Healthcare-Associated Pneumonia Does Not Accurately Identify Potentially Resistant Pathogens: A Systematic Review and Meta-Analysis

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(See the editorial commentary by Restrepo and Aliberti on pages 340–1.)

Background. The 2005 American Thoracic Society/Infectious Diseases Society of America guidelines introduced a concept of healthcare-associated pneumonia (HCAP) to define patients at higher risk of antibiotic-resistant pathogens, thus requiring broad spectrum therapy. There has been no systematic evaluation of the ability of this definition to identify antibiotic-resistant pathogens.

Methods. We conducted a systematic review and meta-analysis of studies comparing the frequency of resistant pathogens (defined as methicillin-resistant *Staphylococcus aureus*, Enterobacteriaceae, and *Pseudomonas aeruginosa*) in populations with HCAP compared with populations with community-acquired pneumonia (CAP). Predictive accuracy was evaluated using the area under the receiver operator characteristic curve (AUC). The frequencies of pathogens in each group were pooled using a random effects model.

Results. Twenty-four studies were included (n = 22 456). Overall study quality was poor. HCAP was associated with an increased risk of methicillin-resistant *S. aureus* (odds ratio [OR], 4.72; 95% confidence interval [CI], 3.69–6.04) enterobactericeae (OR, 2.11; 95% CI, 1.69–2.63), and *P. aeruginosa* (OR, 2.75; 95% CI, 2.04–3.72; all *P* < .0001), but these analyses were confounded by publication bias. The discriminatory ability of HCAP for resistant pathogens was low (AUC, 0.70; 95% CI, 0.69–0.71) and was lower in high-quality (AUC, 0.66; 95% CI, 0.62–0.70) and prospective studies (AUC, 0.64; 95% CI 0.62–0.66). After adjustment for age and comorbidities, mortality was not increased in HCAP (OR, 1.20; 95% CI, 0.85–1.70; *P* = .30).

Conclusions. The HCAP concept is based on predominantly low-quality evidence and does not accurately identify resistant pathogens. Mortality in HCAP does not appear to be due to a higher frequency of resistant pathogens.

Keywords. healthcare-associated infection; pneumonia; mortality; meta-analysis; guidelines.

Pneumonia has traditionally been classified as either community or hospital-acquired or as pneumonia in the immunosuppressed host. These distinctions are important because community-acquired pneumonia (CAP) is typically caused by organisms such as *Streptococcus pneumoniae*, which are sensitive to first-line antibiotics, whereas hospital-acquired pneumonia (HAP) is typically caused by *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), Gram-negative Enterobacteriaceae, and *Pseudomonas aeruginosa* [1, 2]. Pathogens in immunosuppressed patients are even more diverse and include opportunistic pathogens. Immunosuppressed patients and those with HAP therefore require broad-spectrum initial antibiotic treatment and are at higher risk of treatment failure and mortality.

In 2005, the American Thoracic Society/Infectious Diseases Society of America guidelines introduced a

new classification of pneumonia: healthcare-associated pneumonia (HCAP) [2]. This group included those patients presenting from the community with pneumonia but who had frequent contacts with healthcare. The definition includes nursing-home residents, patients hospitalized for >2 days the preceding 90 days, patients receiving home infusion therapy and domiciliary wound care, and patients attending a hemodialysis center within the preceding 30 days [2].

A multicenter study published around the same time indicated that these patients had an excess of mortality due to a high frequency of potentially resistant pathogens not covered by initial empiric antibiotics [3]. It was recommended, therefore, that these patients should therefore receive broad-spectrum antibiotic therapy similar to HAP [3].

This concept has been very controversial [4, 5]. Most studies, particularly from Europe, have not replicated the higher frequency of drug-resistant pathogens in HCAP [6–9]. The quality of HCAP studies has been strongly criticized. A causal association between excess mortality in HCAP patients and a failure to cover potentially-drug resistant pathogens has not been established [4]. Others have argued that the value of the HCAP concept varies by geographical region, being more useful in the United States than elsewhere [10, 11].

There is no agreement on the value of the HCAP concept to identify drug-resistant pathogens. We therefore sought to systematically evaluate the literature to determine how accurately HCAP identifies patients with potentially resistant pathogens, to systematically evaluate the quality or potential for bias in HCAP studies, and to thereby validate or reject the HCAP concept.

METHODS

This study was a systematic review and meta-analysis conducted according to MOOSE (meta-analysis of observational studies in epidemiology) guidelines [12].

Search Criteria
The study was based on a search of the PUBMED database (January 1980–January 2013). The following search strategy was used: ("healthcare" OR "health-care" OR "hospital" OR "nursing-home") AND ("associated" OR "acquired" OR "related") AND pneumonia. Additional searches were performed based on the following search terms that form part of the HCAP definition: "care facility," "infusion therapy," "wound care," "dialysis," and "pneumonia." No language criteria were applied. Full articles of potentially appropriate abstracts were reviewed. Conference abstracts were excluded. The search was repeated in EMBASE and Web of Science and supplemented by reviewing of reference lists, bibliographies, and investigator files.

