CLINICAL FORUM

Hospital-acquired pneumonia: coverage and treatment adequacy of current guidelines

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ABSTRACT: The American Thoracic Society (ATS) guideline for hospital-acquired pneumonia (HAP) released in 1996 and the Trouillet classification published in 1998 supply different rational foundations for the classification of patients with HAP and for the selection of initial antibiotic therapy. The aims of this study were to assess the level of bacterial coverage and to assess and validate the adequacy of antibiotic strategy of each of these classifications.

Intensive care unit-admitted patients (n=71) with suspicion of HAP were evaluated. The ATS and Trouillet classifications demonstrated an accuracy to predict the causative microorganism of 91% and 83%, respectively. The ATS and Trouillet antibiotic treatment recommendations were adequate in 79% and 80% of the patients, respectively. The microorganisms implicated in the treatment inadequacy of the ATS guideline were *Pseudomonas aeruginosa* (n=3), *Acinetobacter baumanii* (n=1), *Stenotrophomonas maltophilia* (n=1) and methicillin-resistant *Staphylococcus aureus* (n=1). *P. aeruginosa* was implicated with Trouillet treatment inadequacy.

The current recommendations for empirical antibiotic treatment of hospital-acquired pneumonia (American Thoracic Society and Trouillet) showed a good ability to predict the involved pathogen. However, considering the resistance pattern of the isolated pathogens, both classifications demonstrated a rather lower treatment adequacy; the main reason was the failure to treat highly resistant strains.
Eur Respir J 2003; 22: 876–882.

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The American Thoracic Society (ATS) statement for the management of hospital-acquired pneumonia (HAP) released in 1996, appeared to be extremely well-documented material and a highly useful tool for the treatment of HAP [1]. In 1998, TROUILLET *et al.* [2] also proposed a classification for patients with ventilator-associated pneumonia (VAP) based on two additional risk factors in order to support another rational basis for initial antibiotic therapy selection.

Despite the creation of these recommendations, studies have confirmed a prominent rate of inappropriate initial treatment [3], which could occur as a result of the presence of an unexpected pathogen or the isolation of a resistant strain of an expected microorganism. In fact, the increasing emergence of bacterial resistance over the last decade could result in a higher level of inadequacy of these initial recommendations for antibiotic treatment. Moreover, the microbial pattern may vary according to different countries and settings, as a result of different strategies for preventing microbial resistance or occurrence of nosocomial infection [4], and this should also be taken into account during the process of choosing the initial therapy.

The mortality rate of HAP remains high at ∼30% [5]. Higher mortality rates are reported in pneumonia caused by *Pseudomonas aeruginosa* [6] and among patients that receive initial inappropriate antibiotic treatment [3]. The choice of an adequate antimicrobial therapy clearly reduces the hospital stay and further complication [7], and has favourable consequences on the microbial ecology.

The capacity of the ATS guidelines and the Trouillet classification to predict resistant pathogens in patients with HAP and the appropriateness of different antimicrobial regimens in those patients was evaluated by LEROY *et al.* [8] in 2002, but retrospectively and not taking a clinical outcome into account.

The present study prospectively assessed the level of bacterial coverage of the ATS guidelines and Trouillet classification for HAP and VAP, respectively. Assuming that the changes in the profile of the microbial resistance could alter the adequacy of any therapeutic approach, the adequacy of both ATS and Trouillet antibiotic strategies for nosocomial pneumonia was also assessed and validated.

Methods

A prospective study was conducted during a 12-month period in the intensive care unit (ICU) of the Hospital Clinic, Barcelona, Spain. The study was approved by the local Ethical Committee.

Patients

All consecutive patients admitted to the ICU, hospitalised for >48 h and with suspicion of HAP were included. The diagnosis of pneumonia was based on the detection of a

new, persistent pulmonary infiltrate and at least two of the following clinical criteria: 1) fever or hypothermia (temperature >38° or <35.5°); 2) leukopaenia or leukocytosis (white blood cells $\leqslant 4 \times 10^9 \cdot L^{-1}$ or $\geqslant 12 \times 10^9 \cdot L^{-1}$); or 3) purulent respiratory secretions [9]. Pneumonia was considered ventilator-associated when it occurred after intubation and was judged not to have been incubated previously. Patients with severe immune suppression (solid organ or bone marrow transplant, human immunodeficiency virus infection, severe neutropaenia, immunosuppressive treatment) were excluded. Patients were followed until hospital discharge or death. Only the first episode of HAP was evaluated.

