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Hospital-acquired pneumonia: microbiological data and potential adequacy of antimicrobial regimens

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ABSTRACT: Adequate antimicrobial therapy is a main approach employed to decrease the mortality associated with hospital-acquired pneumonia (HAP). All methods that optimise empirical treatment without increasing antibiotic selective pressure are relevant. Categorisation of patients according to HAP time of onset, severity and risk factors (American Thoracic Society (ATS) classification) or duration of mechanical ventilation and prior antibiotics (Trouillet's classification) are two such methods. The aim of this study was to catagorise patients with HAP according to these classifications and to determine the frequency of resistant pathogens and the most adequate antimicrobial regimens in each group.

A total 124 patients with bacteriologically proven HAP were studied. The ATS classification categorised patients by increasing frequency of resistant pathogens from 0–30.3%. The ATS empirical antibiotic recommendations appeared valid but proposed combinations including vancomycin for 72.5% of patients. Trouillet's classification categorised patients into four groups with a frequency of resistant pathogens from 4.9–35.6%. Vanomycin was proposed for 48.5% of patients.

The American Thoracic Society classification appears to be more specific than Trouillet's for predicting the absence of resistant causative pathogens in hospital-acquired pneumonia but could lead to a greater use of vanomycin. Stratification combining the two classifications is an interesting alternative.

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Hospital-acquired pneumonia (HAP) remains the most severe nosocomial infection in intensive care units (ICUs). Although mortality rates vary from one study to another and its prognostic impact is debated [1–7], it is recognised that one-third to one-half of all HAP deaths are directly attributable to infection [8]. Some factors influencing mortality have been identified. Bacteraemia and *Pseudomonas aeruginosa* or *Acinetobacter* spp. as causative agents increase mortality [3, 9]. Conversely, adequate and prompt initial antimicrobial therapy reduces mortality [10, 11].

Treatment instituted before knowing the aetiology and antimicrobial sensitivities is empirical. In order to choose the correct antibiotics, different means could be proposed. Firstly, guidelines such as those proposed by the American Thoracic Society (ATS) [8] can be used. These guidelines are based on patient classification into three categories according to the severity of HAP, the time of onset and the presence or absence of specific risk factors. In each group, different possible causative pathogens are incriminated and different antimicrobial regimen are proposed. Secondly, specific epidemiological data from each ICU can be studied and hence antibiotic regimens can be tailored. Such work performed by TROUILLET *et al.* [12], who studied patients with ventilator-associated pneumonia (VAP). According to the duration of mechanical ventilation (MV) prior to the VAP onset and the presence or absence of prior antibiotic(s), patients were separated into four different groups in which the frequency of potentially resistant organisms and their antimicrobial susceptibility varied.

In addition to the adequacy of the initial antimicrobial therapy, physicians must consider the problem of bacterial resistance. In particular, the use of wide-spectrum agents and vancomycin have been incriminated in the occurrence and increase of resistance [13].

Consequently, all methods optimising the choice of an adequate HAP antimicrobial treatment and decreasing the selective pressure appear relevant.

The aim of this study was to retrospectively categorise all patients exhibiting HAP, in the current authors unit, according to the ATS [8] and TROUILLET *et al.* [12] classifications and to determine microbial epidemiology and potentially the most adequate antimicrobial regimen.

Methods and materials

Selection of patients

From January 1994–December 1999, all patients admitted to the current authors ICU for HAP or exhibiting HAP during their ICU stay were enrolled.

HAP was considered when new and/or progressive chest radiographical infiltrates occurred $\geqslant$48 h after hospital admission, in conjunction with at least two of the following criteria: purulent respiratory secretions, temperature >38.5 or <35°C, blood leucocyte count >10,000 or <1,500·mm^{-3}. Only patients with bacteriologically documented HAP were studied. Establishing an aetiological diagnosis required isolation of bacteria in significant quantity from a sample of lower respiratory tract secretions (endotracheal aspiration $>1\times10^6$ colony forming units (cfu)·mL^{-1}, protected brush catheter $>1\times10^3$ cfu·mL^{-1} or bronchoalveolar lavage $>1\times10^4$ cfu·mL^{-1}) or isolation of a definitive pathogen from a blood or pleural fluid culture. These latter cultures were considered significant when the same organism, as recovered from the sample of respiratory secretion, was identified.

