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Should Empyema with or without Necrotizing Pneumonia in Children Be Managed Differently?

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Abstract

Background: Necrotizing pneumonia (NP) is an increasing lung infection mostly associated with pleural empyema. **Objectives:** We aimed to compare children with empyema with and without concomitant NP, in terms of risk factors, management and outcome. **Methods:** We retrospectively included children hospitalized between 2005-2014 with empyema to whom a computed tomography was performed. We recorded patient characteristics, clinical, biological (blood and pleural fluid) and radiological findings, medical and surgical treatments, and clinical, radiological and functional follow-up. **Results:** 35 children with empyema were included, including 25 with a concomitant NP. Patients with or without NP were undistinguishable, in terms of characteristics, symptoms at admission or detected pathogens. Pleural leucocytes were significantly higher in the empyema group (p = 0.0002) as pleural LDH (p = 0.002), and pleural/blood LDH ratio (p = 0.0005). Medical and surgical managements were similar between both groups. Complications occurred in 1/10 children with empyema alone (pneumatocele) and 5/25 with concomitant NP (bronchopleural fistula (n = 3), lobectomy, pneumothorax). The hospital length of stay and delay for chest X-ray normalization were similar in both groups. **Conclusion:** Except for minor biological parameters, the presence of concomitant NP in case of empyema does not change the presentation, clinical features, management and outcome, suggesting that the presence of additional NP to empyema should not be managed differently. Therefore, in case of empyema with suspected concomitant NP, chest CT should probably be restricted to abnormal worsening or when mandatory for surgical treatment.

1. Introduction

Necrotizing pneumonia (NP) is a fairly rare but increasing lung infection mostly associated with pleural empyema (94% - 97%) [1]-[6].

NP is characterized by a loss of architecture and pulmonary tissue associated with the formation of thin-walled cavities full of air or liquid without enhancing border [7]. The physiopathology of NP is not yet completely understood, as the reason for its increasing incidence. Some authors argue a selection of more virulent serotypes of *Streptococcus pneumoniae* [1] [2] [4] [8] [9] [10], or a better identification of NP considering the easier resort to chest computed tomography (CT) [1] [11] [12]. Others theorized that a raising virulence of *Staphylococcus aureus*, especially when producing Panton-Valentine leukocidin (PVL) known to induce cellular lysis, is responsible for the increasing incidence of NP [13] [14]. But this last hypothesis seems doubtful as *Staphylococcus aureus* is implicated in only 2% to 32% of empyema [3] [4] [6] [12] [15].

There are only few studies focusing on empyema with NP that have been published [2] [5] [16] [17] [18] [19]. Macedo *et al.* reported, among patients with empyema, prolonged duration of pleural drainage and hospital length of stay in case of concomitant NP [18], while other authors found no difference [17] [19]. In 2012, the American Pediatric Surgical Association (APSA) published a review on the management of empyema and pointed out, that in case of NP, "there are no published data informing the choice of treatment for this specific condition" [16].

These discordant results regarding empyema with NP led us to compare risk factors, management and outcomes of children with pleural empyema with or without concomitant NP.

2. Patients and Methods

We performed a retrospective study at the University Children's Hospital of Geneva (Switzerland). From the institutional diagnosis registration (CIM10), we selected all children below 16-years old hospitalized between the 1st January 2005 and the 31st December 2014 with the diagnosis of pleural effusion and an available chest CT. All medical records were reviewed by two physicians (AS.K and B.S), in order to only include patients with a confirmed diagnosis of empyema, based on Hardie's criteria [20]. Diagnosis of concomitant NP was confirmed by two certified paediatric radiologists (A.M, K.A) who blindly reviewed all CT, according to published criteria of Donelly *et al.* [21]. CT was mostly performed because of clinical worsening, otherwise because of suspicion of parenchymal necrosis on standard chest X-ray or on surgeon request before procedures.

Among 102 selected children with pleural effusion during the inclusion period to whom a CT was performed, we finally included 35 patients with a confirmed empyema: 25 patients had a concomitant NP (empyema + NP group) and 10 patients had empyema alone (empyema group), as illustrated in the CT images in Figure 1.

