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EDITORIAL

A new category — healthcare-associated pneumonia: a good idea, but problems with its execution

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In regards to community-acquired pneumonia (CAP), a plethora of observational studies have defined the etiologies of CAP with surprising consistency [1]. The discovery that had the most impact on management was the recognition of atypical pathogens (especially *Legionella pneumophila* and *Chlamydia pneumoniae*) as common pathogens of CAP in the immunocompetent host. Major advances in rapid diagnosis, especially the urinary antigen test for *L. pneumophila* and *Streptococcus pneumoniae*, have occurred in the past decade. Two classes of antimicrobial agents, which targeted both the classical "typical" pathogens (*S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*) and atypical pathogens, were commercially released: the newer macrolides and quinolones. With a clearer delineation of pathogens, the development of diagnostic methods to identify the pathogens and effective therapy, a golden era of progress regarding CAP occurred. This culminated in the formulation of three influential consensus guidelines for management: the Canadian Consensus guidelines [2], the American Thoracic Society guidelines [3], and the Infectious Diseases Society of America guidelines [4]. Guidelines from Europe, Asia, and other countries soon followed.

In the past decade, two interesting developments unfolded simultaneously in the field of hospital-acquired pneumonia (HAP): (1) the emergence of multidrug-resistant hospital-acquired pathogens and (2) the recognition that these occur with different frequencies in defined hospital populations. The clinical subsets that were most distinct were patients hospitalized in intensive care units (ICUs) and patients residing in long-term care facilities and nursing homes. The latter group was often placed as a subset of patients with CAP, but it was soon clear that the pathogens of pneumonia in nursing homes were more similar to those of HAP rather than CAP, simply because the risk factors of comorbidity, instrumentation, and prolonged prior antibiotic use were more similar to HAP than CAP.

Research in the fields of HAP and ventilator-associated pneumonia (VAP) has been far more challenging given the difficulties in establishing a reference standard that could be widely accepted. Patients with HAP were much more heterogeneous than patients with CAP, and the reason for the heterogeneity was the clinical setting (hospitalization in the ICU vs. a general ward vs. residence in a nursing home). Moreover, there were other subsets of patients that did not fit well into the categories of HAP and VAP. So, a new category was proposed — healthcare-associated pneumonia (HCAP).

This new category was formally sanctified in the 2005 ATS Guidelines for Management of Adults with HAP, VAP, and HCAP [5]. One important feature of HCAP relevant to management was that this patient population was likely to have a higher frequency of multidrug-resistant pathogens as compared to CAP, but a lower frequency than patients with VAP. Pathogens that are commonplace in the ICU may not be so common in other areas of the hospital. This is intuitively obvious and logical, and has implications for targeted antibiotic therapy.

A number of studies have been performed using the conceptual classification of HCAP. Here, we will review

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three large-scale studies of HCAP or HAP: (1) A prospective multicenter study of 12 Spanish academic hospitals evaluating HAP in 165 patients. By definition, none were in the ICU [6]. (2) A retrospective study involving 165 hospitals in the USA, taken from a large multi-institutional database [7]: 988 patients were classified as HCAP, 835 were HAP, and 499 were VAP. (3) A study published in this issue of EJCMID in which 69 hospitals were evaluated in a multicenter international prospective study [8]. Unlike the first two studies mentioned above, the study of Yakovlev et al. [8] is a milestone since it applies the concept of HCAP to case management. This is the first interventional comparative study of two antibiotics for the treatment of patients with HAP and HCAP (the authors labeled these patients as having hospital/healthcare-associated pneumonia, abbreviated as HHCAP). The study group included patients hospitalized with HAP in wards other than ICUs and cases of pneumonia occurring in nursing homes/long-term care facilities.

In the HCAP study of Kollef et al. [7], 50% of pneumonia cases occurred in nursing home and long-term care facilities. For those patients with HAP, the pneumonias were not ventilator-associated. The classifications for pneumonia contracted in nursing home/long-term care facilities in this large retrospective study were not mutually exclusive, since 10% of HAP and 50% of HCAP infections occurred in patients in nursing home/long-term care facilities. In terms of overall HAP in all three studies, pneumonia contracted in nursing home or long-term care facilities ranged from 10% [7] to 24% [8].