On ICU admission, age and sex as well as severity of illness and vital sign abnormalities were recorded, and then evaluated by Simplified Acute Physiology Score (SAPS II) [14]. When HAP occurred, the time of onset from hospital admission, temperature, chest radiographical involvement and leucocyte count were recorded.

Definition of groups of patients

The ATS guidelines [8] stratify patients with HAP into three groups, according to its severity, time of onset, and presence or absence of specific risk factors. All patients exhibiting HAP, whether the pneumonia is ventilator associated or not, are classified. Group 1 includes "patients without unusual risk factors who present with mild-to-moderate HAP with onset at any time during hospitalisation or severe HAP with early onset". Group 2 includes "patients with specific risk factors who present with mild-to-moderate HAP occurring at any time during hospitalisation". Group 3 includes "patients with severe HAP either of early onset with specific risk factors or of late onset" [8]. As previous antimicrobial treatment is a risk factor for selecting resistant pathogens, subjects in group 3 were further divided into subgroups according to the absence or presence of prior antibiotic(s) within 1 month before HAP.

TROUILLET *et al.* [12] proposed a classification for patients with VAP based on duration of MV (<7 days or $\geqslant$7 days before VAP onset) and presence or absence of antibiotic treatment within the 15 days preceding VAP. Four groups were defined. In the present study, any antibiotic treatment within 1 month before HAP onset was taken into account and all patients with HAP were studied, whether ventilator associated or not. Consequently, nonventilated and ventilated patients with HAP occurring before the seventh day of MV were included in groups A and B. In group A, patients had not received antibiotic(s) within 1 month preceding HAP, while the subjects in group B had. Groups C and D included ventilated patients with MV duration $\geqslant$7 days before HAP onset. In group C, patients had not received antibiotic(s) within the month preceding HAP while in group D they had.

Microbial epidemiology

In each HAP episode, all significant isolates were identified by standard laboratory techniques. For each pathogen, its antimicrobial susceptibility was studied. Criteria propsed by the Comité de l'Antibioprogramme de la Société Française de Microbiologie [15] were used. Antibiotics tested were amoxycillin/clavulanic acid, cefotaxime, ceftazidime, cefepime, piperacillin, piperacillin/tazobactam, imipenem, ciprofloxacin, vancomycin and amikacin.

According to the definition of TROUILLET *et al.* [12], methicillin-resistant *Staphylococcus aureus, P. aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia* were considered as "potentially resistant" bacteria. For the purpose of this study, methicillin-resistant *S. aureus*, ticarcillin-resistant *P. aeruginosa*, extended-spectrum β-lactamase producing *Enterobacteriaceae* and all *S. maltophilia* and *Acinetobacter* spp. strains were considered as "truly resistant" bacteria.

The distribution of causative organisms, "potentially resistant" and "truly resistant" bacteria, was studied in each group defined by the ATS [8] and TROUILLET *et al.* [12] classifications.

Potential adequacy of antibiotic regimens

An adequate antimicrobial regimen for HAP was defined as the use of at least one antibiotic to which all isolates were susceptible *in vitro*. In the presence of *P. aeruginosa*, a combination of at least two active agents was required [16]. In the presence of methicillin-resistant *S. aureus*, vancomycin was required.

To assess the potential adequacy of antimicrobial regimens, an analysis based on three steps was performed. First, the susceptibility of all organisms was determined. Second, HAP episodes and antibiotic monotherapy were considered. Betalactams were always considered inadequate when *P. aeruginosa* and/or methicillin-resistant *S. aureus* were implicated as pathogen(s) or copathogen(s). For other organisms, any antibiotic was inadequate if the pathogen or one of the pathogens was resistant to this antibiotic. The third step was to study antimicrobial combinations in a HAP episode. All pathogens implicated in an episode and the respective adequacy of each antibiotic used in combination were examined. For all pathogens, except *P. aeruginosa* and methicillin-resistant *S. aureus*, a regimen was adequate when no organism was resistant to all antibiotics used in combination. In the presence of *P. aeruginosa*, two combined active agents were required. In the presence of methicillin-resistant *S. aureus*, vancomycin was required.

Among regimens recommended by the ATS [8], some antibiotics were not available in the current author's hospital. Consequently, only the adequacy of amoxycillin/clavulanic acid, piperacillin/tazobactam, cefotaxime and ciprofloxacin for patients classified in ATS group 1 were tested. In group 3, piperacillin, piperacillin/tazobactam, ceftazidime, cefepime and imipenem, combined with amikacin or ciprofloxacin, and each combination with and without vancomycin were tested.

