Effect of Previous Antimicrobial Therapy on the Accuracy of the Main Procedures Used to Diagnose Nosocomial Pneumonia in Patients Who Are Using Ventilation

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We evaluated the effect of antibiotic treatment received before the suspicion of pneumonia on the diagnostic yield of protected specimen brush (PSB), direct examination (BAL D) and culture (BAL C) of lavage fluid on consecutive mechanically ventilated patients with suspected nosocomial pneumonia. Bronchoscopy was always performed before any treatment for suspected pneumonia. One hundred and sixty-one patients with suspected pneumonia underwent PSB and BAL before any institution or change in antibiotic therapy (AB). Sixty-five patients received AB for an earlier septic episode (ON AB group) and 96 patients did not (OFF AB group). All but two strains recovered were highly resistant to previous AB. Sensitivity and specificity of each test were not different between the ON AB and OFF AB groups as well as the percentage of complete agreement between the 3 procedures, 74 and 67% respectively. We conclude that previous AB received to treat an earlier septic episode unrelated to suspected pneumonia do not affect the diagnostic yield of PSB and BAL. ***(CHEST 1995; 108:1036-40)***

AB=antibiotic therapy; BAL D=direct examination of centrifuged BAL fluid; BAL C=BAL fluid culture; CFU=colony-forming unit; OFF AB=patients who did not receive AB; ON AB=patients who received AB for an earlier episode; PSB=protected specimen brush

Key words: bronchoalveolar lavage; nosocomial pneumonia; previous antibiotics; protected specimen brush

Previous antibiotherapy has been shown to decrease the accuracy of the distal procedures used to diagnose nosocomial pneumonia in ventilated patients.[1-3] Moreover, the agreement of results of protected specimen brush (PSB) and direct examination of centrifuged BAL (BAL D) also seems to be decreased by the use of antimicrobials before these procedures.[4] If this is true, distal procedures would be unreliable in at least half of ICU cases.

However, the meaning of the term "previous antibiotic" is unclear in the literature. Previous antibiotic therapy could include either new antimicrobials instituted empirically or recently to treat the suspected pneumonia, or antimicrobials armed to treat another infectious focus and started before any sign of pneumonia. The purpose of our study was to test the effect of previous antibiotic treatment not directed against suspected pneumonia on the accuracy of the main distal procedures used when pneumonia is suspected in ICU patients.

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Materials and Methods

Every patient hospitalized and mechanically ventilated for more than 48 h in our ICU was prospectively included in the study when nosocomial pneumonia was suspected. Clinical suspicion of pneumonia was based on the appearance of new and persistent infiltrate on the chest x-ray film during the ICU stay and on at least two of the following clinical criteria:[5] fever >38.5°C or hypothermia <36.5°C; leukocytosis ($>10\times10^9$/L) or neutropenia ($<4\times10^9$/L); and purulent tracheal aspirates. When pneumonia was suspected, fiberoptic bronchoscopy was immediately performed on each patient before any change of antibiotic therapy.

Patients were premedicated with phenoperidine, midazolam, and pancuronium bromide. Topical anesthetics were never used. Immediately after endotracheal aspiration via a sterile tube, the bronchoscope was introduced through a special adaptator (Bodaï, Suction Safe Y. Sontek; Medical Lexington, Mass) and advanced, without suction, to the bronchial orifice of the lung segment identified radiographically as containing the new infiltrate. The PSB was then inserted into the inner suction channel and advanced to a 3-cm peripheral position before dislodging. The PSB was then removed and placed on a sterile operative field.

The bronchoscope was then positioned in the adjacent subsegment and BAL was performed by infusing a total of six 20 mL aliquots of sterile non bacteriostatic saline. The lavage recovered after the first aliquot was discarded and the remaining lavage aliquots were pooled. When the fiberoptic bronchoscopy was finished, the specimens were separately prepared as follows. Using strict aseptic conditions for the PSB, the distal portion of the outer and inner cannulas were sequentially cleaned with a 70% alcohol sponge, dried with sterile compresses, and discarded with sterile scissors,

Table 1—*Criteria for the Diagnostic Categories: Presence of Pneumonia, Absence of Pneumonia, and Uncertain Status*

