Impact of guidelines for stratification of community acquired and hospital pneumonia severity and treatment

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IMPACT OF GUIDELINES OF STRATIFICATION OF COMMUNITY AND HOSPITAL ACCQUIRED PNEUMONIA SEVERITY AND TREATMENT

DOCTORAL THESIS

of

Liapikou Adamantia in order to obtain the degree of Doctor of Medicine.

Supervised by:

Professor Dr. Antoni Torres Marti,

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To my Supervisors

Professor Antoni Torres

and

Dr. Miquel Ferrer

AUTHORIZATION OF THE DIRECTOR THE DOCTORATE

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CERTIFICATE that the doctoral thesis with the title: "Impact of guidelines of stratifications of community and hospital acquired pneumonia severity and treatment" presented for obtain the degree of Doctor of Medicine has been realized under my supervision. Once authorize its submission to be judged by the court.

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Doctoral Thesis Supervisor

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I N D E X

ABBREVIATIONS

ATS/IDSA	American Thoracic Society/Infectious Diseases Society of America
COPD	Chronic Obstructive Pulmonary Disease
CAP	Community Acquired Pneumonia
CURB-65	Confusion/Urea/Respiratory rate/Blood Pressure
PSI	Pneumonia Severity Index
CPIS	Pulmonary Infection Score
PaCO2	Partial Pressure of arterial carbon dioxide
PaO2/FiO2	Ratio of arterial oxygen tension to inspired oxygen fraction
WBC	White Blood Cells
SBP	Systolic Blood Pressure
CRP	C-reactive protein

PRESENTATION

This doctoral thesis has been structured following the guidelines of the rules for submission of doctoral theses as a compendium of publications, adopted by the Council, Department of Medicine, University of Barcelona.

The studies are part of this thesis belong to the same line of research, validated the current guidelines of pneumonia-community acquired and hospital acquired. The results of the studies have provided relevant and innovative in this field and were collected in 2 original articles published in international journals with a widespread global impact factor of 16, 37 points.

INTRODUCTION

1. Community Acquired Pneumonia (CAP)

CAP is a significant cause of morbidity and mortality and the most common infectious cause of death in the developed word (1). When combined with influenza, it is currently the eighth leading cause of death in the United States and the most common infectious cause of death in the developed world. Although the greatest incidence of CAP occurs in the outpatient environment (2-12cases/1000p), an estimated 20% of the patients with CAP require admission to the hospital. Furthermore, the number of hospitalizations increases with age (1.29 per 1,000 in patients from 18 to 39 years of age versus 13.21 per 1,000 in those who are 55 years old or older). The mortality rate of patients who require admission to the hospital averages 12% overall but increases to 30%-40% for those with severe CAP who require admission to the ICU. This compares to a mortality rate of less than 1% among patients with CAP treated on an outpatient basis. But, mortality of CAP in the intermediate and long term is high with figures showing 8% at 90 days, 21% per year and 36% at the end of 5 years (3).

Site of care in patients with CAP impacts the overall cost of treatment, the intensity of diagnostic testing and options for empiric antimicrobial selection. The decision to admit a patient with CAP is based on: (**a)** mortality prediction rules, such as the PORT (Pneumonia Outcomes Research Team) Severity Index (**PSI**) score, developed in the USA or the British Thoracic Society **CURB-65** (Confusion, Urea concentration, Respiratory rate, Blood pressure and age>65) **(b)** social circumstances of the patient and **(c)** co-existing conditions (4, 5). Prognostic scales for severity have been developed to solve this problem whose purpose is to classify patients into difference risk groups according to the probability of death within 30 days or to specify a more aggressive treatment such as assisted ventilation or the administration of vasopressor drugs.

Twenty (20) weighted variables are used to calculate the PSI score which includes age, sex, co-morbidities, vital signs and analytical and radiological changes. According to the total score, the patients are stratified into 5 classes (I-V). Classes I-III refer to patients with mild CAP

(mortality 0.1-2.8%), Class IV are patients with an intermediate risk (mortality 8.2-9.3%) and Class V are patients at high-risk (mortality 27-31%). Hospitalization is recommended for Classes III-IV-V.

The calculation of the CURB65 score (5) is carried out by adding one point for each variable present with a range between 0 and 5 points. This scale stratifies patients into three groups or risk classes: 0 to 1 low risk (mortality 1.5%), 2 is an intermediate risk (mortality 9.2%) and 3 to 5 is high-risk (mortality 22%). Hospitalization is recommended when the score is >1, especially if other factors are present associated with severity such as hypoxemia or multilobar involvement in the chest x-ray (3).

Although each of the two approaches has been proposed as a tool to guide the site of care decision, neither is ideal by itself, and both can be regarded only as providing decision support information that must be supplemented by clinical assessment and judgment. In fact, the two scoring approaches should be viewed as being complementary, as each has different strengths and weaknesses (6). This is primarily because the PSI except from its complexity, heavily weights age and co morbidity, and does not directly measure CAP-specific disease severity. The PSI appeared to be more discriminating in identifying the low mortality risk patients (7). In contrast, the CURB- 65 approach may be ideal for identifying high mortality risk patients with severe illness due to CAP. CURB-65 approach is that it does not generally account for co morbid illness, and thus may not be easily applied in older patients who may still have substantial mortality risk, even if a mild form of CAP destabilizes a chronic, but compensated, disease process.

The use of objective admission criteria clearly can decrease the number of patients hospitalized with CAP but neither can be used to define the site of care without considering other clinical and social variables.

1.a. Defining severe cap

The evaluation of severity of CAP, the decision about the antibiotic treatment and the overall management until complete resolution all play a key role in the prognosis of the disease. Severe CAP (SCAP) has been defined as those cases that require admission to the ICU (8), because they require intensive therapies or monitoring of vital signs. The proper use of resources for critically-ill patients is important to avoid either unnecessary occupation of ICU beds or the increased mortality associated with delayed ICU admission. Evidence from observational studies suggest that patients transferred ‘‘late’’ to the ICU and subsequently requiring MV/VS have a sub-optimal treatment and care, worse mortality rate, arguing that more of these patients should be initially treated in the ICU from admission (9). Delayed ICU admission for any cause may occur in at least 30% patients with severe CAP and is associated with 2 to 2.6-fold increase risk for hospital mortality in two recent studies, compared with direct admission from the emergency room (9,10). The proper use of resources for critically-ill patients is important to avoid either unnecessary occupation of ICU beds or the increased mortality associated with delayed ICU admission.

Many investigators in order to define SCAP evaluated different parameters of severity: Leroy et al (11) evaluated mechanical ventilation, shock, or medical complications to define SCAP, whereas Buising and colleagues (12) proposed mortality, ICU admission, mechanical ventilation, or inotrope/ vasopressor therapy. Charles and colleagues (13) used mechanical ventilation (invasive or noninvasive) and vasopressors, regardless of site of care.

In addition to problems with determining the best definition, SCAP has proved difficult to predict. Most of the studies comparing the PSI and CURB65 resulted that they are not appropriate for the decision of ICU admission. In a study of Angus and coauthors (14) included 170 SCAP patients , only 27% belonged to PSI I - III . In another Spanish Study of Valencia et al, found that from 457 CAP patients class V only 92 (20%) admitted to the ICU (15).

The Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) had many attempts to define severe CAP, beginning in 1993(16). This first guideline-based definition of severe CAP involved 10 criteria. The presence of only one criterion was enough for ICU admission, and thus this rule was highly sensitive (98%) but insufficiently specific (32%) (17). A new score was proposed relying on one of two major criteria (mechanical ventilation, septic shock) or two of three minor criteria and was adopted in the 2001 ATS guidelines (18). This modified ATS score achieved a sensitivity of 69%, and specificity of 97% in predicting ICU admission, while the prediction of mortality yielded a sensitivity of 94% and a specificity of 93% in a study of Ewig et al on 2004 (19).

The modified ATS score showed better discriminatory capacity for ICU admission than the PSI and the CURB scores (12). However, none of the prediction rules was particularly good in one study, mainly due to their poor positive predictive value, in such a way that most patients who met the criteria were never admitted to an ICU. This study concluded that the discrimination of the scores appeared too low to guide individual decision-making for ICU admission.

A the mentioned earlier study by Angus et al. (14) comparing the outcomes of hospitalized patients with CAP who received ICU care with the outcomes of those who did not and compared the predictive characteristics of the original and revised ATS criteria, the BTS criteria, and the PSI criteria for ICU admission, receipt of mechanical ventilation, medical complications and death. They concluded that none of the available prediction rules for severe CAP were “adequately robust to guide clinical care at the current time”. Ewig et al (19), in a subsequent article, confirmed the ability of the modified ATS rule to predict severe pneumonia. In a multicenter prospective study in 23 hospitals, Bodi et al (20) investigated the prognostic factors related to outcome in CAP patients admitted to the ICU. This study, which included only severe CAP with a high mortality rate, analyzed adherence to the IDSA guidelines and confirmed the lower mortality in the adherent group of patients (24% *vs.* 33%).

On 2007 the IDSA/ATS issued guidelines (8) on the management of CAP that include specific criteria to identify patients for ICU admission. The major criteria of the IDSA/ATS guidelines for ICU admission of CAP refer to patients with acute respiratory failure requiring

invasive mechanical ventilation or septic shock. The ATS minor criteria and the CURB variables were included in the new proposed minor criteria. The recent IDSA/ATS rule recommended that the presence of three or more of the nine minor criteria would indicate ICU admission (**Table 1**).

The priority of the two major criteria is out of question but whether each of the minor criteria is of equal weight is not clear. Therefore, the guidelines recommended a prospective validation of this set of criteria, which is the aim of my first study (21).

Table 1: **Criteria for severe CAP according to the IDSA/ATS guidelines (6)**

Major Criteria
Invasive mechanical ventilation
Septic Shock with the need for vasopressors
Minor criteria
• Respiratory rate ≥30 breaths/min *
• PaO_2/FiO_2 ≤250 *
• Multilobar infiltrates
• Confusion-disorientation
• Uremia (BUN level ≥20 mg/dL)
• Leucopenia (WBC count <$4x10^9$/L)
• Thrombocytopenia (platelet count <$100x10^9$/L)
• Hypothermia (core temperature <36ºC)
• Hypotension SBP <90 mmHg) requiring aggressive fluid resuscitation

Definition of abbreviations: PaO_2/FiO_2 = ratio of arterial oxygen tension to inspired oxygen fraction; BUN = blood urea nitrogen; WBC = white blood cells; SBP = systolic blood pressure.

2. Hospital Acquired Pneumonia (HAP)

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection accounts for approximately one fourth of all infections in the ICU (22) and more than 50% of the antibiotics prescribed. When HAP occurs in mechanically ventilated patients this is called ventilation-acquired pneumonia (VAP) and its incidence ranges between 10-30% in patients that require mechanical ventilation for more than 48 hours, with an incidence of 7.6 cases per thousand days of mechanical ventilation (MV) (3). In mechanically ventilated patients, the incidence increases with duration of ventilation. Cook and coworkers (23) demonstrated in a large series of 1014 mechanically ventilated patients that the VAP rate was 18%, and although the cumulative risk for developing VAP increased over time, the daily hazard rate decreased after day 5. The risk per day was evaluated at 3% on day 5, 2% on day 10, and 1% on day 15. The risk of VAP is highest early in the course of hospital stay, and is estimated to be 3%/day during the first 5 days of ventilation, 2%/day during days 5 to 10 of ventilation, and 1%/day after this (22). Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation.

Studies have consistently shown that VAP increases morbidity, typically prolongs the duration of hospitalization for an average of 7–9 days per patient and constitutes a serious burden for the healthcare system. The mortality rate in VAP ranges from 24% to 76% in several studies (24, 25). ICU ventilated patients with VAP may have a 2- to 10-fold higher risk of death than patients without it. In some series the attributable mortality of VAP may reach 30% (25). Several case-matching studies have estimated that one- third to one-half of all VAP-related deaths are the direct result of infection, with a higher attributable mortality in cases of

bacteraemia or in which the aetiological agent are multidrug resistant (MDR) pathogens, especially *P. aeruginosa* or *Acinetobacter* spp and *MRSA* (22, 26,27).

Moreover, studies have shown that adequacy of empiric antibiotic treatment and the time period between VAP diagnosis and treatment are strong predictors of mortality (28). With mini-BAL fluid cultures, Kollef and Ward (29) reported that inappropriate antibiotic therapy was associated with an OR for death of 3.28. Alvarez-Lerma et al (30) evaluated 430 patients with VAP and reported that patients receiving appropriate empiric antibiotic therapy had lower mortality(16.3% vs.24.7%,p=0.039) in comparison to patients in whom adequate antibiotic treatment was delayed. In the above study, it was found that empirical antibiotic treatment must be modified in 43.7% of the cases. Kollef and Ward (29) found a high prevalence (73.3 %) of inadequate initial antibiotic therapy in a study of 130 patients with VAP. The percentage of inadequate treatment has varied in the literature between 22 and 73%. Iregui et al (31) studied 107 patients with VAP and found that 33 patients (31%) received delayed antibiotic treatment, mostly due to delay in writing antibiotic orders. Those patients had 7.68-fold increase in mortality in comparison to patients receiving appropriate antibiotics in a timely manner. Moreover, it could be shown by Luna et al (32), that even if the initially inappropriate, antimicrobial treatment is corrected according to diagnostic results; there still remains an excess mortality as compared to the group treated appropriately from the beginning.

The treatment guidelines published by scientific societies are an invaluable help to begin an adequate empirical antimicrobial therapy in infected critically - ill patients. The ATS released in 1996 (33) and later in 2005 jointly with the IDSA guidelines (22) for the management of adults with HAP. The stratification into different groups for initial treatment varied when comparing the 1996 and 2005 recommendations.

In 1996, the guidelines recommended stratifying patients according to severity of illness (mild to moderate or severe), presence of risk factors and the time onset of pneumonia (early and late onset). Comorbidities and medical interventions were associated with specific pathogens (***Table 2***). For instance, coma, head trauma, diabetes and renal failure were all risk factors for acquiring

S. aureus. Also, prolonged ICU stay, steroids, antibiotics and structural lung disease increased risk for acquiring *P. aeruginosa.*

A French important study, published on 1998, of 135 patients with VAP (34) found that nearly 60% of the microorganisms tested were potentially PRM, being particularly high in patients who had received ventilation for >7 days and in those receiving antibiotic treatment prior to the development of VAP.

The current 2005 ATS/ IDSA guidelines for the management of adults with HAP, VAP, and health care associated pneumonia (HCAP) emphasized modifiable risk factors for infection, and reviewed the microbiology of HAP with an emphasis on "potentially-resistant" microorganisms (PRM)(***Table 3).***

The new concept of healthcare-associated pneumonia (HCAP) is based on three crucial notions: 1) a subgroup of patients with on-going contact with healthcare presents with community-acquired infections but nosocomial microbial patterns; The presence of an HCAP risk factor at admission is recent hospitalization, admission from a nursing home/long-term care facility, chronic dialysis, outpatient infusion therapy, home wound care or family member with a multidrug-resistant (MDR) pathogen.