In the groups determined by the classification by TROUILLET *et al.* [12], the adequacy of amoxycillin/clavulanic acid, cefotaxime, piperacillin, piperacillin/tazobactam, ceftazidime, cefepime or imipenem, used as single agent, were tested. Then, all of them combined with amikacin or ciprofloxacin were tested. Finally, all these combinations with vancomycin were tested.

The results were expressed as percentages of adequate regimens in HAP episodes.

Statistical analysis

The distribution of organisms was compared in groups according to the classification used. Either the Chi-squared test or the Fisher's exact test was used. A p-value $\leqslant 0.05$ was considered as a significant difference.

Results

Study population

During the study period, 172 HAP episodes were evaluated. Pathogen(s) were identified in 124 episodes that occurred in 124 patients (mean age 64±14 yrs, 89 males). On ICU admission, the mean SAPS II was 44±12. The mean time of HAP onset from hospital admission was 15.4±12.2 days. A total 103 of the HAP cases (83%) were VAP. The mean duration of MV before HAP onset was 10.3±11.0 days. When HAP occurred, the temperature was >38.5°C in 107 patients and <35°C in four. All patients had purulent respiratory secretions. The leucocyte count was >10,000 mm^{-3} in 109 cases and <1,500 mm^{-3} in one case. Radiographical infiltrates were bilateral in 39 patients. During the HAP episode, MV was required for 117 patients.

Distribution of patients

According to the ATS classification [8], no patient was included in group 2. Six patients were included in group 1 and 118 in group 3. In group 3, 90 patients had received antibiotic(s) within 1 month prior to HAP onset. In the classification by TROUILLET *et al.* [12], 31, 33, 3 and 57 patients were included in groups A, B, C and D, respectively. In groups A and B respectively, 7 of 31 (22.6%) and 13 of 33 (39.4%) patients were nonventilated when HAP occurred.

When patients were analysed for both the ATS [8] and TROUILLET *et al.* [12] classifications, it was observed that all patients (n=6) included in group 1 were included in group A. In group 3 (n=118), the distribution of patients in groups A, B, C and D was 25, 33, 3 and 57, respectively.

Microbiological data and distribution of microorganisms responsible for hospital-acquired pneumonia

A total 154 pathogens were isolated (table 1). Infection was polymicrobial in 32 cases. The main organisms were *P. aeruginosa* (31.2%), *Enterobacteriaceae* spp. (20.8%), *S. aureus* (18.8%) with 33% methicillin-resistant strain, *Haemophilus influenzae* (6.5%), *Streptococcus pneumoniae* (5.8%), *Acinetobacter* spp. (5.8%) and *S. maltophilia* (5.2%).

The distribution of causative pathogens, according to the ATS classification [8], is detailed in table 1. In group 3, almost one-half of organisms were "potentially resistant", but only 23.4% were "truly

Table 1. – Bacteria isolated in the 124 episodes of hospital-acquired pneumonia

	Total	Group 1	Group 3	Group A	Group B	Group C	Group D
Number of episodes	124	6	118	31	33	3	57
Number of bacteria	154	8	146	41	36	4	73
Organisms							
S. pneumoniae[#]	9	2	7	5	2		2
Streptococcus spp.	2		2	1			1
MSSA	19	3	16	12[¶]	1	1	5
MRSA	10		10		1	1	8[+]
CNS	1		1		1		
M. catarrhalis	5	1	4	4			1
E. coli	8		8	4	3		1
Enterobacter spp.	7		7	1	4		2
Klebsiella spp.	5		5		1		4
Serratia spp.	7		7		2	1	4
Proteus spp.	5		5		1		4
H. influenzae	10	2	8	8	1		1
P. aeruginosa	48		48	5	16[§,*f*]	1	26[*f*]
S. maltophilia	8		8	1	3		4
Acinetobacter spp.	9		9				9
Corynebacterium spp.	1		1				1

S. pneumoniae: *Streptococcus pneumoniae*; MSSA: methicillin sensitive *Staphylococcus aureus*; MRSA: methicillin resistant *Staphylococcus aureus*; CNS: coagulase negative staphylococci; *M. catarrhalis*: *Moraxcella catarrhalis*; *E. coli*: *Escherichia coli*; *H. influenzae*: *Haemophilus influenzae*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. maltophilia*: *Stenotrophomonas maltophilia*. [#]: $p<0.05$ groups A+B *versus* groups C+D; [¶]: $p<0.01$ *versus* group B and $p<0.01$ *versus* group D; [+]: $p<0.001$ *versus* group A and and *versus* group B; [§]: $p<0.01$ *versus* group A; [*f*]: $p<0.01$ groups B+D *versus* groups A+C.

