Pleural Parapneumonic Spill in Pediatrics

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Abstract

The special idiosyncrasies of children and their particular physiology force them to think of them as an independent entity and different from adults, so we need specific paediatric clinical guidelines and not adapt adult guidelines to the use of children. In order to manage the parapneumonic pleural effusion, these guidelines have been lacking due to the lack of controlled studies on this pathology and specifically aimed at children.

The child is not an adult in small, generally his health status is less conditioned to external factors which allows a morbidity and mortality much lower than that of the adult, so the prognosis is usually good and the recovery almost complete in the vast majority of cases.

In the last decade there has been a change in epidemiology increasing the prevalence of pneumonia and its complications, from an annual incidence of parapneumonic effusions of 18 to 42/100,000 children and even as a complication of admitted patients has increased from 0.76 to 3.3%, due to variations in responsible germs and their serotypes due to multiple factors such as antibiotic resistance, new vaccines that select serotypes, etc. Thus, it can be specified that pneumonia is one of the most frequent causes of pleural effusion in children, 40% of pneumonia requiring hospitalization in children develop pleural effusion and 0.6-2% of pneumonia are complicated by empyema.

The pleural fluid is considered an ultrafiltration of the plasma that originates in both pleural leaves with a volume that does not exceed 5 - 15 ml in the adult without pathology; its reabsorption is carried out lymphatically, mostly through the parietal pleura, with a daily exchange flow of only a few millilitres a day. Pleural effusion occurs when there is an imbalance between the production and reabsorption of pleural fluid.

Parapneumonic pleural effusions evolve naturally, without therapeutic intervention, from a phase of dry pleurisy where there is a local pleuritic reaction, to an exudative (spill) phase, through a fibropurulent phase to an organizational phase where fibroblasts grow in exudate from the parietal and visceral pleural surfaces transforming fibrin into a thick and non-elastic tissue, which can functionally translate into pulmonary restriction. Depending on the stage of the diagnosis, the therapeutic approach should be different.

Keywords: Pleural Parapneumonic; Pediatrics

Etiology

In children, the possibility of isolating the etiological cause starting from cultures of pleural fluid or blood cultures is 32%, and pleural fluid culture with a positive predictive index of 31% is more effective [1,2].

The most frequently isolated bacteria in pleural empyema in children are:

1. *Streptococcus pneumoniae*
2. *Staphylococcus aureus*
3. *Streptococcus pyogenes*

Less frequent are other infectious causes of pleural effusion such as viruses (adenovirus, influenza, parainfluenza), *Mycoplasma* and *Mycobacterium tuberculosis*. Gram-negative bacilli, anaerobes and polymicrobial infections are much less frequent than in adults.

And sometimes we can find negative results of the cultures, even in pneumococcal pneumonias. Paediatric series of pneumococcal pneumonia have been published with 29% of patients who had a pleural effusion corresponding to empyema in 13.8%; Pneumococcus was isolated in 67% of children in whom thoracentesis was performed. Although there may be regional differences, 91% of pneumococci are sensitive to penicillin and 75% to Erythromycin, indicating a low degree of resistance.

The frequency of different germs in all paediatric age groups is as follows: *Staphylococcus aureus* 35% (infants 50%), *Streptococcus pneumoniae* 35%, *Streptococcus* sp. 15%, *Haemophilus* 5%, *Pseudomonas* 5%, anaerobes 5%.

However, in recent years there has been an epidemiological change so that *Streptococcus pneumoniae* is becoming the most isolated germ being responsible for more than 70% of cases.

Clinical Study

Patients with parapneumonic effusions present a clinical symptomatology similar to those who have pneumonia without effusion: fever, tachypnea, chest pain, expectoration and leucocytosis. Series have been published that show an incidence of pleuritic pain of 59% in 113 patients without effusion and 64% in 90 patients with pleural effusion.

