

ORIGINAL ARTICLE

Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2013-203384>).

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Received 6 February 2013

Revised 9 April 2013

Accepted 16 May 2013

To cite: Aliberti S, Cilloniz C, Chalmers JD, et al. *Thorax* Published Online First: [please include Day Month Year] doi:10.1136/thoraxjnl-2013-203384

ABSTRACT

Background Probabilistic scores have been recently suggested to identify pneumonia caused by multidrug-resistant (MDR) bacteria. The aim of the study was to validate both Aliberti and Shorr scores in predicting MDR pneumonia, comparing them with healthcare associated pneumonia (HCAP) classification.

Methods Two independent European cohorts of consecutive patients hospitalised with pneumonia were prospectively evaluated in Barcelona, Spain (BC) and Edinburgh, UK (EC). Data on admission and during hospitalisation were collected. The predictive value of the three scores was explored for correctly indicating the presence of MDR pneumonia via a receiver-operating characteristic (ROC) curve.

Results A total of 1591 patients in the BC and 1883 patients in the EC were enrolled. The prevalence of patients with MDR pathogen among those with isolated bacteria was 7.6% in the BC and 3.3% in the EC. The most common MDR pathogen found in both cohorts was MRSA, followed by MDR *P aeruginosa*. A significantly higher prevalence of MDR bacteria was found among patients in the intensive care unit (ICU). The two probabilistic scores, and particularly the Aliberti one, showed an area under the ROC curve higher than the HCAP classification in predicting MDR pneumonia, especially in the ICU.

Conclusions Risk scores able to identify MDR pneumonia could help in developing strategies for antimicrobial stewardship.

INTRODUCTION

The presence of multidrug-resistant (MDR) organisms causing pneumonia in the community has emerged over the past decades as a critical problem.¹ Studies performed in the USA clearly documented the increasing prevalence of resistant organisms in patients with community-acquired pneumonia (CAP).² Data from European studies are limited and generally suggest a low frequency of MDR organisms in patients coming from the community with pneumonia.³⁻⁴ Two probabilistic scores have been developed to assess the potential for MDR pathogens in CAP patients: the Aliberti score was prospectively derived from a European cohort of patients with CAP, while the Shorr score was derived from a retrospective analysis of patients with CAP in the USA.³⁻⁵ However, neither

Key messages

What is the key question?

Can we use probabilistic scores to predict the presence of multidrug-resistant (MDR) organisms in hospitalised patients coming from the community with pneumonia?

What is the bottom line?

Two probabilistic scores perform better than the healthcare-associated pneumonia classification in predicting the presence of pneumonia due to MDR bacteria in patients hospitalised both in the ward and in the intensive care unit.

Why read on?

The application of risk scores able to predict the presence of a MDR pneumonia in patients coming from the community could help to balance the need to treat infections appropriately while avoiding the overuse of broad-spectrum antibiotics.

score has been prospectively validated in large and independent European cohorts of CAP patients.

The aims of the present study were (a) to externally validate the Aliberti and Shorr scores in predicting pneumonia caused by MDR bacteria and to compare them with the healthcare-associated pneumonia (HCAP) classification; (b) to evaluate the prevalence of *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and other MDR bacteria in two independent European cohorts of hospitalised patients coming from the community with pneumonia; and (c) to study characteristics and clinical outcomes of patients with pneumonia caused by MDR versus non-MDR bacteria.

MATERIALS AND METHODS

Two independent European cohorts of consecutive patients coming from the community and admitted with a diagnosis of pneumonia were prospectively evaluated in Barcelona, Spain, and Edinburgh, UK. The Barcelona cohort (BC) included patients admitted with a diagnosis of pneumonia to the Hospital Clínic in Barcelona, Spain, between January 2007 and March 2012. Patients who were

Respiratory infection

hospitalised in the previous 21 days, as well as those with a diagnosis of active tuberculosis or infection with fungi were excluded from the study. The Edinburgh cohort (EC) included patients admitted to National Health Service hospitals in **Edinburgh** with a diagnosis of pneumonia between **January 2005** and **December 2009**. Exclusion criteria were (a) immunosuppression, defined as current, >28 days, use of oral prednisolone at any dose or other immunosuppressive drugs or (b) patients with solid organ transplantation; (c) known thoracic malignancy and (d) patients in whom active treatment was not considered appropriate; (e) hospitalisation in the preceding 14 days; and (f) patients who developed pneumonia >48 h after hospital admission.

