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3 **Increased incidence of bronchopulmonary fistulas complicating paediatric pneumonia.**
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Abstract

Background. The frequency of complicated pneumococcal disease, including necrotising pneumonia, has increased over the last decade. During 2008-9, 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 2002-7, compared with 2008-9. 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 2008-9. 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.

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].

Cavitary disease is another complication of pneumococcal pneumonia, and it has become increasingly recognised since first reported in 1994 [4]. It is characterised 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 pulmonary 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 USA [1-3]. In terms of necrotising pneumonia, a series from Northern England reported that 20% of their empyemas were complicated by cavitary disease, but this was not associated with any particular pneumococcal serotype [9]. However, in Utah USA, Bender *et al.* demonstrated a positive association between pulmonary necrosis and *S.pneumoniae* serotype 3 [10]. The relevance of these serotypes is that the heptavalent pneumococcal conjugate vaccine Prevenar® (Wyeth, Maidenhead UK) introduced into the UK's childhood immunisation 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 be rare. However in the last two years we noted a marked rise in the

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2
3 number of children with empyemas who had fistulas leading to long hospital stays and an
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5 increase in the surgical intervention rate. We aimed to ascertain whether this was a genuine
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7 rise and whether there was an associated cause.
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10 11 12 **Methods**

13 14 **Subjects**

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16 We have maintained a database of all paediatric empyema cases (aged <17.0 years) admitted
17
18 to the tertiary unit at the Royal Brompton Hospital since January 2002. All children had a
19
20 clinical history of parapneumonic effusion confirmed by a chest ultrasound, and we included
21
22 those treated conservatively who did not require a chest drain. For this study, children were
23
24 recorded as having a fistula if there was radiological evidence (on a plain chest radiograph) of
25
26 free air within the pleural space, or air bubbling into the underwater seal bottle attached to the
27
28 chest drain (other than very briefly). This had to be noted either before or at least 24 hours
29
30 after drain insertion, to ensure the air was not iatrogenic arising during the placement of the
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32 drain. Chest radiographs were taken routinely immediately after drain insertion; later ones
33
34 would only be taken if there was air bubbling into the drain or if other complications arose.
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41 **Chest CT scans were not routinely performed as per current UK guidelines [3].**
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46 A retrospective review of cases from 1st January 2002 to 31st December 2009 was conducted
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48 using our database and case notes, supplemented by the hospital's IT system. For each case,
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50 the data collected included patient demographics, clinical outcomes, haematology &
51
52 inflammatory markers, radiology, and microbiology. The latter included blood and pleural
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54 fluid cultures, but from 2005, 16s rDNA PCR was also performed, and from 2006 detection of
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56 specific capsular pneumococcal antigens was included, both on pleural fluid.
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Statistical analysis

Demographic, clinical and laboratory variables were summarised by standard descriptive statistics, and comparison was made between cases occurring during the 6 years of 2002-7 and the 2 years of 2008-9. A further comparison was made of the children who developed a fistula and those who did not, for the period of 2008-9. SPSS (Statistical Package for the Social Sciences) software (SPSS version 17.0, Chicago, IL, USA) was used for all statistical analysis. Differences were considered statistically significant if $p < 0.05$ (using Fisher's exact and Mann Whitney tests). 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 3 children from analysis as it was possible that their fistulas were iatrogenic in origin (1 had surgical intervention elsewhere) so data is presented on 307 children. The median age was 4.6 yrs (range 0.2-15.7 yrs) and the male to female ratio was 1.6:1. We have no information regarding their pneumococcal immunisation 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 6 doses administered (range 1-10, and only

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3 8% receiving more than 6 doses). Urokinase was stopped when an air leak was noted on the
4
5 theoretical basis it might impede plugging off and healing of a fistula. Only 12 (4%) children
6
7 required surgery (video assisted thoracoscopic surgery or thoracotomy), always as second line
8
9 management to chest drain and fibrinolytics. **Surgery was considered when there was either**
10
11 **significant clinical deterioration or failure to progress in the treatment of sepsis.**
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16 17 **Microbiology**

