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Resistance to Co-Amoxiclav (Augmentin) in Community-Acquired and Nosocomial Pleural Infections

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Abstract

Objective: To describe the ecology in pleural infections, where nosocomial and community-acquired infections may have different ecology.

Methods: retrospective single center study. Any subject admitted in intensive care unit with a diagnosis of complicated pleural effusion (presence of macroscopic pus, or sero-fibrinous pleural effusion with pH <7.2 or LDH >1000 or pleural glucose <0, 4 g/L, and signs of infection or positive bacteriological sampling) were included.

Results: From 2006 to 2012, 57 patients were included. Four strains of "Multi-resistant" bacteria were reported in 3 patients with community-acquired pleural infection. As a whole 3 out of 57 (5%) patients had microorganisms (not including candida and mycobacteria) resistant to co-amoxiclav. It was not different between nosocomial and community-acquired pleural infections.

Conclusion: Our study found resistance to co-amoxiclav in 14% and "multi-drug resistance" in 8% of the patients with community-acquired pleural infection.

Keywords: Empyema; Nosocomial; Pleural; Infection; Antibiotics; Co-amoxiclav; Thoracocentesis

Introduction

Empyema thoracis are rarely seen in the intensive care unit (ICU). They are reported to correspond to an unfavorable evolution of lung infection [1]. Bacterial ecology was largely described in ancient series [2-4]. The flora found in the condition of community-acquired was gladly polymorphic and often included Gram-positive cocci and anaerobes. This feature was acknowledged in more recent studies [5,6]. In empyema thoracis, systemic antibiotic therapy is recommended. However, the choice of the antibiotics is still matter of debate, including recommendation of the association of penicillin with a beta-lactamase inhibitor for community-acquired pleural infections [7,8]. However, recently, the resistant bacteria encountered in nosocomial thoracic empyema was emphasized, in up to 40% of the patients [6,9]. Consequently, owing to the expansion of the use of antibiotics and the frequent "multi-resistant" bacteria, increasing surveillance of susceptibility of the bacteria should be considered. Indeed, significant increase in mortality rate related to empyema was noticed in a study over 100 years. The authors speculated that changes in micro-organisms, with perhaps more antibiotic resistance, might cause this increased mortality rate [10]. Accordingly, increased numbers of pleural infections due to *Staphylococcus aureus* [11,12], *Streptococcus milleri* [1], and *Pseudomonas aeruginosa* [11,13] was acknowledged.

Purpose of the study

To describe the ecology in empyema thoracis and complicated pleural effusion, and resistance to common antibiotics with emphasize on sensitivity to co-amoxiclav.

Material and Methods

Patients

The research protocol was consistent with the declaration of Helsinki and was approved by Ethics Committee. Over a period of 6 years, from 2006 to 1012, any admitted subjects in our medical ICU with a diagnosis of empyema thoracis and/or complicated pleural effusion were retrospectively included according to the following criteria:

-Presence of frank pus in the pleural cavity macroscopically during thoracocentesis, or

-positive bacteriological sample (culture or direct examination) of the pleural fluid (PF), or

-sero-fibrinous pleuritis with a PF pH <7.2, or LDH >1000, or a glucose concentration <0. 4 g/L, and signs of infection (fever, biological inflammatory syndrome).

Exclusion criteria were subjects minor or without a pleural sample realized.

PF was immediately examined for Gram-stain and inoculated for aerobic and anaerobic growth. Antimicrobial susceptibility was tested by disks, according to the French guidelines. Resistance to different antibiotics was defined by resistance *in vitro* of at least a strain among the germ (s) found (s) in the samples.

Pleural infection was considered nosocomial if it did not exist or was not incubating prior to hospital admission. It was secondary to a pleural gesture burglary or to nosocomial pneumonia. Otherwise, infections were considered community-acquired.

Data Collected

Subjects were identified using the Fusion F software program. The following parameters were collected; age, gender, underlying disease (including cancer, diabetes, neurological disease advanced, heart

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failure, chronic renal failure, cirrhosis, chronic respiratory failure, long-term corticosteroids treatment, transplantation, HIV/AIDS, malignant hematology disease, chemotherapy) or another past history (including chronic alcoholism, smoking, malnutrition, antecedent of thoracic surgical or trauma), previous antibiotic administration in the 14 days prior to admission, hospitalization, and nosocomial or community-acquired infection. Clinical data (respiratory functional signs, temperature, blood pressure, heart rate, respiratory rate, oxygen saturation), biological data (number of white blood cells, hemoglobin, albumin, red blood cell counts, distribution width, C-reactive protein, alkaline phosphatase, lactate dehydrogenase), and radiological findings (side of achievement, volume) were reported.

