Pediatric Pleural Empyema in the Province of Quebec: Analysis of a 10-Fold Increase Between 1990 and 2007

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Background. Although the frequency of pneumonia has decreased over time, an increase in pleural empyema has been observed in different settings worldwide. This study assessed the epidemiology of community-acquired pediatric pleural empyema in the province of Quebec through validation of cases found in a hospitalization discharge database.

Methods. We used the national administrative database of hospitalization to identify children (6 months–14 years) hospitalized for pleural empyema or pleural effusion with drainage from January 1990 until December 2007 and reviewed their medical charts. Patients with pleural effusion secondary to chest trauma, thoracic surgery, malignancies, cardiac failure, or metabolic disorders were excluded.

Results. Predictive positive value (PPV) of empyema code in any position among discharge diagnostics in the administrative database was 86.5% (95% confidence interval: 81.9%–90.3%). After chart revision, 292 met the inclusion criteria. Age-adjusted incidence of pleural empyema in the pediatric population increased from 0.23 in 1990 to 4.01/100,000 person-years in 2007. A bacterial pathogen was identified in 46.5%; Streptococcus pneumoniae (Sp) (42%) and S pyogenes (30%) were most frequent. There was no obvious change in the PPV and proportions of children with chronic disease or asthma and in identified pathogens over time, but an increase in pre-admission respiratory symptoms duration (from 3.8 days to 5.7) and nonsteroidal anti-inflammatory drug use (from 0% to 19%) was observed.

Conclusions. From 1990 to 2007, we observed a 10-fold increase in the incidence of pediatric hospitalizations associated with pleural empyema. This increase preceded the introduction of a pneumococcal conjugated vaccine program in Quebec. Sp remained the major pathogen identified.

Key words. database validation; epidemiology; pediatric population; pleural empyema.

Pleural empyema is one of the main complications of pneumonia [1, 2], causing significant morbidity and prolonged hospitalization. Although the frequency of childhood community-acquired pneumonia has decreased over the last few years subsequent to the introduction of the heptavalent conjugated pneumococcal vaccine (PCV7) in routine vaccination schedules [3, 4], an increasing incidence of hospitalization associated with pleural empyema has been observed in North America [1, 2, 5–10] and worldwide [11–15]. In Canada, an increased incidence of admissions for pleural empyema has been reported in the 1- to 14-yearold age group over the period 1995–2003 [16]. However, this study was solely based on hospital administrative databases; medical records were not reviewed. A Canadian study of empyemas from 8 tertiary pediatric hospitals (2000–2003) detailed some epidemiological and clinical characteristics and management of cases using chart review, but was not population-based [17].
The validity of administrative databases in identifying community-acquired pleural empyema has not been assessed: variation in the chart review process and coding may affect reported rates. In the province of Quebec, a time-series analysis did not show any significant trend in the incidence rate of hospital admission for pleural effusion over the period 1997–2005 [4]. However, clinicians had the impression that rates of hospitalizations due to community-acquired empyema were increasing in recent years. The objective of this study was to assess the incidence rate of community-acquired pediatric pleural empyema in the province of Quebec, Canada, over an 18-year period, and validate the use of administrative data for ascertainment of pleural empyema through a review of medical records.

METHODS

Identification of Cases
Using the hospital administrative database Med-Echo (discharge abstract database), cases of empyemas were identified to form the basis for a population-based retrospective cohort study. The Med-Echo database includes all admissions to acute-care hospitals in the province of Quebec and incorporates data from medical records reviewed by certified medical archivists. One main diagnosis and up to 15 secondary diagnoses are assigned and coded according to the International Classification of Disease (9th Revision up to March 31, 2006, and 10th revision thereafter).

