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► To cite this version:

David Luque-Paz, Marie-Clémence Verdier, Charles R Lefevre, Pierre Chauvin, Thomas Goter, et al.. Pleural penetration of amoxicillin and metronidazole during pleural infections: an ambispective cohort study. *International Journal of Antimicrobial Agents*, 2023, 62 (6), pp.107004. 10.1016/j.ijantimicag.2023.107004 . hal-04282984

HAL Id: hal-04282984

<https://hal.science/hal-04282984v1>

Submitted on 11 Jan 2024

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Highlights

- Intravenous amoxicillin at 6 g/d allowed detectable concentration in pleural fluid in 90% of cases
- Amoxicillin coefficient of diffusion in pleural fluid was 68%
- Metronidazole achieved excellent pleural diffusion, highly correlated with plasma levels

- Considering causative pathogens MICs, an amoxicillin target of C_{min} or $C_{ss} \geq 5\text{mg/L}$ in pleural fluid seems appropriate

Manuscript (including the abstract): 2679 words

Abstract: 214 words

Pleural penetration of amoxicillin and metronidazole during pleural infections: an ambispective cohort study

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Keywords: pleural infection, pleural empyema, amoxicillin, pharmacokinetics, pleural fluid, metronidazole

Abstract

Introduction. Pharmacokinetics of antibiotics in pleural fluid during pleural infections have been poorly described. We aimed to explore amoxicillin and metronidazole diffusion into pleural space.

Methods. This is an ambispective, single-center study. We included patients with complicated parapneumonic effusion or pleural empyema managed with repeated therapeutic thoracentesis as first-line treatment between 2014 and 2022. Pleural steady-state or trough concentrations of amoxicillin and metronidazole were measured with a lower limit of quantification of 5 mg/L.

Results. Seventy paired samples of blood and pleural samples were analyzed, in 40 patients. Median age was 55 years [interquartile range, 45 – 67] and 88% of patients were men. Median weight was 65.8 kg [57.3 – 82] and median plasma albumin concentration was 29.7 g/L [23.7 – 33.9]. Median creatinine clearance was 106 mL/min [95 – 117]. Median amoxicillin pleural concentrations in patients treated with oral, bolus, and continuous intravenous administrations (6 g/day) were, respectively, 5.2 [<5 –6.4], 9.4 [8–13.1], and 10.8 [7.1–13.1] mg/L. Pleural concentrations were <5 mg/L in 5/11 samples (45%) with oral treatment, and 6/59 (10%) with intravenous treatment. Median metronidazole pleural concentrations were 18.4 mg/L [15.7–22.8], all patients being treated orally, 1.5 g/day.

Conclusion. Oral metronidazole (1.5 g/d) and intravenous amoxicillin (6 g/d) achieved therapeutic targets on pleural fluid in most cases, but not oral amoxicillin.

1. Introduction

Pleural infection is a life-threatening and difficult-to-treat infection due to the necessity of drainage combined with effective anti-infective treatment [1]. Optimal drainage of infected fluid is particularly important in the early stages, while antibiotics have the crucial role of sterilizing the pleural space [2]. Research about methods of drainage, or intrapleural fibrinolytic therapy received considerable attention over the last few years [3]. On the other hand, research on anti-infective treatment of pleural infections has been neglected and is based on low quality evidence [4]. The current guidelines provide suggestions about the choice of antibiotic regimen but do not address the recommended antibiotic dosages for treating community-acquired pleural empyema [5–7]. While optimizing antibiotic therapy remains a key issue in pleural empyema, it has been poorly studied, especially in the field of pharmacokinetics (PK). Indeed, PK data of antibiotics in the pleural fluid are notably scarce for amoxicillin and metronidazole, mostly based on single-centre and limited sample size clinical studies, or experimental studies [8–12].

For severe infections, recommended beta-lactam concentration target is between four and eight times the minimal inhibitory concentration (MIC) during 100% of the dosing interval in order to obtain a maximal bactericidal effect [13]. In the setting of pleural infections, there is no consensus on antibiotic dosages nor administration mode (intermittent *versus* continuous infusion) for the anti-infective treatment in order to achieve this target. In this study, we aimed to explore PK parameters of two antibiotics widely used in the treatment of pleural infection, amoxicillin and metronidazole.