We excluded all patients from whom the CT was missing in order to avoid any undiagnosed NP in the empyema group. The design of the study and the flowchart of patient inclusions are summarized in Figure 2.

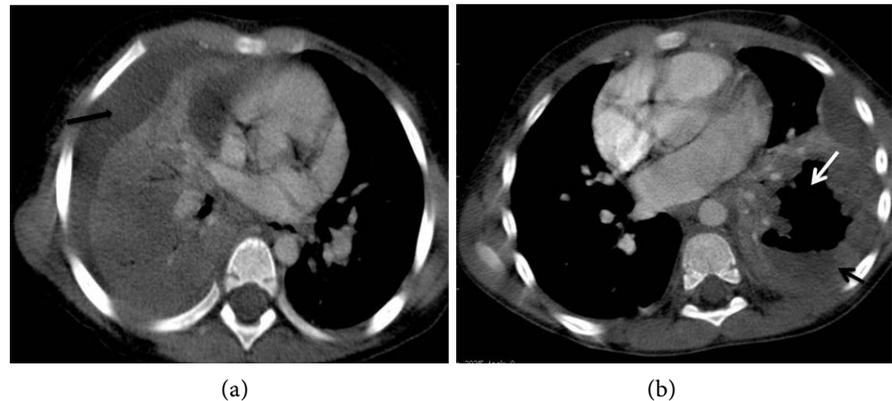(a)   (b)

Figure 1. Contrast enhanced axial chest CT images. Left panel (a): pleural effusion (black arrow) and enhancing lung consolidation with no sign of cavitation. Right panel (b): pleural effusion (black arrow) and adjacent non-enhancing parenchyma with a large cavitary necrosis suggesting necrotizing pneumonia (white arrow).
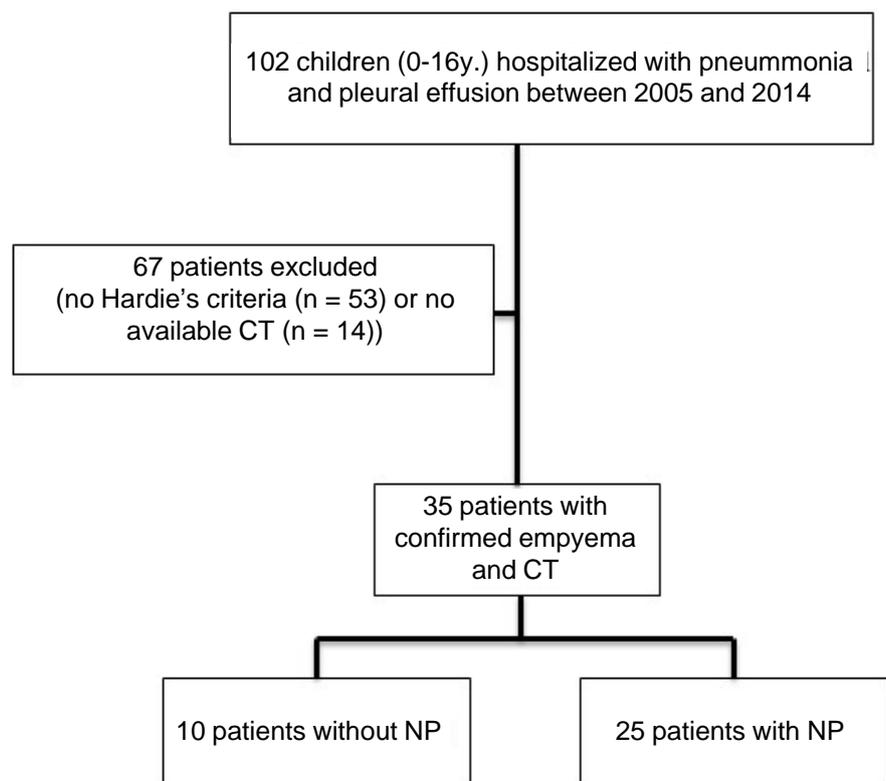

Figure 2. Design study. NP: Necrotizing pneumonia, CT: computed tomography.

