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Impact of empirical treatment recommendations from 2017 European guidelines for nosocomial pneumonia

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Title: Impact of empirical treatment recommendations from 2017 European guidelines for nosocomial pneumonia*Short title: Impact of 2017 European guidelines for HAP/VAP*

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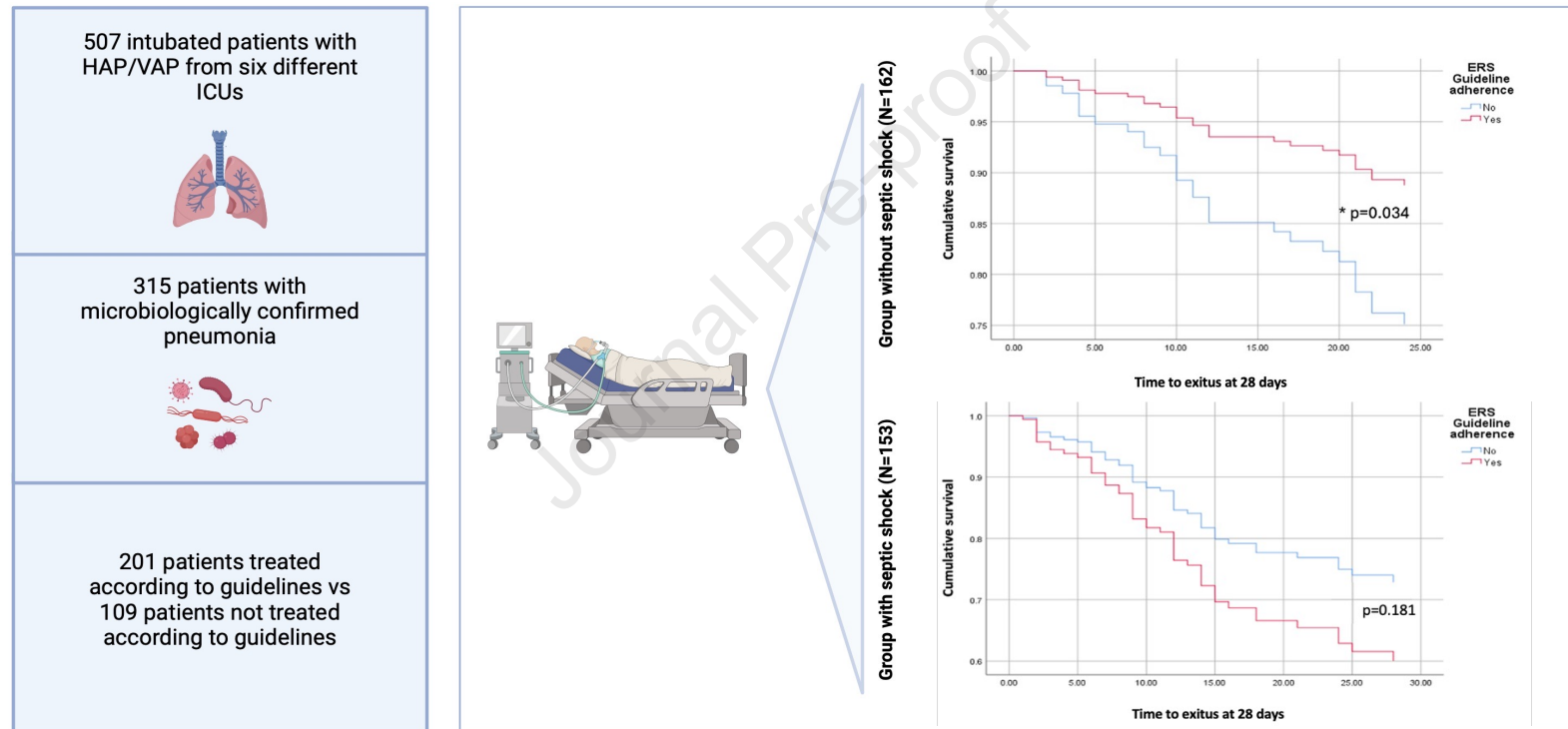
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Impact of empirical treatment recommendations from European guidelines for nosocomial pneumonia

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GRAPHICAL ABSTRACT The treatment algorithm proposed by European guidelines appears to be effective, being able to reduce mortality in population without septic shock. However, it was not possible to confirm this superiority in patients with septic shock at the diagnosis and future studies should determine its efficacy in this group.

Title: Impact of empirical treatment recommendations from 2017 European guidelines for nosocomial pneumonia

Short title: Impact of 2017 European guidelines for HAP/VAP

Davide Calabretta¹, Catia Cilloniz², Albert Gabarrus³, Ana Motos⁴, Flavia Galli³, Miquel Ferrer⁵, Laia Fernandez-Barat⁶, Andrea Palomeque⁷, Giovanni Mistraretti⁸, Mauro Panigada⁹, Cristina Pitart¹⁰, Mateu Espasa¹⁰, Ignacio Martin-Loeches¹¹, Antoni Torres¹²

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34 **KEYWORDS LIST**

- 35 • Hospital acquired pneumonia
- 36 • Ventilator associated pneumonia
- 37 • Intensive care medicine
- 38 • Nosocomial infection
- 39 • Septic shock
- 40 • Antimicrobial treatment
- 41

Patients hospitalized for more than 48 hours are at increased risk of the potentially life-threatening lung infections hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)¹. These are the leading cause of ICU-acquired infections, the second leading causes of nosocomial infection^{2,3}, and are associated with a high incidence of adverse outcomes and increased healthcare costs⁴. The pathogens involved in HAP/VAP are often typical of the hospital environment and characterized by drug resistance, making their treatment a major challenge⁵⁻⁷. Physicians should avoid overtreatment and limit the use of ineffective empirical antibiotic therapy due to the association of these factors with antimicrobial resistance and increased mortality⁸⁻¹⁰.

In 2017, the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Asociación Latinoamericana del Tórax (ALAT) published a joint European guideline on the management of HAP/VAP¹¹. This proposed a new algorithm for empirical antimicrobial therapy based on the medical history, local ecology, and disease severity defined by the presence or absence of septic shock (Figure 1). Although the guidelines had low accuracy for predicting multidrug resistant (MDR) pathogens in HAP/VAP¹², their impact on clinical outcomes has never been investigated.

The present study assessed the efficacy of the 2017 ERS/ESICM/ESCMID/ALAT European guideline implementation on mortality, treatment adequacy, treatment failure, and overtreatment among patients with nosocomial pneumonia treated in intensive care units (ICU).

STUDY DESIGN AND METHODS

Study design and cohort

We performed a retrospective analysis of prospectively collected data from a cohort of 507 patients admitted between 2004 and 2017 to Hospital Clinic of Barcelona (Spain). Patients from six different ICUs (2 medical, 3 mixed, 1 postoperative) were included if they were age ≥ 18 years, stayed in ICU for ≥ 48 hours, and had a microbiologically confirmed diagnosis of HAP/VAP. Only the first episode of HAP/VAP was considered in those with ≥ 2 episodes during an ICU stay. Patients with neutropenia, drug-induced immune suppression, and human immunodeficiency virus infection were excluded.

Outcome variables

The primary outcome was the 28-day mortality after the diagnosis of pneumonia. Secondary outcomes included the 90-day mortality, ICU mortality, treatment adequacy, and antibiotic overtreatment. We compared the incidence of each outcome between two patient groups, defined as follows: (1) guideline adherence, if treated according to the 2017 European guideline; and (2) guideline nonadherence, if not treated according to the 2017 European guideline or if treated according to different guidelines, local protocols, or the treating physician's clinical judgment.

Definitions

Cases of VAP/HAP case were identified using the definition set out in the European guidelines¹¹. Microbiological confirmation was defined by the results from different sources, including sputum, tracheobronchial aspirates, and bronchoalveolar lavage¹³, and was confirmed only when the number of colony-forming units was significant¹⁴. Patients were considered at high mortality risk ($\geq 15\%$) if they had an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≥ 10 when pneumonia was diagnosed¹⁵.