Microbiological testings were conducted according to British Thoracic Society and European Respiratory Society recommendations. **MRSA**, ***P aeruginosa*** resistant to antipseudomonal penicillins, cephalosporins, carbapenems and quinolones, ***Stenotrophomonas maltophilia***, **vancomycin-resistant *Enterococcus***, ***Acinetobacter baumannii***, **Enterobacteriaceae** producing extended-spectrum B-lactamases (ESBL) and other non-fermenting Gram-negative bacilli were considered to be MDR pathogens. Among patients with isolated bacteria, two study groups were identified: patients whose pneumonia was caused by at least one MDR bacteria and those whose pneumonia was caused only by non-MDR bacteria. Among patients with isolated bacteria, three risk scores were evaluated and tested against the isolation of MDR bacteria: the Aliberti and Shorr scores and HCAP classification, see online supplementary material.

The χ^2 test was used to compare categorical data between groups. The Mann-Whitney U test was used to compare two groups of non-parametric data. The area under the receiver-operating characteristic (ROC) curves, together with its 95% CIs, was calculated for the three scores.

RESULTS

A total of 1591 consecutive patients with pneumonia (63% men, median age: 70 years) in BC and 1883 patients (51% men, median age: 68 years) in EC were enrolled during the study periods. Demographics, severity of disease, clinical, laboratory and radiological findings on admission, initial antibiotic therapy and clinical outcomes of both study populations are summarised in the online supplementary material. A causative organism for pneumonia was identified in 691 patients (43%) in BC and in 557 patients (30%) in EC.

The prevalence of patients with at least one MDR pathogen was 2.4% in BC and 0.9% in EC and among those with isolated bacteria, 7.6% in BC and 3.3% in EC. The most common MDR pathogen found in both cohorts was MRSA, followed by MDR

P aeruginosa and **ESBL+** pathogens. Characteristics and outcomes of patients whose pneumonia was due to *P aeruginosa* and MRSA are reported in the online supplementary material. A significantly higher prevalence of MDR bacteria was found among patients admitted to the intensive care unit (ICU) in comparison with those admitted to the ward in both cohorts. In comparison with patients with pneumonia caused by non-resistant bacteria, those with a least one MDR bacteria came more frequently from a nursing home, had been more frequently hospitalised in the prior 90 days, were more immunosuppressed (in BC) and had more severe pneumonia on admission in terms of use of mechanical ventilation, acidemia and alteration of gas exchange. Patients with MDR bacteria also showed a significant longer hospital stay, a significant higher frequency of treatment failure and higher mortality, up to 40%, in comparison with subjects with a pneumonia caused by a non-resistant bacteria.

At least one risk factor for MDR organisms was identified in 41% and 31% of the patients in BC and EC, respectively. The ROC curves evaluating the performance of the three scores with respect to the presence of MDR bacteria are reported in table 1 for both study cohorts. In the entire BC, the area under the ROC curve for the Aliberti score was 0.89, the Shorr score was 0.89 and HCAP classification was 0.77. In the entire EC, the area under the ROC curve for the Aliberti score was 0.77, the Shorr score was 0.75 and HCAP classification was 0.66. The performance of the three scores was evaluated among patients admitted to ICU and among those admitted to the ward. The Aliberti score showed a higher area under the curve in both populations of patients in BC admitted to ICU and ward patients and in ICU patients in EC in comparison with the Shorr score and HCAP classification.

DISCUSSION

This study shows a low prevalence of MDR bacteria in CAP patients in three hospitals in a single Scottish region in Northern Europe and in one hospital in Barcelona in Southern Europe. Patients suffering from pneumonia caused by MDR bacteria show more severe disease on presentation and worse clinical outcomes in comparison with those with non-MDR bacteria. Finally, two probabilistic scores (Aliberti and Shorr) perform better than HCAP classification in predicting the presence of pneumonia due to MDR bacteria. The Aliberti score shows a slightly better performance in both the entire population of patients with pneumonia and among ICU patients in comparison with the Shorr score.