During the study period, 75 patients with suspicion of HAP were initially included. Four patients were excluded within the following 48 h because of evidence of an alternative aetiology or complete radiological resolution. In this study, 71 patients were included. The diagnosis of pneumonia was confirmed by the isolation of a potentially pathogenic microorganism or, among those without a defined aetiology, by one of the following: 1) classical clinical presentation associated with adequate response after the beginning of antibiotics; 2) histological confirmation of pneumonia; or 3) exclusion of additional diagnosis. Initial antibiotic treatment was chosen according to the attending physician, without influence of the investigators.

Diagnostic procedures

Respiratory, blood and urine samples were obtained from the 71 patients before initiating antimicrobial treatment whenever possible. Respiratory samples were obtained by endotracheal aspirate (ETA), protected specimen brush (PSB) and bronchoalveolar lavage (BAL). Collected specimens were processed according to procedures described previously [10]. Respiratory samples were considered valid based on criteria described elsewhere [7]. The significant thresholds defining infection were PSB, BAL and ETA cultures yielding $\geqslant 10^3$, $\geqslant 10^4$ and $\geqslant 10^5$ colony-forming units·mL^{-1}, respectively. Blood cultures, urinary *Legionella pneumophila* antigen test and detection of *Aspergillus* sp. antigen in serum was also performed. Thoracentesis with pleural fluid analysis was performed when applicable.

Definition of groups of patients

Based on initial characteristics each patient was categorised according to the ATS classification [1]. Those patients with VAP were also categorised according to the classification of TROUILLET *et al.* [2].

The ATS guideline classifies patients into three different groups based on time of onset (before or after 5 days of hospitalisation), severity criteria and the presence of risk factors. Group 1 included patients with mild-to-moderate pneumonia, without risk factors with onset at any time, or severe pneumonia without risk factors with early onset. Group 2 included those with mild-to-moderate pneumonia with risk factors with onset at anytime. Group 3 included those with severe pneumonia without risk factors with late onset, or severe pneumonia with risk factors with onset at any time.

The Trouillet classification stratifies patients with VAP based on the prior duration of mechanical ventilation and the prior use of antibiotic in the previous 15 days. Groups 1 and 2 included patients ventilated for <7 days. Group 1 patients had not received prior antibiotic therapy within the last month while group two patients had. Groups 3 and 4 included patients ventilated for $\geqslant 7$ days. Group 3 patients had not received prior antibiotic therapy within the last month while group 4 patients had.

Definitions

Bacterial coverage. Isolated pathogens from each patient were compared with the predicted spectrum of microorganism according to each patient's category in the ATS and Trouillet classifications. When the isolated pathogen corresponded to the expected one, the bacterial coverage of the ATS or Trouillet classification was considered adequate.

Guideline adherence. Patients were also aggregated into different groups depending on whether the initial empirical treatment chosen by the attending physicians suited the antibiotic treatment suggested by the previously mentioned guidelines or not. Those groups were ATS or non-ATS groups and Trouillet or non-Trouillet groups.

Treatment adequacy. Empirical treatment was considered adequate when the isolated pathogens were susceptible *in vitro* to at least one of the antibiotics administrated. In case of infection by *P. aeruginosa*, adequate treatment had to consist of at least two active drugs against the isolated strain.

Treatment failure. Treatment was considered to have failed if after 72 h following initiation, the presence of at least one of the following was defined: 1) persistence of fever ($\geqslant 38°C$) or hypothermia (<35.5°C) plus purulent respiratory secretions; 2) worsening of the pulmonary infiltrates with or without worsening in oxygenation; 3) occurrence of septic shock or multiple organ dysfunction syndrome not present on the first day; or 4) death attributable to pneumonia [7].