We should suspect the presence of a parapneumonic effusion if the fever is maintained for more than 48 hours after starting the antibiotic treatment of pneumonia, although the diagnosis of parapneumonic effusion should be established at the time of the initial examination and evaluation of the patient. If the amount of fluid accumulated is very important, dyspnoea on exertion or rest and signs of respiratory distress may appear [3].

Anaerobic bacterial infections are rare in children, but they have special characteristics. Most children have perverse infections, neurological problems or dysphagia. They are presented with more subacute symptoms, generally more than seven days old, with fever, weight loss, leucocytosis and slight anemia.

Up to 20% of empyema are complicated with necrotizing pneumonias, which was previously common for Staphylococcus Aureus is now being for pneumococcus, although it does not seem to correlate with any specific serotype [4-6].

Diagnosis

The study of the patient with suspected parapneumonic pleural effusion should include the following examinations: blood count, C-reactive protein, blood biochemistry including proteins and LDH, blood culture, tests for the detection of capsular polysaccharide antigen from *Streptococcus pneumoniae*, imaging techniques, thoracentesis and tuberculin test [7,8].

We should not delay the diagnosis and the start of treatment as this may condition the need to use surgical treatments later. One of the complementary tests that we must perform is a chest ultrasound in which if we observe the presence of loculations it will be a bad factor for the evolution of the disease.

Chest x-ray

Anteroposterior chest radiography in standing position is not the most sensitive technique for detecting small amounts of fluid. The occupation of the costophrenic sinus is the earliest sign of pleural effusion. If the effusion is moderate, the typical aspect of the effusion is

that of an opacification in the pulmonary base that occupies the costophrenic sinus and erases the diaphragm, concave, with its highest part in the lateral wall of the thorax for what is most needed 200 ml.

If the spill exceeds that amount then an increase in intercostal spaces will occur and the mediastinum will be displaced. If the patient is supine as usual in children, it can be manifested as an erasure of the costophrenic sinus, increased homogeneous density of the hemithorax with decreased visibility of the vasculature and appearance of a pleural line on the lateral part of the hemithorax.

The lateral chest x-ray helps distinguish if there is a significant amount of fluid. Lateral recumbent radiography on the affected side allows small amounts of effusion to be seen. If the distance between the inside of the chest wall and the lower area of the lung is less than 10 mm, it can be assumed that the effusion is not clinically significant and diagnostic thoracentesis is not indicated.

Thoracic ultrasound

Ultrasound is the most useful exploration in the management of parapneumonic pleural effusions since it allows to detect quantities of 10 ml and can even be helpful in different actions such as:

- Identify the appropriate point for a thoracentesis, or to place a thoracic drain.
- Identify images of partitions of the pleural fluid.
- Differentiate between pleural fluid and increased pleura thicknesses. Ultrasound can even see if a pleural effusion is free of echoes (anechoic), with free bands floating inside an anechoic pleural effusion, with simple linear septa and complex septations. The presence on ultrasound of echogenic bands or partitions corresponds to an exudate. The finding of an anechoic pleural effusion may correspond to a transudate or an exudate. In fact, the echogenic aspect of parapneumonic effusions is a key factor in deciding which treatment should be applied in a patient. In addition, it is possible to differentiate stages of the effusion that allow a drainage to be placed, avoiding subsequent surgical treatments and helping to make decisions regarding the use of fibrinolytic or the need for a thoracotomy.

Thoracic computed tomography (CT)

Free pleural fluid manifests on CT as a sickle-shaped opacity in the most declining and posterior parts of the thorax. The partitioned liquid collections are observed as fixed position lenticular opacities. CT is not indicated systematically in patients with suspected pleural disease. It does not allow to distinguish between transudates and empyema, and neither is it very accurate in defining the presence of partitions. CT is effective in demonstrating anomalies of the pulmonary parenchyma occasionally not visible on a simple chest x-ray due to the presence of pleural effusion. It is particularly useful in differentiating empyema with hydro-air levels from a lung abscess. CT also gives additional information about the effect of pleural effusion on the underlying lung, often observing atelectasis, especially of the lower lobe [9].