Table 2. – Numbers and percentages of "potentially" and "truly resistant" bacteria isolated in 124 episodes of hospital-acquired pneumonia according to the American Thoracic Society classification

	Total	Group 1	Group 3		
			Overall	No prior antibiotics	Prior antibiotics
Organisms n	154	8	146	37	109
"Potentially resistant" bacteria	75 (48.8)	0	75 (48.8)	8 (21.6)[#]	67 (61.5)
P. aeruginosa	48 (31.2)	0	48 (31.2)	6 (16.2)	42 (38.5)
Acinetobacter spp.	9 (5.8)	0	9 (5.8)	0	9 (8.3)
S. maltophilia	8 (5.2)	0	8 (5.2)	1 (2.7)	7 (6.4)
MRSA	10 (6.5)	0	10 (6.5)	1 (2.7)	9 (8.3)
"Truly resistant" bacteria	36 (23.4)	0	36 (23.4)	3 (8.1)[¶]	33 (30.3)
Ticarcillin resistant *P. aeruginosa*	5 (3.2)	0	5 (3.2)	1 (2.7)	4 (3.7)
Acinetobacter spp.	9 (5.8)	0	9 (5.8)	0	9 (8.3)
S. maltophilia	8 (5.2)	0	8 (5.2)	1 (2.7)	7 (6.3)
MRSA	10 (6.5)	0	10 (6.5)	1 (2.7)	9 (8.3)
ESBL producing enterobacteriaceae	4 (2.6)	0	4 (2.6)	0	4 (3.7)

Data are presented as n (%). *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. maltophilia*: *Stenotrophomonas maltophilia*; MRSA: methicillin resistant *Staphylococcus aureus*; ESL: extended-spectrum β-lactamase. [#]: $p<0.0001$ *versus* patients with prior antibiotics; [¶]: $p=0.003$ *versus* patients with prior antibiotics.

resistant" (table 2). If the presence or absence of prior antibiotic(s) were taken into account, the incidence of "potentially resistant" pathogens (21.6 *versus* 61.5%, $p<0.0001$) and "truly resistant" pathogens (8.1 *versus* 30.3%, $p=0.003$) was significantly less in the subgroup of patients without prior antibiotics (table 2). Thus in the patients in this study, ATS classification [8] was able to detect HAP episodes due to resistant organisms with a negative predictive value of 100% since no "potentially or truly resistant" organism was implicated in group 1.

In the classification by TROUILLET *et al.* [12], *S. pneumoniae* was more frequently isolated when the duration of MV was <7 days (groups A+B *versus* C+D, $p<0.05$). Methicillin-susceptible *S. aureus* was found more often in group A than in B ($p<0.01$) and D ($p<0.01$). Methicillin-resistant *S. aureus* was predominant in group D ($p<0.001$). *P. aeruginosa* was incriminated as a causative bacterium in all groups. In patients with a duration of MV of <7 days and without prior antibiotics (group A), *P. aeruginosa* accounted for 12.2% of the total number of bacteria. However, *P. aeruginosa* was isolated more frequently when HAP occured after prior antibiotic(s) (groups B+D *versus* A+C, $p<0.01$).

The distribution of "potentially and truly resistant" pathogens is reported in table 3. In group A, the incidence of "potentially resistant" organisms was low (14.7%). In groups B, C and D, the incidence of "potentially resistant" organisms was >50%. Finally, an increasing incidence of "truly resistant" pathogens from group A (4.9%) to groups B (19.5%), C (25%) and D (35.6%) was found. Thus in this series, this classification was unable to distinguish a group without resistant causative organisms.

