

Etiology of Childhood Bacteremia and Timely Antibiotics Administration in the Emergency Department

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abstract

BACKGROUND: Bacteremia is now an uncommon presentation to the children's emergency department (ED) but is associated with significant morbidity and mortality. Its evolving etiology may affect the ability of clinicians to initiate timely, appropriate antimicrobial therapy.

METHODS: A retrospective time series analysis of bacteremia was conducted in the Alder Hey Children's Hospital ED between 2001 and 2011. Data on significant comorbidities, time to empirical therapy, and antibiotic susceptibility were recorded.

RESULTS: A total of 575 clinical episodes were identified, and *Streptococcus pneumoniae* ($n = 109$), *Neisseria meningitidis* ($n = 96$), and *Staphylococcus aureus* ($n = 89$) were commonly isolated. The rate of bacteremia was 1.42 per 1000 ED attendances (95% confidence interval: 1.31–1.53). There was an annual reduction of 10.6% (6.6%–14.5%) in vaccine-preventable infections, and an annual increase of 6.7% (1.2%–12.5%) in Gram-negative infections. The pneumococcal conjugate vaccine was associated with a 49% (32%–74%) reduction in pneumococcal bacteremia. The rate of health care-associated bacteremia increased from 0.17 to 0.43 per 1000 ED attendances ($P = .002$). Susceptibility to empirical antibiotics was reduced (96.3%–82.6%; $P < .001$). Health care-associated bacteremia was associated with an increased length of stay of 3.9 days (95% confidence interval: 2.3–5.8). Median time to antibiotics was 184 minutes (interquartile range: 63–331) and 57 (interquartile range: 27–97) minutes longer in Gram-negative bacteremia than in vaccine-preventable bacteremia.

CONCLUSIONS: Changes in the etiology of pediatric bacteremia have implications for prompt, appropriate empirical treatment. Increasingly, pediatric bacteremia in the ED is health care associated, which increases length of inpatient stay. Prompt, effective antimicrobial administration requires new tools to improve recognition, in addition to continued etiological surveillance.



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WHAT'S KNOWN ON THIS SUBJECT: Childhood bacteremia caused by vaccine-preventable organisms has substantially declined over the last decade. Recognition of bacteremia in children is difficult, and delayed administration of antibiotics is associated with poor outcomes. Adults with health care-associated Gram-negative bacteremia experience delays in receiving appropriate antibiotics.

WHAT THIS STUDY ADDS: Bacteremia in children presenting to the emergency department is increasingly health care associated and resistant to empirical antibiotics. These infections are associated with increased length of stay. Rates of Gram-negative bacteremia have increased, and children with Gram-negative bacteremia experience delayed antibiotic administration.

Acute infections are a common reason for presentation to the children's emergency department (ED).¹ In young children presenting with an acute febrile illness, serious bacterial infection occurs in ~7%. Bacteremia occurs in 1 in 250 febrile children aged <5 years and may be difficult to recognize.²

Bacteremia is associated with significant mortality and morbidity in children. Immediately before the introduction of the pneumococcal vaccine in the United Kingdom, 20% of childhood mortality was infection related, with "septicemia" the most commonly documented cause of death.³ The etiology of pediatric bacteremia in the United Kingdom has evolved substantially as the immunization schedule has expanded. The incidence of vaccine-preventable infections has declined,⁴ while that of Gram-negative infections has increased.⁵

Timely, effective antimicrobial therapy is fundamental to the management of serious infections in children. Delayed recognition of meningococcal disease,⁶ and suboptimal resuscitation of septic shock, contribute to mortality in children.^{7,8} The Surviving Sepsis Campaign recommends administration of antibiotics within 1 hour of recognition of severe sepsis.⁹

Historically, serious infections have been categorized according to the timing of their identification into "community-acquired" and "hospital-acquired" infection. These categories were used to inform the likely etiology and to guide empirical treatment. There is an increasing awareness of patients who, although they acquire serious infections in the community, share the characteristics of patients with "hospital-acquired" infections. Such occurrences have been termed health care-associated (HCA) infections.¹⁰ In adults, HCA bacteremia is associated with delayed administration of appropriate antibiotics.¹¹ To date, no validated

definition of HCA bacteremia is in use in children.¹²

The objective of the present study was to describe the etiology of bacteremia by using data from children presenting to the Alder Hey Children's Hospital ED between 2001 and 2011. Our goal was to explore the impact of temporal changes on outcomes, including the timeliness and appropriateness of empirical antibiotic therapy.

