ERJ Express. Published on November 8, 2012 as doi: 10.1183/09031936.00100812

Title

Criteria for clinical stability in hospitalized patients with community-acquired pneumonia

Authors

Stefano Aliberti MD[1,2], Anna Maria Zanaboni PhD[3], Tim Wiemken PhD[2], Ahmed Nahas MD[2], Srinivas Uppatla MD[2], Letizia Corinna Morlacchi MD[4], Paula Peyrani MD[2], Francesco Blasi MD, PhD[4] and Julio Ramirez MD[2]

Affiliations

[1] Department of Clinical Medicine and Prevention, University of Milan-Bicocca, Respiratory Department, AO San Gerardo, Via Pergolesi 33, 20052, Monza, Italy

[2] Division of Infectious Diseases, Department of Medicine, University of Louisville, Louisville, Kentucky, USA

[3] Computer Science Department, University of Milan, Via Comelico 39, Milan, Italy

[4] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, University of Milan, IRCCS Fondazione Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy

Corresponding Author

Stefano Aliberti, MD. Department of Clinical Medicine and Prevention, University of Milan-Bicocca, Respiratory Department, AO San Gerardo, Via Pergolesi 33, 20052, Monza, Italy Phone: 00390392339284 Fax: 00390392339437 email: stefano.aliberti@unimib.it

This work was presented as oral communication at the European Respiratory Society Annual Congress 2011, Amsterdam, Nederland. No personal or financial support or author involvement with organization(s) with financial interest in the subject matter –or any actual or potential conflict of interest- exists. A statement to that effect is included for each author.

ABSTRACT

Background The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) suggested two sets of criteria in 2001 and 2007 to define clinical stability (CS) in community-acquired pneumonia (CAP). We aim to evaluate the level of agreement between these two sets of criteria and how well they can predict clinical outcomes.

Methods A retrospective cohort study of 487 consecutive patients hospitalized with CAP. Level of agreement was tested using a survival curve analysis, while prediction of outcomes at 30-day follow-up was evaluated through receiver-operator curves (ROC).

Results A discrepancy between ATS 2001 and ATS/IDSA 2007 criteria in identifying CS was detected in 62% of the patients. The median (IQR) time to CS was 2 (1-4) days based on ATS 2001 and 3 (2-5) days based on ATS/IDSA 2007 criteria (p=0.012). The daily distribution of patients who reached CS evaluated with both sets was different (p=0.002). The ROC analysis showed an area under the curve of 0.705 for the ATS 2001 criteria and 0.714 for ATS/IDSA 2007 criteria, p=0.645.

Conclusion ATS 2001 and ATS/IDSA 2007 criteria for CS in hospitalized patients with CAP are clinically equivalent and both can be used in clinical practice as well as in clinical research.

Keywords: bacterial infections; bacterial pneumonia; biomarkers; community-acquired infections; infections

INTRODUCTION

Community-acquired pneumonia (CAP) occurs in up to 5.6 million patients every year in the United States and more than one million require hospitalization [1]. After initiation of appropriate empiric antibiotic therapy, the majority of patients who are hospitalized show evidence of clinical improvement. The process of clinical improvement starts when a patient with CAP becomes clinically stable. Identification of clinical stability has several implications in clinical practice and clinical research. In clinical practice, time to clinical stability is used to guide the switch from intravenous to oral antibiotic therapy and it can also help to define time for hospital discharge, as well as adverse events after hospitalization [2, 3]. In clinical trials, patient's clinical stability is an early outcome used to compare antibiotic treatments in CAP patients. Recently, the US Food and Drug Administration (FDA) acknowledged clinical stability as one of the most important endpoints for patients with bacterial pneumonia [4].

