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Healthcare-associated pneumonia: Diagnostic criteria and distinction from community-acquired pneumonia

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SUMMARY

Background: Traditionally, pneumonia developing in patients who receive healthcare services in the outpatient environment has been classified as community-acquired pneumonia (CAP). However, recent investigations suggest that this type of infection, known as healthcare-associated pneumonia (HCAP), is distinct from CAP in terms of its epidemiology, etiology, and risk for infection with multidrug-resistant (MDR) pathogens.

Methods: A Medline literature review of available clinical studies using the term HCAP was conducted to determine outcomes compared to CAP and effective empiric treatment strategies.

Results: Analysis of multi-institutional clinical data showed that mortality in hospitalized patients with HCAP is greater than that in CAP, and patients with HCAP received inappropriate initial empiric antibiotic treatment more frequently than CAP patients. The bacterial pathogens associated with HCAP also differed from CAP with potentially MDR Gram-positive and Gram-negative bacteria being more common in HCAP.

Conclusions: All patients hospitalized with suspected HCAP should be evaluated for their underlying risk of infection with MDR pathogens. Because HCAP is similar to hospital-acquired pneumonia (HAP), both clinically and etiologically, it should be treated as HAP until culture data become available.

1. Introduction

In recent years, the traditional distinction between community-acquired and hospital-acquired infections has become less clear, with some infections having mixed characteristics of both types.[1,2] Pneumonia occurring before hospital admission in patients with recent contact with the health system has been termed 'health-care-associated pneumonia' (HCAP), and has been proposed as a new category of respiratory infection that needs a distinct approach when selecting empiric antibiotic therapy.[3–9]

Since the publication of the 2005 update of the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) nosocomial pneumonia guidelines, which incorporated for the first time the concept of HCAP, 12 studies have provided original data on HCAP.[4,6,10–19] 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 multi-drug resistant (MDR) pathogens.[3,4] These pathogens are frequently not covered by the initial antimicrobial treatment recommended in guidelines for community-acquired pneumonia (CAP).[7] Many physicians are also unaware of the risk factors for HCAP and the clinical relevance of distinguishing it from CAP.[9,20] 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.[21]

Therefore, the aim of this paper is to critically review the available evidence on HCAP and to propose a summary of recommendations regarding the definition of HCAP.

2. Methods

A Medline literature review of available clinical studies using the term HCAP was conducted to determine outcomes compared to CAP and to identify risk factors for HCAP. The references of the identified citations were also reviewed for additional pertinent studies.

3. Results and discussion

3.1. Definitions of HCAP: the body of evidence

A correct recognition of risk factors for HCAP is crucial, because acceptance of a broader definition of HCAP could potentially

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Table 1
Definitions of HCAP used in different studies according to four criteria

Study [Ref.]	Previous hospitalization	Hemodialysis; home infusion therapy	Residence in a nursing home or LTCF	Immunosuppression
ATS/IDSA guidelines	At least 2 days in the preceding 90 days	Yes; within 30 days	Yes	Immunosuppressive disease and/or therapy[a]
Kollef et al. 2005	In the preceding 30 days	Yes	Yes	No
Micek et al. 2007	In the preceding 360 days	Yes	Yes	Corticosteroids (5 mg/day or more), HIV infection, solid organ or bone marrow transplant, radiation or chemotherapy for cancer in the past 6 months, inherited or acquired immunodeficiency
Carratalà et al. 2007	At least 2 days in the preceding 90 days	Yes; within 30 days	Yes	Intravenous chemotherapy in the 30 days before pneumonia
Webster et al. 2007	At least 2 days in the preceding 30 days	Yes; within 30 days	Yes	Intravenous chemotherapy in the 30 days before pneumonia
Shorr et al. 2008	In the preceding 90 days	Yes	Yes	Presence of neutropenia, concurrent use of an oral corticosteroid (at least 5 days of therapy) or other immunosuppressive agent, active chemotherapy for malignancy, or infection with HIV
Venditti et al. 2009	At least 2 days in the preceding 180 days	Yes; within 30 days	Yes	Intravenous chemotherapy in the 30 days before pneumonia
Shindo et al. 2009	At least 2 days in the preceding 90 days	Yes; within 30 days	Yes	No
Rello et al. 2010	At least 2 days in the preceding 90 days	Yes; within 30 days	Yes	Intravenous chemotherapy in the 30 days before pneumonia
Schreiber et al. 2008	In the preceding 90 days	Yes; within 30 days	Yes	Immunosuppressive therapy in the 30 days before pneumonia
Cecere et al. 2010	In the preceding 90 days	Yes	Yes	HIV infection, neutropenia in the past 2 weeks, use of $\geq$20 mg of prednisone per day, or other immunosuppressant drugs