Patients at high risk for MDR pathogens according to guideline required the presence of

septic shock or positivity for at least one VAP risk factor, including antibiotic use in the 90 days before hospitalization, prior isolation of MDR pathogens, hospitalization in the last 90 days, and an hospital setting with a $\geq 25\%$ prevalence of MDR pathogens (both methicillin-resistant *Staphylococcus aureus* [MRSA] and resistant gram-negative strains). MDR and extensively drug-resistant (XDR) pathogens were defined according to standard definitions as nonsusceptibility to at least one antibiotic drug in three or more antimicrobial categories¹⁶.

Septic shock was defined as a state of sepsis with persistent hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg, according to what is stated in the 2017 European guideline.

Patients were treated according to guidelines if they complied with the indications of the treatment algorithm (Figure 1). All medical and mixed ICUs had a $\geq 25\%$ prevalence of MDR pathogens, with only the postoperative ICU showing lower levels. None of the antipseudomonal antibiotics used for empirical treatment had a $>90\%$ efficacy on local gram-negative organisms; therefore, only patients treated with dual antipseudomonal therapy were considered adherent to the guidelines¹¹. Antibiotic therapy was considered adequate if it covered all isolated pathogens, but it was considered inadequate if at least one pathogen was not susceptible to any of the prescribed empirical antibiotics¹⁷. Treatment failure was defined according to clinical, radiological, microbiological, and laboratory criteria at 72–96 hours after starting antibiotic therapy¹⁸.

Finally, in the absence of a universally accepted definition of antibiotic overtreatment¹⁹, we defined unnecessary antibiotic treatment as follows:

- anti-gram-positive agents used in the presence of only gram-negative bacteria
- anti-gram-negative agents used in the presence of only gram-positive bacteria
- antipseudomonal treatment used in the presence of non-MDR gram-negative bacteria
- anti-MRSA treatment used in the presence of non-MDR gram-positive bacteria

- antimicrobial combination therapy when a monotherapy could have been adequate
- antibiotic treatment in the presence of only viruses or fungi
- when all pathogens in polymicrobial infection were treated with unnecessary therapy.

Statistical analysis

We report the number and percentage of patients for categorical variables and the median and interquartile range (IQR) for continuous variables. To compare categorical variables, we used the chi-squared test or the Fisher exact test for contingency tables, as appropriate. To compare continuous variables, we used the non-parametric Mann–Whitney test. The assumption of normality was checked with Kolmogorov–Smirnov tests.

Survival curves were obtained using the Kaplan–Meier method and compared using the Gehan–Breslow–Wilcoxon test²⁰. We analyzed the association between guideline adherence and 28-day mortality using a Cox regression multivariable model²¹ with adjustment for potential confounders. The following variables, selected according to their potential clinical relevance, were included: age, sex, VAP, diabetes mellitus, chronic renal failure, solid tumor, chronic heart disease, chronic respiratory disease, chronic hepatopathy, APACHE II at diagnosis, *P. aeruginosa*, and MDR pathogens. Effect modification by clinical factors (e.g., septic shock) potentially associated with the primary patient outcome (i.e., 28-day mortality) and guideline adherence were assessed by an interaction term, with subgroup analyses based on this factor. Single collinearity in the multivariable analysis was evaluated by Spearman correlation (r) and multicollinearity was examined by the variance inflation factor. Proportional hazard assumptions were tested with log minus log plots. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Assessment of discrimination in the multivariable model was measured using Harrell’s C and Somers’ D. We used the multiple imputation method^{22,23} for missing data to generate five datasets, replacing missing values with plausible estimates. The model for multiple imputation included all covariates from the

135 multivariable analyses.

136 Patients lost to follow-up were censored in the survival analyses. The level of significance
137 was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS version 26.0 (IBM Corp.,
138 Armonk, NY, USA).

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RESULTS

Descriptive characteristics of the population

As shown in the flowchart (Figure 2), we excluded patients with no information on septic shock ($n = 2$), low mortality risk and low MDR risk ($n = 2$), and without an isolated pathogen ($n = 187$). In total, 315 patients were included in the analysis and categorized into a group without septic shock ($n = 162$) and a group with septic shock ($n = 153$) at the diagnosis of pneumonia.¹¹

Table 1 describes the cohort's characteristics at ICU admission, and Table 2 describes the incidence of microorganisms. The population characteristics at the diagnosis of pneumonia are reported in e-Table 1 of the electronic supplementary material. Most patients in our study were males (72%), the median age was 66 years, and the most frequent comorbidity was chronic lung disease (34%). VAP accounted for most cases ($n = 217$; 69%) and *P. aeruginosa* was the most frequently isolated pathogen (33%).

Comparison between treatment groups

Table 3 shows the main outcome measures. Of the 315 patients, 206 received treatment in accordance with the 2017 European guideline and 109 received treatment not in accordance with the guideline. No statistically significant differences in the main or secondary outcomes emerged when comparing these groups, except for antibiotic overtreatment, which was more prevalent in patients treated according to the guidelines (42.5% vs 66.3%; $p < 0.001$). The comparison was repeated after excluding two-drug combinations with aminoglycosides, confirming these results (e-Table 2).

Cox regression was performed to assess the impact of variables on mortality 28 days after the diagnosis of pneumonia. Table 4 shows the impact of variables considered in our predictive model, and e-Figure 1 shows the survival curves by whether patients were treated according to the 2017 European guideline. Significant effect modification was found for guideline adherence and

septic shock after adjustment for covariates ($p = 0.027$), prompting further analyses to evaluate the incidence of the main outcomes by the presence of septic shock at the diagnosis of pneumonia. e-Table 3 and e-Table 4 report the number of valid variables considered by the model and the Akaike information criterion (AIC) used for model choice.

Subgroup analyses

All patients treated according to the 2017 European guidelines received combination therapy and more often required treatment with three or four antibiotics ($p < 0.001$ in both groups, e-Table 5 and e-Table 6); all other patients received monotherapy or combinations of antimicrobials that are not included in the recommendations. Tables 5 and 6 summarize the results of key outcome comparisons by treatment adherence in subgroups without and with septic shock, respectively. As expected, the group with septic shock showed a higher incidence of adverse outcomes.

In patients without septic shock, statistically significant differences emerged between the adherence and nonadherence groups for ICU mortality (28.8% vs 14.5%; $p = 0.031$) and overtreatment (38.8% vs 65.1%; $p = 0.002$). However, those differences were not observed for 28-day mortality (25.0% vs 14.5%; $p = 0.105$), 90-day mortality (44.2% vs 30.6%; $p = 0.073$), inadequate treatment (15.4% vs 16.4%; $p = 0.874$), or treatment failure (55.8% vs 49.1%; $p = 0.427$) (Table 5). Among patients with septic shock, the only significant difference emerged for overtreatment, which was again better represented in patients treated according to the guidelines (45.6% vs 67.7%; $p = 0.007$) (Table 6).

The predictive model was also applied to predict the impact of septic shock on 28-day mortality. The relevant survival curves are shown in Figure 3, showing a significant difference in favor of guideline adherence for patients without septic shock (HR 0.42; 95%CI 0.18-0.93; $p = 0.034$); however, no significant difference existed for patients diagnosed with septic shock (HR 1.57; 95%CI 0.81-3.05; $p = 0.181$). Because this result was unexpected, we conducted further analysis to identify

possible factors that may have influenced outcomes in the population with septic shock. No difference emerged based on the APACHE II, Sequential Organ Failure Assessment (SOFA), and Clinical Pulmonary Infection Score (CPIS) severity scores at diagnosis. The incidence of MDR also did not differ significantly between the two groups. However, when considering the incidence of risk factors for nosocomial pneumonia, patients treated according to the 2017 European guideline showed a higher incidence of hospitalization ≥ 5 days (75.0% vs 49.1%; $p < 0.001$) and higher percentages of infection by *P. aeruginosa* (47.9% vs 21.0%; $p < 0.001$), MDR *P. aeruginosa* (22.9% vs 5.3%; $p = 0.004$), and XDR pathogens (25.0% vs 5.3%, $p = 0.002$).

e-Table 7 and e-Table 8 show the etiology of HAP/VAP by treatment arm in patients without and with septic shock, while e-Table 9 and e-Table 10 show the antimicrobials prescribed in the different groups, including the incidence of treatment de-escalation and escalation in the different groups.

