-orbital tissues	POS	n.d	n.d	n.d	n.d	n.d
# 12	*S. pneumoniae*	Lung	NEG	n.d	NEG	POS	n.d	POS

POS = positive; NEG = negative; n.d. = not done

ear and peri-orbital tissues (1 patient each) (Table 2). No antibiotic-resistant strains were isolated. Empiric antibiotic therapy prescribed at diagnosis was found appropriate to microbiological results in all cases; it was administered for a mean time of 17.7±10.1 days (median 14.5 days, range 7-42 days). Mean length of hospitalization was 23.4±15.5 days (median 17 days, range 9-56). All patients had a good outcome.

DISCUSSION

Albeit small, our case series provides an interesting overview on CA-LBSIs in paediatric age: definitions of the study cases were established a priori, and the prospective way of collecting data gave full epidemiological information of the episodes concerned. However, few cases were involved: most children admitted to the Emergency Department for fever are generally already pre-treated with oral antimicrobials at home; secondly, patients with symptoms and signs of sepsis at clinical examination often undergo blood cultures after starting IV antibiotic therapy. In our opinion, both of these reasons contribute to reduce chances dramatically for bacteria identification through blood cultures. As isolation of the responsible pathogen was the first step to identify the patient and essential to define CA-LBSIs. Cases of clinical sepsis were consequently excluded [5]. Comparison with other European surveys is often difficult, as they are population-based studies, they group together adults and children, or they include early onset neonatal sepsis in CA-LBSIs [3, 4, 7, 8]. Importantly, about 50% of observed cases were caused by potential vaccine-preventable pathogens; moreover, the majority of episodes regarded children under two years old, confirming that this age group is at great risk of CA-LBSIs, probably due to an incomplete vaccine schedule [2-4, 9]. However, vaccinations against *S. pneumoniae, H. influenzae* and

N. meningitidis should be strongly implemented among the paediatric population of Piedmont, as evident in Table 1. Our survey recognized *S. pneumoniae* as the commonest isolated pathogen. The European Centre for Disease Prevention and Control (ECDC) reported an overall confirmed case rate of 4.3 per 100,000 population for invasive pneumococcal disease (IPD) in 2009 [1]. A general decline in IPD burden was observed after introduction of PCV-7 in different European States, but this led to the emergence of previously secondary serotypes (1, 19A, 3, 6A, and 7F), now included in PCV-13 [10]. Likewise, the widespread of vaccinations against *H. influenzae* type b and *N. meningitidis* group C made invasive diseases incidence rates decrease in Europe in recent years [1]. However, the World Health Organization (WHO) registered an incidence of meningococcal disease from 0.2 to 14 cases per 100,000 population in Europe, with the majority of cases caused by serogroup B strains, particularly in those countries which have introduced serogroup C conjugate vaccines in recommended schedule [11]. Indeed, the sole case of CA-LBSI by *N. meningitidis* of our survey was caused by serogroup B.
We found that *Escherichia coli* was the second most frequently isolated pathogen (3 cases), giving importance to appropriate coverage of this Gram negative pathogen upon prescription of the empiric antibiotic therapy: an Italian multicentre study noted that *E. coli* obtained the same prevalence among CA-LBSIs and hospital-acquired ones, with urinary tract infections representing the main source for *E. coli* BSIs in the community setting [8].
Blood culture is the current *gold standard* for BSI diagnosis, able to provide bacteria isolation together with antibiotic susceptibility tests. In addition, current guidelines strongly recommend a careful search of the primary infective focus of BSIs, in order to collect other specimens and increase the chances of bacteria identification [12, 13]. Our survey noted 50% of negative blood cultures: previous antibiotic treatment and low bacteria loads can lead to negative results, first of all in paediatric patients where samples are often poor. In this *scenario*, collection of multiple blood samples for culture before starting therapy can represent a helpful strategy, although this can be rarely applicable in debilitate children. New methods such as the Septifast test will represent a valid support for pathogen identification: it may increase sensitivity of blood cultures and give swift results in order to guide antimicrobial drug choice, as seen in one child of the present case series [14].
Among our patients, empiric antibiotic therapy prescribed at the time of diagnosis was found adequate to microbiological results, setting a broad spectrum monotherapy or a combination of antibiotics according to current guidelines (12). Although a total duration of 7-10 days of antibiotic therapy is generally recommended, we reserved a prolonged treatment for children under 2 years old and complicated patients, as longer courses are justified in cases of slow clinical response, undrainable foci of infection, or immunological disorders [13, 15]. We found no antibiotic-resistant strains: Italy still registers a limited number of antibiotic non-susceptible pathogens among bacteria species isolated in our patients, and the Italian paediatric population maintains a lower proportion compared to the adult one [16]. No patients died of CA-LBSIs. A low mortality rate is expected in cases of prompt diagnosis and appropriate antibiotic treatment [2-4, 9].
In conclusion, the prompt collection of blood samples and specimens from primary foci of infection together with the rapid institution of empiric antibiotic therapy is essential for sound management of CA-LBSIs in paediatric patients. Implementation of vaccinations against the main pathogens responsible is the most important prevention strategy, most of all in categories at risk. However, continuous surveillance is required to notice global changes in invasive bacterial disease epidemiology.

