# Patients Hospitalized With Pneumonia: Determining the Need for Broad-Spectrum Antibiotic Therapy

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**(See the Major Article by Aliberti et al, on pages 470–8.)**

Physicians are increasingly faced with the dilemma of deciding between broad-spectrum empiric antimicrobial therapy and narrow-spectrum treatment for patients hospitalized with serious infections. In the balance of this dilemma are the need to treat serious infections with an initial appropriate antibiotic regimen to optimize the likelihood of a good clinical outcome and the need to avoid unnecessary antimicrobial exposure to minimize the emergence of antimicrobial resistance [1]. A number of different strategies for antimicrobial stewardship can be used to achieve this balance [2]. In this issue of *Clinical Infectious Diseases*, Aliberti et al report a prospective observational study identifying risk factors for infection with multidrug resistant (MDR) bacteria in patients hospitalized with pneumonia [3]. These authors found that hospitalization in the preceding 90 days, together with residency in a nursing home or extended care facility (ECF), were the strongest independent predictors for infection with MDR pathogens. The authors concluded that physicians treating hospitalized patients with pneumonia should be familiar with these MDR risk factors in order to guide the appropriate use of empiric antimicrobial therapy.

The findings from Aliberti et al confirm our prior observation that specific risk factors can be used to determine the presence of infection with MDR bacteria in patients hospitalized with pneumonia [4]. We have subsequently refined the accuracy of our prediction model using the following weighted point assignments: 4 – recent hospitalization, 3 – admission from a nursing home or ECF, 2 – chronic hemodialysis, 1 – critically ill [5]. As a screening test for MDR bacteria, a score of zero had a high negative predictive value (84.5%) and could potentially be used to avoid the unnecessary use of broad-spectrum antibiotics.

The clinical relevance of studies such as that by Aliberti et al is their provision of a strategy for healthcare workers to balance the need to treat infections appropriately while avoiding the overuse of broad-spectrum antibiotics. Implicit in such a strategy is that physicians should be aware of the risk factor profile of the patients they are treating as well as the local patterns of MDR infection. Absence of risk factors for infection with MDR bacteria, especially in areas where the prevalence of such pathogens is low, should result in the primary use of more narrow-spectrum empiric antibiotic regimens for hospitalized patients with pneumonia. However, in critically ill patients where there is doubt or uncertainty regarding the presence of infection with MDR bacteria, a strategy of de-escalation after starting with a broad-spectrum regimen may be prudent [5, 6].

Since the publication of the 2005 update of the American Thoracic Society and Infectious Diseases Society of America nosocomial pneumonia guidelines, which incorporated for the first time the concept of healthcare-associated pneumonia (HCAP) [6], numerous studies and reviews have provided original data on the concept of HCAP as an infection occurring outside of the hospital setting that is often attributed to MDR pathogens [3–5, 7–20]. These pathogens are frequently not susceptible to the initial antimicrobial regimens recommended in guidelines for community-acquired pneumonia [21]. Many physicians are also unaware of the importance of the criteria for healthcare-associated infections and their clinical relevance for distinguishing patients at risk for MDR bacteria from those with community-acquired infections [22]. Because patients classified as having HCAP are often heterogeneous, and the studies published on HCAP sometimes differ in setting and methodology, some authors have criticized the overall concept of HCAP [23–25]. However, the number of investigations from diverse geographic locations supporting the clinical utility of the HCAP criteria for predicting infection with MDR pathogens adds credence to the

Received 12 October 2011; accepted 18 October 2011; electronically published 21 November 2011.

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**Clinical Infectious Diseases 2012;54(4):479–82**

DOI: 10.1093/cid/cir848

validity of HCAP as a distinct category of pneumonia [9, 14–16, 18, 26]. The most recent studies of HCAP have helped to further refine the relative importance of the individual HCAP criteria for identifying the presence of MDR infections, thus making them more useful for clinical decision making [3–5, 18, 26].

It is evident that hospital or healthcare exposure creates an opportunity for pathogens not commonly present in the community to colonize patients. This phenomenon seems to be primarily caused by the widespread use of antibiotics, often for prolonged periods of time, that select for MDR pathogens [27]. Admission to a room previously occupied by a methicillin-resistant *Staphylococcus aureus* (MRSA)–positive patient or a vancomycin-resistant *Enterococcus* (VRE)–positive patient significantly increases the odds of acquiring MRSA and/or VRE [28]. Additionally, prolonged MRSA carriage is 2relatively common, with 40% of patients who became colonized by MRSA during hospitalization remaining colonized for a median time of 7.4–8.5 months [29, 30]. New MRSA carriers also have a high risk of developing sterile-site MRSA infections in the year following acquisition [31, 32].

Hospitalized patients can also become colonized by MDR gram-negative bacilli. It has been estimated that 8% of patients newly admitted to general medical wards become carriers of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae during their hospitalization [33]. Risk factors for rectal carriage of ESBL-producing Enterobacteriaceae include nursing home residence, recent antibiotic treatment, and concomitant nasal carriage of MRSA and/or ESBL-producing Enterobacteriaceae [33]. Zahar et al found that the median duration of ESBL carriage was 132 days and that patients readmitted between 6 months and 1 year after their last positive culture were still positive 50% of the time [34].