METHODS

A retrospective time series analysis was conducted of all clinically significant episodes of bacteremia presenting via the Alder Hey Children's Hospital ED. This children's ED is the busiest in the United Kingdom, with ~60 000 attendances per year. All positive results of blood culture isolates from 2001 to 2011 (inclusive) were identified. Positive culture results isolated >48 hours after presentation, or associated with a hospital admission in the previous month, were considered hospital-acquired and excluded. Isolates commonly considered commensals were included if they were cultured on >1 occasion within 48 hours.¹³

Clinical data relating to each episode were extracted from clinical notes and the hospital electronic database. Recorded data included demographic characteristics and significant comorbidities, including the presence or absence of a central venous line (CVL). Commonly used markers of infection (white blood cell count, neutrophil count, platelets, and C-reactive protein) were extracted electronically.

To examine trends and to compare our data with published evidence, we grouped episodes of *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* as vaccine-preventable infections; Gram-negative infections were similarly grouped. For the remaining Gram-positive infections, we differentiated

between typically pathogenic organisms in healthy children such as *Staphylococcus aureus* (typical Gram-positive) and those considered to be associated with the health care setting, such as coagulase-negative *Staphylococcus* (ie, other Gram-positive).

Definitions

Community-acquired bacteremia was defined as the identification of a significant pathogen in a blood culture taken within 48 hours of presentation to the ED (in the absence of admission to the hospital in the previous month).

HCA bacteremia was defined as the identification of a significant pathogen in a blood culture taken within 48 hours of presentation to the ED in the following children: those with an indwelling device (eg, CVL, ventriculoperitoneal shunt, prosthetic material); those with primary or acquired immunodeficiency; those requiring regular hospital-based intervention (eg, hemodialysis, intravenous therapies); and preterm infants <12 months from discharge from the neonatal unit.

Empirical therapy was defined as therapy instituted before microbiologic evidence of infection, limited to 24 hours from presentation to the ED. Therapy instituted beyond this period, or where there was documentation of microbiological advice, was termed "directed."

Susceptibility to empirical therapy was defined as susceptibility to the empirical therapy initiated by the clinical team. Susceptibility was determined by breakpoints in use at the time of isolation, according to methods of the British Society for Antimicrobial Chemotherapy.¹⁴

Statistical Methods

Statistical analysis was undertaken in R version 3.0.1.¹⁵ A detailed explanation of the statistical methods is described in the Supplemental Appendix.

Continuous data were described according to medians and interquartile ranges, and comparison between groups was performed by using the Kruskal-Wallis test. Categorical variables were expressed as percentages with 95% confidence intervals (95% CIs). Groups were compared by using the χ^2 test.

Time Series Analysis

Poisson regression was used to model weekly counts of bacteremia with weekly ED attendance as an offset. Logistic regression was used to model the likelihood over time (ie, the fitted likelihood) that each clinical episode occurred in a child with an indwelling CVL or that the isolate was susceptible to empirical antibiotic therapy.

Inspection of these models suggested an initial increase in the likelihood of a clinical episode occurring in a child with an indwelling CVL, with a subsequent reduction from 2008. In parallel, there was an initial reduction in the likelihood of an isolate being susceptible to empirical antibiotics, with an increase after 2008. Late in 2007, the hospital increased investment in specialist intravenous nurses, with responsibility for training in the management of CVLs. We considered this intervention to be a plausible explanation for the observed variation, and we implemented a piecewise fit of time with the breakpoint specified according to the time of the clinical

intervention. Inclusion of the piecewise variable improved the fit of the model to the data.

