

## Healthcare-associated pneumonia: a never-ending story

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In recent years, the changes in the healthcare system have shifted a considerable part of patients care from hospitals to the community, and the traditional distinction between community- and hospital-acquired infections has become less clear.<sup>1,2</sup> For this more frequent healthcare contact, patients, especially the frail elderly patient, have an higher risk of multidrug-resistant (MDR) colonization and to develop a more severe pneumonia, with a real risk to receive an inadequate empiric antibiotic therapy and, therefore, to have a fatal outcome.<sup>3</sup>

Pneumonia occurring before hospital admission in patients with recent contact with the health system has been termed *healthcare-associated pneumonia* (HCAP), and has been proposed as a new category of respiratory infection that needs a distinct approach when selecting empiric antibiotic therapy.<sup>4-7</sup> Since the publication of the 2005 update of the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) nosocomial pneumonia guidelines,<sup>8</sup> which incorporated for the first time the concept of HCAP, studies have provided original data on HCAP.<sup>9,10</sup> On the basis of the published data, patients with recent or chronic contact with the healthcare system appear to be at increased risk of infection with MDR pathogens. These pathogens are frequently not covered by the initial antimicrobial treatment recommended in guidelines for community-acquired pneumonia (CAP).<sup>11</sup> Many physicians are also unaware of the risk factors for HCAP and the clinical relevance of distinguishing it from CAP.<sup>12</sup> Since 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 concept of HCAP.<sup>13</sup> Recently Chalmers *et al.*<sup>14</sup> conducted a systematic review and meta-analysis of studies comparing the frequency of resistant pathogens (defined as methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae*, and *Pseudomonas aeruginosa*) in populations with HCAP compared with populations with CAP. In this study the rate of mortality was not increased in HCAP compared to CAP. The authors concluded that the HCAP concept is based on predominantly low-quality evidence and does not accurately identify resistant

pathogens, and mortality in HCAP does not appear to be due to a higher frequency of resistant pathogens. In a correspondence about this study,<sup>15</sup> we assessed that is very difficult to identify the main endpoint of this systematic review since no studies have been specifically designed to identify microbiology patterns of CAP and HCAP; as a matter of fact in all studies causative pathogens have been identified only in a minority of cases and no studies used, by protocol, invasive diagnostic procedures (*e.g.* bronchoscopy) to ascertain etiologies. Not all eligible papers were included in this meta-analysis and in the last year were published important retrospective and, especially, prospective study that confirmed a higher frequency of MDR pathogens in patients with healthcare contacts.<sup>16,17</sup>

Most studies observed statistically significant differences in terms of mortality between patients with CAP and HCAP. Some authors attributed this increased mortality to differences existing in terms of median age or presence of comorbidities,<sup>18</sup> but other studies confirmed that patients with HCAP had a worse prognosis independent of differences in age, comorbidities, or immunosuppression.<sup>6</sup> A critical disparity appears to be the greater administration of inappropriate initial antimicrobial therapy in patients with HCAP compared to those with CAP, as a result of a higher incidence of infection with antibiotic-resistant pathogens among patients with HCAP.<sup>19,20</sup> Pathogens associated with inappropriate antibiotic treatment in patients with HCAP are most often MRSA, *P. aeruginosa* or other non-fermenting Gram-negative rods, and antibiotic-resistant *Enterobacteriaceae*. In a Japanese study, HCAP patients with potentially drug-resistant pathogens (including MRSA, *P. aeruginosa*, and ESBL-producing *Enterobacteriaceae*) had a risk ratio of 14.0 with respect to inappropriate initial antibiotic treatment. Of importance, a comparison between these studies is very difficult, due to methodological differences and number of patients enrolled.

For this reason, recent studies have been published in order to provide scores based on epidemiological criteria and clinical clues for an early identification of patients with pneumonia due to MDR pathogens (Table 1).<sup>21-25</sup> In these studies were analyzed CAP and HCAP populations of patients and was observed that patients with risk factors for MDR had higher mortality rate than those who had not. Exposure to the hospital environment creates an opportunity for pathogens not commonly present in the community to colonize the upper respiratory and gastrointestinal tracts of patients.<sup>26</sup> Colonization and subsequent microaspiration of MDR pathogens acquired during healthcare exposure has been proposed as the mechanism for the occurrence of HCAP attributed to MDR pathogens. Admission to a