Thoracentesis

Diagnostic thoracentesis is indicated in parapneumonic pleural effusions to identify the etiologic agent and differentiate uncomplicated from complicated effusions, since neither the clinical nor the radiological study allows us.

Among the aspects to consider before proceeding to perform this technique, we must assess whether there are alterations of the coagulation and correct them, skin disease at the point of entry, or mechanical ventilation with very high pressures.

Diagnostic thoracentesis will only require a few cubic centimetres of pleural fluid. The profitability of the crops in case of suspected tuberculosis requires the extraction of a greater quantity of liquid. Sometimes the therapeutic thoracentesis will be required with the extraction of as much liquid as possible although we must consider the possibility that the withdrawal of a large amount of fluid, if the effusion is of long evolution, can cause unilateral pulmonary oedema and even hypotension, so it is sometimes necessary to remove enough fluid to improve dyspnoea without emptying the spill completely, however if the spill is purulent, we should remove as much as possible

using if temporary drainage is necessary except in cases of tuberculous empyema because it can increase the risk of bacterial spread and worsen the evolution of the disease [10].

For the study and differential diagnosis of a parapneumonic effusion, the following studies are advised: Biochemistry: pH, glucose, LDH, proteins, cell count and formula, and assess ADA, amylase, cholesterol and triglycerides. Microbiology: Gram and Ziehl stains, Aerobic, anaerobic, Lowenstein and fungal cultures.

Parapneumonic effusions are exudates

The differential diagnosis of pleural exudate is extensive. It is caused by an increase in capillary permeability caused by infection, neoplasia, collagenous, abdominal involvement or drugs; In addition to other causes such as trauma, arrival of transdiaphragmatic fluid, esophageal lesions or the thoracic duct.

The following table 1 shows the differential biochemical characteristics between a transudate and an exudate [11].

	Exudate	**Transudate**
Proteins	≥ 3 g/dL	< 3 g/d1.
Relation pleural proteins/serum proteins	> 0,5	≤ 0,5
LOH	> 200 UI/L	< 200 UI/L
Relation LDH pleural/ serum	≥ 0.6	< 0,6
pH	< 7,3	≥ 7,3
Glucose	< 60 mg/dl	> 60 mg/d1.
Cholesterol	> 60 mg/di.	< 60 mg/dL
Leucocites	> 1.000/mμ³	< 1.000/mμ³

Table 1

The most widespread criteria to differentiate between transudate and exudate are those of Light that allow identifying a spill as exudate in more than 95% of cases if at least one of these three criteria is met:

a) Pleural fluid proteins/blood proteins > 0.5;

b) LDH in pleural fluid/LDH in blood > 0.6;

c) LDH in pleural fluid greater than two thirds of the maximum values considered normal (depending on the technique used in each laboratory tends to be considered positive value for exudate greater than 1000 IU/L).

When these determinations are doubtful then it is recommended to resort to the measurement of cholesterol in the pleural fluid, usually establishing the cut-off point between transudates and exudates at 60 mg/dL (1.55 mmol/L).

It would be a transudate when none of these criteria is met. The pleural fluid sample must be obtained under anaerobic conditions. The pH analysis must be performed in a blood gas machine with the sample in a heparinized syringe and must be immediate or the sample must be stored on ice.

The valuation of these parameters can be summarized as follows: The pH must be measured unless the appearance of the liquid is frankly purulent. Glucose measurement is useful when there is doubt about the quality of the pH measurement. Patients with pH < 7.0 have a high risk of developing empyema and partitions with conservative treatment and should be drained. In cases where the pH is between 7.0 and 7.2, conservative treatment and thoracentesis should be repeated. Spills with a pH value > 7.2 usually follow a benign course and must be treated with antibiotics only.