PF: pH, lactate dehydrogenase, glucose, white cell and neutrophil counts, bacteriological findings (direct examination; cultures, and *in vitro* antimicrobial sensitivity with in particular, the 'first line' antibiotic resistance).

Support: antibiotic therapy, clinical efficacy (apyrexia timeout defined as obtaining a temperature <37.8°C during 48 h), duration of stay in ICU, in-hospital survival, complications (loculation, sepsis, infection from another site...), pleural fibrinolysis, surgery.

Statistical analysis

Data are expressed as median (IQR: 25; 75 percentiles) for continuous variables and number (percent) for binary variables. Qualitative values were compared with Chi-2 tests and quantitative values with Mann-Whitney tests as appropriate. Odds ratios (OR) for hospital mortality were calculated with their 95% confidence intervals (CI). A p value <0.05 was considered significant. Statistical analysis was performed with Statview 5.0.

Results

Subjects

During the 6 year-period of time 57 subjects were included (Table 1). They had a significant underlying pathology for 34 of them (60%) including: cancer (n=5); malignant hemopathy (n=3); chemotherapy (n=3); long-lasting corticosteroid therapy (n=3); previously known AIDS (n=4); diabetes mellitus (n=9); respiratory (n=4), heart (n=9), or renal (n=4) failure; hepatic cirrhosis (n=1); advanced neurological disease (n=9). It was not noted pleural infection related to drug-induced aspiration or to thoracic surgery.

Prior to admission, 23 subjects (40%) received antibiotics for a median duration of 7 days (5; 11). Most of the subjects had community-acquired infections (91%). Pleural infection was classified nosocomial in 5 subjects (9%). PF was bilateral in two subjects. The side of pleural infection was not recorded in one subject. PF concerned the right and left side in 35 and 23 subjects (62% and 41%) respectively. The outpouring was considered of small (n=7), medium (n=34) or large (n=15) abundance, in 56 subjects for which chest imagery was available. PF was collected in all the subjects. The characteristics of the PF are summarized in Table 2.

Microbiology

While 23 subjects were on antibiotics prior to admission, at least one microorganism was found in 39 subjects (68%). For these subjects, the number of responsible microorganisms was one (30 subjects), two (8 subjects), and four (1 subject). Found microorganisms are described in Table 3, depending on nosocomial (n=5) or community-acquired infection (n=34 found germs on 52 community-acquired empyema). No fermenting Gram-negative bacilli (GNB) (*Pseudomonas aeruginosa*,

	Population (n=57)
Male (%)	36 (63%)
Age (years)	54 (40; 69)
Underlying pathology (%)	34 (60%)
Malnutrition (%)	15 (26%)
Alcoholism (%)	10 (18%)
Smoking (%)	24 (42%)
Thoracic antecedent (%)	5 (9%)
SAPS II*	27 (21; 42)
APACHE II†	11 (8; 17)
Temperature (°C)	38 (37.4; 38.4)
Heart rate (/min)	105 (90; 116)
Blood pressure (mmHg)	
- Systolic	120 (108; 135)
- diastolic	70 (60, 77)
SpO$_2$ (%)‡	96 (95; 99)
Respiratory rate (/min)	30 (22; 35)
Leukocyte count (/mm^3)	12700 (10000, 18000)
Hemoglobin (g/L)	112 (89; 121)
Red blood cells distribution width	13.2 (12.6; 14.6)
Platelet count	382 (277; 567)
CRP (mg/L)§	240 (147; 314)
Plasma albumin (g/L)	20 (16; 26)
Plasma LDH‖	252 (206; 299)
Alkaline phosphatase	122 (87; 212)
Septic shock (%)	6 (11%)
Respiratory distress (%)	19 (33%)
Chest tube drainage (%)	50 (88%)
Use intra-pleural fibrinolysis (%)	27 (47%)
Use of thoracic surgery (%)	11 (19%)
Length of stay (days)	
- Intensive care unit	7 (4, 10)
- Hospital	18 (15; 30)
Invasive mechanical ventilation (%)	9 (16%)
Duration of ventilation (days)	5 (3; 11)
Hospital mortality (%)	5 (9%)

*SAPS II, simplified acute physiology score II; †APACHE II, acute physiology and chronic health evaluation II; ‡SpO$_2$, percutaneous oxygen saturation; §CRP, C-reactive protein; ‖LDH, lactate dehydrogenase.
Table 1: Demographic characteristics of the overall population (57 patients) with pleural infection.