Data collection and end-points

Demographic and clinical parameters included the Acute Physiology and Chronic Health Evaluation II [11], time of pneumonia onset, severity criteria and risk factors [1], microbiological results, antimicrobial treatment for nosocomial pneumonia, lengths of mechanical ventilation, ICU and hospital stay.

The end-points analysed were adequate bacterial coverage, treatment adequacy, treatment failure, hospital mortality and lengths of ICU and hospital stay. Hospital mortality was defined as death by any cause that occurred within hospitalisation.

Statistical analysis

Results are expressed as percentage and mean±SD. The continuous variables were compared using the Mann-Whitney U-test and categorical variables were contrasted by the Chi-squared test or Fisher's exact test. The level of significance was set at 5%.

Results

Seventy-one patients with HAP were evaluated. Epidemiological characteristics at the time of ICU admission are detailed in table 1. Of these patients, 29 (40.8%) cases of HAP were ventilator-associated. The mean duration of mechanical ventilation before VAP onset was 5.4±2.7 days (range 1–11 days). Nineteen (26.8%) patients required intubation after

Table 1. – Intensive care unit (ICU) admission characteristics of 71 patients studied prospectively

Characteristic	Value
Age yrs	62.7±13.9
Male	55 (77.5)
APACHE II	14.9±5.6
Comorbid conditions	
Coma	10 (14.1)
Head trauma	5 (7.0)
Renal failure	3 (4.2)
Diabetes mellitus	7 (9.9)
Underlying lung disease	23 (32.4)
Recent surgery	38 (53.5)
Aspiration	11 (15.5)
Antibiotics during previous month	50 (70.4)
Cause of ICU admission	
Postoperative	38 (53.5)
Exacerbated COPD	4 (5.6)
Pneumonia	3 (4.2)
Neurological	5 (7.0)
Trauma	5 (7.0)
Other pulmonary disease	4 (5.6)
Miscellaneous	12 (16.9)
Severity criteria	57 (80.3)
Definitive aetiology	33 (46.5)
VAP	29 (40.8)

Data are presented as mean±SD or n (%) unless otherwise stated. APACHE: Acute Physiology and Chronic Health Evaluation; COPD: chronic obstructive pulmonary disease; VAP: ventilator-associated pneumonia.

onset of HAP, and in this group the mean time of mechanical ventilation was a 9.0±3.8 days.

Microbiological findings

An aetiological diagnosis was achieved in 33 patients (46.5%) and a total number of 48 pathogens were isolated. Polymicrobial pneumonia was diagnosed in 14 patients (19.7%). The most frequently isolated microorganisms were *P. aeruginosa* (n=9, 18%) and methicillin-resistant *Staphylococcus aureus* (MRSA; n=8, 16%). Positive blood cultures with agents considered as causative of pneumonia were found in six patients (*Klebsiella oxytoca, Enterobacter aerogenes, P. aeruginosa, Escherichia coli, Enterobacter cloacae* and MRSA). Aetiological diagnosis of pleural empyema was achieved in three of five cases, and the causative agents were MRSA in two cases and coinfection of *Streptococcus milleri* and *E. coli* in another case. Four patients with negative serum Aspergillus antigen had *Aspergillus fumigatus* isolated in association with a Gram-negative strain and were not considered pathogenic. One patient submitted to surgical resection of lung aspergiloma developed a postoperative pneumonia with no other microorganism isolated besides Aspergillus, had a positive serum Aspergillus antigen, and therefore the fungus was considered the causative agent. Legionella urinary antigen was performed in 49% of patients, without any positive results.