Potential adequacy of antimicrobial regimens in hospital-acquired pneumonia episodes

For patients in ATS group 1, adequacy levels of amoxycillin/clavulanic acid, piperacillin/tazobactam, cefotaxime and ciprofloxacin were 100, 100, 100 and 50%, respectively. In group 3, adequacy levels are

Table 3. – Numbers and percentages of "potentially" and "truly resistant" bacteria isolated in 124 episodes of hospital-acquired pneumonia classified according to the duration of mechanical ventilation and prior antimicrobial therapy

	Total	Group A	Group B	Group C	Group D
Organisms n	154	41	36	4	73
"Potentially resistant" bacteria	75 (48.8)	6 (14.7)	20 (55.6)	2 (50)	47 (64.4)
P. aeruginosa	48 (31.2)	5 (12.2)	16 (44.5)	1 (25)	26 (35.6)
Acinetobacter spp.	9 (5.8)	0	0	0	9 (25)
S. maltophilia	8 (5.2)	1 (2.4)	3 (8.3)	0	4 (11.1)
MRSA	10 (6.5)	0	1 (2.8)	1 (25)	8 (22.2)
"Truly resistant" bacteria	36 (23.4)	2 (4.9)	7 (19.5)	1 (25)	26 (35.6)
Ticarcillin resistant *P. aeruginosa*	5 (3.2)	1 (2.4)	0	0	4 (5.5)
Acinetobacter spp.	9 (5.8)	0	0	0	9 (12.3)
S. maltophilia	8 (5.2)	1 (2.4)	3 (8.3)	0	4 (5.5)
MRSA	10 (6.5)	0	1 (2.8)	1 (25)	8 (11)
ESBL producing Enterobacteriaceae	4 (2.6)	0	3 (8.3)	0	1 (1.4)

Data are presented as n (%). *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. maltophilia*: *Stenotrophomonas maltophilia*; MRSA: methicillin resistant *Staphylococcus aureus*; ESL: extended-spectrum β-lactamase.

Table 4. – Potential adequacy of selected antimicrobial combination therapies in 118 episodes of hospital-acquired pneumonia (group 3 according to American Thoracic Society classification)

	Patients without prior antimicrobial therapy %	Patients with prior antimicrobial therapy %
Episodes of HAP n	28	90
Combinations with amikacin		
Piperacillin	78.6	56.7
Piperacillin+vancomycin	82.1	63.3
Piperacillin/tazobactam	82.1	62.2
Piperacillin/tazobactam+vancomycin	85.7	68.9
Ceftazidime	92.9	61.1
Ceftazidime+vancomycin	96.4	68.9
Cefepime	92.9	63.3
Cefepime+vancomycin	96.4	70.0
Imipenem	85.7	62.2
Imipenem+vancomycin	89.3	67.9
Combinations with ciprofloxacin		
Piperacillin	75.0	47.8
Piperacillin+vancomycin	75.0	55.6
Piperacillin/tazobactam	78.6	60.0
Piperacillin/tazobactam+vancomycin	78.6	67.8
Ceftazidime	89.3	56.7
Ceftazidime+vancomycin	92.9	65.6
Cefepime	85.7	61.1
Cefepime+vancomycin	89.3	68.9
Imipenem	85.7	62.2
Imipenem+vancomycin	89.3	68.9

reported in table 4. In the subgroup of patients without prior antibiotic(s), only cefepime and ceftazidime combined with amikacin reached a level of >90%. With the addition of vancomycin, the improvement of adequacy level was always <5%. For patients with prior antibiotic(s), levels were lower, ranging from 47.8% for piperacillin/ciprofloxacin combination to 70% for cefepime/amikacin/vancomycin combination.

The potential adequacy of regimens in groups of TROUILLET's *et al.* [12] classification is reported in table 5. In group A, all betalactams except piperacillin, used as monotherapy, reached a level of >74%. Levels of piperacillin/tazobactam, ceftazidime, cefepime and imipenem, combined with amikacin were >90%. Combinations with ciprofloxacin had lower levels than combinations with amikacin. The addition of vancomycin to betalactam/amikacin or ciprofloxacin combinations left levels unchanged. In group B, no betalactam used as monotherapy reached a level >45%. Levels reached by piperacillin, piperacillin/tazobactam, ceftazidime, cefepime or imipenem, combined with amikacin, were >75%. When betalactams were combined with ciprofloxacin, only imipenem had a level of >75%. Levels reached by betalactam/ciprofloxacin combinations were lower than respective levels reached by the same betalactam combined with amikacin. Finally, when vancomycin was added to betalactam/amikacin or ciprofloxacin combinations, improvement of levels was close to 3%. In group C, there were only three episodes, a figure too low to comment. In group D, levels of all regimens were low, close to 30% for monotherapies, to 50% for the most adequate betalactam combined with amikacin, and to 55% for the most adequate betalactam combined with ciprofloxacin. When vancomycin was added, improvement of levels was near to 10%. However, the best regimen exhibited a level of <70%.