Inclusion criteria were patients aged 6 months to 14 years with a hospital discharge date between January 1, 1990, and December 31, 2007 (18 years). Records with a code for empyema (ICD-9 code 510.X or ICD-10 code J86.X) or for pleural effusion associated with a procedure used to manage pleural effusions, including thoracocentesis, chest tube placement for pleural drainage, decortication procedure, transpleural thoracoscopy, and thoracotomy (corresponding to ICD-9 511.X with codes 46.04, 46.09, 46.41, 46.81, 46.91, and ICD-10 J90 or R09.1 with the codes 1GV33HA1C, 1GV38.X, 1GV52.X, 1GV54.X, 1GV87.X, 1GV89.X) were extracted. Multiple hospitalizations in a unique patient could be linked using the unique provincial health insurance number; only the first episode was retained for incidence rate calculations. Transfers and multiple admissions within a 7-day period were considered to be a single episode.

Medical Records Review
Trained research assistants reviewed medical records of identified children and completed a standardized data collection form for each patient. All cases, discharged from any hospital in the province, with a code for empyema in any position were reviewed. However, as the positive predictive value of pleural effusion codes with drainage was found to be low and as the vast majority of cases identified with this code in the Med-Echo database had been referred to 1 of the 4 tertiary-care pediatric centers in the province of Quebec, we only reviewed charts coded as pleural effusions with drainage in tertiary care centers. The information gathered included demographic, clinical, and microbiological data for bacterial isolates from blood samples and pleural fluid, when available.

Case Definition
Only community-acquired pleural empyema was included; patients with pleural effusion and empyema secondary to chest trauma, thoracic surgery, malignancies, cardiac failure, or metabolic disorders were excluded. Pleural empyema was defined by the presence of one or more of the following features: (1) pleural fluid with any of the following empyema features: purulent appearance, white blood cell count >50,000×10^9/L, pH <7.1, glucose ≤2.1 mM/L, lactate dehydrogenase >1000 IU/L, Gram-positive stain or culture; (2) loculated pleural fluid demonstrated by ultrasound or CT scan; and (3) diagnosis during a surgical procedure by thoracotomy or video-assisted thoracoscopic surgery. These criteria were in accordance with those previously described by others [1, 2, 6, 14].

Statistical Analyses
Crude incidence rates were computed using 6 months to 14 years population denominators for each age and calendar year provided by the Quebec Statistics Institute. Confidence intervals around crude rates were computed using normal approximation after square-root transformation. Age-specific and age-standardized incidence rates were also computed using the year 2007 as the reference year for standardization (n = 1,044,526 persons at risk). To account for the minimal proportion of empyema cases that may have been missed in nonreviewed charts, we computed corrected rates, using the predictive value of diagnostic codes for the nonreviewed charts. Statistical comparisons of proportions were performed using χ^2 test, Fisher’s exact test, or Cochran-Armitage test for trends over the 18 years, by 3-year periods. Variation in the age distribution of cases over time was analyzed using the Kruskall-Wallis test. We used linear regression to test for the significance of secular trends in rates or continuous variables, and Poisson regression was used to determine the age-adjusted relative risks. All P-values were two-sided.

SAS 9.2 software (SAS Institute, Cary, NC) was used for statistical analyses.

The study was approved by the provincial Commission d’Accès à l’Information du Québec and by the Research Ethics Board of the CHU-Sainte-Justine.
RESULTS

Ascertainment of Cases

A total of 915 Med-Echo records, representing 834 patients, met the initial selection criteria. A total of 713 medical records were reviewed and a total of 292 episodes of community-acquired pleural empyema were confirmed (Fig. 1). The medical records of 281 of 302 patients (93.0%) with a primary or secondary diagnosis of pleural empyema were available for review, resulting in 243 cases classified as community-acquired pleural empyema. Among the 532 cases with a code of pleural effusion associated with a surgical procedure without an empyema code, 432 (81.2%) were reviewed, with 49 being classified as community-acquired pleural empyema. The positive predictive value (PPV) of a pleural empyema code in any position was 86.5% (95% CI: 81.9–90.3). When this was the main diagnostic code, the PPV was 95.2% (95% CI: 89.0–98.4%), and when it was in any other position it was 81.5% (95% CI: 75.0–86.9%). The PPV of a pleural effusion code was only 11.3% (95% CI: 8.5–14.7%). No significant trend in the PPVs of various codes over time was observed during the study period.