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19 Overall, an organism was identified in only 70 children (23%). *S.pneumoniae* was the most
20
21 frequently isolated, occurring in 44 children (14%), followed by β -haemolytic Group A
22
23 Streptococcus in 13 (4%), and *Staphylococcus aureus* in 8 (3%). *Mycoplasma pneumoniae*,
24
25 *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus milleri*, and
26
27 *Haemophilus influenzae* were isolated in single patients.
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34 **Comparison of 2002-7 vs 2008-9**

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36 There was a marked and statistically significant rise in frequency of bronchopleural fistulas in
37
38 the later period, rising from 1% (2/258) in 2002-7 to 33% (16/49) in 2008-9, $p < 0.0001$ (table
39
40 1). The 2 fistulas occurring during the initial 6-year period were in 2004 and 2005, so it seems
41
42 this represents a genuine sudden increase rather than a gradual rise; **microbiology was**
43
44 **negative for both those cases.** The rise in frequency of fistula formation was matched by a
45
46 significant increase in median length of hospital stay (7 vs 10 days, $p < 0.0001$). Length of stay
47
48 for children without fistulas was no different in the two time periods (median 7 vs 8.5 days),
49
50 **nor was there a difference in length of pleural drainage (5 vs 5.5 days),** suggesting the
51
52 increased hospital stay in the latter 2 years was likely to have been associated with the air
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54 leaks (median 26.5 days), rather than any change in management. There were no age or sex
55
56 differences between the two time periods. Initial management was the same in the two groups
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3 with a similar use of chest drains and intrapleural fibrinolytics. However there was a 7-fold
4
5 increase in surgical intervention rate (see table 1 for procedures) in the 2008-9 period (2% vs
6
7 14%, p=0.001), with a corresponding increase in admission to the paediatric intensive care
8
9 unit (PICU) (2% vs 10%, p=0.02).

15 **Analysis of patients with bronchopleural fistulas vs those without, in 2008-9**

17 There were 49 cases of empyema analysed in the 2 years; 16 (33%) had a bronchopleural
18
19 fistula. An aetiological organism was identified in 32/49 (65%) of cases during this time
20
21 period, with *S.pneumoniae* responsible for 28/32 (89%) (table 2). Capsular specific antigen
22
23 testing was available for 20 of these samples: serotype 1 accounting for 7, serotype 3 for 11
24
25 and serotype 7a/7f and 19a accounting for single cases; in 2 cases there was no serotype
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27 identified and 6 cases were not tested. Pneumococcal serotype 3 was identified in 10/16
28
29 (63%) children with a bronchopleural fistula and 1/33 (3%) without (<0.0001). The 3 cases of
30
31 fistulas excluded as possibly iatrogenic included two who developed an air leak immediately
32
33 following drain insertion (one with *Staphylococcus aureus*, one with an unidentified
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35 organism), and one case referred to us following decortication and rib resection who had non-
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37 serotyped *S.pneumoniae*.
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46 There were no differences between the two groups with respect to age and gender or in the
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48 use of antibiotics prior to admission (table 3). Markers of disease severity were similar with
49
50 respect to highest C-reactive protein (CRP), highest neutrophil count and lowest serum
51
52 albumin. However those with bronchopleural fistulas had significantly lower Hb levels; out of
53
54 16 patients, 1 required a blood transfusion, 1 had erythropoietin (refusing transfusion) and 4
55
56 had oral iron, whereas only 1/33 without a fistula required therapy (a blood transfusion).
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3 Children with bronchopleural fistulas were more likely to have initial treatment with a drain
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5 (p=0.02) but there was no difference in the use of intrapleural fibrinolytics. The median length
6
7 of time for a bronchopleural fistula to become apparent was 5 days following insertion of the
8
9 drain, with a range of 3-10 days; one child had the leak noted before drain insertion. Children
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11 with bronchopleural fistulas had a more protracted and complicated clinical course (table 3).
12
13 Drains remained in place for a median of 21.5 days (range 7-46), compared to 5.5 days (range
14
15 0-16), hence there was a much longer length of stay, 26.5 days vs 8.5 days. Complicated
16
17 fistulas were managed in conjunction with the thoracic surgeons, using large calibre drains
18
19 until the air leaks resolved. Ten cases were managed successfully this way, but 5 required
20
21 surgical intervention with video-assisted thoracoscopy **only**, and one required a decortication
22
23 **as well as VATS** (none required lung resection). No child without a fistula required surgery.
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25 All children have been followed up for at least 6 months and chest radiographs have shown
26
27 complete resolution in every child.
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36 Discussion