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room previously occupied by an MRSA-positive patient or a vancomycin-resistant *Enterococcus* (VRE)-positive patient significantly increased the odds of acquisition of MRSA and VRE.<sup>27</sup> However, a prospective study that evaluated 1100 patients with MRSA infections found that 131 (12%) were community-associated without any identifiable healthcare exposure (*i.e.*, no history of hospitalization, surgery, dialysis, or residence in a long-term care facilities (LTCF) within the previous 12 months).<sup>28</sup> Prolonged MRSA carriage does not appear to be rare, with 40% of patients who became colonized by MRSA during hospitalization remaining colonized for a median time of 8.5 months.<sup>29</sup> A retrospective cohort study from Switzerland found that the median time to clearance of MRSA colonization was 7.4 months, and that independent determinants for longer carriage duration were the receipt of antibiotics, use of an indwelling vascular device, presence of a skin lesion, immunosuppressive therapy, and hemodialysis.<sup>30</sup> New MRSA carriers also have a high risk of developing a sterile-site MRSA infection in the year following acquisition.<sup>31,32</sup>

Hospitalized patients can also be colonized *de novo* by MDR Gram-negative bacilli. It has been estimated that 8% of patients newly admitted to general medical wards become carriers of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* during their hospitalization.<sup>33</sup> 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*. 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.<sup>34</sup> To date, a limited number of good quality studies

have reported on the relationship between prescribing antibiotics and prevalence of antibiotic resistance for individuals treated in the primary care setting. Costelloe and co-workers systematically reviewed the literature and performed a meta-analysis describing the occurrence of antibiotic resistance in individuals prescribed antibiotics in primary care.<sup>35</sup> Among patients with respiratory infections, there was evidence of an association between antibiotics and resistance between 0 and 1 month, 0 and 2 months, and 0 and 12 months. Thus the effects of previous antibiotic prescription on resistance emergence were strongly detectable for up to 12 months after exposure, even in primary care.

Shorr *et al.* examined the individual risk factors for HCAP in an attempt to identify their relative importance for the presence of infection attributed to antibiotic-resistant bacteria. Overall, 639 patients were included in their study, and drug-resistant pathogens were found in 289 (45.2%) patients. Multivariate analysis identified recent hospitalization, residing in a nursing home, undergoing hemodialysis, and admission to an intensive care unit (ICU) as independent risk factors for antibiotic-resistant infection.<sup>15</sup> Similarly, a prospective observational study evaluating the accuracy of the ATS/IDSA criteria in predicting infection or colonization with MDR bacteria at the time of ICU admission found recent hospitalization, prior antimicrobial treatment, and residence in a nursing home as independent predictors of infection with MDR bacteria.<sup>36</sup> These criteria had high sensitivity (89%) and negative predictive value (96%), but low specificity (39%) and positive predictive value (18%) for the prediction of MDR bacteria. Another retrospective study of 190 patients

with nosocomial pneumonia and respiratory failure analyzed the factors associated with respiratory infection due to MDR bacteria. The presence of antibiotic-resistant infection was more common in patients meeting the HCAP definition (78% *vs.* 44%;  $P=0.001$ ). Multivariate analysis identified immunosuppression, LTCF admission, and prior broad-spectrum antibiotics in the previous 30 days as independent risk factors for infection with an antibiotic-resistant pathogen.<sup>37</sup> Infections occurring in LTCFs are likely to have a significant impact on the mortality rate of residents.<sup>38</sup> Older patients living in LTCFs frequently have a deterioration of consciousness, and are likely to aspirate oropharyngeal contents at night, usually without documentation of its occurrence. A previous study analyzing swallowing function reported a high incidence of aspiration pneumonia among hospitalized patients with a history of prior hospitalization of at least 2 days in the preceding 90 days or a stay at a nursing home or extended care facility.<sup>39</sup> Patients with dysphagia and feeding tubes are also at high risk of silent aspiration. There is evidence that residents of LTCFs are an important reservoir of MDR pathogens and contribute to the influx of MDR bacteria into the hospital setting.<sup>40</sup> Major sites of colonization are nares and wounds, and, in some institutions, up to 80% of decubitus ulcers were colonized. In addition, European studies have evaluated the prevalence of MRSA colonization in LTCFs, describing ranges between 8.6% and 22% of inhabitants.<sup>41,42</sup> MRSA colonization in LTCFs may have less severe consequences than in acute-care hospitals. MRSA carriers have a 30-60% risk of developing an infection during hospitalization in an acute-care hospital, whereas this risk is only 5-10% during a

