

Ventilator-associated Sinusitis

Microbiological Results of Sinus Aspirates in Patients on Antibiotics

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Background: **The efficacy of systemic antibiotics on the treatment of ventilator-associated infectious maxillary sinusitis (VAIMS) is debated. The objective of this study was to determine the etiologic diagnosis of VAIMS in patients receiving antibiotics.**

Methods: **Patients mechanically ventilated for more than or equal to 72 h, who had persistent fever while on antibiotics for more than or equal to 48 h, underwent computed tomography scan followed by transnasal puncture of involved maxillary sinuses. VAIMS was defined as follows: fever greater than or equal to 38°C, radiographic signs (air fluid level or opacification of maxillary sinuses on computed tomography scan), and a quantitative culture of sinus aspirate yielding more than or equal to 10^3 colony-forming units/ml.**

Results: **Twenty-four patients had radiographic signs of sinusitis. The mean ± SD prior durations of mechanical ventilation and antibiotic exposure were 9.5 ± 4.7 days and 6 ± 4 days, respectively. Six unilateral and nine bilateral VAIMS were diagnosed in 15 patients. The median number of etiologic organisms per patient was two (range, one to four). The bacteriologic cultures yielded gram-positive bacteria (n = 21), gram-negative bacteria (n = 22), and yeasts (n = 5). Forty percent of causative agents were susceptible to the antibiotics prescribed. Seven patients with VAIMS developed 10 concomitant infections: ventilator-associated pneumonia (n = 5), urinary tract infection (n = 3), catheter infections (n = 2). In all cases of ventilator-associated pneumonia, the implicated agents were the causative agents of VAIMS.**

Conclusion: **In VAIMS patients on antibiotics, quantitative cultures of sinus aspirates may contribute to establish the diagnosis. The frequent recovery of microorganisms susceptible to the antimicrobial treatment administered suggests that therapy of VAIMS with systemic antibiotics may not be sufficient. (Key words: Microorgnisms; pneumonia; quantitative culture.)**

VENTILATOR-ASSOCIATED infectious maxillary sinusitis (VAIMS) is a frequently unrecognized cause of fever in critically ill patients.[1–6] Nasal intubation is an acknowledged risk factor.[1] In a recent study, VAIMS was observed in 40% of patients with nasotracheal intubation.[2] VAIMS may lead to sepsis, intracranial infections,[3] bacteremia,[1,4,5] thoracic empyema,[6] and pneumonia.[2] The systematic search for and treatment of VAIMS was found to be associated with a decrease in overall mortality.[2] However, the explanations for this improved survival rate remain speculative.[7]

The definition of VAIMS in the literature is elusive and variable.[8] Sinus aspiration and positive culture are required for accurate diagnosis.[8] Some investigators have recommended quantitative culture of sinus aspirate[1,2,8] because of the risk of specimen contamination by nasal flora.[1]

Opinions differ on the best therapeutic strategy for VAIMS. Some investigators recommend intravenous antimicrobial treatment in addition to sinus aspiration,[2,8] whereas others have shown that successful treatment can be achieved by sinus lavage using topical antibiotics.[1] Recent studies that focused on the concentration of antibiotics in sinus secretions and mucosa in patients treated with systemic antibiotics showed that adequate levels can be achieved.[10–12] VAIMS has been reported in patients on antibiotics.[1] One may speculate that antibiotics predispose to the overgrowth of resistant bacteria or that antibiotics are only partially effective in suppressing susceptible microorganisms caused by the presence of a closed space infection. We therefore studied the microbiological results of sinus aspirate cultures in patients who were receiving systemic antimicrobial treatment.

Methods

Study Population

This prospective study was conducted from April 1, 1995, to March 31, 1996, in a 10-bed medical–surgical intensive care unit (ICU) at the teaching hospital of Clermont-Ferrand in France. Patients enrolled in the study fulfilled the following six criteria: (1) age more than 18 yr, (2) endotracheal intubation, (3) mechanical ventilation for more than 72 h, (4) temperature greater than 38°C, (5) leukocytosis greater than 12,000/μl, and (6) antibiotic treatment for more than 2 days without change in the previous 48 h. All patients underwent a routine fever workup that included chest roentgenogram, urine analysis with culture, and blood cultures. When these studies failed to identify the source of the fever or if fever was persistent despite administration of antibiotics effective against isolated causative organisms of a diagnosed infection, a computed tomography (CT) of the paranasal sinuses (5-mm incremental thickness scans in the axial plane) was performed within 48 h.