Although a general agreement exists on the importance of the recognition of clinical stability as an early outcome in patients with CAP, there is surprisingly little scientific literature on how its evaluation should be performed [5]. Guidelines on the management of CAP published by the American Thoracic Society (ATS) in 2001 suggested a definition of clinical stability that was based on patient symptoms, such as cough and shortness of breath, along with signs of systemic response, such as fever and white blood cell count [1]. These criteria were initially reported by Ramirez et al. in 1995 [2]. The latest American Thoracic Society and the Infectious Diseases Society of America (IDSA) guidelines, published in 2007, define clinical stability as a decrease under fixed thresholds of vital parameters, including temperature, heart rate, respiratory rate, blood pressure, mental status and oxygenation [6]. This new approach developed from physician-based observations, as originally described by Halm et al. in 1998 [7].

The ATS 2001 criteria are based on patient symptomatology, while the ATS/IDSA 2007 definition of clinical stability is based on objective parameters. Although these are the two most common

3

criteria used to define clinical stability, they have never been evaluated in a head-to-head comparison in the same population of hospitalized patients with CAP.

The aim of our study was to compare the ATS 2001 and ATS/IDSA 2007 criteria for clinical stability in hospitalized patients with CAP in an attempt to: 1) define the level of agreement between the two sets of criteria in relation to time to clinical stability (TCS); 2) define how well these criteria can identify patients with good clinical outcome during a 30-day follow-up period.

4

MATERIAL AND METHODS

Study design

This was an observational, retrospective study of consecutive patients admitted with a diagnosis of CAP at the Veterans Administration Medical Center (VAMC) in Louisville, Kentucky, USA, between June 2001 and March 2006. Patients enrolled in this study are part of the Community-Acquired Pneumonia Organization (CAPO) database [8]. The study protocol, data collection form and all the data collection form are available on the study website (www.caposite.com). Details about data collection and management have been described previously [9]. The Institutional Review Board of the VAMC approved the study (Human Study Subcommittee, CAPO IRB #: 0061).

Study population and measurements

Patients ≥ 18 years of age who met the criteria for CAP were included in this study. Patients in whom findings to identify clinical stability were missing were excluded from the study. The records of all enrolled patients were reviewed. Data from the VAMC system were extracted pertaining to patient demographics, medical comorbidities, clinical and laboratory variables, radiographic findings, the pneumonia severity index (PSI), the CURB-65 score, microbiologic and in-hospital treatment data, clinical stability, length of hospital stay (LOS), adverse outcomes during hospitalization and within 30 days after hospital discharge [10, 11]. Two investigators (AN and SU) independently reviewed the electronic charts of all the enrolled patients and collected data on clinical stability.

Study definitions

CAP was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with at least one of the following: 1) new or increased cough; 2) an abnormal temperature (<35.6ºC or >37.8ºC); 3) an abnormal serum leukocyte count (leukocytosis,

left shift, or leucopenia defined by local laboratory values). Severe CAP was defined based on the ATS/IDSA guidelines published in 2007 [6].

Criteria to define clinical stability were evaluated daily during the first seven days of hospitalization. Clinical stability was defined according to two criteria: ATS guidelines published in 2001 and ATS/IDSA guidelines published in 2007 [1, 6]. Table 1 depicts the two sets of criteria for clinical stability. Time to clinical stability was calculated as the number of days from the date of hospital admission to the date that the patient met clinical stability criteria. LOS was calculated as the number of days from the date of admission to the date of discharge. LOS was censored at 14 days in an effort to capture only CAP-related LOS.

Outcome definition

The presence of clinical failure either during hospitalization or after hospital discharge was defined as the outcome of interest. Clinical failure during hospitalization was considered if any of the following took place after patient admission to the floor and initial stabilization, and during hospitalization: 1) acute pulmonary deterioration with the need for either invasive or non-invasive mechanical ventilation; 2) acute hemodynamic deterioration with the need for aggressive fluid resuscitation (approximately 40 ml/kg of colloids or crystalloids), vasopressors or invasive procedures (e.g.: pericardial drainage, electrical cardioversion); 3) in-hospital death up to 28 days after admission. Clinical failure after discharge was defined as either readmission or death for any reason within 30 days after hospital discharge.