2) failure to cover multidrug-resistant (MDR) pathogens leads to inadequate initial antimicrobial coverage and, subsequently, accounts for excess mortality; and 3)HCAP patients must, therefore, be identified and treated with initial broad spectrum antimicrobial treatment covering MDR pathogens (22).

But, today, the original data on which the concept of HCAP was originally based have been subject to a detailed critique. The HCAP concept is based on varying definitions poorly predictive of MDR pathogens. The appropriate management of HCAP remains questionable because of the controversial status of its microbial etiology and the paucity of clinical trials. Data from the USA (22, 35) indicate an excess of MDR pathogens in these patients, but studies from Europe don't confirm this (36, 37). There is no consistent proof that HCAP is associated with an excess of inadequate treatment and HCAP guideline-concordant treatment could not be shown to be associated with improved outcomes (38). Instead, after adjustment for confounders, mortality might be related to hidden or documented treatment restrictions in elderly and severely disabled

patients. Therefore, a careful individual assessment of risk factors associated with an increased risk of MDR pathogens justifying broader antimicrobial coverage is mandatory, along with a de-escalation of antimicrobial treatment in patients ultimately not revealing a MDR pathogen (39). There are suggestions from experts to reconsider the concept of HCAP in terms of definition and management (36, 40).

About the HAP, these guidelines classified patients into two groups based on time-onset (early-onset or late-onset) and the presence of risk factors to be infected with PRM. AThese, PRM, are *Pseudomonas aeruginosa, MRSA, Acinetobacter spp., Stenotrophomonas malthophilia, Burkholeria cepacia* and extended spectrum *b-lactamase (ESBLþ) Klebsiella pneumoniae*. Conversely, *Streptococcus pneumoniae, Haemophilus influenzae*, methicillin-sensitive *S. aureus* and antibiotic-sensitive *Enterobacteriaceae* are considered non-PRM pathogens (***Table 4***).

Guidelines for VAP have two primary goals: to reduce overall incidence of VAP via implementation of preventive strategies, and to improve morbidity and mortality by recommending appropriate management and treatment (41). The recent guidelines did not address several features related to severity of illness for risk stratification and called attention to prior antibiotic treatments and recent stay in hospital and healthcare-associated facilities as major risks for acquiring MDR pathogens. The 2005 guidelines also emphasized the importance of choosing specific antimicrobials based on local microbiology.

Thus, two treatment groups have been designed: a schedule for patients with NP of early onset without risk factors for MDR which may be treated with antibiotics in monotherapy with ceftriaxone, respiratory fluoroquinolone, amoxicillin/clavulanic or ertapenem; and a second schedule for patients with risk factors for PRM or with late onset pneumonia (***Table 5***).

Table 2. Potential etiology of HAP according to ATS guidelines 1996 (32)

Group I	
Patient characteristics	***Core organisms (PLUS)***
Patients with mild to moderate hospital-acquired pneumonia, no unusual risk factors, onset any time or patients with severe disease and early onset	Enteric gram-negative bacilli *(non-Pseudomonal)* *Enterobacter spp* *E. coli* *Klebsiella spp.* *Proteus spp.* *Serratia marcescens* *Haemophilus influenzae* *Staphylococcus aureus* *(Methicillin-sensitive)* *Streptococcus pneumoniae*
Early onset VAP in patients with previous antibiotic therapy (last 15d)	Risk of multiresistant pathogens ->Pseudomonas, Acinetobacter, S. maltophilia (30%) ->MRSA (5-18%) [7;10]
Late onset, non-ventilated	Risk of resistant GNB (?)
Group II	
Patients with mild to moderate hospital-acquired pneumonia, with risk factors, onset any time	*Anaerobes* recent abdomial surgery witnessed aspiration
	Staphylococcus aureus (coma, head trauma, diabetes mellitus, renal failure)
	Legionella spp. (high dose steroids)
	Pseudomonas aeruginosa (prolonged ICU stay, steroids, antibiotics, structural lung disease, COPD)
Specific comments	
In case of previous antibiotic treatment	Risk of multiresistant pathogens
Contact with children, >65 yrs, co-morbid	Resistant *S. pneumoniae* (?)
Group III	
Patients with severe hospital-acquired pneumonia,	*P. aeruginosa*

with risk factors, early onset or patients with severe HAP with late onset	*Acinetobacter spp.* S. maltophilia *MRSA*

TABLE 3. Risk factors for multigrug –resistant pathogens causing HAP, HCAP and VAP

• Antimicrobial therapy in preceding 90 d
• Current hospitalization of 5 d or more
• High frequency of antibiotic resistance in the community or
in the specific hospital unit
• **Presence of risk factors for HCAP:**
Hospitalization for 2 d or more in the preceding 90 d
Residence in a nursing home or extended care facility
Home infusion therapy (including antibiotics)
Chronic dialysis within 30 d
Home wound care
Family member with multidrug-resistant pathogen
• Immunosuppressive disease and/or therapy

Table 4. Potential Pathogens according to time onset of HAP.

Early onset HAP	***Late Onset HAP***
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Klebsiella pneumoniae (ESBL)*
Methicillin-sensitive Staphylococcus aureus	*Acinetobacter species*
Antibiotic-sensitive enteric gram-negative bacilli : *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter species* *Proteus species* *Serratia marcescens*	*Methicillin-resistant Staphylococcus aureus (MRSA)*
	Legionella pneumophila

Table 5: Initial empiric antibiotic treatment for PN and VAP of late onset or in patients with risk factors for infection by PRM and with any degree of severity.

Probable microorganism	**Combined antibiotic treatment**
Microorganisms from table 3 plus: ***Pseudomonas aeruginosa*** ***Klebsiella pneumoniae* (ESBL+)** ***Serratia marcescens*** ***Acinetobacter* spp.** **MRSA** ***Legionella pneumophila*** **Other non fermentative GNB**	Antipseudomonic cephalosporin (ceftazidime or cefepime) or Carbapenem (imipenem, meropenem) or Betalactamic / betalactamase inhibitor (piperacillin / tazobactam) + Antipseudomonic fluoroquinolone (ciprofloxacin, levofloxacin) or Aminoglycoside (amikacin) ± linezolid or vancomycin

The utility of a clinical guideline for the treatment of VAP was evaluated by Ibrahim et al (42), in 2001, in a prospective study of 50 patients in a medical ICU treated before the guideline was implemented and 52 patients treated after the guideline was implemented. The specific goals were to provide an initial administration of adequate antimicrobial treatment and to reduce potentially unnecessary antimicrobial use. The guideline suggested empiric treatment with vancomycin, ciprofloxacin, and imipenem, which could be modified after 24 to 48 hours based on cultures and clinical findings. Initial duration of treatment was 7 days, except for those patients with persistent signs and symptoms of infections. The data indicate that adequate antimicrobial therapy was significantly higher in the guideline group (94% vs. 48%, $P < 0.001$), duration of therapy was shorter (9 days vs. 15 days, $P < 0.001$), and second episodes of pneumonia were significantly reduced (8% vs. 24%, $P = 0.030$). These data indicate that the use of a clinical guideline for therapy can increase the rate of appropriate initial antimicrobial therapy, decrease the duration of therapy, and prevent second episodes of pneumonia.

With the aim to evaluate an antibiotic treatment protocol based on local microbiology data, Soo-Hoo et al (43) studied the treatment adequacy and outcome of 56 pre-guideline episodes and 61 guideline-treated cases of severe HAP. With that purpose, they implemented an antibiotic protocol for HAP based on the 1996 ATS guidelines, adjusted according to local microbiological and resistance patterns. With the implementation of the local protocol the adequacy of treatment increased from 46% to 81%. The 14-day mortality decreased from 27 to 8%, but not the 30-day mortality.

Despite extensively diffused, the current guidelines of 2005 have never been validated in the clinical practice. We therefore assessed the efficacy of the current ATS/IDSA guidelines to predict the infecting pathogens and validated the adequacy of these guidelines for the choice of the empirical antibiotic strategy and outcome in ICU patients. Because the 2005 guidelines introduced substantial changes in the risk factors for infection by PRM, we also compared these

guidelines with the former 1996 ATS guidelines for HAP in adults (44).

PUBLICATIONS

The results of the studies that form the base of the present Doctoral Thesis been have gathered in the following publications:

1) **Liapikou A**, Ferrer M, Polverino E, Balasso V, Esperatti M, Piñer R, Mensa J, Luque N, Ewig S, Menendez R, Niederman MS, Torres A. Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. Clin Infect Dis. 2009 Feb 15; 48(4): 377-85 (Impact Factor= 8,18)*.

1.b. Lionel A. Mandell. Severe Community-Acquired Pneumonia (CAP) and the Infectious Diseases Society of America/American Thoracic Society CAP Guidelines Prediction Rule: Validated or Not. Editorial Commentary. CID 2009:48 (15 February)

2) Ferrer M, **Liapikou A**, Valencia M, Esperatti M, Theessen A, Antonio Martinez J, Mensa J, Torres A. Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit. Clin Infect Dis. 2010 Apr 1; 50(7):945-52 (Impact factor= 8,18)*

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PRESENTATIONS IN CONGRESSES

1. Ferrer M, **Liapikou A**, Polverino E, Balasso V, Esperatti M, Piñer R, Mensa J, Marcos M.A, Torres A. (Barcelona, ES) << Severe community-acquired pneumonia: validation of the ATS/IDSA guidelines to predict admission to the ICU >>,ATS Congress, 2008 May, Toronto.
2. Ferrer M, **Liapikou A**, Polverino E, Balasso V, Esperatti M, Piñer R, Mensa J, Marcos M.A, Torres A. (Barcelona, ES) << Severe Community-Acquired Pneumonia (CAP): Validation of the ATS/IDSA Guidelines To Predict Admission to the ICU >> ECCMID Congress, 2008 April, Barcelona ,Spain.
3. **Liapikou A**, Ferrer M, Polverino E, Balasso V, Piner R, Mensa J, Marcos MA, Torres A. S. Pneumologia, Hospital Clinic, Barcelona, Spain. <<Severe Community-Acquired Pneumonia (CAP): Validation of the ATS/IDSA Guidelines To Predict Admission to the ICU >> ,October 2008,ERS Congress, Berlin.
4. Ferrer M, **Liapikou A**, Valencia M, Esperatti M, Theessen A, Piñer R, Mensa J, Torres A. <<Validation of the ATS/IDSA guidelines for Hospital-Acquired Pneumonia in the ICU>>, 13^{o} State of the Art, Athens, April 2009.
5. Ferrer M, **Liapikou A,** Valencia M, Esperatti M, Theessen A, Martinez, Mensa JA, Torres A. <<Validation of the ATS/IDSA guidelines for Hospital-Acquired Pneumonia in the ICU>>, accepted for oral presentation in Vienna ERS Congress, September

3. *HYPOTHESES AND OBJECTIVES*

3.1. 1st Study

Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. Clin Infect Dis. 2009 Feb 15; 48 (4):377-85.

Hypothesis

We hypothesize that the predictive rule consists of at least 1 of 2 major (septic shock and invasive ventilation) or 3 of 9 minor severity criteria to identify severe CAP is more accurate for ICU admission and prediction of mortality than the previous ATS guidelines (12).

Objectives

The aims of this study were to validate our cohort of 2102 consecutively hospitalized episodes of CAP during 3 years:

- We assessed whether this predictive rule, fits with the clinical practice of our institution, as well as the relevance of minor criteria in the need for ICU admission.
- Whether the prediction of this rule is better for hospital mortality.

3.2. 2st Study

Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit. Clin Infect Dis. 2010 Apr 1; 50 (7):945-52

Hypothesis

We suppose that the 2005 ATS/IDSA guidelines predict potentially-resistant microorganisms in ICU patients with HAP better than the 1996 ones.

Objectives

We prospectively followed 276 patients with intensive care unit-acquired pneumonia. We classified patients into Group 1 (early-onset without risk factors for potentially-resistant microorganisms, n=38) and Group 2 (late-onset or risk factors for potentially-resistant microorganisms, n=238).

- We determined the accuracy of guidelines to predict causative microorganisms
- We validated the adequacy of these guidelines for the choice of the empiric antibiotic strategy and outcome in ICU patients
- The influence of guidelines adherence in patients' outcome.

ARTICLES

ARTICLE 1

MAJOR ARTICLE

Severe Community-Acquired Pneumonia: Validation of the Infectious Diseases Society of America/ American Thoracic Society Guidelines to Predict an Intensive Care Unit Admission

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(See the editorial commentary by Mandell on pages 386–8)

Background. The recent Infectious Disease Society of America/American Thoracic Society guidelines for the management of community-acquired pneumonia (CAP) in adults defined a predictive rule to identify patients with severe CAP to determine the need for intensive care unit (ICU) admission. We clinically validated this rule.

Methods. We analyzed 2102 episodes of CAP in consecutively hospitalized patients over a 7-year period. The predictive rule consists of at least 1 of 2 major severity criteria (septic shock and invasive mechanical ventilation) or at least 3 of 9 minor severity criteria. We assessed the association of the predictive rule with ICU admission and mortality.

Results. A total of 235 episodes of CAP (11%) occurred in patients who were admitted to the ICU, whereas the predictive rule identified 397 (19%) of 2102 episodes as severe CAP. The predictive rule and the decision for ICU admission agreed in 1804 (86%) of the episodes (κ coefficient, 0.45), with a sensitivity of 71% and a specificity of 88%, similar to the 2001 American Thoracic Society guidelines (sensitivity, 66%; specificity, 90%) in predicting ICU admission. Severe CAP criteria had higher sensitivity (58% vs. 46%) and similar specificity (88% vs. 90%), compared with the 2001 American Thoracic Society guidelines in predicting hospital mortality. Invasive mechanical ventilation was the main determinant for ICU admission, followed by septic shock. In the absence of major criteria, ICU admission was not related to survival of patients with minor severity criteria.

Conclusions. The predictive rule to identify severe CAP is accurate for ICU admission and improved the prediction of mortality, compared with the previous American Thoracic Society guidelines. The need for ICU admission derived from minor severity criteria alone is uncertain and deserves further investigation.

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality in all age groups [1–4]. The assessment of severity is crucial in the management of CAP. To aid in deciding whether a given patient can be treated as an outpatient or should be admitted to the hospital, severity scores (such as the Pneumonia Severity Index [PSI] [5]; the confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure [CURB] score; and the CURB plus age ≥65 years [CURB 65] score [6, 7]) have been described; these scores stratify patients with CAP into mortality risk groups. These scores, however, were not developed to identify specifically those patients with severe CAP or to decide the site of inpatient care (ward or intensive care unit [ICU]) [5, 8].