Group distribution

The distribution of patients and their pathogens according to the ATS guideline is described in table 2. No patient complied with ATS group 1 criteria. Of the 29 cases of VAP, 18 (62.1%) had a defined aetiological diagnosis. These

Table 2. – Distribution of pathogens according to American Thoracic Society (ATS) statement

	Total	ATS guideline	
		Group 2	Group 3
Total patients	71	14	57
Patients with defined aetiology	33	6	27
Isolated microorganism	48	9	39
Potentially resistant	20	4	16
Pseudomonas aeruginosa	9	3	6
Acinetobacter sp.	1		1
Stenotrophomonas maltophilia	2		2
MRSA	8	1	7
Other	28	5	23
Klebsiella sp.	1		1
Escherichia coli	5	2	3
Enterobacter sp.	1		1
Serratia sp.	1		1
Proteus sp.	1		1
Citrobacter sp.	2		2
Haemophilus influenzae	4	1	3
Streptococcus pneumoniae	2	1	1
Moraxella catarrhalis	1		1
MSSA	4		4
Aspergillus	5		5
Streptococcus milleri	1	1	

Data are presented as n. MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensible *Staphylococcus aureus*.

patients were also classified according to the Trouillet classification and their distribution is shown in table 3.

The empirical therapy chosen by the attending physician fulfilled the ATS treatment recommendation in 52 (73.2%) patients, who were designated ATS group. Conversely, those 19 (26.8%) who were not treated according to the ATS recommendation were designated non-ATS group. Only eight of the 29 (27.6%) patients with VAP received an initial antibiotic therapy that followed the Trouillet suggested treatment (Trouillet group), whereas 21 patients received a different sort of treatment (non-Trouillet group). All the different antibiotic combinations employed are shown in table 4.

Bacterial coverage

The ATS classification could correctly predict the isolated microorganisms in 30 of 33 (90.9%) patients. It failed to predict the pathogens isolated from two patients classified in the ATS group 2 (*P. aeruginosa* and MRSA) and one pathogen from an ATS group 3 patient (Aspergillus). The specific risk factors of each pathogen were *P. aeruginosa* (use of corticoids), MRSA (postoperative lung cancer resection, alcohol ingestion and chronic obstructive pulmonary disease (COPD)), Aspergillus (postoperative pulmonary aspergiloma resection).

The use of the Trouillet classification could properly predict the isolated microorganism in 15 of 18 (83.3%) patients, only failing to predict three pathogens: one MRSA in a Trouillet group 1 patient (postoperative lung cancer resection, alcohol ingestion), one MRSA in a Trouillet group 2 patient (previous hospitalisation and previous use of antibiotics), and an Aspergillus in a Trouillet group 4 patient (postoperative pulmonary aspergiloma resection).

Treatment adequacy

The ATS antibiotic treatment strategy was adequate in 19 of 24 (79.1%) patients that had a defined aetiological diagnosis.

Table 3. – Distribution of pathogens according to Trouillet classification

	Total	Trouillet classification			
		Group 1	Group 2	Group 3	Group 4
Total patients	29	6	11	2	10
Patients with defined aetiology	18	3	6	1	8
Isolated microorganism	25	5	8	1	11
Potentially resistant	8	1	3		4
Pseudomonas aeruginosa	3		2		1
Acinetobacter sp.	1				1
Stenotrophomonas maltophilia	1				1
MRSA	3	1	1		1
Other	17	4	5	1	7
Klebsiella sp.					
Escherichia coli	2	1	1		
Enterobacter sp.	1	1			
Serratia sp.	1				1
Proteus sp.	1				1
Citrobacter sp.	2		1		1
Haemophilus influenzae	3	1	1		1
Streptococcus pneumoniae					
Moraxella catarrhalis					
MSSA	4	1	1	1	1
Aspergillus	3		1		2
Streptococcus milleri					

Data are presented as n. MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensible *Staphylococcus aureus*.

Among those patients treated according to the ATS recommendation, treatment inadequacy occurred in six patients, all of them from ATS group 3. The six implicated pathogens were three resistant strains of *P. aeruginosa* (postoperative lung cancer resection, alcohol ingestion, neoplasia, prolonged use of corticoids, previous antibiotics), one of *A. baumannii* (alcohol ingestion, COPD), one of *Stenotrophomonas maltophilia* (alcohol ingestion, prolonged use of corticoids, previous antibiotics) and one MRSA (postoperative lung resection, alcohol ingestion).