The table 2 summarizes the biochemical characteristics of pleural fluid in the different types of parapneumonic effusion.

	Simple Parapneumonic pleural effusion	Complex Parapneumonic pleural effusion	Empyema
pH	<7,3	< 7,2	< 7,0
Leucocites/mμ³	> 10.000	> 10.000	15.000
Glucose	< 60 mg/dL	< 40 mg/dL	< 40 mg/dL
Culture	Negative	Positive	Positive
LOH	< 1.000 UI/L	> 1.000 UI/L	> 1.000 UI/L

Table 2

It has been determined that pH < 7.27 in pleural fluid is the only significant factor for fibrin formation with or without septa. Cytology, sediment, cultures and Gram staining should always be performed. In all patients with parapneumonic pleural effusion, blood cultures should be performed and when possible to achieve good quality it would be advisable to collect sputum culture.

A pH < 7.1 and severe clinical involvement are good predictors of poor evolution. An early thoracotomy should be considered in these cases no later than 7 days if antibiotic treatment and fibrinolytic drainage fail in order to minimize morbidity.

Treatment

An adequate treatment implies an early diagnosis that avoids future complications.

The exudative pleural effusion circulates freely through the pleural cavity and is resolved with antibiotics and pleural tube drainage. In the organizational phase, surgical debridement is necessary.

In the fibropurulent phase (in which complications due to the formation of septa and loculations can take place) is where there is the greatest controversy in the literature regarding its management; While some authors defend the combination of antibiotics with pleural tube ± fibrinolytic drainage, other authors consider the early surgical approach by debridement by means of thoracoscopy or thoracotomy decortication. Most authors agree that antibiotic treatment and thoracic drainage with the administration of intrapleural fibrinolytic when indicated is the best clinical practice in complicated DPPs and that their application is associated with a good medium-term prognosis in paediatrics [12].

The classification proposal made by Light is one of the best approaches to the treatment of these patients, both in the categorization of parapneumonic effusion and in the proposed treatment protocol.

Although this scheme has been developed for adult patients and no equivalent studies have been conducted in the paediatric population, it provides a reasonable framework for action that is followed by many paediatricians.

Figure 1 summarizes the treatment scheme that we believe is recommended, which is based on the one proposed by Light with some modifications. Grewal., *et al*. based on the sonographic aspect of the effusion, they propose the early use of thoracoscopy in order to reduce the days of admission [13,14].

Antibiotics

Intravenous antibiotic treatment is mandatory in all cases and keep several days after the fever subsides and the drainage of the liquid, a minimum of 10 days of intravenous antibiotics, then completing it with one or two weeks of oral antibiotics. Empirical treatment should include effective antibiotics against *Streptococcus pneumoniae* and *Staphylococcus aureus*. In patients who are fully vaccinated against Haemophilus influenzae and in whom Gram staining is negative, coverage against this germ is not required.

