ORIGINAL ARTICLE

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

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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.

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.

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 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 Clinìc in Barcelona, Spain, between January 2007 and March 2012. Patients who were

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 baumanii*, 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

		Area under the curve		
Study cohorts	Score	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.

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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.

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Competing interests None.

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Title

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

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What is the key question?

Can we use probabilistic scores to predict the presence of multidrug-resistant (MDR) organisms in hospitalized 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 hospitalized 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.

Abstract

Background: Probabilistic scores have been recently suggested to identify pneumonia caused by multidrug-resistant (MDR) bacteria. The aim of the study was to evaluate the prevalence and characteristics of MDR pneumonia in hospitalized patients coming from the community and 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 hospitalized with pneumonia were prospectively evaluated in Barcelona, Spain (BC) and Edinburgh, UK (EC). Data on admission and during hospitalization 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 1,591 patients in the BC and 1,883 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 United States of America (US) clearly documented the increasing prevalence of resistant organisms in patients with community-acquired pneumonia (CAP).[2-4] A new classification of pneumonia, health-care associated pneumonia (HCAP), has been introduced in 2005 to identify different risk factors for resistant organisms related to frequent contact with the health system.[5] Studies performed after 2005 confirmed differences between HCAP and CAP patients in terms of causative organisms, severity of the disease and clinical outcomes.[3]

The scenario outside the US seems to be quite different. Data from European studies are limited and generally suggest a low frequency of MDR organisms in patients coming from the community with pneumonia.[6-9] Some concerns have also been raised on the HCAP criteria as a screening test for MDR pathogens, mainly because their application could lead to substantial misclassification of patients unnecessarily receiving broad-spectrum antibiotics.[10]

Specific and weighed analysis of each risk factor for MDR organisms has been recently suggested. 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 US.[6,11] However, neither 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 HCAP classification; b) to evaluate the prevalence of *P. aeruginosa*, methicillin-resistant *S. aureus*

(MRSA) and other MDR bacteria in two independent European cohorts of hospitalized patients coming from the community with pneumonia; b) to study characteristics and clinical outcomes of patients with pneumonia caused by MDR vs. non-MDR bacteria.

MATERIALS AND METHODS

Study design and study patients

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 Clinìc in Barcelona, Spain, between January 2007 and March 2012. The Institutional Review Board of the Hospital Clinic approved the study. A written informed consent was waived due to the non-interventional design of the study. Pneumonia was defined as the presence of a new pulmonary infiltrate on a chest radiograph performed on hospital admission *plus* symptoms and signs of low respiratory tract infection without other alternative diagnosis during the follow up. Patients ≥ 18 years of age and satisfying the criteria for pneumonia were included in the study. Patients who were hospitalized 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 NHS hospitals in Edinburgh with a diagnosis of pneumonia between January 2005 and December 2009. The study was approved by the local research ethics committee. The methodology has been previously described.[12] Pneumonia was defined as the presence of a new infiltrate on chest radiograph *plus* three or more of the following signs or symptoms: cough, sputum production, breathlessness, pleuritic chest pain, or signs consistent with pneumonia on auscultation. Exclusion criteria were: a) immunosuppression, defined as current, >28 day, 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) hospitalization in the preceding 14 days; f) patients who developed pneumonia >48 hours after hospital admission.

Data collection and study definitions

The following data were recorded in both cohorts of patients: demographics, past medical history, severity on admission, the pneumonia severity index (PSI), physical, laboratory, and radiological findings on admission, microbiological data, empiric antibiotic therapy, treatment failure, length of stay in the hospital (LOS), and mortality (in-hospital for the BC and 30-day mortality for the EC).[13] LOS was calculated as the number of days from the date of admission to the date of discharge. Treatment failure was defined as clinical deterioration within 72 hours of treatment caused by one or more of the following: hemodynamic instability, worsening or appearance of respiratory failure, radiographic progression, or the appearance of new metastatic infectious foci.[14]