The pathogens of pneumonia can be classified as endogenously or exogenously acquired. Endogenous microorganisms are colonizing microflora of the patients, while exogenous microorganisms are transmitted to the host from an external source, such as food or water. In CAP, the endogenous microorganisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*, both of which colonize elderly patients. One exogenous pathogen is *Legionella*, which is transmitted via aspiration from contaminated drinking water (aerosols from air conditioners and cooling towers are actually much less common than currently believed).

In HAP, HCAP, and VAP, the major pathogenic mechanism is aspiration, in which colonization of the oropharynx is an important antecedent event. The colonizing flora is endogenous gastrointestinal flora emerging under the pressure of broad-spectrum antibiotics (e.g., EBSL-producing *Klebsiella* spp) or exogenous waterborne pathogens (*Acinetobacter* spp, *Stenotrophomonas maltophilia*, *Legionella pneumophila*). In HAP, especially VAP, the use of multiple empiric antibiotics for a prolonged duration has long been employed, leading to the ready emergence of antibiotic-resistant microorganisms.

The changing bacterial flora of the oropharynx is linked to duration of hospitalization and severity of illness. In one oft-cited study, gram-negative bacilli colonizing the oropharynx were found to be present in 6% of healthy non-hospitalized subjects, 35% of moderately ill hospitalized patients, and 63% of critically ill hospitalized patients [9]. In addition, the frequency of pneumonia caused by gram-negative bacilli increased along with an increase in oropharyngeal colonization [10]. Microaspiration occurs in patients with states of altered consciousness including those caused by sedation, seizures, or neurologic diseases in which the protective gag reflex may be compromised. In the context of HAP and VAP, nasogastric tubes and endotracheal tubes are established precipitating factors for aspiration.

Many of the more resistant organisms, especially the Enterobacteriaceae including *Serratia*, *Providencia*, *Enterobacter*, and *Proteus vulgaris* are relatively avirulent, but they have the capacity to acquire genetic elements that convey antibiotic resistance. Thus, while they are less invasive in causing life-threatening disease, they pose a problem because of their tendency to be multidrug resistant.

The three pathogens that are prominent examples of multidrug resistance in the ICU are *Pseudomonas aeruginosa*, *Acinetobacter* spp, and methicillin-resistant *Staphylococcus aureus* (MRSA). *P. aeruginosa* and *Acinetobacter* are also ready colonizers of the respiratory tract, such that definitive diagnosis of pneumonia is challenging. The key point of the study of Yakovlev et al. [8] is that the investigators assumed that empiric antibiotic coverage for these three colonizers/pathogens was unnecessary.

P. aeruginosa and MRSA are the most common causative organisms of nosocomial pneumonia according to National Nosocomial Infection Surveillance data [11], and initial antibiotic treatment is often inadequate for treating them [12, 13]. *P. aeruginosa* is also the most common multidrug-resistant gram-negative bacterial pathogen, and it is often quite virulent. A small study of 48 patients conducted using fiberoptic bronchoscopy (bronchoalveolar lavage and/or protected specimen brush) showed that crude mortality of VAP caused by *P. aeruginosa* and/or other non-fermentative gram-negative bacilli was 71% and attributable mortality was 43% [14].

The main problem associated with *Acinetobacter* spp resides in its ability to acquire antibiotic-resistant genes extremely rapidly [15] and its propensity to cause outbreaks in the ICU setting [16]. However, colonization is common and attributable mortality is low [16].

Fifty percent of *S. aureus* strains involved in VAP proved to be MRSA in one study [17], and the mortality was significantly higher in patients with VAP if MRSA was the culprit [18]. Furthermore, MRSA strains are often resistant to other antibiotics, with 80% being macrolide resistant and 90% being quinolone resistant [19].

In the study of 165 non-ICU pneumonia cases conducted by Sopena et al. [6], strict criteria were used for defining etiology in 60 patients, and *S. pneumoniae* was the most common pathogen (10%) followed by *Legionella pneumophila* (4%). Gram-negative bacilli included the Enterobacteriaceae (*E. coli*, *Serratia marcescens*, *Enterobacter* spp, *K. pneumoniae*) (5%), *P. aeruginosa* (4%), *Acinetobacter* spp (3%), and MRSA (1%) [6] (Table 1). These incidence rates are similar to those found in the study of Yakovlev et al. [8]: *P. aeruginosa* (6%), *Acinetobacter* spp (2%), and MRSA (7%) (Table 1).