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Patients with CT maxillary sinusitis (CTMS) underwent a transnasal puncture of the maxillary sinus involved and were included in the study. Patients were excluded from the study if they met at least one of the following criteria: (1) a history of sinusitis, (2) a transfer to the radiology department (considered by the attending physician as a high risk of morbidity because of severe respiratory or hemodynamic instability), and (3) coagulation disorders contraindicating transnasal puncture.

Using protected-brush specimens obtained under fiberoptic examination, lower respiratory tract secretions in the affected pulmonary lobe as seen on the chest radiograph were obtained from patients with suspected ventilator-associated pneumonia.

Patients receiving mechanical ventilation in our ICU are usually placed in a semirecumbent position. There is no written protocol concerning the route for endotracheal and nasal intubations, and the choice is left at the discretion of the attending physician. In practice, the oral route is mostly used for tracheal intubation and the nasal route for gastric intubation. In nasotracheally intubated patients, the nasogastric tube is inserted in the opposite naris to the nasotracheal tube.

The Ethics Committee of the hospital (Hôpital G. Montpied, Clermont-Ferrand, France) approved the study protocol. However, informed consent was not requested because all procedures applied were considered routine medical practice.

Study Protocol

Patients were adequately premedicated with intravenous midazolam and were either paralyzed with intravenous atracurium or further sedated with fentanyl. To conduct a large disinfection, in patients intubated through the nose the tubes were removed and placed *via* the oral route. The nasal secretions were washed out with saline. The nasal cavity and the surrounding facial area were thoroughly disinfected with a chlorhexidine alcoholic solution, and the nose was surgically draped. The maxillary sinus was then punctured under visual control at the inferior meatus with a sterile trocar. Any fluid present in the sinus was suctioned through a sterile catheter. The aspirate was then immediately sent to the laboratory, and the catheter was left in place. A sinus lavage was performed through the catheter every 8 h using 5–10 ml of warm sterile saline.

Specimen Processing

The specimens were sent directly to the laboratory in sterile tubes. Samples were Gram-stained and examined microscopically for bacteria. Aerobes were cultured on enriched chocolate agar, anaerobes on 5% sheep blood agar under anaerobic conditions, and fungi on Sabouraud's dextrose agar. Growth density was determined by a quantitative technique that consisted in serial 10-fold dilution of the original specimens. Results were expressed in colony-forming units (cfu) per milliliter. Isolated organisms were identified by standard techniques. Susceptibility to antibiotics was determined by the disk diffusion test.

Data Collection

The following data were collected on standardized forms designed for the purpose of the study: patient name, date of birth, gender, date and time of admission to the ICU, indication for ICU admission, simplified acute physiology score on admission,[13] routes of endotracheal and enteric intubations, date and time of insertion, date and time of mechanical ventilation, type of antimicrobial agents with course duration, indications for antimicrobial therapy, date of CT scans, date of sinus punctures, infections diagnosed at sites other than sinuses, and microbiological results within a week of sinus punctures, date of discharge, or death. In the event of recurrent sinusitis, only the first sinus puncture was taken into account.

Definitions

Computed tomography maxillary sinusitis was diagnosed by a team of senior physicians from the radiology and the otolaryngology wards based on CT findings. CTMS was defined as a total opacity of one or both maxillary sinuses or as the presence of an air-fluid level within one or both maxillary sinuses.

Criteria for VAIMS were as follows: (1) CTMS, (2) macroscopic purulent sinus aspiration, and (3) quantitative cultures of transnasal maxillary sinus punctures yielding at least one isolate with a bacterial growth more than or equal to 10^3 cfu/ml. Pneumonia was diagnosed when the quantitative culture of protected-brush specimens was more than or equal to 10^3 cfu/ml. The diagnostic criteria of other nosocomial infections were based on Centers for Disease Control criteria.