Microbiological analysis and empiric antibiotic therapy

Microbiological testings were conducted according to British Thoracic Society (BTS) and European Respiratory Society recommendations [1,15,16] Microbiological examinations were performed on sputum, urine, and blood during the first 24 hours after admission and according to standard of practice. Pleural aspiration, tracheobronchial aspirates, and bronchoalveolar lavage fluid (BAL), when available, were also collected and cultured. Identification of microorganisms and susceptibility testing were performed according to standard methods. The etiology was considered definite if one of the following criteria was met: positive blood culture in the absence of an apparent extrapulmonary focus; positive bacterial culture of pleural fluid; positive urinary

antigen for *Legionella pneumophila* (Binax Now, Trinity Biotech, Bray, Ireland); positive urinary antigen for *Streptococcus pneumoniae* (Binax Now, Emergo Europe, The Netherlands); a bacterial yield in cultures of valid sputum (> 25 polymorphonuclear cells and < 10 epithelial cells per power field, total magnification x 100) of at least 10^6 CFU/mL, tracheobronchial aspirates of at least 10^5 CFU/mL, bronchoalveolar lavage fluid of at least 10^4 CFU/mL and protected specimen brush cultures of at least 10^3 CFU/mL; seroconversion (a 4-fold rise in IgG titers for *C. pneumoniae* [1:512], *L. pneumophila* or a rise in IgM titers for *C. pneumoniae* [1:32] and *M. pneumoniae* [any titer]) occurred.

All of the tests described above were performed in both cohorts of patients, with the exception of Pneumococcal urinary antigen which was not available in the EC during the study. When two or more microbiological causes were present, the patient was considered to have a polymicrobial infection. Patients for whom no microbiological tests were performed, and patients with negative microbiogical results, were considered to have disease of an unknown etiology.

MRSA, *Pseudomonas aeruginosa* resistant to antipseudomonal penicillins, cephalosporins, carbapenems, and quinolones, *Stenotrophomonas maltophilia*, vancomycin-resistant *Enterococcus*, *Acinetobacter baumanii*, *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. Empiric antibiotic therapy was administered as soon as the diagnosis of pneumonia was reached in accordance with Spanish and BTS guidelines.[1,17]

Risk factors and scores to predict MDR pneumonia

The following risk factors for MDR pathogens were recorded among the study population: hospitalization for two days or more in the preceding 90 days, residency in a nursing home (NH) or long term care facility (LTCF), chronic renal failure and chronic dialysis within 30 days, antimicrobial therapy in preceding 30 days, and immunosuppression. Immunosuppression was collected only in the BC and was 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 (≥ 10 mg of oral prednisolone or equivalent daily for at least two weeks). 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 Table 1.[5,6,11]

Statistical Analysis

All data were analyzed using SPSS (version 19.0; SPSS Inc., Chicago, IL, USA) for Mac. Descriptive statistics of demographic and clinical variables are presented as median (interquartile range -IQR) for continuous variable and categorical data expressed as counts (%). The Chi-squared 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 curves (ROC) together with its 95% confidence intervals (CI) was calculated for the three scores. A test of significance for the difference of the area under two ROC curves was performed using the pROC package of the R environment.[18] A two-tailed p value <0·05 was assumed to represent statistical significance for all analysis.

RESULTS

Study cohorts

A total of 1,591 consecutive patients with pneumonia (63% males, median age: 70 years) in the BC and 1,883 patients (51% males, median age: 68 years) in the 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 summarized in Table 2. The percentage of patients who underwent blood culture, sputum, BAL and urinary antigen investigations were 875 (55%), 391 (25%), 120 (7.5%) and 1124 (71%) respectively in the BC and 1019 (54%), 1084 (58%), 96 (5.1%), and 698 (37%) respectively in the EC. A causative organism for pneumonia was identified in 691 patients (43%) in the BC and in 557 patients (30%) in the EC, see Table 3.