Residents of nursing homes and ECFs also appear to be an important reservoir of MDR pathogens and therefore contribute to the influx of MDR bacteria into the hospital setting [35–38]. Studies performed >10 years ago at Veterans Affairs facilities in the United States showed a high prevalence of MRSA colonization among residents, with rates ranging from 13% to 35% [39, 40]. Major sites of colonization were nares, wounds, and decubitus ulcers [39, 40]. European studies have also evaluated the prevalence of MRSA colonization in ECFs and described ranges of 8.6%–22% of inhabitants [41–45]. Elderly residents living in ECFs are also at high risk of colonization and infection with MDR gram-negative bacteria [46]. Diagnoses of advanced dementia and nonambulatory status were significant risk factors for harboring these pathogens [46]. Subsequent studies have confirmed these observations [38, 47–49]. However, El-Solh et al found that patients with both antibiotic exposure in the previous 6 months and an activities of daily living (ADL) score ≥12.5 showed a 90% probability of having infection caused by MDR bacteria, while patients without these risk factors had a 0% probability of infection with MDR bacteria [50].

In summary, empiric antibiotic therapy for serious infections in hospitalized patients requires careful clinical consideration in order to provide appropriate initial coverage for the majority of patients infected with MDR pathogens. Equally important, the absence of risk factors for MDR pathogens, especially preceding hospitalization or admission from a nursing home or ECF, should at least question the need for initial broad-spectrum antibiotic therapy. A good understanding of the patient's risk factor profile for infection with MDR bacteria and the prevailing local patterns of infection with these pathogens is required to balance the needs of the patient (administration of appropriate antibiotic therapy) with those of the hospital environment (preventing the emergence of antibiotic resistance). Last, physicians caring for patients with pneumonia need to be aware of the changing global patterns of pathogens accounting for these infections, which may require rethinking of current antibiotic practice patterns [51].

## Notes

***Financial support.*** Dr Kollef's efforts are supported in part by the Barnes-Jewish Hospital Foundation.

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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MAJOR ARTICLE

# Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia

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**(See the Editorial Commentary by Kollef, on pages 479–82.)**

***Background.*** Not all risk factors for acquiring multidrug-resistant (MDR) organisms are equivalent in predicting pneumonia caused by resistant pathogens in the community. We evaluated risk factors for acquiring MDR bacteria in patients coming from the community who were hospitalized with pneumonia. Our evaluation was based on actual infection with a resistant pathogen and clinical outcome during hospitalization.

***Methods.*** An observational, prospective study was conducted on consecutive patients coming from the community who were hospitalized with pneumonia. Data on admission and during hospitalization were collected. Logistic regression models were used to evaluate risk factors for acquiring MDR bacteria independently associated with the actual presence of a resistant pathogen and in-hospital mortality.

***Results.*** Among the 935 patients enrolled in the study, 473 (51%) had at least 1 risk factor for acquiring MDR bacteria on admission. Of all risk factors, hospitalization in the preceding 90 days (odds ratio [OR], 4.87 95% confidence interval {CI}, 1.90–12.4]; $P = .001$) and residency in a nursing home (OR, 3.55 [95% CI, 1.12–11.24]; $P = .031$) were independent predictors for an actual infection with a resistant pathogen. A score able to predict pneumonia caused by a resistant pathogen was computed, including comorbidities and risk factors for MDR. Hospitalization in the preceding 90 days and residency in a nursing home were also independent predictors for in-hospital mortality.

***Conclusions.*** Risk factors for acquiring MDR bacteria should be weighted differently, and a probabilistic approach to identifying resistant pathogens among patients coming from the community with pneumonia should be embraced.

Pneumonia caused by multidrug-resistant (MDR) pathogens traditionally has been confined to the hospital setting. In view of the diffusion of healthcare delivery and technology outside the hospital, resistant pathogens have extended beyond the confines of the inpatient setting. The rapid emergence of MDR bacteria that cause pneumonia in the community has created the need to identify risk factors for acquiring resistant pathogens by evaluating the contacts patients have with the healthcare environment as well as the patient's characteristics [1].

Pneumonia that occurs in outpatients who have been in contact with the healthcare system is termed healthcare-associated pneumonia (HCAP) [2]. Prior hospitalization, residency in a nursing home, going to hemodialysis centers, and receiving domiciliary care are some of the risk factors for acquiring the resistant

Received 11 August 2011; accepted 7 October 2011; electronically published 21 November 2011.

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**Clinical Infectious Diseases 2012;54(4):470–8**



DOI: 10.1093/cid/cir840

pathogens included in the HCAP classification. Beyond these risk factors, immunosuppression, severe underlying diseases, and the patient's functional status also have been recognized as conditions that could lead to acquisition of MDR pathogens [3]. The American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recognize that pneumonia in patients with these risk factors who come from the community shares bacteriologic features with nosocomial pneumonia and thus should be treated with broad-spectrum empiric antibiotic therapy [2].

It has been demonstrated that a large group of patients with risk factors for acquiring MDR bacteria may present with differences in terms of epidemiology, impact on the actual acquisition of a resistant pathogen, and response to therapy [4, 5]. Recently, concern has been raised because all risk factors for MDR acquisition are classified within the same category and a definition of different subpopulations of patients is needed [6, 7].