2. Methods

2.1 Study population

We performed an ambispective study of patients managed with repeated therapeutic thoracentesis as first-line treatment for pleural infections in the Rennes University Hospital,

France [14,15]. Data were collected retrospectively for patients managed between 2014 to 2017, and prospectively during years 2018-2022. Non-complicated parapneumonic effusions were excluded from the study. We included all adult patients with at least one clinical symptom suggestive of lung infection (fever, cough, or/and dyspnea) and at least one of the following characteristics for pleural fluid: frank pus, presence of intrapleural loculations or identification of a pathogen. Only patients with at least one concomitant determination of amoxicillin or metronidazole concentrations in blood and pleural fluid were eligible. Pleural fluid samples were retrieved using thoracentesis only (no chest tube). Data were collected on a standardized questionnaire including demographic, clinical, and biological data.

2.2 Antibiotic measurement method

Blood samples were collected in heparinized tubes and pleural samples in sterile tubes (Falcon 15mL), immediately transported on ice to the laboratory and centrifuged for 10 min at 3,000g and 4°C. Then, plasma and pleural samples were stored at -20°C until analysis as routine drug monitoring (maximum storage time of 72 hours).

Amoxicillin concentrations in plasma and pleural fluid were measured by a validated routine liquid chromatography method with an ultra-violet detection derived from a previously published method [16]. After protein precipitation with acetonitrile, the compounds were separated on an Nucleoshell RP18 plus analytical column (Macherey-Nagel, Hoerd, France) and amoxicillin was monitored at 230 nm. The range of measurable concentrations extended from 5 to 250 mg/L. When clavulanic acid was administered in combination with amoxicillin, we could not measure clavulanic acid concentrations. Metronidazole concentrations were measured by a validated routine liquid chromatography method coupled with a tandem-mass spectrometer, after protein precipitation by acetonitrile. The range of measurable concentrations extended from 1 to 120 mg/L. For amoxicillin and metronidazole, all plasma and pleural concentrations were determined after at least 48 h on a steady antibiotic regimen.

Steady-state concentrations (C_{ss}) were measured on samples obtained at any time point when amoxicillin was administered by continuous intravenous infusions. Trough concentrations (C_{min}) were measured on samples obtained just before the next injection or oral intake when antibiotics (amoxicillin or metronidazole) were given orally or using intermittent intravenous infusions. The lower limit of quantification (LLOQ) was defined as the first concentration with a peak height of at least three times the baseline value. LLOQ was 5 mg/L for amoxicillin and 1 mg/L for metronidazole. In reproducibility tests, the coefficient of variation was $< 8\%$. The coefficient of diffusion in pleural space was calculated according to the formula $(C_{pleura} / C_{plasma}) \times 100$.

2.3 Statistical analysis

Descriptive results were expressed as median and interquartile range [IQR] for quantitative variables, and numbers (%) for qualitative variables. Missing data for each variable were excluded from the denominator. The Student *t*-test or Mann-Whitney test, and Fisher's exact test were used, as appropriate. The relationship between amoxicillin plasma and pleural concentrations was assessed by Pearson's correlation analysis. Two-tailed *p*-values inferior to 0.05 were considered as statistically significant. Statistical analysis was carried out using R-Studio 2015, Integrated Development for R (R-Studio, Boston, MA, USA). Figures were performed with GraphPad Prism v.9.2 software (GraphPad Software, San Diego, CA, USA).

2.4 Ethics

The study was approved by the Ethics Committee of Rennes University Hospital (approval number 18.77). Patients were informed and could refuse to be enrolled in the study.

3. Results

3.1 Baseline characteristics

A total of 70 paired (*i.e.* blood and pleural) samples were obtained from 40 patients with pleural infections: 14 retrospectively and 26 prospectively. Median age was 55 years [45 – 67]

and thirty-five patients were men (88%). Median weight was 65.8 kg [57.3 – 82] and median plasma albumin concentration was 29.7 g/L [23.7 – 33.9]. At baseline, median creatinine clearance was 106 mL/min [95 – 117] using the Cockcroft-Gault estimation. Half of patients (n=20/40, representing 34 samples) received amoxicillin in combination with clavulanic acid. Four (10%) patients had a creatinine clearance < 60 mL/min, but no patient had a creatinine clearance < 30 mL/min. Twenty-four patients had pleural empyema and 16 had complicated parapneumonic effusion. Surgical referral and 3-month mortality were respectively 10% (n=4/40) and 5% (n= 2/40)