HCAP, healthcare-associated pneumonia; ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; LTCF, long-term care facility; HIV, human immunodeficiency virus.
[a] Not included in the definition, but considered a risk factor for multidrug-resistant pathogens.

increase the use of antimicrobial drugs, produce selection pressure for MDR organisms, and increase the cost of healthcare.[21] According to the 2005 ATS/IDSA guidelines, HCAP includes any patient presenting with pneumonia with one of the following features: (1) hospitalization for two or more days in an acute care facility within 90 days of infection, (2) patients from a nursing home or long-term care facility (LTCF), (3) patients who attended a hospital or hemodialysis clinic, and (4) those who received intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection.[3] These definitions have been incorporated by different authors in clinical studies (Table 1). Most studies considered prior hospitalization of at least 2 days in the 90 days preceding hospitalization as an important risk factor (Table 2).[12,15,16] However, other authors have found it useful to expand this interval to 180–360 days.[6,10] All HCAP studies are concordant in considering residence in a nursing home or in a LTCF and hemodialysis as risk factors for HCAP, and most authors also included immunosuppression as a potential risk factor.[6,10–12,14,16,18,19]

4. Role of MDR pathogens in patients with risk factors for HCAP

4.1. Previous hospitalization and previous antibiotic treatment

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. This

Table 2
Percentage of patients included in four criteria for HCAP (including overlapping cases)

Study [Ref.]	Previous hospitalization	Hemodialysis	Residence in a nursing home or LTCF	Immunosuppression
Kollef et al. 2005	Not reported	11.6%[a]	49.6%	23.2%
988 patients (median age 73 years)				
Micek et al. 2007	93.3%	10%	28.1%	39.7%
431 patients (mean age 59.8 years)				
Carratalà et al. 2007	43.7%	31.7%	25.4%	11.9%[b]
126 patients (mean age 69.5 years)				
Webster et al. 2007	25%	0%	44%	31%
28 patients (mean age 67.8 years)				
Shorr et al. 2008	63%	6.7%	18.9	30%
639 patients (mean age 59.7 years)				
Venditti et al. 2009	80%	3.3%	10%	6.7%
90 patients (mean age 62.2 years)				
Shindo et al. 2009	39%	7.1%	61%	9.2%
141 patients (mean age 81.3 years)				
Rello et al. 2010	56.8%	2.3%	38.5%	18.2%
44 patients[c] (median age 77 years)				
Schreiber et al. 2008	22.1%	15.3%	26.8%	22.1%
190 patients (mean age 60.9 years)				
Cecere et al. 2010	24%	5%	30%	58%
164 patients (mean age 46.1 years)				

HCAP, healthcare-associated pneumonia; LTCF, long-term care facility.
[a] Patients with a history of chronic renal disease, not specified if undergoing hemodialysis therapy.
[b] Long-term corticosteroid use.
[c] Only cases of pneumococcal HCAP.

phenomenon is primarily caused by the widespread use of antibiotics, often for prolonged periods of time, which select for drug-resistant pathogens.[22]

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.[5] Admission to a room previously occupied by a methicillin-resistant *Staphylococcus aureus* (MRSA)-positive patient or a vancomycin-resistant Enterococcus (VRE)-positive patient significantly increased the odds of acquisition of MRSA and VRE.[23] 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 LTCF within the previous 12 months).[24] 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.[25] 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.[26] New MRSA carriers also have a high risk of developing a sterile-site MRSA infection in the year following acquisition.[27,28]

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.[29] Risk factors for rectal carriage of ESBL-producing *Enterobacteriaceae* include female sex (odds ratio (OR) 11), nursing home residence (OR 6.9), recent antibiotic treatment (OR 9.8), and concomitant nasal carriage of MRSA and/or ESBL-producing *Enterobacteriaceae* (OR 5.8).[29] 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.[30]

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.[31] Very recently, 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.[32] Among patients with respiratory infections, there was evidence of an association between antibiotics and resistance between 0 and 1 month (with an OR of 2.1, 95% confidence interval (CI) 1.0–4.2), 0 and 2 months (pooled OR 2.4, 95% CI 1.4–3.9), and 0 and 12 months (pooled OR 2.4, 95% CI 1.3–4.5). 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.[14] Overall, 639 patients were included in their study, and drug-resistant pathogens were found in 289 (45.2%) patients. Multivariate analysis identified recent hospitalization (OR 4.2), residing in a nursing home (OR 2.7), undergoing hemodialysis (OR 2.11), and admission to an intensive care unit (ICU) (OR 1.62) as independent risk factors for antibiotic-resistant infection. 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 (OR 3.9), prior antimicrobial treatment (OR 2.3), and residence in a nursing home (OR 2.0) as independent predictors of infection with MDR bacteria.[33] 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.[33]