Keywords: community acquired, bloodstream infections, children, vaccinations.

Conflict of interest
The authors declare that they have no conflict of interest.

RIASSUNTO

Invasive bacterial diseases continue to represent a significant burden in paediatric age, and the emergence of previously secondary bacteria and antibiotic-resistant strains requires continuous surveillance. In this context, a one-year prospective survey on laboratory confirmed community-acquired bloodstream infections (CA-LBSIs) cases admitted to an Italian tertiary referral paediatric hospital. In all, twelve cases were documented, with an incidence rate of 0.39/1,000 admissions to the Emergency Department, and 2.9/1,000 hospitalizations to general and specialized wards. Mean age at diagnosis was 5.2±5.9 years, with 58.3% of episodes regarding children <2 years. Six episodes were caused by Gram positive and six by Gram negative bacteria, with potential vaccine-preventable pathogens responsible for 50% of CA-LBSIs. Empiric antibiotic therapy prescribed on admission was found appropriate to microbiological results in all cases and administered for a mean time of 17.7±10.1 days. No resistant strains were found. All patients had a good outcome. Prompt collection of samples for microbiological tests together with the rapid institution of empiric antibiotic therapy is therefore essential for sound management of CA-LBSIs in paediatric patients. Implementation of vaccinations against the main pathogens responsible remains the most important prevention strategy.

SUMMARY

Introduzione. *Le infezioni batteriche invasive continuano a rappresentare un'importante causa di morbilità in età pediatrica; inoltre, l'emergere di patogeni un tempo secondari e di ceppi antibiotico-resistenti richiede una sorveglianza continua.*
Materiali e metodi. *Studio prospettico osservazionale dei casi di sepsi comunitaria microbiologicamente documentata (CA-LBSIs) afferenti a un Centro specialistico pediatrico di Terzo Livello in un anno.*
Risultati. *Dodici casi di CA-LBSIs documentati: incidenza di 0,39/1.000 accessi in Pronto Soccorso, e 2,9/1.000 ricoveri nei reparti generali e specialistici. Età media alla diagnosi: 5,2±5,9 anni, con il 58,3% degli episodi riguardante bambini <2 anni. Batteri Gram positivi e Gram negativi hanno determinato 6 episodi ciascuno, il 50% dei quali dovuti a patogeni potenzialmente prevenibili con vaccinazione. La terapia antibiotica empirica prescritta all'ingresso, e somministrata per una media di 17,7±10,1 giorni, è risultata adeguata al dato microbiologico nella totalità dei casi. Nessun isolamento di ceppi antibiotico-resistenti. La guarigione senza reliquati è stata osservata nella totalità dei casi.*
Conclusioni. *La sollecita raccolta dei campioni biologici per i test microbiologici, unitamente alla rapida istituzione di una terapia antibiotica empirica, sono essenziali per la corretta gestione delle CA-LBSIs. La diffusione della pratica vaccinale verso i maggiori patogeni responsabili rimane la più importante strategia preventiva.*

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