Our data confirm a low percentage of pneumonia caused by MDR bacteria in Europe: 7.6% in Spain and 3.3% in the UK. A difference seems to be emerging in the prevalence of CAP

Table 1 Area under the receiver-operating characteristic curve in the entire population, patients admitted to the intensive care unit (ICU) and those admitted to the ward in the Barcelona cohort (BC) and Edinburgh cohort (EC) according to the Aliberti and Shorr scores and healthcare-associated pneumonia (HCAP) classification

Study cohorts	Score	Area under the curve		
		Entire population	ICU patients	Ward patients
BC	Aliberti score	0.89 (0.83–0.95)	0.85 (0.75–0.96)	0.91 (0.84–0.98)
	Shorr score	0.89 (0.82–0.96)	0.77 (0.58–0.96)	0.89 (0.80–0.97)
	HCAP classification	0.77 (0.69–0.83)	0.83 (0.71–0.95)	0.75 (0.68–0.83)
EC	Aliberti score	0.77 (0.71–0.84)	0.79 (0.68–0.89)	0.77 (0.70–0.84)
	Shorr score	0.75 (0.68–0.81)	0.74 (0.63–0.86)	0.80 (0.73–0.87)
	HCAP classification	0.66 (0.59–0.73)	0.60 (0.49–0.71)	0.73 (0.64–0.82)

caused by MDR bacteria between the USA and Europe. Reasons for this finding could be related to the enrolment of **more severe** and immunocompromised patients in the **US** studies as well as the presence of some differences in the organisation of healthcare systems in terms of decentralisation of care on the territory and different policies and guidelines related to the use of antibiotics (11, 18). These final considerations could be also responsible for the slight **difference** in **MDR** prevalence between **Southern** (Spain and Italy) Europe and **Northern** (UK) Europe (6).

We showed a superiority of both Aliberti and Shorr scores in comparison with HCAP classification. Differences in ROC values of both Aliberti and Shorr scores between the two study cohorts could be mainly due to the **difference** in **prevalence** of MDR bacteria. The knowledge of population characteristics, the presence and degree of immunosuppression and background resistance rates is therefore critical to optimise the use of these scores.

We found a **high prevalence of MDR** bacteria among patients with pneumonia who were **admitted to ICU** and, particularly, those who received mechanical **ventilation**. These findings raise the **question** whether **all severe patients** with pneumonia admitted to ICU **should** receive a **broad-spectrum** antibiotic treatment against MDR bacteria **regardless** of the presence of **risk factors**. Although in daily clinical practice patient disease severity often leads physicians to prescribe a broad-spectrum antibiotic coverage in order to prevent excess mortality due to treatment failure, a probabilistic approach based on score system could be suggested. The **Aliberti** score has been proved to have a role in evaluating the presence of MDR infection also in CAP patients admitted to ICU.

In conclusion, a low prevalence of MDR organisms could be found among patients coming from the community and who are hospitalised because of an episode of pneumonia, with **MRSA** identified as the **most frequent pathogen**. The application in clinical practice of risk scores able to predict the presence of

MDR pneumonia in patients coming from the **community** could help in developing strategies for healthcare workers to balance the need to treat infections appropriately while avoiding the overuse of broad-spectrum antibiotics.

Acknowledgements The authors acknowledge the assistance of Anna Maria Brambilla, MD (Emergency Medicine Department, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy).

Contributors SA proposed the initial idea for the study, designed the study, performed data analysis and interpretation and wrote the first and all drafts. CC and JDC designed the study, recruited patients, managed the data, participated in data analysis and interpretation. AMZ conducted the statistical analysis, data analysis and interpretation. FB, AT, RC, PT and AP participated in the analysis and interpretation of the results. FB and AT designed and coordinated the study. All authors interpreted the data and contributed to the write-up of all the drafts.

Funding This work was supported by Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028). JDC was supported by a fellowship from the Medical Research Council (UK). All authors have no conflict of interest.

Competing interests None.

Ethics approval Institutional review board of the Hospital Clinic.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lim WS, Baudouin SV, George RC, *et al*. Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;64 (Suppl 3):iii1–55.
- 2 Kollef MH, Shorr A, Tabak YP, *et al*. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005;128:3854–62.
- 3 Aliberti S, Di Pasquale M, Zanaboni AM, *et al*. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012;54:470–8.
- 4 Chalmers JD, Taylor JK, Singanayagam A, *et al*. Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. *Clin Infect Dis* 2011;53:107–13.
- 5 Shorr AF, Zilberberg MD, Micek ST, *et al*. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 2008;168:2205–10.