Discussion

In this study, the classifications of the ATS [8] and TROUILLET *et al.* [12] were used to categorise patients. With the ATS classification [8], patients were included into classes with an increasing frequency of "truly resistant" pathogens from 0–30.3%. Current ATS therapeutic recommendations appeared valid, with a treatment based on a single antibiotic (amoxycillin/clavulanic acid or piperacillin/tazobactam or cefotaxime) for 5% of patients, two antibiotics (broad spectrum betalactam combined with amikacin or ciprofloxacin) for 22.5% of patients and three antibiotics (broad spectrum betalactam plus amikacin or ciprofloxacin plus vancomycin) for 72.5% of patients. With the classification of TROUILLET *et al.* [12], patients were categorised into four groups with an increasing frequency of "truly resistant" pathogens from 4.9–35.6%. Using this classification, an empirical antimicrobial treatment, based on two antibiotics (broad spectrum betalactam combined with amikacin), could be proposed for 51.5% of patients. Combinations, including a broad-spectrum betalactam, amikacin or ciprofloxacin and vancomycin, were proposed for 48.5% of patients.

Categorisation of patients with HAP was proposed by the ATS to approach HAP microbial epidemiology and to guide initial antimicrobial treatment. In this series, all HAP episodes were considered to be severe since they occurred during ICU stay or were the indication of ICU admission. Consequently, no patient was categorised in group 2. Ninety-five per cent of

Table 5. – Potential adequacy of selected antimicrobial regimens in 124 episodes of hospital-acquired pneumonia classified according to the duration of mechanical ventilation and prior antimicrobial therapy

	Group A	Group B	Group C	Group D
Episodes of HAP n	31	33	3	57
Single antimicrobial agent				
Amoxycillin/clavulanic acid	74.2	15.2	33.3	10.5
Cefotaxime	83.9	33.3	33.3	26.3
Piperacillin	25.8	15.2	0	8.8
Piperacillin/tazobactam	77.4	30.3	33.3	29.8
Ceftazidime	77.4	36.4	33.3	26.3
Cefepime	83.9	42.4	33.3	29.8
Imipenem	83.9	39.4	33.3	35.1
Combinations with amikacin				
Amoxycillin/clavulanic acid	80.7	33.3	33.3	29.8
Cefotaxime	83.9	39.4	33.3	29.8
Piperacillin	87.1	75.7	33.3	42.1
Piperacillin/tazobactam	90.3	78.9	33.3	52.6
Ceftazidime	90.3	78.9	66.7	50.9
Cefepime	96.8	84.9	66.7	50.9
Imipenem	93.6	78.9	33.3	52.6
Combinations with amikacin and vancomycin				
Amoxycillin/clavulanic acid	80.7	36.4	66.7	36.8
Cefotaxime	83.9	42.4	66.7	36.8
Piperacillin	87.1	78.8	66.7	50.9
Piperacillin/tazobactam	90.3	81.8	66.7	61.4
Ceftazidime	90.3	81.8	100	61.4
Cefepime	96.8	87.9	100	59.7
Imipenem	93.6	81.8	66.7	59.7
Combinations with ciprofloxacin				
Amoxycillin/clavulanic acid	80.7	33.3	33.3	21.1
Cefotaxime	83.8	39.4	33.3	29.8
Piperacillin	80.7	60.6	33.3	38.6
Piperacillin/tazobactam	87.1	63.6	33.3	57.9
Ceftazidime	83.9	63.6	33.3	52.6
Cefepime	90.3	69.7	33.3	56.1
Imipenem	87.1	75.8	33.3	54.4
Combinations with ciprofloxacin and vancomycin				
Amoxycillin/clavulanic acid	80.7	36.4	33.3	28.1
Cefotaxime	83.8	42.4	33.3	36.8
Piperacillin	80.7	63.6	33.3	49.1
Piperacillin/tazobactam	87.1	66.7	33.3	68.4
Ceftazidime	83.9	66.7	33.3	64.9
Cefepime	90.3	72.7	66.7	66.7
Imipenem	87.1	78.8	66.7	61.4