| Classification	Characteristics	Actuation
Type 1: Parapneumonic effusion not important	Little, < 10 mm X-ray in lateral decubitus	Antibiotics
Type 2: Parapneumonic effusion not complex	>10 mm. Glucose > 40 mg/dl, pH > 7,2, LDH < 1000. Gram and cultures negatives	Antibiotics
Type 3: Slight complex pleural effusion	7,0 < pH < 7,2 y/o, LDH >1000 y, glucose > 540 mg/dl. Gram and cultures negatives	Antibiotics+thoracocentesis
Type 4: Simple pleural effusion	pH < 7.0, LDH >1000, glucose < 40 mg/dl y/o. Gram or cultures positives. Not partitions. Not purulences	Antibiolics+pleural drainage
Type 5: Complex pleural effusion	pH < 7,0, LDH > 1000, glucose < 40 mg/dl y/o. Gram or cultures positives. Partitions. Not purulence	Antibiotics+pleural drainage+fibrinolytics
Type 6: Empyema not complex	Free purulent or ono partition	Antibiotics+ pleural drainage
Type 7: Complex empyema	Purulent liquid with many partitions	Antibiotics+pleural drainage+fibrinolytics. Use need thoracoscopic
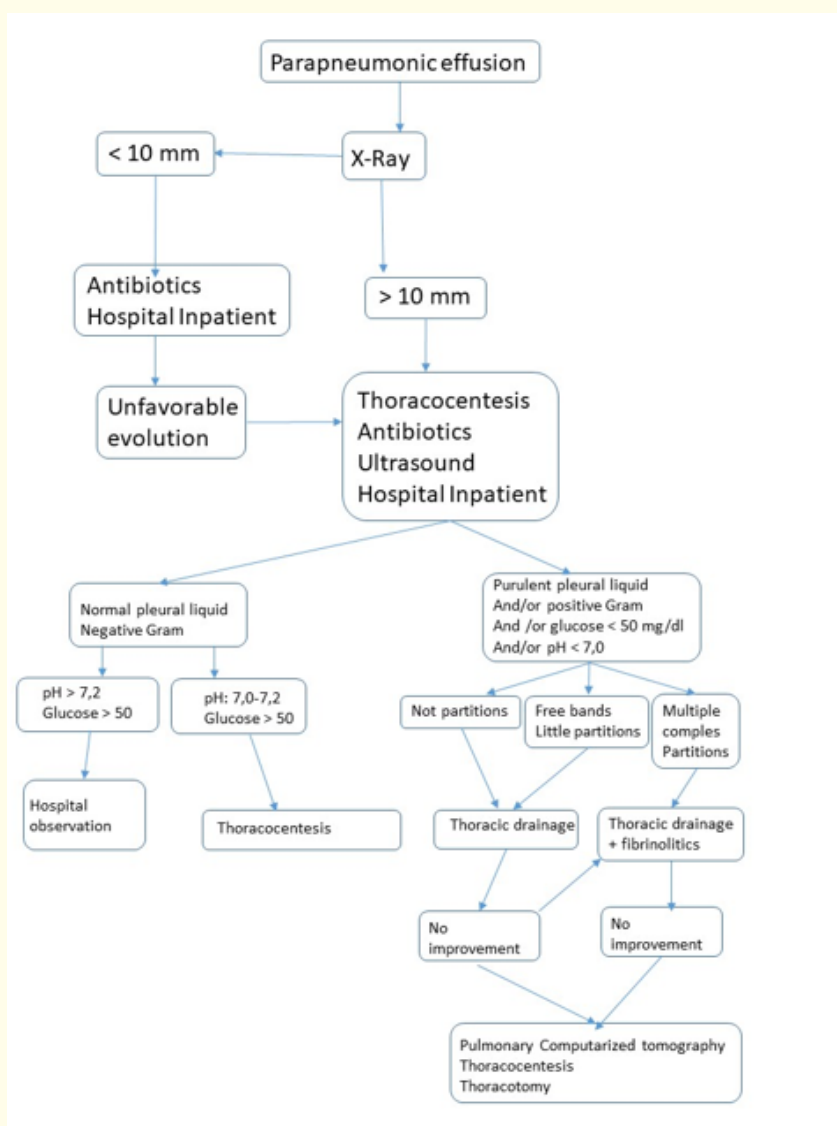
Table 3

Figure 1

A suitable initial empirical pattern would be the combination of cefotaxime (200 mg/kg/day) or ceftriaxone (100 mg/kg/day) with clindamycin (40 mg/kg/day). Alternatively, amoxicillin clavulanic acid (100 mg/kg/day of amoxicillin) could be used [15].

In patients with *Streptococcus pneumoniae* confirmed the antibiotic to be used would depend on the value of the minimum inhibitory concentration (MIC) to penicillin: a) MIC < 0.06 mg/L: penicillin or amoxicillin at conventional doses; b) MIC between 0.12 and 1 mg/L: high doses of penicillin, ampicillin or amoxicillin; MIC between 2 - 4 mg/L or > 4 mg/L: they usually respond well to cefotaxime or ceftriaxone; You can also use vancomycin and lastly carbapenems. Oral treatment for 1 - 4 weeks after discharge, even more if there is no complete resolution.

