Moxifloxacin vs Ampicillin/Sulbactam in Aspiration Pneumonia and Primary Lung Abscess

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Abstract

Background: Aspiration pneumonia (AP) and primary lung abscess (PLA), are diseases following aspiration of infectious material from the oropharynx or stomach. An antibiotic therapy, also covering anaerobic pathogens, is the treatment of choice. In this study we compared moxifloxacin (MXF) and ampicillin/sulbactam (AMP/SUL) concerning efficacy and safety in the treatment of AP and PLA.

Methods: Patients with pulmonary infections following aspiration were included in a prospective, open-label, randomized, multicenter trial. Sequential antibiotic therapy with MXF or AMP/SUL was administered until complete radiologic and clinical resolution.

Results: A total of 139 patients with AP and PLA were included, 96 were evaluable for efficacy (EE, 48 patients in each treatment group). The overall clinical response rates in both groups were numerically identical (66.7%). MXF and AMP/SUL were both well tolerated, even after long-term administration [median duration of treatment (range) in days MXF versus AMP/SUL: AP 11 (4–45) vs 9 (3–25), PLA 30.5 (7–158) vs 35 (6–90)].

Conclusion: In the treatment of aspiration-associated pulmonary infections moxifloxacin appears to be clinically as effective and as safe as ampicillin/sulbactam; but, however, having the additional benefit of a more convenient (400 mg qd) treatment.

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Introduction

Aspiration pneumonia (AP) and primary lung abscess (PLA) are rare diseases, but they can result in life-threatening complications, including severe hemoptysis [1]. Mortality rates of up to 15–20% have been reported in the literature [2, 3]. The initial step in the pathogenesis of these diseases is aspiration of infectious material from the oropharynx or stomach. Therefore the expected microbiological flora generally comprises a mixed spectrum, including anaerobic, microaerobic and aerobic microorganisms [4–6]. A number of risk factors for aspiration are known such as compromised consciousness, esophageal diseases, alcoholism, drug overdosage, seizure disorders, general anesthesia and neurological disorders [7–9]. Generally, AP and PLA present as subacute infections and the clinical signs are comparable to those of other forms of pneumonia. The primary therapeutic strategy for AP and PLA is an antibiotic treatment, which needs to be prolonged in the presence of abscess formation. Because of its good in-vitro activity against anaerobes, Penicillin G has been the drug of choice for a long time, until it has been outperformed by clindamycin or ampicillin + sulbactam in a more recent study [10]. Beside this, a number of other antibiotics such as third-generation cephalosporins, piperacillin or fluorquinolones are recommended [11], although there are no data available to date that support the use of any of these regimens on the basis of recent and adequate clinical trials. In the last years, the problem of changing patterns of antimicrobial resistance has become common and it seems to be important to add other antibiotics to the standard treatment regimens based on valid data. Therefore, the present study compared the clinical efficacy and safety of moxifloxacin (MXF) with that of one of the established regimens consisting of ampicillin + sulbactam (AMP/SUL).

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Materials and Methods

Study Subjects and Study Design

From February 2001 to January 2005 patients with AP or PLA or both (inclusion and exclusion criteria see table 1) were recruited from 15 centers in Germany (1–33 patients per center) and were included in a prospective, randomized, open-label and comparative multicenter study with a parallel group design. Patients admitted to hospital with radiographic and clinical signs of AP or PLA following proven or highly suspected aspiration requiring initial parenteral antibiotic treatment were randomized to receive sequential therapy (switch from parenteral to oral therapy) consisting of either MXF or AMP/SUL. Randomization was performed locally on the basis of a centrally established code. A random list by investigator was generated centrally and the local investigator selected chronologically random numbers in ascending order. Antibiotics were administered until complete resolution of the clinical, radiological, and laboratory alterations or until no further regression could be observed. Bacteriological samples were cultured in all patients prior to treatment. Vital signs, i.e., temperature, heart rate, respiratory rate, and blood pressure, were monitored daily up to the time of patient's discharge from the hospital or to the end of treatment (EOT). A standard 12-lead electrocardiogram was to be performed pretreatment and within 30 min after intravenous application of the first dose of study medication on days 1 and 3. Adverse events were assessed up to the test-of-cure (TOC) visit, planned 5–14 days after the EOT visit. The primary efficacy variable was the clinical response determined at the TOC visit. Secondary endpoints were the clinical and bacteriological response and safety, being evaluated at EOT and TOC visit. A written informed consent in accordance with the declaration of Helsinki was obtained prior to therapy and the trial was approved by the ethics commitees of all participating centers. The study was conducted under GCP guidelines.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:
Age > 18 years
Radiographic signs of pneumonia and/or lung abscess after witnessed or suspected aspiration
At least two of the following symptoms:
Cough
Dyspnea
Crackles
Pleuritic pain
Dullness of percussion
At least one of the following clinical signs:
Fever (> 38 °C)
Leukocytosis (> 10/nl)
Purulent sputum
Hypothermia (< 36.5 °C)
Leukopenia (< 4/nl)
Written informed consent in accordance with the Declaration of Helsinki
Exclusion criteria:
Retrostenotic pneumonia
Tuberculosis
Endocarditis
iv drug abuse
Antibiotic treatment within 24 h prior to inclusion
Pregnant or nursing women
Severe hepatic or nephrologic disorders
HIV infection
Mechanical ventilation > 48 h prior to enrolment
Known congenital or sporadic syndrome of QTc prolongation or concomitant medication known to increase the QTc interval