Collected data were age, gender, past medical history, underlying disease, clinical features at admission, biological findings (blood and pleura), chest imaging (X-ray and CT), pathogens, medical and surgical management, and outcomes (oxygenotherapy, chest tube duration, surgery, fever duration, Intensive Care Unit (ICU) and hospital length of stay, radiological (at 6 and 12 months) and functional follow-up).

No supplemental examination and visit, blood test, CT or lung function test, were required for this study. The Ethical Committee of the University Hospital of Geneva approved this study on 04th July 2012 (CER12-116R).

Results were expressed as median [range] or number (percentage) unless indicated. To compare patients presenting empyema with or without concomitant NP, Fisher's test was applied to categorical factors and Mann-Whitney U test to continuous factors. Confidence interval was 95% and p-value < 0.05 was considered significant. The time to X-ray normalization was assessed using Kaplan-Meier estimate of survival for interval-censored data since the date of normalization likely occurred between two visits [22].

3. Results

Patient characteristics and clinical features at admission are summarized in Table 1; there was no difference between the two groups. Past pulmonary medical history was only found in four patients from the empyema + NP group, including bacterial pneumonia (n = 1) and viral bronchitis or bronchiolitis (n = 3). Besides pulmonary diagnoses, one patient from the empyema group presented an hydronephrosis. The median delay time from first symptoms to admission was five days in both groups (from 1 to 5 days in the empyema group and from 0 to 9 days in the empyema + NP group).

Except one patient in the empyema + NP group, all patients underwent blood sample at admission and pleural fluid analysis. The pleural fluid was obtained by thoracocentesis (3 patients in the empyema group and 7 in the empyema + NP group), or during surgical insertion of a chest tube. The results of blood and pleural fluid tests are presented in Table 2. Regarding the blood tests at admission, including white cell count and inflammatory markers such as C reactive protein, we found no difference between the two groups. In the pleural fluid, white blood cells (WBC) and lactate dehydrogenase (LDH) were significantly lower in the empyema + NP group as well as pleura/blood LDH ratio. The pathogens were identified in the pleural fluid for all patients except one in the empyema + NP group (identified in the broncho-alveolar lavage). The involved micro-organisms are described in Table 2 and no difference was found between both groups regarding the proportion or type of pathogens, or the way to identify them.

The medical and surgical management, summarized in Table 3, was not different between the two groups, except the fibrinolytic agents more prescribed in the empyema group (p = 0.047). The initial intravenous antibiotherapy was modified for three patients in the empyema group and seven patients in the

Table 1. Patient characteristics and clinical features at admission. Data are expressed as median [range] or n (%).

	Empyema n = 10	Empyema + NP n = 25	p-value
Age (year)	3.0 [0.6 to 8.1]	3.6 [0.8 to 10.2]	0.99
Gender female	2/10 (20.0%)	11/25 (44.0%)	0.26
Weight (standard deviation)	0.25 [−1.50 to 3.00]	0.25 [−1.50 to 3.00]	0.59
Past pulmonary medical history	0 (0.0%)	4/25 (16.0%)	0.30
Concomitant extra-pulmonary infection	3/10 (30.0%)	6/25 (24.0%)	0.69
Anti-pneumococcal vaccine pneumocoquevaccine = yes = 1, 2, 3	3/10 (30.0%)	11/21 (52.4%)	0.28
Symptoms			
Fever	9/9 (100.0%)	24/25 (96.0%)	1
Cough	5/10 (50.0%)	20/25 (80.0%)	0.11
Dyspnea	2/10 (20.0%)	5/25 (20.0%)	1
Lethargy	9/10 (90.0%)	22/25 (88.0%)	1
Chest pain	3/10 (30.0%)	2/25 (8.0%)	0.13
Abdominal pain	4/10 (40.0%)	10/25 (40.0%)	1
Clinical features			
Tachycardia	6/9 (66.7%)	15/23 (65.2%)	1
Tachypnea	10/10 (100.0%)	23/24 (95.8%)	1
Hypoventilation	7/10 (70.0%)	20/25 (80.0%)	0.66
Rales	2/10 (20.0%)	8/25 (32.0%)	0.69
Tubular sounds	4/10 (40.0%)	7/25 (28.0%)	0.69
Wheezing	2/10 (20.0%)	1/25 (4.0%)	0.19
$SpO_2 < 92\%$	1/10 (10.0%)	2/19 (10.6%)	1

Table 2. Results of blood and pleural investigations. Data are expressed as median [range] or n (%).