Statistical Analysis

The categoric data were compared using the chi-square test with Yate's correction. The continuous data were compared using the Mann–Whitney U test. All averages are reported as the arithmetic mean ± SD. Data were analyzed with EPI-INFO software, version 6 (Centers for Disease Control).

Results

Study Population

A total of 49 patients were enrolled during the 1-yr period of the study. In 13 of the patients, CT was not performed because of severe respiratory or hemodynamic instability (n = 11) or profound coagulation disorders (n = 2). Thirty-six patients underwent CT of the paranasal sinuses. Evidence of CTMS was obtained in 24

Table 1. Clinical Characteristics of the 24 Patients with Computed Tomography Maxillary Sinusitis, Comparing Patients with or without Ventilator-associated Infectious Maxillary Sinusitis

Patient Characteristics	VAIMS (n = 15)	No VAIMS (n = 9)	*P* Value
Age (yr), mean ± SD	66 ± 14	55 ± 7	0.02
Sex (% male)	80	78	0.89
SAPSII at admission	57.6 ± 18.5	49.2 ± 12.1	0.24
Admission diagnosis (N)			ND
Stroke	3	0	
Cardiac arrest	2	0	
Meningitis–encephalitis	2	1	
Sepsis	2	1	
Acute respiratory failure	2	3	
Acute pancreatitis	1	0	
Abdominal surgery	1	2	
Vascular surgery	1	2	
Polytrauma	1	0	
Intubation under emerging circumstances (N)	8*	2†	0.13
Nasotracheal tube (N)	1	1	0.7
Orotracheal tube (N)	14	8	
Previous ventilator (days)	10.3 ± 5.0	8.2 ± 4.1	0.57
Nasogastric tube (N)	15	8‡	ND
Previous antibiotics indications			ND
Community-acquired infection (N)	6§	7‖	
Nosocomial infection (N)	9#	2**	
Previous antibiotic (days)	4.7 ± 4.5	7.3 ± 3.7	0.03
Deaths (N)	9	3	0.2

* Because of coma (N = 5), cardiac arrest (N = 2), aspiration pneumonia (N = 1), or polytrauma (N = 1). † Because of coma (N = 1) or aspiration pneumonia (N = 1). ‡ One additional patient had a gastrostomy. § Including meningitis-encephalitis (N = 2), septic shock (N = 2), pneumonia (N = 1), and polytrauma (N = 1). ‖ Including meningitis–encephalitis (N = 1), septic shock (N = 1), pneumonia (N = 4), and peritonitis (N = 1). # Including ventilator-associated pneumonia (N = 4), septic shock (N = 3), peritonitis (N = 1), and catheter-related bacteremia (N = 1). ** Including ventilator-associated pneumonia (N = 1) and endocarditis (N = 1).

VAIMS = ventilator-associated infectious maxillary sinusitis; SAPS = simplified acute physiology score; ND, not done.

patients. CTMS was unilateral in 10 patients and bilateral in 14; therefore, the overall number of transnasal punctures performed was 38. In 6 of the 10 patients with unilateral CTMS, the gastric tube was placed in the corresponding naris. The clinical characteristics of the 24 patients with CTMS are shown in table 1. A diagnosis of VAIMS was made in 15 patients.

Microbiological Results

A diagnosis of VAIMS was ruled out in nine patients, four with unilateral and five with bilateral CTMS. The quantitative cultures of the 14 sinus punctures were sterile in 13 cases and yielded *Klebsiella oxytoca* and *Enterobacter aerogenes* with growth less than 10^3 cfu/ml in the remaining case, who had been receiving amoxicillin for 7 days to treat community-acquired pneumonia. In the nine patients who did not fulfill VAIMS criteria, fever was attributed to urinary tract infection (n = 3), ventilator-associated pneumonia (n = 3), or mesenteric ischemia (n = 1). In the other two patients, the cause of the fever was unknown.