Severe CAP has been defined as those cases that require admission to the ICU [9]. Direct admission to an ICU is required for patients with septic shock or acute respiratory failure requiring invasive mechanical ventilation, which are defined as major severity criteria

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Table 1. Criteria for severe community-acquired pneumonia according to the Infectious Diseases Society of America/American Thoracic Society guidelines.

Type of criteria	Severity criteria
Minor	Respiratory rate ≥30 breaths/min[a]
	P_{AO_2}/F_{IO_2} ≤250[a]
	Multilobar infiltrates
	Confusion and/or disorientation
	Uremia (BUN level ≥20 mg/dL)
	Leukopenia (WBC count <4 × 10^9 cells/L)
	Thrombocytopenia (platelet count <100 × 10^9 platelets/L)
	Hypothermia (core temperature <36°C)
	Hypotension (SBP <90 mm Hg; requiring aggressive fluid resuscitation)
Major	Receipt of invasive mechanical ventilation
	Septic shock with the need for vasopressors[b]

NOTE. Adapted from Mandell et al. [11]. BUN, blood urea nitrogen; P_{AO_2}/F_{IO_2}, ratio of arterial oxygen tension to inspired oxygen fraction; SBP, systolic blood pressure.

[a] The need for noninvasive mechanical ventilation can substitute for respiratory rate ≥30 breaths/min or P_{AO_2}/F_{IO_2} ≤250.

[b] Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid replacement, in combination with hypoperfusion abnormalities [13].

in the modified score of the American Thoracic Society (ATS) guidelines that are used to define severe CAP [10]. Admission to an ICU was also recommended for patients with other minor severity criteria. However, none of those minor severity criteria adequately distinguish patients for whom ICU admission is necessary.

The recent Infectious Diseases Society of America (IDSA)/ATS guidelines for the treatment of adults with CAP retained the same major severity criteria and developed a new set of minor severity criteria on the basis of data on individual risks to identify patients with severe CAP [11]. Whether each of the minor severity criteria is of equal weight is not clear. Therefore, the guidelines recommended a prospective validation of this set of criteria but consideration of ICU admission if ≥3 minor severity criteria were present [11].

Because ICU resources are often scarce in many institutions, admission of patients with CAP who would not benefit from ICU care is problematic. Moreover, the predictive potential of this rule, particularly the importance of the individual minor severity criteria, has not been validated in an individual hospital setting. Therefore, we assessed whether this predictive rule fits with the clinical practice of our institution (Hospital Clinic, Universitat de Barcelona; Barcelona, Spain), as well as the relevance of minor severity criteria in the need for ICU admission.

METHODS

Study population. We prospectively observed consecutive patients aged >15 years who were admitted to the emergency department for >12 h in an 850-bed tertiary care university hospital from January 2000 through January 2007 and who received a diagnosis of CAP. Pneumonia was defined as a new pulmonary infiltrate found on the hospital admission chest radiograph and symptoms and signs of lower respiratory tract infection. We excluded patients with immunosuppression (e.g., patients with neutropenia after chemotherapy or bone marrow transplantation, patients with drug-induced immunosuppression as a result of solid-organ transplantation or corticosteroid or cytotoxic therapy, and patients with HIV-related disorders) [12]. The decision for admission to an ICU or ward was made by the attending physicians in all cases.

Data collection and evaluation. The following parameters were recorded at admission: age, sex, tobacco use, alcohol and drug consumption, comorbidities (heart, renal, liver, lung, neurological, and neoplastic diseases, diabetes mellitus, and hypertension), previous use of antibiotics, treatment with corticosteroids, clinical symptoms and features (fever, cough, pleuritic chest pain, dyspnea, mental confusion, and aspiration), clinical signs (blood pressure, body temperature, respiratory rate, and heart rate), arterial blood gas measurements, chest radiograph findings (number of lobes affected, pleural effusion, and atelectasis), laboratory parameters (hemoglobin level, WBC count, platelet count, serum creatinine level, C-reactive protein level, and other biochemical parameters), diagnostic procedures, and therapy. Septic shock [13], the need for invasive mechanical ventilation, complications, duration of treatment, length of hospital stay, and 30-day in-hospital mortality were noted. We also calculated the PSI [5] and the CURB 65 [7] scores at hospital admission.

Definition of severe CAP. According to the prediction rule of the IDSA/ATS guidelines [11], those cases that met at least 1 of 2 major severity criteria or 3 of 9 minor severity criteria (table 1) at hospital admission were defined as severe CAP. Because blood urea nitrogen level is not systematically deter-

mined in our hospital, we accepted, in its place, serum creatinine level >2 mg/dL, as in previous studies [14, 15].

Statistical analysis. For comparisons between groups, qualitative or categorical variables were compared with use of the χ^2 or Fisher's exact tests, when appropriate. Quantitative continuous variables were compared using the unpaired Student's *t* test. All data were analyzed and processed using SPSS software, version 14.0 (SPSS). The level of statistical significance was set at $P = .05$ (2-tailed).

To determine the predictive capacity of severe CAP criteria for ICU admission and hospital mortality, we determined sensitivity, specificity, and positive and negative likelihood ratio [16], and we compared the findings with the modified score of the ATS guidelines [10]. The coincidence between the predictive rule and the clinical decision for ICU admission was assessed with the κ coefficient of agreement. The univariate association of the predictive rule and of each of the severity criteria with ICU admission or mortality are expressed as the relative risk and the 95% CI.

Impact of ICU admission on hospital mortality for patients with minor severity criteria only. All patients with minor severity criteria and without major severity criteria were categorized on the basis of the number of individual minor severity criteria. The mortality rates of patients with different numbers of minor severity criteria who were hospitalized in the ICU and not hospitalized in the ICU were compared.

RESULTS

Patient characteristics. We identified 2391 episodes of CAP among patients admitted to our hospital during the study period. Complete data to evaluate the IDSA/ATS prediction rule to define severe CAP were available for 2102 episodes. According to the attending physicians, 235 (11%) of the episodes occurred in patients who were admitted to an ICU, 194 (9%) occurred in patients treated in the emergency department, and 41 (2%) occurred in patients from other wards who experienced clinical deterioration. Patient characteristics are shown in table 2. The patients who were admitted to the ICU were younger; were more likely to have a smoking history, consume alcohol, and abuse drugs; were more likely to have pleural effusion; had higher C-reactive protein levels; had worse oxygenation; had higher PSI and CURB 65 risk classes; and had a longer mean length of hospital stay, compared with patients who were not admitted to the ICU.

The predictive rule identified 397 (19%) of the patients as having severe CAP; 8 (2%) had major severity criteria only, 219 (55%) had minor severity criteria only, and 170 (43%) had both major and minor severity criteria. Of those 397 patients who were defined as having severe CAP, 167 were admitted to the ICU. Only 68 (4%) of the 1705 patients who were defined as not having severe CAP were admitted to the ICU.

Severe CAP and prediction of ICU admission. The predictive rule and the decision for ICU admission agreed in 1804 (86%) of the episodes (table 3); the κ coefficient was 0.45 ($P < .001$). The predictive rule overestimated ICU admission; although 230 patients with severe CAP criteria were not admitted to ICUs, 68 patients with nonsevere CAP criteria were admitted to ICUs. As expected, severe CAP and all severity criteria, except hypothermia, were more frequent among patients who were admitted to the ICU.

The sensitivity for ICU admission was 71%, and the specificity was 88%. When considering admission to the ICU directly from the emergency department, the sensitivity (75%) and specificity (87%) were similar. The likelihood ratios show that severe CAP was 5.77-fold more frequent among patients admitted to the ICU than it was among those not admitted to the ICU; likewise, the probability that patients hospitalized in the ICU, compared with those who were not hospitalized in the ICU, had nonsevere CAP was only 33%. Patients with severe CAP, compared with patients with nonsevere CAP, had a relative risk of being admitted to an ICU of 17.5. In our population, the criteria of the modified score of the 2001 ATS guidelines [10] yielded a sensitivity (66%) and specificity (90%) that were similar to those of the IDSA/ATS prediction rule.

Severe CAP and prediction of mortality. The 30-day hospital mortality was higher among patients admitted to the ICU than it was among those who were not admitted to the ICU ($P < .001$; table 2). Mortality, assessed at 7 days and 30 days, was similar among patients with severe CAP criteria, regardless of whether they were admitted to the ICU; mortality was similar among patients with no criteria of severe CAP and was lower for such patients than it was among patients with severe CAP, regardless of whether the patient was admitted to an ICU (table 4).

The association between the predictive rule and mortality is shown in table 5. Severe CAP and the presence of either of the 2 major severity criteria had the strongest association with mortality. Not all of the minor severity criteria were individually predictive of death. The presence of hypotension, thrombocytopenia, and multilobar involvement were not associated with mortality. However, the remaining minor severity criteria were significantly associated with death.

The sensitivity of severe CAP criteria in predicting hospital mortality was 58%, and the specificity was 88%. The modified score of the 2001 ATS guidelines [10] had a lower sensitivity (46%) and a similar specificity (90%) in predicting hospital mortality.

Severity criteria and outcome variables for patients admitted and patients not admitted to the ICU. The major severity criteria had the highest association with ICU admission; in particular, all patients who received invasive mechanical ventilation except 1 were admitted to an ICU. However, 57 (43%)

Table 2. Characteristics of the study population.

Variable	Patients not hospitalized in the ICU (n = 1867)	Patients hospitalized in the ICU (n = 235)	P
Age, mean years ± SD	67 ± 18	64 ± 17	.006
Sex, M/F	1147/720	144/91	>.99
History of smoking	1060 (57)	161 (69)	<.001
History of alcohol abuse	282 (16)	57 (26)	.001
History of injection drug abuse	8 (0.4)	4 (1.7)	.034
Comorbidity			
Chronic heart failure	372 (20)	41 (18)	.43
Chronic renal failure	133 (7)	17 (7)	>.99
Chronic liver disease	74 (4)	15 (6)	.12
Chronic pulmonary disease	834 (45)	109 (47)	.56
Diabetes mellitus	352 (19)	48 (21)	.59
Neurological disease	359 (19)	45 (19)	>.99
Cancer	131 (7)	12 (5)	.34
Clinical and laboratory characteristics at hospital admission			
C-reactive protein level, mean mg/dL ± SD	18 ± 12	23 ± 14	<.001
WBC count, mean value × 10^9 cells/L ± SD	14.2 ± 7.0	14.2 ± 7.8	.93
Platelet count, mean value × 10^9 platelets/L ± SD	249 ± 107	255 ± 128	.49
P_{AO_2}/F_{IO_2}, mean value ± SD	301 ± 68	231 ± 81	<.001
Pleural effusion	252 (14)	61 (26)	<.001
Aspiration	200 (11)	26 (11)	.91
Cavitation	22 (1.2)	4 (2)	.53
Atelectasis	61 (3)	11 (5)	.33
Length of hospital stay, mean days ± SD	7.1 ± 6.5	18.0 ± 14.8	<.001
Hospital mortality			
At 30 days	79 (4)	30 (13)	<.001
At 7 days	44 (2)	6 (3)	>.99
Pneumonia Severity Index			
Mean value ± SD	97 ± 40	120 ± 38	<.001
Risk class I-III	875 (47)	50 (22)	
Risk class IV	620 (34)	91 (39)	
Risk class V	353 (19)	91 (39)	
CURB 65 score, mean value ± SD	1.2 ±1.0	1.8 ± 1.0	<.001
Etiologic diagnosis			
Any	737 (40)	102 (43)	.28
Polymicrobial	88/737 (12)	22/102 (22)	
Streptococcus pneumoniae	410/737 (56)	59/102 (58)	
Viruses	126/737 (17)	17/102 (17)	
Legionella pneumophila	61/737 (8)	13/102 (13)	
Haemophilus influenzae	46/737 (6)	7/102 (7)	
Mycoplasma pneumoniae	40/737 (5)	2/102 (2)	
Chlamydia pneumoniae	23/737 (3)	4/102 (4)	
Staphylococcus aureus	18/737 (2)	7/102 (7)	
Pseudomonas aeruginosa	17/737 (2)	3/102 (3)	
Other	90/737 (12)	15/102 (15)	

NOTE. Data are no. (%) of episodes, unless otherwise indicated. ICU, intensive care unit; P_{AO_2}/F_{IO_2}, ratio of arterial oxygen tension to inspired oxygen fraction; CURB 65, confusion, urea, respiratory rate, blood pressure plus age ≥65 years.

Table 3. Infectious Diseases Society of America/American Thoracic Society guidelines criteria for severe community-acquired pneumonia (CAP) and operative indices to predict intensive care unit (ICU) admission.

Variable	No. (%) of patients		Sensitivity, %	Specificity, %	Likelihood ratio		Risk ratio (95% CI)	*P*
	Not hospitalized in the ICU (*n* = 1867)	Hospitalized in the ICU (*n* = 235)			Positive	Negative		
Severe CAP	230 (12)	167 (71)	71	88	5.77	0.33	17.5 (12.8–23.9)	<.001
Nonsevere CAP	1637 (88)	68 (29)						
Major severity criteria								
Receipt of mechanical ventilation	1 (0.1)	86 (37)	37	99.9	683.24	0.63	1077 (149–7788)	<.001
Septic shock	57 (3)	75 (32)	32	97	10.45	0.70	14.9 (10.2–21.8)	<.001
Minor severity criteria								
SBP <90 mm Hg	57 (3)	28 (12)	12	97	3.90	0.91	4.3 (2.7–6.9)	<.001
Respiratory rate >30 breaths/min	485 (26)	128 (55)	55	74	2.10	0.62	3.4 (2.6–4.5)	<.001
P_{AO_2}/F_{IO_2} <250	398 (21)	144 (61)	61	79	2.87	0.49	5.8 (4.4–7.8)	<.001
Temperature <36°C	74 (4)	15 (6)	6	96	1.61	0.97	1.7 (0.93–2.9)	.12
WBC count <4000 cells/mm^3	25 (1)	18 (8)	8	99	5.72	0.94	6.1 (3.3–11.4)	<.001
Platelet count <100,000 platelets/mm^3	44 (2)	14 (6)	6	98	2.53	0.96	2.6 (1.4–4.9)	.003
Creatinine level >2 mg/dL	171 (9)	49 (21)	21	91	2.28	0.87	2.6 (1.8–3.7)	<.001
Multilobar involvement	401 (22)	116 (49)	49	78	2.30	0.64	3.6 (2.7–4.7)	<.001
Mental confusion	345 (19)	79 (34)	34	81	1.82	0.81	2.2 (1.7–3.0)	<.001

NOTE. P_{AO_2}/FIO_2, ratio of arterial oxygen tension to inspired oxygen fraction; SBP, systolic blood pressure.

of the patients with septic shock, whose cases were initially managed and stabilized in the emergency department, were not subsequently admitted to an ICU (table 3). Of 132 patients with septic shock, 91 (69%) did not receive invasive mechanical ventilation. Patients with septic shock who did not receive mechanical ventilation who were hospitalized in the ICU and such patients who were not hospitalized in the ICU had similar severity scores, such as PSI (mean score ± SD, 124 ± 37 vs. 117 ± 46) and CURB 65 (mean score ± SD, 2.5 ± 1.0 vs. 2.2 ± 1.3). However, the 30-day in-hospital mortality was lower among patients who were hospitalized in the ICU than it was among patients who were not hospitalized in the ICU (2 [6%] vs. 17 [30%]; $P = .014$), suggesting a possible benefit of ICU care for patients with septic shock.