The aim of our study was to evaluate risk factors for acquiring MDR bacteria among patients coming from the community who were hospitalized with pneumonia on the basis of infection with a resistant pathogen and patient clinical outcome during hospitalization. A second purpose was to develop a risk-scoring tool that could be used to identify subjects who come from the community to the hospital with pneumonia caused by resistant organisms.

## MATERIALS AND METHODS

### Study Design and Study Patients

This was an observational, prospective study of consecutive patients coming from the community who were admitted to the Policlinico Hospital, Milan, Italy, with a diagnosis of pneumonia between April 2008 and April 2010. The Institutional Review Board of the Policlinico Hospital approved the study. Patients ≥18 years of age who satisfied the criteria for pneumonia were included in the study. Patients who were hospitalized in the previous 15 days were excluded. The patient enrollment process is detailed in the online supplement. The following data were recorded: demographics; past medical history; severity of symptoms on admission; pneumonia severity index (PSI) and CURB-65 score (confusion, urea nitrogen, respiratory rate, blood pressure, ≥65 years of age); physical, laboratory, and radiological findings on admission; microbiological data; empiric antibiotic therapy; and in-hospital mortality [8, 9].

### Study Definitions

Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with ≥1 of the following: (1) new or increased cough with/without sputum production; (2) fever (≥37.8°C) or hypothermia (<35.6°C); or (3) abnormal white blood cell count (either leukocytosis or leukopenia), or C-reactive protein values above the local upper limit. Severe community-acquired pneumonia (CAP) was defined according to the latest ATS guidelines [10]. Severe sepsis was defined as sepsis plus ≥1 signs of organ hypoperfusion or organ dysfunction, as previously reported [11]. Length of stay was calculated as the number of days from the date of admission to the date of discharge.

### Risk Factors for Acquiring MDR Pathogens

The following risk factors for acquiring MDR pathogens were recorded among the study population according to the ATS/IDSA guidelines: hospitalization for ≥2 days in the preceding 90 days, residency in a nursing home or extended-care facility, home infusion therapy (including antibiotics), home wound care, chronic dialysis within 30 days, family member with an MDR pathogen, antimicrobial therapy in the preceding 90 days, and immunosuppression [2]. Severe immunosuppression was defined by the presence of ≥1 of the following factors: active hematologic malignancy, transplantation, immunosuppressive therapy, chemotherapy, and radiotherapy. Mild-to-moderate immunosuppression was defined by the presence of ≥1 of the following factors: chronic systemic steroid therapy (prednisone ≥25 mg/day), active solid malignancy, splenectomy, and autoimmune disease.

### Microbiological Analysis and Empiric Antibiotic Therapy

Microbiological examinations were performed on sputum, urine, and blood during the first 24 hours after admission and according to standards of practice. Pleural puncture, tracheobronchial aspirates, and bronchoalveolar lavage fluid, when available, were also collected and cultured. Identification of microorganisms and susceptibility testing were performed according to standard methods [12]. Microbiological results were reviewed, and a microbiological cause was assigned independently by 2 of the investigators (M. D. P. and S. S.). The etiology was considered definite if 1 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); positive urinary antigen for *Streptococcus pneumoniae* (Binax Now, Emergo Europe); a bacterial yield in cultures of valid sputum (>25 polymorphonuclear cells and <10 epithelial cells per power field, total magnification ×100) of $\geq 10^6$ colony-forming units (CFU)/mL, tracheobronchial aspirates of $\geq 10^5$ CFU/mL, bronchoalveolar lavage fluid of $\geq 10^4$ CFU/mL, and protected specimen brush cultures of $\geq 10^3$ CFU/mL; and occurrence of seroconversion (a 4-fold rise in immunoglobulin G [IgG] titers for *Chlamydophila pneumoniae* [1:512] and *L. pneumophila* or a rise in immunoglobulin M [IgM] titers for *C. pneumoniae* [1:32] and *Mycoplasma pneumoniae* [any titer]). When ≥2 microbiological causes were present, the

**Table 1. Demographics; Severity of Disease; and Clinical, Laboratory, and Radiological Findings on Admission of the Study Population, According to the Presence of Risk Factors for Multidrug-Resistant Organisms (Group A: Absence of Risk Factors; Group B: Presence of ≥1 Risk Factors)**