Data Extraction
Articles were independently reviewed by 2 investigators. Nonrelevant studies were excluded based on title and abstract review alone. Data extraction and quality assessment were performed in a blinded fashion. The modified Hayden's criteria were used to assess quality [13]. Disagreement between investigators was resolved independently by a third investigator.

Study Inclusion and Exclusion Criteria
Studies were considered eligible if they fulfilled the following criteria: original publications; inclusion of a cohort of patients with HCAP or nursing home–acquired pneumonia (for the nursing home–acquired pneumonia subanalysis) compared with a CAP cohort; and reporting of 1 of the study outcomes (microbiology or clinical outcomes).

Study Outcomes
Primary Analysis
The primary outcome was the frequency of potentially resistant microorganisms in the HCAP group compared with the CAP group. Potentially resistant microorganisms were defined as MRSA, Gram-negative Enterobacteriaceae, and *Pseudomonas aeruginosa* because these organisms have been the focus of previous studies in HCAP and often require different empirical therapy from CAP [2–4].

Secondary analyses were each of these organisms individually, the frequency of typical CAP pathogens (*S. pneumoniae*, *Haemophilus influenzae*, and *S. aureus*) and atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*).

The denominator for the frequency of pathogens in each group was the total number of patients with HCAP or CAP. Clinical outcomes were mortality and intensive care unit (ICU) admission.

Subanalysis
A priori, the authors proposed several subgroup analyses to answer questions identified from the literature and explore sources of heterogeneity:

1. Analysis of studies limited to Europe, North America (United States and Canada), and Asia because it has been proposed that HCAP may be more useful as a concept in North America than in other regions.
2. Analysis limited to prospective studies and those rated as high quality.
3. Analysis of studies of NHAP.

Statistical Analysis
Odds ratios (ORs) comparing the incidence of each organism in HCAP vs CAP were calculated. Odds ratios were then pooled using a Mantel–Haenszel random effects model. The same analysis was used for categorical outcomes (mortality and

intensive care unit [ICU] admission). To analyze for possible effect modifiers, such as geographical region or study quality, ORs were compared using interaction testing as described [14].

Because the HCAP concept was designed to predict patients likely to have potentially resistant pathogens, we used diagnostic meta-analysis to calculate pooled positive and negative likelihood ratios and the area under the summary receiver operator characteristic curve (AUC) for HCAP [15, 16]. Authors suggest that a positive likelihood ratio >10 or a negative likelihood ratio <0.1 is likely to identify a clinically useful test [17] and that an AUC <0.75 is not regarded as clinically useful [18]. The number needed to treat was calculated from the OR as the average number of patients who would need to be treated with antipseudomonal or anti-MRSA antibiotics to prevent 1 additional treatment failure in the HCAP group compared with the CAP group.

Statistical heterogeneity was assessed using the Higgins I^2 tests. Publication bias was assessed using Eggers test [19]. Analyses were conducted using Review Manager 5, Metadisc, and SPSS version 21 for Windows.

RESULTS

The initial search identified 16 520 potential publications. Six hundred twenty-seven potentially relevant articles were reviewed in depth. The majority of studies were excluded because they did not contain microbiology data, did not include patients with HCAP, or did not include a comparator population of CAP patients.

The characteristics of the included studies are shown in Table 1. The meta-analysis included 24 studies with a total study population of 22 456 patients [3, 6, 7, 9, 20–39]. A full description of the included studies is shown in the online supplementary material (Supplementary Table 1). Fifteen (62.5%) studies were retrospective [3, 20, 26–34, 36–39]. Fifty percent of studies were from Asia [23, 27–33, 36–38]. Only 4 studies were rated to be at low risk of bias, whereas 10 studies (41.7%) were rated as being at high risk of bias. The frequency of HCAP in the included studies ranged from 67.4% of patients [20] at its highest to 14.3% at its lowest [29]. Only 5 studies used the original American Thoracic Society/Infectious Diseases Society of America definition of HCAP [6, 24, 30, 33, 35]; the other studies applied a modified definition, mainly by inclusion of immunosuppressed patients.

Comparison of Microbiology in HCAP vs CAP
In the raw analysis, there were statistically significant differences in the frequency of pathogens isolated in the HCAP group compared with the CAP group. *S. pneumoniae* and the atypical pathogens (*L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*) were all less frequent in the HCAP group ($P < .05$ for all comparisons). *S. aureus,* MRSA, Enterobactericeae, and *P. aeruginosa* were more frequent in the HCAP group compared with the CAP group ($P < .0001$ for all comparisons).

Table 1. Characteristics of the Included Studies

Characteristics	Number of Studies
Total	24
Design	
Prospective	9
Retrospective	15
Definition of HCAP	
ATS/IDSA definition	5
Alternative definition	19
Geography	
North America	3
Europe	9
Asia	12
Duration of follow-up for outcome assessment	
In hospital	11
30 days	11
Unclear	2
Quality assessment	
Good	4
Moderate	10
Poor	10

Abbreviations: ATS, American Thoracic Society; HCAP, healthcare-associated pneumonia; IDSA, Infectious Diseases Society of America.