Pneumonia caused by *P. aeruginosa*

Among patients who had a bacteria isolated, the prevalence of *P. aeruginosa* was 6·5% (32/496 patients) in the BC and among those 12 had a MDR *P. aeruginosa*. In the EC cohort, 9 patients (1·6%) had *P. aeruginosa* and among those 3 had a MDR *P. aeruginosa*. At univariate analysis, risk factors associated with a pneumonia caused by *P. aeruginosa* were nursing home residency (p=0·003 in BC), hospitalization in the previous 90 days (p<0·001 in the BC and p=0·01 in EC) and a history of chronic lung disease (p=0·007 in EC). In the BC cohort, patients with *P. aeruginosa* showed a significant higher treatment failure in comparison to those with other bacteria (11/32 patients, 34% vs. 40/464, 8·6%, p<0·001) and a higher, but not statistically

significant, in-hospital mortality (3/32, 9·4%, CI: 0%-21%, vs. 20/464, 4·3%, CI: 2.5%-6.2%, p=0·179). In the EC cohort, 2 out of 9 patients (22%) had treatment failure, compared to 70/548 patients, 13%, p=0·4, and 3 out of 9 patients (33%) died within 30 days, compared to 58/548 patients, 11%, p=0·03.

Pneumonia caused by MRSA

Among patients with a bacterial isolate, the prevalence of MRSA was 4·9% (24/492 patients) in the BC and 1·3% (7/557 patients) in the EC. At univariate analysis, risk factors associated with a pneumonia caused by MRSA in the BC were diabetes (p=0·026), immunosuppression (p=0·011), nursing home residency (p=0·003) and hospitalization in the previous 90 days (p<0·001). In the BC, patients with MRSA showed a significant higher treatment failure in comparison to those infected by other bacteria (10/24 patients, 42% vs. 41/472, 8·7%, p<0·001) and a higher, but not statistically significant, in-hospital mortality (3/24, 13% vs. 20/472, 4·2%, p=0·11). In the EC, the mortality rate was 43% (3/7 patients) compared to 11% (58/550 patients), p=0·007, while treatment failure occurred in 43% (3/7 patients) vs 13% (69/550 patients) p=0·02. Co-infection with MRSA and *P. aeruginosa* was found in 4 patients in the BC.

Pneumonia caused by MDR bacteria

The prevalence of patients with at least one MDR pathogen was 2·4% in the BC and 0·9% in the EC and, among those with isolated bacteria, 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* and ESBL+ pathogens. In the BC, a total of 10 patients had bacteremia caused by MRSA, one patient by Proteus ESBL+, one by E. coli ESBL+ and one by MDR *P. aeruginosa*. Co-infection of MRSA and MDR *P. aeruginosa* was detected in four patients in the BC. In the EC, 4 patients had

a bacteremia caused by MRSA, 2 patients had bacteraemia caused by MDR *E.coli* and 1 patient had *Pseudomonas* bacteraemia. There were no polymicrobial bacteraemias with MDR pathogens, although one patient with MRSA bacteraemia also had a positive throat swab for influenza A.

Characteristics and outcomes of patients with MDR bacteria

Distribution of MDR bacteria in both study cohorts is depicted in Figure 1 according to PSI risk classes, need of mechanical ventilation or the presence of shock on admission. A significantly higher prevalence of MDR bacteria was found among patients admitted to ICU in comparison to those admitted to the ward in both cohorts: 14/116 (12%) vs. 24/380 (6·3%), p=0·041, in the BC, and 7/102 (6·9%) vs. 11/589 (1·9%), p=0·009, in the EC.

In comparison to 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 hospitalized in the prior 90 days, were more immunosuppressed (in the BC), and had more severe pneumonia on admission in terms of use of mechanical ventilation, acidemia and alteration of gas exchange, see Table 4.

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 to subjects with a pneumonia caused by a non-resistant bacteria, see Table 4.

Predicting pneumonia caused by MDR bacteria: validation of three scores

At least one risk factor for MDR organisms was identified in 41% and 31% of the patients in the BC and EC, respectively. Prevalences of each risk factor for MDR organisms in both study cohorts are depicted in Table 5.

Distributions of the prevalence of MDR pathogens among patients in both cohorts who had isolated bacteria are depicted in Figure 2 according to the risk stratification of the three evaluated scores. As the scores increased, so did the prevalence of MDR bacteria for all the three scores in both study cohorts.