Patients

Sample size calculation was made according to the formula published by *Farrington* and *Manning* [12]. For sample size estimation a clinical cure rate of 85% in both treatment arms was assumed. In addition an indifference delta of 20%, an α-level of 0.05, a power of 80%, and a validity rate of 80% was preconditioned. This calculation resulted in a number of a least 154 subjects, who should be included. All patients, who were enrolled and randomized, were included into the intention-to-treat (ITT) population. As all randomized subjects received at least one dose of study medication the valid-for-safety population was the same as that for the ITT analysis. The evaluable for efficacy (EE) population contained all subjects of the ITT population who were evaluable for efficacy. From all patients of the EE population valid data were available regarding the primary endpoint.

Inclusion and exclusion criteria are shown in table 1.

Study Medication

After randomization therapy was initially given intravenously. A switch to oral administration could be made after at least 6 days of parenteral therapy at the investigators' discretion. The minimum treatment period was 48 h in case of treatment failure. A maximal treatment duration was not specified in the protocol.

Patients in the MXF group received 400 mg of MXF (Avelox®, Bayer HealthCare) intravenously every 24 h, administered over 60 min. Thereafter, MXF was given orally as a 400-mg tablet once a day. AMP/SUL (Unacid®, Pfizer) was given intravenously at a dose of 2 g AMP + 1 g SUL over 20 min thrice a day and after conversion to oral therapy twice a day at a dose of 750 mg sultamicillin (two tablets of 375 mg).

Collection of Data

Clinical and laboratory examinations were performed pretreatment, at follow-up visits during treatment, at the EOT visit, and at the TOC visit.

Bacteriological Sampling

From all patients microbiological samples were obtained before treatment and if possible at EOT. Invasive techniques were not required but it was tried to obtain valid material from the lower respiratory tract (LRT) by bronchoscopy whenever possible. From all samples a gram-staining and aerobic, and anaerobic cultures, were carried out. Anaerobic cultures were performed for material from the LRT, which was gained by bronchoalveolar lavage (BAL), protected specimen brush (PSB) or transthoracic puncture only. Bacteria isolated from these samples were considered to be definite causative pathogens. If valid material from the LRT could not be obtained, a sputum sample or bronchial secretion was used for microbiological procedures (except of anaerobic culture) and considered to be representative if > 25 polymorphonuclear leukocytes and < 10 squamous epithelial cells/low-power field were found. In order to receive valid bacteriological results the transportation time of microbiological

samples was minimized by performing the microbiological testing at the laboratory institutions of each clinical center.

Evaluation of Efficacy

The primary efficacy variable was the clinical response 5–14 days after the end of the study drug period (TOC) in the EE-population. The disappearance of acute signs, symptoms, and laboratory alterations related to infection in combination with resolution of radiographic abnormalities to a degree that was considered normal for the individual patient was defined as clinical cure. A clinical response with partial resolution of clinical, radiographic, and laboratory abnormalities was classified as an improvement. Any failure to respond or insufficient responses to the study drug that required a modification treatment or resulted in death from the primary diagnosis were considered a clinical failure.