Among the *P. aeruginosa* infections in the studies of Yakovlev et al. [8] and Sopena et al. [6], none were bacteremias. It is notable that *P. aeruginosa* was isolated from two patients who were randomized to receive ertapenem, a non-antipseudomonal antibiotic, which has little in vitro activity against *P. aeruginosa*; both patients responded, thus underscoring the difficulty in distinguishing colonization from pathogenicity [8]. Surprisingly, in the patients classified as HCAP or HAP in the study of Kollef et al. [7], the frequency of *P. aeruginosa* was 25% and 18%, respectively. *Acinetobacter* was rare in all three studies (3% Sopena et al. [6], 2% Yakovlev et al. [8], and 3% HCAP and 2% HAP in the Kollef et al. study [7]). So, the assumption that empiric coverage for *Acinetobacter* is unnecessary for non-VAP pneumonia was confirmed in all three studies.

The widest variation of results amongst the three studies was seen for *Staphylococcus aureus*. Pneumonia due to *S. aureus* occurred infrequently in the studies of Sopena et al. [6] (1%) and Yakovlev et al. [8] (7%) (Table 1), while in the study of Kollef et al. [7], the incidence of *Staphylococcus aureus* was a staggering 27% in HCAP and 23% in HAP. It was also the most frequent pathogen in CAP. Such a high incidence of *S. aureus* has not been duplicated in most published studies of HAP or CAP. It should be noted that the data from this study was retrospectively retrieved from a large inpatient database in the USA without the use of uniform criteria for distinguishing colonizing bacteria from pathogens.

The issue of *Legionella pneumophila* as a pathogen in both HAP and HCAP is dealt with inadequately in the ATS guidelines [5]. *L. pneumophila* will never be diagnosed in investigations of pneumonia unless diagnostic tests for it are routinely performed [1]. *L. pneumophila* cannot be diagnosed with confidence on the basis of clinical manifestations and general laboratory tests [20, 21]. This weakness was conceded in both the Yakovlev et al. [8] and Kollef et al. [7] studies, and this point is particularly pertinent for the Yakovlev et al. [8] study, since neither of the two study drugs (cefepime and ertapenem) is active against *Legionella*. In the study of Sopena et al. [6], the authors performed both sputum cultures for *Legionella*, using specialized media, and the urinary antigen test for *Legionella*. In that study, the second most common etiology

Table 1 Comparison of three studies of healthcare-associated pneumoniae (HCAP) and hospital-acquired pneumonia (HAP)

Reference[a]	Country	No. of hospitals	Design	No. of patients	Location		Organism[b]			Crude mortality
					Hospital	Nursing home	*P. aeruginosa*	*Acinetobacter* sp	*S. aureus*	
HCAP										
[6]	Spain	12	Prospective; cohort	165	NA	NA	4% (7/165)	3% (5/165)	1% (1/165)	18% (30/165)
[8]	International (12 countries)	69	Prospective; randomized, double blind	303	67% (202/303)	24% (74/303)	6% (11/195)	2% (3/195)	7% (14/195)	5% (14/303)
[7]	USA	165	Retrospective; cohort	988	NA	50%	25%	3%	27%	20%
HAP										
[7]	USA	165	Retrospective; cohort	835	NA	10%	18%	2%	23%	19%
VAP										
[7]	USA	165	Retrospective; cohort	499	NA	9%	21%	3%	15%	29%

[a] Caution must be used in comparing figures since definition of HCAP and HAP differed in the three studies, as did microbiologic criteria and number of evaluable patients

[b] Numerator/denominator were not explicitly given in the Kollef study

VAP ventilator-associated pneumonia

was *L. pneumophila*! For future controlled studies of HCAP, we recommend, at a minimum, that the *Legionella* urinary antigen test be performed routinely, especially if the hospital water supply is colonized by *L. pneumophila* [22].

Antibiotics with specific anaerobic activity have not been routinely recommended and may be indicated in patients with risk factors, such as severe periodontal disease, putrid sputum, or radiological evidence of necrotizing pneumonia or lung abscess [23]. In a study of aspiration pneumonia in VAP, 25 patients had blinded protected specimen brush and mini-BAL and only one non-pathogenic anaerobic organism was isolated [23]. Thus, the addition of metronidazole at the discretion of the investigator for patients in the cefepime arm of the study of Yakovlev et al. [8] may not necessarily have led to an improved outcome. Ertapenem has respectable coverage for anaerobes.