Minor severity criteria were associated with ICU admission less often than were major severity criteria. Among the 219 patients with severe CAP defined by the presence of minor severity criteria only, 47 (21%) were admitted to an ICU (table 6). The number of minor severity criteria, as well as the PSI risk classes and hospital mortality, were similar between patients hospitalized in the ICU and patients who were not hospitalized in the ICU. Patients with hypoxemia were more likely to be admitted to the ICU, and those with mental confusion were less likely to be admitted to the ICU. The remaining minor severity criteria were as common among those admitted to the ICU as they were among those who were not admitted to the ICU.

Among the patients with nonsevere CAP, 1012 (59%) met 1 or 2 of the minor severity criteria. Again, the number of minor severity criteria, as well as the PSI risk classes and mortality, were similar between patients hospitalized in the ICU and those who were not hospitalized in the ICU (table 6). Only leukopenia was more common among patients with nonsevere CAP who were admitted to the ICU than it was among patients with nonsevere CAP who were not admitted to the ICU.

In our population, 1924 patients had no major severity criteria. Of these, 115 were admitted to the ICU, and 1809 were not admitted to the ICU. Among this population, the number of minor severity criteria with the best discriminative capacity to predict ICU admission was 2, with a sensitivity of 64% and a specificity of 72%. The number of minor severity criteria was related to hospital mortality (relative risk, 1.97 for each of the criteria; 95% CI, 1.63–2.37; $P < .001$). However, there were no differences in hospital mortality between patients admitted to the ICU and patients not admitted to the ICU according to the different number of minor severity criteria present (table 7).

DISCUSSION

The definition of severe CAP in the current IDSA/ATS guidelines for the management of adults with CAP is accurate for predicting ICU admission. Of the 235 patients who were admitted to the ICU, 167 (71%) met severe CAP criteria. Compared with the modified score of the 2001 ATS guidelines [10], the current IDSA/ATS guidelines [11] are similar in predicting ICU admission and better in predicting hospital mortality. However, the predictive rule identified 230 patients with severe CAP criteria who were not admitted to the ICU. These patients had a higher mortality rate than did patients who did not meet

Table 4. Characteristics of patients with severe and nonsevere community-acquired pneumonia (CAP) in relation to hospital site of care.

Variable	Patients with severe CAP			Patients with nonsevere CAP		
	Not hospitalized in the ICU (n = 230)	Hospitalized in the ICU (n = 167)	P	Not hospitalized in the ICU (n = 1637)	Hospitalized in the ICU (n = 68)	P
Hospital mortality						
At 30 days	36 (16)	27 (16)	>.99	43 (3)	3 (4)	.43
At 7 days	19 (8)	6 (4)	.093	25 (2)	0 (0)	.62
Age, mean years ± SD	75 ± 16	65 ± 16	<.001	66 ± 18	59 ± 17	.003
Length of hospital stay, mean days ± SD	10 ± 8	20 ± 17	<.001	7 ± 6	14 ± 9	<.001
Pneumonia Severity Index risk class, mean value ± SD	3.9 ±1.3	4.2 ± 1.0	.003	3.2 ± 1.4	3.7 ± 1.1	<.001
CURB 65 score, mean value ± SD	2.4 ± 1.0	2.0 ± 0.9	<.001	1.0 ± 0.8	1.1 ± 0.8	.64
Major severity criteria for severe CAP						
Septic shock	57 (25)	75 (45)	<.001	...	...	
Receipt of mechanical ventilation	1 (0.4)	86 (52)	<.001	...	...	
Minor severity criteria for severe CAP						
Systolic blood pressure <90 mm Hg	37 (16)	28 (17)	.96	20 (1)	0 (0)	>.99
Respiratory rate >30 breaths/min	140 (61)	106 (64)	.67	345 (21)	22 (32)	.039
P_{AO_2}/F_{IO_2} <250	135 (59)	126 (75)	.001	263 (16)	18 (27)	.036
Temperature <36°C	30 (13)	15 (9)	.27	44 (3)	0 (0)	.42
WBC count <4000 cells/mm^3	13 (6)	15 (9)	.28	12 (1)	3 (4)	.020
Platelet count <100,000 platelets/mm^3	17 (7)	13 (8)	>.99	27 (2)	1 (1)	>.99
Creatinine level >2 mg/dL	78 (34)	42 (25)	.077	93 (6)	7 (10)	.11
Multilobar involvement	113 (49)	92 (55)	.28	288 (18)	24 (35)	<.001
Mental confusion	131 (57)	69 (41)	.003	214 (13)	10 (15)	.84

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit; CURB 65, confusion, urea, respiratory rate, blood pressure plus age ≥65 years; P_{AO_2}/F_{IO_2}, ratio of arterial oxygen tension to inspired oxygen fraction.

severe CAP criteria who were admitted to the ICU (table 4). Thus, although this predictive rule overestimated ICU admission in clinical practice, many of these patients may have benefited from ICU care, and our findings may reflect a lack of availability of ICU beds for the management of these patients.

Approximately 10% of hospitalized patients with CAP (for whom a higher rate of complications, higher mortality rate, and prolonged hospital stay are expected) require admission to an ICU [17–19]. However, the optimal management of CAP requires that seriously ill patients be recognized as such in the emergency department, which allows appropriate site-of-care decisions to be made. The site-of-care (home, hospital ward, or ICU) often determines the extensiveness of the diagnostic evaluation, the choice and route of antimicrobial therapy, the intensity of clinical observation, and the economic cost [8].

Prognostic scoring systems are used to define the predicted mortality rate associated with CAP and, by inference, the site-of-care, suggesting hospitalization for those patients who are expected to have higher mortality rates. The PSI [5] and the CURB 65 scores [7] are designed for recognizing those patients whose cases can safely be managed outside the hospital if serious vital sign abnormalities or comorbidities are absent. However, the likelihood of receiving ICU care is poorly predicted by these severity scores [14, 15, 20]. A wrong decision regarding ICU admission could result in underuse or overuse of the ICU, with consequences including delayed or inadequate treatment for some patients and excessive resource use for other patients (keeping in mind that the cost of inpatient care for pneumonia is as much as 25 times greater than the cost of outpatient care) [21].

Creating accurate and objective prediction models for ICU admission has several advantages. First, the appropriate placement of patients optimizes the use of limited ICU resources, selecting those patients who would actually benefit from ICU care or high-level monitoring. Second, an accurate prediction model avoids the delayed ICU transfer of patients who are initially placed in other hospital units, which is associated with increased mortality [22]. Third, correct site-of-care can optimize initial antibiotic treatment, because the microbial etiologies of severe CAP differ from those associated with CAP in general [23, 24]. Avoidance of initial inappropriate antibiotic treatment is associated with lower mortality [25, 26].

The first guideline-based definition of severe CAP involved 10 criteria [9]. The presence of only 1 criterion was enough to

Table 5. Association of the predictive rule of severe community-acquired pneumonia (CAP) and other indices with 30-day in-hospital mortality.

Variable	Patients alive at 30 days: Yes (n = 1993)	Patients alive at 30 days: No (n = 109)	Risk ratio (95% CI)	P
Age, mean years ± SD	66 ± 18	77 ± 13	1.043 (1.027–1.058)	<.001
Severe CAP criteria	343 (17)	63 (58)	6.8 (4.6–10.1)	<.001
Major severity criteria for severe CAP				
Septic shock	102 (5)	30 (28)	7.0 (4.1–11.9)	<.001
Receipt of mechanical ventilation	66 (3)	21 (19)	6.9 (4.2–11.5)	<.001
Minor severity criteria for severe CAP				
Systolic blood pressure <90 mm Hg	78 (4)	7 (6)	1.7 (0.8–3.7)	.21
Respiratory rate >30 breaths/min	552 (28)	61 (56)	3.3 (2.2–4.9)	<.001
P_{AO_2}/F_{IO_2} <250	487 (24)	55 (51)	3.2 (2.1–4.6)	<.001
Temperature <36°C	80 (4)	9 (8)	2.2 (1.1–4.4)	.046
WBC count <4000 cells/mm^3	36 (2)	7 (6)	3.7 (1.6–8.6)	.006
Platelet count <100,000 platelets/mm^3	54 (3)	4 (4)	1.4 (0.5–3.8)	.54
Creatinine level >2 mg/dL	191 (10)	29 (27)	3.4 (2.2–5.4)	<.001
Multilobar involvement	483 (24)	34 (31)	1.4 (0.9–2.2)	.13
Mental confusion	370 (19)	54 (50)	4.3 (2.9–6.4)	<.001
Pneumonia Severity Index risk class, mean value ± SD	3.3 ± 1.4	4.0 ± 1.1	1.62 (1.35–1.95)	<.001
CURB 65 score, mean value ± SD	1.2 ± 1.0	2.2 ± 1.0	2.48 (2.06–2.98)	<.001

NOTE. CURB 65, confusion, urea, respiratory rate, blood pressure plus age ⩾65 years; P_{AO_2}/F_{IO_2}, ratio of arterial oxygen tension to inspired oxygen fraction.

recommend ICU admission; therefore, this rule was highly sensitive (98%) but insufficiently specific (32%) [20]. A new score was proposed that relied on 1 of 2 major severity criteria (receipt of mechanical ventilation and septic shock) or 2 of 3 minor severity criteria [20], and this score was adopted in the 2001 ATS guidelines [10]. This modified ATS score achieved a sensitivity of 69% and a specificity of 97% in predicting ICU admission, whereas the prediction of mortality yielded a sensitivity of 94% and a specificity of 93% [14].

The modified ATS score showed better discriminatory capacity for ICU admission than did the PSI, CURB, and CURB 65 scores [8, 14]. However, one study found that none of the prediction rules were particularly good, largely because of their poor positive predictive value; in this study, most patients who met the criteria were never admitted to an ICU [8]. This study concluded that the discrimination of the scores appeared to be too low to guide individual decision making for ICU admission.

To achieve better prediction for ICU admission, the IDSA/ATS adopted a new prediction rule for defining severe CAP, with the inclusion of a new set of minor severity criteria [11]. We have evaluated, for the first time, to our knowledge, how this predictive rule fits with the clinical practice in a large population of patients with CAP who were hospitalized before the IDSA/ATS guidelines were published (and therefore, a population in which the decisions regarding ICU admission were not affected by the guidelines). This predictive rule has a good sensitivity and specificity in identifying ICU admission, but it does not improve substantially the discriminative capacity of the modified ATS rule [10].

The presence of 1 of the 2 major criterion (in particular, receipt of invasive mechanical ventilation) was a major determinant in the decision for ICU admission. This is obvious, because patients who need invasive mechanical ventilation cannot be treated outside the ICU in most hospitals. The worse outcomes among patients with septic shock who were not treated in an ICU after the initial stabilization in the emergency department confirm the need for close monitoring and ICU care of these patients.

A significant number of patients in our population who met the criteria for severe CAP were not admitted to the ICU. We identified the absence of major severity criteria or hypoxemia, together with older age and lower score on the severity indices, as the main reasons that they were treated outside the ICU. The higher proportion of mental confusion in patients who were not treated in the ICU is explained by the fact that this subset of patients was older, with the highest proportions of limitation in the activities of the daily life, witnessed aspiration, and neurological comorbidity. Likewise, several patients with nonsevere CAP were actually admitted to the ICU. ICU admission was related to the presence of minor severity criteria,

Table 6. Characteristics of patients with severe and patients with nonsevere community-acquired pneumonia (CAP) who met minor severity criteria but not major severity criteria.

Variable	Patients with severe CAP			Patients with nonsevere CAP		
	Not hospitalized in the ICU (n = 172)	Hospitalized in the ICU (n = 47)	P	Not hospitalized in the ICU (n = 954)	Hospitalized in the ICU (n = 58)	P
Hospital mortality						
At 30 days	19 (11)	4 (9)	.79	38 (4)	3 (5)	.51
At 7 days	9 (5)	0 (0)	.21	22 (2)	0 (0)	.63
Age, mean years ± SD	77 ± 15	66 ± 18	<.001	69 ± 17	59 ± 17	<.001
Length of hospital stay, mean days ± SD	10 ± 6	15 ± 8	<.001	8 ± 7	14 ± 9	<.001
Pneumonia Severity Index risk class, mean value ± SD	3.9 ± 1.2	4.2 ± 1.0	.095	3.4 ± 1.2	3.7 ± 1.1	.12
CURB 65 score, mean value ± SD	2.6 ± 0.8	2.3 ± 0.9	.019	1.4 ± 0.9	1.1 ± 0.8	.027
Mean no. of minor severity criteria ± SD	3.3 ± 0.5	3.4 ± 0.6	.33	1.4 ± 0.5	1.5 ± 0.5	.16
Systolic blood pressure <90 mm Hg	15 (9)	3 (6)	.77	20 (2)	0 (0)	.62
Respiratory rate >30 breaths/min	118 (69)	38 (81)	.14	345 (36)	22 (28)	.90
P_{AO_2}/F_{IO_2} <250	112 (65)	41 (87)	.006	263 (28)	18 (31)	.17
Temperature <36°C	28 (16)	4 (9)	.27	44 (5)	0 (0)	.42
WBC count <4000 cells/mm^3	11 (6)	4 (9)	.53	12 (1)	3 (5)	.050
Platelet count <100,000 platelets/mm^3	16 (9)	5 (11)	.78	27 (3)	1 (2)	.93
Creatinine level >2 mg/dL	61 (36)	13 (28)	.41	93 (10)	7 (12)	.73
Multilobar involvement	99 (58)	32 (68)	.26	288 (30)	24 (41)	.10
Mental confusion	108 (63)	20 (43)	.020	214 (22)	10 (17)	.45

NOTE. Data are no. (%) of patients, unless otherwise indicated. CURB 65, confusion, urea, respiratory rate, blood pressure plus age ≥65 years; ICU, intensive care unit; P_{AO_2}/F_{IO_2}, ratio of arterial oxygen tension to inspired oxygen fraction.

particularly tachypnea, hypoxemia, leukopenia, and multilobar involvement, together with younger age and higher PSI risk classes. Other clinical prediction rules for severe CAP that include factors similar to the minor severity criteria of the IDSA/ATS guidelines have been proposed [27]. These investigators weighted each variable and created a quantitative score. However, we think that their results cannot be compared with those of the present study, because they used hospital mortality, receipt of mechanical ventilation, and septic shock to define severe CAP, which does not correspond to published guidelines.