There was significant heterogeneity in the majority of analyses, as shown in Table 2. The increased risk of MRSA was consistent across the studies ($I^2 = 16\%$), as were the lower incidences of *M. pneumoniae* and *C. pneumoniae*.

In the analysis of prospective studies, there were only 9 studies with 8902 participants [6, 7, 9, 21, 22, 25, 35]. In these studies, the estimates were more consistent with lower I^2 values. The frequency of *S. pneumoniae* was lower in HCAP than CAP. HCAP was associated with a higher risk of *S. aureus*, MRSA, *H. influenzae*, Enterobacteriaceae, and *P. aeruginosa* (Table 2). In all of these analyses, the I^2 test of heterogeneity was ≤50%.

Prevalence of Multidrug-Resistant Pathogens in HCAP and CAP Groups
There was large variation in the reported prevalence of multidrug-resistant (MDR) pathogens in both the HCAP and CAP groups. The MRSA prevalence varied 0.7%–30% in HCAP and 0%–12% in CAP. *P. aeruginosa* prevalence varied from 0.7%–23% in HCAP and 0%–8% in CAP. For Enterobactericeae, the prevalence varied 2%–46% in HCAP and 0%–28% in CAP (Figure 1).

Studies with high prevalence of MDR pathogens in the HCAP group typically also showed a high prevalence of MDR pathogens in the CAP group (Figure 1).

Analysis for Sources of Bias
A detailed discussion of sources of bias is presented in the online supplementary material.

Table 2. Comparison of the Microbiology Results in Patients With Healthcare-Associated Pneumonia Compared With Community-Acquired Pneumonia in All Included Studies and in an Analysis Limited to Prospective Studies

Organism	All Included Studies						Prospective Studies					
	Studies	No.	HCAP	CAP	HCAP vs CAP OR (95% CI)	I^2	Studies	No.	HCAP	CAP	HCAP vs CAP OR (95% CI)	I^2
S. pneumoniae	24	22 456	1003/7388	3299/15 068	0.61 (0.49–0.75)	82%	9	8902	493/2576	1789/6326	0.79 (0.65–0.97)	50%
S. aureus	23	20 711	713/6917	811/13 794	1.71 (1.23–2.37)	65%	8	7157	50/2105	54/5052	2.67 (1.40–5.08)	44%
MRSA	20	17 670	624/6368	280/11 302	4.72 (3.69–6.04)	16%	5	4116	34/1556	7/2560	5.87 (2.57–13.42)	0%
H. influenzae	22	19 941	309/6624	1032/13 317	0.73 (0.52–1.02)	75%	8	6656	98/1925	169/4731	1.49 (1.09–2.05)	11%
P. aeruginosa	22	20 594	589/6878	555/13 716	2.75 (2.04–3.72)	58%	8	7309	46/2179	47/5130	2.11 (1.08–4.10)	43%
M. catarrhalis	10	5621	56/2440	62/3181	1.06 (0.73–1.54)	0%	2	1033	11/318	10/715	1.47 (0.21–10.1)	69%
Enterobacteriaceae	21	20 281	1119/6866	1488/13 415	2.11 (1.69–2.63)	72%	7	6996	97/2167	96/4829	1.88 (1.23–2.87)	40%
L. pneumophila	16	13 202	70/4810	350/8392	0.43 (0.25–0.73)	54%	8	8589	39/2486	305/6103	0.41 (0.26–0.65)	30%
M. pneumoniae	16	9262	15/3920	159/5342	0.26 (0.12–0.55)	41%	5	3945	9/1375	44/2570	0.47 (0.17–1.30)	26%
C. pneumoniae	11	7548	20/3127	72/4421	0.40 (0.19–0.81)	27%	5	3945	4/1375	12/2570	0.79 (0.13–4.94)	52%

The number of included subjects varies in each analysis because some studies did not report specific organisms. As described in the methods, the denominator for this analysis was the percentage of patients in each group.

Abbreviations: C. pneumoniae, Chlamydophila pneumoniae; CAP, community-acquired pneumonia; CI, confidence interval; H. influenzae, Haemophilus influenzae; HCAP, healthcare-associated pneumonia; L. pneumophila, Legionella pneumophila; M. catarrhalis, Moraxella catarrhalis; M. pneumoniae, Mycoplasma pneumoniae; MRSA, methicillin-resistant Staphylococcus aureus; OR, odds ratio; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; S. pneumonia, Streptococcus pneumoniae;

Immunosuppression

Immunosuppression was not included in the original HCAP definition but was included in the HCAP group in 15 studies [3, 7, 9, 20, 21, 23, 25–28, 30, 32, 34, 36, 39]. Only 4 studies explicitly excluded immunosuppression [6, 24, 30, 35].

Frequency of Testing for Micro-organisms

Pooled analysis showed a 23% higher rate of testing for aetiological diagnosis in the HCAP group compared with the CAP group (OR, 1.23; 95% confidence interval [CI], 1.07–1.41; $P = .003$) and a significantly higher frequency of positive microbiology tests in the HCAP group (OR, 1.35; 95% CI, 1.15–1.59; $P = .0003$). This would tend to exaggerate any increased frequency of pathogens identified in the HCAP group.

