Clinico-epidemiological profile and risk factors associated with failure of conservative therapy in pediatric empyema patients

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ABSTRACT

Objective: The objective is to study the clinico-epidemiological profile and risk factors associated with failure of conservative therapy in pediatric empyema patients and to correlate the Light's criteria in the same. **Materials and Methods:** A hospital-based prospective observational study was performed in the pediatric department of a tertiary care hospital, New Delhi. A total of 74 children of ≤12 years of age having either macroscopic frank pus in pleural tap or a positive Gram-stain or positive culture in pleural fluid were enrolled in the study. Those empyema patients who fail to improve with antibiotics and chest tube drainage after 7–14 days (4 weeks for *Staphylococcus aureus* and 6–12 weeks for anaerobic organisms, respectively) or develop some complications in the mean time were considered as a failure of therapy. **Results:** Head nodding, lethargy and inability to feed/drink, prior antibiotic therapy, duration of illness (>7 days) before presenting to the hospital, and growth on the cultures were the main factors associated with the failure of conservative therapy. *S. aureus* is the most common organism causing empyema. Considering Light's criteria, significant results were obtained and almost all the enrolled empyema patients found to have exudative pleural fluid. In the study, failure of conservative therapy occurred in 27.03%, prolonged hospitalization was seen among 48.65 % children, 28.38% needed change in antibiotics, and 1.35% children expired. **Conclusion:** History of prior antibiotic therapy, long duration of illness, and clinical features at admission along with the microorganism involved affect the conservative therapy response and may predispose to complications. Light's criteria were very well validated in the study for its use in pediatric population.

Key words: *Complications, Empyema, Failure, Pediatric*

Empyema thoracis is defined as a collection of pus in the pleural space usually in the context of pneumonia and is a major global health problem causing morbidity among children in the most developing countries. The mortality rate from empyema remains high ranging between 6% and 24% [1-4]. The incidence of pediatric empyema is increasing substantially over the past few years in the developing countries, like India, and lack of consensus on the proper management of empyema has generated a renewed interest in the research of the subject.

There are a number of epidemiological and clinical factors that determine the severity of the illness and show association with the failure of conservative therapy such as prior antibiotic therapy, duration of illness, head nodding, lethargy, and refusal to feed [5-8]. These factors can predict the progression and requirement of aggressive treatment during the course. The causative organism of empyema is also important in determining the prognosis and response to treatment. *Staphylococcus aureus* is the most common organism in India causing empyema [9,10]. However, due to prior antibiotic use, cultures are sterile in 30–50% of the cases which make the isolation of causative organism difficult [11-13]. Approximately 60–80% of cases are recovered by conservative

treatment with antibiotics and chest tube drainage, but 11–17% of cases may require surgical interventions [1,14].

Light's criteria are used to classify the nature of the pleural fluid in adult pleural effusion patients, and there is a lack of studies in the paediatric population to prove its role [15]. Hence, we planned to study the clinico-epidemiological profile and risk factors associated with failure of conservative therapy in pediatric empyema patients and also to correlate the Light's criteria in the same population.

MATERIALS AND METHODS

The study was conducted in the department of pediatrics in a tertiary care hospital, New Delhi. It was a prospective observational study carried out from November 2014 to April 2016 after taking prior approval from the institutional ethics committee. The pediatric patients (≤12 years), who had either macroscopic frank pus in pleural tap or a positive gram stain or positive culture in pleural fluid, were admitted in pediatric wards and were included in the study. Cases with intercostal drainage (ICD) *in situ* from outside at the time of admission, transudative/tubercular pleural

effusion, patients with congenital malformations, and patients on cardiopulmonary resuscitation at the time of admission were excluded from the study. Children who fulfill the inclusion criteria were taken for the study after taking informed consent from the parents/guardian.

A pre-designed proforma was used to record the details of personal and demographic profile, clinical presentation, underlying disease, laboratory investigations, treatment, and course in hospital and final outcome. A detailed examination was done at the first contact with the patients. All relevant investigation reports were noted if done within 24 h of admission, and these include complete blood count, chest X-ray, and pleural fluid culture. The treatment given and progress notes were recorded at 48 h, 7th day, or as required. Patients were observed until the day of discharge or death.

In the mean time, those empyema patients who failed to improve with antibiotics and chest tube drainage for 7–14 days (4 weeks for *S. aureus* and 6–12 weeks for anaerobic organism respectively) or developed some complications (e.g. pneumothorax, empyema developing in contralateral side, pericardial effusion, bronchopleural fistula, or death) were taken as the cases who failed conservative therapy [16]. Light *et al.* used a pleural fluid lactate dehydrogenase (LDH) (IU/L) to serum LDH ratio >0.6 (or levels of pleural fluid LDH >2/3 of upper range of serum LDH) or pleural fluid proteins (g/dl) to serum proteins ratio more than 0.5 to define exudative pleural effusion [15].