3.2 Pharmacokinetics of amoxicillin in pleural fluid.

All pleural concentrations of amoxicillin are represented in Figure 1. Pleural C_{ss} of amoxicillin for continuous infusions, and pleural C_{min} for oral intake or intermittent intravenous infusions, according to the route of administration and daily dose, are summarized in Table 1. The median time from initiation of amoxicillin to sample collection was 80 hours [53 – 153]. The median time from last dose to sample collection to determine C_{min} was 6 hours [4.2 – 8.0]. When administered orally at 2 g t.i.d (6 g/d), median pleural C_{min} of amoxicillin was 5.2 mg/L [<5 – 6.4], with 5/11 (45%) samples under LLOQ (Table 1). Intermittent intravenous administration of 2 g amoxicillin infusions t.i.d (6 g/d) resulted in median pleural C_{min} of 9.4 mg/L [7.1 – 13.1]. Of 29 paired samples analyzed, five (17%) revealed pleural concentrations of amoxicillin under LLOQ. Four of the 22 patients (18%) initially treated by intermittent infusions of amoxicillin - 6 g/d t.i.d – were switched to continuous infusions after results of pleural concentrations.

Using continuous intravenous infusions of amoxicillin 6 g/d, the median pleural C_{ss} of amoxicillin was 10.8 mg/L [7.1 – 13.1] and only one pleural sample of the 21 analyzed was under LLOQ. Five out of 13 patients (38%) received increasing doses of amoxicillin after blood and pleural samples were analyzed. Median C_{ss} of amoxicillin in pleural fluid was

higher with 9 g/d (12.4 mg/L [9.4 – 16.3], $P= 0.32$). With continuous administration, the median amoxicillin coefficient of diffusion in pleural space was 68% [49 – 82].

Pleural concentrations of amoxicillin did not significantly differ between continuous and intermittent infusions ($P= 0.34$). This comparison remained non-significant even using multiple analyses: using single-sample patient or keeping all samples, removing data under LLOQ or keeping them uncoded as null (worst-case scenario).

Amoxicillin concentrations in pleural fluid were similar with 6 g or 9 g per day ($P= 0.47$). Oral administration resulted in lower pleural fluid concentrations than continuous or intermittent infusions ($P< 0.01$ for each).

Pleural and plasma concentrations of amoxicillin were correlated with intermittent intravenous ($r= 0.64$; $P< 0.01$) and with intravenous continuous administration ($r= 0.54$; $P= 0.03$), but not with oral administration ($P= 0.17$).

3.3 Metronidazole

Metronidazole C_{min} in blood and pleural fluid were measured in eleven paired samples, from seven patients (Supplementary Table S1). Metronidazole was orally given (1.5 g per day, t.i.d). Median creatinine clearance was 110 mL/min [96 – 115] with only one patient having acute renal failure ($Cl_{creat} = 33$ ml/min). Median albumin concentration was 24 g/L [20 – 26] and median weight was 79 kg [75 – 89].

The median time from initiation of metronidazole to sample collection was 84 hours [68 – 112]. The median time from last dose to sample collection to determine C_{min} was 4 hours [3.8 – 5.8]. Plasma and pleural fluid median C_{min} were, respectively, 20 mg/L [17.5 – 24.2] and 18.4 mg/L [15.7 – 22.8]. The median coefficient of diffusion for metronidazole in pleural space was 96% [93 – 98]. Blood and pleural concentrations of metronidazole were highly correlated ($r = 0.97$, $P < 0.001$).

4. Discussion

The primary findings of this study focusing on amoxicillin and metronidazole PK in pleural infections are as follows: i) the median coefficient of diffusion in pleural fluid was 67% and 96% for amoxicillin and metronidazole, respectively; ii) in most cases, a regimen of intravenous amoxicillin 6 g/d achieved pleural concentrations within the therapeutic target; iii) although unquantifiable concentrations were less frequent with continuous infusions of amoxicillin, pleural concentrations did not significantly increase, in comparison with intermittent infusions.