	Empyema n = 10	Empyema + NP n = 25	p-value
Blood at admisssion			
Hemoglobin (g/l)	104 [100 to 130]	102 [79 to 123]	0.13
Platelets (G/l)	328 [237 to 629]	266 [143 to 999]	0.08
WBC (G/l)	18.3 [10.0 to 29.9]	13.2 [0.6 to 33.8]	0.22
WBC > 15 G/l	6/9 (66.7%)	10/24 (41.7%)	0.26
CRP (mg/l)	193 [138 to 200]	200 [60 to 200]	0.41
Pleural fluid			
WBC (G/l)	66.5 [12.1 to 137.6]	1.1 [0.03 to 72.0]	**0.0002**
pH	6.8 [6.8 to 7.0]	7.5 [6.4 to 8.0]	0.07
LDH (U/l)	18040 [7128 to 31416]	3138 [586 to 39525]	**0.002**
LDH pleura/blood ratio	63.0 [15.1 to 101.3]	4.8 [2.6 to 19.5]	**0.0005**
Glucose (mmol/l)	0.8 [0.3 to 1.1]	1.8 [0.3 to 4.8]	0.08
Pathogens	9/10	23/25	
Streptococcus pneumoniae	7/9 (77.8%)	22/23 (95.7%)	0.18
Other Streptococcus	1/9 (11.1%)	1/23 (4.3%)	
*Staphylococcus aureus**	1/9 (11.1%)	0/0 (0.0%)	

WBC: White blood cell count, CRP: C-reactive protein, LDH: lactate dehydrogenase, *: including 1 Methicillin Resistant Staphylococcus aureus.

Table 3. Management and outcomes. Data are expressed as median [range] or n (%).

	Empyema n = 10	Empyema + NP n = 25	p-value
Medical and surgical management			
IV β-lactamines	10/10 (100.0%)	25/25 (100.0%)	1
Duration (d)	12.5 [8 to 22]	12 [6 to 56]	0.69
Oral β-lactamines after IV treatment	10/10 (100.0%)	22/24 (91.7%)	1
Duration (d)	16 [7 to 30]	21 [9 to 45]	0.15
O_2 requirement	7/10 (70.0%)	10/25 (40.0%)	0.15
Duration (d)	10 [2 to 10]	8 [2 to 40]	0.59
Chest tube	10/10 (100.0%)	24/25 (96.0%)	1.00
Insertion delay after admission (d)	2 [1 to 15]	2 [0 to 8]	0.64
Duration (d)	7 [3 to 12]	5 [2 to 128]	0.67
Intrapleural urokinase	4/5 (80.0%)	3/13 (23.1%)	**0.047**
VATS	8/10 (80.0%)	21/25 (84.0%)	1.000
Outcomes			
Fever duration (d)	15 [12 to 28]	14 [9 to 36]	0.73
Fever duration after admission (d)	10 [3 to 25]	9 [3 to 30]	0.74
ICU admission	6/10 (60.0%)	12/25 (48.0%)	0.71
ICU length of stay (d)	3 [1 to 5]	2 [1 to 33]	0.92
Hospital length of stay (d)	15 [9 to 42]	15 [8 to 140]	0.71
Delay of X-ray normalization (d)	288	126	0.28

IV: intravenous, d: day, VATS: video-assisted thoracoscopic surgery, ICU: intensive Care Unit.

empyema + NP group, according to the anti-microbial susceptibility testing or in order to treat a secondary infection.

