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Pneumonia in Intensive Care Unit Patients: Incidence, Risk Factors and Outcomes Related to Multidrug-Resistant Organisms

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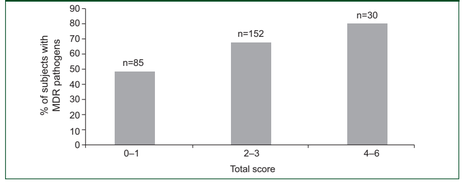
ABSTRACT

Background: Hospital-acquired (HAP), ventilator-associated (VAP) and healthcare-associated pneumonia (HCAP) are caused by a wide spectrum of bacterial pathogens. Rates of infection due to multidrug-resistant pathogens (MDRs) have increased dramatically in hospitalized patients, especially in intensive care (ICU). While multiple risk factors exist for MDRs infection, we wished to assess which risk factors were most likely associated with pneumonia due to MDRs in ICU patients.
Methods: Retrospective, multicenter observational evaluation of ICU patients with pneumonia enrolled in the IMPACT-HAP study (02/06 – 07/07). We used CDC criteria for the diagnosis of pneumonia and ATS/IDSA definitions for HAP, VAP, and HCAP. All patients had a confirmed microbiologic diagnosis. MDRs included: methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter* species. Pneumonia patients with MDRs were compared with those with no MDRs.
Results: 278 ICU patients (HAP=43, VAP=189, HCAP=46) had pneumonia and ≥1 pathogen identified. MDRs were found in 64% (n=178) of subjects. Variables independently associated with recovery of MDRs in logistic regression: history of COPD (OR, 2.52; 95% CI, 1.17–5.43; p=0.018), antimicrobial therapy in preceding 30 days (OR, 1.9; 95% CI, 1.02–3.54; p=0.042). Residence in a nursing home or extended care facility approached statistical significance (OR, 2.3; 95% CI, 0.90–5.84; p=0.080). We used these 3 variables to create a point score to determine risk of pneumonia due to MDRs (**Figure 1**). Initial empiric therapy included ≥1 antibiotic active against the first (91.6%) and second (81.5%) pathogen(s) recovered from the 278 patients. Clinical success at day 14 (72% vs 62%, p=0.1), day 28 (65% vs 58%, p=0.25), and mortality day 28 (15% vs 14%, p=0.89) were comparable between MDRs/non-MDRs groups.

Figure 1. Point score to determine risk of pneumonia due to MDR pathogens (p<0.001 for trend)



Conclusions: Patients with HAP/VAP/HCAP in the ICU have at least 50% chance of pneumonia with MDRs. Presence of additional risk factors can elevate likelihood of MDRs to 80%. The comparable outcomes may suggest that MDR pathogens are not inherently more virulent that non-resistant bacteria when treated correctly.

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INTRODUCTION

- The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) published guidelines for treating nosocomial pneumonia in 2005.[1] In addition to recommendations for patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), these guidelines identified a new cohort of patients at risk for multidrug-resistant (MDR) pathogens that should be included in the spectrum of HAP and VAP: healthcare-associated pneumonias (HCAP).
- Several studies, predominantly from the United States, have found drug-resistant pathogens in patients with HCAP,[2-5] supporting the recommendation that HCAP patients should receive antimicrobial therapy directed against drug-resistant pathogens. In contrast, European reports have shown a lower frequency of drug-resistant pathogens.[6-9]
- The ATS/IDSA guidelines identified multiple risk factors for infection with MDR pathogens. We postulate that selected risk factors may play a greater role than others.
- Our objective was to assess which risk factors are most predictive for infection with MDR pathogens in patients with pneumonia in the intensive care unit (ICU). We used these risk factors to develop a scoring tool to determine the risk of MDR pneumonia in the ICU. Additionally, we describe clinical and healthcare utilization outcomes of ICU patients with pneumonia caused by MDR pathogens.