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean±standard deviation and median. Normality of data was tested by Kolmogorov–Smirnov test and non-parametric test was used when the normality was rejected.

RESULTS

Of 74 patients enrolled as per the inclusion criteria, 39 (52.70%) were male in which 15 (20.27%) patients were below 1 year of age and 51 (68.92%) were between 1 and 5 years. A total of 36 (48.65%) children stayed in hospital for more than 14 days, which also includes *Staphylococcus* and *Pseudomonas* cases, who normally require antibiotics for longer duration as mentioned before, 21 (28.38%) needed change in antibiotics, and 20 (27.03%) cases who failed to conservative therapy (including complications such as pneumothorax in 7 (35%) cases, bilateral empyema in 4 (20%) cases, pericardial effusion in 1 (5%) case, and bronchopleural fistula in 1 (5%) case and 1 (1.35%) patient) expired.

Sociodemographic characteristics such as patient's age, parental age and education, overcrowding at home, immunization, and breastfeeding were not significantly associated with the development of complications (p>0.05). Males were more commonly affected with empyema as compared to females; however, no prediction for complications can be made based on the gender. In this study, all of the above-mentioned epidemiological factors were not found associated with the failure of conservative therapy.

With respect to clinical features, significant association of complications was found with head nodding, lethargy, and inability to intake orally (p<0.05). Other significant variables were duration of illness before presenting to the hospital and history of prior antibiotic therapy (p<0.05) (Table 1). Those cases, who had longer duration of illness (>7 days) or who received antibiotic therapy before admission in the hospital, had more chances of long hospital stay, upgradation of antibiotics, and to develop complications. Other clinical features such as wheezing, cyanosis, lymphadenopathy, edema, icterus, clubbing, and pallor were not significantly associated with failure of therapy (p>0.05).

Laboratory parameters such as hemoglobin level or total leukocytes count had no association with the outcome. Important laboratory variables were the blood and pleural fluid cultures. The organism isolated found to be deciding the duration of hospital stay, need of changing antibiotics, longer duration of antibiotics or ICD, and development of complications. Most of the samples were sterile but, among the samples which grew organism, *S. aureus* was the most common organism causing empyema followed by alpha hemolytic *Streptococci*, methicillin-resistant *S. aureus* (MRSA), and *Pseudomonas* (Table 2).

To look for the applicability of Light's criteria in the pediatric population, we studied and analyzed the levels of serum proteins, serum LDH, pleural fluid proteins, and pleural fluid LDH level. On further evaluating these values as per Light's criteria, significant results were obtained in which almost all the enrolled empyema patients were found to have exudative pleural fluid considering either the proteins or LDH criteria. However, no significance was seen in view of predicting failure of conservative therapy using these criteria. In the presence of macroscopic frank pus, pleural fluid level of LDH was found to be present in thousands, i.e., several times higher than serum LDH levels.

Table 1: Association between clinical characteristics of patients and complications of empyema

Characteristics	Complications N (%)		p value
	Yes	**No**	
Head nodding			
Yes	14 (40.0)	21 (60.0)	0.017
No	6 (15.38)	33 (84.62)	
Inability to feed/drink			
Yes	17 (39.53)	26 (60.47)	0.007
No	3 (9.68)	28 (90.32)	
Lethargy			
Yes	16 (40.0)	24 (60.0)	0.008
No	4 (11.76)	30 (88.24)	
Duration of illness			
Yes	14 (38.89)	22 (61.11)	0.025
No	6 (15.79)	32 (84.21)	
Prior antibiotic therapy			
Yes	15 (51.72)	14 (48.28)	0.0001
No	5 (11.11)	40 (88.89)	

Table 2: Association between laboratory findings of patients and complications of empyema

Characteristics	Complications N (%)		p value
	Yes	No	
Pleural fluid culture			
Alpha-hemolytic streptococci	2 (16.67)	10 (83.33)	0.561
MRSA	3 (50.00)	3 (50.00)	
Staphylococcus aureus	5 (29.41)	12 (70.59)	
Pseudomonas	1 (50.00)	1 (50.00)	
Sterile	9 (24.32)	28 (75.68)	
Blood culture			
Alpha hemolytic streptococci	1 (100.0)	0 (0.00))	0.251
Staphylococcus aureus	2 (28.57)	5 (71.43)	
Sterile	17 (25.76)	49 (74.24)	
Light's criteria on proteins			
No	4 (26.67)	11 (73.33)	1.000
Yes	16 (27.12)	43 (72.88)	
Light's criteria on LDH			
No	1 (50.00)	1 (50.00)	0.470
Yes	19 (26.39)	53 (73.61)	

LDH: Lactate dehydrogenase

DISCUSSION

This was a prospective observational study where we observed the frequency of failure of conservative therapy or development of the complications in the meantime, i.e., during the hospital stay and the risk factors associated with it, by analyzing various epidemiological, clinical, and laboratory parameters as mentioned in the result section. The results obtained were significant for some variables such as head nodding, lethargy, duration of illness, and inability to feed and drink in the clinical section.