The outcomes are detailed in Table 3. We did not observe any difference between the two groups regarding the fever duration and the ICU or hospital length of stay. Complications occurred in seven patients, but only one (10%) in the empyema group, as a secondary pneumatocele requiring thoracoscopy and two chest tubes for 10 days. In the empyema + NP group, complications occurred in five (20%) patients: one patient presented a pneumothorax during the chest tube removal, one patient required a right superior lobectomy for persistent compressive pneumothorax possibly related to an unconfirmed broncho-pleural fistula, and three other patients developed a broncho-pleural fistula. The first one of these last three patients underwent a thoracotomy 89 days after admission and multiple chest tube insertions for a total of 128 days. The second one required two chest tubes for 20 and 26 days. The last one required a chest tube for 19 days. Furthermore, one patient in the empyema + NP group presented a pneumococcal septic shock. No statistical comparison was feasible, considering the small number of patients with complication. Radiological follow-up was available in all patients, and delay of chest X-ray normalization was not different between both groups (p = 0.28) (Table 3 and Figure 3).
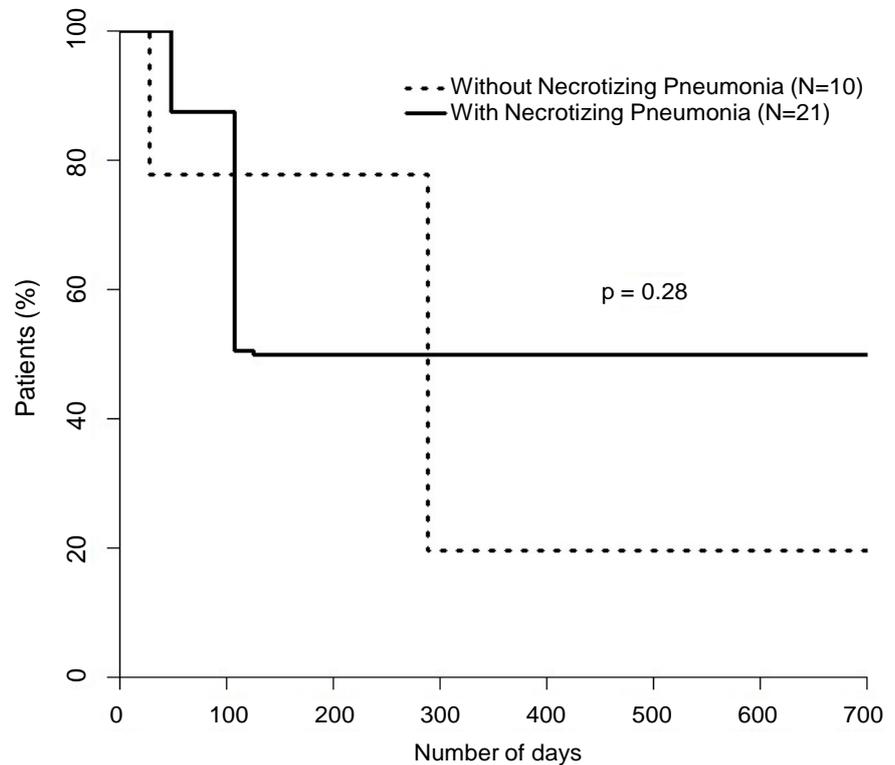
Figure 3. Kaplan-Meier curves of the delay of chest X-ray normalization in the empyema group (dashed line) and the empyema + NP group (solid line) (p = 0.28).

Among the seven patients with complications, the last available X-ray was still abnormal for two of them from the empyema + NP group: the patient requiring a lobectomy (radiological follow-up at 505 days showed a condensation of the right apex) and the patient requiring a thoracotomy (radiological follow-up at 488 days showed blebs in the right apex). Pulmonary function tests were available in five patients from the empyema group and for three patients from the empyema + NP-group, performed between 1 and 12 months after discharge, and were normal.

4. Discussion

This paediatric retrospective study aims to evaluate the morbidity effect of concomitant NP in case of empyema. Interestingly, we found similar clinical and biological features, pathogens, management and outcomes in both groups, except for minor biologic parameters in pleural fluid.