Multivariable Analysis of Clinical Outcomes

Length of stay (LOS) and time to empirical antibiotic administration were assessed by using multivariable linear regression. Both factors were log-transformed to meet the assumption of linearity between outcome and explanatory variables. In the model assessing time to antibiotic administration, a piecewise fit for platelets was undertaken and found to improve the fit of the model. A maximal model of all variables with a *P* value <.1 was fit before model simplification was undertaken in a backward stepwise process.

The use of anonymized data was approved by the research department of the Alder Hey Children's Hospital.

RESULTS

Between 2001 and 2011, a total of 692 clinically significant blood cultures were identified in children sampled within 48 hours of presentation to the ED. These cultures represented 575 episodes of bacteremia in 525 children.

Clinical Characteristics of Children

The characteristics of the 525 children presenting with bacteremia are summarized in Table 1. Significant comorbidities were

present in 151 children (29%). The most common comorbidities were gastrointestinal (Supplemental Table 5), and many of these children (22 of 25) had indwelling CVLs for the purpose of parenteral nutrition. Children with Gram-negative isolates were younger and more likely to have significant comorbidities or an indwelling CVL than those with vaccine-preventable or typical Gram-positive isolates. Mortality in children with other Gram-positive infections was higher (6 of 37) than in other groups (odds ratio: 5.15 [95% CI: 1.60–15.8] vs vaccine-preventable isolates).

Children with HCA bacteremia were older than those with community-acquired bacteremia. LOS in children with HCA bacteremia was prolonged by 3.9 days versus community-acquired bacteremia (95% CI: 2.3–5.8). Mortality and admission to the PICU did not differ between these groups (Table 2).

Etiology of Bacteremia in the Children's ED

Isolated organisms varied according to age (Fig 1). In early infancy, the most common organisms were *Escherichia coli* and Group B streptococcus. There were 47 presentations of neonatal sepsis, including 1 of early-onset disease (Group B streptococcus). *S pneumoniae* was most common overall. *S pneumoniae* and *N meningitidis* occurred more

TABLE 1 Clinical Characteristics of 525 Children Presenting to the ED With Bacteremia According to Type of Organism

Variable	Median	IQR	Vaccine-Preventable (n = 221)	Typical Gram-Positive (n = 149)	Gram-Negative (n = 118)	Other Gram-Positive (n = 37)	<i>P</i>
Age, y	1.52	0.42–4.27	1.80 (0.83–3.88)	1.58 (0.13–6.82)	0.82 (0.20–3.08)	1.64 (0.69–11.45)	<.001 ^a
LOS, d	6	3–10	6 (4–9)	7 (3–13)	6 (4–10)	7 (2–11)	.5 ^a
	%	95% CI	n (%)	n (%)	n (%)	n (%)	
CM	28.8	25.1–32.8	36 (16.3)	42 (28.2)	51 (43.2)	22 (59.5)	<.001 ^b
CVL	9.0	6.80–11.7	3 (1.40)	6 (4.02)	26 (22.0)	12 (32.4)	.001 ^c
PICU	18.9	15.8–22.5	56 (25.3)	23 (15.4)	13 (11.0)	7 (18.9)	.007 ^b
Mortality	4.57	3.09–6.71	8 (3.62)	6 (4.02)	4 (3.39)	6 (16.2)	.005 ^c

CM, significant comorbidity; IQR, interquartile range.

^a Kruskal-Wallis test.

^b χ^2 test.

^c Monte Carlo simulation.

TABLE 2 Clinical Characteristics of Community-Acquired Bacteremia and HCA Bacteremia

Characteristic	Community-Acquired (<i>n</i> = 444)	HCA (<i>n</i> = 81)	<i>P</i>
Median age, y (IQR)	1.43 (0.35–3.88)	2.32 (0.96–6.48)	.001 ^a
Median LOS, d (IQR)	6 (3–9)	9 (4–18)	<.001 ^a
PICU, % (95% CI)	19.0 (15.6–22.9)	18.5 (11.6–28.3)	.15 ^b
Mortality, % (95% CI)	4.1 (2.6–6.3)	7.4 (3.4–15.2)	.25 ^c
Group			<.001 ^b
Vaccine-preventable	207	14	
Typical Gram-positive	133	16	
Gram-negative	82	36	
Other Gram-positive	22	15	
Median time to antibiotics, min (IQR)	181 (59–321)	218 (91–353)	.15 ^a

IQR, interquartile range.

