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Increased Incidence of Bronchopulmonary Fistulas Complicating Pediatric Pneumonia

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Summary. Background: The frequency of complicated pneumococcal disease, including necrotizing pneumonia, has increased over the last decade. During 2008–2009, we noted an increase in the number of children whose empyema was complicated by the development of a bronchopleural fistula and air leak. We studied these children to see if there was an associated cause. Methods: This was a retrospective case note and database review of children admitted to our tertiary unit with a parapneumonic effusion or empyema from 2002 to 2007, compared with 2008 to 2009. For the latter period, we also compared the outcomes of those with a bronchopleural fistula to those without. Results: During the 8-year period, 310 children were admitted. In the first 6 years, the frequency of air leaks was 1% (2/258) rising to 33% (16/49) in the last 2 years ($P < 0.0001$). Three children were excluded as their fistulas were possibly iatrogenic. This was associated with a significant increase in median hospital stay (7 vs. 10 days, $P < 0.0001$) and surgical intervention rate (2% vs. 14%, $P = 0.001$). In the latter 2 years, *S. pneumoniae* serotype 3 was identified in 10/16 (91%) of those with a bronchopleural fistula compared to 1/33 (3%) of those without. Conclusions: The frequency of bronchopleural fistulas increased markedly in the 2 years 2008–2009. Although these cases were associated with pneumococcal serotype 3 infection, which was not covered by the heptavalent pneumococcal vaccine Prevenar® in use at that time, we do not know whether the increased incidence of fistulas was due to a change in serotype 3 prevalence. **Pediatr Pulmonol. 2011; 46:717–721.** © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Childhood community-acquired pneumonia may be complicated by a parapneumonic effusion or empyema, and these cases are most frequently caused by *Streptococcus pneumoniae*.[1–3] Cavitatory disease is another complication of pneumococcal pneumonia, and it has become increasingly recognized since first reported in 1994.[4] It is characterized by abscess formation and is likely to be a consequence of pulmonary gangrene, parenchymal liquefaction, and subsequent necrosis.[5] It is thought this may be due to either an abnormal cytokine-driven inflammatory response,[6] or pulmomary infarction secondary to a thrombotic process.[7] When necrosis and abscess formation arise adjacent to the pleura, bronchopleural fistulas can form, leading to air leaks. These are more properly called alveolar-pleural fistulae, as the communication to the pleural space is usually distal to the segmental bronchi.[8] Whilst the majority resolves with conservative management, the clinical course can be complicated and lengthy.

To date, *S. pneumoniae* serotype 1 has accounted for most cases of empyema in the UK and the USA.[1–3] In terms of necrotizing pneumonia, a series from Northern England reported that 20% of their empyemas were complicated by cavitatory disease, but this was not associated with any particular pneumococcal serotype.[9] However, in Utah USA, Bender et al.[10] demonstrated a positive association between pulmonary necrosis and *S. pneumoniae* serotype 3. The relevance of these serotypes is that the heptavalent pneumococcal conjugate vaccine Prevenar® (Wyeth, Maidenhead, UK) introduced into the UK's childhood immunization programme in 2006 does not cover either serotype 1 or 3.

The frequency of bronchopleural fistulas complicating childhood pneumonia is unknown but generally thought to

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be rare. However, in the last 2 years we noted a marked rise in the number of children with empyemas who had fistulas leading to long hospital stays and an increase in the surgical intervention rate. We aimed to ascertain whether this was a genuine rise and whether there was an associated cause.

METHODS

Subjects

We have maintained a database of all pediatric empyema cases (aged <17.0 years) admitted to the tertiary unit at the Royal Brompton Hospital since January 2002. All children had a clinical history of parapneumonic effusion confirmed by a chest ultrasound, and we included those treated conservatively who did not require a chest drain. For this study, children were recorded as having a fistula if there was radiological evidence (on a plain chest radiograph) of free air within the pleural space, or air bubbling into the underwater seal bottle attached to the chest drain (other than very briefly). This had to be noted either before or at least 24 hr after drain insertion, to ensure the air was not iatrogenic arising during the placement of the drain. Chest radiographs were taken routinely immediately after drain insertion; later ones would only be taken if there was air bubbling into the drain or if other complications arose. Chest CT scans were not routinely performed as per current UK guidelines.[3]

A retrospective review of cases from January 1, 2002 to December 31, 2009 was conducted using our database and case notes, supplemented by the hospital's IT system. For each case, the data collected included patient demographics, clinical outcomes, hematology and inflammatory markers, radiology, and microbiology. The latter included blood and pleural fluid cultures, but from 2005, 16s rDNA PCR was also performed, and from 2006 detection of specific capsular pneumococcal antigens was included, both on pleural fluid.