To the best of our knowledge, this is the largest report of PK data of antibiotics in pleural fluid to date. However, pleural infections are common with an increased incidence in recent years [17]. Despite the pivotal role of drainage in the early stage of management of pleural infections, a well-conducted antimicrobial therapy is requested to obtain clinical cure and avoid relapse. This is why optimizing antibiotic therapy in the setting of pleural infections is crucial. In a landmark study using a rabbit model of pleural empyema, the concentrations of several antibiotics have been measured in pleural fluid (ceftriaxone, penicillin, metronidazole, vancomycin and clindamycin), with striking heterogeneities [8]. Another experimental model using four healthy horses confirmed favorable metronidazole pharmacokinetics in pleural fluid, which achieved an AUC_{24}/MIC_{90} ratio for 22 clinical *Bacteroides* isolates of 84.9% [18]. However, to our knowledge, no measure of metronidazole diffusion in pleural fluid has been reported in humans. A recent review of antibiotics PK in humans highlighted the scarcity of data for amoxicillin diffusion in infected pleural fluid, despite this antibiotic is part of first-line choice for pleural infections worldwide (in combination with clavulanic acid) [4]. In our study, we showed that intravenous amoxicillin frequently reached pleural concentrations target (>5 mg/L), with a median coefficient of diffusion at 68% in pleural fluid when administered continuously. However, our ambispective cohort was composed mostly of

patients without kidney failure nor obesity. These characteristics could affect our findings making them non-generalizable in patients with renal failure or high body mass index (BMI). Continuous or intermittent infusions were associated with comparable pleural concentrations of amoxicillin, but our study was underpowered to compare these two modes of infusion due to limited sample size. Despite the short half-life of amoxicillin in patients with normal renal function (1 h), trough concentrations in pleural fluid were surprisingly high, which suggests a much longer half-life in pleural fluid as compared to blood [19].

Pleural infections are often polymicrobial, but with no pathogen identified on pleural fluid culture in almost half of pleural infections. Consequently, minimal inhibitory concentrations (MICs) are not available. Based on the known epidemiology, the main pathogens are streptococci (*Streptococcus anginosus* group or *S. pneumoniae*) and anaerobes in community-acquired infections [20]. Most of these streptococci have low aminopenicillin MIC, but *S. mitis/oralis* or *S. pneumoniae* may present with amoxicillin MICs equal or greater than 1 mg/L in nearly 10% of cases [21]. In this setting, the empirical antibiotic regimen in pleural infections, including the choice of the drug and the appropriate dose, is challenging. The current guidelines recommend, for time-dependent antibiotics, target concentrations between four and eight times the MIC, for 100% of the dosing interval in order to obtain a maximal bactericidal effect [13]. Considering the global microbiology, and amoxicillin MIC for streptococci involved in pleural infections, a target of at least 5 mg/L in pleural fluid seems to be appropriate. However, precise estimation of the percentage of time above the MIC can only be achieved through PK modeling. In addition, this threshold may be overestimated for non-continuous administration of a short half-life antibiotic like amoxicillin (approximately one hour) in the setting of bacterial species highly susceptible to penicillin. The findings of this study advocate for initial treatment with intravenous amoxicillin 6 g/day. Oral switch should be considered only once infection is controlled, given the sub-optimal PK data with

oral amoxicillin (i.e, 45% of patients with pleural concentrations <5 mg/L). Our results suggest that the monitoring of antibiotic concentrations in pleural fluid can be useful in the management of pleural infections. In our center, we performed repeated therapeutic thoracenteses as a first-line method of drainage for complicated parapneumonic effusion and most pleural empyema, which provides easy access for therapeutic drug monitoring in pleural fluid. This would not be feasible with chest tube flushing.

This work has limitations. First, as an observational single-center study, our findings may not be generalizable. Underlying comorbidities of patients having pleural infection may differ according to case mix. For example, severe malnutrition, high BMI or renal failure could affect PK parameters of antibiotics. In addition, our study did not explore the protein binding in pleural fluid, the role of vascular permeability or the influence of pleural thickness. Second, this study was ambispective, and so, suffers from inherent biases due to a partial retrospective design. However, the proportion of missing data for the retrospective part of the cohort was low. Third, the sample size of this study remains limited to 40 patients with multiple antibiotic regimens, which cannot allow us to build a PK model of amoxicillin into the pleura.

Nevertheless, we report the largest data of amoxicillin in pleural space and deliver some important messages. Fourth, we were unable to measure clavulanic acid concentrations in pleural fluid. This would have been of interest, and the rare available data suggest good diffusion of clavulanic acid in pleural fluid in animals [22]. Fifth, LLOQ generated an area of uncertainty by the absence of precise quantification below the admitted cut-off. However, the sensitivity of the method used in the present study allows to quantify antibiotic concentrations above the predefined target of 5 mg/L.