Incidence Rates

The age-adjusted incidence of pleural empyema in the pediatric population increased from 0.23/100 000 person-years in 1990 to 4.01/100 000 person-years (p-y) in 2007, a 17-fold increase (Fig. 2a). Adjusted relative risk comparing the 1990–1992 to the 2005–2007 period was 8.9
The average absolute increase in rate was 0.19 per 100,000 per year (linear scale), and the mean annual relative risk increase was 1.16 (95% CI: 1.10–1.22; \( P < .001 \)) (geometric scale).

As 21 charts with empyema code and 100 charts with pleural effusion and drainage code were not reviewed, we estimated based on PPV that 29 real cases of empyema were not reviewed for the 18-year study period. Correction of rates for possible under-ascertainment did not substantially change results as nonreviewed cases were evenly distributed across the study period (Fig. 2a).

Characteristics of Patients
As shown in Figure 2b, rates were higher in younger compared to older children. The absolute increase in rate was also higher in younger children, but there was no gradient in the relative risk increase. Patients’ median age was 4.2 years, and the age distribution did not significantly change over the study period (\( P = .40 \)). Three (1%) patients died and 97 (33%) were admitted to the intensive care unit; no temporal trend was observed in these proportions.

A total of 212 cases (73%) had loculated pleural fluid, as demonstrated by ultrasound or CT scan, and 277
(95%) presented compatible pleural fluid anomalies. Seventy-five patients (26%) had only pleural fluid anomalies without loculation. Five patients (2%) had only a surgical diagnosis. The proportion of patients with demonstration of loculations in pleural fluid slightly increased over the study period, from 66.7% in 1990–1992 to 81.7% in 2005–2007 ($P = .06$), but there was no trend in the proportion of children with demonstrated pleural fluid anomalies. A medical history of risk factor for a severe respiratory infection was reported in 94 cases (32% of total). Asthma was the most frequently reported condition (21% of all cases, with or without other condition), and 17.8% presented other medical conditions. No significant change was observed over time in the proportions of underlying medical conditions. An influenza-like illness or other upper respiratory tract infection in the month preceding the hospital admission for empyema was reported in 150 children (51% of the total, no temporal trend observed). In the month preceding admission, 7.9% reported a history of varicella, 12.3% had used a nonsteroidal anti-inflammatory drug (NSAID), and 33.9% had taken antibiotics. There was a significant increasing trend in the proportion of NSAID use, with 0.0% report of use from 1990 to 1992, and 19.3% in 2005–2007 ($P < .001$). A moderate trend was observed for antibiotics use (from 25.0% to 37.6%, $P = .04$, for the same periods), but the proportion of patients with a history of varicella decreased (from 16.7% to 0%, $P < .001$, for the same periods). The average time elapsed between fever onset or respiratory symptoms and admission were, respectively, 5.4 (SD: 4.42) and 5.4 days (SD: 6.0). Both increased over the study period, and the increase in time interval between respiratory symptoms and admission was significant (mean number of days was 3.8 in 1990–1992 and 5.7 in 2005–2007; mean increase of 0.17 day/year, $P = .02$).

**Microbiological Characteristics**

Microbiological results were available for 288 patients (98.6%); a bacterial involvement was found in 134 cases (134/288 = 46.5%): by culture (124 cases) or only by direct examination of pleural fluid or surgical sample (10 cases). Blood cultures were positive in 53 cases (53/288 = 18.4%) and pleural fluid cultures in 79 cases (27.4%). Isolate identification was available for 122 cases; *Streptococcus pneumoniae* ($Sp$) represented 42% (51/122) and *Group A Streptococcus* (GAS) 30% (37/122) of these isolates. $Sp$ serotypes were available for 17 cases only, all but 1 after the year 2000: serogroup 14 (5 cases, all before 2005), serotypes 3, 7F, and 19A (3 each), and serogroup 1 (2).