Statistical Analysis

Demographic, clinical, and laboratory variables were summarized by standard descriptive statistics, and comparison was made between cases occurring during the 6 years of 2002–2007 and the 2 years of 2008–2009. A further comparison was made of the children who developed a fistula and those who did not, for the period of 2008–2009. Statistical Package for the Social Sciences (SPSS) software (SPSS version 17.0, Inc; Chicago, IL) was used for all statistical analysis. Differences were considered statistically significant if $P < 0.05$ (using Fisher's exact test and Mann–Whitney *U*-test). The opinion of the Local Research Ethics Committee was that this project was a service evaluation and that formal approval was not required.

RESULTS

Demographics

A total of 310 cases were reviewed covering the 8-year period; we excluded three children from analysis, as it was possible that their fistulas were iatrogenic in origin (1 had surgical intervention elsewhere) so data are presented on 307 children. The median age was 4.6 years (range 0.2–15.7 years) and the male to female ratio was 1.6:1. We have no information regarding their pneumococcal immunization status.

Management

All children received intravenous antibiotics with cefuroxime or co-amoxiclav, plus oral azithromycin. Seventy-three (24%) children were managed conservatively and the remaining 234 (76%) had a chest drain inserted using the standard Seldinger technique.[3] The intrapleural fibrinolytic, urokinase was used in 211 (69%) cases (90% of those with a drain), using the standard regimen[3] with a median of six doses administered (range 1–10, and only 8% receiving >6 doses). Urokinase was stopped when an air leak was noted on the theoretical basis it might impede plugging off and healing of a fistula. Only 12 (4%) children required surgery (video-assisted thoracoscopic surgery or thoracotomy), always as second-line management to chest drain and fibrinolytics. Surgery was considered when there was either significant clinical deterioration or failure to progress in the treatment of sepsis.

Microbiology

Overall, an organism was identified in only 70 children (23%). *S. pneumoniae* was the most frequently isolated, occurring in 44 children (14%), followed by β-hemolytic Group A Streptococcus in 13 (4%), and *Staphylococcus aureus* in 8 (3%). *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus milleri*, and *Haemophilus influenzae* were isolated in single patients.

Comparison of 2002–2007 Versus 2008–2009

There was a marked and statistically significant rise in frequency of bronchopleural fistulas in the later period, rising from 1% (2/258) in 2002–2007 to 33% (16/49) in 2008–2009, $P < 0.0001$ (Table 1). The two fistulas occurring during the initial 6-year period were in 2004 and 2005, so it seems this represents a genuine sudden increase rather than a gradual rise; microbiology was negative for both those cases. The rise in frequency of fistula formation was matched by a significant increase in median length of hospital stay (7 days vs. 10 days, $P < 0.0001$). Length of stay for children without fistulas

TABLE 1— Comparison of Clinical Outcomes in Children Admitted From 2002 to 2007 Versus 2008–2009

	2002–2007 (n = 258)	2008–2009 (n = 49)	*P*-value
Age (median and range) years	4.7 (0.3–15.7)	3.6 (0.2–15.2)	ns
Male	160 (62%)	28 (57%)	ns
Air leak	2 (1%)	16 (33%)	<0.0001
Chest drain inserted	195 (76%)	39 (80%)	ns
Intrapleural fibrinolytic	174 (67%)	37 (76%)	ns
Surgery	6 (2%)	6 (14%)	0.001
Decortication	2	1	
VATS	4	5	
Length of pleural drainage (median and range) days	5 (1–23)	9 (1–46)	<0.0001
Length of stay (median and range) days	7 (1–42)	10 (4–48)	<0.0001
PICU admission	6 (2%)	5 (10%)	0.02

was no different in the two time periods (median 7 days vs. 8.5 days), nor was there a difference in length of pleural drainage (5 days vs. 5.5 days), suggesting the increased hospital stay in the latter 2 years was likely to have been associated with the air leaks (median 26.5 days), rather than any change in management. There were no age or sex differences between the two time periods. Initial management was the same in the two groups with a similar use of chest drains and intrapleural fibrinolytics. However, there was a sevenfold increase in surgical intervention rate (see Table 1 for procedures) in the 2008–2009 period (2% vs. 14%, $P = 0.001$), with a corresponding increase in admission to the pediatric intensive care unit (PICU; 2% vs. 10%, $P = 0.02$).