Comparison between ATS 2001 and ATS/IDSA 2007

The level of agreement between ATS 2001 and ATS/IDSA 2007 criteria was detected by the evaluation of the joint distribution of time to clinical stability in the study population according to both scores. Survival curve analysis was used to compare between the two scores the daily distribution of patients who reached clinical stability during the first week of hospitalization.

6

ATS 2001 and ATS/IDSA 2007 criteria for clinical stability with respect to clinical outcome was compared through receiver-operator curve analysis of their predictive value with respect to clinical failure either during hospitalization or after hospital discharge.

Statistical analysis

All data were statistically analyzed using SPSS (version 18.0) for Mac. Descriptive statistics were reported at baseline, with continuous data expressed as a median (interquartile range -IQR- 25th-75th percentile) and categorical data expressed as frequencies and percentages. A generalized Wilcoxon test was performed to compare the survival curves (Kaplan Meier). The difference of median (IQR) time to clinical stability according to the ATS 2001 and ATS/IDSA 2007 criteria was evaluated by the the Wilcoxon–Mann–Whitney U two-sample test. The predictive value of the ATS 2001 and ATS/IDSA 2007 criteria for clinical stability was explored for indicating the presence of a clinical failure via a ROC curve. Each point of the ROC curve corresponds to a specific TCS value (e.g. t days). The coordinates of each point of the ROC curve were computed as follows: the sensitivity of TCS was calculated as the frequency of patients who did not reach clinical stability within t days among those who had a clinical failure The specificity of TCS was calculated as the frequency of patients who reached clinical stability within t days among those who did not have a clinical failure. The difference of areas under the curve (AUC) was tested according to DeLong et al [12]. All tests were 2-tailed and a p value <0.05 was considered statistically significant.

7

RESULTS

Study population

A total of 500 consecutive patients with CAP were enrolled during the study period. The final study population consisted of 487 patients, due to lack of data in 13 patients. Characteristics of the study population are summarized in Table 2. Among the entire study population, median (IQR) length of stay in the hospital was 4 (3-7) days. A total of 64 patients (13%) experienced a clinical failure during hospitalization: 39 (8%) had a respiratory instability, 10 (2%) had hemodynamic instability and 33 (7%) died. A total of 71 patients (15%) experienced a clinical failure 30 days after discharge: 71 (15%) were re-hospitalized and 17 (3.5%) died.

Level of agreement between ATS 2001 and ATS/IDSA 2007 criteria

After initiation of empiric antibiotic therapy, a total of 429 patients (88%) reached clinical stability during the first seven days of hospitalization according to the ATS 2001 criteria and 410 patients (84%) according to the ATS/IDSA 2007 criteria. The level of agreement between the two sets of criteria with regard to time to clinical stability detected in the study population is shown in Table 3. A discrepancy between ATS 2001 and ATS/IDSA 2007 criteria in identifying clinical stability within the first week of hospitalization was detected in 301 patients (62%).

Among those who reached clinical stability within the first week of hospitalization, the median (IQR) TCS was 2 (1-4) days based on ATS 2001 criteria and 3 (2-5) days based on ATS/IDSA 2007 criteria (p=0.012). ATS 2001 criteria identified clinical stability earlier than ATS/IDSA 2007 criteria in 40% of the study population. Clinical stability was reached one day before based on ATS 2001 criteria, in comparison to ATS/IDSA 2007 criteria in 23% of the population, two days before in 11% of the population, 3 days before in 4% of the population. The daily distribution of patients

8

who reached clinical stability during the first week of hospitalization is depicted in Figure 1, showing a significant difference with regard to ATS 2001 and ATS/IDSA 2007 criteria (Breslow Generalized Wilcoxon: p=0.002).