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38 In a single tertiary centre, we have demonstrated a marked increase in the frequency of
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40 bronchopleural fistulas complicating paediatric empyema in the last two years. This
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42 complication was associated with greater length of hospital stay, increased PICU requirement
43
44 and an increased need for surgical intervention. Furthermore *S.pneumoniae* serotype 3 was
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46 isolated frequently in those with fistulas compared to those without, suggesting a strong
47
48 association **which may possibly have been causal but we cannot prove this**. This is in keeping
49
50 with Bender *et al* who demonstrated an increase in the frequency of necrotising pneumonia in
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52 one state in the USA, which they attributed to both an increase in recognition and an
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54 alteration in invasiveness of certain strains of *S.pneumoniae* [10]. However since we do not
55
56 have complete data on serotypes from both time periods, we can not say whether there was an
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3 increase in prevalence of serotype 3 in our patients to account for the dramatic rise in air leaks
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5 in the last two years.
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10 We do know that our treatment protocols have not changed (and there is nothing to suggest
11 that use of urokinase was associated with fistula formation), nor our admission criteria (the
12 patient demographics were similar over the two time periods), so it is quite possible the
13 appearance of fistulas is due to an inherent feature of the infecting organisms. It has been
14 shown that pneumococcal serotype 3 has a greater content of capsular polysaccharide when
15 compared to serotype 1 which leads to increased resistance to phagocytosis, and
16
17 consequentially it is more virulent [11]. A recent systematic review and meta-analysis pooled
18 study-specific estimates of risk of death from 9 studies of pneumococcal pneumonia and
19 meningitis, and found that the outcome of invasive pneumococcal disease was associated with
20 the specific serotype in a stable manner; serotype 3 was amongst those that were associated
21 with an increased risk of death (serotypes 3, 6A, 6B, 9N & 19F), and serotypes 1, 7F and 8
22 had a decreased risk [12]. Harboe *et al* reviewed 30-day mortality following invasive
23 pneumococcal disease in patients over 5 years; pneumococcal serotype 3 infections resulted in
24 a significantly greater adjusted mortality than serotype 1 (odds ratio 3.6) [13]. Serotype 3 is
25 thought to account for 1-2% of paediatric invasive pneumococcal disease, although is
26 significantly more prevalent in adult populations [14].
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50 Epidemiological data from the Health Protection Agency has shown a significant decline in
51 the frequency of invasive pneumococcal disease caused by those serotypes (4, 6B, 9V, 14,
52 18C, 19F, 23F) covered by heptavalent Prevenar® with a corresponding rise in the frequency
53 of serotypes not included [15]. In Utah, 86% of empyema cases and 88% of necrotising
54 pneumonia cases occurring from January 2001 to March 2006, were related to *S.pneumoniae*
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3 serotypes not in Prevenar® [10]. A more recent paper from the same group in Utah has
4 suggested that serotype replacement was occurring rather than serotype switch, and that
5
6 serotype 3 emerged in 2001 as an important cause of paediatric pneumococcal empyema [16].
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10 Further epidemiological information for the UK is likely to become available as a result of the
11
12 ongoing national programme for enhanced pneumococcal surveillance
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15 (www.public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=7229).
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20 In April 2010, as a response to the rising frequency of non-vaccine serotypes, the childhood
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22 immunisation programme in the UK has replaced the heptavalent Prevenar® with a 13-valent
23
24 vaccine, Prevenar 13® (Wyeth, Maidenhead UK). This contains all of the serotypes in
25
26 Prevenar® plus serotypes 1, 3, 5, 6A, 7F and 19A [15]. Time will tell whether this leads to a
27
28 decrease in incidence of childhood empyemas in the UK, now that serotypes 1 and 3 are
29
30 included, or whether yet another serotype becomes predominant. Ultimately a non-serotype
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32 specific vaccine may offer a better solution to invasive pneumococcal disease, and to this end
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34 there are a number of collaborative teams using either inactivated whole cell or common
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36 proteins to develop non-serotype specific vaccines [17].
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Competing interests

None

For Peer Review

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Abstract

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Methods. This was a retrospective case note and database review of children admitted to our tertiary unit with a parapneumonic effusion or empyema from 2002-7, compared with 2008-9. 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 2008-9. 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.