Several studies showed that children developing NP were previously healthy [5] [9] [15] [23], and reported no difference in terms of comorbidities and age between patients with simple or complicated pneumonia, including NP [1] [8] [9] [23] [24]. Our results are in accordance with the study of Macedo *et al.* reporting no difference in age and gender between patients presenting an empyema with or without concomitant NP [18].

Concerning the biological findings, although we did not find any difference in blood inflammatory parameters, WBC tended to be more elevated in the em-

pyema group as published by Wexler *et al.* [23]. Ulloa-Gutierrez reported a very high level of LDH in patients with pneumococcal empyema with concomitant NP, but no value or comparison was available [25]. To our knowledge, no previous study compared pleural findings between patients with empyema associated or not with NP. According to the Light's criteria that differentiate exudative from transudative pleural effusion with three severity stages of inflammation [26] [27], the pleural fluid showed a lower inflammatory level in case of concomitant NP group. These findings concurred with the hypothesis that NP is probably not due to an increased inflammatory process, but is mainly due to an inadequate local leukocyte response, accompanied by vasculitis, gangrene or venous thrombosis [28] [29].

Our results agree with the published data, reporting an increasing predominance of *Streptococcus pneumoniae* in complicated pneumonia [9] [30]. *Staphylococcus aureus* infection is reported in 2% of adult and pediatric community-acquired pneumonia [3] [4] [12], but Lemaitre *et al.* identified *Staphylococcus aureus* in 32% of NP in a pediatric cohort, and all were PVL producers [15]. Against all odds, *Staphylococcus aureus* was never evidenced in the empyema + NP group, and only in one patient from the empyema group. Since the serotype of *Streptococcus pneumoniae* was not available in most of our patients, we could not evaluate the potential role of specific serotypes, but we did not observe any difference in anti-pneumococcal vaccination (Prevenar 7®) between the two groups.

The Pediatric Infectious Diseases Society and the Infectious Diseases Society of America recommend to treat hospitalized children with community-acquired pneumonia with an anti-staphylococcal antibiotic in case of clinical, biologic or radiologic suspicion [31]. Moreover, the British Thoracic Society guidelines on pleural infection in children as well as a recent review on pediatric NP recommend to consider *Staphylococcus aureus* in the treatment strategy [3] [32]. According to our microbiological findings and the limited role of Staphylococcus aureus in complicated pneumonia in previous studies [4] [6], we might reconsider at least in Switzerland to systematically include an anti-staphylococcal treatment as first choice regimen in case of empyema even with concomitant NP. We did not find any difference in terms of antibiotherapy, oxygenotherapy, chest tube requirement/duration or VATS. To our knowledge, the only available recommendations on empyema treatment in children have been published by the British Thoracic Society in 2005 and the Thoracic Society of Australia and New-Zealand in 2011, but without any special focus on empyema associated with NP [32] [33]. Recently the APSA pointed out the lack of data on paediatric empyema management, and recommended caution in case of NP if fibrinolysis/VATS is necessary due to concomitant pleural space disease [16]. Our management was conducted in agreement with the available recommendations, as medical management was our first line of treatment. Fibrinolytic agents have been prescribed more easily in case of empyema without NP, as this treatment is classically used with caution if not avoided in case of NP. However, in this study,

a large majority of patients underwent a VATS in a second line after failure of medical management, as recommended by the APSA, and in the same proportion in the two groups [16]. We did not observe any difference in the frequency of VATS between the 2005-2009 and the 2009-2013 periods (data not shown). This is surprising, given that VATS was widely put forward in the early 2000's as a treatment of choice for empyema, but was progressively challenged by the chemical debridement, the fibrinolytic agents and a conservative treatment. Paediatric studies showed contradictory conclusion regarding the surgery (including chest tube, VATS and thoracotomy): one study suggested that surgery was not better than thoracocentesis alone [12], and another supported early VATS as a valuable option to avoid prolonged recovery and late thoracotomy compared to conservative treatment [18]. Since 2008, three randomized studies compared the effectiveness of fibrinolytic agents versus VATS in childhood empyema [34] [35] [36], two of them including also children with concomitant NP [35] [36]. All of them concluded that the two treatments are equivalent and that fibrinolytic treatment is less invasiveness and expensive compared to VATS. Finally, during the last three years, we dramatically decreased the number of VATS in our institution.