ATS 2001 *versus* ATS/IDSA 2007 criteria with respect to clinical outcomes

A total of 11 patients (2.6%) experienced a clinical failure during hospitalization after reaching clinical stability according to the ATS 2001 criteria and 69 patients (16%) experienced a clinical failure after discharge. A total of 5 patients (1.2%) experienced a clinical failure during hospitalization after reaching clinical stability according to the ATS 2007 criteria and 64 patients (16%) experienced a clinical failure after discharge.

Table 4 depicts clinical outcomes both during hospitalization and 30 days after discharge among those who reached clinical stability within the first week of hospitalization according to both scores. Among the 429 patients who reached clinical stability within the first week of hospitalization, based on the ATS 2001 criteria, 19% underwent a clinical failure either during hospitalization or after discharge. Among the 410 patients who reached clinical stability within the first week of hospitalization, based on the ATS/IDSA 2007 criteria, 17% underwent a clinical failure either during hospitalization or after discharge. The difference was not significant (p=0.491).

The ROC curves for both ATS and ATS/IDSA criteria for clinical stability with respect to the clinical outcome are shown in Figure 2. ATS 2001 criteria showed an AUC of 0.705 (95% CI: 0.649-0.671), while ATS/IDSA 2007 criteria had an AUC of 0.714 (95% CI: 0.657-0.771); their difference was not significant (p=0.645).

9

DISCUSSION

This study shows a discrepancy in identifying clinical stability between the criteria recommended by the ATS in 2001 and ATS/IDSA in 2007 in more than 60% of patients who are hospitalized because of an episode of CAP. Criteria recommended by the ATS in 2001 identify clinical stability significantly earlier than those recommended by the ATS/IDSA 2007 guidelines. Finally, ATS/IDSA 2007 criteria show a slightly, but not significant, better performance in comparison to ATS 2001 criteria with regard to clinical outcomes at 30-day follow up.

The definition suggested by the ATS in 2001 uses only three criteria to identify a patient with CAP who reaches clinical stability, while the definition proposed by the ATS/IDSA in 2007 includes six criteria. It is expected that as more criteria are added to the definition of clinical stability, it will become more difficult for a patient to reach all the criteria. This most likely explains our finding that the ATS 2001 criteria tend to identify patients' clinical stability earlier in comparison to the ATS/IDSA 2007 criteria. On the other hand, as more criteria are used to define clinical stability, patients will be in a more advanced period of clinical improvement, thus, will be less likely to experience further clinical deterioration. This could explain the fact that in our population, if clinical stability during hospitalization was defined using the ATS/IDSA 2007 criteria, fewer patients had an evidence of clinical deterioration at 30-day follow up after discharge.

Several implications of our results can be identified from research and clinical perspectives. In the field of clinical research, when comparing time to clinical stability as the early clinical outcome in patients with CAP, both sets of clinical criteria could be applied equally. The advantage of the ATS/IDSA 2007 criteria is that they are based on objective parameters that can be easily derived from most available electronic medical records. On the other hand, the ATS 2001 criteria use symptoms of pneumonia, such as cough and shortness of breath, that need to be assessed daily and then compared day-by-day. These patient-based criteria may be difficult to detect in a retrospective study. On the other hand, symptoms of pneumonia could be easily obtained in a prospective study.

In its recent document, “Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia”, the FDA emphasized symptoms resolution as objective evidence of clinical improvement in patients with CAP [4]. Following these recommendations, it seems that the ATS 2001 criteria for clinical stability using the improvement of subjective criteria that are directly collected from the patient, are more in line with the FDA requirements than the ATS/IDSA 2007 criteria.

From a clinical point of view, it should be reassuring for the practicing physician that that the ATS 2001 and ATS/IDSA 2007 criteria equally define clinical stability and perform similarly in hospitalized patients with CAP. During daily clinical practice, it may not be necessary to remember specific thresholds of vital parameters to define clinical stability in hospitalized patients with CAP. A patient with improving signs and symptoms of pneumonia in comparison with the previous day could be safely considered clinically stable.