^a Kruskal-Wallis test.^b χ^2 test.^c Monte Carlo simulation.

commonly between the ages of 1 and 5 years, whereas *S aureus* was the most common organism in children aged >5 years. Most meningococcal isolates (87 of 96) were Group B; the remainder were Groups C (*n* = 5), W135 (*n* = 3), and Y (*n* = 1). Two episodes of methicillin-resistant *S aureus* bacteremia occurred over the 11-year period; 1 episode was associated with ventriculitis in a child with a ventriculoperitoneal shunt, and 1 episode was in a previously well child. There were 17 polymicrobial infections in 13 children; 12 had significant comorbidities, and 8 had CVLs in situ. Isolated organisms are summarized in Table 3.

Time Series Analysis

The rate of clinically significant bacteremia in children presenting to the ED was 1.42 per 1000 attendances (95% CI: 1.31–1.53).

The cumulative frequency plot reveals a declining rate of vaccine-preventable isolates, including *S pneumoniae*, and an increasing rate of Gram-negative isolates (Supplemental Fig 4).

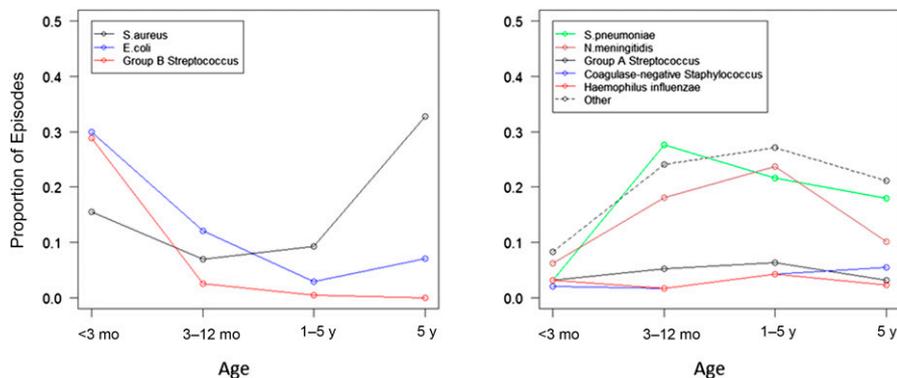
Poisson regression was used to model the observed rate of bacteremia (Fig 2). For the overall rate of bacteremia, neither the trend over time (*P* = .18) nor the seasonal effect (*P* = .17) was statistically significant. Bacteremia caused by vaccine-preventable isolates including *S pneumoniae* was highly seasonal (*P* < .001). From 2001 to 2011, its rate declined from 1.32 to 0.37 per 1000 ED attendances at an annual rate of reduction of 10.6% (95% CI: 6.6–14.5). The pneumococcal conjugate vaccine (PCV) was introduced into the UK immunization schedule in September 2006. When incorporated into the regression model, PCV was associated with

a 49% reduction in pneumococcal bacteremia (95% CI: 32–74) from 0.50 to 0.25 per 1000 attendances. By contrast, the rate of Gram-negative bacteremia increased from 0.24 to 0.53 per 1000 ED attendances (*P* = .007). The fitted seasonal effect in the Gram-negative model, although not statistically significant (*P* = .07), exhibited a peak in summer, in contrast to that of the vaccine-preventable model, which peaked in winter.