Drainage with pleural tube

Its placement is indicated in all complicated pleural effusions early, as soon as the diagnosis of complicated parapneumonic effusion is established because if it is delayed it can be very difficult to perform a good drainage of the liquid, since a spill with free liquid can transform in a few hours in a spill with partitions.

The indications to place a thoracic drain would be:

1. Presence of pus in the pleural space.

2. Gram stain of the positive pleural fluid.

3. Pleural fluid glucose < 50 mg/dl.

4. Pleural fluid pH < 7.

5. Presence of bands or partitions in the pleural fluid on ultrasound.

The tube should be placed in a declining portion of the chest and initially connected to aspiration (20 cm H_2O), since the negative pressure facilitates pulmonary expansion and tends to close the empyema cavity. In loculated spills it may be necessary to place more than one drain.

The usefulness of drainage must be assessed within 24 hours when clinical and radiological improvement should occur; if this is not the case, either the drainage is ineffective or the antibiotic is inadequate. If after 24 - 48 hours of drainage the fever persists, the debit is scarce or the radiological image has not been reduced, the permeability of the drainage must be confirmed and an ultrasound or CT scan to rule out:

a) Persistence of partitioned liquid;

b) Tube obstruction due to thick pus, bending or poor placement;

c) The existence of a necrotizing or extensive underlying pneumonia.

If there is no evidence of a mechanical problem that can be resolved by mobilizing drainage, the use of fibrinolytic or surgical treatment should be assessed. The drain must be maintained until the liquid evacuation is less than 25 - 50 mL/day or less than 1 - 1.5 mL/kg/day.

Sometimes the patient responds clinically and radiologically, but the drainage is still purulent, so it would be necessary to perform a surgical cleaning. Regarding the size of the drainage pipe, large-gauge tubes tend to be used to prevent blockage of the same by thick liquid. However, good results have also been reported with the use of small tubes (8 to 16 F) even placed by percutaneous puncture guided by CT or ultrasound [16-19].

The administration of fibrinolytic can increase pain, favouring immobility and the slower resolution of the process. You have to try a quick mobilization and the realization of physical exercise, physiotherapy can be of help if there is an atelectic component.

Fibrinolytic

The use of locally administered fibrinolytic in the effusion decreases the need for surgical treatment. The favourable rate of results ranges between 38 and 100%, depending on how advanced the stage of the spill is used. Comparative studies have shown that streptokinase and urokinase are both effective equally. Some authors recommend the use of urokinase, although its cost is slightly higher, since it has less allergenic and pyrogenic effects. No effect on blood clotting has been seen with any of them.

The dose of streptokinase is 250,000 units/day while the dose of urokinase ranges between 50,000 and 250,000 units/day. It is recommended to perform 3-day treatments and if there is no response proceed to perform a surgical treatment, although some authors recommend performing a second round of treatment. Streptokinase or urokinase are administered by the pleural drainage tube diluted with 50 - 100 mL of physiological serum. The drain is then closed for 2-4-6 or 12 hours making postural changes to the patient during this time. Finally, it reopens and connects to aspiration. If there is pain when urokinase is instilled, an oral analgesic can be administered or bupivacaine introduced through the drain (0.25 mg). Contraindications to its use include a history of allergic reactions to the preparation, trauma or recent surgery, cerebral haemorrhagic infarction, blood clotting disorder, thrombopenia, liver failure, pregnancy, recent major surgery and bronchopleural fistula [18].