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Thorax published online June 17, 2013
doi: 10.1136/thoraxjnl-2013-203384

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TABLES

Table 1. Scoring systems to evaluate the presence of multidrug resistant pathogens in patients with pneumonia hospitalized from the community

The Aliberti score		The Shoor score		HCAP classification*	
Variable	Point	Variable	Point	Variable	Point
No risk factors for MDR pathogen (including comorbidities)	0	Recent hospitalization	4	None of the following	0
At least one among: cerebrovascular disease; diabetes; chronic obstructive pulmonary disease; antimicrobial therapy in preceding 90 days; immunosuppression; home wound care; home infusion therapy (including antibiotics)	0.5	Nursing home or extended care facility	3	At least one among: Hospitalization for at least 48 hours during the preceding 90 days; Nursing home or extended care facility; Hemodialysis; Immunosuppression; Antimicrobial therapy in the preceding 90 days	1
Nursing home or	3	Chronic	2		

extended care facility		hemodialysis	
Hospitalization for two days or more in the preceding 90 days	4	Admitted to the ICU within 24 hours of evaluation in the ED	1
Chronic renal failure	5		

MDR: Multidrug resistant; ICU: intensive care unit; ED: Emergency Department; * A comprehensive definition of healthcare associated pneumonia (HCAP) was used [5].

Table 2. Demographics, severity of disease, clinical, laboratory, radiological findings on admission, initial empiric antibiotic treatment and clinical outcomes of the study cohorts.

Characteristic	Barcelona Cohort	Edinburgh Cohort
n. (%)	1591 (100)	1883 (100)
Demographics, n. (%)		
Male	1001 (63)	961 (51)
Age, median (IQR) years	70 (50-82)	68 (62-79)
Active smokers	406 (26)	650 (35)
Active alcohol abuser	240 (15)	189 (10)
Comorbidities, n. (%)		
Congestive heart failure	268 (17)	390 (21)
COPD	208 (13)	496 (26)
Diabetes mellitus	288 (18)	245 (13)
Aspiration	203 (13)	318 (17)
Neurological diseases	133 (9)	226 (12)
Cerebrovascular disease	62 (3·9)	191 (10)
Chronic renal failure	96 (6)	124 (7)
Liver disease	140 (9)	98 (5)
Bronchiectasis	59 (4)	61 (3)
Asthma	60 (4)	48 (3)
Severity on admission, n. (%)		

Admission to ICU	198 (12)	181 (10)
Admission to RH DU	123 (8)	132 (7)
PSI Risk Class IV and V	784 (49)	667 (50)
Altered mental status	299 (19)	281 (15)
Invasive Mechanical ventilation	88 (6)	121 (7)
Non-Invasive Mechanical Ventilation	38 (2.4)	86 (5)
Septic shock	80 (5)	98 (5)
Physical findings on admission, n. (%)		
Temperature, median (IQR) °C	37.2 (36.3-38.1)	37.5 (36.9-38.4)
Hypotension [#]	238 (15)	444 (24)
Heart rate, median (IQR) beats/minute	98 (84-111)	104 (89-118)
Heart rate > 125 beats/minute	119 (8)	252 (13)
Respiratory Rate, median (IQR)	24 (20-28)	25 (20-32)
breath/minute		
Respiratory Rate > 30 breath/minute	273 (17)	451 (24)
Alteration of gas exchange*	701 (44)	697 (37)
SpO ₂ , median (IQR)	93 (90-95)	94 (91-95)
Laboratory values, median (IQR)		
Arterial pH	7.44 (7.40-7.47)	7.43 (7.40-7.45)
Arterial pH < 7.35, n. (%)	121 (8)	247 (13)
White blood cells, cell/L ⁻¹	12000 (8500-16900)	14200 (9200-19500)
Platelet, cell/L ⁻¹	237000 (178000-244000)	322000 (192000-306000)