DISCUSSION

The choice of empirical antimicrobial therapy is a critical moment in the early management of patients with HAP/VAP. A well-designed therapeutic algorithm needs to exert a positive impact on outcomes without adding unnecessary treatment^{3,8}. Applying the 2017 ERS/ESICM/ESCMID/ALAT European guidelines in our cohort did not improve any mortality outcomes. This included when we considered the incidence of inadequate therapy, cases of treatment failure, and when adjusting for confounders. Given that combination antibiotic treatments with aminoglycosides have been associated with adverse outcomes²⁴, we conducted additional analyses excluding these patients, but this approach also failed to demonstrate benefits (Table S2).

Nevertheless, the significant interaction between guideline application and presence or

212 absence of septic shock at diagnosis suggested an effect that cannot be attributed to chance. When
213 the groups with and without septic shock were analyzed separately, the results of the chi-squared
214 test and predictive model analysis differed. Whereas guideline adherence in those without septic
215 shock appeared to confer advantages, such as the significant reduction in ICU mortality ($p = 0.031$),
216 it did not improve any of the main outcomes in those with septic shock. Curiously, our model
217 indicated that a history of chronic heart failure was also associated with better survival; however,
218 this could be explained by a high proportion of these being post-surgical (39/95), a factor associated
219 with a better prognosis compared with the general ICU population.

220 Guideline adherence seemed to offer improved 28-day cumulative mortality in patients
221 without septic shock, but not in those with septic shock. Indeed, the survival curves may suggest
222 that the 2017 European guideline recommendations had a negative impact (Figure 3). A similar
223 result was obtained by Kett et al., who observed a higher incidence of adverse outcomes in patients
224 who adhered to American guidelines. They attributed excessive antibiotic therapy as a possible
225 explanation²⁵. Consistent with this, we found that guideline adherence resulted in a higher
226 incidence of overtreatment because of the indication to receive antipseudomonal therapy plus an
227 anti-MRSA agent where there was a possible high prevalence of MDR organisms.

228 The rationale for combined antimicrobial treatment may be appropriate for nosocomial
229 pneumonia to obtain synergy between different antibiotic classes, especially for severe infections
230 due to *P. aeruginosa*. However, this approach lacks consensus, and recent studies show an overlap
231 in the incidence of adverse events when comparing single and combination therapy^{26–31}. Although
232 our results appear to contradict such evidence, with most patients receiving combination therapy
233 when treated according to the 2017 European guideline, it must be stressed that several patients in
234 the control group also received combination treatment. The observed difference due to guideline
235 adherence must therefore be attributable to the type of combination therapy recommended. It is

possible that the choice of certain drugs impacted the outcomes for groups with and without septic shock. Furthermore, overtreatment due to guideline adherence in our cohort was significantly higher in both the groups without and with septic shock, failing to explain the different impacts of the guidelines in these treatment arms.

Finally, when analyzing the characteristics of patients with septic shock, those treated according to the 2017 European guideline recommendations showed a higher prevalence of hospitalization for ≥ 5 days, despite the absence of differences in severity scores. This is relevant because prolonged hospitalization is a critically important risk factor for MDR pathogens; and, in our population, it is likely that it led to an increased incidence of *P. aeruginosa*, MDR *P. aeruginosa*, and XDR pathogens in the group with septic shock treated according to the guidelines. Furthermore, major guidelines for the treatment of nosocomial pneumonia agree that more aggressive therapy is appropriate when this risk factor is present³. Due to the retrospective nature of our analysis, we cannot exclude the possibility that this influenced treatment arm assignment, resulting in the allocation of patients with a higher intrinsic risk to the group treated according to the 2017 European guidelines.

To the best of our knowledge, this is the first study to investigate the impact of empirical treatment recommendations from the 2017 ERS/ESICM/ESCMID/ALAT European guideline on the outcomes of patients with HAP/VAP. The retrospective analysis benefited from the prospective data collection by a dedicated investigator, thereby limiting the biases of retrospective data collection from medical records. It is also well known that a variable percentage of patients with HAP/VAP without microbial diagnosis do not have pneumonia, giving them a better prognosis³²; by including only patients with microbiological confirmation of nosocomial pneumonia, we increased the relevance of our findings.

Despite these strengths, some limitations may have impacted on our results. First, the patient

inclusion period ranged from 2004 to 2017, precluding assessment of the impact of guideline recommendations in a population treated according to current best practice. However, no significant changes in the empirical treatment of nosocomial pneumonia were introduced during the following years and our local guidelines were in line with what was published in 2017, thus we do not believe that the standard of care in the study period affected our results. Second, the retrospective nature of the analysis meant that we did not calculate the sample size, which may have resulted in low study power to estimate the true impact of guideline adherence. Third, our study was performed in an ICU population, meaning that we cannot generalize our conclusions to all the patients with HAP. Fourth, we considered the definition of septic shock in accordance with 2017 guidelines, however further validation studies could consider the new definition of septic shock in the decision-making algorithm for empirical treatment of nosocomial pneumonia. Fifth, our definition of treatment adequacy did not account for timing, pharmacokinetics, treatment duration, and antibiotic synergy, which may have led to the failure to detect differences between groups. Sixth, different ICUs exhibited heterogeneous characteristics, with different levels of antibiotic resistance in different settings leading to different guideline application.

CONCLUSIONS

The development of effective recommendations for empirical antimicrobial treatment poses a critical challenge in the management of nosocomial pneumonia in ICU. In our general ICU population, the empirical treatment algorithm for HAP/VAP proposed by the ERS/ESICM/ESCMID/ALAT guidelines was ineffective for reducing the incidence of adverse outcomes and increased the risk of overtreatment. However, algorithm use had differing efficacies depending on the presence or absence of septic shock at diagnosis. In patients without septic shock, the ICU mortality and adjusted 28-day mortality rates were significantly lower with guideline adoption, whereas in those with septic shock, guideline adoption was not associated with improved

284 outcomes, possibly due to the retrospective nature of our analysis. Nevertheless, we cannot at
285 present endorse the ERS/ESICM/ESCMID/ALAT guidelines in these patients. Future guideline
286 authors should therefore focus on improving recommendations and on integrating biomarkers to
287 guide treatment decisions, with special attention given to patients with septic shock at time of
288 diagnosis.

289

TAKE HOME POINTS

STUDY QUESTION: We performed a retrospective analysis of a perspective cohort including 315 ICU patients with microbiologically confirmed HAP/VAP to assess the impact on clinical outcomes of the recommendations for empirical antibiotic treatment from 2017 ERS/ESICM/ESCMID/ALAT guidelines.

RESULTS: Despite having led to an increased incidence of overtreatment, the application of the guidelines reduced ICU mortality and 28-day adjusted mortality in patients without septic shock but provided no benefit to those with septic shock at the diagnosis of pneumonia.

INTERPRETATION: Our study demonstrated the usefulness of the guidelines and supports their use in patients without septic shock but does not allow us to recommend their application in those with septic shock at the time of diagnosis.

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LEGEND FIGURES**Figure 1. Treatment algorithm for empirical antibiotics in nosocomial pneumonia**

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recommendations¹¹. # low risk for mortality is defined as a $\leq 15\%$ chance of dying, a mortality rate

that has been associated with better outcome using monotherapy than combination therapy

when treating serious infection¹⁵. Abbreviations: ICU, intensive care unit; MDR, multidrug

resistant; MRSA, methicillin-resistant *S. aureus*.

Figure 2. Study flowchart

Abbreviations: ICU, intensive care unit; MDR, multidrug resistant.

Figure 3. Survival curves for 28-day mortality by guideline adherence

(A) patients without septic shock. (B) patients with septic shock. Significance levels for the

comparison are reported per figure. * indicates the presence of a statistically significant difference

between the two groups.