The rate of community-acquired bacteremia was reduced from 0.93 to 0.57 per 1000 ED attendances (*P* = .005) between 2001 and 2011, while the rate of HCA bacteremia increased from 0.17 to 0.43 per 1000 (*P* = .002). The proportion of clinical episodes occurring in children with an indwelling CVL increased from 3.2% in 2001 (95% CI: 1.47–6.84) to a peak of 26.5%, before declining to 21.8% in 2011 (95% CI: 12.9–34.3). In parallel, the likelihood that an isolate was susceptible to empirical therapy was reduced from 96.3% (95% CI: 92.1–98.2) to 82.6% (95% CI: 69.8–90.7) between 2001 and 2011; it reached a nadir of 74.4% in 2008. These trends are illustrated in Fig 3. LOS, likelihood of PICU admission, and mortality did not change over time.

Timeliness and Appropriateness of Empirical Antibiotics

The empirical antibiotic protocol was documented in 563 of 575 clinical

**FIGURE 1**

Proportion of bacteremia episodes of each isolate according to age group.

TABLE 3 Predominant Organisms According to Group

Organism	N	%
Vaccine preventable, n = 223		
<i>S pneumoniae</i>	109	19.0
<i>N meningitidis</i>	96	16.7
<i>H influenzae</i> (type B)	18	3.1
Typical Gram-positive, n = 149		
<i>S aureus</i>	89	15.4
Group B streptococcus	32	5.6
Group A streptococcus	28	5.9
Gram-negative, n = 152		
<i>E coli</i>	59	10.3
<i>Klebsiella</i> sp	26	4.5
<i>Acinetobacter</i> sp	11	1.9
<i>Enterobacter</i> sp	10	1.7
<i>Pseudomonas</i> sp	10	1.7
<i>Salmonella</i> sp	9	1.6
<i>Moraxella catarrhalis</i>	9	1.6
Other	18	3.2
Other Gram-positive, n = 51		
Coagulase-negative <i>staphylococcus</i>	21	3.5
<i>Enterococcus</i> sp	19	3.3
Nonpyogenic <i>streptococcus</i>	6	1.0
Other	5	0.9

episodes (Supplemental Table 6). For children with no indwelling CVL, 375 of 480 received monotherapy (most commonly, cefotaxime [289 of 393]). In combination treatments, cefotaxime was also invariably used, along with gentamicin, benzylpenicillin, or amoxicillin. In children with an indwelling CVL, combination therapy was commonly used (46 of 83), particularly with teicoplanin and gentamicin.

We were able to define empirical susceptibility in 527 of 575 cases.

Vaccine-preventable isolates were almost universally susceptible to empirical therapy (217 of 219), whereas 22% (29 of 131) of Gram-negative isolates were resistant ($P < .001$). Data on time to antibiotic administration were available for 78% (444 of 575) of all episodes. Median time to antibiotic administration was ~3 hours and varied according to the type of organism (Table 4). Children with vaccine-preventable infections received empirical antibiotics more quickly than children with other types of infection.

To explore this relationship, a multivariable model of time to antibiotics was developed (Supplemental Table 7). After adjustment for other explanatory variables, time to antibiotics was increased by 57 minutes for Gram-negative infections compared with vaccine-preventable infections. Older children received antibiotics later than younger children. Overall, time to antibiotics increased by ~3 minutes per year of the study ($P = .006$ for linear trend).

DISCUSSION

In describing the changing etiology of bacteremia in the busiest children's ED in the United Kingdom, we have shown a reduction in vaccine-

preventable bacteremia, coincident with an increase in Gram-negative bacteremia. The rate of pneumococcal bacteremia has been halved since the introduction of the PCV. These trends affirm data from surveillance studies of invasive bacterial infections internationally.^{4,5,16-18} We identified a seasonality to Gram-negative bacteremia with a summer peak; although not statistically significant, this finding is consistent with other published data.^{19,20}

Our analysis illustrates the changing characteristics of children presenting to the ED with bacteremia. Increasingly, these are children with underlying comorbidities and indwelling CVLs. The rate of HCA bacteremia is increasing. The proportion of episodes involving children with CVLs increased to a peak in 2008 before declining toward the end of the study. This finding occurred in parallel with an initial reduction in antibiotic susceptibility, which also improved after 2008. This outcome likely reflects more children with CVLs receiving total parenteral nutrition in the community. Unpublished data from Alder Hey Children's Hospital (S. Melville, personal communication, 2013) reveals a threefold increase in CVL-associated infection rates with the use of total parenteral nutrition (from 3.3 to 10.4 per 1000 line-days). At the end of 2007, the hospital increased investment in specialist intravenous nurses, with responsibility for training in the management of CVLs. This intervention may explain the later reduction in children with CVL-associated infections presenting to the ED.