Criteria to define the presence of pneumonia
• Foci of consolidation with intense polymorphonuclear leukocyte accumulation in the bronchioles and alveolar spaces within 8 d after bronchoscopy.
• Positive culture of the lung parenchyma.
• Positive culture of empyema fluid.
• Rapid cavitation on chest x-ray film or CT scan.
• Complete resolution with appropriate antibiotic therapy with no other disease explaining chest radiograph abnormality.
Criteria to define the absence of pneumonia
• Complete resolution without antibiotics and other disease of the chest explaining chest radiograph abnormality.
• Absence of histologic signs of pneumonia within 3 d after bronchoscopy if antimicrobials have been administered or within 7 d, if not.
Criteria to define uncertain status
• Appropriate treatment but histology unavailable or unconclusive (greater than 7 d after bronchoscopy).
• Appropriate treatment but other disease of the chest simultaneously treated (such as cardiac failure).
• No treatment, unfavorable outcome, but histology unavailable (greater than 7 d or not performed).

distal to the brush so that the brush would not come into contact with the possibly contaminated distal portion of the inner cannula. The brush was then advanced and severed with sterile scissors into numbered screw capped glass vials containing 1.0 mL of sterile Ringer's lactate solution.[1] The pooled BAL fluid was divided in three samples: one for cytologic examination, one for BAL C, and one for and BAL D. The containers were then sent to the laboratory for immediate processing. Microbiologic procedures were performed by experienced technicians, according to the protocol previously described.[6]

The patients were classified into three diagnostic categories during the follow up (Table 1): pneumonia, absence of pneumonia and uncertain status. One hundred and sixty-one episodes of suspected pneumonia in ventilated patients were studied. Ninety-six patients did not received any antimicrobial over the last 3 days or longer (OFF AB). Among the OFF AB group, 29 never received antimicrobials and for 67 received their last antimicrobials since 6.8±4 d (range: 3-29 d). Sixty-five patients (41%) (ON AB) were on antibiotics during the 48 h preceding bronchoscopy. Previous antibiotic therapy was never related to septic signs associated with nosocomial pneumonia. Patients were treated with monotherapy in 35 cases and with combination in 30 cases. Antimicrobials used were penicillin G, amoxicillin, oxacillin (n=10), penicillin A/clavulanate (n=10), other penicillin (n=7), carbapenems (n=2), cephalosporins (n=12), aminoglycosides (n=6), fluoroquinolones (n=13), macrolides (n=6), glycopeptides (n=21), fucidic acid (n=5), other (n=7). The mean duration of previous antibiotic treatment was 8±4 days (range: 2-17 d).

There was no difference in age (OFF AB, 65 yr vs ON AB, 66 yr, p=0.7), simplified acute physiologic score[7] (OFF AB, 14 vs ON AB, 14.5, p=0.5) or duration of mechanical ventilation (OFF AB, 12 and ON AB, 10 d, p=0.6) between the 2 groups. The criteria for the diagnosis are detailed in Tables 2 and 3.

Results

Accuracy of the distal samples was not modified by previous antimicrobials (Table 4), using classical thresholds, *ie*, 10^3 CFU/mL for PSB, 10^4 CFU/mL for BAL C, and 5% cells containing bacteria for BAL D. Moreover, the results of the 3 examinations are in accord, *ie*, positive according to the thresholds, in 11/19 and in 24/46 episodes of pneumonia in the ON AB and the OFF AB group respectively (p=0.91).

Microorganisms recovered during episodes of pneumonia are detailed on Table 4. *Heamophilus influenzae*, methicilline sensitive *Staphylococcus aureus*, and *Streptococcus pneumoniae* were more frequent in the OFF AB group and methicilline resistant *S aureus* was mostly recovered from the ON AB group. Moreover all but two microorganisms, *ie*, methicillin-resistant *S aureus* twice, Table 2) recovered from distal samples of definite pneumonia were highly resistant to previous antimicrobial treatment.

To assess the influence of the patients whose diagnosis remained uncertain, we evaluated, independently of any definite diagnosis, the percentage of complete agreement between the three procedures between ON AB and OFF AB groups. The percentage of complete agreement was similar in the ON AB and the OFF AB group (74% and 67% respectively, p=0.74).