Table 1. Demographic and baseline characteristics of the population

Variable	N = 315
Age, median (Q1–Q3), years	66 (53–75)
Sex, M, n (%)	226 (71.5)
Smoking (current or former), n (%) [†]	163 (51.7)
Alcohol abuse (current or former), n (%) [‡]	79 (25.1)
Recent corticosteroid use, n (%) [§]	33 (11.3)
Comorbidities, n (%)[*]	
Diabetes mellitus	71 (22.5)
Chronic renal failure	25 (7.9)
Solid cancer	53 (16.8)
Chronic heart disease	95 (30.1)
Chronic lung disease	106 (33.5)
COPD	74 (23.4)
Chronic liver disease	57 (18.0)
Causes of ICU admission n (%)	
Hypercapnic respiratory failure	45 (14.3)
Hypoxemic respiratory failure	57 (18.0)
Acute coronary syndrome	10 (3.1)
Polytrauma	30 (9.5)
Postsurgical	66 (21.0)
Cardiac arrest	22 (7.0)
Altered consciousness	43 (13.6)
Abdominal disease (nonsurgical)	14 (4.4)
Other	28 (8.9)

Abbreviations: COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; Q1 = first quartile; Q3 = third quartile.

[†]Percentages calculated from available data of 314 patients

[‡] Percentages calculated from available data of 314 patients

[§]Percentages calculated from available data of 292 patients

*Patients could have more than one comorbidity condition.

Table 2. Etiology of HAP/VAP

Variable	N = 315
Microorganism, n (%)	
<i>Staphylococcus aureus</i>	84 (26.6)
<i>Pseudomonas aeruginosa</i>	103 (32.6)
<i>Klebsiella spp.</i>	34 (10.8)
<i>Escherichia coli</i>	22 (7.0)
<i>Streptococcus pneumoniae</i>	18 (4)
<i>Enterobacter spp.</i>	17 (5.4)
<i>Serratia spp.</i>	15 (4.7)
<i>Proteus spp.</i>	7 (2.2)
<i>Stenotrophomonas spp.</i>	22 (7.0)
<i>Aspergillus spp.</i>	13 (4.1)
Respiratory viruses	8 (2.5)
Others*	29 (9.2)
MDR pathogens, n (%)	
<i>Pseudomonas aeruginosa</i>	40 (12.7)
Methicillin-resistant <i>Staphylococcus aureus</i>	27 (8.5)
<i>Enterobacteriaceae</i>	23 (7.3)
XDR pathogens	49 (15.5)
PDR <i>Acinetobacter baumannii</i>	1 (0.3)

Definition of abbreviations: MDR = multidrug resistant; spp. = species; PDR = pandrug resistant; XDR = extensively drug resistant.

* Aetiological agents poorly represented in our population and/or of uncertain clinical significance were considered in this category, including both bacteria (*Bacteroides* spp., *Citrobacter* spp., coagulase-negative *Staphylococci*, *Streptococcus* spp., *Neisseria* spp.) and mycetes (*Candida* spp.).

Table 3. Comparison of the main outcomes in the general population based on guideline adherence or nonadherence

Outcomes	Guideline nonadherence N = 109	Guideline adherence N = 206	p-value
28-day mortality, n (%)	28 (25.7)	52 (25.2)	0.931
90-day mortality, n (%)	53 (49.1)	84 (41.8)	0.219
ICU mortality, n (%)	38 (34.9)	61 (29.6)	0.340
Inadequate treatment, n (%)	23 (20.9)	32 (15.5)	0.229
Treatment failure 3-4 days, n (%)	62 (56.9)	118 (57.3)	0.945
Overtreatment, n (%)	45 (42.5)	136 (66.3)	<0.001

Abbreviations: ICU = intensive care unit. Percentages were calculated on non-missing data.

Table 4. Multivariate Cox regression models assessing factors associated with 28-day mortality

Variables	Guideline adherence and treatment group			
	Without interaction*		With interaction [§]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Interaction: guideline adherence and treatment group	-	-	3.07 (1.13-7.85)	0.027
Guideline adherence	0.92 (0.56-1.51)	0.748	0.47 (0.22-1.00)	0.050
Treatment group	1.84 (1.14-2.98)	0.013	0.92 (0.43-1.97)	0.834
Age	1.02 (1.01-1.04)	0.011	1.02 (1.00-1.04)	0.014
Sex	1.29 (0.77-2.14)	0.332	1.35 (0.81-2.25)	0.248
VAP	0.74 (0.44-1.23)	0.241	0.71 (0.42-1.17)	0.181
Diabetes mellitus	0.81 (0.46-1.44)	0.474	0.83 (0.47-1.48)	0.535
Chronic renal failure	1.52 (0.69-3.35)	0.299	1.42 (0.64-3.14)	0.389
Solid tumor	0.86 (0.45-1.63)	0.634	0.72 (0.46-1.70)	0.794
Chronic heart disease	0.44 (0.25-0.79)	0.006	0.43 (0.24-0.77)	0.004
Chronic respiratory disease	1.59 (0.98-2.60)	0.062	1.68 (1.05-2.79)	0.004
Chronic hepatopat	1.30 (0.75-2.28)	0.350	1.27 (0.73-2.22)	0.345
APACHE II at the diagnosis	1.01 (0.96-1.05)	0.819	1.00 (0.96-1.05)	0.836
P. aeruginosa	1.27 (0.79-2.04)	0.316	1.22 (0.76-1.96)	0.404
Prevalence of MDR pathogen	1.03 (0.64-1.66)	0.905	1.06 (0.65-1.71)	0.820

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; HR = hazard ratio; MDR = multidrug resistant; VAP = ventilator-associated pneumonia.

* Harrell's C statistic is 0.69 and Somers' D statistic is 0.37.

§ Harrell's C statistic is 0.69 and Somers' D statistic is 0.38.

Table 5. Comparison of the main outcomes in patients without septic shock

Outcomes	Guideline nonadherence N = 52	Guideline adherence N = 110	p-value
28-day mortality, n (%)	13 (25.0)	16 (14.5)	0.105
90-day mortality, n (%)	23 (44.2)	33 (30.6)	0.073
ICU mortality, n (%)	15 (28.8)	16 (14.5)	0.031
Inadequate treatment, n (%)	10 (19.2)	18 (16.4)	0.652
Treatment failure 3-4 days, n (%)	29 (55.8)	54 (49.1)	0.427
Overtreatment, n (%)	19 (38.8)	71 (65.1)	0.002

Abbreviations: ICU = intensive care unit.

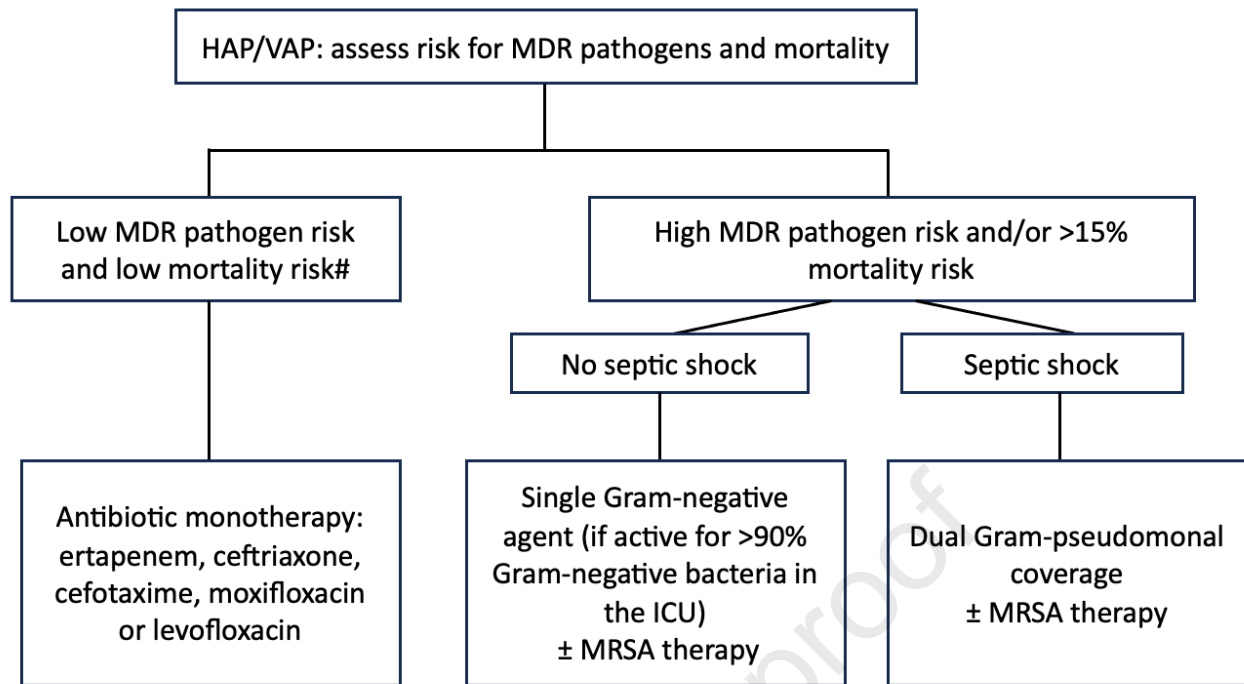
Percentages were calculated on non-missing data.