METHODS

- IMPACT-HAP (Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia) is a multicenter initiative aimed at improving the care of ICU patients with pneumonia in four academic medical centers: University of Louisville Medical Center (Louisville, KY, USA), Ohio State University Medical Center (Columbus, OH, USA), Henry Ford Health System (Detroit, MI, USA), and University of Miami/ Jackson Memorial Hospital (Miami, FL, USA).
- Adult ICU patients were eligible for inclusion if there was clinical suspicion of pneumonia.
- Data collected included demographics and comorbid conditions, risk factors for MDR infection, healthcare utilization prior to the diagnosis of pneumonia, and all-cause mortality at day 28.
- Microbiology laboratories at all four centers provided semiquantitative cultures of tracheal aspirates or either semiquantitative or quantitative cultures of bronchoalveolar lavage specimens. All culture results were reviewed by the study coordinator and principal investigator at each site to classify identified microorganisms as pathogenic or not pathogenic.
- We defined MDR pathogens as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Acinetobacter* species.

Pneumonia definitions

- HCAP was defined as pneumonia acquired in a long-term care or subacute/intermediate healthcare facility; following a recent hospitalization (discharged within 90 days of current admission and previously hospitalized for >48 hours); or in a patient who received chronic dialysis care within the 30 days before study enrollment.
- VAP was defined based on the presence of clinical signs and symptoms of pneumonia, along with a new or evolving radiographic infiltrate, in patients who had undergone >48 hours of mechanical ventilation.
- HAP was defined as pneumonia with clinical onset >48 hours after hospitalization in an acute inpatient healthcare facility.

Statistical analysis

- Baseline characteristics and severity of illness of ICU patients with pneumonia, with or without MDR organisms, were compared using chi-square or Fisher exact tests for categorical variables and the Student *t* and nonparametric Wilcoxon tests, where appropriate, for continuous variables.
- Variables with *P* values <0.20 on bivariate analyses and those designated a priori based on our review of the literature (eg, late-onset pneumonia, nursing home residence) were included in a logistic regression model that examined their relationship with recovery of MDR pathogens.
- *P* values ≤0.05 were considered statistically significant.
- Statistical Analysis Software (SAS) version 9.2 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

RESULTS

- We identified 279 ICU patients who were diagnosed with pneumonia and had at least 1 pathogen identified.
  - Characteristic MDR organisms (MRSA, *P. aeruginosa*, *Acinetobacter* spp.) were found in 178/279 (63.8%) patients.
  - The proportion of patients with HCAP was the same in patients with and without MDR organisms (16.9% vs 15.8%; *P*=0.811).
- When patients who had pneumonia caused by MDR pathogens were compared with the rest of the ICU patients with pneumonia, we found only modest differences in baseline characteristics and severity of illness (**Table 1**).
  - Patients with MDR pathogens were more likely to present with a history of respiratory comorbidities (eg, chronic obstructive pulmonary disease [COPD]).

Table 1. Baseline characteristics and severity of illness of ICU patients with pneumonia, with or without MDR organisms[a]

Characteristic	MDR pneumonia (N=178)	Non-MDR pneumonia (N=101)	*P* value
Mean age ± SD, y	56.2 ± 18.3	59.8 ± 16.7	0.106
Median age (IQR), y	57 (44,72)	60 (50,76)	0.095
Age ≥65 years, n (%)	61 (34.3)	42 (41.6)	0.224
Gender, n (%)			0.134
Male	113 (63.5)	73 (72.3)	
Female	65 (36.5)	28 (27.7)	
Race, n (%)			0.453
White	119 (66.9)	63 (62.4)	
African American	51 (28.7)	29 (28.7)	
Hispanic	7 (3.9)	8 (7.9)	
Other	1 (0.6)	1 (1.0)	
Mean weight ± SD, lb	179.6 ± 56.5	181.2 ± 66.0	0.834
Mean CPIS ± SD at day 0	6.6 ± 1.8	6.3 ± 1.7	0.149
Mean APACHE II score ± SD	20.6 ± 7.6	21.2 ± 6.7	0.526
Bacteremia	20 (11.2)	13 (12.9)	0.684
Comorbidities, n (%)[b]			
Cardiac disease	30 (17.1)	28 (27.7)	0.035
Respiratory	45 (25.3)	14 (13.9)	0.025
Vascular disease	31 (17.6)	34 (33.7)	0.002
Renal disease	35 (19.9)	17 (16.8)	0.531
Diabetes	52 (29.6)	32 (31.7)	0.709
Pneumonia type, n (%)			
HCAP	30 (16.9)	16 (15.8)	0.811
HAP + VAP, combined	147 (83.1)	85 (84.2)	0.811
Mean LOS ± SD, hospital before diagnosis of pneumonia, d	11.6 ± 16.4	8.8 ± 9.4	0.115
Mean LOS ± SD, ICU before diagnosis of pneumonia, d	8.6 ± 11.9	6.5 ± 9.0	0.119
Mean LOS ± SD, MV before diagnosis of pneumonia, d	7.8 ± 12.5	5.3 ± 7.3	0.068