Discussion

In our study, previous antibiotherapy used for other infections before suspicion of nosocomial pneumonia appears not to modify the diagnostic yield of PSB, BAL D, and BAL C. This result seems opposite from those obtained in other studies.[1,2,8]

But the definition of previous antibiotherapy is unclear: Is a patient treated for a few days by a beta-lactamine and an aminoglycoside for an *Enterococcus faecalis* endocarditis *similar* to a patient empirically treated with betalactamine and aminoglycoside for 1 day because of a nosocomial septic shock? When nosocomial pneumonia develops in patients receiving a course of antibiotics for a previous infection, however, the causing organisms are likely to be resistant to the antibiotics and their growth remain unaffected by them.[2,9]

Rello et al[10] have shown that the rate of nosocomial pneumonia caused by Gram-positive cocci or *H influenzae* was statistically lower in the patients who had previously received antibiotics while the rate of nosocomial pneumonia caused by *Pseudomonas aeruginosa* was higher. In our study, the overall rate of Gram-positive cocci was similar in the two groups with a higher rate of methicilline sensitive *S aureus* and *S pneumoniae* but a lower rate of methicilline resistant *S aureus*.

We did not observe a significant increased incidence of *P aeruginosa* and *A baumannii* nosocomial pneumonia as described by Fagon et al.[6] The variation of the microorganisms recovered is probably highly depen-

Table 2—*Results of PSB, BAL, and Type of Previous Antibiotic Therapy (ON AB Group)

Patient No.	Microorganisms	PSB, CFU/mL	BAL C, CFU/mL	BAL D† % infected cells	Dx‡	Previous Antibiotics	Days on Anti-biotics	Previous Antibiotic Treatment Cause
Confirmed VNP§								
1	*A baumannii*	50	400	0	1,2	amoxicillin+clavulanate	6	COPD superinfection
2	*E coli*	50	10^4	0	1,3	vancomycin, piperacillin	4	Nosocomial peritonitis
	MRSA	30	10^5					
	Streptococcus sp	10	10^4					
3	*E aerogenes*	No growth	10^5	1	1	amoxicillin+clavulanate	7	COPD superinfection
4	MRSA	10^5	10^6	33	1	ciprofloxacin+tobramycin	5	Catheter related septicemia
5	MRSA	6×10^4	10^5	9	1,2	ciprofloxacin+erythromycin	12	Legionellosis
6	*M morganii*	2×10^3	10^4	0	4	amoxicillin+clavulanate	3	Peritonitis
	MRSA	7×10^2	5×10^3					
7	*A baumannii*	3×10^4	7×10^4	36	1	vancomycin	4	Nosocomial bacteremia
8	*P aeruginosa*	10^5	10^5	12	1	erythromycin	13	Interstitial pneumonia
9	MSSA	8×10^3	5×10^4	7	4	penicillin G	8	Splenectomy
10	*A baumannii*	2.5×10^3	1.2×10^4	2	1	vancomycin	3	Nosocomial bacteremia
11	*P aeruginosa*	10^5	10^4	5	1	trimethoprim-sulfamethoxazole	17	*Pneumocystis carinii* pneumonia
12	*E coli*	1.1×10^3	10^5	2	1	vancomycin	4	Nosocomial bacteremia
13	*P aeruginosa*	8×10^2	6×10^3	2	1	amoxicillin	5	Meningitis
Probable VNP								
14	*H influenzae*	8×10^4	10^5	6	5	vancomycin	8	Catheter related septicemia
15	MRSA	1.6×10^3	6×10^3	4	5	amoxicillin	8	Community acquired pneumonia
16	MRSA	1.4×10^3	10^5	10	5	teicoplanin+fucidic acid	4	Nosocomial bacteremia
17	MRSA	10^4	10^5	5	5	cefotaxime	8	Pyelonephritis
18	MSSA	1.6×10^3	10^5	5	5	piperacillin	5	Nosocomial peritonitis
19	*P aeruginosa*	5×10^2	4×10^4	6	5	vancomycin	4	Nosocomial bacteremia
Uncertain status								
20	*S epidermidis*	20	5,000	0	8	vancomycin+fucidic acid	4	Catheter related sepsis
21	*P aeruginosa*	1,800	1.3×10^4	ND	8	trimethoprim-sulfamethoxazole+ vibramycin	5	HIV pneumonia
22	*P aeruginosa*	0	300	0	10	cefotaxime+erythromycin	5	Community acquired pneumonia
23	*A baumannii*	500	10^5	4	9	oxacillin+netilmicin	17	Endocarditis
24	MRSA	400	0	0	9	vancomycin	3	Nosocomial bacteremia
	S epidermidis	0	4×10^3			amoxicillin+clavulanate		
25	*K pneumoniae*	0	10^4	1	8	vancomycin	3	Nosocomial bacteremia
26	MRSA	3,700	ND		8	amoxicillin+clavulanate+ norfloxacin	4	Community acquired pneumonia
27	Streptococcus sp	0	2,600	6	8	ceftriaxone+erythromycin	5	Meningitis
Excluded VNP§								
33	*P aeruginosa*	20	10^5	0	6	amoxicillin+clavulanate	6	COPD superinfection
34	Candida sp	400	5×10^3	0	7	amoxicillin+clavulanate	2	Antibioprophylaxis
35	*A baumannii*	10	3×10^3	0	7	oxacillin+pefloxacin	10	Mediastinitis
36	*P aeruginosa*	0	500	0	6	penicillin G	6	Community acquired pneumonia
	MRSA	40	30					
37	*P aeruginosa*	20	900	0	7	cefotaxime+vancomycin	12	Infected aortic aneuvrism
38	*P aeruginosa*	0	10^4	0	7	vancomycin+fucidic acid	3	Gram-positive cocci bacteremia
39	*P aeruginosa*	0	700	0	7	vancomycin	3	Nosocomial bacteremia
40	*S epidermidis*	120	20	0	6	cefotetan	2	Antibioprophylaxis
	P aeruginosa	30	20					