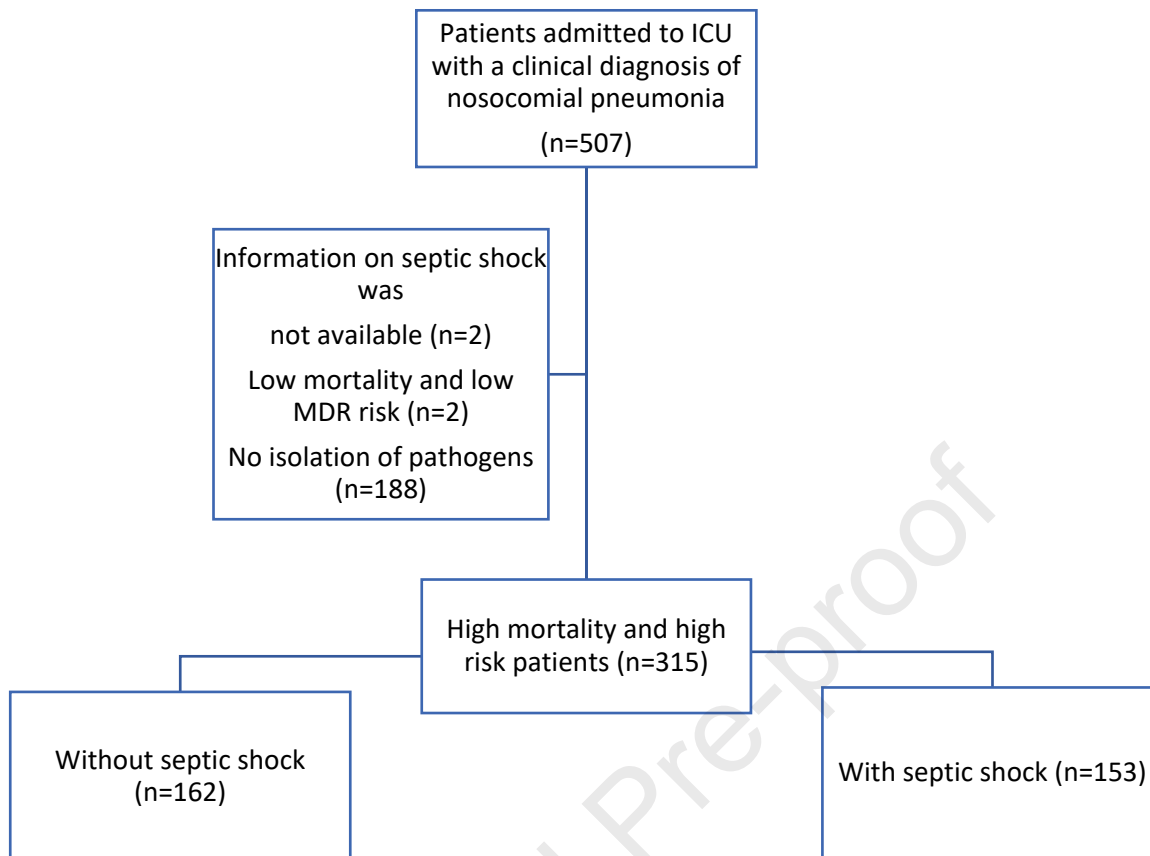
Table 6. Comparison of the main outcomes in patients with septic shock

Outcomes	Guideline nonadherence N = 57	Guideline adherence N = 96	p-value
28-day mortality, n (%)	15 (26.3)	36 (37.5)	0.156
90-day mortality, n (%)	30 (52.6)	51 (54.8)	0.792
ICU mortality, n (%)	23 (40.4)	45 (46.9)	0.432
Inadequate treatment, n (%)	13 (22.4)	14 (14.6)	0.216
Treatment failure 3-4 days, n (%)	33 (57.9)	64 (66.7)	0.427
Overtreatment, n (%)	26 (45.6)	65 (67.7)	0.007

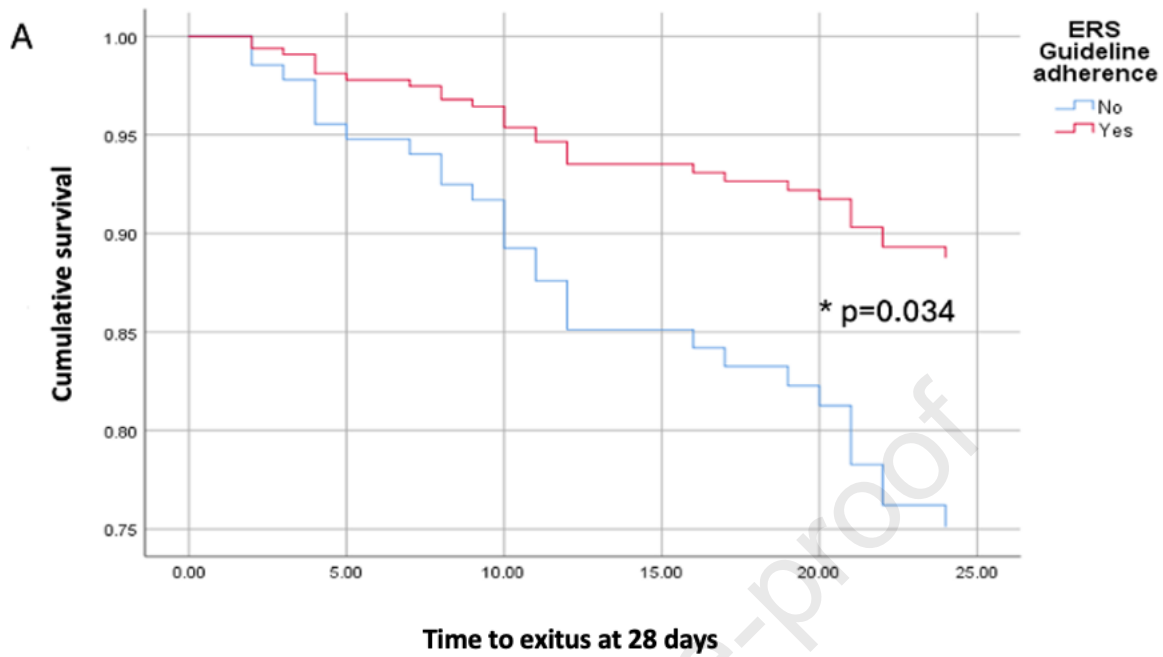
Abbreviations: ICU = intensive care unit.

Percentages were calculated on non-missing data.