The ROC curves evaluating the performance of the three scores with respect to the presence of MDR bacteria are reported in Table 6 for both study cohorts. In the entire BC, the area under the ROC curve for the Aliberti score was of 0·89 (95% CI, 0·83-0·95), the Shorr score of 0·89 (95% CI, 0·82-0·96) and the HCAP classification of 0·77 (95% CI, 0·70-0·83). In the entire EC, the area under the ROC curve for the Aliberti score was of 0·77 (95% CI, 0·71-0·84), the Shorr score of 0·75 (95% CI, 0·68-0·81) and the HCAP classification of 0·66 (95% CI, 0·59-0·73). Differences between ROC curves for the entire population of patients in both study cohorts are depicted in Table 7. The performance of the three scores was evaluated among patients admitted to the ICU and among those admitted to the ward. The Aliberti score showed a higher AUC in both populations of patients in the BC admitted to the ICU (0·85) and ward (0·91) patients and in the ICU patients (0·79) in the EC, in comparison to the Shorr score and the HCAP classification, see Table 6.

DISCUSSION

This study shows a low prevalence of MDR bacteria in CAP patients in three hospitals in a single Scottish region in North Europe and in one hospital in Barcelona in South Europe. Patients suffering of pneumonia caused by MDR bacteria show more severe disease on presentation and worse clinical outcomes in comparison to those with non-MDR bacteria. Finally, two probabilistic scores (Aliberti and Shorr) perform better than the 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 to the Shorr score.

Several data from retrospective studies conducted in the US have shown percentage of patients with MDR pathogens among those with an isolated bacteria up to 48%.[19] On the other hand, a retrospective study in Asia and both prospective and retrospective studies in Europe showed a lower prevalence of MDR bacteria in patients with CAP.[6-9,20] Our data confirm a low percentage of pneumonia caused by MDR bacteria: 7·6% in Spain and 3·3% in UK. Furthermore, these percentages are likely to be an overestimate of the true prevalence of MDR pathogens because positive microbiology is more frequent in severely ill and ICU patients. A difference seems to be emerging in the prevalence of CAP caused by MDR bacteria between US and Europe. Reasons for this finding could be related to the enrollment of more severe and immunocompromised patients in the US studies as well as the presence of some differences in the organization of healthcare systems, in terms of decentralization of care on the territory and different policies and guidelines related to the use of antibiotics [11, 19]. These final

considerations could be also responsible for the slight difference in MDR prevalence between Southern (Spain and Italy) and Northern (UK) Europe.[6]

We validated two clinical risk scores able to identify patients with pneumonia caused by MDR bacteria. We showed a superiority of both scores in comparison to the HCAP classification. If AUC value higher than 0.75 is usually suggested for predictive scores to be potentially useful in clinical practice, the AUC of the HCAP classification in the EC did not exceed the 0.75 cut-off in any CAP groups. On the other hand, both Aliberti and Shorr scores categorized patients as to the potential for an MDR in two separate populations and this suggests the robustness of both models. Although both scores were able to differentiate among low and high-risk patients, fewer patients with MDR bacteria were classified in the high class using the Shorr score in comparison to the Aliberti score. The slight superiority of the Aliberti over the Shorr score was also testified by a better performance at the ROC curves among all the study population as well as among patients admitted to the ICU. 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 optimize the use these scores. Specifically, it could be reasonable to suggest their use in clinical practice if the expected prevalence of MDR bacteria is more than 5%

Our data suggest that if a CAP caused by an MDR pathogen is suspected, one out of two patients may have MRSA. This finding could be of a certain importance in deciding the initial antibiotic therapy because two of the most important risk factors (nursing home residency and previous hospitalization) are related to all MDR bacteria and *P. aeruginosa* infection. If our data will be confirmed in further studies, someone could suggest that, facing with a high suspicion of MDR

bacteria in a CAP patient, an antibiotic against MRSA could be added to the empiric antibiotic regimen.

The role of MDR bacteria in critically ill patients is not completely clear. Schreiber reported resistant organisms in approximately one-third of patients who presented to the ED with pneumonia necessitating mechanical ventilation.[21] We also found a high prevalence of MDR bacteria among patients with pneumonia who were admitted to the 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 the ICU.

