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Targeted empiric antibiotic therapy for children with non-oncological comorbidities and community-onset invasive bacterial infections

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Summary *Objectives:* To describe the aetiology, risk factors, treatment and outcome of children with community-onset invasive bacterial infections (IBI) and determine the appropriateness of the nationally recommended empiric antibiotic therapy in children with non-oncological comorbidities.
Method: The CABIN network prospectively collected clinical information for all positive blood and cerebrospinal fluid cultures in children aged 1 month to 15 years in southwest London over three years.
Results: During 2009–11, 119 healthy children each had a single IBI episode and 61 children with non-oncological comorbidities had 83 IBI episodes. The pathogens causing IBI in children with comorbidities and no central venous catheter (CVC) were similar to those causing IBI in healthy children. However, those with a CVC had multiple IBI episodes, often with pathogens usually associated with nosocomial infection. In particular, gastro-intestinal commensals were frequently responsible for IBI in TPN-dependent children with gastro-intestinal disease (16/43 episodes) and those with liver disease (8/43). Nationally recommended antibiotics were commenced empirically in 93%, with additional or alternate antibiotics more likely to be prescribed in children with comorbidities or those requiring intensive care. Fifteen children died (11 healthy, 4 with comorbidity), including 12 who died before arrival or in the Emergency Department.

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Conclusion: Increasing care of children with comorbidities in the community has resulted in a significant proportion of community-onset IBI occurring in this group. Children with a CVC *in situ* — particularly those with gastro-intestinal and liver disease — were infected with a wider range of potentially more virulent pathogens. They might benefit from more broad-spectrum antimicrobial cover.

Introduction

In the United Kingdom, serious infections are responsible for around 20% of all childhood deaths, with half the deaths occurring in children with underlying comorbidity.[1] Given that the vast majority of UK children are healthy, these studies and others suggest a substantially higher risk of an infection-related death in children with comorbidities compared to healthy children.[2,3] Moreover, the pathogens responsible differ between these two groups, with Gram-negative and fungal infections recorded more frequently on death certificates of children with comorbidities.[1]

There are several reasons why children with comorbidities have increased risk of invasive bacterial infection (IBI), more severe disease and worse outcomes. In some children, the primary comorbidity or its treatment renders the child immunodeficient and thus, more vulnerable to IBI. In conditions not associated with immunodeficiency, the increased risk may be attributable to weakening of physical innate immune protection (e.g. neuromuscular disorder and recurrent respiratory tract infections). Repeated hospital contact and exposure to multiple and prolonged antibiotic courses may also increase their risk of infection. At the same time, children with comorbidities may present with more non-specific symptoms and/or signs, leading to a delay in diagnosis and initiation of appropriate antimicrobial therapy.

In 2009, a Childhood Acute Bacterial Infection Network (CABIN) was set up in southwest London to describe the epidemiology, clinical characteristics and outcomes of laboratory-confirmed IBI within a geographically defined population.[4] In that study, we observed that two-thirds of IBI episodes had a community-onset and, within this group, two-thirds occurred in children with comorbidities. Currently, the Children's British National Formulary (BNFc) recommends treatment with specific antimicrobials depending on site of suspected infection, but does not differentiate between previously healthy children and those with comorbidities.[5] Although larger tertiary paediatric units and regional networks may have their own empiric antibiotic guidelines reflecting their specialist expertise and/or local antimicrobial data, most paediatric units in the UK rely on the BNFc for empiric antibiotic treatment for children with suspected IBI.

This study, therefore, aimed to describe the aetiology, comorbidity status, focus of infection, treatment and outcome of children with community-onset IBI and determine whether the empiric antibiotic therapy recommended in the BNFc is appropriate for children with comorbidities.

Methods

CABIN was a web-based, prospective surveillance project collecting data on children aged one month to 15 years with a positive blood/cerebrospinal fluid (CSF) culture during 2009—11 at five National Health Service (NHS) hospitals (St George's, Kingston, Epsom and St. Helier and Croydon University Hospitals) that provide medical care for about 600,000 children in southwest London. St George's Hospital is a tertiary paediatric referral hospital with multiple specialties including endocrine, haemato-oncology, infectious diseases, intensive care, gastroenterology, surgery and neurosurgery. The remaining four hospitals are district general hospitals (DGH) that routinely seek specialist advice from St. George's hospital and refer patients for specialist care. Within each hospital, the microbiology laboratory identified positive cultures at monthly intervals. Medical notes were then collected and a standard web-based questionnaire completed by the lead clinician at each site. Data were anonymised at source.[4]

A positive culture was considered significant if the clinical presentation was consistent with infection caused by that pathogen. Community-onset IBI was defined as a significant culture obtained $\leq$48 h of admission. Children with cancer were excluded because specific national and local guidelines are already in place for febrile illnesses in this group.[6] Multiple positive cultures from the same patient within seven days were considered the same episode. IBI was considered to be CVC-related if a child was managed with antimicrobial therapy directed towards the causative pathogen ($\pm$CVC removal) and the diagnosis was documented contemporaneously in the child's notes. It is not routine practice in southwest London for children with CVCs to have central catheter infection prophylaxis such as antibiotic locks, recombinant tissue plasminogen activator (rTPA) or ethanol locks, although this information was not specifically requested in the CABIN questionnaire. Data are described for three age groups ($<$1, 1—4 and 5—15 years) because the pathogens responsible, comorbidity prevalence, risk factors and outcomes are different in these age-groups.[4] The majority of children aged 16—18 years are managed by adult physicians and, therefore, not included this study. Formal statistical analyses were not undertaken because of small number of cases when sub-grouped by age, comorbidity status and other parameters.

Results

During 2009—11, there were 319 community-onset IBI episodes in 270 children. Manual inspection of reported comorbidities resulted in four children (with autism, gastro-oesophageal reflux, laryngomalacia and sickle cell trait) recategorised into the 'previously healthy' group. After excluding children with malignancy, 119 previously healthy children had a single IBI episode and 61 children with comorbidities had 83 IBI episodes. Twenty-four of the 61