In the absence of major severity criteria, we could not demonstrate that ICU admission resulted in reduced mortality for patients with minor severity criteria. In addition, the number of minor severity criteria could not discriminate which patients could benefit from ICU admission.

Several limitations of this study deserve comment. First, blood urea nitrogen level was not systematically determined in our hospital; therefore, we used serum creatinine level as a surrogate, as we have done in previous studies [14, 15]. Therefore, we cannot exclude the possibility that some cases did not entirely meet the definitions given in the guidelines. Second, information regarding "do not intubate" (DNI) decisions was available for only 856 (41%) of the episodes. Previous DNI orders may influence the decision for ICU admission. However, among patients for whom such information was available, the rate of previous DNI orders did not substantially differ between patients who were hospitalized in the ICU and patients who were not (6% and 10%, respectively). The proportion of ICU admissions did not differ substantially between patients with and patients without a previous DNI decision (9% and 14%, respectively). After excluding patients with a previous DNI decision, the sensitivity (72%) and specificity (88%) of the IDSA/ATS guidelines were similar to the sensitivity and specificity among the overall population. Third, we used the decision for

Table 7. Thirty-day in-hospital mortality among patients without major severity criteria, according to the number of minor criteria present.

No. of minor severity criteria	No. of patients	30-day mortality, no. (%) of patients		
		Not hospitalized in the ICU (n = 1809)	Hospitalized in the ICU (n = 115)	P
0	693	5/683 (1)	0/10 (0)	>.99
1	633	17/602 (3)	0/31 (0)	>.99
2	379	21/352 (6)	3/27 (11)	.24
3	158	12/126 (10)	2/32 (6)	.74
4	52	7/41 (17)	1/11 (9)	>.99
5	8	0/1 (0)	1/4 (25)	>.99
6	1	0 (0)	...	
Total	1924	62/1809 (3)	7/115 (6)	.19

NOTE. ICU, intensive care unit.

ICU admission as the gold standard, because this reflected the actual clinical practice. However, the variability of clinicians' judgment and the frequent constraints on the availability of ICU beds may have influenced the site-of-care decisions.

In conclusion, the predictive rule of the IDSA/ATS guidelines for identification of severe CAP is accurate, but it slightly overestimates ICU admission in clinical practice. Compared with the previous ATS guidelines, the current IDSA/ATS guidelines are similar at defining the need for ICU admission and are better at predicting hospital mortality. Although ICU admission is clearly indicated for patients who require invasive mechanical ventilation or experience septic shock, the need for ICU admission derived from minor severity criteria alone is uncertain in our population and deserves further prospective evaluation.

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EDITORIAL COMMENTARY

Severe Community-Acquired Pneumonia (CAP) and the Infectious Diseases Society of America/American Thoracic Society CAP Guidelines Prediction Rule: Validated or Not

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(See the article by Liapikou et al. on pages 377–85)

Identifying patients with severe community-acquired pneumonia (CAP) who require admission to an intensive care unit (ICU) can, at times, be a difficult and daunting task. It is not always clear which patients will benefit from the additional diagnostic, treatment, and management protocols and procedures of the ICU, and the consequences of a poor selection process can be disastrous.

ICU facilities, resources, and personnel are relatively limited in most hospitals. Therefore, the inappropriate admission to the ICU of patients with CAP who do not require such care may prevent a patient who does require such care from accessing it. The subsequent transfer of patients with CAP who are first admitted to a hospital ward to the ICU for delayed onset of respiratory failure or septic shock is associated with increased mortality [1]. To anyone who cares for patients who may have severe CAP, it is obvious that the course of the disease is dynamic and that neither clinical nor laboratory values remain static. It can be difficult to differentiate between individuals who require ICU care at the time of assessment in the emergency department and those whose conditions will worsen after admission to the hospital. Ideally, we would like to identify patients who require ICU care as early as possible. Having an accurate prediction rule that allows physicians to select patients with severe CAP who require ICU treatment early in the course of illness facilitates the appropriate initial management and antibiotic treatment and is an important strategy for mortality reduction [2].

The decision regarding site of care (i.e., whether the patient should be treated as an outpatient, in a hospital ward, or in the ICU) carries with it a number of important implications. It is for these reasons that having an accurate and reliable prediction rule is important. The site of care determines the type and extent of diagnostic testing, the spectrum and route of administration of antibiotics, and the overall treatment costs. Rules that are overly sensitive or insufficiently specific help no one.

A number of criteria have been developed over the years to help with the definition of severe CAP and/or to identify patients who require admission to an ICU. These include the original American Thoracic Society (ATS) guidelines published in 1993 and the revised version published in 2001; the confusion, elevated blood urea nitrogen, respiratory rate, and blood pressure [CURB] score; the CURB plus age ≥65 years [CURB 65] score; and the Pneumonia Severity Index (PSI). All of these guidelines and measures attempted to deal with the concept of CAP severity [3–7]. Some, such as the CURB and CURB 65 scores, were in fact severity-of-illness scores, whereas the PSI was a prognostic model that was originally developed to identify patients who could be managed at home.

Part of the problem has been that there has not been a universally agreed upon definition of severe CAP. An examination of North American guidelines published over the past 14 years shows a process that has been slowly but progressively evolving. The original ATS CAP guidelines listed 9 criteria, and the presence of any 1 of these criteria implied that the patient had severe CAP. Such an approach, however, resulted in a definition that was extremely sensitive but not specific [8]. The ATS guidelines of 2001 modified the definition of severe CAP to include the presence of ≥2 minor criteria (respiratory rate ≥30 breaths per min, ratio of arterial oxygen tension to inspired oxygen fraction <250, bilateral or

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multilobar pneumonia, systolic blood pressure ≤90 mm Hg, and diastolic blood pressure ≤60 mm Hg) or the presence of 1 major criterion (the need for mechanical ventilation, septic shock or the need for vasopressors for >4 h, an increase in the size of infiltrates by >50% within 48 h, and acute renal failure).

A study by Angus et al. [9] compared the outcomes of hospitalized patients with CAP who received ICU care with the outcomes of those who did not. Angus et al. [9] compared the predictive characteristics of the original and revised ATS criteria, the British Thoracic Society criteria, and the PSI criteria for ICU admission, receipt of mechanical ventilation, medical complications, and death. They found that, with ICU admission and receipt of mechanical ventilation as the outcome measures, the revised ATS guidelines were the best predictor; when medical complications and death were the outcome measures, the PSI was the best predictor. It is important to note that the authors stipulate that, in both situations, none of the prediction rules were found to be particularly effective.

Angus et al. [9] concluded that none of the available prediction rules for severe CAP were "adequately robust to guide clinical care at the current time" [9, p. 717]. Ewig et al. [10], in a subsequent article, confirmed the ability of the modified ATS rule to predict severe pneumonia.

The Infectious Disease Society of America (IDSA)/ATS CAP guidelines are quite explicit about what constitutes major criteria for either severe CAP or direct admission to the ICU [11]. Either the need for mechanical ventilation with endotracheal intubation or the presence of septic shock requiring receipt of vasopressors are absolute indications. The minor criteria, however, are less clear-cut. A total of 9 such criteria are given in the guidelines, and the presence of ≥3 criteria was considered to provide sufficient evidence for admission to an ICU or high-level monitoring unit.

The 9 criteria are respiratory rate ≥30 breaths per min, ratio of arterial oxygen tension to inspired oxygen fraction ≤250, multilobar infiltrates, confusion and/or disorientation, uremia (blood urea nitrogen level ≥20 mg/dL), leukopenia (WBC count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 platelets/mm^3), hypothermia (core temperature <36°C), and hypotension requiring aggressive fluid resuscitation. The reader is referred to the IDSA/ATS CAP guidelines for a discussion of the minor criteria and the reasons for their inclusion [11].

The study by Liapikou et al. [12] in this issue of *Clinical Infectious Diseases* is an attempt to validate the predictive rule suggested by the IDSA/ATS CAP guidelines for the identification of patients with severe CAP and the selection of those individuals who require ICU admission. The study is an important one from both academic and clinical standpoints, and it is the first study, to our knowledge, to validate the recent prediction rule. The authors prospectively observed consecutive patients with CAP who met predefined criteria. The study took place over a 7-year period from January 2000 through January 2007, at which time the new guidelines were first published online, followed shortly thereafter by publication in print. The IDSA/ATS prediction rule was retrospectively applied to the patient database, but such an approach should have no bearing on the results. The main outcomes of interest were the predictive capacity of severe CAP criteria for ICU admission and hospital mortality and the impact of ICU admission on hospital mortality for patients who met only minor severity criteria and no major criteria.

For the relationship between severe CAP criteria and ICU admission, the sensitivity and specificity were 71% and 88%, respectively, whereas for mortality, the sensitivity and specificity were 58% and 88%, respectively. The rule tended to overestimate ICU admission somewhat, but overall, when compared with the modified ATS criteria of 2001, the IDSA/ATS prediction rule was equally good at predicting ICU admission and better at predicting hospital mortality. As might be expected, severity determined on the basis of a major criterion had the strongest association with mortality.

As for the predictive value of the minor criteria only, the authors were unable to document a reduction in mortality among patients who were admitted to the ICU, nor did the number of minor criteria present predict any benefit from ICU admission. The authors concluded that the need for ICU management was clear when either of the major criteria were employed but that the need for ICU care when only the minor criteria were used was not unequivocally supported by their data.

If we examine the IDSA/ATS criteria for severe CAP, the value of the major criteria is self evident. It goes without saying that a patient who requires intubation and mechanical ventilation or a patient with septic shock who requires vasopressors would need treatment in an ICU. The minor criteria, however, are not as obvious in terms of their relationship to mortality or the necessity for ICU care. I would agree with the authors when they state that "the need for ICU admission derived from minor criteria alone is uncertain in our population and deserves further prospective evaluation" [12, p. 377]. This is virtually identical to a statement made in the IDSA/ATS guidelines themselves; when referring to the minor criteria, the committee wrote that "prospective validation of this set of criteria is clearly needed" [11, p. 539].

There are 2 questions that can be asked of the article by Liapikou et al. [12] that relate to the minor criteria and to 1 of the major criteria. We are told that 235 patients were admitted to the ICU and that this included 41 patients from other wards who were admitted to the ICU after their condition deteriorated. In the absence of any major criteria, how many and/or what types of the minor criteria did these specific 41 patients meet?

It is also reported that 57 (43%) of the patients with septic shock were initially treated and stabilized in the emergency de-

partment and did not require subsequent admission to the ICU. This seems like a high percentage of such patients to do so well. We are then told, however, that the poorer outcome in such patients "confirms the need for close monitoring and ICU care of these patients" [12, p. 383]. This suggests that too many patients with septic shock were admitted to hospital wards when they might have benefitted from ICU admission instead.

It is unfortunate that studies of ICU admission do not account for patients who have a "do not resuscitate" status. Such patients may, in fact, meet severity criteria and die without being considered for ICU admission.

The article by Liapikou et al. [12] describes a nicely performed study that validates the IDSA/ATS prediction rule when it comes to major criteria but fails to confirm the validity of the minor criteria. These findings are welcome but are not very surprising, and it is incumbent upon investigators to continue to explore the usefulness of the minor criteria.

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Potential conflicts of interest. L.A.M.: no conflicts.

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ARTICLE 2

MAJOR ARTICLE

Validation of the American Thoracic Society–Infectious Diseases Society of America Guidelines for Hospital-Acquired Pneumonia in the Intensive Care Unit

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Background. The 2005 guidelines of the American Thoracic Society–Infectious Diseases Society of America Guidelines for Hospital for managing hospital-acquired pneumonia classified patients according to time of onset and risk factors for potentially drug-resistant microorganisms to select the empirical antimicrobial treatment. We assessed the microbial prediction and validated the adequacy of these guidelines for antibiotic strategy.

Methods. We prospectively observed 276 patients with intensive care unit–acquired pneumonia. We classified patients into group 1 (early onset without risk factors for potentially drug-resistant microorganisms; 38 patients) and group 2 (late onset or risk factors for potentially drug-resistant microorganisms; 238 patients). We determined the accuracy of guidelines to predict causative microorganisms and the influence of guidelines adherence in patients' outcome.

Results. Microbial prediction was lower in group 1 than in group 2 (12 [50%] of 24 vs 119 [92%] of 129; $P < .001$) mainly because of potentially drug-resistant microorganisms in 10 patients (26%) from group 1. Guideline adherence was higher in group 2 (153 [64%] vs 7 [18%]; $P < .001$). Guideline adherence resulted in more treatment adequacy than did nonadherence (69 [83%] vs 45 [64%]; $P = .013$) and a trend toward better response to empirical treatment in group 2 only but did not influence mortality. Reclassifying patients according to the risk factors for potentially drug-resistant microorganisms of the former 1996 American Thoracic Society guidelines increased microbial prediction in group 1 to 21 (88%; $P = .014$); all except 1 patient with potentially drug-resistant microorganisms were correctly identified by these guidelines.

Conclusions. The 2005 guidelines predict potentially drug-resistant microorganisms worse than the 1996 guidelines. Adherence to guidelines resulted in more adequate treatment and a trend to a better clinical response in group 2, but it did not influence mortality.

Hospital-acquired pneumonia (HAP) is a frequent and severe infection in intensive care units (ICU), with important morbidity, mortality, and economic cost [1–3]. Although the mortality rate has decreased in recent years, it is still substantial [4].

The institution of a timely and appropriate antimicrobial therapy is crucial to decrease the rates of complications and mortality related to pneumonia [5–8]. Thus, knowledge about the microbial epidemiology of each intensive care unit (ICU) is extremely important to ensure the choice of an appropriate empirical antimicrobial therapy. However, microbiology and the resistance patterns are not the same in different hospitals or between different departments within a hospital [9]. In addition, the etiology of ventilator-associated pneumonia (VAP) may vary substantially between different geographic sites in patients with similar epidemiological risk factors [10].

The treatment guidelines published by scientific societies are an invaluable help to begin an adequate empirical antimicrobial therapy in infected critically-ill

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patients. The current 2005 American Thoracic Society (ATS)–Infectious Disease Society of America (IDSA) guidelines for the management of adults with HAP, VAP, and health care–associated pneumonia focused on the epidemiology and pathogenesis of HAP, emphasized modifiable risk factors for infection, and reviewed the microbiology of HAP with an emphasis on "potentially drug-resistant" microorganisms (PRMs) [1]. These guidelines classified patients into 2 groups on the basis of time of onset of infection (early onset vs late onset) and the presence of risk factors for infection with a PRM.

Despite extensively diffused, these guidelines have never been validated in the clinical practice. We therefore assessed the efficacy of the current ATS/IDSA guidelines to predict the infecting pathogens and validated the adequacy of these guidelines for the choice of the empirical antibiotic strategy and outcome in ICU patients. Because the 2005 guidelines introduced substantial changes in the risk factors for infection by PRM, we also compared these guidelines with the former 1996 ATS guidelines for HAP in adults [11].