Data are presented as %.

patients were included in group 3 and 5% in group 1. The late onset of HAP, with a delay from hospital admission of 15.4±12.2 days, and the fact that the ATS guidelines [8] including all HAP was not specific to VAP explain the disparate number of patients included in each group. Conversely, with TROUILLET'S *et al.* [12] classification, distribution of patients was more homogeneous, with ~25% in group A, 25% in B and 50% in D. However, it must be emphasised that this classification was devised for VAP. In the current study, 21 patients did not have VAP. They were included in groups A or B since the duration of MV before HAP was obviously <7 days, but this point could, perhaps, be considered as an incorrect use of this classification.

In most ICUs, clinical problems are associated with the emergence of pathogens with increased antibiotic resistance [17]. All methods able to predict that a causative pathogen is resistant could optimise initial therapy. In this series, among 154 causative pathogens, 75 were "potentially resistant". The use of broad-spectrum antimicrobial therapy is regularly incriminated as one of the factors increasing resistance [13]. In the current group, 90 patients had received antibiotics prior to HAP onset. In these patients, 61.5% of pathogens were "potentially resistant" whereas, in patients without prior antibiotics, 17.8% were "potentially resistant". If only "truly resistant" pathogens are considered, 36 (23.4%) were incriminated. Their frequency was significantly higher in patients with prior antimicrobial treatment (30.3%) than in patients without (6.7%). However, prior antimicrobial therapy on its own was associated with a poor specificity in predicting infection due to resistant organisms since some resistant pathogens were incriminated in patients without prior antibiotic(s). Thus, other characteristics should be taken into consideration. The ATS guidelines [8]

recommend stratification of patients according to the time of HAP onset, HAP severity and prior antimicrobial therapy. In this study group, 5% of patients were included in group 1. No resistant causative pathogen was incriminated in this group. In patients included in group 3, the frequency of "truly resistant" pathogens was 23.4% with a significant difference between patients with and without prior antibiotics. Consequently in this series, this classification was able to identify a group where the likehood of a resistant causative organism was nil. In the series by TROUILLET *et al.* [12], it was demonstrated that no "potentially resistant" pathogen was incriminated in VAP episodes with a duration of MV <7 days and without prior antibiotics. In such a group in this study, the frequency of "potentially resistant" pathogens was 14.7% and the rates of "truly resistant" pathogens in the four groups were, 4.9, 19.5, 25 and 35.6%, respectively. These results show that, in this series, the classification by TROUILLET *et al.* [12] exhibits a lower negative-predictive value than the ATS classification [8] in the detection of HAP episodes due to resistant pathogens. Some conflicting results between the study by TROUILLET *et al.* [12] and the current study suggest additional comments. In the study by TROUILLET *et al.* [12], there were no precise data on antimicrobial susceptibility. Pathogens were classified as "potentially resistant" or not. Among all *Enterobacteriaceae* spp., classified as no "potentially resistant" pathogens, the presence of extended-spectrum β-lactamase producing strains was possible. Consequently, the absence of resistant pathogens in patients with duration of MV <7 days and without prior antibiotic(s) was surprising. Moreover, with the same definition of "potentially resistant" pathogens, the frequency of such pathogens was different in the two studies. In the current study as compared to the study by TROUILLET *et al.* [12], any prior antibiotic(s) within 30 days before HAP instead of 15 days were considered. This shorter period, rather than decreasing would have increased the risk of isolation of "potentially resistant" pathogens in patients falsely considered as having no prior treatment. Consequently, this can not be considered as a possible explanation. The most satisfying explanation is that the duration of MV before the onset of pneumonia is not, perhaps, relevant in this series. As reported, the mean time of HAP onset from hospital admission was 15.4±12.2 days. Consequently, some patients included in groups A or B, because pneumonia occurred before the seventh day of MV, developed pneumonia later than the seventh day of hospitalisation. This could explain the isolation of resistant pathogens in patients in the current series without prior antibiotics and with a short duration of MV. In summary, it seems better to evaluate HAP onset from hospital admission, as in ATS guidelines [8], rather than from the start of MV, as in the study by TROUILLET *et al.* [12].

