A Critical Evaluation of Healthcare-Associated Pneumonia and the Need for Anti-pseudomonal Therapy, Including Double Coverage

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Abstract In 2005, healthcare-associated pneumonia (HCAP) was described as a distinct entity, reflecting the concern that patients with HCAP have mortality rates and microbiologic culprits more akin to patients with hospital-acquired pneumonia (HAP) and, thus, warrant treatment similar to HAP, including empiric broad spectrum antibiotics. Increasing evidence suggests that the HCAP definition and criteria are insufficient predictors of which patients are at highest risk of being infected with a multi-drug resistant organism (MDRO); this lack of accuracy leads to overuse of broad spectrum antibiotics. New risk stratification schemes have been proposed that may supplant our current reliance on HCAP criteria for identifying patients who may be infected with an MDRO. Regardless of the risk stratification method used, antibiotic decisions must account for local MDRO prevalence rates. In settings where *P. aeruginosa* resistance to anti-pseudomonal therapies is high or in patients who are critically ill, empiric combination therapy for *P. aeruginosa* may be considered. However, therapy should be narrowed to a single agent once an effective agent has been identified from culture susceptibility data.

Keywords Healthcare-associated pneumonia (HCAP) · Healthcare-associated infections · Multi-drug resistant · *Pseudomonas aeruginosa* · Combination therapy · Double coverage

Introduction

Pneumonia and influenza together are the leading infectious cause of death worldwide [1], including in developed nations such as the United States [2]. In 2005, the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) described healthcare-associated pneumonia (HCAP) as an entity distinct from community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). Patients who were previously described as having CAP were redefined as having HCAP if they were hospitalized for at least 48 hours in the prior 90 days; were a resident of a nursing home or extended care facility; received intravenous antibiotic therapy, chemotherapy, or wound care in the prior 30 days; or attended a hospital or hemodialysis clinic in the prior 30 days [3•]. This new terminology and clinical approach to such patients reflected the concern that although patients with HCAP may come from the community, they have mortality rates [4, 5] and microbiologic culprits more akin to patients with HAP [5] and thus warrant treatment similar to HAP, including empiric broad spectrum antibiotics as initial therapy [3•]. This concept and the therapeutic recommendations stemming from it are controversial [6–8]. In the face of increasing data that suggest current treatment guidelines lead to antibiotic overtreatment without mortality benefit [9•], we anticipate the next revision of guidelines will be less prescriptive about empiric antibiotic coverage for HCAP and will place greater emphasis on more accurate

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patient risk stratification for infection with multi-drug resistant organisms (MDRO) as well as greater emphasis on understanding local microbiological epidemiology and antibiotic resistance patterns to guide antibiotic choice for patients with HCAP. Additionally, accounting for the severity of illness in the antibiotic selection process may help to avoid overtreatment of patients with HCAP who have milder clinical syndromes.

Due to an aging population and medical advances, more people are in contact with healthcare settings including hospitals, rehabilitation facilities, nursing homes, dialysis centers, and intravenous infusion centers. This increases their exposure to MDRO and healthcare-associated infections (HAI). Thus, the percentage of patients hospitalized with pneumonias that are characterized as HCAP is expected to grow. Given the increased mortality [4, 5, 10] and cost [11] associated with HCAP compared to CAP, it is of utmost clinical and economic importance that guidelines for HCAP treatment are evidence-based and support appropriate antibiotic use and healthcare utilization.

Controversy Surrounding HCAP

The main rationale for distinguishing HCAP from CAP was to help identify patients who would be at increased risk of infection with MDRO and, therefore, benefit from broad spectrum antibiotics, with the ultimate goal of reducing morbidity and mortality. Surprisingly, important assumptions underlying the 2005 guidelines have not proven true, namely that the HCAP criteria accurately identify those at high risk for infection with MDRO and that mortality is reduced by giving broad spectrum antibiotics.

Mortality and HCAP

One of the chief reasons for creating the 2005 ATS/IDSA guidelines which encouraged treating HCAP similarly to HAP was the recognition that the mortality and microbiologic agents in HCAP and HAP appeared to be similar [3•]. Mortality is certainly increased in patients with HCAP compared to CAP in univariate analyses [4, 5, 9•, 12–14], with rates similar to HAP [4, 5]. However, in multivariate analyses that adjusted for age, comorbidities, and, in some cases, severity of disease at presentation, patients with HCAP did not have excess mortality compared to patients with CAP [9•, 12]. The studies by Kollef et al. and Gross et al. were among the minority that showed increased mortality even after adjusting for age, comorbidities, and pneumonia severity [5, 10•]. The current data suggest that patient characteristics have more bearing on mortality than the presence of HCAP versus CAP.

Although Gross et al. did find increased 30-day mortality in the HCAP groups compared to CAP (5.8 % vs. 0.4 %, $p < 0.001$) that persisted after propensity-adjusted multivariate logistic regression analysis (AOR 11.60; 95 % CI 1.48–90.75; $p = 0.02$), this did not seem to be mediated by the presence of increased MDRO in the HCAP group. The 30-day mortality rate was not statistically significantly higher in patients in whom MDRO was isolated (10 % vs. 2.8 %; $p = 0.122$) [10•]. Again, these findings support the idea that underlying patient characteristics are a primary contributor to mortality and that full adjustment may be difficult.