Publication Bias

Publication was not evident for the majority of pathogens, but there was significant asymmetry for the analysis of S. aureus, MRSA, Enterobacteriaceae, and P. aeruginosa and statistically significant evidence of publication bias by Eggers test.

Analysis by Geographical Region

The ORs for MDR pathogens derived from Europe, North America, and Asia were compared using interaction testing, but none of the interactions were statistically significant ($P > .05$).

Prediction of Potentially Resistant Pathogens by the HCAP Definition

Table 3 shows the performance of HCAP as a predictor of resistant pathogens. HCAP did not achieve the threshold AUC of 0.75 in any of the analyses. In addition, the positive likelihood ratios and negative likelihood ratios did not suggest a clinically useful test (Table 3).
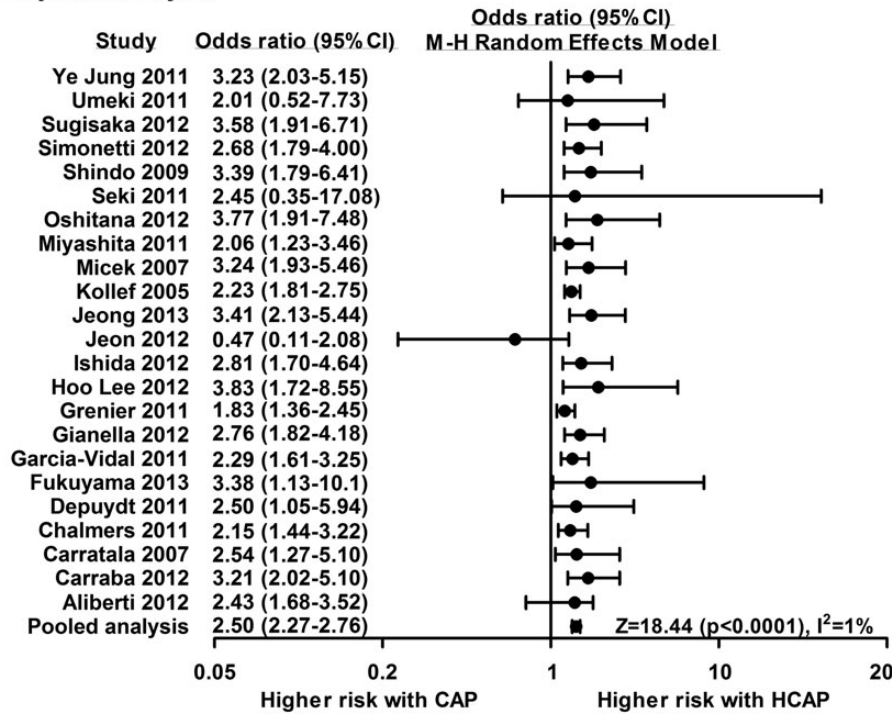
Subanalysis by region found that HCAP performed poorly in European studies and in prospective/high-quality studies. Performance in North American and Asian studies was significantly better (AUC comparison vs European studies, $P < .05$) but did not reach the predetermined threshold of clinical usefulness (Table 4).

The subanalysis of nursing home-acquired pneumonia alone is shown in the online supplementary material.

Number Needed to Treat

Assuming that the recommended CAP regime did not cover MRSA or P. aeruginosa, the number needed to treat for 1 to benefit in the HCAP group compared with the CAP group is shown in Figure 2. This varied from 4 to 499 for MRSA, from 5 to 330 for P. aeruginosa, and from 6 to 282 for Enterobacteriaceae, largely depending on the background prevalence of MDR pathogens.

Unadjusted analysis

Study	Odds ratio (95% CI)
Ye Jung 2011	3.23 (2.03–5.15)
Umeki 2011	2.01 (0.52–7.73)
Sugisaka 2012	3.58 (1.91–6.71)
Simonetti 2012	2.68 (1.79–4.00)
Shindo 2009	3.39 (1.79–6.41)
Seki 2011	2.45 (0.35–17.08)
Oshitana 2012	3.77 (1.91–7.48)
Miyashita 2011	2.06 (1.23–3.46)
Micek 2007	3.24 (1.93–5.46)
Kollef 2005	2.23 (1.81–2.75)
Jeong 2013	3.41 (2.13–5.44)
Jeon 2012	0.47 (0.11–2.08)
Ishida 2012	2.81 (1.70–4.64)
Hoo Lee 2012	3.83 (1.72–8.55)
Grenier 2011	1.83 (1.36–2.45)
Gianella 2012	2.76 (1.82–4.18)
Garcia-Vidal 2011	2.29 (1.61–3.25)
Fukuyama 2013	3.38 (1.13–10.1)
Depuydt 2011	2.50 (1.05–5.94)
Chalmers 2011	2.15 (1.44–3.22)
Carratala 2007	2.54 (1.27–5.10)
Carraba 2012	3.21 (2.02–5.10)
Aliberti 2012	2.43 (1.68–3.52)
Pooled analysis	2.50 (2.27–2.76)