The first success stories have been published in the treatment of a complicated parapneumonic pleural effusion in children with the use of fibrinolytic as the plasminogen activator (alteplase), administered by catheter in the pleural space. Recent studies confirm that the use of urokinase is effective and safe in the treatment of complicated DPP, facilitates the drainage of more fluid and shortens the need to maintain the drainage catheter. The recommended doses in these paediatric studies would be urokinase 1 or 2 times a day for 3 days at 40,000 U in 40 ml of physiological serum in children older than 10 kg and 10,000 U in 10 ml of serum in children under 10 kg are the doses currently recommended. Although a Cochrane review confirms the small number of controlled clinical trials adequate to assess the use of fibrinolytic, they demonstrate a benefit of its use in relation to saline, considering it as an additional treatment for beneficial drainage in this group of patients. Intrapleural fibrinolytic instillation is shown as an effective and less invasive alternative than surgical drainage in children with complicated pleural effusion that does not drain properly with the isolated thoracotomy tube [19,20].

Thoracoscopy debridement

Thoracoscopy debridement is useful in the fibrinopurulent phase with tabs and adhesions. Its advantages over thoracotomy are less invasiveness and less postoperative pain. Instead, it is not useful in the organizational phase, and is only possible in patients who tolerate selective lung ventilation. Its effectiveness in children varies with the precocity of its realization, between 30 -100%. Thoracotomy should be reserved for medical treatment failures (antibiotics + drainage + fibrinolytic) and thoracotomy and decortication for thoracotomy failures. If it fails, it is necessary to resort to performing a thoracotomy [19,21].

Thoracotomy decortication

In this procedure, all fibrous tissue is removed from the visceral pleura and all pus is drained from the pleural space. To perform it, the practice of a complete thoracotomy incision is required. In the acute phase it is indicated only to control the pleural infection if it is not possible to achieve it with other more conservative measures. It should not be done just for the existence of a pleural thickening, because it resolves spontaneously in the course of several months.

In the chronic phase it allows the removal of fibrotic tissue that causes functional restriction. It is very effective with resolution of 90 - 95% of empyema. An empyema organized in a symptomatic child will need a thoracotomy and decortication. A lung abscess coexisting with empyema does not necessarily need to be drained surgically [22,23].

Evolutionary tracking

The patient must be checked once he is discharged until his complete recovery and his radiology is practically normal. The possibility of underlying debilitating diseases should be considered if there is a more torpid evolution than expected.

Conclusion

The annual incidence of pneumonia is increasing exponentially in recent years due to the abuse of antibiotics that are generating increasingly complicated and difficult to overcome bacterial resistance and therefore the complications of such pneumonia are becoming more frequent, including the spills.

The work as paediatricians should be to try to avoid the most aggressive techniques in children, so an early diagnosis and an adequate management of complementary techniques can allow the adequate treatment of these patients, without forgetting that in the last case we can and must apply techniques invasive that allow an adequate end of these processes [24,25].

This article has tried to make a general review of one of the complications of pneumonia in order to serve as a reference for those professionals who face patients with these conditions.

Bibliography

1. Mahon C., *et al*. "Incidence, aetiology and outcome of pleural empyema and parapneumonic effusion from 1998 to 2012 in a population of New Zealand children". *Journal of Paediatrics and Child Health* 52.6 (2016): 662-668.

2. Krenke K., *et al*. "Etiology of parapneumonic effusion and pleural empyema in children. The role of conventional and molecular microbiological tests". *Respiratory Medicine* 116 (2016): 28-33.

3. Griffith D., *et al*. "Evolution of practice in the management of parapneumonic effusion and empyema in children". *Journal of Pediatric Surgery* 3.4 (2018): 644-646.

4. Santana Hernández M., *et al*. "Paediatric invasive pneumococcal disease on the island of Gran Canaria: 16-year prospective study (2001-2016)". *Enfermedades Infecciosas y Microbiología Clínica* 36.10 (2018): 607-611.

5. Osowicki J and Steer AC. "International survey of paediatric infectious diseases consultants on the management of community-acquired pneumonia complicated by pleural empyema". *Journal of Paediatrics and Child Health* 55.1 (2019): 66-73.