| Characteristic | Study Population | Group A | Group B | *P* Value[a] |
|---|---|---|---|---|
| No. (%) | 935 (100) | 462 (49) | 473 (51) | |
| Male, no. (%) | 504 (54) | 225 (49) | 279 (59) | .001 |
| Age, years, mean ± SD | 76 ± 15 | 76 ± 16 | 76 ± 13 | .627 |
| Comorbidities, no. (%) | | | | |
| Congestive heart failure | 264 (28) | 117 (25) | 147(31) | .050 |
| COPD | 270 (29) | 121 (26) | 149 (32) | .071 |
| Diabetes mellitus | 140 (15) | 64 (14) | 76 (16) | .360 |
| Cerebrovascular disease | 40 (4.3) | 19 (10) | 21 (11) | .517 |
| Chronic renal failure[b] | 147 (16) | 62 (13) | 85 (18) | .059 |
| Liver disease | 53 (5.7) | 16 (3.5) | 37 (8) | .004 |
| Severity on admission, no. (%) | | | | |
| PSI risk class IV–V | 711 (76) | 309 (67) | 402 (85) | <.001 |
| CURB-65 score 3, 4, and 5 | 352 (38) | 147 (32) | 205 (43) | <.001 |
| Altered mental status | 255 (27) | 110 (24) | 145 (31) | .019 |
| Severe CAP | 348 (37) | 135 (29) | 213 (45) | <.001 |
| Need of ventilatory support | 99 (11) | 51 (11) | 48 (10) | .750 |
| Need of blood pressure support | 101 (11) | 48 (10) | 53 (11) | .200 |
| Severe sepsis | 243 (26) | 96 (21) | 147 (31) | <.001 |
| Physical findings on admission, no. (%) | | | | |
| Hypotension[c] | 180 (19) | 71 (16) | 109 (23) | .003 |
| Heart rate, beats/min, mean ± SD | 97 ± 22 | 96 ± 21 | 98 ± 22 | .264 |
| Alteration of gas exchange[d] | 416 (45) | 207 (48) | 209 (48) | .609 |
| $SpO_2$ %, mean ± SD | 92 ± 6 | 93 ± 6 | 92 ± 6 | .074 |
| Laboratory values, mean ± SD | | | | |
| Arterial pH | 7.44 ± 0.08 | 7.44 ± 0.08 | 7.44 ± 0.08 | .591 |
| $PaCO_2$, mm Hg | 36 ± 11 | 36 ± 11 | 36 ± 12 | .681 |
| $PaO_2$, mm Hg | 64 ± 20 | 65 ± 20 | 63 ± 20 | .270 |
| WBC count, cells/$L^{-1}$ | 12 374 ± 7134 | 12 089 ± 5227 | 12 651 ± 8594 | .229 |
| Platelet count, cells/$L^{-1}$ | 232 487 ± 115 443 | 231 257 ± 91 022 | 233 701 ± 135 386 | .748 |
| Hemoglobin, g/dL | 12.6 ± 2 | 13 ± 1.8 | 12.1 ± 2.2 | <.001 |
| Hematocrit, % | 39 ± 13 | 37 ± 6 | 41 ± 16 | .001 |
| Urea, mg/dL | 62 ± 44 | 57 ± 39 | 66 ± 49 | .003 |
| Creatinine, mg/dL | 1.4 ± 1.6 | 1.2 ± 0.7 | 1.5 ± 2.1 | .013 |
| Sodium, mEq/L | 137 ± 6 | 137 ± 6 | 137 ± 6 | .368 |
| C-reactive protein, g/dL | 13 ± 12 | 13 ± 13 | 13 ± 12 | .524 |
| Chest radiographic findings, no. (%) | | | | |
| Multilobar involvement | 332 (36) | 148 (44) | 184 (48) | .296 |
| Pleural effusion | 316 (34) | 143 (31) | 173 (37) | .072 |

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urea nitrogen, respiratory rate, blood pressure, 65 years of age and older; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaO_2$, partial pressure of oxygen in arterial blood; PSI, pneumonia severity index; SD, standard deviation; $SpO_2$, oxygen saturation; WBC, white blood cell.

[a] Difference between group A and group B.

[b] Chronic renal failure defined as creatinine >1.2 mg/dL.

[c] Hypotension defined as systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg.

[d] Alteration of gas exchange defined as $PaO_2$ <60 mm Hg, $PaO_2$/fraction of inspired oxygen <300, or $O_2$ saturation <90%.

patient was considered to have a polymicrobial infection. Patients for whom no microbiological tests were performed and patients with negative microbiological results were considered to have disease of an unknown etiology.

Methicillin-resistant *Staphylococcus aureus* (MRSA); *Pseudomonas aeruginosa* resistant to antipseudomonal penicillins, cephalosporins, carbapenems, and quinolones; *Stenotrophomonas maltophilia*; vancomycin-resistant *Enterococcus*; *Acinetobacter*

*baumanii*; extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae; and other nonfermenting gram-negative bacilli were considered to be MDR pathogens.

Empiric antibiotic therapy was administered as soon as the diagnosis of pneumonia was reached in the emergency department. The empiric antibiotic treatment was evaluated for compliance with the European Respiratory Society guidelines [13].

### Study Groups and End Points

Two study groups were identified among the study population according to the presence of risk factors for acquiring MDR bacteria: group A, patients without risk factors, and group B, patients with ≥1 risk factors for resistant pathogen. The microbiological end point was the actual isolation of an MDR pathogen. The clinical end point was the in-hospital mortality.