continued

**A baumannii=Acinetobacter baumannii; E aerogenes=Enterobacter aerogenes; E cloacae=Enterobacter cloacae; E coli=Escherichia coli;* Dx=diagnosis; *E faecium=Enterococcus faecium; H influenzae=Haemophilus influenzae; K pneumonia=Klebsiella pneumonia; M morganii=Morganella morganii;* MRSA=methicillin resistant *Staphylococcus aureus;* MSSA=methicillin sensitive staphylococcus; ND=not done; *P aeruginosa=Pseudomonas aeruginosa; S epidermidis=Staphylococcus epidermidis;* sp=species.

†Expressed as percentage of cells containing bacteria.

‡Diagnosis categories are in Table 1.

§VNP=nosocomial pneumonia in ventilated patients.

Table 2—*Continued*

Patient No.	Microorganisms	PSB, CFU/mL	BAL C, CFU/mL	BAL D† % infected cells	Dx‡	Previous Antibiotics	Day on Anti-biotics	Previous Antibiotic Treatment Cause
41	MRSA	0	10	0	6	cefotaxime+pefloxacin	5	Community acquired pneumonia
42	MRSA	0	800	0	6	piperacillin+amikacin	4	Mesenteric infarction
	E faecium	0	200					
43	*P aeruginosa*	0	100	0	7	piperacillin+pefloxacin+ vancomycin	7	Nosocomial peritonitis
44	*E cloacae*	0	100	0	6	amoxicillin+clavulanate	6	COPD superinfection
45	MRSA	4×10^3	100	0	7	isoniazid+rifampicin+ ethambutol	14	Community acquired pneumonia
	S epidermidis	2×10^3	10					
46	*P aeruginosa*	50	10^5	0	6	vancomycin+fucidic acid	4	Nosocomial bacteremia
47	*P aeruginosa*	10^4	10^3	1	7	penicillin G	7	Splenectomy
	Proteus sp	2,400	60					
	K pneumoniae	1,200	500					
48	—	0	0	1	6	vancomycin	7	Catheter related septicemia
49	Streptococcus sp	1.8×10^5	10^5	2	7	amoxicillin+gentamicin	16	Endocarditis
	K pneumoniae	10^3	10^4					
51	MRSA	3×10^3	100	0	6	ceftriaxone	8	Cholangitis

**A baumannii=Acinetobacter baumannii; E aerogenes=Enterobacter aerogenes; E cloacae=Enterobacter cloacae; E coli=Escherichia coli;* Dx=diagnosis; *E faecium=Enterococcus faecium; H influenzae=Haemophilus influenzae; K pneumonia=Klebsiella pneumonia; M morganii=Morganella morganii;* MRSA=methicillin resistant *Staphylococcus aureus;* MSSA=methicillin sensitive staphylococcus; ND=not done; *P aeruginosa=Pseudomonas aeruginosa; S epidermidis=Staphylococcus epidermidis;* sp=species.