Hematocrit, %	40 (37-43)	39.1 (35-42)
Creatinine, mg/dL	1 (0·8-1·4)	1 (0·8-1·4)
Glucose, mg/dL	122 (103-156)	117 (101-142)
Sodium, mEq/L	136 (133-139)	137 (134-140)
C-reactive protein, mg/dL	17 (8·7-27)	16 (7·5-30)
Radiology findings on CXR, n (%)		
Pleural effusion	224 (14)	385 (20)
Initial empiric antibiotic treatment, n (%)		
Ceftriaxone	990 (62)	305 (16)
Levofloxacin	925 (58)	0
Azithromycin	465 (29)	0
Clarithromycin	1 (0·06)	1099 (69)
Amoxicillin/clavulanate	140 (8·8)	893 (47)
Amoxicillin	0	652 (35)
Clindamycin	36 (2·3)	12 (0·6)
Piperacillin/tazobactam	28 (1·8)	56 (2·9)
Doxycycline	0	55 (2·9)
Meropenem	19 (1·2)	9 (0·5)
Ciprofloxacin	15 (0·9)	31 (1·6)
Trimetoprin/sulfametazol	11 (0·7)	10 (0·5)
Vancomycin	11 (0·7)	16 (0·8)
Others	52 (3·3)	112 (5·9)
Clinical outcomes, n (%)		

Length of stay in the hospital, median8 (5-12)		5 (3-11)
(IQR) days		
Treatment failure	144 (9)	201 (11)
In-hospital mortality	91 (6)	169 (9)

IQR: interquartile range; COPD: Chronic obstructive pulmonary disease; PSI: pneumonia severity index; CAP: community-acquired pneumonia; SpO₂: oxygen saturation; PaCO₂: arterial partial pressure of carbon dioxide; PaO₂: arterial partial pressure of oxygen; ICU: intensive care unit; RHDU: respiratory high dependency unit; PSI: Pneumonia Severity Index; CXR: chest radiograph; #Hypotension defined as systolic blood pressure <90 mmHg or diastolic blood pressure < 60 mmHg; *Alteration of gas exchange defined as PaO₂ < 60 mm Hg, PaO₂/fraction of inspired oxygen < 300, or O₂saturation < 90%.

Table 3. Microbiological findings in the study cohorts

Characteristic	Barcelona Cohort	Edinburgh Cohort
n. (%)	1591 (100)	1883 (100)
Patients with at least one isolated pathogen	691 (43)	557 (30)
Patients with at least one MDR bacteria	38 (2.4)	18 (0.9)
MDR bacteria		
Methicillin-resistant <i>S. aureus</i>	25	7
<i>P. aeruginosa</i> MDR+	12	3
<i>E. coli</i> ESBL +	3	4
<i>Proteus mirabilis</i> ESBL +	2	0
<i>K. pneumoniae</i> ESBL+	2	1
<i>Enterobacter</i> MDR+	1	0
<i>Enterococcus</i> MDR+	1	0
<i>Stenotrophomonas maltophilia</i>	1	3
<i>Acinetobacter baumannii</i>	1	0
Non-MDR bacteria		
<i>S. pneumoniae</i>	327	332
<i>H. influenzae</i>	34	54
<i>Legionella pneumophila</i>	28	19
<i>P. aeruginosa</i> MDR-	20	6
Methicillin-sensible <i>S. aureus</i>	15	44
<i>M. pneumoniae</i>	15	28
<i>C. pneumoniae</i>	9	3

<i>K. pneumoniae</i> ESBL-	7	8
<i>Coxiella</i>	5	0
<i>E. coli</i> ESBL -	5	10
<i>M. Catarrhalis</i>	4	6
<i>Proteus mirabilis</i> ESBL -	2	1
<i>Enterococcus</i> MDR-	2	0
<i>Enterobacter</i> MDR-	1	1
<i>Other bacteria</i>	36	12
Virus		
<i>Influenza A virus</i>	16	32
<i>Rinovirus</i>	16	1
<i>Parainfluenza virus</i>	5	2
<i>Adenovirus</i>	3	2
<i>Influenza B virus</i>	2	3
<i>Coronavirus</i>	2	0
<i>Respiratory syncytial virus</i>	2	2
<i>Other virus</i>	116	1
Other		
<i>Pneumocystis</i>	40	0
<i>Nocardia</i>	1	0
Polymicrobial infection	72 (4·5)	30 (1·6)
Bacteremia	129 (8)	88 (5)

ESBL: extended-spectrum beta-lactamase; MDR: multidrug resistant

Table 4. Characteristics and outcomes of patients with and without a multidrug- resistant (MDR) bacteria in the Barcelona (BC) and Edinburgh cohort (EC).