MDR, multidrug resistant; SD, standard deviation; IQR, interquartile range; CPIS, Clinical Pulmonary Infection Score; APACHE, Acute Physiology And Chronic Health Evaluation; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; LOS, length of stay; ICU, intensive care unit; MV, mechanical ventilation.
[a] MDR pathogens: methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
[b] Missing or unknown values were excluded from the analyses.

- Analysis of potential MDR risk factors (**Table 2**) revealed:
  - Patients with MDR organisms were more likely to have used antibiotics in the previous 30 days (69.5% vs 52.1%; *P*<0.005).
  - A greater number patients with MDR organisms had at least 1 risk factor for infection with MDR pathogens (96.6% vs 88.1%; *P*<0.01).
  - Both groups of ICU patients had high frequencies of late-onset HAP/VAP (≥5 days), previous hospitalization within the previous 90 days, and immunosuppressive disease and/or therapy.

Table 2. Frequencies of potential risk factors for MDR pathogens[a,b]

Risk factor	MDR pneumonia, n (%) (N=178)	Non-MDR pneumonia, n (%) (N=101)	*P* value
Antibiotics within prior 30 days	121 (69.5)	50 (52.1)	<0.005
Hospitalized for >5 days before diagnosis of pneumonia	119 (66.9)	64 (63.4)	0.556
Hospitalized ≥2 days within the prior 90 days	72 (40.7)	37 (37.0)	0.547
Immunosuppressive disease and/ or therapy	66 (37.7)	37 (38.5)	0.897
Residence in a nursing home or extended-care facility	31 (17.8)	12 (12.0)	0.203
Chronic dialysis within the prior 30 days	11 (6.3)	4 (4.0)	0.583
Home infusion therapy (including antibiotics)	5 (2.8)	6 (5.9)	0.216
Home wound care	3 (1.7)	5 (5.0)	0.147
Known family member with MDR pathogen	1 (0.8)	0	1
Any risk factor	172 (96.6)	89 (88.1)	<0.010

MDR, multidrug resistant.
[a] MDR pathogens: methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
[b] Missing or unknown values were excluded from the analyses.

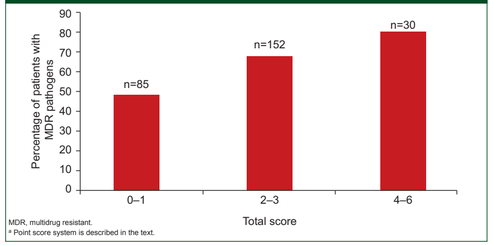
Logistic regression model

- Variables independently associated with the recovery of MDR organisms by in logistic regression:
  - History of COPD (odds ratio [OR], 2.52; 95% confidence interval [CI], 1.17 to 5.43; *P*=0.018)
  - Antimicrobial therapy in preceding 30 days (OR, 1.9; 95% CI, 1.02 to 3.54; *P*=0.042).
  - Residence in a nursing home or extended-care facility approached statistical significance (OR, 2.3; 95% CI, 0.90 to 5.84; *P*=0.080).
- We used these 3 variables to create a point score to determine the risk of ICU pneumonia due to MDR organisms (next section).