### Statistical Analysis

All data were statistically analyzed using SPSS (version 18.0) for Mac. Descriptive statistics were reported at baseline, with continuous data expressed as a mean ± SD and categorical data expressed as counts. Patient characteristics were compared between group A and group B: all continuous explanatory variables were presented as means, with differences between the 2 groups compared by means of independent *t* tests. Categorical explanatory variables were summarized as frequencies and percentages, with differences between the 2 groups analyzed using the $\chi^2$ test and Fisher exact test when appropriate. Risk factors for acquiring MDR bacteria independently associated with the actual presence of a resistant pathogen were evaluated by a logistic regression model, using the forward method. Goodness of fit was explored based on the Hosmer-Lemeshow test. Interactions between terms within the logistic model were also tested. Based on the logistic regression findings, a predictive additive scoring tool was developed to identify the presence of MDR pathogens. Coefficients from the logistic regression were converted to whole integers and 0.5 points were defined for the presence of ≥1 risk factors not included in the final regression model. Risk classes (low vs high) were defined by the inspection of the prevalence of MDR pathogens given the different score values. The predictive value of the scoring tool was explored for correctly indicating the presence of MDR pathogens via a receiver-operating characteristic (ROC) curve. Independent predictors for in-hospital mortality were evaluated in the entire study population by a logistic regression model, using the forward method. All tests were 2-tailed, and a *P* value <.05 was considered statistically significant.

## RESULTS

A total of 935 consecutive patients with pneumonia were enrolled during the study period (54% males, mean ± SD age: 76 ± 15 years). Demographics; severity of disease; and clinical, laboratory, and radiological findings on admission of the study population are summarized in Table 1. Within the study population, 473 patients (51%) had ≥1 risk factors for acquiring MDR bacteria on admission (Table 2). A total of 271 patients (29%) had 1 risk factor, 129 (14%) had 2 risk factors, 54 (6%) had 3 risk factors, and 19 (2%) had ≥4 risk factors. The most common associations among risk factors were previous hospitalization plus previous antimicrobial therapy (10%) and previous hospitalization plus immunosuppression (8%).

Demographics; comorbidities; severity of disease; and physical, laboratory, and radiological findings on admission of patients with and without risk factors are depicted in Table 1. Patients in group B showed a more severe disease on admission compared with group A, with a higher prevalence of severe sepsis. *S. pneumoniae* was the most common pathogen isolated in both study groups. A higher prevalence of MDR bacteria was found in patients in group B compared with those in group A (6.1% vs 0.9%, respectively; $P < .001$) (Table 3). Among patients with an isolated resistant pathogen, 7 had bacteremia on admission: 3 due to ESBL-positive *Escherichia coli*, 2 due to MRSA, 1 due to *Providencia stuartii*, and 1 due to *Proteus* species. A combined etiology of resistant pathogens was identified in 3 patients among those in group B: MRSA plus *S. maltophilia* in 2 cases and ESBL-positive *E. coli* plus MRSA in 1 case.

**Table 2. Risk Factors for Multidrug-Resistant Pathogens Among the Study Population**

| Risk Factor for MDR | Prevalence, No. (%) |
|---|---|
| Risk factors for HCAP | 284 (30) |
| Hospitalization for ≥2 days in the preceding 90 days | 200 (21) |
| Residency in a nursing home or extended-care facility | 66 (7) |
| Home infusion therapy (including antibiotics) | 39 (4) |
| Home wound care | 36 (4) |
| Chronic dialysis within 30 days | 8 (0.9) |
| Family member with MDR pathogen | 0 (0) |
| Immunosuppression | 267 (29) |
| Severe immunosuppression[a] | 135 (15) |
| Mild-to-moderate immunosuppression[b] | 132 (14) |
| Other | |
| Antimicrobial therapy in preceding 90 days | 155 (17) |

Abbreviations: HCAP, healthcare-associated pneumonia; MDR, multidrug resistant.

[a] Severe immunosuppression defined as hematologic malignancy, transplantation, immunosuppressive therapy, chemotherapy, radiotherapy.

[b] Mild-to-moderate immunosuppression defined as chronic systemic steroid therapy (prednisone ≥25 mg/day), solid malignancy, splenectomy, autoimmune diseases.

**Table 3. Microbiological Findings and Empiric Antibiotic Therapy of the Study Population and According to the Presence of Risk Factors for Multidrug-Resistant Pathogens (Group A: Absence of Risk Factors; Group B: Presence of ≥1 Risk Factors)**