The changing etiology of childhood bacteremia in the ED was not associated with temporal changes in mortality or PICU admission. HCA bacteremia was associated with an increased LOS, irrespective of the responsible organism. Other investigators have related increased

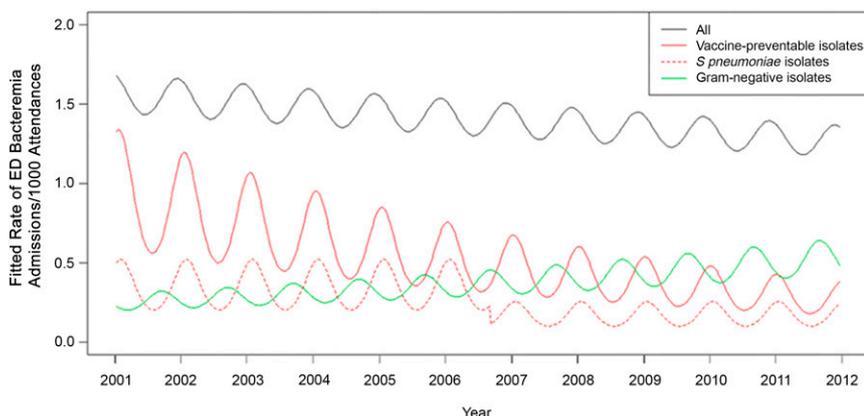


FIGURE 2

Fitted rate of pediatric bacteremia per 1000 attendances to the Alder Hey Children's Hospital ED between 2001 and 2011. The discontinuity in the fit for *S pneumoniae* is due to the introduction of the PCV in September 2006.

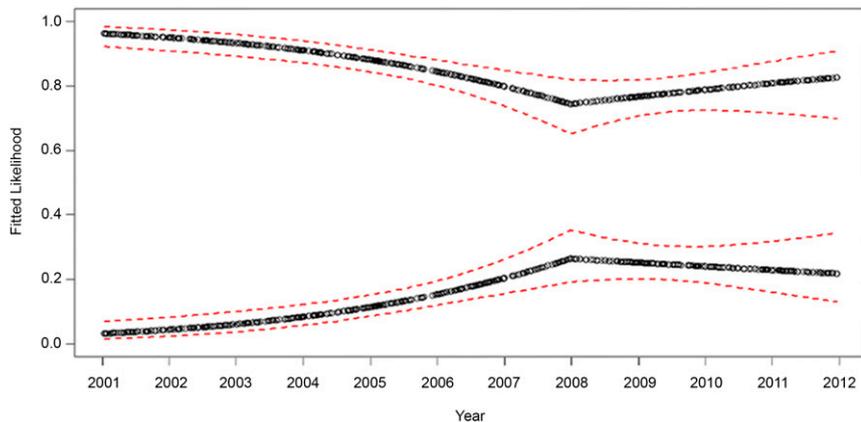


FIGURE 3

Fitted likelihood over time that an isolate was susceptible to empirical therapy (top) and that an episode occurred in a child with an indwelling CVL (bottom). Time was fit as a piecewise term to incorporate a clinical intervention. Inclusion of the piecewise term improved the model fit. Dotted red lines are 95% CIs.

LOS in adults to HCA bacteremia,²¹ but we are unaware of pediatric data detailing the same. To date, this category of infection remains poorly defined in children.