Z=18.44 (p<0.0001), I²=1%

Adjusted analysis

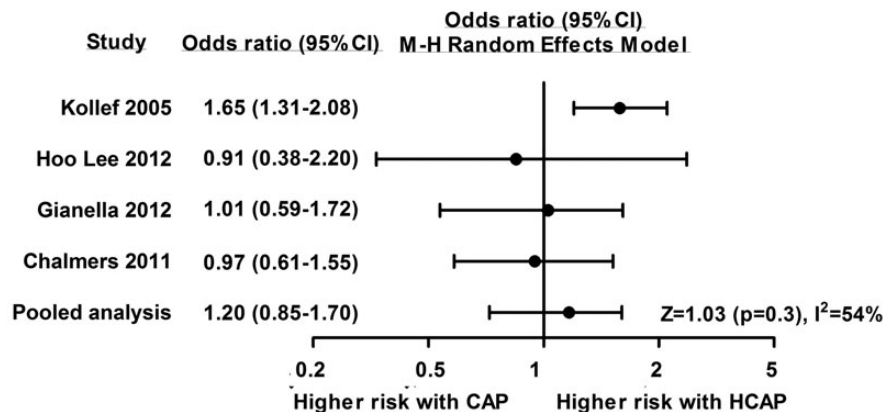| Study	Odds ratio (95% CI)
Kollef 2005	1.65 (1.31–2.08)
Hoo Lee 2012	0.91 (0.38–2.20)
Gianella 2012	1.01 (0.59–1.72)
Chalmers 2011	0.97 (0.61–1.55)
Pooled analysis	1.20 (0.85–1.70)

Z=1.03 (p=0.3), I²=54%

Figure 1. Prevalence of potential multidrug-resistant pathogens in each of the included studies. Data are shown as prevalence (percentage of patients in each group) in the healthcare-associated pneumonia (open bars) and community-acquired pneumonia (black bars) groups. *A*, Methicillin-resistant *Staphylococcus aureus. B, Pseudomonas aeruginosa. C*, Enterobactericeae. Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; HCAP, healthcare-associated pneumonia.

Outcomes in HCAP vs CAP

HCAP was associated with a statistically significant and consistent increase in mortality across all studies (n = 23 studies, 20 181 participants; OR, 2.44, 95% CI, 2.20–2.69; *P* < .0001; $I^2 = 0\%$). This was also evident in prospective studies (n = 7, 8283 participants; OR, 2.52, 95% CI, 2.15–2.95; $I^2 = 0\%$). Evaluating studies using in-hospital or 30-day mortality separately did not impact these findings.

Because nearly all studies reported a higher mean age and a higher frequency of comorbidities in the HCAP group compared with the CAP groups, the analysis was limited to those studies that provided adjusted ORs after accounting for age and comorbid illnesses. There were only 4 studies with available adjusted data for meta-analysis [3, 6, 25, 27]. This showed no significant increase in mortality associated with HCAP (OR, 1.20; 95% CI, 0.85–1.70; *P* = .30). There was significant heterogeneity

Table 3. Discrimination of the Healthcare-Associated Pneumonia Concept for Identifying Potentially Resistant Microorganisms Across All Included Studies

Organisms	PLR (95% CI)	NLR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
All resistant microorganisms	1.94 (1.67–2.24)	0.57 (0.50–0.66)	53.7 (52.2–55.2)	71.2 (70.5–71.9)	0.70 (0.69–0.71)
MRSA	1.97 (1.74–2.22)	0.44 (0.35–0.55)	69.0 (65.9–72.0)	65.7 (65.0–66.4)	0.74 (0.72–0.76)
Enterobacteriaceae	1.37 (1.26–1.49)	0.76 (0.69–0.84)	42.9 (41.0–44.8)	66. 1 (65.5–66.8)	0.60 (0.58–0.62)
P. aeruginosa	1.68 (1.53–1.84)	0.62 (0.52–0.74)	52.2 (49.2–55.1)	67.7 (67.1–68.4)	0.68 (0.66–0.70)

Abbreviations: AUC, area under the curve; CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; NLR, negative likelihood ratio; *P. aeruginosa*, *Pseudomonas aeruginosa*; PLR, positive likelihood ratio.

in this analysis, which was resolved by excluding the study by Kollef et al, which was limited to culture-positive cases [3]. Excluding this study, the OR was 0.98 (95% CI, 0.70–1.36; $P = .90$) with no heterogeneity ($I^2 = 0\%$). The unadjusted and adjusted ORs are shown in Figure 3.

In the crude pooled analysis, HCAP was associated with a statistically significant increase in risk of ICU admission (n = 12, 15 201 participants; OR, 1.39, 95% CI, 1.08–1.78; $P = .01$; $I^2 = 78\%$). Limiting the analysis to prospective studies identified no increase in ICU admission (n = 4 studies, 5821 patients; OR, 0.99, 95% CI, 0.45–2.17; $P = .98$; $I^2 = 78\%$).