Table 2. Microorganisms Isolated from the 24 Sinus Aspirates with Growth Greater Than 10^3 cfu/ml in 15 Patients with Ventilator-associated Infectious Maxillary Sinusitis

Microorganisms	No. (%) of Isolates
Gram-negative bacteria	
Pseudomonas aeruginosa	12 (25)
Enterobacter aerogenes	6 (12.5)
Escherichia coli	3 (6.3)
Stenotrophomonas maltophilia	1 (2)
Gram-positive bacteria	
Enterococcus species	7 (14.6)
Coagulase-negative staphylococci	5 (10.4)
Streptococcus species	5 (10.4)
Staphylococcus aureus	4 (8.3)
Yeasts	
Candida albicans	5 (10.4)
Total	48 (100)

cfu = colony-forming unit.

Fifteen patients, six with unilateral and nine with bilateral CTMS, fulfilled the VAIMS criteria. The 24 sinus aspirates were macroscopically purulent, and quantitative cultures yielded 48 isolates with a concentration of more than or equal to 10^3 cfu/ml. Nine cultures were monomicrobial and 15 were polymicrobial. Gram-negative bacilli accounted for 45.8% of isolates, gram-positive cocci 43.8%, and fungi 10.4%. *Pseudomonas aeruginosa* and enterococci were the most commonly identified organisms. The microorganisms isolated are shown in table 2. Because several isolates were found in both sinuses, the mean number of etiologic organisms recovered per patient was 2 ± 1 (n = 31) (table 3). In five of the patients in whom aspirates were obtained from both maxillary sinuses, different species were cultured from the two sinuses.

In 10 of 15 patients, at least one etiologic organism, for an overall total of 19 (39.6%), was sensitive to prior antibiotic treatment. The characteristics of the causative agents of VAIMS according to prior antimicrobial treatment are shown in table 3. The median duration of previous antibiotic therapy (3 days) was comparable in these 10 patients and in the other 5 VAIMS patients who had no etiologic organism sensitive to prior treatment.

Of the 15 patients with VAIMS, 7 developed 10 coinfections: ventilator-associated pneumonia (n = 5), urinary tract infection (n = 3), and catheter infection (n = 2). In four patients, the diagnosis of coinfection was made 48 h before VAIMS, and in the other three at the time of VAIMS. In 9 of 10 coinfections, and in all ventilator-associated pneumonia coinfections, the causative agents were VAIMS etiologic organisms. In the five patients with both VAIMS and ventilator-associated pneumonia, the latter occurred before VAIMS in three and on the same day in two. In four patients, the same organism was isolated from the lung and sinus: *P. aeruginosa* was

Table 3. Etiologic Diagnosis of Ventilator-associated Infectious Maxillary Sinusitis According to Previous Antimicrobial Treatments

Patient No.	Etiologic Diagnosis	Previous Antibiotics	Duration
1	*Streptococcus* species* *E. Coli*	Penicillin, metronidazole	3 days
2	*Streptococcus* species* *E. aerogenes*	Piperacillin, gentamicin	2 days
3	*Streptococcus* species* *Enterococcus* *E. aerogenes* *P. aeruginosa*	Cefotaxime, ofloxacin	3 days
4	*Streptococcus* species* MRSA* *P. aeruginosa*	Cefotaxime, vancomycin, amphotericin B	6 days
5	*Enterococcus** MRSA* *C. albicans*	Penicillin, metronidazole, pristinamycin	4 days
6	*Enterococcus** *P. aeruginosa*	Vancomycin	3 days
7	*S. maltophilia**	Cefpirome, amikacin	4 days
8	*E. aerogenes** *Enterococcus** *P. aeruginosa* *C. albicans*	Vancomycin, imipenem	3 days
9	MSCoNS* Enterococcus*	Vancomycin	3 days
10	*P. aeruginosa** MRCoNS	Piperacillin, tazobactam, amikacin, fluconazole	2 days
11	*P. aeruginosa*	Imipenem, gentamicin	5 days
12	*E. coli*	Vancomycin, metronidazole	8 days
13	*C. albicans*	Amoxicillin, clavulanate, ofloxacin	3 days
14	*P. aeruginosa*	Amoxicillin, antituberculous	2 days
15	MRSA MRCoNS	Piperacillin, tazobactam	20 days

* Organism sensitive to one or more antibiotics previously given.