For the primary efficacy variable a two-sided 95% confidence interval (CI) for the true difference of the two clinical success rates (the success rate for MXF minus the rate of the comparator group) was calculated using Mantel–Haenszel weights. If the lower limit of this CI was > –20%, MXF had proven to be clinically not less effective than the comparator regimen. MXF was deemed to be superior to AMP/SUL if the lower limit of this CI was > 0. In this analysis any clinical failures occurring before the TOC visit were counted as clinical failure at the TOC visit. The secondary efficacy variables were analyzed exploratively in the same way as the primary efficacy variable. All tests were two-sided and performed at the 0.05-significance level. The primary efficacy analysis was in the EE population, the ITT-analysis was supportive. Statistical analyses were adjusted to the subindications (AP, PLA, and AP with abscess-formation).

Demographic and baseline characteristics were summarized by treatment group using mean and standard deviation for quantitative data or frequency counts for categorical data. Comparability of treatment groups was established for both the EE and ITT analyses (test for homogeneity between treatment groups with Fisher's exact test).

The safety of both treatment groups was described by summary statistics and no formal analyses were performed.

Results

According to the initial sample-size calculation, at least 154 individuals should have been included in this trial. But during the course of recruitment evidence emerged indicating a lower validity rate as expected (i.e., 12 patients were excluded from the study after randomization because a previously unknown bronchial malignancy was diagnosed). In order to achieve the required number of valid patients, the total sample size would have had to be substantially increased. Taking into account the slow recruitment rate up to this time, this appeared to be infeasible. Therefore, the study was prematurely terminated with a total of 139 subjects enrolled. All of the 139 subjects were valid for ITT analysis. The study was analyzed as planned.

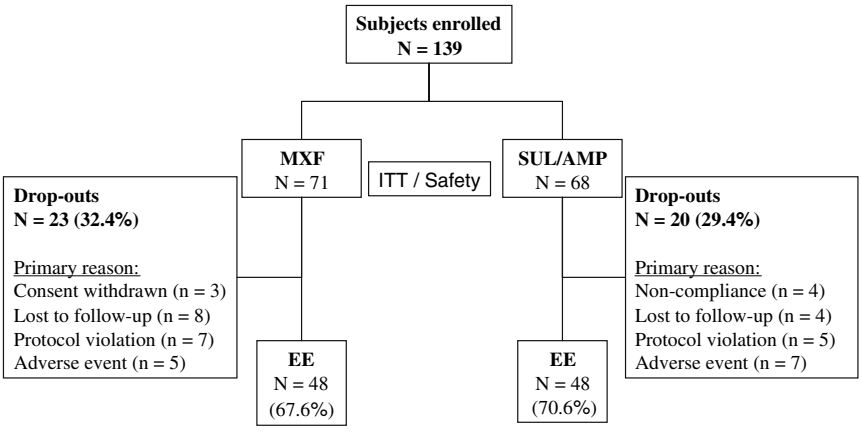

Figure 1. Overview of subject disposition.

Of the 139 subjects enrolled, 71 subjects were randomly assigned to the treatment with MXF and 68 to the treatment with AMP/SUL. Seventy-six subjects of the total subject population (54.7%) did not complete the whole study course, mainly because of treatment failure (18.7%) or adverse events (13.7%). The percentages of premature terminations as well as the primary reasons for discontinuation were comparable between the two treatment groups ($p > 0.05$). The disposition of subjects by treatment groups is displayed in figure 1. All 139 randomized subjects received at least one dose of study medication.

Of the 96 subjects in the EE population, 48 were receiving MXF, and 48 were randomized to AMP/SUL. The baseline characteristics of the patients included in the EE analysis are summarized in table 2, and testing for homogeneity showed that they were comparable in the two groups. There was no statistically significant imbalance found between the two treatment arms according to laboratory abnormalities, clinical signs and symptoms, and vital signs at pre-treatment visit or at follow-up-visits, including EOT and TOC visits (data not shown). All patients in EE population received a full course of study medication in accordance to the protocol. The treatment periods of the study subjects were rather variable and ranged between 1 and 158 days (safety/ITT population). For details on duration of therapy see table 3.