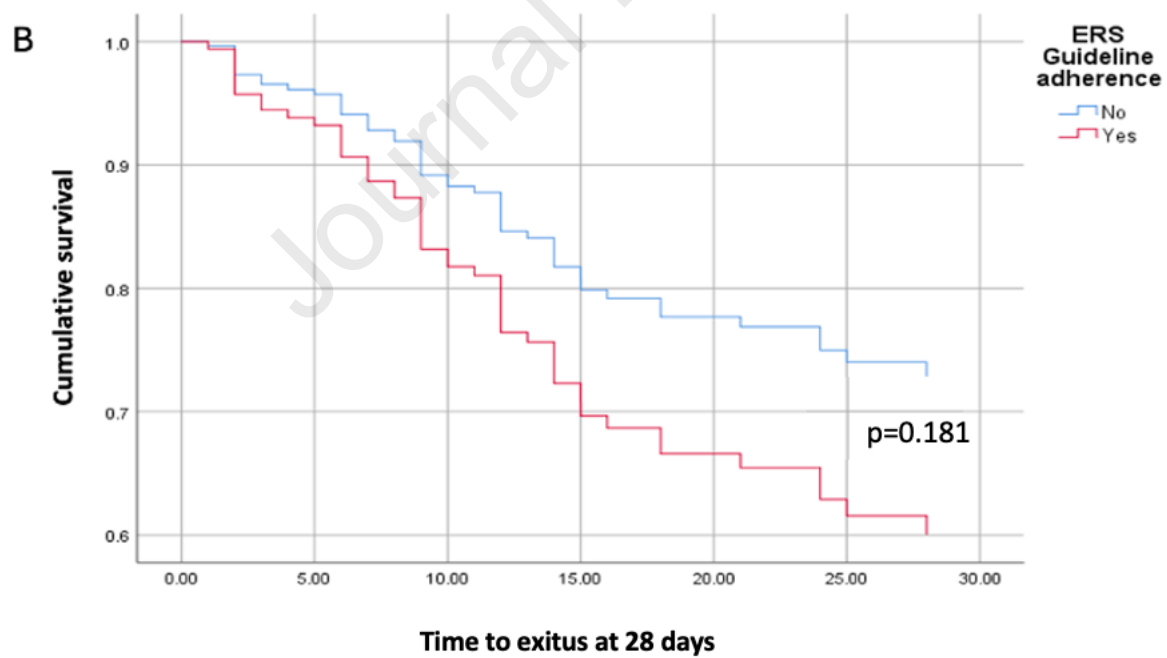




Survival curves – patients without septic shock



Survival curves – patients with septic shock



Summary conflict of interest statements: The authors declare no conflict of interest

Conflict of interests:

Davide Calabretta: declares no conflict

Catia Cilloniz: declares no conflict

Ana Motos: declares no conflict

Flavia Galli: declares no conflict

Miquel Ferrer: declares no conflict

Laia Fernandez-Barat: declares no conflict

Andrea Palomeque: declares no conflict

Giovanni Mistraletti: declares no conflict

Mauro Panigada: declares no conflict

Cristina Pitart: declares no conflict

Mateu Espasa: declares no conflict

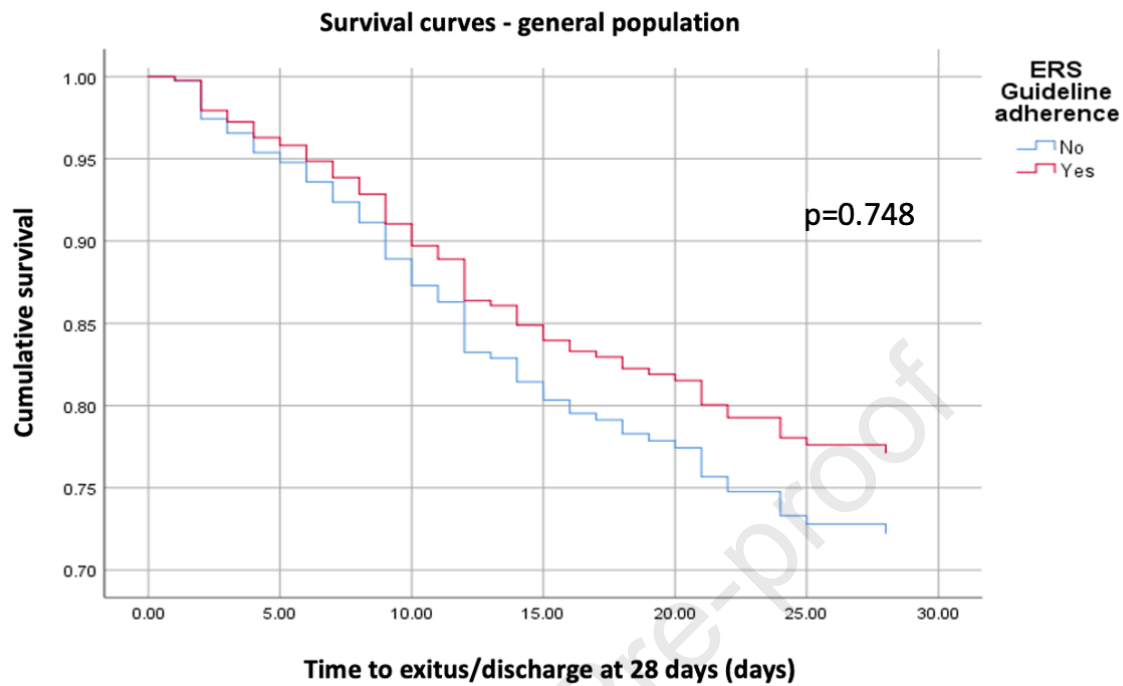
Ignacio Martin-Loeches: declares no conflict

Antoni Torres: declares no conflict

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e-Figure 1. Survival curves related to 28-day mortality for the two cohorts of patients treated or not according to guidelines.



ELECTRONIC SUPPLEMENTARY MATERIALS

e-Table 1. Baseline characteristics at time of diagnosis of pneumonia

Type of pneumonia, n (%)	
Ventilator-associated pneumonia	217 (68.7)
Hospital-acquired pneumonia	99 (31.3)
Severity assessment of pneumonia	
CPIS, median (Q1–Q3)	7 (5–10)
APACHE II, median (Q1–Q3)	16 (12–20)
SOFA score, median (Q1–Q3)	7 (5–9)
Temperature, median (Q1–Q3), C°	37.0 (35.8–38.0)
Multilobar pneumonia, n (%)	144 (45.6)
Presence of ARDS, n (%)	38 (12.1)
Pleural effusion, n (%)	99 (32.0)
Laboratory variables, median (Q1–Q3)	
Creatinine, mg/dl	0.9 (0.6–1.5)
Hemoglobin, g/dl	10.3 (9.1–11.7)
White blood cell count, 10 ⁹ cells/L	12.1 (9.1–17.3)
Lymphocytes, n/mm ³	819 (528–1202)
PaO ₂ /FIO ₂ , mmHg	192 (142–260)

Definition of abbreviations: APACHE = acute physiology and chronic health evaluation; CPIS = clinical pulmonary infection score; PaO₂/FIO₂ = ratio of arterial oxygen tension to fraction of inspired oxygen; Q1= first quartile; Q3= third quartile; SOFA = sequential organ failure assessment. Percentages were calculated on non-missing data.

e-Table 2. Comparison of the main outcomes, following exclusion of cases treated with combination therapy with a beta-lactam or carbapenemics in exclusive association with aminoglycosides

Outcomes	Guideline	Guideline adherence	p-value
	nonadherence	N = 137	
	N = 109		
28-day mortality, n (%)	28 (25.7)	34 (24.8)	0.876
90-day mortality, n (%)	53 (49.1)	58 (43.3)	0.369
ICU mortality, n (%)	38 (34.9)	45 (32.8)	0.740
Inadequate treatment, n (%)	23 (20.9)	25 (18.2)	0.575
Treatment failure 3-4 days, n (%)	62 (56.9)	83 (60.6)	0.558
Overtreatment, n (%)	45 (42.5)	136 (66.3)	<0.001

Abbreviations: ICU = intensive care unit. Percentages were calculated on non-missing data.

e-Table 3. AIC (Akaike Information Criterion) of different survivals models considered for multivariate analysis.