Recent literature in pneumonia has identified several biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT) and pro-adrenomedullin that can help manage patients with low respiratory tract infections [13]. Menendez et al. found that low levels of CRP and PCT, in addition to clinical criteria, seem to increase the likelihood of an absence of severe complication in hospitalized patients with CAP [14]. Furthermore, repeat measurements of CRP after 72 or 96 hours from initiation of antibiotic therapy seem to be helpful in identifying patients with treatment failure [15, 16]. Future research is needed to define if the addition of serum biomarkers to current criteria of clinical stability will be beneficial in the management of CAP patients. The advantage of current criteria for clinical stability is that they are based on signs and symptoms that could be easily obtained in every clinical setting.

Most of the original works in the field of clinical stability were focused on the development of criteria to define when a CAP patient was stable enough to be switched to oral antibiotic. When patients were followed from the time that they reach stability until the time that they were discharged from the hospital, it was found that clinical deterioration from the time to clinical stability to hospital discharge occurred in less than 2% of the cases. Based on these data, it was

considered that at the point of clinical stability not only the switch to oral therapy can occur, but also it was safe to discharge the majority of patients, since clinical deterioration in the days following stability was a rare event. The original works on clinical stability did not evaluate clinical outcomes after hospital discharge. In our current study we evaluated each stability criteria for negative outcomes during hospitalization as well as negative outcomes after discharge within 30 days. Our data evaluating 30-day outcomes indicate that both criteria have similar rate of failure after hospital discharge. The fact that approximately 20% of patients have evidence of deterioration after hospital discharge emphasizes the concept that patients reaching clinical stability will not have early deterioration, but these patients may still develop clinical deterioration after hospital discharge. Data from Guertler et al. clearly showed that significant medical conditions, such as COPD, cardiac disease and malignancy, are some of the reasons behind adverse outcomes after discharge in CAP patients [17]. The majority of clinical failures after discharge in our population were due to re-hospitalizations. Our data are in line with those reported by recent literature [18-21]. Particularly, Jasti and coworker found that 12% of patients discharged after hospitalization for CAP were re-hospitalized within 30 days and most of them were comorbidity-related and not pneumonia-related [18]. Our findings suggest that current criteria for clinical stability, as windows of the early response to infection and inflammation, cannot predict the subsequent impact of the pneumonia on the deterioration of comorbities after discharge that could be responsible for both deaths and readmissions. At the moment, the time in which a CAP patient reaches clinical stability during hospitalization, in addition to the presence of signs of instability at discharge, seems to be the only tool that can help physicians in predicting adverse outcomes after discharge [20, 22].

One important limitation of our study is its retrospective design. Furthermore, the population belonged to a single hospital and was composed primarily of elderly people, particularly men, with a markedly higher number of comorbidities. This may affect the generalizability of our findings. Our study is strengthened by the evaluation of the two most used criteria for clinical stability among the same population of consecutive patients hospitalized for an episode of CAP.

In conclusion, we identified only minimal differences in the performances of ATS 2001 and ATS/IDSA 2007 criteria in defining clinical stability in hospitalized patients with CAP. Both criteria can identify early clinical stability and can be used in clinical practice as well as in clinical trials of patients with CAP.

Acknowledgements

The authors acknowledge the assistance of Mehdi Mirsaeidi MD and Asad Amir (Division of Infectious Diseases, University of Louisville), and Elizabeth Smigielski, MSLS (Associate Professor, Kornhauser Health Sciences Library, University of Louisville).

REFERENCES

1. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J, Sarosi GA, Torres A, Wilson R, Yu VL; American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163:1730–1754.
2. Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. Arch Intern Med 1995; 155(12): 1273-1276.
3. Ramirez JA, Vargas S, Ritter GW, Brier ME, Wright A, Smith S, Newman D, Burke J, Mushtaq M, Huang A. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Intern Med 1999; 159(20): 2449-2454.
4. Division of Anti_infective Products / Office of Antimicrobial Products. Anti-Infective Drugs Advisory Committee. Endpoints and Clinical Trial Issues in Community-Acquired Bacterial Pneumonia. November 3, 2011. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm275823.pdf (last access, May 15th, 2012)
5. Musher DM. Clinical and microbiological end points in the treatment of pneumonia. Clin Infect Dis 2008; 47 Suppl 3: S207-209.
6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society .Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 Suppl 2: S27-72.

7. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, Singer DE. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998;279(18): 1452-1457.
8. Ramirez JA. Fostering international multicenter collaborative research: the CAPO Project. Int J Tuberc Lung Dis 2007; 11(10): 1062-1065.
9. Aliberti S, Amir A, Peyrani P, Mirsaeidi M, Allen M, Moffett BK, Myers J, Shaib F, Cirino M, Bordon J, Blasi F, Ramirez JA. Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. Chest 2008; 134(5): 955-962.
10. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336:243–250
11. Lim WS, Lewis S, Macfarlane JT. Severity prediction rules in community-acquired pneumonia: a validation study. Thorax 2000; 55: 219–223
12. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44: 837-845.
13. Schuetz P, Amin DN, Greenwald JL. Role of procalcitonin in managing adult patients with respiratory tract infections. Chest 2012; 141(4): 1063-1073.
14. Menéndez R, Martinez R, Reyes S, Mensa J, Polverino E, Filella X, Esquinas C, Martinez A, Ramirez P, Torres A. Stability in community-acquired pneumonia: one step forward with markers? Thorax 2009; 64(11): 987-992.
15. Gómez J, Baños V, Ruiz Gómez J, Soto MC, Muñoz L, Nuñez ML, Canteras M, Valdés M. Prospective study of epidemiology and prognostic factors in community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 1996;15(7):556-560.
16. Menéndez R, Cavalcanti M, Reyes S, Mensa J, Martinez R, Marcos MA, Filella X, Niederman M, Torres A. Markers of treatment failure in hospitalised community acquired

1

pneumonia. Thorax 2008; 63(5): 447-452.

17. Guertler C, Wirz B, Christ-Crain M, Zimmerli W, Mueller B, Schuetz P. Inflammatory responses predict long-term mortality risk in community-acquired pneumonia. Eur Respir J 2011; 37(6): 1439-1446.
18. Jasti H, Mortensen EM, Obrosky DS, Kapoor WN, Fine MJ. Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia. Clin Infect Dis. 2008; 46: 550-556.
19. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. Arch Intern Med. 2002; 162:1278-1284.
20. Capelastegui A, España PP, Bilbao A, Martinez-Vazquez M, Gorordo I, Oribe M, Urrutia I, Quintana JM. Pneumonia: criteria for patient instability on hospital discharge. Chest. 2008; 134: 595-600.
21. Capelastegui A, España PP, Quintana JM, Gallarreta M, Gorordo I, Esteban C, Urrutia I, Bilbao A. Declining length of hospital stay for pneumonia and postdischarge outcomes. Am J Med 2008; 121(10): 845-852.
22. Aliberti S, Peyrani P, Filardo G, Mirsaeidi M, Amir A, Blasi F, Ramirez JA. Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. Chest 2011; 140(2): 482-488.

TABLES

Table 1. American Thoracic Society 2001 and American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria for clinical stability in hospitalized patients with community-acquired pneumonia.

ATS 2001 criteria*	ATS/IDSA 2007 criteria[#]
Improved symptoms of pneumonia (cough and shortness of breath)	Temperature ≤ 37.8 °C
Lack of fever for at least eight hours	Heart rate ≤ 100 beats/min
Improving leukocytosis (decreased at least 10% from the previous day)	Respiratory rate ≤ 24 breaths/min
	Systolic blood pressure ≥ 90 mmHg
	Arterial oxygen saturation ≥ 90% or a partial pressure of oxygen (PaO_2) ≥ 60 mmHg on room air
	Normal mental status

*All the criteria should be present during the same day in comparison to the previous day to define clinical stability. [#]All the criteria should be present during the same day to define clinical stability.