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Whilst the majority resolves with conservative management, the clinical course can be complicated and lengthy.

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10 11 12 **Methods**

13 14 15 **Subjects**

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17 We have maintained a database of all paediatric empyema cases (aged <17.0 years) admitted
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19 to the tertiary unit at the Royal Brompton Hospital since January 2002. All children had a
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21 clinical history of parapneumonic effusion confirmed by a chest ultrasound, and we included
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23 those treated conservatively who did not require a chest drain. For this study, children were
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25 recorded as having a fistula if there was radiological evidence (on a plain chest radiograph) of
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27 free air within the pleural space, or air bubbling into the underwater seal bottle attached to the
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29 chest drain (other than very briefly). This had to be noted either before or at least 24 hours
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31 after drain insertion, to ensure the air was not iatrogenic arising during the placement of the
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33 drain. Chest radiographs were taken routinely immediately after drain insertion; later ones
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35 would only be taken if there was air bubbling into the drain or if other complications arose.
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37 Chest CT scans were not routinely performed as per current UK guidelines [3].
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46 A retrospective review of cases from 1st January 2002 to 31st December 2009 was conducted
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48 using our database and case notes, supplemented by the hospital's IT system. For each case,
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50 the data collected included patient demographics, clinical outcomes, haematology &
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52 inflammatory markers, radiology, and microbiology. The latter included blood and pleural
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54 fluid cultures, but from 2005, 16s rDNA PCR was also performed, and from 2006 detection of
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56 specific capsular pneumococcal antigens was included, both on pleural fluid.
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Statistical analysis

Demographic, clinical and laboratory variables were summarised by standard descriptive statistics, and comparison was made between cases occurring during the 6 years of 2002-7 and the 2 years of 2008-9. A further comparison was made of the children who developed a fistula and those who did not, for the period of 2008-9. SPSS (Statistical Package for the Social Sciences) software (SPSS version 17.0, Chicago, IL, USA) was used for all statistical analysis. Differences were considered statistically significant if $p < 0.05$ (using Fisher's exact and Mann Whitney tests). 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 3 children from analysis as it was possible that their fistulas were iatrogenic in origin (1 had surgical intervention elsewhere) so data is presented on 307 children. The median age was 4.6 yrs (range 0.2-15.7 yrs) and the male to female ratio was 1.6:1. We have no information regarding their pneumococcal immunisation 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 6 doses administered (range 1-10, and only

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3 8% receiving more than 6 doses). Urokinase was stopped when an air leak was noted on the
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5 theoretical basis it might impede plugging off and healing of a fistula. Only 12 (4%) children
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7 required surgery (video assisted thoracoscopic surgery or thoracotomy), always as second line
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9 management to chest drain and fibrinolytics. Surgery was considered when there was either
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11 significant clinical deterioration or failure to progress in the treatment of sepsis.
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17 **Microbiology**

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19 Overall, an organism was identified in only 70 children (23%). *S.pneumoniae* was the most
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21 frequently isolated, occurring in 44 children (14%), followed by β -haemolytic Group A
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23 Streptococcus in 13 (4%), and *Staphylococcus aureus* in 8 (3%). *Mycoplasma pneumoniae*,
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25 *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus milleri*, and
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27 *Haemophilus influenzae* were isolated in single patients.
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34 **Comparison of 2002-7 vs 2008-9**

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36 There was a marked and statistically significant rise in frequency of bronchopleural fistulas in
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38 the later period, rising from 1% (2/258) in 2002-7 to 33% (16/49) in 2008-9, $p < 0.0001$ (table
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40 1). The 2 fistulas occurring during the initial 6-year period were in 2004 and 2005, so it seems
41
42 this represents a genuine sudden increase rather than a gradual rise; microbiology was
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44 negative for both those cases. The rise in frequency of fistula formation was matched by a
45
46 significant increase in median length of hospital stay (7 vs 10 days, $p < 0.0001$). Length of stay
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48 for children without fistulas was no different in the two time periods (median 7 vs 8.5 days),
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50 nor was there a difference in length of pleural drainage (5 vs 5.5 days), suggesting the
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52 increased hospital stay in the latter 2 years was likely to have been associated with the air
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54 leaks (median 26.5 days), rather than any change in management. There were no age or sex
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56 differences between the two time periods. Initial management was the same in the two groups
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3 with a similar use of chest drains and intrapleural fibrinolytics. However there was a 7-fold
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5 increase in surgical intervention rate (see table 1 for procedures) in the 2008-9 period (2% vs
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7 14%, p=0.001), with a corresponding increase in admission to the paediatric intensive care
8
9 unit (PICU) (2% vs 10%, p=0.02).