The strength of this study is the evaluation of two large cohorts of consecutive, prospectively enrolled patients in two regions of Europe in very large and robust data collections. The fact that both probabilistic scores work better than HCAP classification in two different cohorts of patients is very important since scores should be validated in different healthcare settings and in populations with different background prevalences of MDR pathogens. One limitation of our study is the relatively low frequency of positive microbiology in both cohorts, although this is consistent with many large observational studies and reflects the limitations of the currently available etiological tests.

In conclusion, a low prevalence of MDR organisms could be found among patients coming from the community and who are hospitalized 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 a 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.

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; Hemodyalisis; Immunosuppression; Antimicrobial therapy in the preceding 90 days	1
Nursing home or	3	Chronic	2		

extended care facility		hemodyalisis	
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 RHDU	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) breath/minute	24 (20-28)	25 (20-32)
Respiratory Rate > 30 breath/minute	273 (17)	451 (24)
Alteration of gas exchange*	701 (44)	697 (37)
SpO2, 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 (178000-306000)	244000 (192000-322000)

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, median (IQR) days	8 (5-12)	5 (3-11)
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; SpO_2: oxygen saturation; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: 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 PaO_2 < 60 mm Hg, PaO_2/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 *S. aureus*	25	7
P. aeruginosa MDR+	12	3
E. coli ESBL +	3	4
Proteus mirabilis ESBL +	2	0
K. pneumoniae ESBL+	2	1
Enterobacter MDR+	1	0
Enterococcus MDR+	1	0
Stenotrophomonas maltophilia	1	3
Acinetobacter baumanii	1	0
Non-MDR bacteria		
S. pneumoniae	327	332
H. influenzae	34	54
Legionella pneumophila	28	19
P. aeruginosa MDR-	20	6
Methicillin-sensible *S. aureus*	15	44
M. pneumoniae	15	28
C. pneumoniae	9	3

K. pneumoniae ESBL-	7	8
Coxiella	5	0
E. coli ESBL -	5	10
M. Catarrhalis	4	6
Proteus mirabilis ESBL -	2	1
Enterococcus MDR-	2	0
Enterobacter MDR-	1	1
Other bacteria	36	12
Virus		
Influenza A virus	16	32
Rinovirus	16	1
Parainfluenza virus	5	2
Adenovirus	3	2
Influenza B virus	2	3
Coronavirus	2	0
Respiratory syncytial virus	2	2
Other virus	116	1
Other		
Pneumocystis	40	0
Nocardia	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

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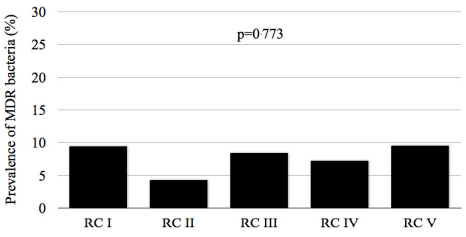
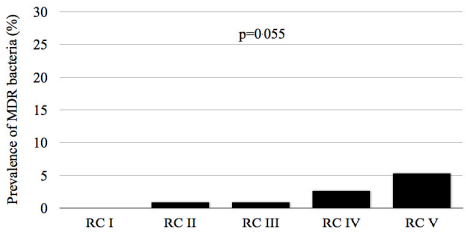
Pneumonia Severity Index

Barcelona Cohort



MDR	6	3	10	13	6
Total	64	69	119	181	63

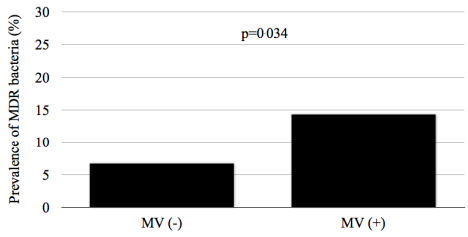
Edinburgh Cohort



MDR	0	1	1	6	10
Total	48	113	108	234	188

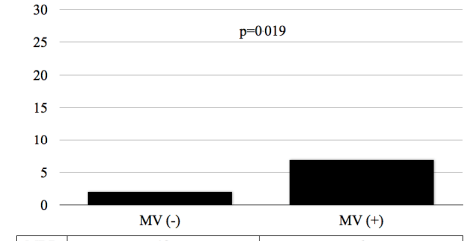
Mechanical ventilation (MV)