The absolute number of cases with a presumptive bacterial pathogen over the study period is shown in Figure 3. The global proportion of cases according to different pathogens and the proportion of nonidentified pathogens did not statistically change over time, but there was a borderline trend for a decrease in the proportion of those with GAS compared to all others ($P = .05$).

The proportion of children with recent varicella was significantly higher in patients with GAS pleural empyema (24%) compared to patients with pneumococcal empyema (2%, $P < .0001$).

**Discussion**

This is the first population-based study on the epidemiology of community-acquired pleural empyema in Canada based on medical charts review. Results show more than a 10-fold increase in the annual incidence of children admitted with pleural empyemas between 1990 and 2007, and this increase is particularly affecting the younger children (Fig. 2b). An observation similar to ours was reported in

![Figure 3. Distribution of community-acquired pleural empyema cases by year according to results of bacteriologic investigations and streptococcal strains identified as the causal infectious agent, in the province of Quebec, 1990–2007.](image-url)
Scotland, where the admission rate for childhood pleural empyema (in the 1-to-4-year-old age group) rose from an average of 6.5 per million per year between 1981 and 1998 to 66 per million in 2005 [18]. The magnitude of increase observed in our study from 1996 to 2007 may also be compared to what was observed in the United States between 1996 and 2007 [10, 19]. We observed an absolute increase in incidence rate of 1.8 per 100 000 p-y from the 1996–1998 period to the 2005–2007 period, while a difference of 1.5/100 000 was observed in the U.S. pediatric population between 1997 and 2006 [10]. In our study, strict criteria were used to exclude coding errors and cases of pleural effusion or empyema secondary to chest trauma, thoracic surgery, malignancies, cardiac failure, or metabolic disorders. The PPV of ICD codes for pleural empyema in this hospital administrative database was found to be high (86.5%) and constant over time; it therefore cannot explain the observed increase. As patients were selected according to two diagnostic codes that we thought would predict real empyema, the proportion of real cases with an empyema code is likely higher among our study cases compared to all cases and controls in the base population; therefore, no sensitivity, specificity, and negative predictive value can be adequately estimated in this study [20].

It is possible that some cases were not caught by the hospital database searches based on discharge diagnostic codes of empyema and pleural effusion with drainage because of lack of sensitivity. Adding pleural effusion and drainage to the empyema code allowed us to find an additional 49 cases (16.8% of our cases). The correction of incidence rates for nonreviewed charts did change the observed epidemiology, as expected by the low PPV of the ICD code for pleural effusion with drainage for empyema. There is, however, a possible underestimate on the number of cases, particularly in the earlier time period, because ultrasound and CT scans were less available. Therefore, empyema may have been more likely miscoded as pneumonia or pleural effusion. However, the proportion of patients with demonstrated loculation increased only slightly over time (from 66.7% in 1990–1992 to 81.7% in 2005–2007), while the PPV of pleural effusion and drainage did not change (11.1% in the first 9 years of the study and 11.6 in the 9 last years). Moreover, in the hospitalization database, the incidence of hospitalization with a discharge diagnostic code of pleural effusion with drainage (without empyema code) was also lower before 1995 (1.5/100 000 p-y) and remained stable (around 2.5/100 000) since. Although an underestimate of the number of cases earlier in time may have contributed to the increase in incidence of empyema, we do not believe that it is the main explanation. The possibility that some cases could be hospitalized outside the province or that non-Quebec residents could be hospitalized for empyema in the province is also a possible source of bias but, as this is a marginal phenomenon, it would not exceed 1% or 2% of the estimates [21, 22].