| Characteristic | Study Population | Group A | Group B |
|---|---|---|---|
| No. (%) | 935 (100) | 462 (49) | 473 (51) |
| Microbiological finding, no. (%) | | | |
| Blood culture performed | 500 (53) | 244 (53) | 256 (54) |
| Patients with isolated bacteria | 170 (18) | 73 (16) | 97 (21) |
| *Streptococcus pneumoniae* | 63 (37) | 27 (37) | 36 (37) |
| Methicillin-susceptible *Staphyloccocus aureus* | 21 (12) | 9 (12) | 12 (12) |
| Methicillin-resistant *S. aureus* | 16 (9.4) | 2 (2.7) | 14 (14) |
| *Legionella pneumophila* | 26 (15) | 14 (19) | 12 (12) |
| *Escherichia coli* ESBL$^+$ | 5 (2.9) | 1 (1.4) | 4 (4.1) |
| *E. coli* ESBL$^-$ | 10 (5.9) | 3 (4.1) | 7 (7.2) |
| *Pseudomonas aeruginosa* MDR$^+$ | 7 (4.1) | 0 | 7 (7.2) |
| *P. aeruginosa* MDR$^-$ | 5 (2.9) | 1 (1.4) | 4 (4.1) |
| *Klebsiella pneumoniae* ESBL$^+$ | 0 | 0 | 0 |
| *K. pneumoniae* ESBL$^-$ | 13 (7.6) | 6 (8.2) | 7 (7.2) |
| *Haemophilus influenzae* | 6 (3.5) | 5 (6.8) | 1 (1) |
| *Mycoplasma pneumoniae* | 5 (2.9) | 3 (4.1) | 2 (2.1) |
| *Chlamydophila pneumoniae* | 4 (2.4) | 4 (5.5) | 0 |
| *Bordetella bronchiseptica* | 1 (0.6) | 0 | 1 (1) |
| *Stenotrophomonas maltophilia* | 2 (1.2) | 0 | 2 (2.1) |
| *Enterococcus* MDR$^+$ | 1 (0.6) | 0 | 1 (1) |
| *Enterococcus* MDR$^-$ | 2 (1.2) | 1 (1.4) | 1 (1) |
| *Proteus mirabilis* ESBL$^+$ | 2 (1.2) | 1 (1.4) | 1 (1) |
| *Providencia stuartii* ESBL$^+$ | 1 (0.6) | 0 | 1 (1) |
| *Acinetobacter baumanii* | 1 (0.6) | 0 | 1 (1) |
| Patients with ≥1 MDR organisms | 33 (3.3) | 4 (0.9) | 29 (6.1) |
| Polymicrobial infection | 17 (1.8) | 4 (0.9) | 13 (2.8) |
| Initial empiric antibiotic treatment, no. (%) | | | |
| Ceftriaxone | 434 (46) | 278 (60) | 156 (33) |
| Azithromycin | 384 (41) | 250 (54) | 134 (28) |
| Levofloxacin | 288 (31) | 116 (25) | 172 (36) |
| Piperacillin/tazobactam | 188 (20) | 54 (12) | 134 (28) |
| Vancomycin | 22 (2) | 3 (0.7) | 19 (4) |
| Ampicillin/sulbactam | 29 (3) | 18 (4) | 11 (2) |
| Metronidazole | 25 (3) | 12 (3) | 13 (3) |
| Ceftazidime | 16 (2) | 4 (1) | 12 (2) |
| Imipenem | 16 (2) | 5 (1) | 11 (2) |
| Amikacin | 13 (1) | 2 (0.4) | 11 (2) |
| Clarythromycin | 13 (1) | 8 (2) | 5 (1) |
| Ciprofloxacin | 8 (1) | 1 (0.2) | 7 (2) |
| Others | 16 (2) | 9 (2) | 7 (2) |
| Compliant with ERS guidelines | 672 (72) | 370 (80) | 302 (64) |

Abbreviations: ERS, European Respiratory Society; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant.

A multivariable logistic regression model was performed for the 170 patients who had a bacterium isolated. Among all risk factors for acquiring MDR bacteria, hospitalization in the preceding 90 days (odds ratio [OR], 4.87 [95% confidence interval {CI}, 1.90–12.4]; $P = .001$) and residency in a nursing home or extended-care facility (OR, 3.55 [95% CI, 1.12–11.24]; $P = .031$) were independent predictors for an actual infection with a resistant pathogen, after adjustment for sex, age, and comorbidities such as diabetes, cerebrovascular disease, chronic renal failure (OR, 3.90 [95% CI, 1.35–11.99]; $P = .014$), and chronic obstructive pulmonary disease (Hosmer-Lemeshow test, 0.829; Nagelkerke $R^2$, 0.299; omnibus $\chi^2$ test, 0.021).

**Table 4. Scoring System to Evaluate the Presence of Multidrug-Resistant Pathogens in Patients With Pneumonia From the Community Who are Hospitalized**

| Variable | Score |
|---|---|
| No risk factors for MDR pathogen (including comorbidities) | 0 |
| ≥1 of the following: cerebrovascular disease, diabetes, COPD, antimicrobial therapy in preceding 90 days, immunosuppression, home wound care, home infusion therapy (including antibiotics) | 0.5 |
| Residence in a nursing home or extended-care facility | 3 |
| Hospitalization for ≥2 days in the preceding 90 days | 4 |
| Chronic renal failure | 5 |

Abbreviations: COPD, chronic obstructive pulmonary disease; MDR, multidrug-resistant.

A score for predicting the risk of infection with resistant bacteria, including factors related to contact with the healthcare environment as well as patients' comorbidities, was computed (Table 4). The scores ranged from 0 to 12.5. Based on visual inspection, patients were grouped into low-risk and high-risk classes as a function of their overall score (Figure 1). Among patients with a score ≤0.5 on entry, the prevalence of a resistant bacteria was 8% (95% CI, 2%–13%), compared with 38% (95% CI, 25%–50%) in those with a score of ≥3 ($P < .001$). Figure 2 depicts the ROC curve for the score. The area under the ROC curve is 0.79 (95% CI, .71–.87). A score >0.5 was associated with the best balance between sensitivity (0.75) and specificity (0.71).

Data on the initial antimicrobial treatment are given in Table 3. Of the 33 patients who had ≥1 MDR organisms, the pathogen was susceptible to the empiric antibiotic therapy in 22 subjects (66%). Mean ± SD length of stay in the hospital was 15 ± 11 days for the entire study population: patients in group B had a longer hospital stay compared with those in group A (15.3 ± 12.3 vs 13.8 ± 8.9 days, respectively; $P = .037$). In-hospital mortality for the entire study population was 16% (n = 161). Among patients in group A (n = 48), mortality was 10%; among those in group B (n = 104), mortality was 22% ($P < .001$). Mortality was 48% for patients coming from a nursing home and 26% for patients who were hospitalized in the preceding 90 days.