Although it has been widely published that complicated pneumonia (e.g. empyema), compared with simple pneumonia, is associated to prolonged hospital length of stay [1] [8] [23], higher rate of complications [1] [6] [8] and delayed clinical and radiological recovery [1] [12] [21], the results regarding the outcomes of empyema with concomitant NP are very few and controversial. One retrospective study specifically reported that empyema associated with NP required a longer hospitalisation than empyema without NP [18], when the sole prospective study showed no difference in hospital length of stay [17], in line with our data. We could not complete the functional follow-up due to the small number of patients, but we found no difference in radiological follow-up between both groups. Krenke *et al.* showed a complete or almost complete radiological recovery at 6 months post NP [5]. Despite pleural scarring in lung MRI several years after, Honkinen *et al.* showed a good long-term outcome in case of empyema with rare functional alteration [37].

Chest CT is the accepted gold standard to confirm NP [1] [11] [12]. CT allows earlier and more accurate diagnosis of NP and detects more precisely the parenchymal abnormalities, making CT superior to X-ray or ultra-sound (US) in identifying parenchymal lung diseases [38] [39] [40] [41]. The role of CT in case of empyema has been questioned by Jaffe *et al.*, as these additional findings do not change the management or the outcome of the patient. Thus, the authors concluded that CT should not be performed as a routine investigation for patients with empyema [17]. Used since decades for pleural investigations, US are progressively used for parenchymal analysis given his high accuracy for detecting consolidation and interstitial lung disease. In complicated pneumonia, Kurian *et al.* showed that US was as effective as CT to evaluate pleural fluid, as well as the underlying parenchyma [42]. Other authors showed a high correlation

between US and CT for NP diagnosis and recommended routine US in case of severe pneumonia [43]. Given the widely recognized radiation-induced risk of malignancy in children [44], it is of importance to assess and clearly confirm the usefulness of CT. Since we found no relevant difference between the 2 groups, we question the usefulness of confirming, by an irradiating chest CT, a suspected concomitant NP in case of empyema. Therefore, we suggest that CT might be restricted to abnormal worsening of pleural empyema or when mandatory for surgical treatment, until it could be eventually replace by US in the future.

We are aware that this study presents several limitations. We included a limited number of patients due to the mono-centric and retrospective nature of the study. In order to detect a difference of hospital length of stay, 89 patients per group would have been necessary to obtain a power of 80% with an alpha risk of 0.05, but empyema associated to NP is a rare pathology and no one of the few published studies was able to gather data from a suitable number of patients. Due to the necessity to confirm/infirm NP by a chest CT, considering the poor accuracy of X-ray for detecting NP [17], we clearly selected particularly severe patients especially in our empyema group. This recruitment bias could explain the high proportion of chest tube insertion, fibrinolytic treatment and VATS in this latter group. Furthermore, we did not include a severity scoring of the disease, as the extend of the necrotizing zones, in order to compare patients with extensive necrotizing pneumoniae or with only a small area of necrotizing pneumonia. Finally, we were unable to collect functional follow-up. Indeed, pulmonary function tests after complete recovery would be interesting to study the potential long-term sequela.

5. Conclusion

As a conclusion, this paediatric survey is the first study comparing as many parameters in empyema associated or not with NP, and showing no difference regarding risk factors, clinical and biological features, pathogens, management and outcome. Empyema with concomitant NP is rarely due to *Staphylococcus aureus*, leading to recommend the same empiric antibiotic therapy as empyema without NP. Finally, in case of empyema with suspected concomitant NP, chest CT should probably be restricted to abnormal worsening or when mandatory for surgical treatment.

Acknowledgements

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