Characteristic	Barcelona Cohort		p	Edinburgh Cohort		p
	MDR bacteria	Non-MDR bacteria		MDR bacteria	Non-MDR bacteria	
n. (%)	38 (100)	458 (100)		18 (100)	673 (100)	
Demographics						
Male	29 (76)	275 (60)	0.048	11 (61)	359 (53)	0.5
Age, median (IQR) years	58 (44-81)	64 (47-79)	0.778	69 (59-79)	66 (51-77)	0.3
Characteristics on admission						
Residency in a nursing home or extended care facility	9 (24)	15 (3.3)	<0.001	3 (17)	35 (5.2)	0.04
Hospitalization for 2 days or more in the preceding 90 days	26 (68)	19 (4.1)	<0.001	5 (28)	63 (9.4)	0.01
Immunosuppression	13 (34)	62 (14)	0.001	NA	NA	NA
Liver disease	9 (24)	53 (12)	0.032	2 (11)	39 (5.8)	0.3
Pneumonia Severity Index, median (IQR)	3.5 (2.75-4)	3 (2-4)	0.781	5 (4-5)	4 (2-4)	<0.0001

Use of mechanical ventilation on admission	9 (24)	54 (12)	0·034	6 (33)	74 (11)	0·003
Acidemia on admission	6 (24)	35 (9·8)	0·027	5 (28)	82 (12)	0·05
Alteration of gas exchange	21 (84)	216 (61)	0·023	12 (67)	259 (39)	0·02
Septic Shock	5 (13)	37 (8·3)	0·309	5 (28)	53 (8)	0·003
Outcomes						
Length of stay in the hospital	16 (12-24)	8 (5-13)	0·001	19 (9-29)	7 (3-15)	<0·0001
Treatment failure [#]	16 (42)	35 (7·6)	<0·001	7 (39)	72 (11)	<0·0001
Mortality*	4 (11)	19 (4·1)	0·072	7 (39)	61 (9·1)	<0·0001

IQR: interquartile range; NA: not applicable; [#]Treatment failure defined as a clinical deterioration within 72 hours of treatment caused by one or more of the following: hemodynamic instability, appearance or impairment of respiratory failure, radiographic progression, or the appearance of new metastatic infectious foci; *In-hospital mortality for the BC and 30-day mortality for the EC. NB: patients with immunosuppression were excluded from the EC.

Table 5. Prevalence of patients with risk factors for multidrug-resistant pathogens among the two study cohorts

Risk factor for MDR	Barcelona Cohort	Edinburgh Cohort
n. (%)	1593 (100)	1883 (100)
Antimicrobial therapy in preceding 90 days	299 (19)	297 (16)
Residency in a nursing home or extended care facility	103 (7)	128 (7)
Chronic renal failure	96 (6)	124 (7)
Hospitalization for 2 days or more in the preceding 90 days	79 (5)	156 (8)
Chronic dialysis within 30 days	5 (0.3)	18 (0.9)
Immunosuppression*	199 (13)	NA

MDR: multi-drug resistant pathogen; NA: not applicable; *Immunosuppression defined by the presence of at least one among: neutropenia after chemotherapy or bone marrow transplantation, HIV infection, immunosuppressive therapy, chemotherapy, transplantation, cytotoxic therapy, chronic systemic steroid therapy (prednisone > 10 mg daily).

Table 6. Area under the receiving operator characteristics curve in the entire population, patients admitted to the intensive care unit (ICU) and those admitted to the ward in the Barcelona and Edinburgh cohorts according to the Aliberti and Shorr scores and healthcare-associated pneumonia (HCAP) classification.