E. coli = *Escherichia coli*; *E. aerogenes* = *Enterobacter aerogenes*; *P. aeruginosa* = *Pseudomas aeruginosa*; MRSA = methicillin-resistant *Staphylococcus* aureus; *C. albicans* = *Candida albicans*; *S. maltophilia* = *Stenotrophomonas maltophilia*; MSCoNS = methicillin-sensitive coagulase-negative *Staphylococcus*; MRCoNS = methicillin-resistant coagulase-negative *Staphylococcus*.

found in two patients, *Stenotrophomonas maltophilia* in one, and *Escherichia coli* in one other. In the fifth patient, sinus punctures yielded *E. aerogenes*, *Enterococcus* species, *P. aeruginosa*, and *Candida albicans*, and protected-brush specimens yielded *E. aerogenes* and *Enterococcus* species.

Discussion

The results of the study demonstrate the following: (1) infectious maxillary sinusitis may occur in mechanically ventilated patients receiving antibiotics; (2) causative agents are typically nosocomial bacteria; and (3) in numerous cases VAIMS emerges despite prior antibiotics to which the etiologic organisms are susceptible.

In critically ill patients with a clinical suspicion of infection and radiologic evidence of sinusitis, the diagnosis of VAIMS is established or refuted based on microbiologic cultures and Gram staining from sinus aspirates.[8] Because of the high colonization of the airway, a rigorous disinfection protocol using wide-area disinfection of the nasal mucosa is required to prevent the risk of introducing bacteria during the transnasal sinus puncture procedure. The efficacy of nasal disinfection before sinus aspirates was demonstrated in a previous study in which nasal disinfection was performed in 179 nares of 133 patients and failed in only 11%.[1] The explanations for the lack of efficacy in these few cases can only be speculative because no mention was made of the pathogens isolated and their antiseptic susceptibility, nor of the relationship between the type of pathogens found on nasal swab after nare disinfection and the subsequent transnasal quantitative cultures.[1]

In our study, we adopted a strict disinfection protocol using wide-area disinfection of the nasal mucosa with a chlorhexidine alcoholic solution before sinus puncture. The VAIMS etiologic organisms isolated from sinus punctures were not tested for chlorhexidine alcoholic susceptibility but seemed to be classically susceptible to chlorhexidine alcoholic solution.[14] In addition, to limit the risk of contamination we used as diagnostic criteria both the presence of pus at direct examination and transnasal sinus quantitative culture yielding more than or equal to 10^3 cfu/ml. This definition of VAIMS is con-

sistent with that used in most relevant studies performed on VAIMS in the ICU setting.[1,2,9,15]

Although most of our patients were orally intubated, we found a high rate of CTMS (24 of 36 patients; 67%) and VAIMS (15 of 36 patients; 42%). A possible explanation is that nearly all patients had gastric intubation *via* the nasal route and that nasogastric intubation is a risk factor for sinusitis.[16] The VAIMS/CTMS ratio (62.5%) we observed was similar to that calculated with the combined results of the studies using nasal disinfection before transnasal puncture and quantitative cultures for case definition: 61.9% (176/284).[1,2,9] The microbiological findings of this present study are consistent with the etiology of nosocomial sinusitis commonly reported.[1,2,4,8,9,16–19] However, in our study *Proteus* species, *Klebsiella* species, *Acinetobacter* species, and anaerobes were not isolated from quantitative sinus cultures and we found a higher incidence of infection with *P. aeruginosa*, coagulase-negative *Staphylococcus*, and *Streptococcus* species. The limited number of patients with nosocomial sinusitis reported in our study may explain these differences.