†Expressed as percentage of cells containing bacteria.

‡Diagnosis categories are in Table 1.

§VNP=nosocomial pneumonia in ventilated patients.

dent on the class of antibiotic used. Moreover, the effects of the prior antibiotic therapy, stopped for 3 days for some patients of the OFF AB group, could have endured until the time that the nosocomial pneumo-

Table 3—*Effect of Previous Antimicrobials on the Accuracy of the Distal Samples Used to Diagnose Nosocomial Pneumonia on Patients Who Are Ventilated*

	Diagnosis (according to Table 1)		1,2,3,4 (n=13)	5 (n=6)	6,7 (n=34)	8,9,10 (n=12)	Diagnostic Yield*, %
ON AB (n=65)	PSB	No growth	1	0	23	7	Sensitivity, 74
		$<10^3$ CFU/mL	3	1	7	3	Specificity, 88
		$\geq10^3$ CFU/mL	9	5	4	2	
		ND	0	0	0	0	
	BAL C	No growth	0	0	17	5	Sensitivity, 79
		$<10^4$ CFU/mL	3	1	11	4	
		$\geq10^4$ CFU/mL	10	5	4	3	Specificity, 88
		ND	0	0	2	0	
	BAL D	0%	3	0	28	7	Sensitivity, 56
		<5%	3	2	3	1	
		≥5%	7	4	0	2	Specificity, 100
		ND	0	0	3	2	
			(n=19)	(n=27)	(n=33)	(n=17)	
OFF AB (n=96)	PSB	No growth	1	4	24	7	
		$<10^3$ CFU/mL	4	5	5	8	Sensitivity, 70
		$\geq10^3$ CFU/mL	14	18	4	2	Specificity, 88
		ND	0	0	0	0	
	BAL C	No growth	0	0	15	6	
		$<10^4$ CFU/mL	2	6	10	4	Sensitivity, 82
		$\geq10^4$ CFU/mL	15	21	6	6	Specificity, 81
		ND	2	0	2	1	
	BAL D	0%	1	7	26	9	
		<5%	3	4	2	4	
		≥5%	11	15	1	3	Sensitivity, 63
		ND	4	1	4	1	Specificity, 97

*The 29 patients with the 8,9,10 diagnosis criteria are excluded from the analysis.

Table 4—*Recovered Microorganisms From the ON AB Group or the OFF AB Group**

Microorganisms†	ON AB Group, 19 Episodes (%)	OFF AB Group, 46 Episodes (%)
MSSA	2 (10)	7 (15)
MRSA*	8 (42)	6 (13)
S pneumoniae	0	5 (11)
Other Gram positive	1 (5)	6 (13)
B catarrhalis	0	4 (9)
H influenzae	1 (5)	9 (20)
P aeruginosa	4 (21)	9 (20)
A baumannii	3 (16)	4 (9)
E coli	2 (10)	3 (7)
Klebsiella sp	0	3 (7)
Other Gram negative	2 (10)	4 (9)
Total	23	60

*The number of patients with MRSA strains recovered was significantly lower in the OFF AB group (p=0.02). There was more than one microorganism by episode of nosocomial pneumonia.

†*B catarrhalis=Branhamella catarrhalis; E coli=Escherichia coli;* MRSA=methicillin-resistant *Staphylococcus aureus;* MSSA=methicillin-sensitive *Staphylococcus aureus;* ND=not done.

nia was documented and diagnosed.

We conclude that, regarding mechanically ventilated patients, nosocomial pneumonia occurring in patients already treated with antimicrobials are due to resistant microorganisms and that previous antibiotic therapy if not related to septic signs associated to nosocomial pneumonia does not influenced the accuracy of protected specimen brush, BAL direct examination, and culture. The conclusion is probably different when empirical antimicrobials have been started, recently, before bronchoscopy, because of a suspected pneumonia.[9] These two different types of "previous antibiotherapies" should be clearly differentiated in further studies dealing with nosocomial pneumonia.

In the management of nosocomial pneumonia, the issue of pretreatment for suspected pneumonia vs nonspecific antibiotic therapy must be considered as two distinct entities. Many techniques either blind or directed by a bronchoscopy currently are available and must be performed before any new antibiotic treatment for suspected pneumonia is initiated.

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