Barcelona Cohort



MDR	29	9
Total	433	63

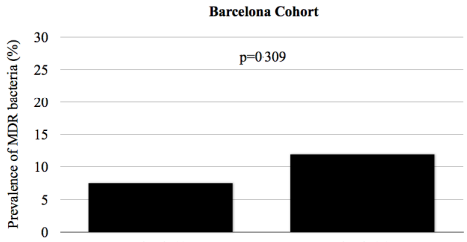
Edinburgh Cohort



MDR	12	6
Total	604	87

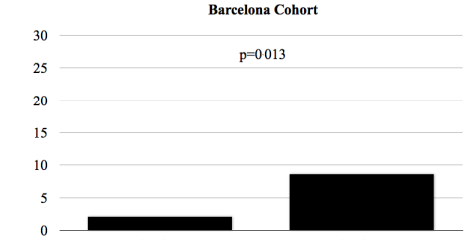
Shock

Barcelona Cohort



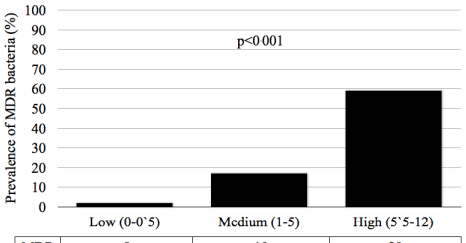
MDR	33	5
Total	441	42

Barcelona Cohort

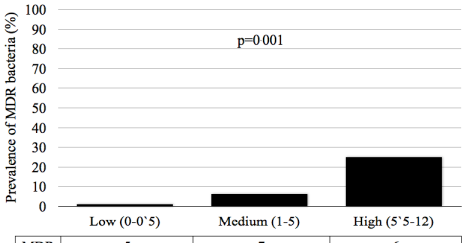


MDR	13	5
Total	633	58

Aliberti Score

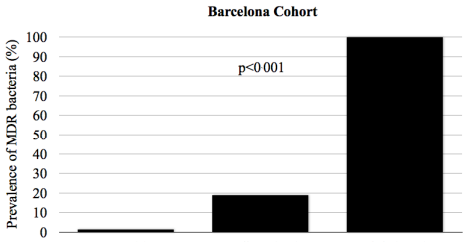


MDR	8	10	20
Total	400	59	34

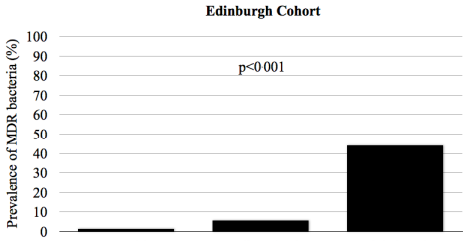


MDR	5	7	6
Total	420	113	24

Shorr Score

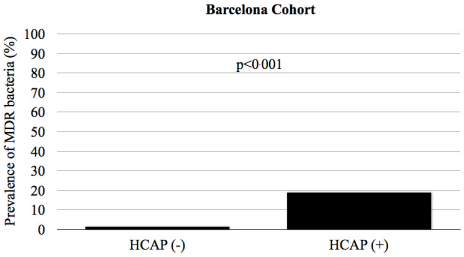


MDR	5	27	6
Total	348	139	6

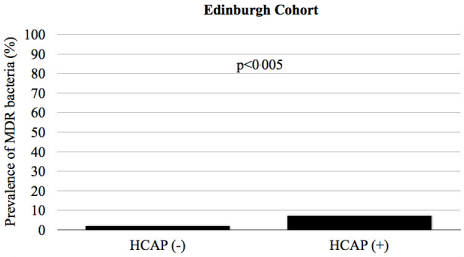


MDR	5	9	4
Total	387	161	9

HCAP classification



MDR	4	34
Total	309	184



MDR	8	10
Total	418	139