A limitation of the Yakovlev et al. study [8] was the large number of exclusions, which included malignancy, rapidly progressive diseases (undefined), acute hepatic failure, dialysis, diseases with hepatic dysfunction, and neutropenia. The authors were able to recruit only 303 patients from 69 institutions over 3 years. So, the authors' findings cannot be extrapolated to a broader group of patients. Excluding neutropenic patients and dialysis patients is understandable, because of their predilection for *P. aeruginosa* and MRSA, respectively. The Clinical Pulmonary Infection Score might be a more useful criterion for inclusion criteria for this type of study, since it allows enrollment of many more patients. Its use has been notably successful in studies of ICU pneumonia [24, 25].

Nevertheless, the implications from the Yakovlev study [8] are clear and clinically significant. Defining a group of patients with pneumonia outside of the ICU can allow the use of antibiotic monotherapy without compromising the efficacy of therapy. Emergence of resistance would theoretically be expected to be lower.

While the intent of defining HCAP and HAP is rational and logical, the definitions varied amongst the three studies. In fact, the classification schemes are inherently imprecise, because patient groups overlap in the HCAP category (Fig. 1). For example, non-ICU pneumonia in the Sopena et al. study [6] was not identical to non-VAP. In the study of Kollef et al. [7], cases of pneumonia occurring in nursing home/long-term care facilities enrolled in the retrospective study included those patients who were transferred to the acute-care hospitals; it did not include those who remained in the nursing home/long-term care facilities. With the overlapping categories, data from the three studies were difficult to compare (Table 1).

The best-defined group was patients residing in long-term care facilities or nursing homes, and we suggest this should be a distinct category in future studies. We believe a more precise classification that minimizes overlapping categories will allow easier comparison between studies so a rigorous database can be accumulated for future investigations (Fig. 1). The Yakovlev et al. study [8], despite its limitations, is an important preliminary proof-of-concept study that shows that monotherapy without the use of anti-pseudomonal antibiotics is feasible for a notable segment of hospitalized patients with pneumonia.

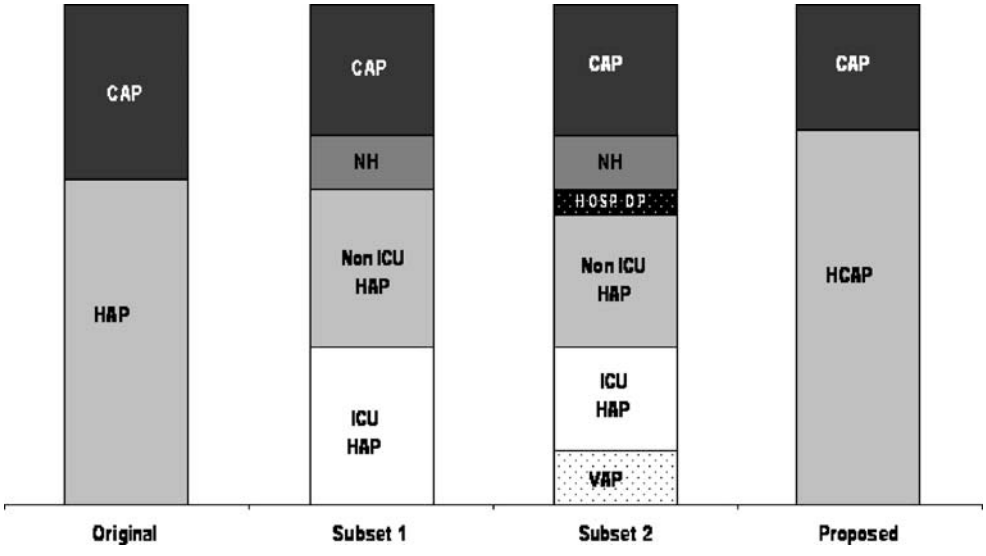

Fig. 1 The original histogram depicts the earlier simplified perspective of pneumonia. Histograms labeled as Subsets 1 and 2 show the complexity of the categorization of patients more likely to have multidrug-resistant pathogens. The proposed histogram shows the numerous subsets that are now covered by the single category, HCAP. *CAP* community-acquired pneumonia, *HAP* hospital-acquired pneumonia, *ICU* intensive care unit, *HCAP* healthcare-associated pneumonia, *Hosp OP* hemodialysis unit patients or outpatients receiving home IV therapy, wound care or having a percutaneous device, *NH* nursing home, *VAP*, ventilator-associated pneumonia

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