6. de Benedictis FM., *et al*. "Prospective evaluation of lung function in children with parapneumonic empyema". *Pediatric Pulmonology* 54.4 (2019): 421-427.

7. Ferreiro L., *et al*. "Advances in pleural effusion diagnostics". *Expert Review of Respiratory Medicine* 22 (2019).

8. Alcoba G., *et al*. "A three-step diagnosis of pediatric pneumonia at the emergency department using clinical predictors, C-reactive protein, and pneumococcal PCR". *European Journal of Pediatrics* 176.6 (2017): 815-824.

9. Andronikou S., *et al*. "Computed tomography in children with community-acquired pneumonia". *Pediatric Radiology* 47.11 (2017): 1431-1440.

10. Chen M., *et al*. 'Thoracoscopy in diagnosis and treatment of pleural diseases in children". *Zhonghua Er Ke Za Zhi* 55.9 (2017): 695-699.

11. Stankey CT., *et al*. "Blood Culture and Pleural Fluid Culture Yields in Pediatric Empyema Patients: A Retrospective Review, 1996-2016". *The Pediatric Infectious Disease Journal* 37.9 (2018): 952-954.

12. Godfrey MS., *et al*. "Medical and Surgical Management of Empyema". *Seminars in Respiratory and Critical Care Medicine* 40.3 (2019): 361-374.

13. Feola GP., *et al*. "Quality Improvement Standards for the Treatment of Pediatric Empyema". *Journal of Vascular and Interventional Radiology* 29.10 (2018): 1415-1422.

14. Dorman RM., *et al*. "Trends in treatment of infectious parapneumonic effusions in U.S. children's hospitals, 2004-2014". *Journal of Pediatric Surgery* 51.6 (2016): 885-890.

15. Segerer FJ., *et al*. "Therapy of 645 children with parapneumonic effusion and empyema-A German nationwide surveillance study". *Pediatric Pulmonology* 52.4 (2017): 540-547.

16. Cherian SV., *et al*. "Empyema "Necessitated" by Indwelling Pleural Catheter: A Unique Complication". *American Journal of Respiratory and Critical Care Medicine* 28 (2019).

17. Haggie S., *et al*. "Increasing Rates of Pediatric Empyema and Disease Severity with Predominance of Serotype 3 S. pneumonia: An Australian Single-Center, Retrospective Cohort 2011 to 2018". *The Pediatric Infectious Disease Journal* 15 (2019).

18. Kanellakis NI., *et al*. "Biological effect of tissue plasminogen activator (t-PA) and DNase intrapleural delivery in pleural infection patients". *BMJ Open Respiratory Research* 6.1 (2019): 24.

19. Reichert M., *et al*. "Stage-directed therapy of pleural empyema". *Langenbeck's Archives of Surgery* 402.1 (2017): 15-26.

20. Livingston MH., *et al*. "Intrapleural Dornase and Tissue Plasminogen Activator in pediatric empyema (DTPA): a study protocol for a randomized controlled trial". *Trials* 18.1 (2017): 293.

21. Kelly MM., *et al*. "Trends in Hospital Treatment of Empyema in Children in the United States". *The Journal of Pediatrics* 202 (2018): 245-251.

22. Redden MD., *et al*. "Surgical versus non-surgical management for pleural empyema". *Cochrane Database Systematic Review* 17.3 (2017).

23. Tantraworasin A., *et al*. "Factors associated with recurrent bacterial empyema thoracis". *Asian Journal of Surgery* 41.4 (2018): 313-320.

24. Krenke K., *et al*. "Risk factors for local complications in children with community-acquired pneumonia". *The Clinical Respiratory Journal* 12.1(2018): 253-261.

25. Breuer O., *et al*. "Predictors of Prolonged Hospitalizations in Pediatric Complicated Pneumonia". *Chest* 153.1 (2018): 172-180.