METHODS

Study population. The study was conducted in 6 specialized ICUs of an 800-bed university hospital. The investigators made daily rounds in the different ICUs. Patients aged >18 years who had been admitted to these ICUs for ≥48 h with clinical suspicion of HAP were prospectively and consecutively included in the study. Patients with major immunosuppression [12] were excluded. The ethics committee of the institution approved the study, and written informed consent was obtained from patients or relatives.

Definition of pneumonia, microbiologic processing, and antimicrobial treatment. The clinical suspicion of pneumonia was based on either (1) clinical criteria (new or progressive radiological pulmonary infiltrate plus ≥2 of the following characteristics: temperature, >38°C or <35.5°C; leukocyte count, >12,000 cells/mm^3 or <4000 cells/mm^3; or purulent respiratory secretions [13, 14]) or (2) a simplified Clinical Pulmonary Infectious Score >5 points [15]. VAP was diagnosed in patients with previous invasive mechanical ventilation for ≥48 h.

The microbiologic evaluation included the collection of at least 1 lower respiratory airway sample by sputum, tracheobronchial aspirate, or bronchoscopy [16] or by blind bronchoalveolar lavage [17] within the first 24 h after inclusion. The same sampling method was performed after 3 days if clinically indicated. Blood cultures and cultures of pleural fluid specimens, if puncture was indicated, were also undertaken. Microbiologic confirmation of pneumonia was defined by the presence of ≥1 potentially pathogenic microorganism (PPM) in respiratory samples above predefined thresholds (for bronchoalveolar lavage specimens, >10^4 CFU/mL; for sputum or tracheobronchial aspirate specimens, >10^5 CFU/mL) [18]; in pleural fluid specimens; or in blood cultures, if an alternative cause of bacteremia was ruled out. Microbial identification and susceptibility testing were performed by standard methods [19]. Pneumonia was considered to be caused by PRM if methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Acinetobacter baumannii,* or *Stenotrophomonas maltophilia* were identified [1, 20, 21]. Polymicrobial pneumonia was defined as identification of >1 PPM as causative agents.

The initial empirical antimicrobial treatment was administered in accordance with local adaptation of the ATS/IDSA guidelines [1] and was subsequently revised according with the microbiologic results.

Validation of the ATS/IDSA guidelines. According to the guidelines, we aggregated patients into group 1 (early-onset pneumonia without risk factors for PRM infection) and group 2 (late-onset pneumonia or early-onset pneumonia with risk factors for PRM infection) [1]. We assessed the adequacy of the guidelines to predict the isolated pathogens according to each patient's category [1]. If the isolated pathogen corresponded to the expected one, the microbial prediction was considered adequate.

Patients were also aggregated into different groups depending on whether the initial empirical antimicrobial treatment chosen by the attending physicians fitted the treatment suggested by the guidelines. These were classified as adherence or not to the guidelines. The prediction of the isolated pathogens and the treatment adherence were also assessed for the previous 1996 ATS guidelines on HAP [11]. These guidelines classified patients into 3 groups, as follows: group 1, mild-to-moderate HAP, no usual risk factors, onset any time, or early-onset, and severe HAP; group 2, mild-to-moderate HAP with risk factors and onset any time; and group 3, late-onset, severe HAP or early-onset HAP with risk factors.

The empirical antimicrobial treatment was considered adequate when the isolated pathogens were susceptible in vitro to ≥1 of the antimicrobials administrated. For *P. aeruginosa* infection, adequate treatment needed a combination of 2 active antibiotics against the isolated strain [22].

The initial response to treatment was evaluated after 72 h of antimicrobial treatment. Nonresponse was considered if ≥1 of the following criteria were present: (1) no improvement of the arterial O_2 tension to inspired O_2 fraction ratio or need for intubation because of pneumonia (defined as need for intubation after 24 h after the commencement of antibiotics); (2) persistence of fever (temperature, ≥38°C) or hypothermia (temperature, <35.5°C), together with purulent respiratory secretions; (3) increase in the pulmonary infiltrates on chest radiograph of ≥50%; or (4) occurrence of septic shock [23] or multiple-organ dysfunction syndrome, defined as ≥3 organ system failures [24] not present on day 1 [25, 26]. An effort was made to rule out causes not related to pneumonia. In

Table 1. Baseline Characteristics of Patients at Admission to the Intensive Care Unit (ICU)

Characteristic	Group 1 (n = 38)	Group 2 (n = 238)[a]	P
Age, mean years ± SD	62 ± 13	64 ± 14	.55
Sex			
Male	29	172	
Female	9	66	.75
Current or former smoking habit	26 (68)	130 (55)	.16
Current or former alcohol abuse	17 (45)	85 (36)	.37
Mean APACHE II score ± SD	17 ± 5	16 ± 6	.26
Comorbidity			
Diabetes mellitus	9 (24)	42 (18)	.51
Chronic renal failure	1 (3)	17 (7)	.49
Chronic liver disease	5 (13)	22 (9)	.65
Chronic lung disease	9 (24)	75 (32)	.43
Chronic heart disorders	13 (34)	39 (16)	.017
Solid cancer	7 (18)	50 (21)	.88
Recent surgery	14 (37)	125 (53)	.11
Receipt of antibiotics in previous 90 days	0 (0)	163 (69)	<.001
Previous hospital admissions	2 (5)[b]	72 (30)	.002
Previous use of corticosteroids	7 (18)	91 (38)	.029
Tracheostomy at admission	0 (0)	23 (10)	.053
Cause of ICU admission			.008
Postoperative respiratory failure	8 (21)	78 (33)	
Hypercapnic respiratory failure	4 (11)	24 (10)	
Septic shock	5 (13)	23 (10)	
Decreased consciousness	5 (13)	22 (9)	
Nonsurgical abdominal disease	0 (0)	22 (9)	
Acute hypoxemic respiratory failure	0 (0)	21 (9)	
Acute coronary syndrome	5 (13)	14 (6)	
Multiple trauma	5 (13)	9 (4)	
Other	6 (16)	25 (11)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation.

[a] Among patients from group 2, 101 (42%) had early-onset pneumonia and risk factors for potentially drug-resistant microorganisms; in 20 cases, they had criteria for health care–associated pneumonia.

[b] The durations of previous hospitalizations of patients from group 1 were <2 days.

patients with initial nonresponse to treatment, cultures of respiratory samples and blood were obtained again, and the empirical antimicrobial treatment was revised.

Data collection. All relevant data from the medical records and bedside flow charts of patients, including clinical, laboratory, radiology, and microbiology information, were collected at admission and at onset of pneumonia, and patients' follow-up was extended to death or hospital discharge. Special emphasis was made in searching all risk factors for PRM causing HAP, including those for health care–associated pneumonia, as defined in the 2005 ATS/IDSA guidelines [1].

Statistical analysis. Data were analyzed with SPSS, version 16.0 (SPSS). Data are presented as number (proportions) and mean ± SD, unless otherwise stated. Comparisons were done between groups of patients. Qualitative or categorical variables were compared with the χ^2 test or the Fisher exact test, as appropriate. Quantitative continuous variables were compared using the unpaired Student t test or the Mann-Whitney nonparametric test, as appropriate. Differences between groups were considered statistically significant for variables yielding a 2-tailed P value $\leq .05$.

RESULTS

Patients' characteristics. We included 276 patients; 38 were allocated to group 1, and 238 we allocated to group 2. The patients' characteristics at ICU admission and at onset of pneumonia are shown in Tables 1 and 2. Except for the rates of

Table 2. Patients Characteristics at Onset of Pneumonia

Characteristic	Group 1 (n = 38)	Group 2 (n = 238)	P
Ventilator-associated pneumonia	18 (47)	128 (54)	.58
Septic shock	13 (34)	83 (35)	>.99
Previous re-intubation	3 (8)	46 (19)	.14
Bilateral radiological involvement	9 (24)	49 (21)	.83
Duration of hospitalization before pneumonia, mean days ± SD	2.8 ± 1.5	15.9 ± 23.3	<.001
Pleural effusion	5 (13)	59 (25)	.17
Mean Pao_2/Fio_2 ± SD	173 ± 75	185 ± 87	.43
White blood cell count, mean × 10^9 cells/L ± SD	13.5 ± 5.7	15.4 ± 7.6	.079
C-reactive protein level, mean mg/dL ± SD	18 ± 13	16 ± 9	.52
Mean CPIS ± SD			
Day 1	6.5 ± 1.4	6.4 ± 1.4	.65
Day 3	5.3 ± 1.9	5.3 ± 1.8	.91

NOTE. Data are no. (%) of patients, unless otherwise indicated. CPIS, Clinical Pulmonary Infection Score; Pao_2/Fio_2, ratio of arterial oxygen tension to inspired oxygen fraction; SD, standard deviation.

underlying chronic heart disorders, previous hospital admissions and use of antibiotics and corticosteroids, tracheostomy at admission, and the hospital stay prior to onset of pneumonia, patients from groups 1 and 2 were similar.

Microbiologic findings. Pneumonia was microbiologically confirmed in 153 (55%) cases. The proportion of patients with etiological diagnosis, polymicrobial pneumonia, and the individual PPM isolated, including PRM, were similar between the two groups (Table 3).

Ten patients (26%) from group 1 had PRM, despite the absence of risk factors for these microorganisms according to the guidelines [1]. Their reason for ICU admission was post-

Table 3. Etiologic Diagnosis of Pneumonia

Etiology	Group 1 (n = 38)	Group 2 (n = 238)	P
Etiological diagnosis	24 (63)	129 (54)	.39
Polymicrobial pneumonia	6 (16)	32 (13)	.89
Patients with potentially drug-resistant microorganisms	10 (26)	70 (29)	.84
Potentially drug-resistant microorganism			
Pseudomonas aeruginosa	6 (16)	43 (18)	
Stenotrophomonas maltophilia	...	7 (3)	
Acinetobacter baumannii	...	2 (1)	
Methicillin-resistant *Staphylococcus aureus*	6 (16)	19 (8)	
Non–potentially drug-resistant bacteria, n (%)			
Methicillin-susceptible *S. aureus*	4 (11)	20 (8)	
Escherichia coli	3 (8)	15 (6)	
Enterobacter species	1 (3)	11 (5)	
Klebsiella pneumoniae	1 (3)	8 (3)[b]	
Streptococcus pneumoniae	2 (5)	5 (2)	
Serratia marcescens	...	5 (2)	
Citrobacter freundii	...	5 (2)	
Haemophilus influenzae	2 (5)	6 (3)	
Proteus species	3 (8)	3 (1)	
Other	2 (5)	3 (1)	
Fungus			
Aspergillus fumigatus	...	8 (3)	
Candida species[a]	1 (3)	...	

[a] *Candida* species were isolated from a pleural fluid specimen.
[b] In 1 case, *K. pneumonia* produced extended-spectrum β-lactamase.

Table 4. Outcomes of Patients, According to American Thoracic Society–Infectious Diseases Society of America (ATS/IDSA) Guidelines Group

Characteristic	Group 1 (n = 38)	Group 2 (n = 238)	P
Microbial prediction	12 (50)	119 (92)	<.001
Microbial prediction after patients' reclassification according to the 1996 ATS guidelines	21 (88)	119 (92)	.71
Length of ICU stay, mean days ± SD	15 ± 11	21 ± 16	<.001
Length of hospital stay, mean days ± SD	29 ± 24	43 ± 43	<.001
Hospital mortality	10 (26)	98 (41)	.12
Adequate empirical treatment	18 (75)	96 (74)	>.99
Initial nonresponse to treatment	15 (40)	93 (39)	>.99
Adherence to the 2005 ATS/IDSA guidelines	7 (18)	153 (64)	<.001
Adherence to the guidelines after patients' reclassification according to the 1996 ATS guidelines	16 (42)	155 (65)	.011

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

operative respiratory failure in 4 cases, decreased consciousness and multiple trauma in 2 cases each, and acute coronary syndrome and hypercapnic respiratory failure in 1 each. The patients' comorbidities included chronic heart disease in 5 cases, chronic obstructive pulmonary disease (COPD) and cancer in 3 cases each, and chronic liver disease and diabetes mellitus in 1 case each.

Blood cultures positive for pathogens considered causative of pneumonia were found in 5 patients (13%) from group 1 (methicillin-sensitive *S. aureus* [MSSA], MRSA, *Streptococcus pneumoniae, Enterobacter* species, and *Bacteroides fragilis*) and 23 patients (10%) from group 2 (MSSA and *P. aeruginosa* in 5 cases, and *Klebsiella* species and *Escherichia coli* in 3 cases each, among others). Pleural fluid culture results were positive for 2 patients from group 1 (MRSA and *Candida* species) and 9 patients from group 2 (MRSA and MSSA in 3 cases each, *P. aeruginosa* in 2 cases, and *Streptococcus milleri* in 1 case).

Aspergillus fumigatus was considered the causative agent in 8 patients from group 2. Four of them had COPD, 2 had cancer, and 1 had chronic liver disease. Four had received corticosteroids.

Microbial prediction. The ATS/IDSA guidelines successfully predicted the causative microorganisms in 131 patients (86%) with a defined etiologic diagnosis. The microbial prediction was better for patients from group 2 ($P < .001$) (Table 4). The guidelines failed to predict 14 pathogens in 12 patients allocated to group 1 (MRSA and *P. aeruginosa* in 6 cases; *Candida* species and *B. fragilis* in 1 case each) and in 10 patients allocated to group 2 (*A. fumigatus* in 8; *S. milleri* and *Fusobacterium* species in 1 case each).

Patients were reclassified according to the groups defined in the 1996 ATS guidelines [11]. Thirty-three out of 38 patients from group 1 had risk factors for PRM according to the 1996 guidelines; hence the microbial prediction resulted better than the 2005 guidelines for patients from group 1, in whom microbial prediction increased to 21 (88%) ($P = .014$).

Nine patients from group 1 with etiologic pathogens wrongly predicted by the 2005 guidelines (MRSA in 6 cases and *P. aeruginosa* in 5 cases, with isolation of both pathogens in 2 cases) were correctly predicted by the 1996 guidelines. No patient wrongly predicted by the 1996 guidelines was rightly predicted by the 2005 guidelines.

Length of stay, mortality, treatment adequacy, response to treatment, and adherence to the guidelines. The ICU and hospital stay were longer in patients from group 2 ($P < .001$). There was a nonsignificant trend toward a lower hospital mortality rate for patients from group 1 (Table 4).

The empirical antimicrobial treatment was adequate in 114 patients (75%) who had a defined etiologic diagnosis, and 108 (39%) patients did not respond adequately to the empirical antimicrobial treatment. The adequacy and the initial clinical response to the empirical treatment were similar between groups 1 and 2. Inadequate treatment was associated to more nonresponse to the initial treatment (24 [62%] vs 47 [42%]; $P = .044$) and a nonsignificant trend toward a higher hospital mortality rate (23 [59%] vs 49 [43%]; $P = .12$) than adequate treatment. Likewise, nonresponse to treatment was associated to a higher hospital mortality than adequate clinical response (69 [62%] vs 39 [24%]; $P < .001$).