The Trouillet treatment recommendation was adequate in four of five (80%) patients treated according to this classification and with an aetiological diagnosis defined. Treatment inadequacy among those treated as suggested by this classification occurred in only one patient from Trouillet group 2, who presented with a resistant strain of *P. aeruginosa*, and had risk factors of postoperative lung cancer resection, alcohol ingestion, neoplasia, prolonged use of corticoids, and previous antibiotic use.

Outcomes

There was a tendency toward higher treatment adequacy in the ATS compared with the non-ATS group (79.2% and 55.6%), although significance was not achieved. More patients from the ATS group presented treatment failure (66%), but there was no difference in the overall mortality between the ATS and non-ATS groups. Moreover, no difference in the length of ICU and hospital stay could be demonstrated among patients from both groups. The influence of the adherence to the ATS treatment recommendation on these end-points is detailed in table 5.

The empirical therapy of the Trouillet group also demonstrated a tendency toward superior treatment adequacy compared with the non-Trouillet group (80% and 69.2%), but without significance. Treatment failure occurred in 62.5% of the Trouillet and 52.4% in the non-Trouillet group. No difference in ICU or hospital stay was found between the Trouillet and non-Trouillet groups. There was a 50% mortality in the Trouillet and a 38% in the non-Trouillet groups; however, significance was not achieved. These results are shown in table 6.

Discussion

This study found that the current ATS guideline for the management of HAP has a high accuracy to predict the causative microorganism (91%). In this setting, and taking into account *in vitro* susceptibility of the pathogen, the adequacy of the ATS treatment was rather lower (79%). The ATS guideline mainly failed to cover highly resistant organisms such as *P. aeruginosa*, *S. maltophilia* and MRSA. The Trouillet classification demonstrates an 83% accuracy to predict the causal pathogen. Again, when considering the bacterial resistance profile, treatment recommendations resulted in an 80% adequacy. The Trouillet classification only failed to cover a resistant strain of *P. aeruginosa*. No differences were found in mortality between patients that were treated, or not, according to both recommendations.

The association between mortality of HAP and inappropriate antibiotic therapy has been intensely investigated over the last years. Although some studies [3, 12] found no significant differences, others showed a significantly higher mortality among those patients that received inadequate initial treatment [6, 13] or when there was a delay in initiating treatment [14]. Furthermore, there is a general agreement that inadequate treatment is related to the emergence of resistant pathogens [15, 16] and to a prolonged ICU stay [17]. Inadequacy of the empirical treatment can occur as a result of the presence of an unexpected microorganism or the isolation of a resistant strain of an expected pathogen. The guidelines are developed to predict microbial aetiology and to help clinicians in prescribing initial empirical adequate therapy. Consequently, the clinical validation of guidelines in prospective studies is very important.

Two studies had previously evaluated the adequacy of the ATS and Trouillet classifications regarding the prediction of pathogens, with controversial results. RELLO *et al.* [18] found