Bacteriological Findings

Microbiological procedures were performed from samples of all subjects in the ITT group prior to treatment. A total of 102 causative RTI-pathogens were identified in 70 patients, and are summarized in table 4. In 46 subjects (33.1% of all subjects) only one causative organism was found. The most frequently found pathogens in the ITT population were *Staphylococcus aureus* (14% of all subjects), *Klebsiella pneumoniae* (7%), *Escherichia coli* (7%), anaerobes (6.5%), and *Pseudomonas aeruginosa* (6%). Two subjects in each treatment group of the EE population

Table 2
Characteristics of patients of the EE population, underlying conditions predisposing to aspiration and concomitant diseases; p-values were all >0.05 in Fisher's exact test.

Characteristics	MXF (*n* = 48)	AMP/SUL (*n* = 48)
Mean age in years	59.5 ± 16.8	61.3 ± 14.5
Sex (male)	37 (77.1)	33 (68.8)
Sub-diagnosis:		
Aspiration pneumonia (AP)	29 (60.4)	33 (68.8)
Primary lung abscess	15 (31.3)	11 (22.9)
AP with lung abscess	4 (8.3)	4 (8.3)
Underlying conditions/ concomitant diseases:		
Any finding	47 (97.9)	43 (89.6)
Nervous system disorders	23 (47.9)	22 (45.8)
COPD	11 (22.9)	9 (18.8)
Cardiovascular disorders	9 (18.8)	19 (39.6)
Gastrointestinal disorders	5 (10.4)	6 (12.5)
Diabetes mellitus	8 (16.7)	9 (18.8)
Neoplasm (excl. bronchial carcinoma)	10 (20.8)	8 (16.7)
Antibiotics before study	7 (14.6)	17 (35.4)
Hospitalization > 48 h prior to enrollment	12 (25)	12 (25)

Values given in parenthesis are *n* (%). COPD: chronic obstructive pulmonary disease; MXF: moxifloxacin; AMP/SUL: ampicillin/ sulbactam

Table 3
Duration of antibiotic treatment in days according to the sub-indication and route of administration; p-values were all > 0.05 in Fisher's exact test.

Primary diagnosis and route of administration	MXF mean ± SD	AMP/SUL mean ± SD
All diagnoses		
Intravenous	8.9 ± 3.5 7 (4–20)	8.2 ± 3.1 7 (3–18)
Oral	28.1 ± 33.4 15.0 (2–152)	23.1 ± 24.7 13.5 (2–89)
Combined[a]	26.2 ± 29.2 15 (4–158)	21.1 ± 23.3 11 (3–106)
Aspiration pneumonia (AP)		
Combined	13.1 ± 7.7 11 (4–45)	11.0 ± 6.0 9 (3–25)
Primary lung abscess		
Combined	48.4 ± 40.6 30.5 (7–158)	40.2 ± 27.4 35 (6–90)
AP with cavitation		
Combined	43.3 ± 31.8 36.5 (16–84)	46.5 ± 45.1 35 (10–106)

Values given in parenthesis are median (range), SD: standard deviation; combined: intravenous + oral therapy. [a]Not all patients were switched to oral administration [only 61% patients in the moxifloxacin (MXF) group and 59% in the ampicillin/sulbactam (AMP/SUL) group received oral medication]

presented bacteremia with *Enterococcus* spp., *S. aureus*, *Staphylococcus hemolyticus*, *Staphylococcus hominis*, *Klebsiella oxytoca*, and *P. aeruginosa* (the two subjects in the comparator group had two pathogens each). All four patients were clinical failures.

Clinical Response

The primary efficacy criterion was the comparison of the clinical response rate at the TOC visit. Numerically, the success rates were identical in the two treatment groups with 66.7%. The calculation of the 95% CI for treatment group differences resulted in an interval that almost symmetrically embraced the 0 value, with a lower confidence boundary of –20.8%. The statistical evaluation for the EE population as well as for the ITT population are shown in table 5. In the secondary efficacy analyses (i.e., clinical response at different time points of the study course, concomitant treatment with other antibiotics, length of stay in the hospital, and changes in disease-related laboratory parameters and vital signs) there were no statistical significant differences observed between the two study groups (data not shown).

A total of 20 patients (14.4%) died during the study period, with six receiving MXF and 14 being treated with AMP/SUL. The mortality was considerably higher (but not statistically significant) in the AMP/SUL group than in the MXF group, but none of the reported deaths in any of the treatment groups were considered to be drug-related.