The ATS guidelines recommend various antimicrobial regimens [8]. Most of ATS recommended regimens fit perfectly for the patients in this study. Monotherapy could be proposed in patients from group 1. In group 3, a broad-spectrum betalactam combined with amikacin or ciprofloxacin could be proposed for all patients, with the addition of vancomycin in patients with prior antibiotic(s). However, this latter point could be the major drawback of the ATS guidelines. In the current study, most of the patients were included in this group and, consequently, vancomycin should be used for all these patients. As the widespread use of vancomycin has led to the appearance of resistance in Gram-positive cocci [18], such recommendations could have a negative impact on microbial ecology. Physicians are therefore faced with a dilemma, wide spectrum antimicrobial treatment including vancomycin is required to avoid an increased mortality, but such treatment could lead to an undesirable vancomycin selection pressure. The only way to answer this challenge is de-escalation therapy with initial use of broad-spectrum agents, wait for cultures and, finally, focus on narrow-spectrum agents if possible [19]. The low adequacy level obtained by all regimens in patients in group 3 with prior antibiotic(s) must also be emphasised. The "best" combination was cefepime plus amikacin plus vancomycin, with a level of 70%. Such data emphasise the reality of emergence of resistant pathogens in the current author's unit and explains, perhaps, the high mortality rate associated with such HAP. With TROUILLET's *et al.* [12] classification, a broad-spectrum betalactam combined with amikacin or ciprofloxacin, could be proposed in groups A and B. The addition of vancomycin appears useless in these groups. For the remaining patients, the same agents combined with vancomycin could be proposed. The major drawback of this classification is the absence of monotherapies recommended. Its interest is to limit the recommendation for vancomycin to ~50% of patients. The emergence of vancomycin-resistant strains [20], potentially favoured by excessive use of a glycopeptide, underlines the interest of such a classification.

Numerous limitations of this study must be addressed. First, the analysis of the potential adequacy level of various regimens was retrospective. Second, only antibiotics used in the current authors' hospital and not all agents proposed by the ATS have been tested. Third, the results may be relevant to the current authors unit. Numerous studies have, indeed, demonstrated that HAP-causative organisms vary widely from one site to another [21]. Fourth, the classification by TROUILLET *et al.* [12] was modified to include nonventilated patients and to take into account prior antibiotic(s) within 1 month before HAP onset. Fifth, to assess the aetiological diagnosis, endotracheal aspiration with quantitative culture as a sampling method could be used. As recent recommendations [22] underline that quantitative procedures based on nonbronchoscopic or bronchoscopic techniques have similar sensitivities, specificities and positive-predictive values, this point could not be considered as being a limitation. Sixth, the definition of antimicrobial adequacy used in this study was different from the definitions used by KOLLEF and WARD [10], LUNA *et al.* [11] or TROUILLET *et al.* [12]. However, to the best of the current authors' knowledge there is no clear definition of adequacy. Finally, it is not known how long these results will be

valuable for the current therapeutic approach. Therefore, microbiological ecology must be regularly studied to provide up-to-date information.

To conclude, the American Thoracic Society classification [8] appears more specific than the classification by TROUILLET *et al.* [12] in predicting the absence of resistant causative pathogens in hospital-acquired pneumonia. Retrospectively, all antibiotic schemes recommended by the American Thoracic Society appear adequate in the current authors unit, but could lead to a frequent use of vancomycin. A stratification based on both classifications could be proposed. In patients with early-onset hospital-acquired pneumonia without specific risk factors (American Thoracic Society group 1), monotherapies could be used. In patients with either late onset hospital-acquired pneumonia or specific risk factors (American Thoracic Society group 3), prior antibiotic(s) and duration of mechanical ventilation could be taken into account. In the absence of prior antibiotic(s), a broad-spectrum betalactam combined with aminoglycoside or ciprofloxacin could be proposed. In patients with prior antibiotic(s), a similar regimen could be proposed when duration of mechanical ventilation is <7 days (Trouillet's group B). Vancomycin could be added in the remaining patients (Trouillet's group D). Such a classification would have allowed monotherapy for 5% of the patients in this study and limited vancomycin use for 48.5%. An antibiotic strategy including initial antimicrobial treatment guided by such a stratification and, if possible, a de-escalation when antimicrobial data are available could increase the initial administration of adequate antimicrobial treatment and prevent the emergence of antibiotic resistance. Of course, a prospective validation of such a stratification is required.

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