The pathogens most frequently associated to inadequate treatment were *P. aeruginosa* in 18 cases, MRSA in 11, *A. fumigatus* in 5, and *S. maltophilia* in 4. Likewise, the pathogens most frequently isolated in nonresponders to the initial treatment were *P. aeruginosa* in 26 cases, MSSA in 14, MRSA in 12, *E. coli* and *Enterobacter* species in 7 each, *S. maltophilia* in 5, and *S. pneumoniae* and *A. fumigatus* in 4 each. In 40 nonresponders (36%), no etiologic pathogen was isolated.

Adherence of the empirical antimicrobial treatment chosen

Table 5. Outcomes According to Adherence to Guidelines

Variable	Patients' classification according to the 2005 ATS/IDSA guideline criteria			Patients' classification according to the 1996 ATS guideline criteria		
	Adherence (n = 160)	No adherence (n = 116)	P	Adherence (n = 171)	No adherence (n = 105)	P
Adequate empirical treatment						
All	69 (83)	45 (64)	.013	78 (84)	36 (60)	.002
Group 1	1 (50)	17 (77)	>.99	10 (83)	8 (67)	.64
Group 2	68 (84)	28 (58)	.003	68 (84)	28 (58)	.003
Initial nonresponse to treatment						
All	58 (36)	53 (46)	.15	62 (36)	49 (47)	.11
Group 1	3 (43)	12 (39)	>.99	7 (43)	8 (36)	.90
Group 2	55 (36)	41 (48)	.087	55 (36)	41 (49)	.052
Hospital mortality	59 (37)	49 (42)	.44	65 (38)	43 (41)	.72
Length of hospital stay, mean days ± SD	43 ± 42	40 ± 40	.54	42 ± 42	40 ± 41	.74
Length of ICU stay, mean days ± SD	21 ± 16	20 ± 16	.61	21 ± 15	20 ± 16	.62

NOTE. ATS, American Thoracic Society; ICU, intensive care unit; IDSA, Infectious Disease Society of America.

by the attending physicians to the 2005 ATS/IDSA guidelines occurred in 160 cases (58%); the adherence was higher in patients from group 2 ($P < .001$). Adherence to the guidelines resulted in more frequent treatment adequacy than lack of adherence ($P = .013$) (Table 5); this relationship was observed in patients from group 2 but not in those from group 1. In group 2, guidelines adherence was associated with a trend to better initial response to treatment ($P = .087$).

When patients were reclassified according to the risk factors for PRM defined in the 1996 ATS guidelines, the adherence to the empirical antimicrobial treatment recommended by the 2005 guidelines substantially improved in patients from group 1 (from 7 [18%] to 16 [42%]; $P = .047$) (Table 4). The better treatment adequacy associated with guidelines adherence was more pronounced when patients were classified according to the risk factors for PRM defined by the 1996 ATS guidelines ($P = .002$) (Table 5). Again, this relationship was observed in patients from group 2 only, and guidelines adherence was associated with better initial response to treatment in this group ($P = .052$). However, adherence to both guidelines did not influence the hospital mortality and length of stay.

DISCUSSION

Although the current 2005 ATS/IDSA guidelines for HAP [1] had an overall good rate of microbial prediction, the previous 1996 ATS guidelines [11] yielded better predictions of the presence of PRM. The adherence of the empirical antimicrobial treatment to both guidelines resulted in more treatment adequacy in patients from group 2 only. Guidelines adherence tended to improve the clinical response to the empirical treatment in this group, but did not influence the length of stay or mortality.

The choice of the empirical antimicrobial treatment is often based on the recommendations of published guidelines from scientific societies. However, the guidelines are based on scientific evidence plus experts' recommendations, and therefore, validation in the clinical setting is advisable. We had previously assessed the microbial prediction and treatment adequacy of the previous ATS guidelines for the management of HAP [21]. In this study, the 1996 guidelines [11] showed a good predictive capacity for the infecting pathogens. However, the treatment adequacy was low because of the presence of highly drug-resistant microorganisms in the cohort [21].

These guidelines were subsequently revised jointly with the IDSA with substantial changes in the risk factors for infection caused by PRM [1]. The new 2005 ATS/IDSA guidelines successfully predicted the causative pathogens in 86% cases from the present study. However, 12 cases (50%) from group 1 with a defined etiological diagnosis were wrongly predicted by these guidelines. Among them, the etiology of pneumonia in 9 patients with PRM (MRSA and *P. aeruginosa*) was correctly predicted when the risk factors for PRM defined by 1996 ATS guidelines, instead of those defined by the 2005 guidelines, were applied to our population. These 9 patients had risk factors for infection caused by PRM according with the 1996 ATS guidelines [11], such as previous prolonged and complicated surgery in 5 cases, chronic alcohol abuse in 4, COPD and solid cancer in 3 each, and diabetes mellitus, chronic liver disease, and prolonged treatment with corticosteroids in 1 case each. None of these were considered risk factors for PRM in the 2005 ATS/IDSA guidelines [1].

Both guidelines failed in predicting anaerobes and fungi in our population, particularly *A. fumigatus*. Therefore, predictors for pulmonary aspergillosis in patients without major immu-

nosuppression should be considered in future guidelines. However, etiologies of all patients with PRM except 1 were correctly predicted when the 1996 guidelines were applied [11]. The accuracy of these guidelines, particularly the high specificity in excluding the presence of PRM, had been assessed in previous reports [21, 27]. Therefore, the usual risk factors leading to pneumonia defined by the 1996 guidelines [11] appear more accurate than the risk factors for PRM defined by the 2005 guidelines [1] in predicting the etiology of HAP in the ICU. The usefulness of the 1996 guidelines may also be improved by local adaptations to specific settings as suggested in 2 studies [28, 29].

The reasons for nonadherence to guidelines were different between both groups. The poor microbial prediction of the 2005 ATS/IDSA guidelines for patients from group 1 in our study is in line with the low adherence of the attending physicians to these guidelines. It suggests that there is not much trust among physicians in excluding risk factors for PRM according to the definitions of the 2005 guidelines. Indeed, we observed that most patients from group 1 were treated similarly than patients from group 2, and this was the reason for the low adherence to the 2005 guidelines in this group. By contrast, the 36% lack of treatment adherence in group 2 was mainly due to the use of antibiotic combinations not recommended by the guidelines.

Adherence of the empirical treatment to both guidelines resulted in better treatment adequacy only for patients from group 2, as shown in Table 5. This effect was more pronounced when the risk factors for PRM of the 1996 ATS guidelines were applied in our population. Similar to previous investigations [30, 31], the most frequent pathogens causing pneumonia (*P. aeruginosa*, MRSA, and MSSA) were the same in patients with either early- or late-onset pneumonia. Rather than the time of onset, a proper identification of risk factors for specific pathogens is crucial in choosing an appropriate empirical treatment. Therefore, we suggest that future guidelines for the treatment of patients with HAP consider the risk factors for PRM defined by the 1996 ATS guidelines.

Although mortality was not significantly higher in those patients who were inadequately covered by the initial antimicrobial therapy, we observed a worse initial clinical response, which was strongly associated with higher mortality, in them. This stresses the crucial role of an initial adequate therapy for the outcome of these patients, in line with previous publications [5–8]. However, although the normal pattern of resolution of VAP has been described elsewhere [15, 32], the definition of initial nonresponse to empirical treatment, although used in previous investigations [25, 26], needs further prospectively validation.

A limitation of this study is that our population consists of ICU patients; therefore, it did not include patients with mild-to-moderate HAP. Patients with HAP outside the ICU have lower incidence of PRM and higher incidence of "community-acquired PPM," such as *S. pneumoniae* and *Legionella pneumophila* than in the present study [33]. Whether our findings may be extrapolated to non-ICU patients with HAP needs further assessment. A potential approach for future guidelines is to provide different recommendations for patients inside and outside the ICU. Another limitation is that this is a monocenter study and may not be representative for the majority of ICUs worldwide. Finally, the number of patients in group 1 is small, and therefore, these results should be confirmed in larger populations.

In conclusion, the current 2005 ATS/IDSA guidelines do not provide a good microbial prediction for PRMs in group 1. This prediction resulted better when reclassifying patients according to the 1996 ATS guidelines. The reasons for nonadherence to the antibiotic recommendations were different for both groups. In group 2, adherence to both guidelines resulted in better treatment adequacy and a trend to a better clinical response, but did not influence mortality.

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DISCUSSION

4.1. CAP GUIDELINES

The goals of the scientific guidelines are to improve management and outcome without increasing costs or reducing patient safety.

Creating accurate and objective prediction models for ICU admission is very important and has several advantages. First, the appropriate placement of patients optimizes use of limited ICU resources. Second, an accurate prediction model avoids the delayed ICU transfer of patients initially placed in other hospital units, which is associated with increased mortality. Third, correct site-of-care can optimize initial antibiotic treatment, since microbial etiologies of patients with severe CAP differ from that of CAP in general. Avoidance of initial inappropriate antibiotic treatment is associated with lower mortality (21).

We have evaluated **for the first time** how this predictive rule fits with the clinical practice in a large population of patients with CAP hospitalized before the IDSA/ATS guidelines were published; hence the decisions regarding ICU admission were not affected by these guidelines. Of the 235 patients who were admitted to the ICU 167(71%) met severe CAP criteria. Compared with the previous ATS guidelines, the prediction is similar for defining the need for ICU admission and better for predicting hospital mortality (**Figures 2 & 3**). However, the predictive rule identified 230 patients with SCAP criteria who were not admitted to the ICU, with 91 patients with septic shock among them. While ICU admission is clearly indicated for invasive ventilation and septic shock, the need for ICU admission derived from minor criteria alone is uncertain in our population and deserves further prospective evaluation. The proposed modified rule to define severe pneumonia remains imperfect because the performance relying only on baseline (minor) clinical criteria was limited.

The presence of one major criterion, particularly invasive ventilation, was a major determinant in the decision for ICU admission. This is obvious since patients needing invasive ventilation cannot be managed out of the ICU in most hospitals. The worse outcome of patients

with septic shock who were not managed in an ICU after the initial stabilization in the emergency department confirms the need for close monitoring and ICU care of these patients. ICU admission was related with the presence of minor severity criteria, particularly tachypnea, hypoxemia, leucopenia and multilobar involvement, together with younger age and higher PSI risk classes. Patients with hypoxemia were more likely to be admitted to the ICU, and those with mental confusion were less likely to be admitted to the ICU. From the remaining minor severity criteria hypothermia is not associated with ICU admission, and hypotension, multilobar involvement and thrombocytopenia were not significantly associated with mortality.

In absence of major criteria, we could not demonstrate that ICU admission results in reduced mortality for patients with minor severity criteria. In addition, the number of minor criteria could not discriminate which patients could benefit from ICU admission. Thus, among the 219 patients with SCAP defined by the presence of minor severity criteria only, 47 (21%) were admitted to an ICU.

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Figure 2.Predictive capacity for ICU admission

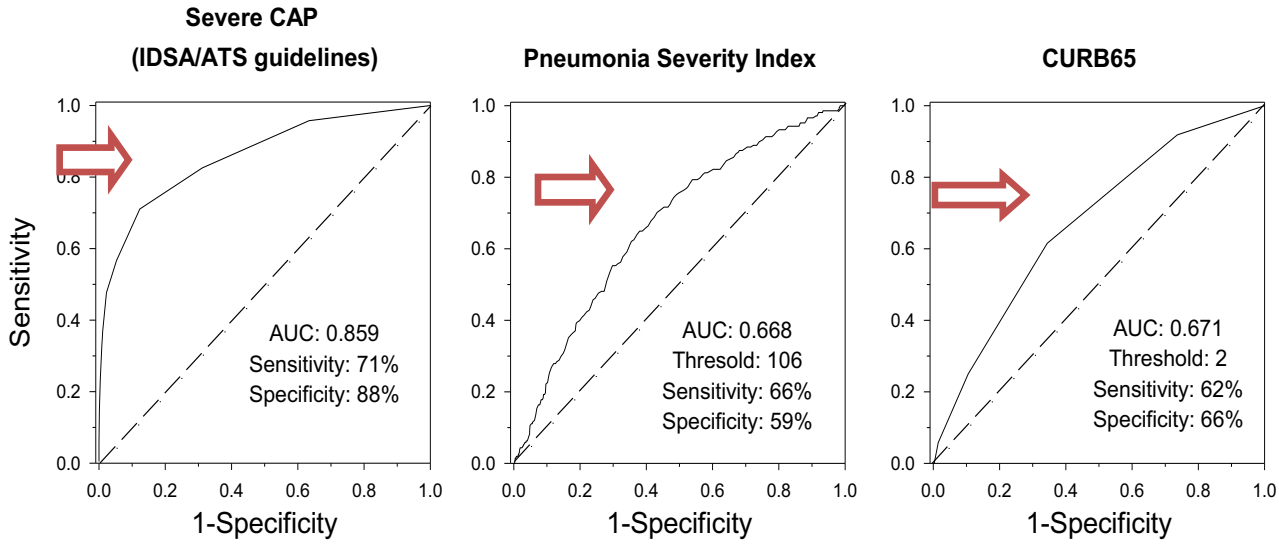
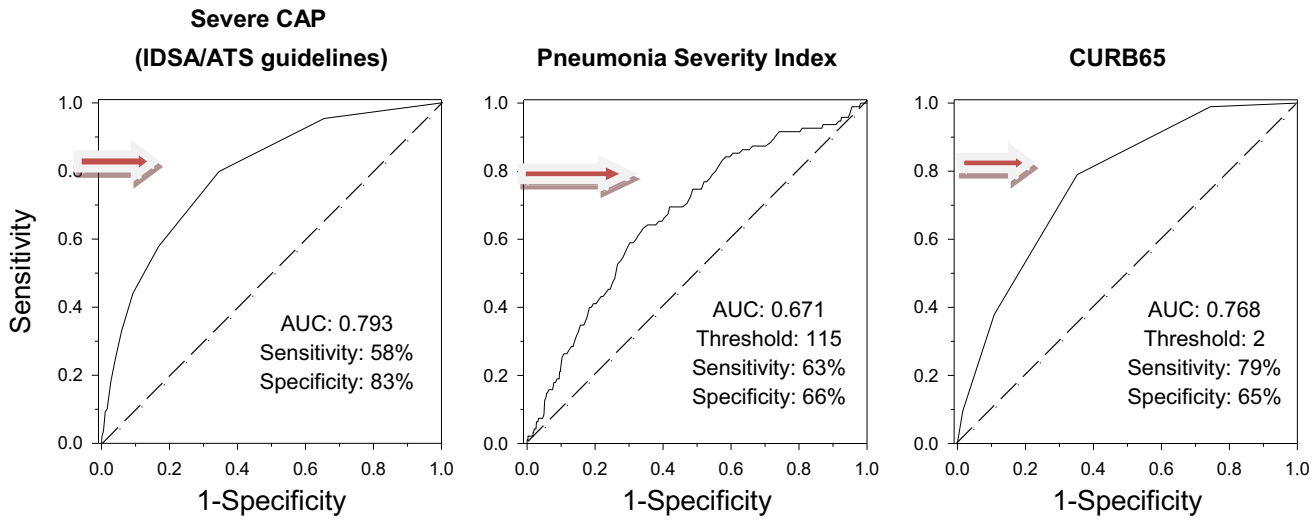


Figure 3.Predictive capacity for hospital mortality



Several limitations of this study deserve comment. First, blood urea nitrogen level was not systematically determined in our hospital; therefore, we used serum creatinine level as a surrogate, as we have done in previous studies (19, 15). Therefore, we cannot exclude the possibility that some cases did not entirely meet the definitions given in the guidelines. Second, information regarding “do not intubate” (DNI) decisions was available for only 856 (41%) of the episodes (21). Previous DNI orders may influence the decision for ICU admission. However, among patients for whom such information was available, the rate of previous DNI orders did not substantially differ between patients who were hospitalized in the ICU and patients who were not (6% and 10%, respectively). The proportion of ICU admissions did not differ substantially between patients with and patients without a previous DNI decision (9% and 14%, respectively). After excluding patients with a previous DNI decision, the sensitivity (72%) and specificity (88%) of the IDSA/ ATS guidelines were similar to the sensitivity and specificity among the overall population.