Table 4. – Isolated microorganisms and empirical antibiotic treatment

Group		Microorganisms	Empirical treatment
ATS	Trouillet		
3#	4#	MRSA	IMI, CIP, VAN
3#	4	P. aeruginosa, Acinotobacter sp.	CEFT, CIP
3		MRSA	CEF, AMI, CLA
2#		No growth	AMI, PIP-TAZ, VAN
3#	2	Citrobacter sp.	IMI, AMI
3#	2#	P. aeruginosa	CEFT, CIP
3#		E. coli, Aspergillus, MRSA	VAN, AMI, PIP-TAZ, AMP B, TMP-SMZ
3#	3	No growth	IMI, AMI
3#		S. pneumoniae, M. catarralis	CEF, CIP
3		No growth	AMP B, CEF, CLIN, PIP-TAZ
3#	1	No growth	CEF, CIP
3		No growth	AZT, CEF
2#	4	No growth	PIP-TAZ, VAN
2#		E. coli	CEF, CIP
2#		No growth	IMI, AMI
3#		No growth	CIP, PIP-TAZ
2		H. influenzae, S. pneumoniae, MRSA	LEV, CLA
3#		No growth	AMI, CEFT, FLU, VAN
3#		No growth	GENT, IMI
2#		P. aeruginosa	CIP, CEFT
3		No growth	IMI
3		MRSA	FLU, CTX
3	1	MRSA	CEF, AMI
3	2	No growth	FLU, PIP-TAZ
3#		P. aeruginosa	PIP-TAZ, AMI
3	4	MSSA	CTX, CLIN
3#		No growth	AMI, IMI
3#	2#	P. aeruginosa	CEF, AMI
3#		No growth	CEFT, CIP
3		No growth	CEF, TEI
3#	4	H. influenzae	CEF, AMI
3#	2	No growth	AMI, IMI
3#	2	MRSA	IMI, CIP
3#		MRSA, S. malthophilia	QUIN-DALF, TOB, AZT, TMP-SMZ
3#	3	MSSA	IMI, AMI
3#		K. oxytoca	IMI, CIP
3		No growth	TMP-SMZ, ERI, FLU, IMI, TB, VAN, ACY
3#		No growth	CEF, AMI
2#		P. aeruginosa	CEF, CIP
2#		No growth	CEFT, CIP
3#		No growth	CIP, IMI
3#	4	S. marcescens	CEF, AMI
2#		No growth	AMI, CEF
3#	2#	No growth	CIP, CEF
3	4	S. maltophilia, Aspergillus	LEV, TMP-SMZ
3#		P. aeruginosa	CEF, CIP
2#		No growth	AMI, CEF
3	4	No growth	AMOX-CLAV
2#		No growth	CIP, IMI, VAN
3#		No growth	CIP, IMI, TEI

(Table 4 continued in right column)

Table 4. – Continued

Group		Microorganisms	Empirical treatment
ATS	Trouillet		
3#		No growth	AMI, IMI
3#		No growth	CIP, IMI, FLU
3#		No growth	CIP, IMI
3#		No growth	AMI, CEFT, VAN
3#	2	No growth	CIP, PIP-TAZ, VAN
3		No growth	IMI, VAN
3#	2#	MSSA, H. influenzae	PIP-TAZ, CIP
3#		P. aeruginosa, Aspergillus	CEF, AMI
3	1#	No growth	AMOX-CLAV
3		No growth	CTX, CLIN
3#		No growth	CEF, AMI
3#	1	No growth	CIP, CEFT
3#	2#	No growth	CEF, CIP
3#	4	Aspergillus	IMI, CIP, AMP B
3	1	E. coli, E. aerogenes	IMI, VAN
3	1#	MSSA, H. influenzae	CTX, CLIN
2#		No growth	CTX, ERI
2#		P. aeruginosa	IMI, VAN, AMI
3	2	E. coli, Aspergillus	VAN
2#		E. coli, S. milleri	IMI, VAN, AMI
3#	4	C. freundii, P. mirabilis	CEF, AMI

MRSA: methicillin-resistant *Staphylococcus aureus*; IMI: imipenem; CIP: ciprofloxacin; VAN: vancomycin; *P. aeruginosa*: *Pseudomonas aeruginosa*; CEFT: ceftazidime; CEF: cefepime; AMI: amikacin; CLA: clarithromycin; PIP-TAZ: piperacillin-tazobactam; *E. coli*: *Escherichia coli*; TMP-SMZ: trimethoprim-sulphamethoxazole; AMP: amphotericin; *S. pneumoniae*: *Streptococcus pneumoniae*; *M. catarrhalis*: *Moraxella catarralis*; CLIN: clindamycin; AZT: aztreonam; *H. influenzae*: *Haemophilus influenzae*; *S. malthophilia*: *Stenotrophomonas malthophilia*; LEV: levofloxacin; FLU: fluconazole; GENT: gentamycin; CTX: ceftriaxone; MSSA: methicillin-sensible *Staphylococcus aureus*; TEI: teicoplamin; QUIN-DALF: quinupristin-dalfopristin; TOB: tobramycin; *K. oxytoca*: *Klebsiella oxytoca*; ERI: erythromycin; TB: tuberculostatics; ACY: acyclovir; *S. marcescens*: *Serratia marcescens*; AMOX-CLAV: amoxacillin-clavulanate; *E. aerogenes*: *Enterobacter aerogenes*; *S. milleri*: *Streptococcus milleri*; *C. freundii*: *Citrobacter freundii*; *P. mirabilis*: *Proteus mirabilis*; #: prescribed antibiotic treatment that suited recommendations.