5. Conclusions

Amoxicillin diffusion to pleural space was appropriate with intravenous dose of 6 g/day, with achievement of therapeutic targets on pleural fluid in most cases. Metronidazole had an

excellent diffusion in pleural fluid, even administered orally. Monitoring antibiotic concentrations at the infected site, especially in severe and difficult-to-treat infections such as pleural infections, may optimize the chances of clinical success. Further PK studies in the field of pleural infections are needed for other antibiotics such as third-generation cephalosporins.

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Declarations

Funding: This work was not funded.

Competing Interests: The authors have nothing to disclose.

Ethical Approval: The study was approved by the Ethics Committee of Rennes University Hospital (approval number 18.77). A written consent to participate was waived.

Sequence Information: Not applicable

Author contributions

DLP, PC, BB and TG collected data. DLP did the analysis and takes responsibility for the integrity of the data. CRL generated the figure. DLP, SJ, MCV and PT co-wrote the original draft. PC, TG, CRL, BB, LA and SB reviewed and edited the manuscript.

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Tables

Table 1. Baseline characteristics including amoxicillin measures in pleural fluid

Variables	Amoxicillin				
	Oral	i.v. intermittent infusions	i.v. continuous infusions		
Pharmacokinetic parameters					
Route of administration					
Doses	2 g t.i.d	2 g t.i.d	6 g per day	9 g per day	12 g per day
Number of patients [#] , n	6	21	13	4	2
Number of samples, n	11	29	21	6	3
Number of samples with pleural concentration < LLOQ, n	5	5	1	0	0
Median time from AMX start to sample collection [IQR], hours	190 [47 - 214]	70 [55 - 144.5]	70 [51.7 - 94.5]	122.3 [117.4 - 136.5]	304 [63.3 - 352]
Median time from last dose to sample collection [IQR], hours	4 [3.2 - 4.1]	6 [5.3 - 8]	-	-	-
Median pleural fluid concentration [IQR], mg/L	5.2 [ND - 6.4]	9.4 [8 - 13.1]	10.8 [7.1 - 13.1]	12.4 [9.4 - 16.3]	31.3 [8.9 - 46]
Median plasma concentration [IQR], mg/L	8.8 [ND - 17.4]	ND [ND - 6.1]	16.6 [13 - 21.6]	18.7 [13.8 - 19.5]	55.4 [35.5 - 75.5]
Median ratio pleural/plasma concentration [IQR]	NC	1.64 [0.8 - 2.3]	0.67 [0.45 - 0.79]	0.84 [0.70 - 0.95]	NC
Characteristics					
Pleural empyema, n (%)	4 (67)	11 (52)	7 (54)	3 (75)	1 (50)
CPPE, n (%)	2 (33)	10 (48)	6 (46)	1 (25)	1 (50)
Renal failure, n (%)	0 (0)	2 (10)	1 (8)	0 (0)	0 (0)
Median GFR [IQR], mL/min	108 [105 - 110]	106 [99 - 131]	103 [94 - 114]	104 [100 - 115]	NA
Median albumin concentration [IQR], g/L	28.2 [24.1 - 33.5]	32.8 [28.3 - 37.6]	25.1 [23.5 - 30.2]	26.1 [24.3 - 31.6]	NA
Median weight [IQR], kg	67.7 [57.9 - 83.7]	63 [57.3 - 65.8]	74 [56.1 - 84.3]	83.3 [73 - 94.5]	NA
Outcomes					
3-month mortality, n (%)	0 (0)	1 (5)	1 (8)	0 (0)	0 (0)
Surgical referral, n (%)	0 (0)	2 (10)	2 (15)	0 (0)	1 (50)
Need of increased doses, n (%)	3 (50)	1 (5)	5 (38)	0 (0)	0 (0)

AMX = amoxicillin

CPPE = complicated parapneumonic effusion

GFR = glomerular filtration rate

IQR = interquartile range

i.v = intravenous

LLOQ = lower limit of quantification

ND = Non determined, under the lower limit of quantification (LLOQ)

NC = Not calculated

NA = Not applicable

t.i.d = thrice a day

Four of 40 patients had paired samples receiving two different regimens during the treatment of pleural infection, and one had samples from three different regimens.

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Figure Legends

Figure 1. Amoxicillin concentrations in pleural fluid by dosage regimen, administration route and sampling time. The hatched area represents the range below the lower limit of quantification.

t.i.d = thrice a day.