15 **Analysis of patients with bronchopleural fistulas vs those without, in 2008-9**

17 There were 49 cases of empyema analysed in the 2 years; 16 (33%) had a bronchopleural
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19 fistula. An aetiological organism was identified in 32/49 (65%) of cases during this time
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21 period, with *S.pneumoniae* responsible for 28/32 (89%) (table 2). Capsular specific antigen
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23 testing was available for 20 of these samples: serotype 1 accounting for 7, serotype 3 for 11
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25 and serotype 7a/7f and 19a accounting for single cases; in 2 cases there was no serotype
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27 identified and 6 cases were not tested. Pneumococcal serotype 3 was identified in 10/16
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29 (63%) children with a bronchopleural fistula and 1/33 (3%) without (<0.0001). The 3 cases of
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31 fistulas excluded as possibly iatrogenic included two who developed an air leak immediately
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33 following drain insertion (one with *Staphylococcus aureus*, one with an unidentified
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35 organism), and one case referred to us following decortication and rib resection who had non-
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37 serotyped *S.pneumoniae*.
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46 There were no differences between the two groups with respect to age and gender or in the
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48 use of antibiotics prior to admission (table 3). Markers of disease severity were similar with
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50 respect to highest C-reactive protein (CRP), highest neutrophil count and lowest serum
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52 albumin. However those with bronchopleural fistulas had significantly lower Hb levels; out of
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54 16 patients, 1 required a blood transfusion, 1 had erythropoietin (refusing transfusion) and 4
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56 had oral iron, whereas only 1/33 without a fistula required therapy (a blood transfusion).
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3 Children with bronchopleural fistulas were more likely to have initial treatment with a drain
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5 (p=0.02) but there was no difference in the use of intrapleural fibrinolytics. The median length
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7 of time for a bronchopleural fistula to become apparent was 5 days following insertion of the
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9 drain, with a range of 3-10 days; one child had the leak noted before drain insertion. Children
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11 with bronchopleural fistulas had a more protracted and complicated clinical course (table 3).
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13 Drains remained in place for a median of 21.5 days (range 7-46), compared to 5.5 days (range
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15 0-16), hence there was a much longer length of stay, 26.5 days vs 8.5 days. Complicated
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17 fistulas were managed in conjunction with the thoracic surgeons, using large calibre drains
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19 until the air leaks resolved. Ten cases were managed successfully this way, but 5 required
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21 surgical intervention with video-assisted thoracoscopy only, and one required a decortication
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23 as well as VATS (none required lung resection). No child without a fistula required surgery.
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25 All children have been followed up for at least 6 months and chest radiographs have shown
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27 complete resolution in every child.
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36 Discussion