Despite acceptance that time to antibiotic administration influences outcome in sepsis,²² few studies have reported time to antibiotic administration in the pediatric ED.^{23,24} We found that the changing nature of bacteremia in the pediatric ED has implications for both recognition and management. A median time to antibiotic administration of 3 hours is comparable with other data.²⁵ Empirical therapy took longer to initiate in children with Gram-negative infections than in children with vaccine-preventable infections, even with adjustment for other explanatory variables. Furthermore, multivariable modeling allowed us to estimate an increase in time to antibiotics of 38 minutes over the

11 years of the study, regardless of changes in etiology. These changes are likely multifactorial, but the implication is that additional resources in diagnostics and training will be required to minimize delays in the treatment of these most invasive infections.

Over 11 years, susceptibility to empirical antibiotic protocols declined. Adults with Gram-negative HCA bacteremia experience delays in appropriate antibiotic therapy,¹¹ and mortality is increased when initial empirical therapy is inadequate.²⁶ Death in children is uncommon even in serious infection, and we failed to draw an association between death or likelihood of PICU admission and inappropriate empirical antibiotics.

The present study had several limitations. It was a retrospective, single-center study of culture-positive bacteremia conducted in the pediatric ED. Blood culture yield is affected by the use of previous antibiotics (more so than polymerase chain reaction

assays).²⁷ Collecting data on previous antibiotics was impractical in this retrospective analysis. Community antibiotic prescribing for children in the United Kingdom decreased substantially in the 1990s,^{28,29} although some data suggest an increase through the course of the present study.³⁰ This finding would not account for the reduction in pneumococcal bacteremia, for which there was no temporal trend before the introduction of the PCV. An increase in prehospital antibiotic use may have affected blood culture yield over time, however, particularly if this use was well targeted toward children with bacteremia.

We have not accounted for changes to the population of the hospital catchment area but have instead incorporated ED attendance. Over time, there was no change in medical attendances to the ED.

Based on the published literature, we developed a pragmatic definition of HCA bacteremia.¹² To date, no such definition has been established in pediatric medicine. We identified a number of surrogate markers of frequent exposure to health care environments but were unable to collect robust data to quantify this occurrence in terms of how frequently or how recently exposure occurred in individual clinical episodes. Understanding this exposure better, thereby establishing a valid definition of HCA bacteremia, would help to guide empirical treatment in the ED. Because our definition was applied consistently across the 11 years of the data set, we believe our description of temporal trends is robust.

Data regarding time to antibiotics were missing in ~20% of clinical cases. We restricted our analysis to time to empirical therapy, although others have reported time to “appropriate” therapy.¹¹ We explored explanatory variables that may influence time to antibiotics and which were available in the clinical

TABLE 4 Time to Antibiotics According to Type of Organism

Organism	Median, min	IQR	P
All	184	62.5–330.5	
Vaccine-preventable	130	34.5–297	<.001
Typical Gram-positive	256	118–376	
Gram-negative	184	95.5–356	
Other Gram-positive	253.5	147–401	

IQR, interquartile range.

notes. Other studies have used validated measures of disease severity (eg, the Glasgow Meningococcal Septicaemia Prognostic Score) and demonstrated an association with time to antibiotic administration.²³ A comparable measure of illness severity may help to explain the variation reported, although no such tool is currently in use in all acutely unwell children in the ED.

We assumed that variation in time to antibiotics was related to clinical recognition. Time to antibiotics is also used as a measure of crowding in EDs. Some investigators have identified an association between

markers of ED crowding and time to antibiotic administration in young infants,³¹ although not consistently.³² We did not collect data on ED crowding. There was no overall increase in numbers presenting to the Alder Hey Children's Hospital ED over the course of the study, nor was there an association between time of day, day of the week, or time of year (all factors that are associated with the volume of ED activity) and time to antibiotic administration.

CONCLUSIONS

We describe the evolving etiology of children with bacteremia presenting

to the UK's busiest children's ED. Increasingly, these infections are considered HCA. They are more likely to be resistant to empirical therapy, more difficult to recognize, and are associated with a prolonged LOS. Prompt and effective antimicrobial treatment of bacteremia requires improved diagnostic tools in addition to continued etiological surveillance.

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