Stenotrophomonas maltophilia or *Acinetobacter sp*) or *S. aureus* resistant to Methicillin were found. Enterobacteriaceae were divided in: Group 1 (4 *Escherichia coli*, 1 *Proteus mirabilis*), group 2 (2 *Citrobacter koseri*, 2 *Klebsiella pneumoniae*, 1 *Klebsiella oxytoca*), group 3 (1 *Citrobacter freundii*, 1 *Enterobacter* cloacae).

Eight subjects had infection with at least a germ resistant to co-amoxiclav, corresponding to 21% of the subjects with PF positivity (8/39) and 14% of our cohort (8/57). Microorganisms resistant to co-amoxiclav were the following: *Mycobacterium tuberculosis* (n=2), *E. cloacae* (n=1), *E. coli* (n=1), *Enterococcus faecium* (n=1), *S. epidermidis* (n=1), and *Candida albicans* (n=2). Fungal infections were observed in one AIDS subject with nosocomial infection and in a subject with community-acquired polymicrobial infection (four microorganisms). Excluding fungi and Mycobacteria, "multi-resistant" bacteria were found (n=4 in 3 subjects) in the community-acquired group and during year 2011 and 2012 (i.e. two last years of survey): *E. cloacae* with derepressed cephalosporinase (n=1), *E. coli* (n=1) with extended-

	N	Pleural fluid
pH	11	7.5 (7.37; 7.9)
Glucose (mg/dL)	49	220 (30; 482)
Proteins (g/L)	51	45 (33; 52)
LDH*	34	3709 (615; 9258)
Leukocytes		
- neutrophils	42	815 (295; 11880)
- lymphocytes	34	144 (49; 500)

*LDH, lactate dehydrogenase

Table 2: biochemical and cytological features in pleural fluid in patients (N=57) in whom it was performed.

	Community-acquired empyema (n=52)	Nosocomial empyema (n=5)	p value
Antibiotic<1 month	20 (38%)	3 (60%)	0.3
Gram stain	18 (35%)	4 (80%)	0.047*
Positive culture	20 (38%)	4 (80%)	0.07
Gram-positive cocci	25/34 (74%)	2 (40%)	0.7
- aerobic Streptococcus (non pneumoniae)	9/34 (26%)	0	-
- *Streptococcus pneumoniae*	15/34 (44%)	0	-
- Anaerobic Streptococcus	3/34 (9%)	0	-
- *Staphylococcus aureus*	2/34 (6%)	2 (40%)	0.02*
- *Non-aureus Staphylococcus*	1 (3%)	0	-
Gram-negative bacilli	11/34 (32%)	2 (40%)	0.3
Enterobacteria group			
- 1	3 (9%)	1 (20%)	0.2
- 2	3 (9%)	2 (40%)	0.01*
- 3	2 (6%)	0	-
Other anaerobes	2/34 (6%)	0	-
Candida albicans	1 (3%)	1 (20%)	0.04*
Mycobacterium tuberculosis	2 (6%)	0	-
Resistance to penicillin G	12/34 (35%)	4 (80%)	0.1
Resistance to amoxicillin	12/34 (35%)	3 (60%)	0.2
Resistance to co-amoxiclav	7/34 (21%)	1 (20%)	1
Resistance to cephalosporins			
- 1era generation	7/34 (21%)	1 (20%)	1
- 2nd generation	6/34 (18%)	1 (20%)	1
- 3rd generation	6/34 (18%)	1 (20%)	1
Resistance to clindamycin	10/34 (29%)	3 (60%)	0.2
Fluoroquinolone resistance	9/34 (26%)	1 (20%)	0.8
No germ	5 (15%)	1 (20%)	0.5
Unfavourable evolution of Empyema	10 (19%)	2 (40%)	0.3
Complication	42 (81%)	5 (100%)	0.3
Death	2 (4%)	3 (60%)	0.001*

*p<0.05.

Table 3: Bacteriological data of pleural fluid according to the community-acquired (n=52 whose 34 germs were found) and nosocomial (n=5 whose 4 germs were found) origins of the pleural infection.

spectrum beta-lactamase, *Enterococcus faecium* resistant to ampicillin and a *S. epidermidis* resistant to Methicillin. As a whole 3 out of 57 (5%) subjects had microorganisms (not including candida and mycobacteria) resistant to co-amoxiclav.