Premature Discontinuation and Adverse Events

The overall incidence of treatment-emergent adverse events (TEAEs) was 54.9% in the MXF group and 54.4% in the AMP/SUL group, with gastrointestinal disorders (five MXF, six AMP/SUL) and investigations (six MXF, two AMP/SUL; p = 0.28), e.g., elevated liver enzymes (three MXF, two AMP/SUL), being the most frequently observed TEAEs. There were five cardiac TEAE in the MXF group (2× pulmonary edema, peripheral edema, sudden cardiac death and angina pectoris) vs eight in the comparator group (2× pulmonary edema, peripheral edema, myocardial ischemia, myocardial infarction, acute cardiac failure, syncope and cardio-respiratory arrest). Twenty-one subjects of the MXF group (29.6%) and 21 subjects of the AMP/SUL group (30.9%) experienced serious TEAEs. Thus, the incidences of TEAEs and serious TEAEs were similar in the two treatment groups.

Twelve subjects in the MXF group (16.9%) prematurely terminated the study because of adverse events. Seven MXF-subjects (9.9%) experienced TEAEs for which a possible relationship to the study medication was assumed. Only in three patients a definite relationship to the study medication was identified, leading to permanent discontinuation of treatment (i.e., drug hypersensitivity and febrile temperature, elevated liver enzymes, pro-

Table 4
Pretherapy bacteriological findings in patients (ITT) with AP and PLA from RTI.

Isolates	All diagnoses (*n* = 102)	AP (*n* = 64)	PLA (*n* = 27)	AP with abscess formation (*n* = 9)
Anaerobes:	9 (9.0)	0 (0)	8 (29.6)	1 (11.1)
Bacteroides fragilis	1	0	1	0
Fusobacterium spp.	2	0	2	0
Fusobacterium nucleatum	1	0	1	0
Prevotella spp.	1	0	0	1
Prevotella intermedia	1	0	1	0
Prevotella denticola	1	0	1	0
Prevotella oralis	2	0	2	0
Aerobes and facultative aerobes:	91 (91.0)	64 (100)	19 (70.4)	8 (88.9)
Gram-positives	41 (41.0)	26 (40.6)	10 (37.0)	5 (55.6)
Staphylococcus aureus	20	15	4	1
Streptococcus spp.	8	5	2	1
Streptococcus pneumoniae	4	1	1	2
Streptococcus mileri	2	0	1	1
Others	7	5	2	0
Gram-negatives	52 (51.0)	38 (59.4)	9 (33.4)	3 (33.4)
Escherichia coli	10	7	1	1
Klebsiella pneumoniae	10	7	2	1
Klebsiella oxytoca	2	2	0	0
Haemophilus influenzae	5	2	2	1
Haemophilus parainfl	2	2	0	0
Pseudomonas aeruginosa	8	7	1	0
Pseudomonas spp.	1	1	0	0
Enterobacter spp.	2	2	0	0
Citrobacter freundii	2	1	1	0
Proteus mirabilis	5	3	1	0
Serratia marcescens	3	2	1	0
Moraxella catharalis	1	1	0	0
Morganella morganii	1	1	0	0

Values given in parenthesis are *n* (%); AP: aspiration pneumonia; PLA: primary lung abscess

longed QT-interval in a patient with multiple cardiovascular comorbidities and concomitant QT-prolonging medication). The outcome of the possible drug-related TEAEs in the MXF group was ''resolved'' in six subjects and ''improved'' in one. In the AMP/SUL group nine subjects (13.2%) were discontinued because of adverse events, with eight (11.8%) considered to be possibly drug related. In four of these patients study medication was permanently discontinued due to definitely drug-related adverse events (i.e., 2× drug hypersensitivity, diarrhea, elevated liver enzymes). In six subjects with assumed drug-related TEAEs the outcome was described as ''resolved'', in one as ''worsened'', and one patient was lost to follow-up. Only in one patient of the ITT/Safety population a surgical intervention was necessary due to pyothorax. Treatment failure leading to premature discontinuation occurred in 11 (15.5%) patients of the MXF group and in 15 (22.1%) subjects receiving AMP/SUL.