This study was published in the Clinical Infectious Disease Journal on May 2009 as a major article and with an editorial also. Its strength has been certified with many references in other articles and books on CAP.

Our results are similar to those of Phua et al (45), who showed good performance of the minor criteria of IDSA/ATS 2007 with AUC=0.88 (95% CI 0.86 to 0.91) and 0.85 (95% CI 0.81 to 0.88) for predicting hospital mortality and ICU admission, respectively (45). A recent study from Japan comes to enhance our results concluded that the individual 2007 IDSA/ATS minor criteria for severe CAP were of unequal weight in predicting hospital mortality (46).

Chalmers et al (47), in 2011, developed another study, to determine the accuracy of the IDSA/ATS 2007 minor criteria for predicting ICU admission or requirement for MV/VS in a population of 1062 CAP patients hospitalized for CAP without contraindications to ICU care. The IDSA/ATS 2007 criteria had an AUR of 0.85 (0.82-0.88) for prediction of MV/VS, 0.85 (0.82-0.88) for prediction of ICU admission, and 0.78 (0.74-0.82) for prediction of 30-day mortality. They reported that the IDSA/ATS 2007 criteria were at least equivalent to more established scoring systems for prediction of MV/VS and ICU admission and equivalent to alternative scoring systems for predicting 30-day mortality in this patient population.

Other models specific to SCAP have been developed, including a recent Australian model called SMART-COP, and two Spanish models called CURXO-80 and PIRO score.

Rello and colleagues (48) developed in 33 ICUs, a severity-assessment score based on the PIRO classification of sepsis generally. The PIRO (predisposition, insult, response, organ dysfunction) score performed better than the APACHE II (Acute Physiology And Chronic Health Evaluation) score and the ATS/IDSA criteria at predicting 28-day mortality. PIRO requires substantial further work to allow implementation in useful predictive models, particularly in light of evidence that acute physiology has the greatest effect on near-term outcomes from CAP (49).

The group of Espana et al, in 2006(50), have published another score CURXO-80 consisted of eight independent predictive factors correlated with SCAP: pH<7.30, BP<90mmHg, confusion,Urea>30 mg/dl,PO2<54mmHg,age>80 years and multilobar lung affection. This model

showed AUR=0.92 and was more accurate than CURB65 and PSI for ICU admission in another validated study (51).But the age limit (80 years) and the variables PO2<54mmHg and RR>30 lowering its sensitivity in younger patients.

Charles and colleagues (13) recently developed a tool for the prediction of which CAP patients will require intensive respiratory or vasopressors support. The SMART-COP score was developed by studying 882 CAP patients in an Australian CAP Study. The tool was then validated in five external databases in patients younger than 50 years old. SMART-COP utilizes the measurement of the following (which are also the origin of the acronym SMART- COP): systolic blood pressure, multilobar chest radiography, low albumin levels, respiratory rate (age adjusted), tachycardia, confusion, low oxygen (age-adjusted), and arterial pH (<7.35). The changes in blood pressure, in pH, in oxygenation scored 2 points and the other variables 1 point. The patients with SMART-COP>3 have sensitivity 92.3% and specificity 62.3% for vasopressor support.

In addition, a retrospective study by Brown et al (52) compared the predictive value of the IDSA/ATS criteria with those of a number of scoring systems, including SMART- COP and the SCAP score. The IDSA/ATS minor criteria predicted better SCAP with AUC=0.88 and optimal cut off four minor criteria instead of three. Importantly, however, this study did not exclude patients unsuitable for ICU care.

There is considerable clinical and research interest in the use of novel biomarkers to diagnose and classify CAP. The abovementioned scales do not take into account the mechanisms of the inflammatory response. Therefore, the role of biomarkers in the inflammatory response and their correlation to the severity of the infection continues to be a subject of growing interest (3). The most studied biomarkers linked to mortality due to CAP are C-reactive protein and procalcitonin, although other biomarkers are also being investigated such as pro-adrenomedullin, neopterin, copeptin and atrial natriuretic pro-peptide (proANP). Evolving data on procalcitonin (53,54) suggest possible utility in deciding the duration of antibiotic therapy and in identifying a bacterial cause of lower respiratory tract infection (or severe sepsis generally).

A report from CAPNETZ study group adding biomarkers to CURB65, suggested that proadrenomedullin improved the prediction of the CURB65 score (55).

Furthermore, Ramirez et al (56, 57), in a recent study of 685 patients with CAP, assessed the prediction for ICU admission of biomarkers and the IDSA/ATS guidelines minor criteria for severe CAP. Concluded, firstly that inflammatory biomarkers (CRP, tumor necrosis factor-a, procalcitonin and interleukin-6) identified patients needing ICU admission, including those with delayed ICU admission and secondly the patients with severe CAP by minor criteria and low levels of procalcitonin may be safely admitted to wards.

And for future research we have to think, that though factors reflecting acute respiratory failure and severe sepsis or septic shock are independent predictors of severity in CAP and sepsis severity at admission significantly affects outcome, such factors have not yet been systematically implemented into risk classification for CAP patients. A possible advance in this area could be the development, validation, and incorporation into management tools of emerging biomarkers for diseases.

4.2. VAP GUIDELINES

To the best of our knowledge, only our study has validated microbial prediction and adequacy of antimicrobial treatment in the 2005 ATS/IDSA guidelines. This study was published in the Clinical Infectious Disease Journal as a major article on April 2010 (44).

In our study microbial prediction by 2005 ATS/IDSA guidelines was lower in group 1 than in group 2 (12 [50%] of 24 vs 119 [92%] of 129; $p<0.001$) mainly because of PRM in 10 patients (26%) from group 1. *Aspergillus fumigatus* was considered the causative agent in the 8 from 12 wrongly predicted patients from group 2. When patients were reclassified according to the groups defined in the 1996 ATS guidelines the microbial prediction resulted better than for patients from group 1, in whom microbial prediction increased to 21 (88%) ($p=0.014$).

In summary, we suggest that the stratification of HAP and VAP in two groups according the 2005 ATS/IDSA guidelines groups probably needs to be revisited in order to define better the risk factors for MDR organisms in the group of early-onset pneumonia.

Previous prolonged and complicated surgery, chronic alcohol abuse, chronic liver disease, advanced COPD, solid cancer and diabetes seem to be associated with higher risk for infection by *MRSA* and *P. aeruginosa* but were not considered as risk factors for PRM in the 2005 ATS/ IDSA guideline. Moreover, all published guidelines failed to predict anaerobes and fungi, mainly *Aspergillus spp*.; therefore, predictors for pulmonary aspergillosis in patients without major immunosuppression should be considered in future guidelines.

In our study adherence of the empiric treatment to guidelines resulted in better treatment adequacy only for patients from Group 2, but did not influenced mortality. The reasons for non-adherence to guidelines were different between both groups. The poor microbial prediction of the 2005 ATS/IDSA guidelines for patients from Group 1 in our study is in line with the low adherence of the attending physicians to these guidelines. It suggests not much trust of physicians in excluding risk factors for PRM according to the definitions of the 2005 guidelines. Indeed, we

observed that most patients from Group 1 were treated similarly than patients from Group 2, and this was the reason for the low adherence to the 2005 guidelines in this group. By contrast, the 36% lack of treatment adherence in Group 2 was mainly due to the use of antibiotic combinations not recommended by the guidelines.

Although mortality was not significantly higher in those patients not-adequately covered by the initial antimicrobial therapy, we observed a worse initial clinical response, which was strongly associated with higher mortality in them. This stresses the crucial role of an initial adequate therapy for the outcome of these patients, in line with previous publications (58).

A limitation of this study is that our population consists of ICU patients and therefore we did not include patients with mild-to-moderate HAP. Patients with HAP outside the ICU have lower incidence of PRM and higher incidence of "community-acquired PPM" such as *S. pneumoniae* and *Legionella pneumophila* than the present study (28). Whether our findings may be extrapolated to non-ICU patients with HAP needs further assessment. A potential approach for future guidelines is to provide different recommendations for patients inside and outside the ICU. Another limitation is that this is a monocenter study and may not be representative for the majority of ICUs worldwide. Finally, the number of patients in Group 1 is small and therefore these results should be confirmed in larger populations.

In any case, the 2005 ATS/IDSA guidelines have several limitations as regards to the definition of patients at risk for MDR pneumonia and possibly promoting unnecessary use of empirical broad-spectrum combination antibiotics (59). In an observational study, ICU patients at risk for MDR pneumonia who were treated according to these guidelines had higher mortality than those with non-adherent treatment (34% vs. 20%) (60). The main reasons for non-compliance in this study were failure to use a secondary anti-Gram-negative drug, or either a primary anti-Gram negative drug or anti-*MRSA* drug, resulting in more patients from the compliant group treated with triple antibiotic coverage.

However, recent reports are challenging such conclusions and demonstrate no association between MDR pathogens and time of onset of pneumonia (61, 62, 63).

For example, in a Greek study of Giantsou et al (61), comparing the causative pathogens of 408 early-onset and late-onset VAP diagnosed by bronchoalveolar lavage quantitative cultures. They concluded that both early-onset and late-onset VAP were mainly caused by PRM bacteria, most commonly *P. aeruginosa* and *MRSA*. Other colleagues doubt the usefulness of this classification. Verhamme et al. reported that pathogens potentially resistant to multiple drugs were isolated in more than half (52%) of cases of early-onset ICU-acquired pneumonia (62). Finally, Gastmeier et al (63), in an large German study, published that the order of the four most frequent pathogens (accounting for 53.7% of all pathogens) was the same in both groups of VAP and was independent of the cutoff categories (early-late onset) applied: *S. aureus* was first, followed by *P. aeruginosa*, *K. pneumoniae*, and *E. coli*. This classification of ATS is no longer helpful for empirical antibiotic therapy, since the pathogens are the same for both groups. These studies suggest the need for extensive research to accurately identify risk factors for harboring MDR pathogens, rather than risk stratification based on nonspecific factors such as severity of pneumonia and time of onset.

In the largest European study performed in 27 sites from nine different countries that were not randomly selected that defines the real antibiotic prescription patterns and the outcomes of therapy in a cohort of critically ill patients with HAP/VAP, suggest that baseline prevalence of *A. baumannii* .10% in pneumonia episodes, severity of sickness and admission category are major determinants of antibiotic choice at the bedside. The association between prevalence of *A. baumannii* >10% in pneumonia episodes and specific antimicrobial agents is new and endorses the importance of local surveillance practices to identify the local flora in each ICU, facilitating appropriate antibiotic prescription in individual patients (64).

Therefore, we suggest that future guidelines for the management of patients with HAP consider the need for extensive research to accurately identify risk factors for harboring MDR pathogens in the Group of early-onset pneumonia. Proposed solutions include the use of individualized assessment of patients in order to avoid antibiotic overuse leading to emergence of

resistance.

Another concept that has to be considered is the subgroup of VAP non intubated (NV) patients in the ICU. In a recent study of Esperatti et al (65) from our group, we compared the microbiology and outcomes of VAP in 164 intubated and 151 non-intubated patients. We found that he relative proportion of most pathogens was essentially similar among patients from both groups, suggesting that the etiology of ICU-acquired pneumonia does not depend on the previous intubation and mechanical ventilation but related to the host factors (severity of pneumonia). Consequently, outcomes of VAP and NV- ICUAP patients in the ICU were similar and in terms of management, VAP and NV-ICUAP patients may be treated with similar empirical antimicrobials. Other studies which will focus in this category of ICU pneumonia is lacking. With the higher incidence of non-invasive ventilation for the treatment of HAP especially in COPD patients, is a necessity to study this subcategory of HAP.

Validation of guidelines in HAP is also important to confirm the reliability of these guidelines in clinical practice and their impact on outcome parameters. Overall, implementing guidelines is followed by an increase in initially adequate antibiotic treatment. In addition, only a few studies have demonstrated that the prediction of microorganisms by HAP guidelines is reliable. Guideline validation studies are not easy and have to take into account different variables potentially related with the outcome of HAP patients, but it is a necessity.

CONCLUSIONS

In conclusion, from the 1st Study the predictive rule of the IDSA/ATS guidelines to identify severe CAP is accurate but slightly overestimates ICU admission in clinical practice. Compared with the previous ATS guidelines, the prediction is similar for defining the need for ICU admission and better for predicting hospital mortality. The need for ICU admission derived from minor criteria alone is uncertain in our population and deserves further prospective evaluation.

From the 2nd Study, the current 2005 ATS/IDSA guidelines do not provide a good microbial prediction for PRM in Group 1. This prediction resulted better when reclassifying patients according to the 1996 ATS guidelines. In group 2, adherence to both guidelines resulted in better treatment adequacy and a trend to a better clinical response, but did not influence mortality.

In summary the current evidence suggests that the stratification of HAP and VAP in two groups according the 2005 ATS/IDSA guidelines probably needs to be revisited in order to define better the risk factors for multi-drug resistant organisms in the group of early-onset nosocomial pneumonia.

Although, the evidence available in few studies also suggests that the implementation of guidelines for CAP, HAP and VAP is followed by a better outcome (41, 66, 67,68).

New studies should taking into account the different components of the recommendations including time to the first dosage, initial adherence, adequacy of antibiotics and the different combinations used.

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