Nosocomial thoracic empyema had more *S. aureus,* Group 2 Enterobacteriaceae, and *C. albicans* (p<0.05 for each) than community-acquired thoracic empyema. The rate of resistance to co-amoxiclav was equivalent to that observed for the community-acquired empyema (20% and 14% respectively).

Antibiotics and efficacy

All subjects received antibiotics from admission. Subjects were treated with co-amoxiclav (n=21), and/or another antibiotics (n=50). After admission, initiation of *in vitro* effective antibiotic therapy was <24 hours in 48 subjects (84%). Apyrexia was obtained after 1 day (0; 3). Noteworthy, despite administration of antibiotics and frequent chest tube drainage, unfavorable development of empyema (encystment, loculation, and lung abscess) was noted during the course in 45 subjects (79%).

Prognosis

Nosocomial empyema was more frequent in subjects with shock (OR=8, CI 1.02-62, p=0.047), intubation (OR=11, CI 1.6-83, p=0.02), anemia (Hemoglobin 88 vs. 122 gr/L, p=0.01), and who received extended prior antibiotic therapy (for 28 vs. 6 days, p=0.02). These parameters were associated with a clear increased risk of in-hospital deaths in subjects with nosocomial empyema (OR=37, CI 3.8-367, p=0.002). Several other items were related to an increase in mortality rate without being bound to the nosocomial infection factor, including: a higher Simplified Acute Physiology Score II (SAPS II), and Acute Physiology And Chronic Health Evaluation II (APACHE II) scores (50 vs. 27, p=0.006 and 28 vs. 10, p=0.003, respectively), malnutrition (OR=15, CI 1.5-143, p=0.02), and advanced neurological disease (OR=6, CI 1.02-42, p=0.048). Interestingly, intra-pleural fibrinolysis was associated with a favorable outcome (27 fibrinolysis / 52 survivors vs. 0 fibrinolysis in 5 non-survivors, p=0.03).

Discussion

Microbiology, antibiotics and prognosis

Refreshing or updating microbiological data seems essential to guide the probabilistic antibiotic therapy in pleural infection. Our study is consistent with the predominance of Gram-positive cocci in community-acquired pleural infections [4,6], even if 60% of our subjects had an underlying disease, increasing the risk of GNB and fungal infection [14]. The rate of PF bacterial "negativity" (32%) found in the present study is also in agreement with previous studies that consistently reported rates of negative PF of about 40 to 50% [1,12].

Our study found resistance to a first line antibiotic – co-amoxiclav – in 14% of so-called community-acquired subjects and in 21% of the PF with bacteriological growth. The differences between nosocomial and community-acquired thoracic empyema included a predominance of infection with *S. aureus* and group 2 enterobacteria in the nosocomial empyema, also found by others [5,15]. We cannot recommend more judicious antimicrobial therapy in the light of our ecology. However, a probabilistic antibiotic with co-amoxiclav is questionable, even in community-acquired empyema. Accordingly, adequate coverage based on *in vitro* susceptibility of micro-organisms found in community-acquired and nosocomial pleural infections, was reported to be only 52% (49% to 53%) and 84% (78% to 86%) with the association of metronidazole and either penicillin (Scandinavian recommended antimicrobial therapy) or cefuroxime, respectively [5].

Tuberculosis infection did not appear to be a concern regarding the immediate risk of sepsis (mortality 0/3, 0% in a medical ICU) [9]. On the other hand, the fungal infection was a real threat, even

among the immune-competent subjects (mortality 2/2 100%, in the same series [9]. One of our subjects with AIDS exhibited *C. albicans* empyema after staying for a long period in hospital and died rapidly. However, the appropriate antifungal treatment was delayed by 2 days. The role of resistant Gram-positive cocci (ampicillin-resistant *E. faecium* and Methicillin-resistant *S. epidermidis* in our cohort) and GNB (Enterobacteriaceae with derepressed cephalosporinase and extended-spectrum beta-lactamase) to front-line antibiotics should be highlighted in the community-acquired empyema in our study.

Before severe sepsis and septic shock related to purulent empyema, especially if the patient has received extended antibiotic therapy, broad-spectrum antibiotic therapy should be recommended, pending the results of the direct examination and culture of PF (and blood), as acknowledged by Tu and colleagues. In immunocompromised patients, the use of the antifungal therapy (fluconazole), especially for nosocomial empyema should be discussed [1,9,16]. Finally, an emergence of drug resistant bacteria is a possible mechanism, as those micro-organisms were found only in the last two years of our study [10].