Another retrospective study of 190 patients with nosocomial pneumonia and respiratory failure analyzed the factors associated with respiratory infection due to MDR bacteria.[34] 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 (adjusted OR 4.85; $p < 0.001$), LTCF admission (adjusted OR 2.36; $p = 0.029$), and prior broad-spectrum antibiotics (adjusted OR 2.12; $p = 0.099$) in the previous 30 days as independent risk factors for infection with an antibiotic-resistant pathogen.[34]

4.2. Residence in a long-term care facility

Infections occurring in LTCFs are likely to have a significant impact on the mortality rate of residents.[35] 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.[36] Patients with dysphagia and feeding tubes are also at high risk of silent aspiration.[3]

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.[37–39] Studies performed more than 10 years ago in Veterans' Affairs facilities in the USA showed a high prevalence of MRSA colonization among residents, with rates ranging from 13% to 35%.[40,41] Major sites of colonization were nares and wounds, and, in some institutions, up to 80% of decubitus ulcers were colonized.[40,41] In addition to studies from the USA, European studies have evaluated the prevalence of MRSA colonization in LTCFs, describing ranges between 8.6% and 22% of inhabitants.[42–46] 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.[47]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*.[48] 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.[48] Subsequent studies have confirmed these observations.[49–51]

Some investigators examining pneumonia occurring among residents of LTCFs have proposed the term 'nursing home-acquired pneumonia' (NHAP). El-Solh et al. conducted a study of 104 elderly patients (aged $\geq$75 years; 55% from the community and 45% from nursing homes) admitted to the ICU with severe pneumonia necessitating mechanical ventilation.[52] 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%).[52] In another study, 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 NHAP caused by drug-resistant pathogens.[53]

Three prospective, randomized trials of therapy for NHAP have provided some insight on HCAP. Unfortunately, these studies included a large proportion of patients not requiring hospitalization, receiving oral or parenteral monotherapies such as levofloxacin,[54] cefepime,[55] or ertapenem[56] (in the latter case patients with pseudomonal risk or severe illness were excluded). Bacteriologic data were not available and patients with mild NHAP had good clinical outcomes when treated with antimicrobial monotherapy.[54–56] This differed from patients with NHAP included in a multicenter prospective study conducted in Germany, who were characterized by a more than four-fold increased mortality rate compared with elderly patients living in the community (28.8% vs. 6.9%).[57] Interestingly, a higher incidence of Gram-negative infections was observed in the NHAP group (18.8% vs. 5.5%), and 39.7% of NHAP patients had a change in their original antibiotics (15.6% due to sequential therapy, 14.1% due to ineffectiveness, 5.5% de-escalation, and 2.0% due to resistance).[57]

More recently, Polverino et al. published data on 150 consecutive cases of NHAP observed over a 10-year period (1997–2007).[58] NHAP patients appeared similar to patients with HAP in terms of age, functional status, and co-morbidities, but the in-hospital mortality was surprisingly low (8.7%).[58] 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 (OR 16.4, 95% CI 2.1–128.9; $p < 0.008$).[58]

4.3. Hemodialysis and patients receiving home intravenous therapy

The population of patients who undergo chronic hemodialysis (CHD) has contributed substantially to the emergence and dissemination of antimicrobial-resistant pathogens. Two essential factors have contributed to this: (1) patient-to-patient transmission of pathogens, and (2) the selective pressure from antibiotic exposure. The dialysis unit and its population provide an ideal setting for cross-transmission of pathogens, because regular hemodialysis is required three times per week in a closed setting and because healthcare workers provide concurrent care to multiple patients. Additionally, patients undergoing CHD require one or two hospital admissions per year.[59] During these hospitalizations, patients are frequently exposed to the ICU, invasive procedures, and antibiotics.[60]

VRE and MRSA are among the antimicrobial-resistant bacteria that have been intensely investigated in this patient population. The prevalence of MDR Gram-positive pathogens is variable. A cross-sectional analysis of 198 hemodialysis outpatients showed low MRSA (5.6%) and VRE (3.14%) colonization rates.[61] However, a 5-year surveillance study on patients undergoing continuous peritoneal dialysis (CPD) found that 76% of patients had at least one nares and/or central venous catheter (CVC) exit culture positive for MRSA; out of these, 44% were persistent carriers, and this status was associated with a three-fold higher risk for CPD-related infections and six-fold higher rates of vancomycin consumption compared to those for the intermittent carriers.[62] Lu et al. found that pulmonary disease (OR 4.8), recent admission to a hospital (OR 2.7), and recent antibiotic usage (OR 2.3) were significantly associated with MRSA carriage among patients undergoing dialysis, their families, and healthcare workers in the dialysis unit.[63] More recently, Mermel et al., in a prospective, multicenter study, identified MRSA colonization in 20% of elderly residents of LTCFs, 16% of HIV-infected outpatients, 15% of outpatients receiving hemodialysis, 14% of inpatients receiving hemodialysis, and 6% of others.[64]