Study cohorts	Score	Area under the curve		
		Entire population	ICU patients	Ward patients
Barcelona cohort	Aliberti score	0.89 (0.83-0.95)	0.85 (0.75-0.96)	0.91 (0.84-0.98)
	Shorr score	0.89 (0.82-0.96)	0.77 (0.58-0.96)	0.89 (0.80-0.97)
	HCAP classification	0.77 (0.69-0.83)	0.83 (0.71-0.95)	0.75 (0.68-0.83)
Edinburgh cohort	Aliberti score	0.77 (0.71-0.84)	0.79 (0.68-0.89)	0.77 (0.70-0.84)
	Shorr score	0.75 (0.68-0.81)	0.74 (0.63-0.86)	0.80 (0.73-0.87)
	HCAP classification	0.66 (0.59-0.73)	0.60 (0.49-0.71)	0.73 (0.64-0.82)

Table 7. P value of differences between ROC curves of the three scores in the entire study population according to the two study cohorts

Scores	p value in the BC	p value in the EC
HCAP vs. Aliberti	0.051	0.053
HCAP vs. Shorr	0.076	0.094
Aliberti vs. Shorr	0.55	0.58

FIGURE LEGENDS

Figure 1. Prevalence of multi-drug resistant (MDR) pathogens in the two study cohorts according to the Pneumonia Severity Index and the presence of mechanical ventilation and septic shock on admission

MDR: number of MDR bacteria isolated; Total: total number of bacteria isolated; RC: risk class.

Figure 2. Prevalence of multi-drug resistant (MDR) pathogens in the two study cohorts according to Aliberti and Shorr scores, and healthcare-associated pneumonia (HCAP) classification.

MDR: number of MDR bacteria isolated; Total: total number of bacteria isolated.

Founding

This work was supported by Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028).

JDC was supported by a fellowship from the Medical Research Council (UK). All authors have no conflict of interest.

REFERENCES

- 1 Lim WS, Baudouin SV, George RC, et al. Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;64 Suppl 3:iii1–5.
- 2 Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005;128:3854–3862.
- 3 Micek ST, Kollef KE, Reichley RM, et al. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. *Antimicrob Agents Chemother* 2007;51:3568–3573.
- 4 Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? *Chest* 2010;137:1283–1288.
- 5 American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
- 6 Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia.

Clin Infect Dis 2012;**54**:470–478.

7 Chalmers JD, Taylor JK, Singanayagam A, et al. Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. Clin Infect Dis 2011;**53**:107–113.

8 von Baum H, Welte T, Marre R, et al. Community-acquired pneumonia through Enterobacteriaceae and Pseudomonas aeruginosa: Diagnosis, incidence and predictors. Eur Respir J 2010;**35**:598–605.

9 Carratalà J, Mykietiuk A, Fernández-Sabé N, et al. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. Arch Intern Med 2007;**167**:1393–1399.

10 Kollef MH, Micek ST. Patients hospitalized with pneumonia: determining the need for broad-spectrum antibiotic therapy. Clin Infect Dis 2012;**54**:479–482.

11 Shorr AF, Zilberberg MD, Micek ST, et al. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. Arch Intern Med 2008;**168**:2205–2210.

12 Chalmers JD, Singanayagam A, Hill AT. Systolic blood pressure is superior to other haemodynamic predictors of outcome in community acquired pneumonia. Thorax 2008;**63**:698–702.

13 Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;**336**:243–250.

14 Menendez R, Torres A, Zalacain R et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 2004;**59**:960–965.

15 Woodhead M, Blasi F, Ewig S, et al. European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of

adult lower respiratory tract infections. *Eur Respir J* 2005;**26**:1138–1180.

16 National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing, 14th informational supplement. Approved standard M100–S14. Wayne, PA: National Committee for Clinical Laboratory Standards 2004.

17 Menéndez R, Torres A, Aspa J, et al. Sociedad Española de Neumología y Cirugía Torácica. [Community acquired pneumonia. New guidelines of the Spanish Society of Chest Diseases and Thoracic Surgery (SEPAR)]. *Arch Bronconeumol* 2010;**46**:543–558.

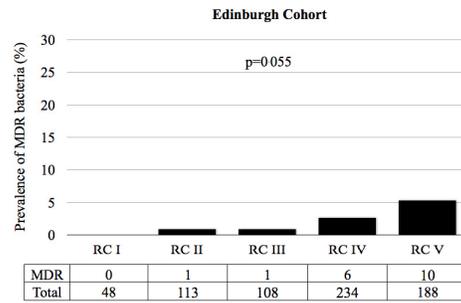
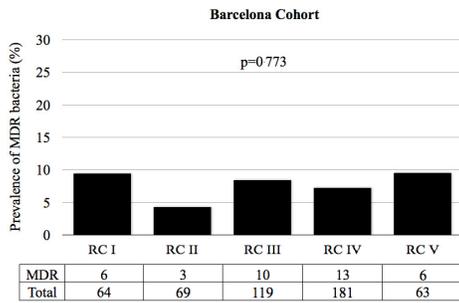
18 Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;**12**:77.