Analysis of Patients With Bronchopleural Fistulas Versus Those Without in 2008–2009

There were 49 cases of empyema analyzed in the 2 years; 16 (33%) had a bronchopleural fistula. An etiological organism was identified in 32/49 (65%) of cases during this time period, with *S. pneumoniae* responsible for 28/32 (89%; Table 2). Capsular-specific antigen testing was available for 20 of these samples: serotype 1 accounting for 7, serotype 3 for 11, and serotype 7a/7f and 19a accounting for single cases; in 2 cases there was no serotype identified and 6 cases were not tested. Pneumococcal serotype 3 was identified in 10/16 (63%) children with a bronchopleural fistula and 1/33 (3%) without (<0.0001). The 3 cases of fistulas excluded as possibly iatrogenic included 2 who developed an air leak immediately following drain insertion (1 with *Staphylococcus aureus* and 1 with an unidentified organism), and 1 case referred to us following decortication and rib resection who had non-serotyped *S. pneumoniae*.

There were no differences between the two groups with respect to age and gender or in the use of antibiotics prior to admission (Table 3). Markers of disease severity were similar with respect to highest C-reactive protein (CRP), highest neutrophil count, and lowest serum albumin. However, those with bronchopleural fistulas had significantly lower Hb levels; out of 16 patients, 1 required a blood transfusion, 1 had erythropoietin (refusing transfusion), and 4 had oral iron, whereas only 1/33 without a fistula required therapy (a blood transfusion).

Children with bronchopleural fistulas were more likely to have initial treatment with a drain ($P = 0.02$) but there was no difference in the use of intrapleural fibrinolytics. The median length of time for a bronchopleural fistula to become apparent was 5 days following insertion of the drain, with a range of 3–10 days; one child had the leak noted before drain insertion. Children with bronchopleural fistulas had a more protracted and complicated clinical course (Table 3). Drains remained in place for a median of 21.5 days (range 7–46), compared to 5.5 days (range 0–16), hence there was a much longer length of stay, 26.5 days versus 8.5 days. Complicated fistulas were

TABLE 2— Pleural Fluid Microbiology Results for Cases Admitted 2008–2009

Bronchopleural fistula (n = 16)		No bronchopleural fistula (n = 33)	
Pneumococcus	13	*Pneumococcus*	15
Serotype 1	0	Serotype 1	7
Serotype 3	10	Serotype 3	1
Serotype 19	1	Serotype 7a/7f	1
Unidentified serotype	1	Unidentified serotype	1
Not tested	1	Not tested	5
Group A *Streptococcus*	0	Group A *Streptococcus*	3
Unknown	2	Unknown	15
Others (*Pseudomonas aeruginosa*)	1	Others	0

TABLE 3— Comparison of Demographics and Clinical Outcomes of Children With or Without a Bronchopleural Fistula for Cases Admitted 2008–2009

	Bronchopleural fistula (n = 16)	No bronchopleural fistula (n = 33)	*P*-value
Age (years)	3.5 (1.3–10.6)	4.6 (0.2–15.2)	ns
Male	10 (63%)	18 (55%)	ns
Antibiotic duration prior to hospital admission (days)	2 (0–12)	0 (0–16)	ns
Drain inserted	16 (100%)	24 (73%)	0.02
Length of pleural drainage (days)	21.5 (7–46)	5.5 (0–16)	<0.0001
Intrapleural fibrinolytic	14 (88%)	23 (70%)	ns
Surgery	6 (38%)	0	0.0006
Length of stay (days)	26.5 (10–48)	8.5 (4–29)	<0.0001
PICU admission	3 (19%)	2 (6%)	ns
Lowest Hb (g/dl)	8.6 (5.1–9.6)	9.8 (6.1–13.8)	0.002
Highest CRP (mg/L)	273 (100–342)	238 (86–500)	ns
Highest neutrophil count ($\times 10^9$/L)	18.7 (9.4–23.0)	15.3 (6.2–40.1)	ns
Lowest serum albumin (g/L)	17 (10–27)	19 (13–31)	0.04