Table 2. Demographics, severity of disease, clinical, laboratory, radiological findings, microbiology and treatment data of the study population

Variable	Overall n = 487
Demographics, n. (%)	
Age, median (IQR) years	73 (61-79)
Male	477 (98)
Current Smoker	204 (42)
Nursing Home residency	21 (4.3)
Comorbidities, n. (%)	
Essential Hypertension	339 (70)
Coronary Artery Disease	206 (42)
Congestive Heart Failure	123 (25)
Chronic Obstructive Pulmonary Disease	241 (50)
Cerebrovascular disease	56 (12)
Diabetes	177 (36)
Renal diseases	74 (15)
Immunocompromized*	83 (17)
Severity of the disease on admission, n. (%)	
ICU admission	85 (18)
Severe CAP^	107 (22)
CURB-65 3, 4 and 5	49 (10)
PSI Risk Class IV and V	282 (58)
Altered mental status	45 (9.2)

Alteration of gas exchange#	169 (35)
Physical findings on admission, n. (%)	
Temperature, median (IQR) F	99 (98-101)
Respiratory Rate >=30 breaths/min	50 (10)
Systolic blood pressure < 90 mmHg	22 (4.5)
Diastolic blood pressure <= 60 mmHg	32 (6.6)
Heart rate >=125 beats/min	51 (11)
Radiological Findings, n. (%)	
Multilobar infiltrates	128 (26)
Pleural effusion	84 (17)
Laboratory values on admission, median (IQR)	
pH < 7.35, no. (%)	23 (4.7)
Albumin, mg/L	3.5 (3.1-3.9)
Creatinine, mg/dL	1.2 (0.9-1.6)
White blood cells count, cell/L	13.1 (10.3-17.2)
Platelets, cell/L	248 (197-337)
Blood urea nitrogen, mg/dL	20 (14-31)
Sodium < 130 mmol/L, no. (%)	32 (6.6)
Hematocrit < 30%, no. (%)	31 (6.4)
Microbiological Profile, n. (%)	
Unknown etiology	385 (79)
S. pneumoniae	36
MRSA	14
MSSA	18
Pseudomonas aeruginosa	11
Haemophilus influenzae	14

Legionella pneumophila	6
Moraxella catarralis	6
Escherichia coli	2
Enterobacter	1
Klebsiella pneumoniae	4
P. carinii	1
Serratia	1
S. pyogenes	1
Virus	1
Other	4
Mixed infection	18 (3.7)
Bacteremia	16 (3.3)
Empiric treatment, n. (%)	
Time to first antibiotic dose, median (IQR) hours	7 (4.5-10)
Compliant to local guidelines	405 (83)
Combination therapy	357 (74)

Continuous data are presented as median (interquartile range 25th-75th percentile); ***** active cancer or HIV or chronic steroids treatment; ^Severe CAP was defined based on the ATS/IDSA guidelines published in 2007; # PaO_2<60 mmHg or PaO2/FiO2 ratio < 300 or SpO_2<90%; SD: Standard deviation; n.: number; ICU: intensive care unit; CAP: community-acquired pneumonia; PSI: pneumonia severity index; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensible *S. aureus*.

Table 3. Joint distribution of time to clinical stability according to American Thoracic Society 2001 and American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria: number of patients in the study population.