a significant variation in the aetiology of microorganisms isolated across three different ICUs (Seville and Tarragona, Spain; Montevideo, Uruguay). They found that both the ATS guideline and the Trouillet classification failed to predict the presence of highly resistant pathogens (Pseudomonas) in some patients belonging to low-risk groups. Contrarily, LEROY et al. [8] found a 100% accuracy of prediction when using the ATS guideline to exclude the presence of resistant pathogens in low-risk patients. In the present study, highly resistant pathogens were found in low-risk patients from the ATS group 2 and the Trouillet groups 1 and 2. The overall rate of prediction was very good for both classifications. Further studies should address the specific risk factors related to the presence of unexpected pathogens in low-risk classes in the ATS guidelines and the Trouillet classification. In this study, most of the unexpected pathogens were isolated in patients that had pulmonary surgery.

One of the problems of the guidelines, when predicting adequate initial antibiotic regimes, is the potential presence of resistance of microorganisms to antibiotics. This issue has

Table 5. – Outcomes according to adequacy of American Thoracic Society (ATS) treatment recommendation

Outcomes	ATS	Non-ATS	p-value
Subjects n	52	19	
Treatment adequacy[#]	19/24 (79.2)	5/9 (55.6)	NS
Failure of treatment	33 (66.0)	10 (47.6)	NS
Mortality	17 (34.0)	7 (33.3)	NS
LOS hospital	33.0±19.4	26.2±10.8	NS
LOS ICU	18.5±12.4	16.4±9.7	NS

Data are presented as n (%) or median±SD unless otherwise stated. LOS: length of stay; ICU: intensive care unit. NS: nonsignificant. [#]: only those with isolated pathogen were included in this analysis.

Table 6. – Outcomes according to adequacy of Trouillet treatment recommendation

Outcomes	Trouillet	Non-Trouillet	p-value
Subjects n	8	21	
Treatment adequacy[#]	4/5 (80)	9/13 (69.2)	NS
Treatment failure	5 (62.5)	11 (52.4)	NS
Mortality	4 (50)	8 (38.1)	NS
LOS hospital	22.7±11	30.8±23.7	NS
LOS UCI	17.1±9.5	21.8±11.6	NS

Data are presented as n (%) or median±SD unless otherwise stated. LOS: length of stay; ICU: intensive care unit. NS: nonsignificant. [#]: only those with isolated pathogen were included in this analysis.

been covered, for example, in the last ATS guidelines on community-acquired pneumonia with regards to *Streptococcus pneumoniae* resistant to antibiotics [19]. However, the issue of resistance in HAP is much more complex due to the tremendous variation of the resistance patterns across units and countries. The knowledge of the risk factors for specific resistances is crucial for the administration of adequate empirical antibiotic regimes in HAP and VAP.

Over the last decade, bacterial resistance in ICUs has been a constant challenge for the clinicians. Since 1995, when the ATS statement for the management of HAP was first released [1], bacterial resistance had a considerable spread [4, 20] and several studies focused on the risks and consequences of infection by resistant strains [21, 22]. In this study, 38% of the isolated strains were resistant and this was the major cause of failure on both strategies of treatment. Basically, three pathogens were involved: *P. aeruginosa*, MRSA and *S. maltophilia*. Concerning *P. aeruginosa*, three of the nine isolated strains showed resistance to both antibiotics used for treatment, resulting in the inadequacy of treatment. As reported in several studies, the leading aetiological organism in HAP appears to be *P. aeruginosa*, isolated in 24% of cases [23], which is also associated with a higher mortality compared with other pathogens [5]. Local and periodical surveillance studies are strongly recommended to determine the antibiotic patterns of sensitivity of this difficult-to-treat microorganism.