However, despite delay in administration of adequate antimicrobial therapy, mortality remained lower in our subjects than that observed in severe complicated parapneumonic effusions (9% vs. 48%) and this discrepancy is questionable [9]. First, population may differ between the centers with different inclusion criteria. Our subjects rarely received catecholamines (11%) or mechanical ventilation (16%). Subjects were admitted in our ICU if chest tube drainage was needed. Though, our subjects did not represent a real ICU population with subsequent elevated mortality, but is in agreement with previous reports accounting for by mortality rates of about 4.7% to 27%, in patients with complicated pleural effusions [5,15,17]. Maskell found a 12-month mortality rate of about 22%, with a significant increase in patients with nosocomial infections (45%; OR 4.24), the mortality rates increased when *S. aureus*, GNB, or mixed aerobic bacteria where found, compared to anaerobes, Streptococcal, or culture-negative infections [6].

Although Tu et al did not report the adequation of "standard" antimicrobial therapy, they reported many "resistant" GNB (fermenting or group 3) along with fungi and a 36% rate of inadequate initial antimicrobial therapy in non-tuberculosis bacteriologically proven pleural infection [9]. The inadequacy between initial antibiotics and in vitro findings was associated with a 60% increase in the mortality rate. Though, their susceptibility to antibiotics antimicrobial therapy might have been even lower than ours. Finally, in contrast with lung infection [18], delay in adequate antimicrobial therapy in PF may not be the point [17], as chest tube drainage is an effective treatment to quickly decrease bacterial load and improve the patients' condition [19-21]. However, some authors recommend not draining every complicated pleural effusion [22]. Accordingly, although ICU patients aforementioned had small bore pleural pigtail catheter, their need for chest tube drainage, intra-pleural fibrinolysis and thoracic surgery was particularly low (9%, 4% and 4% respectively), rendering the characteristics of the pleural infection and its management different from ours. On the other hand, a study found a significant association between adequate empirical therapy and a decrease in hospital mortality (OR 0.43; p=0.02) in the multivariate analysis, consistent with the results of our study [5].

Intra-pleural fibrinolysis with streptokinase resulted in disappointing results [23]. However, the same team showed that adjunction of deoxyribonuclease with recombinant tissue plasminogen activator improved the drainage of infected PF and subsequently decreased the need for thoracic surgery and hospital stay with no change in the mortality rate [24]. Fibrinolysis was realized without

deoxyribonuclease (not available in our hospital) and did not reduce the need for surgery, in our series. However, it was associated with a lower mortality rate, such as in sub-groups of proven loculated/septated effusions in a systematic review [25]. This review showed a significant reduction in surgical intervention. Nevertheless, our retrospective study did not allow concluding on the benefit of fibrinolysis, in terms of mortality or surgical requirements.

The other elements associated with hospital mortality were common. We did not find significant association between red blood cells distribution width or alkaline phosphatase and mortality [15]. However, those variables do not seem valuable tools for prognosis assessment in thoracic empyema. According to pulmonary vasculature and pleural drainage, we found a right predominance as expected [15].

Limitations

Our study is an overview of the ecology of a small series of subjects admitted for empyema thoracis and complicated pleural effusion in a single ICU. It is only a local vision and cannot be extended to the whole spectrum of purulent empyema. Diagnoses on admission were variable and population heterogeneous. Our hospitals having no facility for thoracic surgery, the rare nosocomial thoracic empyema were probably the consequences of complicated pulmonary infections and were not the image of post-operative direct inoculations. However, given the low rate of *S. aureus* resistant to Methicillin and *Streptococcus pneumoniae* with decreased susceptibility in France, our results might encourage other countries screening for bacterial resistance in community-acquired pleural infections.

PF had different characteristics than previous studies [6,17,20]. PF pH and glucose were higher, though, false positive of PF culture might account for misdiagnosis. However, previous studies reported that some patients with PF pH >7.2 do need tube thoracostomy or decortication [26]. Moreover, every subject had clinical signs of overt pleural infection in our series. Clinicians should take into account PF culture despite elevated PF pH and glucose, if clinically indicated [17].

Conclusion

Our study found a resistance to co-amoxiclav in 14% of the subjects with community-acquired thoracic pleural infection and in 21% of found microorganisms. There was no evidence of notable difference in spectrum's between nosocomial and community-acquired pleural infection.

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