The underlying causes for the increase in incidence are not known and various hypotheses have been raised, including a natural change in the epidemiology of bacterial pathogens, the selection of resistant microorganisms resulting from a change in antimicrobial use, or a consequence of the introduction of PCV7 [23]. Delay in hospitalization and longer fever duration before admission were found risk factors for empyema [1, 2, 24, 25]. We found an increase in the time interval between fever or respiratory symptoms onset and admission and also found that an increasing proportion of patients used NSAIDs before admission. An association between NSAIDs administration and the development of pleural empyema pneumonia has been documented by others [1, 25, 26], but our observation could only reflect the increase of NSAID use in the general population. Whether NSAIDs use is associated with a more severe disease is impossible to disentangle in this retrospective study, as systematically obtaining relevant information from medical records is impossible and the NSAID use in the general population was not documented.

Usual risk factors for pneumonia were not found in the majority of our cases as described by others [2, 5, 17, 24, 27–31], and the proportion of cases with underlying conditions did not change over time.

In our study, the increase in incidence began in 2003, 2 years before the introduction of PCV7 to the provincial immunization schedule in December 2004 [4]. Increases in the incidence of empyema before the introduction of PCV7 were also described by others [1, 2, 6, 11, 15, 16].

Conventional culture techniques fail to identify a causative organism in over half of cases, most likely due to previous antibiotic therapy [13, 17, 28, 32–34]. In our study, an infectious agent was isolated in 46.5% of cases. Sp and GAS represented 42% and 30% of the isolates, respectively. Since the implementation of a universal Haemophilus influenza type b vaccine, Sp appears to be the main infectious agent causing pleural empyema in children [1, 6, 27, 28, 30, 32, 33], and the proportion has remained stable over the years. Some recent studies in other settings using molecular biology techniques found that Sp was the most frequent pathogen identified in culture-negative cases, with a proportion of Sp higher than what is observed in culture-positive cases [27, 28, 30, 35]. Only a limited number of serotypes have been associated with pleural
empyemas [1, 2, 5, 31, 32]; in various recent reports, serotypes 1, 3, 5, 7F, and 19A, which are not part of the PCV7 vaccine, accounted for >75% of Sp identified in empyemas [13, 27–30, 35–37], with serotype 1 being the most frequent in many settings. Serotype 14—one of the major serotypes responsible for pneumococcal invasive infection prior to the introduction of PCV7 [38]—is no longer involved in areas where universal pneumococcal immunization has been implemented.

The link between varicella virus infection and the occurrence of invasive GAS infection in children is also well known [39–42]. Almost 8% of our cases reported varicella in the month preceding hospitalization, but the proportion of varicella-associated empyema decreased over the study period, and no case reported varicella in the 2005—2007 period. This proportion was significantly higher in patients with GAS pleural empyema than among patients with pneumococcal empyema. Although this may be secondary to a reporting bias, it is unlikely that this possible bias accounts for the entire difference, as varicella exposure is mandatorily asked about before hospitalization for infection-control purposes. Varicella vaccine was introduced in the routine immunization schedule in the Province of Quebec in January 2006; the impact of this measure requires further evaluation, as it is expected that one of the benefits of universal immunization against varicella would be the reduction in incidence of invasive GAS diseases [41, 42].

It is important to keep in mind the limitations of this study, including its retrospective nature, the absence of standardized diagnostic investigations, and the use of low-sensitivity bacteriologic diagnostic tests, the exclusion of patients not hospitalized, or who might have been discharged from hospital without any code for empyema or pleural effusion with drainage. However, the Med-Echo database includes all admissions in acute-care hospitals in Quebec, and children with complicated lower tract respiratory infections are usually referred to tertiary-care pediatric centers where appropriate imaging and investigations are usually done during admission.

In conclusion, we observed a significant increase of pleural empyemas in the pediatric population of the province of Quebec. No particular cause for the increase could be established. The high PPV of discharge diagnostic code in any position makes administrative databases a useful tool to rapidly and grossly evaluate the epidemiology of the disease. With new diagnostic molecular tests now available to identify pathogens in biologic samples [43], a prospective study relying on these technologies coupled with detailed systematic information on specific risk factors is necessary, to better understand and mitigate the increase in incidence.

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