A surprising finding in the present study was that the traditional risk factors related to highly resistant organisms, especially previous use of antibiotics and prolonged ICU stay [2], were not always present. For example, two of eight patients with an early onset pneumonia and MRSA were not at risk for this specific pathogen. Under these circumstances, the likelihood of spread of resistant strains into the community must be considered. A recent study [24] found a number of community infections by MRSA, drawing attention to the dissemination of this pathogen outside the hospital area. The use of vancomycin in the empirical treatment of VAP has been recommended in a very recent study from IBRAHIM *et al.* [25]. Using this approach the authors achieved a 90% adequacy in the empirical treatment. De-escalation therapy was used subsequently. Interestingly, antibiotics were stopped after 7 days of treatment. With this strategy, they reduced antibiotic resistance when compared with a control population. A more balanced view of the problem of MRSA, instead of giving vancomycin indiscriminately to all patients with suspicion of VAP, should include precautions of the development of *Enterococcus faecium* resistant to vancomycin. In this view, again, the authors' recommendation is to develop better models of prediction for the presence of MRSA infection and to include these models in local guidelines.

Infection by *S. maltophilia* had a slightly higher incidence

in this study compared with other reports (4.1% compared with 1.7% in the pooled incidence calculated by CHASTRE and FAGON [23]). At the moment trimethoprim-sulphamethoxazole (TMP-SMZ) is the antibiotic of choice for the treatment of *S. maltophilia* infections with >90% *in vitro* susceptibility, followed by ticarcillin clavulanate or ceftazidime with 50% susceptibility [26]. Given the relative lack of agents that have significant activity against *S. maltophilia*, it is not surprising that this pathogen is virtually almost never covered by the Trouillet or ATS treatments. In fact, this microorganism and other nonfermenting Gram-negative bacilli are not mentioned in the lists of the ATS guideline and the Trouillet classification. A recent study [27], reports a number of risk factors for nosocomial pneumonia by *S. maltophilia* in trauma patients (cefepime exposure, tracheostomy, pulmonary contusion and increased morbidity) and suggests the association of an agent with activity against this microorganism (preferably TMP-SMZ) when these conditions are present. New guidelines should also cover this problem.

Although *A. fumigatus* was isolated in five patients, only one case was included in the analysis in which it was definitely considered the causative pathogen. Exclusion of the other cases are justified by the following reasons: 1) in most cases the fungus was associated to another organism (*E. coli* and *S. maltophilia*), which was taken into account for the evaluation of the treatment; 2) no specific serum antigen of *A. fumigatus* was detected; and 3) those patients were immunocompetent and did not have previous use of corticoids, a traditional risk factor associated with fungal infection. However, the ATS guidelines and the Trouillet classification do not deal with the problem of Aspergillus and again this issue should be covered in future guidelines.

No differences in mortality or morbidity were found when comparing patients treated, or not, according to the guidelines, and this is probably due to a relatively small sample size. It is also important to note that there were no patients from the ATS group 1, and these conclusions should not be extended to this group. Other studies in community-acquired pneumonia [28] have found that the application of guidelines (in this case from the ATS, 1993) resulted in a lower mortality. In a recent study, applying a specific treatment protocol for VAP resulted in a lower morbidity [25]. Although the ATS guideline and the Trouillet classification adequately predict the aetiological microorganisms of pneumonia in a high percentage of cases, a potential limitation to generalise these results is the variability of the local antimicrobial resistance profiles among different ICUs that may decrease the clinical efficacy of these recommendations.

To conclude, the current classifications for empirical antibiotic treatment of hospital-acquired pneumonia (American Thoracic Society and Trouillet) showed a good ability to predict the involved pathogen. However, considering the resistance pattern of isolated pathogens, both classifications

demonstrated a rather lower treatment adequacy; the main reason was the failure to treat highly resistant strains. Additional parameters, such as local microbial epidemiology and more accurate models of prediction of resistance, should be considered in order to improve the level of coverage and adequacy of the antibiotic treatment. Future guidelines should address the role of other microorganisms such as *Stenotrophomonas maltophilia* and *Aspergillus* sp.

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