ICU admission criteria vary significantly between North America, Europe, and Asia. This was reflected in the results, which showed an increased ICU admission rate in HCAP studies from North America (OR, 1.55; 95% CI, 1.35–1.78; $P < .0001$; $I^2 = 0\%$) but no increase in studies from Asia (OR, 1.47, 95% CI, 0.92–2.36; $P = .1$; $I^2 = 78\%$) or Europe (OR, 1.06, 95% CI, 0.56–2.01; $P = .90$, $I^2 = 88\%$).

DISCUSSION

This is the first study to systematically evaluate the HCAP criteria and their ability to identify potentially resistant pathogens in patients with pneumonia [2, 3]. Our meta-analysis raises

serious questions about the validity of the HCAP concept by demonstrating that it is poorly predictive of resistant pathogens across multiple international studies.

HCAP criteria were initially proposed to identify a cohort of patients with frequent healthcare contacts who require broad-spectrum initial antibiotic therapy because of an increased risk of resistant pathogens and therefore a higher risk of mortality [2, 3]. This analysis suggests that HCAP may not be sufficiently sensitive or specific to identify patients at risk of resistant pathogens. The AUC for HCAP was consistently less than the level of 0.75 reported as clinically useful and was very low in prospective and high-quality studies [6, 7, 9, 21, 22, 25, 35]. The discrimination for MRSA appeared to be better than for the other potentially resistant pathogens but was still poor, with positive and negative likelihood ratios indicating that the concept was unlikely to be useful in clinical practice.

This is not to suggest that MRSA and other MDR pathogens are not a significant problem in some patients presenting with pneumonia. In some studies there are clearly very high rates of MDR pathogens. This analysis, however, shows that the HCAP definition is poor at discriminating between patients requiring MDR therapy and those who do not. Use of the criteria is therefore likely to lead to overtreatment in areas of low MDR prevalence and potentially undertreatment in areas of high MDR

Table 4. Discrimination of the Healthcare-Associated Pneumonia Concept for Identifying All Potentially Resistant Microorganisms in Subgroups of Studies

Subgroups	PLR (95% CI)	NLR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
European studies	1.58 (1.45–1.72)	0.76 (0.66–0.88)	40.0 (46.2–43.9)	75.0 (74.1–75.8)	0.63 (0.61–0.65)
North American studies	2.39 (1.68–3.39)	0.52 (0.35–0.76)	47.3 (45.4–49.2)	83.7 (82.6–84.8)	0.74 (0.68–0.80)
Asian studies	2.00 (1.66–2.41)	0.53 (0.47–0.59)	66.5 (63.8–69.0)	60.3 (58.9–61.6)	0.72 (0.70–0.75)
Prospective studies	1.53 (1.37–1.71)	0.70 (0.56–0.86)	56.3 (50.7–61.7)	70.3 (69.2–71.4)	0.64 (0.62–0.66)
High-quality studies	1.75 (1.37–2.23)	0.67 (0.47–0.98)	51.5 (43.7–59.3)	74.5 (73.2–75.7)	0.66 (0.62–0.70)

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, negative likelihood ratio; PLR, positive likelihood ratio.
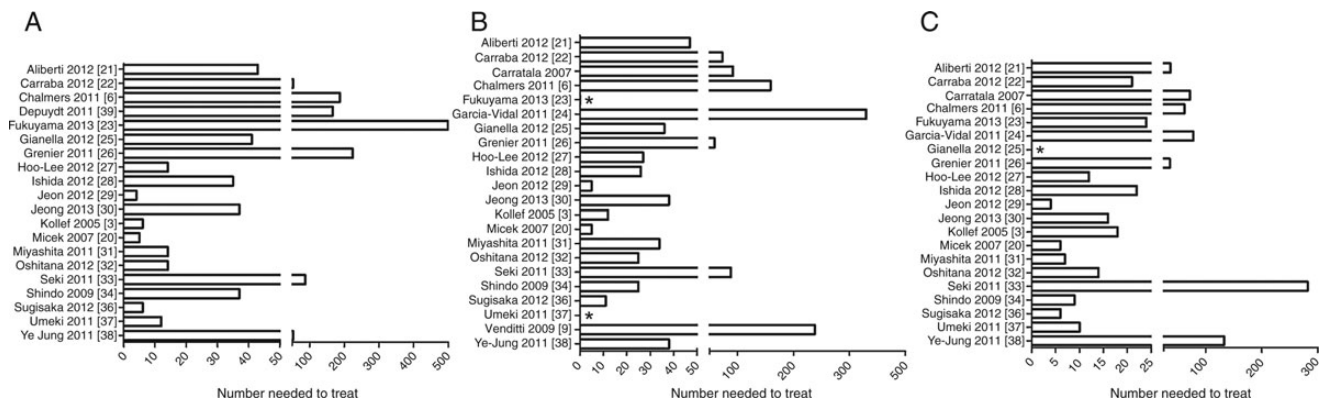
Figure 2. Number needed to treat. *A*, Methicillin-resistant *Staphylococcus aureus*. *B*, *Pseudomonas aeruginosa*. *C*, Enterobactericeae. The * indicates that in these studies, the number needed to treat was inverse (ie, the risk of potential multidrug-resistant pathogens was higher in the community-acquired pneumonia group); these data are therefore not shown.

prevalence. These data suggest the need to understand the local prevalence of MDR pathogens and determine guidelines locally where MDR prevalence is high.