The diagnostic value of sinus aspirate cultures in patients who are receiving antibiotics at the time of sampling is questionable. Our study is the first to focus on the microorganisms isolated from sinus aspirates in mechanically ventilated patients receiving previous antimicrobial treatment and with suspected infectious maxillary sinusitis. The effect of antimicrobial treatment on subsequent cultures of sinus aspirates is an important point, because in the ICU setting many patients who develop a suspected nosocomial infection are already on antibiotics.[20,21]

The direct examination of sinus aspirates is sometimes negative in patients on previous antibiotics,[16] and prior antibiotic therapy may preclude the recovery of organisms in sinus aspirate cultures.[1,16] The negative cultures could represent appropriate clinical response to antibiotics. However, these studies describe neither the preexisting antibiotic regimens nor their indication or duration.

We found that most of the etiologic organisms of VAIMS were resistant to the antibiotics previously given. This suggests that current antibiotic therapy has only a weak impact on the results of sinus aspirate cultures in the diagnosis of VAIMS. If the causative organisms in patients who develop VAIMS while receiving antibiotics are resistant to the antibiotic treatment administered, then their growth is minimally affected by the antibiotics, and cultures of sinus aspirates are therefore a useful tool to diagnose VAIMS. Similar conclusions have been drawn concerning the impact of current antibiotics on the diagnostic accuracy of cultures of protected-brush specimens and bronchoalveolar lavage in critically ill patients with suspected ventilator-associated pneumonia.[21,22]

In our study, we found that a large minority of the pathogens involved (19 of 48; 40%) were sensitive to the antibiotics administered. The sensitivity of VAIMS etiologic organisms to prior systemic antibiotics has been anecdotally reported[19] but has never been extensively studied.

The ability of antibiotics used in the ICU to reach the mucosa of the maxillary sinus has been reported in previous studies. The synthetic penicillins, aminoglycosides, and teicoplanin achieved bactericidal concentrations in sinus fluid.[10,11,23] In the diseased antral mucosa, the extracellular tissue concentration of systemic antibiotics was lower than in serum samples[12] but reached minimal inhibitory concentration levels for the bacteria isolated.[19] The organisms cultured were therefore susceptible to previous antibiotic treatment. The reasons why susceptible organisms were isolated included the following: (1) antibiotic concentration in sinus fluid reported in the literature could be overestimated: the insertion of drains in the sinus cavity to measure antibiotic levels could create an inflammatory reaction responsible for an increased antibiotic concentration that could be much lower before than after drain insertion; and (2) during VAIMS the formation of biofilms could change both the conditions of bacterial propagation[24] and the accessibility of antibiotics to the bacteria.[25]

No prospective study has been performed to assess the efficacy of therapeutic interventions in VAIMS, and hence no consensus has been reached. In general practice, antibiotic treatment was recently shown not to improve the clinical course of acute maxillary sinusitis.[26] Recommendations for VAIMS treatment consist of semirecumbent positioning, removal of nasotracheal or nasogastric tubes, topical decongestants, sinus aspiration, sinus lavage using drains, and parenteral antibiotics. In a recent review on VAIMS, Talmor *et al.*[8] recommended sinus puncture for diagnosis followed by a systemic antibiotics plan and limited drainage for patients without improvement on antibiotics. In our study, several etiologic organisms of VAIMS were susceptible to prior systemic antibiotics. Thus, the delivery of antibiotics may represent an insufficient mechanism for treating sinusitis even if the organism causing the infection is sensitive. Our results suggest that sinus drainage should be adopted as a first-line therapy with or without intravenous antibiotics.

In the present study, we found 10 associated infections in seven patients with VAIMS. In nine cases, identical microorganisms were isolated both in the sinuses and at the other infected sites. The development of VAIMS and ventilator-associated pneumonia with the same pathogens in five patients suggests a possible relation between these two infections. However, there is no documented evidence that the sinus may be the primary septic focus responsible for the occurrence of pneumonia, and the

nature of the link between VAIMS and ventilator-associated pneumonia remains unclear.[2]

In conclusion, our findings suggest that in mechanically ventilated patients, even those on prior antibiotics, quantitative culture of sinus aspirates may be helpful to diagnose infectious maxillary sinusitis. Despite the small size of the study population, our results show that in numerous cases causative organisms are susceptible to previously administered antibiotics, and we therefore recommend that sinus drainage be included in the procedures for the treatment of VAIMS.

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