Hemodialysis patients can also be at risk for colonization and infection with MDR Gram-negative bacteria. A prospective cohort study of an outpatient hemodialysis unit showed that 28% of patients were colonized with one or more MDR bacteria. MDR Gram-negative bacilli were recovered from 16% of patients at enrollment, compared with 13% and 5% of patients with VRE and MRSA, respectively.[65] The subgroup of chronic hemodialysis patients who were at highest risk for harboring MDR Gram-negative bacilli at enrollment were patients who resided in a LTCF and those with antibiotic exposure in the previous 3 months.[65]

Colonization by MDR pathogens in hemodialysis patients is a well recognized risk factor for bloodstream infections, but there are few studies on pneumonia in this category of patients.[66] Berman and co-workers reviewed the infections occurring in 433 patients undergoing chronic hemodialysis at a single hospital-based dialysis program over a 9-year period.[67] Pneumonia accounted for 13% of all infections and was the third most frequent cause of infection. The most common causative pathogens for pneumonia were *S. aureus* (MRSA was involved in 75% of cases), *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, and *E. coli*. Traditional community pathogens such as *Moraxella* species, *Haemophilus influenzae*, and *S. pneumoniae* accounted only for 15% of cases (28 out of 186 episodes).[67]

4.4. Outcome of HCAP in the published studies

Fig. 1 describes the mortality rates for CAP and HCAP observed in the different studies comparing these conditions. Despite some differences regarding the inclusion criteria described above, all 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 co-morbidities,[16] but other studies confirmed that patients with HCAP had a worse prognosis independent of differences in age, co-morbidities, or immunosuppression.[6] 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.[10,12–15]

Fig. 2 describes the odds ratio (OR) for mortality in patients with HCAP treated with inappropriate empiric antibiotic therapy. These data indicate that patients given inappropriate initial antimicrobial therapy are more likely to die during hospitalization. The

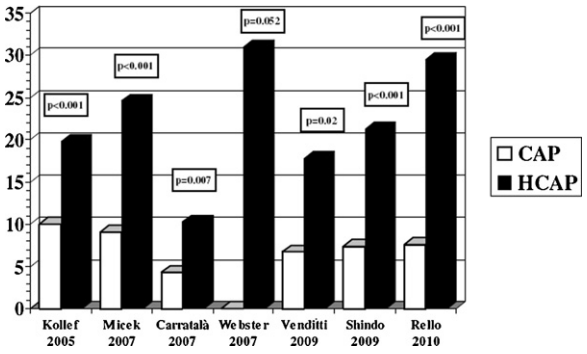

Fig. 1. Mortality rates (%) for community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP) in different published studies.

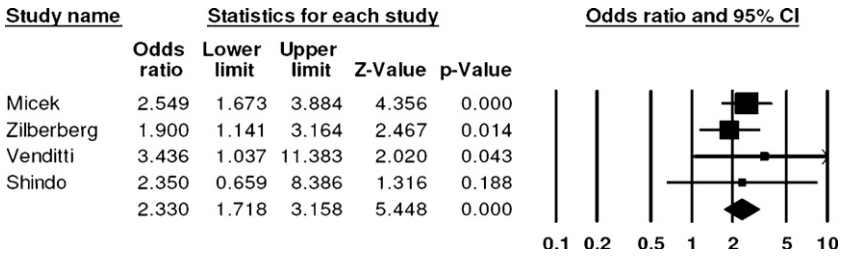

Fig. 2. Odds ratios for mortality in patients with healthcare-associated pneumonia (HCAP) treated with inappropriate antimicrobial therapy or with antibiotics not recommended in the ATS/IDSA guidelines.

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*.[6,10] 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 (95% CI 4.5–43.6; $p < 0.001$) with respect to inappropriate initial antibiotic treatment.[15]

5. Conclusions

The body of evidence presented in this review provides support for the definition of HCAP, which represents a category of pneumonia epidemiologically and microbiologically distinct from CAP.[68] Physicians should correctly identify patients with HCAP in order to provide optimal clinical management. As recommended by the ATS/IDSA nosocomial pneumonia guidelines, an empirical broad-spectrum antibiotic regimen is suggested in most patients with serious HCAP infection, especially those individuals requiring intensive care and mechanical ventilation.[3] However, the selection of initial empiric therapy must be patient-oriented and based on the local patterns of antibiotic resistance.

Conflict of interest

No conflict of interest to declare.

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