Results are given as medians with ranges, unless numbers (%).

managed in conjunction with the thoracic surgeons, using large caliber drains until the air leaks resolved. Ten cases were managed successfully this way, but 5 required surgical intervention with video-assisted thoracoscopy only, and 1 required a decortication as well as VATS (none required lung resection). No child without a fistula required surgery. All children have been followed up for at least 6 months and chest radiographs have shown complete resolution in every child.

DISCUSSION

In a single tertiary center, we have demonstrated a marked increase in the frequency of bronchopleural fistulas complicating pediatric empyema in the last 2 years. This complication was associated with greater length of hospital stay, increased PICU requirement and an increased need for surgical intervention. Furthermore, *S. pneumoniae* serotype 3 was isolated frequently in those with fistulas compared to those without, suggesting a strong association which may possibly have been causal but we cannot prove this. This is in keeping with Bender et al.[10] who demonstrated an increase in the frequency of necrotizing pneumonia in one state in the USA, which they attributed to both an increase in recognition and an alteration in invasiveness of certain strains of *S. pneumoniae*. However, since we do not have complete data on serotypes from both time periods, we cannot say whether there was an increase in prevalence of serotype 3 in our patients to account for the dramatic rise in air leaks in the last 2 years.

We do know that our treatment protocols have not changed (and there is nothing to suggest that use of urokinase was associated with fistula formation), nor our admission criteria (the patient demographics were similar over the two time periods), so it is quite possible the appearance of fistulas is due to an inherent feature of the infecting organisms. It has been shown that pneumococcal serotype 3 has a greater content of capsular polysaccharide when compared to serotype 1 which leads to increased resistance to phagocytosis, and consequentially it is more virulent.[11] A recent systematic review and meta-analysis pooled study-specific estimates of risk of death from nine studies of pneumococcal pneumonia and meningitis, and found that the outcome of invasive pneumococcal disease was associated with the specific serotype in a stable manner; serotype 3 was amongst those that were associated with an increased risk of death (serotypes 3, 6A, 6B, 9N, and 19F), and serotypes 1, 7F, and 8 had a decreased risk.[12] Harboe et al.[13] reviewed 30-day mortality following invasive pneumococcal disease in patients over 5 years; pneumococcal serotype 3 infections resulted in a significantly greater adjusted mortality than serotype 1 (odds ratio 3.6). Serotype 3 is thought to account for 1–2% of pediatric invasive pneumococcal disease, although is significantly more prevalent in adult populations.[14]

Epidemiological data from the Health Protection Agency has shown a significant decline in the frequency of invasive pneumococcal disease caused by those serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) covered by heptavalent Prevenar® with a corresponding rise in the frequency of serotypes not included.[15] In Utah, 86% of empyema cases and 88% of necrotizing pneumonia cases occurring from January 2001 to March 2006, were related to *S. pneumoniae* serotypes not in Prevenar®.[10] A more recent paper from the same group in Utah has suggested that serotype replacement was occurring rather than serotype switch, and that serotype 3 emerged in 2001 as an important cause of pediatric pneumococcal empyema.[16] Further epidemiological information for the UK is likely to become available as a result of the ongoing national programme for enhanced pneumococcal surveillance (www.public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=7229).

In April 2010, as a response to the rising frequency of non-vaccine serotypes, the childhood immunization programme in the UK has replaced the heptavalent Prevenar® with a 13-valent vaccine (Prevenar 13). This contains all of the serotypes in Prevenar® plus serotypes 1, 3, 5, 6A, 7F, and 19A.[15] Time will tell whether this leads to a decrease in incidence of childhood empyemas in the UK, now that serotypes 1 and 3 are included, or whether yet another serotype becomes predominant. Ultimately a non-serotype specific vaccine may offer a better solution to invasive pneumococcal disease, and to this end there are a number of collaborative teams using either inactivated whole cell or common proteins to develop non-serotype-specific vaccines.[17]

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