		ATS/IDSA 2007								
	Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
ATS 2001	**1**	63 (13%)	28 (6%)	15 (3%)	7 (1%)	3 (0.6%)	2 (0.4%)	0	4 (0.8%)	122 (25%)
	2	35 (7%)	48 (10%)	30 (6%)	15 (3%)	8 (2%)	3 (0.6%)	2 (0.4%)	8 (2%)	149 (31%)
	3	11 (2%)	17 (4%)	22 (5%)	15 (3%)	4 (1%)	2 (0.4%)	5 (1%)	5 (1%)	81 (17%)
	4	3 (0.6%)	4 (0.8%)	0	15 (3%)	11 (2%)	5 (1%)	1 (0.2%)	5 (1%)	44 (9%)
	5	2 (0.4%)	3 (0.6%)	0	1 (0.2%)	3 (0.6%)	5 (1%)	1 (0.2%)	3 (0.6%)	18 (4%)
	6	0	0	1 (0.2%)	2 (0.4%)	0	0	1 (0.2%)	2 (0.4%)	6 (1.2%)
	7	0	0	0	0	1 (0.2%)	0	3 (0.6%)	5 (1%)	9 (1.8%)
	8	3 (0.6%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	3 (0.6%)	1 (0.2%)	2 (0.4%)	45 (9%)	58 (12%)
Total		117 (24%)	102 (21%)	69 (14%)	56 (12%)	33 (7%)	18 (4%)	15 (3%)	77 (16%)	487 (100%)

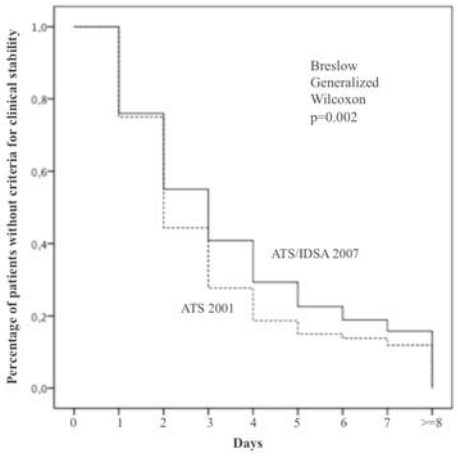
Table 4. Clinical outcomes of patients who reached clinical stability within 7 days from admission according to both American Thoracic Society 2001 and American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria.

Study outcomes	**ATS 2001 criteria** n = 429 pts	**ATS/IDSA 2007 criteria** n = 410 pts
Clinical failure during hospitalization, n. (%)	11 (2.6)	5 (1.2)
Respiratory instability, n. (%)	9 (2.1)	5 (1.2)
Hemodynamic instability, n. (%)	0	0
In-hospital death, n. (%)	4 (1)	0
Clinical failure within 30 days after discharge, n. (%)	69 (16)	64 (16)
Re-hospitalization within 30 days after discharge, n. (%)	62 (15)	59 (15)
Death within 30 days after discharge, n. (%)	14 (3.2)	14 (3.4)
Clinical failure either during hospitalization or within 30 days after discharge, n. (%)	80 (19)	69 (17)

Pts: patients; n: number

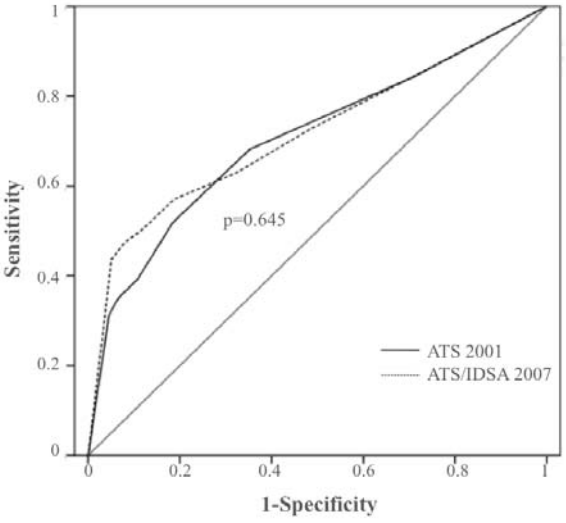
FIGURE LEGENDS

Figure 1. Survival curve showing the percentage of patents who progressively reached clinical stability during the first week of hospitalization according to both sets of criteria



Footnotes. ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America

Figure 2. Receiver operating characteristic curves for American Thoracic Society 2001 and American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2007 criteria with respect to the clinical failure either during hospitalization or after discharge



2