Even the relatively modest discriminatory value reported in this analysis is likely to be an overestimate of the true value of the HCAP concept in clinical practice. First, there was considerable variation in definitions of HCAP applied across studies, with only 4 studies clearly excluding immunosuppression. Second, we identified evidence of publication bias for each of the resistant pathogens. This would suggest that small studies with unusually high frequencies of MDR pathogens in the HCAP group are more likely to be published and will therefore distort the literature, exaggerating the risks associated with HCAP [19]. This analysis also identified a higher frequency of microbiological testing and positive cultures in the HCAP group. This higher frequency of testing will tend to inflate the frequency of pathogens identified in the HCAP group. It is also possible that pathogens such as MRSA, Enterobacteriaceae, and *P.aeruginosa* may be easier to recover in respiratory samples because of their robustness compared with *S. pneumoniae* and *H. influenzae* [40].
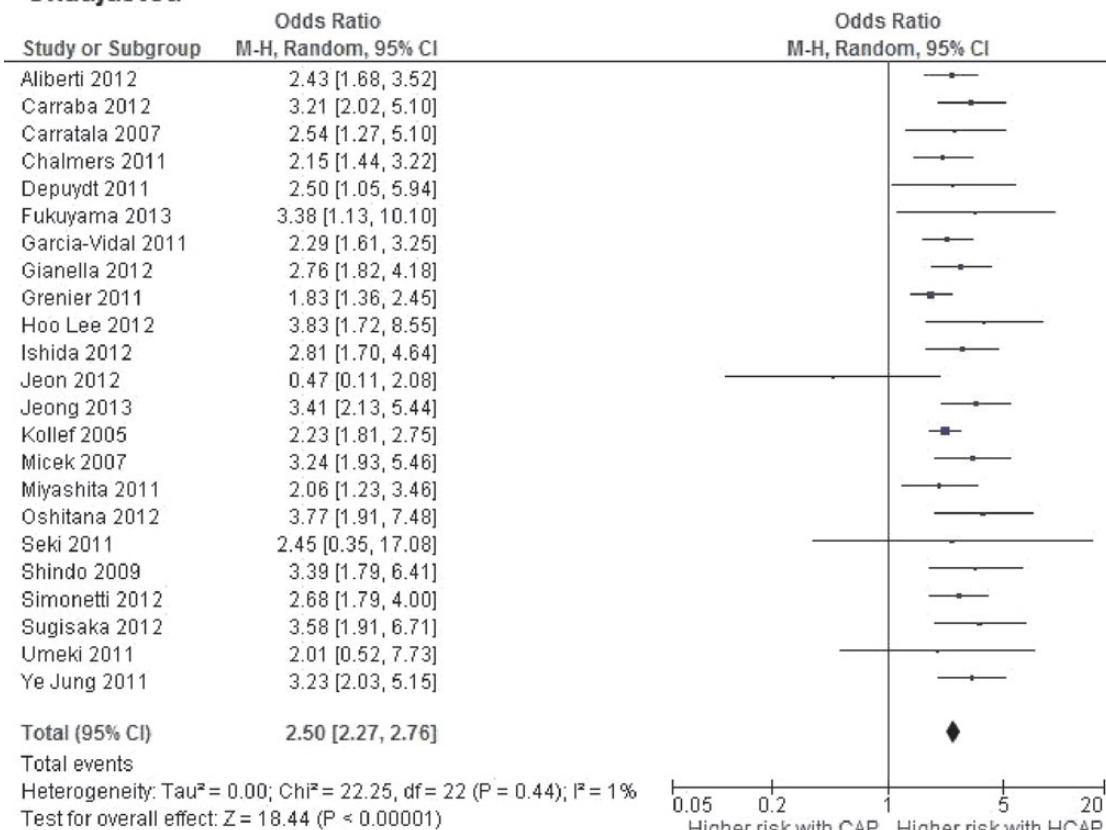
It has been argued that the HCAP concept may be more valuable in North America than elsewhere. Our analysis did not find any evidence to support this, with consistent results obtained from studies in North America, Asia, and Europe. Only 3 eligible studies from North America were identified, and none were prospective, indicating a general lack of evidence in this area [3, 20, 26]. The majority of studies were from Asia, and many used a modified HCAP definition (nursing and healthcare-associated pneumonia) promoted by the Japanese Respiratory Society. The discrimination of HCAP to identify resistant pathogens and the associated positive and negative

likelihood ratios were poor for each continent, and perhaps the only notable difference was the increased frequency of ICU admission in North America. This is consistent with the recognized differences in the use of ICU resources in the United States compared with Europe [15, 41, 42].