Discussion

Aspiration of secretion from the oropharynx or stomach is considered to be the initial step in the pathogenesis of AP and PLA. Therefore coverage of anaerobic bacteria is an important requirement in the antibacterial treatment of aspiration associated pulmonary infections, because of the possible anaerobic colonization of the oral cavity. In this study the data indicated that MXF, compared to AMP/SUL, is clinically at least equally effective in terms of response rates, by achieving a clinical cure in approximately two-thirds (66.7%) of patients. Both treatment regimens were well tolerated with premature discontinuation due to adverse events, definitely considered being drug-related, only seen in seven patients of the ITT population.

The overall clinical response rates observed in this study appear to be relatively low compared to previously published studies, in which success rates of up to 95% were reported [5, 6, 8, 21]. Unfortunately, none of these studies refers to underlying diseases and conditions predisposing to aspiration, severity of the disease, or mortality. *Perlman* et al. [13] demonstrated the impact of underlying diseases and severity of the disease on the outcome of patients with lung abscess. In this report the mortality rate was 1.8% for uncomplicated PLA and 75%

Table 5
Results of the primary efficacy analysis: comparison of clinical success rates at the TOC visit (EE and ITT population).

	EE population (n = 96)		ITT population (n = 139[a]; n = 114[b])	
	MXF	**AMP/SUL**	**MXF**	**AMP/SUL**
All indications:				
Success rate (n/N %)	32/48 (67%)	32/48 (67%)	37/71 (52%)[a] 37/56 (66%)[b]	39/68 (57%)[a] 39/58 (67%)[b]
Difference in success rates estimate[c] 95% CI[c]	−1.6% [−20.8%; 17.6%]		−5.6%[a] [−22.5%; 11.2%][a] −1.2%[b] [−18.9%; 16.5%][b]	
Aspiration pneumonia:				
Success rate (n/N %)	17/29 (59%)	21/33 (64%)	20/39 (51%)[a] 20/32 (63%)[b]	21/40 (53%)[a] 21/33 (64%)[b]
Difference in success rates 95% CI	[−29.7%; 19.7%]		[−23.5%; 21.1%][a] [−25.0%, 22.7%][b]	
Primary lung abscess:				
Success rate[b] (n/N %)	12/15 (80%)	9/11 (82%)	14/25 (56%)[a] 14/20 (70%)[a]	14/21 (67%)[a] 14/19 (74%)[a]
Difference in success rates 95% CI	[−33.6%; 30.0%]		[−39.3%; 18.0%][a] [−32.6%, 25.3%][b]	
Aspiration pneumonia with cavitation:				
Success rate[b] (n/N %)	3/4 (75%)	2/4 (50%)	3/6 (50%)[a] 3/4 (75%)[b]	4/7 (57%)[a] 4/6 (67%)[b]
Difference in success rates 95% CI	[−49.8%; 99.8%]		[−66.2%; 51.9%][a] [−55.8%, 72.4%][b]	

There were neither signs of inhomogeneity of strata in odds ratios [Breslow-Day test: p = 0.71 (PP); p = 0.87(ITT)]: nor signs of a main treatment effect [Cochran-Mantel-Haenszel test: p = 0.87 (PP); p = 0.57 (ITT)]; EE: evaluable for efficacy; ITT: intention to treat; MXF: moxifloxacin; AMP/SUL: ampicillin/sulbactam; [a]Analysis with missing/indeterminate values treated as non-successes; [b]Analysis with missing/indeterminate values being excluded from the analysis; [c]This 95% CI was calculated based on a statistical model considering the 3 indication strata

in immunocompromised patients. These findings were supported by a study from *Mori* et al. [14], who reported a 2.4% mortality rate in patients with community-acquired lung abscess, compared to a 66% mortality rate in hospital-acquired cases with a higher frequency of underlying diseases. In a more recent study, *Allewelt* et al. [10] reported clinical response rates (approx. 70%) comparable to the results of this study. Similar to our study most of the patients in the report of *Allewelt* et al. (94%) presented with at least one underlying disease or condition predisposing to aspiration, and the observed mortality rate (12.9%) was almost identical to the one in this study (14.4%), suggesting comparability of the study populations and that the patients were probably suffering from a more severe course of the disease than in the earlier reports. Furthermore there is evidence indicating a prognostic impact of causative organisms found in patients with lung abscess. *Hirshberg* et al. [15] demonstrated that patients with lung abscess had a worse prognosis if *P. aeruginosa*, *K. pneumoniae* or *S. aureus* were identified. In our study the most frequently isolated bacteria were *S. aureus* (13% of all subjects), *K. pneumoniae* (7%), *E. coli* (7%), and *P. aeruginosa* (6%), thus comprising all microbes mentioned in the report of Hirshberg et al. to be associated with a worse outcome.