19 Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012;**54**:193–198.

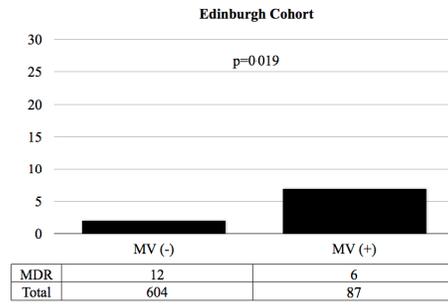
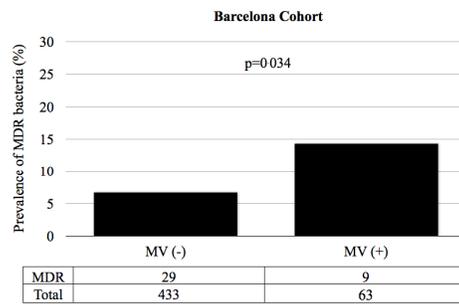
20 Shindo Y, Sato S, Maruyama E, et al.. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. *Chest* 2009;**135**:633–640.

21 Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? *Chest* 2010;**137**:1283–1288.

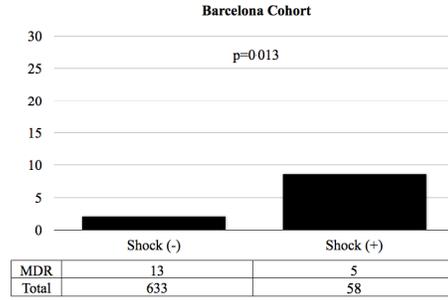
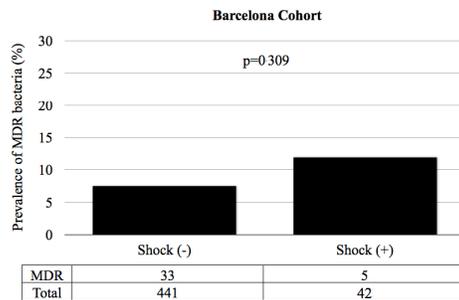
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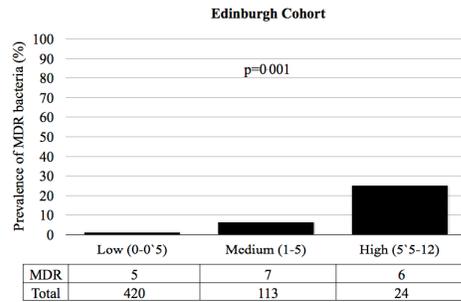
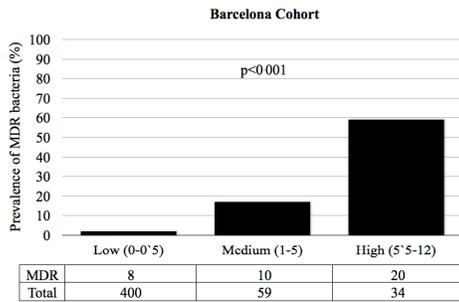
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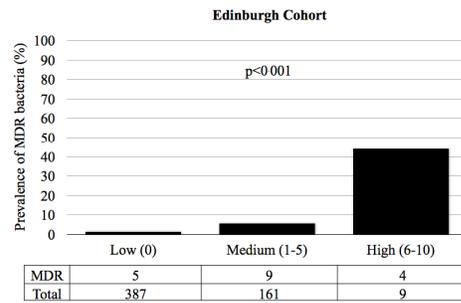
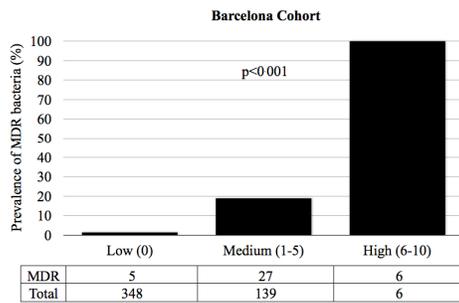
Shock



Aliberti Score



Shorr Score



HCAP classification