Prior antibiotic therapy is an independent risk factor for the failure of therapy or occurrence of complications. Shah *et al.*, in Hyderabad, did a similar study where they found a significant correlation between prior antibiotic therapy and risk of developing more advanced stage of empyema [5]. However, it is mainly concerned with the stage of empyema as compared to our study where we used the variable to predict the failure of conservative therapy. In our study, prior antibiotic therapy (irrational use of antibiotics before admission) is a well-established risk factor for the failure of first-line antibiotics in empyema (p=0.0001). Of 74 total cases, 29 cases (39.19%) had a history of prior antibiotic therapy in which 15 cases (51.72%) developed complications during the hospital stay.

Considering epidemiological variables, the findings of this study were not significantly associated with complications which are somehow similar to the results of Elemraid *et al.* where factors such as age, sex, maternal age, parental smoking, level of socioeconomic status, and household characteristics were not significantly associated with the development of empyema [17]. Tiewsoh *et al.* noted that head nodding is associated with mortality in children with severe pneumonia, and our study had similar findings; 35 cases which presented with head nodding, out of them, 40% of cases (14 cases) failed

to respond conservatively and 60% (21 cases) of the cases responded well (p=0.017) indicating it to be an important factor of outcome. Other clinical parameters, which had a significant association with the failure of conservative therapy, were lethargy and inability to feed/drink. Of 40 (100%) total cases with lethargy, 16 cases (40%) were associated with complications compared to 24 (60%) remaining cases with no association (p = 0.008). Inability to feed/drink was significantly associated with failure of conservative therapy where we found that, of 43 total cases of inability to take orally, 17 cases (39.53%) showed complications and 26 cases (60.47%) showed no complications (p=0.007).

As described in the studies by Shah *et al.,* Narayanappa *et al.*, and Kumar *et al.*, *S. aureus* is the most common organism isolated in empyema in the developing countries [5,9,10]. In our study, based on the culture pattern, response to antibiotic therapy and ICD tube was observed in the form of the duration of ICD requirement, hospital stay, the need to upgrade antibiotics, and the occurrence of complications. In the cases studied (74 cases), 7 cases (4 non-staphylococcal cases and 3 MRSA cases) required prolonged ICD/intravenous antibiotics (i.e., ICD more than 2 weeks in non-staphylococcal cases and more than 4 weeks in staphylococcal cases). All of these 7 cases ultimately required decortications as video-assisted thoracoscopic surgery (VATS) was not performed. Need for the upgradation of antibiotics was also found significantly associated with the organism isolated in the pleural fluid cultures (p=0.010) while blood cultures had no significant association with the hospital stay.

As per the study by Light *et al.*, the criteria were applied on the patients enrolled in our study [15]. In a total of 74 cases of our study, 72 cases (97.30%) followed fluid LDH criteria and 59 cases (79.73%) followed fluid proteins criteria. However, their association with the failure of conservative therapy was not significant as per the study (p=0.470 for LDH and p=1.000 for proteins). As per the study by Iqbal *et al.*, LDH was most sensitive while white blood cell (WBC) >1000/mm^3 was the most specific of all the criteria looked at [18]. The overall accuracy was the highest for Light's criteria of isolated LDH >200 IU/L followed by pleural fluid protein, WBC count, and red blood cell count.

In our study, another important point to ponder was the very high values of pleural fluid LDH in the presence of macroscopic frank pus which was several times higher than serum LDH levels (as one of the Light's criteria is to have pleural fluid LDH >2/3 of the upper limit of serum LDH [15]). However, looking at the trend of Light's criteria in this study, we can conclude it to be applicable on the paediatric population as well and consider both the criteria (LDH and proteins) almost all the enrolled patients with empyema followed Light's criteria.

Strength of the study is its prospective design, and no such prior study as per knowledge and evaluation of Light's criteria was performed earlier. Limitations of the study were the small sample size and reluctance to use VATS in complicated cases.

CONCLUSIONS

In our study, cases with a history of prior antibiotic therapy and long duration of illness before hospital admission were prone to conservative therapy failure. The clinical factors which significantly predict the failure of therapy were head nodding, lethargy, and inability to feed/drink. *S. aureus* was the most common cause of empyema, whereas the duration of hospital stay and need to upgrade antibiotics depend on the invading organism. Light's criteria were very well validated in the study for its use in pediatric population.

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