For the entire study population, a multivariable logistic regression model was used to analyze all risk factors for acquiring MDR bacteria. Hospitalization in the preceding 90 days (OR, 1.63 [95% CI, 1.04–2.54]; $P = .034$) and residency in a nursing home or extended-care facility (OR, 2.83 [95% CI, 1.54–5.2]; $P = .001$) were found to be independent predictors for in-hospital mortality, after adjustment for age, sex, PSI, severe CAP, severe sepsis on admission, and appropriate antibiotic treatment (Nagelkerke $R^2$, 0.234; omnibus $\chi^2$ test, 0.024) (Table 5).

## DISCUSSION

Our study shows that more than half of the patients who were admitted to the hospital from the community because of an episode of pneumonia had risk factors for MDR. Of those patients, hospitalization in the preceding 90 days and residency

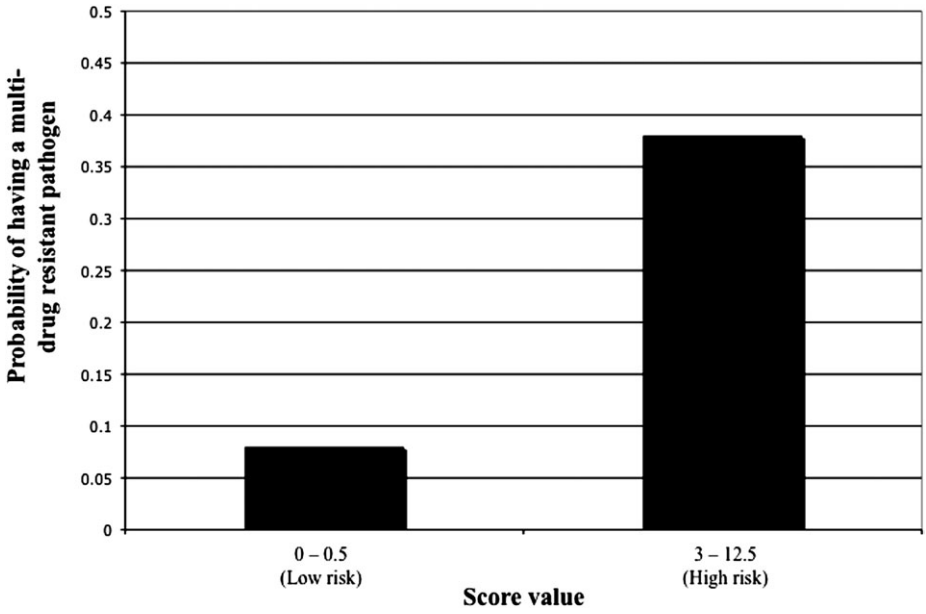


**Figure 1.** Prevalence of multidrug-resistant bacteria in patients with an isolated pathogen, according to the stratification derived from the score (low-risk and high-risk classes).

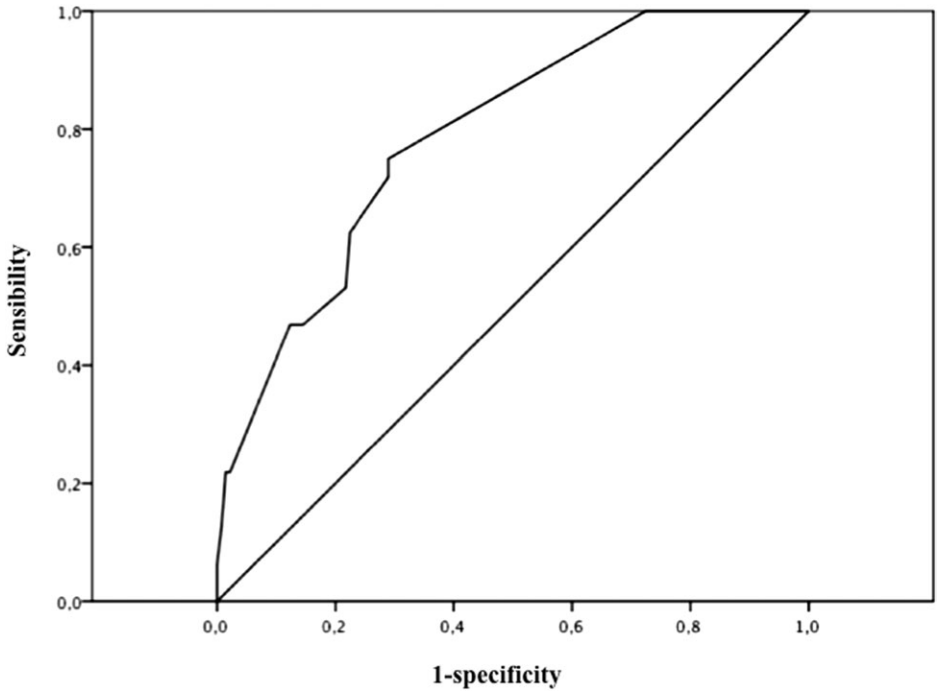


**Figure 2.** Receiver-operating characteristic curve of the score.

in a nursing home or extended-care facility were independently associated with an actual infection with a resistant pathogen, as well as in-hospital mortality. A simple score performed on admission to the hospital that included risk factors and co-morbidities was used to stratify patients into different classes based on the probability of having MDR pneumonia.