stay at a LTCF. Elderly residents living in LTCFs are also at high risk of colonization and infection with MDR Gram-negative bacteria. A cross-sectional study performed in a 648-bed LTCF in Boston, Massachusetts, USA, showed that 51% of residents were colonized by MDR Gram-negative bacilli, the most common species being *Providencia stuartii*, *Morganella morganii*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Enterobacter* spp.<sup>43</sup> The prevalence of Gram-negative bacteria was significantly higher than the prevalence of VRE and MRSA, and a diagnosis of advanced dementia and non-ambulatory status were significant risk factors for harboring these pathogens. Subsequent studies have confirmed these observations.<sup>44,45</sup> Some investigators examining pneumonia occurring among residents of LTCFs have proposed the term *nursing home-acquired pneumonia*. El-Solh *et al.* conducted a study of 104 elderly patients (aged >75 years; 55% from the community and 45% from nursing homes) admitted to the ICU with severe pneumonia necessitating mechanical ventilation.<sup>46</sup> The distribution of infection-associated pathogens in patients admitted from nursing homes was significantly different from that of patients admitted from the community. Among patients with CAP, *Streptococcus pneumoniae* (14%) was the predominant pathogen, whereas among those with NHAP the most common isolated pathogen was *Staphylococcus aureus* (29%). In another study, El-Solh *et al.* showed 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 NHAP caused by drug-resistant pathogens.<sup>47</sup> These differences between the studies of Pop-Vicas and El-solh in term of eti-

**Table 1. Scores proposed for an early identification of patients with community-onset pneumonia due to multidrug-resistant pathogens.**

Author	Variable	Score	Risk stratification
Shindo <i>et al.</i> <sup>22</sup>	Prior hospitalization in the past 90 days	1	≤1 Low risk
	Immunosuppression	1	≥3 High risk
	Antibiotic use in the previous 90 days	1	
	Use of gastric acid-suppressive agents	1	
	Tube feeding	1	
	Non-ambulatory status	1	
Aliberti <i>et al.</i> <sup>24</sup>	No risk factors for MDR pathogen (including comorbidities)	0	≤0.5 Low risk
	≥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	≥3 High risk
	Residence in a nursing home or extended-care facility	3	
	Hospitalization for ≥2 days in the preceding 90 days	4	
	Chronic renal failure	5	
Shorr <i>et al.</i> <sup>25</sup>	Recent hospitalization in the past 90 days	4	<1 Low risk
	Residence in a nursing home or a long-term care facility	3	>5 High risk
	Long-term treatment with hemodialysis	2	
	Patients admitted to the ICU within 24 hours of evaluation in the ED	1	

MDR, multidrug-resistant; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ED, emergency department.

ology, respectively with a higher prevalence of gram-negative and gram-positive, could be explained by a different approach in the collection of samples. These observations foreshadow the non-homogeneity of the studies present in the literature.

Polverino *et al.* published data on 150 consecutive cases of NHAP observed over a 10-year period (1997-2007).<sup>48</sup> NHAP patients appeared similar to patients with HAP in terms of age, functional status, and comorbidities, but the in-hospital mortality was surprisingly low (8.7%). Despite the absence of significant differences between NHAP and CAP in terms of microbial etiology, the authors observed that among the 32 NHAP patients whose pathogens had antimicrobial susceptibility testing performed, initial antibiotic therapy was inappropriate in 12 (38%) patients infected with antibiotic-resistant pathogens. More importantly, the isolation of unusual microorganisms such as Gram-negative bacilli or MRSA was associated with a considerable increase in the mortality risk. Recently, in a new study Polverino *et al.* confirmed a low incidence of MDR pathogens both in CAP and HCAP patients;<sup>49</sup> authors conclude that microbial etiology of HCAP does not differ from CAP, and that HCAP patients in Spain do not need nosocomial antibiotic coverage. Surprisingly, the reported data conflict with a recent prospective study by Giannella *et al.*,<sup>50</sup> conducted in 72 internal medicine wards in Spain, and enrolling 1002 patients; in this study *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) caused 17 and 12.3% of HCAP, respectively; moreover, HCAP was an independent risk factors for pneumonia due do difficult-to-treat microorganisms.

Since data about microbiology of CAP and HCAP are contradictory, probably we need future interventional studies to define the role of MDR pathogens in patients with community-onset pneumonia. Until then, an individualized risk assessment for MDR organisms appears reasonable in patients fulfilling HCAP definition,<sup>51</sup> to determine which patients presenting with pneumonia may require broad-spectrum antibiotic therapy.<sup>52,53</sup> As matter of fact, a systematic, prospective analysis of a large population of patients with community-onset pneumonia is not easy, due to the difficult to reach valid samples, like bronchoalveolar lavage, especially in elderly patients with many comorbidities.

We are not sure that HCAP itself is the most appropriate tool to segregate patients with multidrug-resistant (MDR) etiology, but there is consistent evidence that a percentage of patients with community-onset pneumonia have a MDR infection, and in the majority of cases these patients fulfill HCAP definition. The changing etiology of infections in patients

exposed to the healthcare setting have been clearly demonstrated in various types of infection (including bacteremia, endocarditis, spontaneous bacterial peritonitis, urinary tract infections), but pneumonia remains an unresolved question due to the at least suboptimal quality of diagnostic microbiology investigations of published studies.

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