Model	Without interaction	With interaction
PH	37.54	41.45
AFT (gompertz distribution)	39.12	43.17
AFT (lognormal distribution)	37.74	41.49
AFT (weibull distribution)	39.75	43.92
AFT (ev distribution)	40.08	45.12
AFT (loglogistic distribution)	38.96	42

e-Table 4. Missing data map of variables including in the multivariable analyses

N = 315			
Variable	N Valid	N Missing	% Missing
Age	315	0	0%
Sex	315	0	0%
VAP	315	0	0%
Diabetes mellitus	315	0	0%
Chronic renal failure	315	0	0%
Solid tumor	315	0	0%
Chronic heart disease	315	0	0%
Chronic respiratory disease	315	0	0%
Chronic hepatopathy	315	0	0%
APACHE II at the diagnosis	310	5	1.6%
P. aeruginosa	315	0	0%
Prevalence of MDR pathogen	315	0	0%

Abbreviations: APACHE = acute physiology and chronic health evaluation; MDR = multidrug resistant; VAP = ventilator-associated pneumonia.

e-Table 5. Antimicrobials prescribed in the empirical treatment of patients without septic shock

	No adherence to guidelines N = 52	Adherence to guidelines N = 110	Total N = 162
Beta-lactam, n (%)	9 (17.3)	0 (0.0)	9 (5.6)
Carbapenemic, n (%)	5 (9.6)	0 (0.0)	5 (3.1)
Glycopeptides, n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Linezolid n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Polimixine, n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Quinolone, n (%)	4 (7.7)	0 (0.0)	4 (2.5)
Beta-lactam + aminoglycoside n (%)	0 (0.0)	11 (10.0)	11 (6.8)
Beta-lactam + quinolone, n (%)	0 (0.0)	9 (8.1)	9 (5.6)
Beta-lactam + glycopeptides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Beta-lactam + linezolid, n (%)	2 (3.8)	0 (0.0)	2 (1.2)
Carbapenemic + quinolone, n (%)	0 (0.0)	10 (9.1)	10 (6.1)
Carbapenemic+ aminoglycoside, n (%)	0 (0.0)	7 (6.4)	7 (4.3)
Carbapenemic + glycopeptides, n (%)	3 (5.8)	0 (0.0)	3 (1.9)
Carbapenemic + linezolid, n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Other combination of 2 antibiotics, n (%)	15 (28.8)	0 (0.0)	15 (9.5)
Combination of 3 or 4 antibiotics, n (%)	11 (21.8)	73 (66.4)	84 (51.8)

Definition of abbreviations: MRSA= methicillin-resistant *Staphylococcus aureus*

e-Table 6. Antimicrobials prescribed in the empirical treatment of patients with septic shock

	No adherence to guidelines N = 57	Adherence to guidelines N = 96	Total N = 153
Beta-lactam n (%)	10 (17.5)	0 (0,0)	10 (6.5)
Carbapenemic, n (%)	2 (3.5)	0 (0,0)	2 (1.3)
Glycopeptides, n (%)	2 (5.3)	0 (0,0)	2 (1.3)
Linezolid n (%)	1 (1.8)	0 (0,0)	1 (0.7)
Quinolone, n (%)	2 (3.5)	0 (0,0)	2 (1.3)
Beta-lactam + aminoglycoside n (%)	0 (0.0)	7 (7.3)	7 (4.5)
Beta-lactam + quinolone, n (%)	3 (5.3)	7 (7.3)	7 (4.5)
Beta-lactam + glycopeptides, n (%)	5 (8.8)	0 (0.0)	5 (3.3)
Beta-lactam + linezolid, n (%)	1 (1.8)	0 (0,0)	1 (0.7)
Carbapenemic + quinolone, n (%)	0 (0.0)	3 (3.1)	3 (2.0)
Carbapenemic+ aminoglycoside, n (%)	0 (0.0)	4 (4.2)	4 (2.6)
Carbapenemic + glycopeptides, n (%)	3 (5.3)	0 (0,0)	3 (2.0)
Carbapenemic + linezolid, n (%)	2 (3.5)	0 (0,0)	2 (1.3)
Other combination of 2 antibiotics, n (%)	17 (29.9)	0 (0.0)	17 (13.1)
Combination of 3 or 4 antibiotics, n (%)	9 (15.8)	75 (78.1)	84 (54.9)

Definition of abbreviations: MRSA= methicillin-resistant *Staphylococcus aureus*

e-Table 7. Etiology of HAP/VAP in the group of patients without septic shock. The comparison between non-adherent and adherent patients is reported

Variable	No adherence to guidelines N=52	Adherence to guidelines N=110	p-value
Microorganism, n (%)			
<i>Staphylococcus aureus</i>	13 (25.0)	33 (30.0)	0.510
<i>Pseudomonas aeruginosa</i>	13 (25.0)	32 (29.1)	0.587
<i>Klebsiella spp.</i>	8 (15.4)	14 (12.7)	0.645
<i>Escherichia coli</i>	4 (7.7)	6 (5.5)	0.581
<i>Streptococcus pneumoniae</i>	1 (1.9)	5 (4.5)	0.409
<i>Enterobacter spp.</i>	4 (7.7)	6 (5.5)	0.581
<i>Serratia spp.</i>	6 (11.5)	4 (3.6)	0.051
<i>Proteus spp.</i>	1 (1.9)	1 (0.9)	0.585
<i>Stenotrophomonas spp.</i>	3 (5.8)	9 (8.2)	0.584
<i>Aspergillus spp.</i>	2 (3.8)	5 (4.5)	0.832
Respiratory viruses	0 (0.0)	2 (1.8)	0.328
Others	6 (11.5)	9 (8.2)	0.491
MDR pathogens, n (%)			
<i>Pseudomonas aeruginosa</i>	4 (7.7)	11 (10.0)	0.636
Methicillin-resistant <i>Staphylococcus aureus</i>	4 (7.7)	9 (8.2)	0.915
MDR <i>Enterobacteriaceae</i>	7 (13.5)	6 (5.5)	0.080
XDR pathogens	10 (19.2)	12 (10.9)	0.149
PDR <i>Acinetobacter baumannii</i>	0 (0.0)	0 (0.0)	-

Definition of abbreviations: MDR = multidrug resistant; spp. = species; PDR = pandrug resistant; XDR = extensively drug resistant.

e-Table 8. Etiology of HAP/VAP in the group of patients with septic shock. The p-value for the comparison between the two treatment groups is reported.

Variable	No adherence to guidelines N=57	Adherence to guidelines N=96	p-value
Microorganism, n (%)			
<i>Staphylococcus aureus</i>	19 (33.3)	19 (19.8)	0.001
<i>Pseudomonas aeruginosa</i>	12 (21.1)	46 (47.9)	0.061
<i>Klebsiella spp.</i>	3 (5.3)	9 (9.4)	0.360
<i>Escherichia coli</i>	7 (12.3)	5 (5.2)	0.116
<i>Streptococcus pneumoniae</i>	6 (10.6)	5 (5.2)	0.218
<i>Enterobacter spp.</i>	2 (3.5)	5 (5.2)	0.627
<i>Serratia spp.</i>	2 (3.5)	3 (3.1)	0.897
<i>Proteus spp.</i>	3 (5.3)	2 (2.1)	0.285
<i>Stenotrophomonas spp.</i>	6 (10.5)	4 (4.2)	0.124
<i>Aspergillus spp.</i>	2 (3.5)	4 (4.2)	0.839
Respiratory viruses	3 (5.2)	3 (3.1)	0.510
Others	4 (7.0)	10 (10.4)	0.481
MDR pathogens, n (%)			
<i>Pseudomonas aeruginosa</i>	3 (5.3)	22 (22.9)	0.004
Methicillin-resistant <i>Staphylococcus aureus</i>	4 (7.7)	9 (8.2)	0.301
MDR <i>Enterobacteriaceae</i>	7 (12.3)	7 (7.3)	0.124
XDR pathogens	3 (5.3)	24 (25.0)	0.002
PDR <i>Acinetobacter baumannii</i>	0 (0.0)	1 (1.0)	0.439