Our results argue in favor of an individual evaluation of each patientin order to develop a targeted approach when selecting empiric antibiotic therapy for those patients with CAP. Among known risk factors for acquiring MDR bacteria, hospitalization in the preceding 90 days and residency in a nursing home or extended-care facility were independently associated with pneumonia caused by a resistant pathogen. These findings are in accordance with recent experiences that showed both risk factors to be related to infection with MDR bacteria in different populations, including patients with acute respiratory failure and those admitted to an intensive care unit [6, 7, 14–16]. Although our findings were observed only among patients with an isolated pathogen, previous hospitalization and nursing home residency were also found to be significantly associated with in-hospital mortality among the entire cohort. The double impact of these 2 risk factors on both microbiological and clinical outcomes emphasizes their roles.

There are possible 2 reasons for the impact of previous hospitalization and nursing home residency on resistant pathogen infection. First, the impact could be related to exposure to an extensive antibiotic coverage in these settings that leads to a selecting pressure for resistance. Second, the persistence of MDR pathogens in different wards and transmission between healthcare workers and patients is increasing, and effective healthcare policies are needed to reduce these pathogens [17].

In our population, immunosuppression did not seem to convey an increased risk for infection with a resistant pathogen. This finding is intriguing, although in accordance with recent literature [7]. Immunosuppression needs to be evaluated as the

**Table 5. Independent Predictors for In-Hospital Mortality in the Study Population**

| Variable | OR (95% CI) | *P* Value |
|---|---|---|
| Hospitalization for ≥2 days in the preceding 90 days | 1.63 (1.04–2.54) | .034 |
| Residency in a nursing home or extended-care facility | 2.83 (1.54–5.21) | .001 |
| Pneumonia severity index | 2.19 (1.58–3.03) | <.001 |
| Severe CAP | 2.52 (1.61–3.93) | <.001 |

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; OR, odds ratio.

expression of different disorders, and its association with MDR is based on the type of disease leading to immunosuppression, its severity, and the effectiveness of the treatment chosen. Based on our results, contact with the healthcare system seems to play a more important role in the acquisition of a resistant pathogen than immunosuppression in patients with pneumonia.

We also found chronic renal failure to be an independent risk factor for MDR infection in our cohort. This association has been previously demonstrated in patients infected by *Mycobacterium tuberculosis* and other bacteria [18, 19]. We can also speculate that chronic renal failure represents a window on a patient's functional status. Our finding could reinforce the hypothesis that functional impairment is a crucial determinant of the risk for acquiring drug-resistant pathogens, as recently suggested [3].

As an alternative to a large classification that includes different risk factors, we suggest a probabilistic approach in assuming the presence of MDR-causing pneumonia. The model we developed has the advantage of taking into consideration both the number/type of comorbidities and risk factors and the interaction among them. Recent literature indicates a shift toward this approach [7, 16]. A score to predict MDR pneumonia will allow physicians to develop both diagnostic and treatment protocols. On the one hand, a more rigorous and invasive microbiological workup could be indicated for those patients in the high-risk class. On the other hand, the administration of appropriate empiric antibiotic therapy could be optimized, thus minimizing the unnecessary use of broad-spectrum antibiotics in patients in the low-risk class.

Our study had some limitations. We found a low prevalence of MDR pathogens in our cohort; this finding could be related to the single-center design of the study as well as our healthcare organization and internal policies. Our results should thus be interpreted with caution because different causative organisms or rates of antibiotic resistance may be encountered in other countries. Furthermore, we were not able to directly detect our patients' functional status, and some characteristics of the study population may have limited the ability to identify disease severity as one of the risk factors for MDR infection. In further multicenter studies enrolling a large number of patients, more variables could be evaluated and included in robust prediction models to identify the relationship among different risk factors for MDR organisms. Finally, although our scoring tool appears to perform quite well in identifying patients coming from the community with pneumonia caused by resistant microorganisms, we should acknowledge the absence of a validation of the model in an independent group of patients.

The strength and novelty of our prospective study rely on a specific analysis of all risk factors for acquiring MDR bacteria (including immunosuppression and comorbidities) in a large population of consecutive patients coming from the community with pneumonia and who were hospitalized in different wards. Furthermore, the analysis of risk factors for acquisition of MDR bacteria has been weighted based on both microbiological and clinical outcomes.

Pneumonia caused by an MDR pathogen acquired in the community depends on both patient comorbidities/functional status and previous contact with the healthcare system. However, a different weight of risk factors for MDR should be acknowledged because previous hospitalization and nursing home residency are the main factors leading to both resistant pathogen acquisition and mortality. We suggest that a probabilistic approach to identifying resistant pathogens among patients coming from the community with pneumonia should integrate previous classifications.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

***Acknowledgments.*** We thank all the patients and clinicians in the Policlinico Hospital in Milan, Italy, for their cooperation and participation in the study.

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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