Although one recent study by *Wang* et al. [16] indicates a possible change in the predominant bacterial flora found in patients with lung abscess toward gram-negative enteric bacteria (i.e., *K. pneumoniae*), there is still a broad acceptance of the pivotal role of anaerobic bacteria as the major etiologic agent in PLA and AP [17]. Early studies indicated that anaerobes were causing 60%–80% of cases of lung abscess [4, 18, 19]. Most of the studies, in which anaerobes were isolated in a high number of cases, used representative techniques such as transthoracal puncture, transtracheal aspiration, BAL, or endoscopic PSB to obtain valid samples from the LRT for microbiologic procedures. Compared to these investigations the number of anaerobic bacteria identified in our study was relatively low, probably because invasive techniques were not required in the protocol and therefore a representative sample for anaerobic culture could not be obtained in all cases. Furthermore a large number of our patients were treated with various antibiotic agents prior to enrollment, and it is well established that anaerobic bacteria in lung infections cannot be easily recovered after receipt of any antibiotic treatment, even if valid specimens were obtained [9]. Therefore, the etiologic role of anaerobic bacteria might be underestimated in our investigation. Although bacteriological investigations are not generally

advised in pulmonary infections, in our opinion it seems to be useful to perform representative microbiologic procedures in patients with aspiration associated pulmonary infection to identifiy anaerobes and/or to rule out gram-negative enteric bacteria (like, i.e., *P. aeruginosa*) or methicillin resistant *S. aureus* (*MRSA*), which require a distinct antibacterial therapy. Anyhow, the application of a fiberoptic bronchoscopy is highly advisable in all patients presenting with suspected aspiration associated pulmonary infections, especially when abscess formation is found on a chest radiography, to rule out important differential diagnoses, such as poststenotic cavernous pneumonia, cavernous pulmonary tuberculosis, or necrotizing bronchogenic carcinoma [20]. Nine patients were subsequently excluded from our study, because an underlying bronchogenic carcinoma was diagnosed by fiberoptic bronchoscopy.

Interestingly the number of isolated anaerobic bacteria in our study differed according to the type of infection. While anaerobes were found in almost one third (29.6%) of all cases presenting with solely lung abscess and in 11.1% of all patients suffering from AP with abscess formation, no anaerobic bacteria could be isolated from patients with AP, and gram-negative enteric bacteria (i.e., *E. coli*, *K. pneumoniae*, *P. aeruginosa*, etc.) appeared to be the most frequently identified pathogens (59.4%) in these patients, probably because nosocomial infections (28.8% of all patients (ITT population) were hospitalized > 48 h prior to enrollment) included in this study as well as community-acquired cases. On the other hand, this finding could also suggest that the microbiologic flora found in lung abscess or AP might comprise different bacteria and therefore these diseases should be treated as different entities. Because of the relative inhomogeneity of our study population (including nosocomial cases as well as community acquired), there is a need for further investigations addressing these questions.

The primary therapeutic strategy for AP and PLA is an antibiotic treatment, as widely accepted. Usually, uncomplicated AP needs be treated for 10–14 days [in our study median duration of treatment (in days) of AP: 11 (MXF) and 9 (AMP/SUL)], but in case of abscess formation a prolonged course of treatment is required until complete resolution of radiographic alterations [median duration of treatment (in days) of lung abscess in this study: 30.5 (MXF) and 35 (AMP/SUL)]. In this investigation only in 1/139 patients, a surgical intervention was necessary due to development of pyothorax, which needed to be drainaged.

In conclusion, the findings of this study lend good support to the authors' opinion that an antibiotic treatment, which needs to be given for a sufficient period of time, is the principal therapeutic strategy in the therapy of aspiration-associated pulmonary infections, if no complications occur such as severe hemoptysis, persisting bronchopleural fistulas, or pyothorax. And our results may suggest, that MXF could be an alternative antibiotic regimen for the treatment of AP and PLA, however, having the additional benefit of a more convenient treatment (400 mg qd).

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