Definition of abbreviations: MDR = multidrug resistant; spp. = species; PDR = pandrug resistant; XDR = extensively drug resistant.

e-Table 9. Antimicrobials prescribed in the targeted treatment of patients without septic shock

	No adherence to guidelines N = 52	Adherence to guidelines N = 110	Total N = 162
Beta-lactam, n (%)	5 (9.6)	1 (0.9)	6 (3.7)
Carbapenemic, n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Glycopeptides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Linezolid, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Macrolide, n (%)	1 (1.9)	0 (0.0)	1 (0.6)
Quinolone, n (%)	1 (1.9)	1 (0.9)	2 (1.2)
Beta-lactam + aminoglycoside n (%)	3 (5.8)	14 (12.7)	17 (10.5)
Beta-lactam + quinolone, n (%)	1 (1.9)	11 (10.0)	12 (7.4)
Beta-lactam + glycopeptides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Beta-lactam + linezolid, n (%)	3 (5.8)	3 (2.7)	6 (3.7)
Carbapenemic + quinolone, n (%)	0 (0.0)	2 (1.8)	2 (1.2)
Carbapenemic+ aminoglycoside, n (%)	0 (0.0)	4 (3.6)	4 (2.5)
Carbapenemic + glycopeptides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Carbapenemic + linezolid, n (%)	1 (1.9)	1 (0.9)	2 (1.2)
Other combination of 2 antibiotics, n (%)	10 (19.2)	18 (16.4)	28 (17.3)
Combination of 3 or 4 antibiotics, n (%)	26 (50.0)	55 (50.0)	81 (50.0)
Confirmation of empirical treatment	31 (59.6)	68 (61.8)	99 (61.1)
De-escalation from empirical treatment	12 (23.1)	28 (25.4)	40 (24.7)
Escalation from empirical treatment	9 (17.3)	14 (12.7)	23 (14.2)

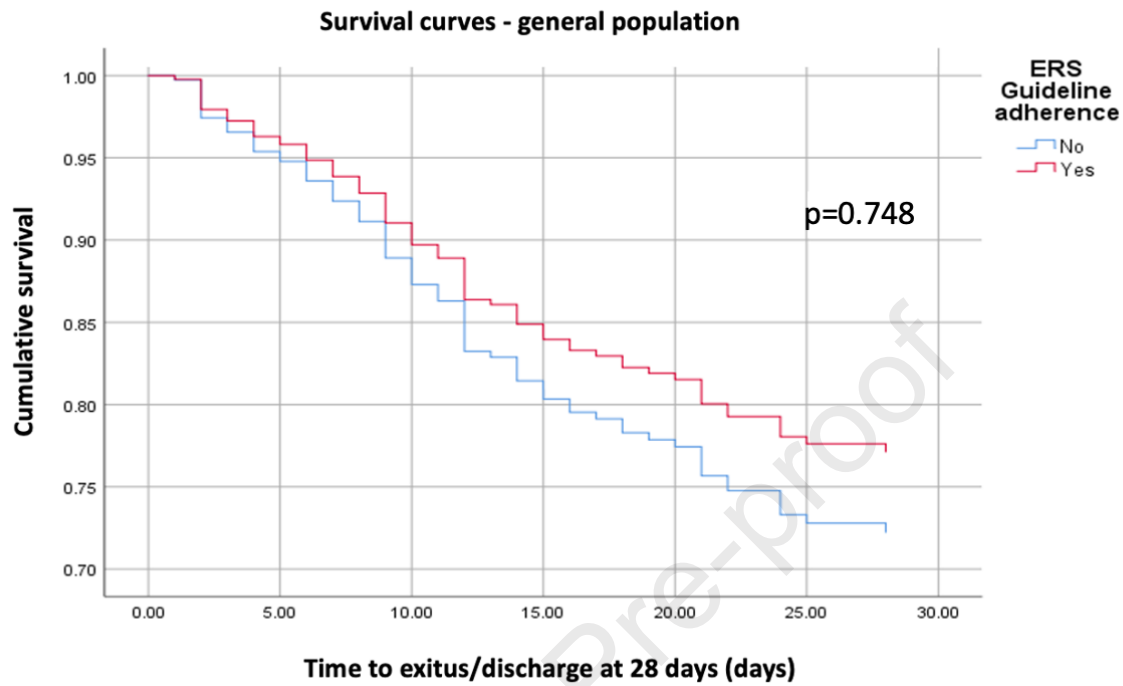
Definition of abbreviations: MRSA= meticilline-resistant Staphylococcus aureus

e-Table 10. Antimicrobials prescribed in the targeted treatment of patients with septic shock

	No adherence to guidelines N = 57	Adherence to guidelines N = 96	Total N = 153
Beta-lactam n (%)	6 (10.5)	1 (1.0)	7 (4.6)
Carbapenemic, n (%)	2 (3.5)	2 (2.1)	4 (2.6)
Glycopeptides, n (%)	1 (1.8)	1 (1.0)	2 (1.3)
Linezolid, n (%)	1 (1.8)	0 (0.0)	1 (0.7)
Quinolone, n (%)	2 (3.5)	1 (1.0)	3 (2.0)
Aminoglycoside n (%)	1 (1.8)	0 (0.0)	1 (0.7)
Beta-lactam + aminoglycoside n (%)	1 (1.8)	7 (7.3)	8 (5.2)
Beta-lactam + quinolone, n (%)	5 (8.8)	6 (6.3)	11 (7.2)
Beta-lactam + glycopeptides, n (%)	2 (3.5)	1 (1.0)	3 (2.0)
Beta-lactam + linezolid, n (%)	0 (0.0)	2 (2.1)	2 (1.3)
Carbapenemic + quinolone, n (%)	1 (1.8)	4 (4.2)	5 (3.3)
Carbapenemic+ aminoglycoside, n (%)	1 (1.8)	4 (4.2)	5 (3.3)
Carbapenemic + glycopeptides, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Carbapenemic + linezolid, n (%)	1 (1.8)	0 (0.0)	1 (0.7)
Other combination of 2 antibiotics, n (%)	10 (17.5)	18 (19.8)	28 (18.3)
Combination of 3 or 4 antibiotics, n (%)	23 (40.4)	49 (51.0)	72 (47.0)
Confirmation of empirical treatment	40 (70.2)	65 (67.7)	105 (68.6)
De-escalation from empirical treatment	11 (19.3)	24 (25.0)	35 (22.9)
Escalation from empirical treatment	6 (10.5)	7 (6.3)	13 (9.6)

Definition of abbreviations: MRSA= meticilline-resistant Staphylococcus aureus

e-Figure 1. Survival curves related to 28-day mortality for the two cohorts of patients treated or not according to guidelines.



Abbreviation list:

ventilator-associated pneumonia (VAP)

hospital-acquired pneumonia (HAP)

Intensive care unit (ICU)

European Respiratory Society (ERS)

European Society of Intensive Care Medicine (ESICM)

European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

Asociación Latinoamericana del Tórax (ALAT)

Acute Physiology and Chronic Health Evaluation (APACHE)

multidrug resistant (MDR)

confidence intervals (CIs)

median interquartile range [IQR])

Sequential Organ Failure Assessment (SOFA)

Clinical Pulmonary Infection Score (CPIS)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	-	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6	
Bias	9	Describe any efforts to address potential sources of bias	5-6	
Study size	10	Explain how the study size was arrived at	5	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7	
		(b) Describe any methods used to examine subgroups and interactions	7	
		(c) Explain how missing data were addressed	7-8	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	8	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	-	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	
		(b) Give reasons for non-participation at each stage	8	
		(c) Consider use of a flow diagram		Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9	Table 2
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10	Table 3
		(b) Report category boundaries when continuous variables were categorized	-	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12	Table 4-5
Discussion				
Key results	18	Summarise key results with reference to study objectives	12-13	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14	
Generalisability	21	Discuss the generalisability (external validity) of the study results	14	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.