Development of a point scoring tool

- Using the 3 variables identified in logistic regression, we designed a point score to determine an ICU patient's risk of pneumonia with a typical MDR pathogen (MRSA, *P. aeruginosa*, *Acinetobacter* spp.). Points were assigned as follows:
  - Presence of a pulmonary comorbidity = 3 points
  - Use of antibiotics in preceding 30 days = 2 points
  - Admission from a nursing home or extended-care facility = 1 point.
- Patients were divided in 3 groups based on total score: 0 to 1 point, 2 to 3 points, and 4 to 6 points. We calculated the frequency of patients with MDR pathogens in each of the 3 scoring groups (**Figure 1**).

Figure 1. Proportion of patients with potential MDR pathogens (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* spp.) as a function of a point score system[a] (*P*<0.001 for trend)



MDR, multidrug resistant.
[a] Point score system is described in the text.

Treatment and outcomes

- Initial empiric therapy included at least 1 antibiotic active against the first (91.6%) and second (81.5%) pathogen(s) recovered from the 279 patients. Clinical success at day 14 (72.0% vs 62.2%; *P*=0.098), day 28 (65.4% vs 57.7%; *P*=0.248), and mortality at day 28 (14.9% vs 14.3%; *P*=0.895) were comparable between MDR/non-MDR pneumonia groups (**Table 3**).

Table 3. Treatment characteristics and outcomes, by presence of MDR organisms[a,b]

Risk factor	MDR pneumonia (N=178)	Non-MDR pneumonia (N=101)	*P* value
Pathogen 1 covered by empiric antibiotic therapy, n/N (%)	116/131 (88.6)	90/94 (95.7)	0.056
Pathogen 2 covered by empiric antibiotic therapy, n/N (%)	29/36 (80.6)	26/32 (81.3)	0.942
Mean LOS ± SD, hospital after diagnosis of pneumonia, d	21.5 ± 19.2	24.0 ± 18.4	0.295
Mean LOS ± SD, ICU after diagnosis of pneumonia, d	16.9 ± 15.3	18.4 ± 14.8	0.411
Mean LOS ± SD, MV after diagnosis of pneumonia, d	13.2 ± 17.2	13.0 ± 11.7	0.895
Clinical success, day 14, n/N (%)	121/168 (72.0)	61/98 (62.2)	0.098
Clinical success, day 28, n/N (%)	87/133 (65.4)	49/85 (57.7)	0.248
Mortality, day 28, n/N (%)	25/168 (14.9)	14/98 (14.3)	0.895

MDR, multidrug resistant; LOS, length of stay; SD, standard deviation; MV, mechanical ventilation.
[a] MDR pathogens: methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.
[b] The denominator for each calculation varies as a function of data available for analysis.

CONCLUSIONS

- Representative MDR organisms (MRSA, *P. aeruginosa*, *Acinetobacter* spp.) were present in 63.8% of ICU patients with HAP/VAP/HCAP in this series.
- The HCAP definition did not help discriminate between patients with MDR and non-MDR pathogens.
- Logistic regression analysis revealed several variables independently associated with recovery of a MDR organism:
  - Respiratory comorbidities (OR, 2.52; 95% CI, 1.17 to 5.43; *P*=0.018)
  - Previous antibiotics use (OR, 1.9; 95% CI, 1.02 to 3.54; *P*=0.042)
  - Residence in a nursing home or extended-care facility approached statistical significance.
- A simple risk score was able to further identify patients with MDR pathogens.
  - With a risk score of 4 to 6, patients have up to 80% chance of having pneumonia due to an MDR pathogen.
  - The risk score used a limited number of easily identifiable patient characteristics (respiratory comorbidity, systemic antibiotics within prior 30 days, admission from nursing home or extended-care facility).
- Patients with HCAP, HAP, and VAP in an ICU setting are at substantial risk for pneumonia due to a MDR pathogens.
  - Even in the 0- to 1-point group, the risk for MDR pathogens is close to 50%.
  - Initial broad-spectrum antibiotic treatment with planned de-escalation should be considered in all cases of ICU pneumonia.
- We observed high rates of active initial empiric therapy against the identified pathogen(s) in both groups, with comparable treatment outcomes.