We did not identify any evidence that the excess mortality in HCAP, which was consistent across all studies, was associated with a higher frequency of resistant pathogens. Instead, the excess mortality appears to be primarily due to age and comorbidities associated with HCAP. It is increasingly recognized that comorbidities account for a large proportion of deaths in patients with pneumonia and that a significant proportion of this mortality cannot be modified with antibiotic treatment [43, 44]. This should lead to a reevaluation of the recommendation to apply HCAP criteria for the selection of patients who generally should receive broad-spectrum antibiotic therapy [2]. This therapy clearly represents heavy overtreatment for the majority of patients and is associated with antibiotic-related side effects, hospital-acquired infections such as *Clostridium difficile*, and promotion of antibiotic resistance [45, 46]. Without clear evidence that such broad-spectrum therapy can improve outcomes in HCAP, it is difficult to see how this recommendation can be justified. In fact, the study including by far the largest population to date indicates that outcomes in patents with nonsevere HCAP are not better when treated with an HCAP guideline–concordant regime compared with a CAP guideline–concordant regime [47].

Limitations of this analysis should be acknowledged. Meta-analysis is dependent on the quality of the source studies, and the general quality identified in this analysis was poor. Methodology of microbiological work-up was heterogeneous, and only a few studies applied strict criteria for classification of isolates

Unadjusted

Study or Subgroup	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Aliberti 2012	2.43 [1.68, 3.52]	
Carraba 2012	3.21 [2.02, 5.10]	
Carratala 2007	2.54 [1.27, 5.10]	
Chalmers 2011	2.15 [1.44, 3.22]	
Depuydt 2011	2.50 [1.05, 5.94]	
Fukuyama 2013	3.38 [1.13, 10.10]	
Garcia-Vidal 2011	2.29 [1.61, 3.25]	
Gianella 2012	2.76 [1.82, 4.18]	
Grenier 2011	1.83 [1.36, 2.45]	
Hoo Lee 2012	3.83 [1.72, 8.55]	
Ishida 2012	2.81 [1.70, 4.64]	
Jeon 2012	0.47 [0.11, 2.08]	
Jeong 2013	3.41 [2.13, 5.44]	
Kollef 2005	2.23 [1.81, 2.75]	
Micek 2007	3.24 [1.93, 5.46]	
Miyashita 2011	2.06 [1.23, 3.46]	
Oshitana 2012	3.77 [1.91, 7.48]	
Seki 2011	2.45 [0.35, 17.08]	
Shindo 2009	3.39 [1.79, 6.41]	
Simonetti 2012	2.68 [1.79, 4.00]	
Sugisaka 2012	3.58 [1.91, 6.71]	
Umeki 2011	2.01 [0.52, 7.73]	
Ye Jung 2011	3.23 [2.03, 5.15]	
Total (95% CI)	**2.50 [2.27, 2.76]**	

Total events
Heterogeneity: Tau² = 0.00; Chi² = 22.25, df = 22 (P = 0.44); I² = 1%
Test for overall effect: Z = 18.44 (P < 0.00001)

Adjusted

Study or Subgroup	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Chalmers 2011	0.97 [0.61, 1.55]	
Gianella 2012	1.01 [0.59, 1.72]	
Hoo Lee 2012	0.91 [0.38, 2.20]	
Kollef 2005	1.65 [1.31, 2.08]	
Total (95% CI)	**1.20 [0.85, 1.70]**	

Heterogeneity: Tau² = 0.06; Chi² = 6.55, df = 3 (P = 0.09); I² = 54%
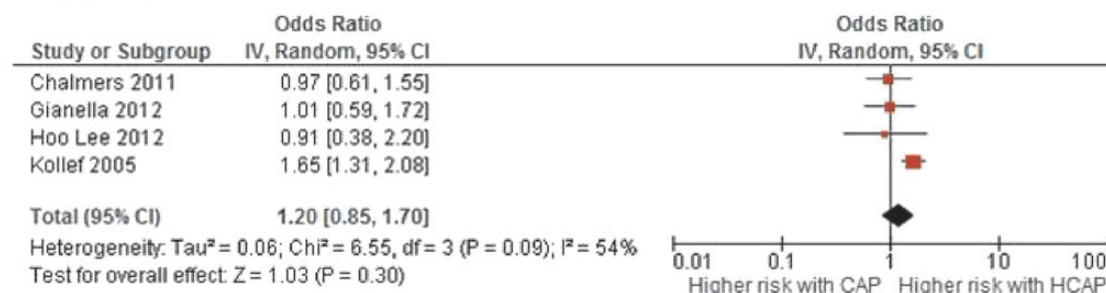Test for overall effect: Z = 1.03 (P = 0.30)

Figure 3. Unadjusted (univariable) and adjusted odds ratios for mortality in studies comparing healthcare-associated pneumonia and community-acquired pneumonia populations. Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; HCAP, healthcare-associated pneumonia; IV, inverse variance; M-H, Maentel–Haentzel.

as true pathogens, which is particularly important regarding the critical pathogens in question. Good-quality studies consistently reported lower frequencies of such pathogens. Enterobacteriaceae were rarely subdivided into extended spectrum beta-lactamase–producing and non-MDR groups and so analysis of this was not possible. Duration of follow-up was variable, and the relationships between specific pathogens and outcomes were rarely investigated.

In conclusion, the HCAP concept discriminates poorly between patients at risk of potentially resistant pathogens, and the excess mortality associated with HCAP is primarily due to age and comorbidities. These findings should be considered in interpreting and revising HCAP recommendations in the future.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). 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

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