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38 In a single tertiary centre, we have demonstrated a marked increase in the frequency of
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40 bronchopleural fistulas complicating paediatric empyema in the last two years. This
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42 complication was associated with greater length of hospital stay, increased PICU requirement
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44 and an increased need for surgical intervention. Furthermore *S.pneumoniae* serotype 3 was
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46 isolated frequently in those with fistulas compared to those without, suggesting a strong
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48 association which may possibly have been causal but we cannot prove this. This is in keeping
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50 with Bender *et al* who demonstrated an increase in the frequency of necrotising pneumonia in
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52 one state in the USA, which they attributed to both an increase in recognition and an
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54 alteration in invasiveness of certain strains of *S.pneumoniae* [10]. However since we do not
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56 have complete data on serotypes from both time periods, we can not say whether there was an
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3 increase in prevalence of serotype 3 in our patients to account for the dramatic rise in air leaks
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5 in the last two years.
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10 We do know that our treatment protocols have not changed (and there is nothing to suggest
11 that use of urokinase was associated with fistula formation), nor our admission criteria (the
12 patient demographics were similar over the two time periods), so it is quite possible the
13 appearance of fistulas is due to an inherent feature of the infecting organisms. It has been
14 shown that pneumococcal serotype 3 has a greater content of capsular polysaccharide when
15 compared to serotype 1 which leads to increased resistance to phagocytosis, and
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17 consequentially it is more virulent [11]. A recent systematic review and meta-analysis pooled
18 study-specific estimates of risk of death from 9 studies of pneumococcal pneumonia and
19 meningitis, and found that the outcome of invasive pneumococcal disease was associated with
20 the specific serotype in a stable manner; serotype 3 was amongst those that were associated
21 with an increased risk of death (serotypes 3, 6A, 6B, 9N & 19F), and serotypes 1, 7F and 8
22 had a decreased risk [12]. Harboe *et al* reviewed 30-day mortality following invasive
23 pneumococcal disease in patients over 5 years; pneumococcal serotype 3 infections resulted in
24 a significantly greater adjusted mortality than serotype 1 (odds ratio 3.6) [13]. Serotype 3 is
25 thought to account for 1-2% of paediatric invasive pneumococcal disease, although is
26 significantly more prevalent in adult populations [14].
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50 Epidemiological data from the Health Protection Agency has shown a significant decline in
51 the frequency of invasive pneumococcal disease caused by those serotypes (4, 6B, 9V, 14,
52 18C, 19F, 23F) covered by heptavalent Prevenar® with a corresponding rise in the frequency
53 of serotypes not included [15]. In Utah, 86% of empyema cases and 88% of necrotising
54 pneumonia cases occurring from January 2001 to March 2006, were related to *S.pneumoniae*
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3 serotypes not in Prevenar® [10]. A more recent paper from the same group in Utah has
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5 suggested that serotype replacement was occurring rather than serotype switch, and that
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7 serotype 3 emerged in 2001 as an important cause of paediatric pneumococcal empyema [16].
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9 Further epidemiological information for the UK is likely to become available as a result of the
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11 ongoing national programme for enhanced pneumococcal surveillance
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15 (www.public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=7229).
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20 In April 2010, as a response to the rising frequency of non-vaccine serotypes, the childhood
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22 immunisation programme in the UK has replaced the heptavalent Prevenar® with a 13-valent
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24 vaccine, Prevenar 13® (Wyeth, Maidenhead UK). This contains all of the serotypes in
25
26 Prevenar® plus serotypes 1, 3, 5, 6A, 7F and 19A [15]. Time will tell whether this leads to a
27
28 decrease in incidence of childhood empyemas in the UK, now that serotypes 1 and 3 are
29
30 included, or whether yet another serotype becomes predominant. Ultimately a non-serotype
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32 specific vaccine may offer a better solution to invasive pneumococcal disease, and to this end
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34 there are a number of collaborative teams using either inactivated whole cell or common
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36 proteins to develop non-serotype specific vaccines [17].
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Competing interests

None

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Table 1

Comparison of clinical outcomes in children admitted from 2002-7 vs 2008-9.

	2002-7	2008-9	p value
	n= 258	n=49	
Age (median & range) yrs	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 & range) days	5 (1-23)	9 (1-46)	<0.0001
Length of stay (median & range) days	7 (1- 42)	10 (4-48)	<0.0001
PICU admission	6 (2%)	5 (10%)	0.02

Table 2

Pleural fluid microbiology results for cases admitted 2008-9.

Bronchopleural fistula		No bronchopleural fistula	
(n=16)		(n=33)	
<i>Pneumococcus</i>	13	<i>Pneumococcus</i>	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
<i>Group A Streptococcus</i>	0	<i>Group A Streptococcus</i>	3
Unknown	2	Unknown	15
Others (<i>Pseudomonas</i>	1	Others	0
<i>aeruginosa</i>)			

Table 3

Comparison of demographics and clinical outcomes of children with or without a bronchopleural fistula for cases admitted 2008-9. Results are given as medians with ranges, unless numbers (%).

	Bronchopleural fistula n=16	No bronchopleural fistula n= 33	p value
Age (yrs)	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