MDRO Definition

One of the difficulties with studying HCAP is a lack of consensus around the definition of MDRO, with most studies including methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae [14•, 15, 16], while others included carbapenem-intermediate or -resistant Enterobacteriaceae (CIRE) [10•], *Acinetobacter* spp. [14•, 16, 17], *Stenotrophomonas maltophilia* [10•, 16], vancomycin-resistant enterococci [16], and other nonfermenting gram negative rods [15, 16]. Shindo et al. defined drug-resistant pathogens by the actual drugs to which they were resistant, including B-lactams, macrolides, and fluoroquinolones [18]. A lack of clear definition makes it difficult to compare results, study epidemiology of MDRO, and, thus, assess risk of infection by MDRO.

Prevalence of MDRO

The positive predictive value of any test is dependent on the prevalence of disease in the population. This is relevant in the management of HCAP in which current recommendations suggest that all patients testing “positive” for HCAP by having one of the defining healthcare exposures be given empiric broad spectrum antibiotics regardless of the prevalence of disease caused by MDRO in the population. A recent retrospective study of cases of CAP and HCAP at a large academic medical center by Gross et al. found MDRO in only 3.8 % of patients with pneumonia; MDRO were isolated in 5.9 % of HCAP cases and 1.9 % of CAP cases [10•]. This low prevalence of MDRO would suggest that patients with HCAP are treated with overly broad antibiotics. In contrast, several studies have shown a markedly higher prevalence of MDRO with approximately one-quarter of HCAP patients with positive bacterial cultures yielding MRSA and one-quarter yielding *P. aeruginosa* and may argue for increased benefit of empiric broad spectrum antibiotic use [5, 17, 19]. However, these

Fig. 1 Variability in prevalence of MRSA and *P. aeruginosa* in healthcare-associated pneumonia (HCAP) and community-acquired pneumonia (CAP). Given the wide range in prevalence of multi-drug resistant organisms in HCAP, in particular MRSA and *P. aeruginosa*, the use of empiric broad spectrum antibiotics in all HCAP cases leads to unnecessary broad coverage, especially in low prevalence areas. Lack of therapy effective against MRSA and *P. aeruginosa* also risks

undertreatment in some CAP patients. One of the reasons for this variability in prevalence stems from differences in methodology; most studies report prevalence of MRSA and *P. aeruginosa* among patients with culture data or other suggestive clinical testing that is positive for a potentially pathogenic bacterial organism rather than among all patients presenting with pneumonia. Prevalence data from Chalmers et al. [9•]. MRSA methicillin-resistant *Staphylococcus aureus*

studies only included patients with positive bacterial cultures whereas Gross et al. included all patients presenting with CAP and HCAP, including those who tested positive for viral pneumonia and those who were culture negative.

The wide variance in MDRO prevalence rates was well summarized by a systematic review and meta-analysis of 24 studies published between December 2005 and January 2013 that showed prevalence rates for MRSA in HCAP ranging from 0.7 to 30 % (compared to 0–12 % in CAP), prevalence of *P. aeruginosa* in HCAP ranging from 0.7 to 23 % (compared to 0–8 % in CAP), and prevalence of Enterobacteriaceae in HCAP ranging from 2 to 46 % (compared to 0–28 % in CAP) (See Fig. 1) [9•]. In general, MDRO prevalence rates have been higher in North American studies compared to East Asian or European studies.

A shortcoming in most studies of MDRO prevalence is the exclusion of patients who do not have culture data or other suggestive clinical testing that is positive for a potentially pathogenic bacterial organism. In clinical practice, many patients with HCAP do not have cultures obtained or specimens are inadequate. Therefore, including only patients with positive cultures creates a cohort that is likely biased toward patients with more severe disease. Also, it has been suggested that MDRO such as *S. aureus* and *P. aeruginosa* are more likely to result in positive cultures than more fastidious organisms, thereby leading to over-representation of MDRO in culture data [20]. In addition, several studies did not test for respiratory viruses which, in at least one study, were the etiologic agents in nearly one third of cases of pneumonia presenting from the

community [10•]. In this study, prevalence of viral pneumonia was almost equally split between patients with CAP and HCAP (19 % vs. 13 %). Another challenge is the difficulty of determining whether a microbe is a true pathogen versus a colonizer when it is isolated from a non-sterile site, such as the respiratory tract. Finally, although cultures are not obtained in many instances of HCAP, a recent meta-analysis found that patients with HCAP had a 23 % increased rate of microbiologic testing (OR 1.23; 95 % CI 1.07–1.41; $p = 0.003$) compared to those with CAP, which likely inflated the prevalence of identified organisms, including MDRO. This study also found statistically significant evidence of publication bias for HCAP studies with respect to resistant organisms, showing an increased likelihood that small studies with a large prevalence of MDRO were published [9•].

HCAP Definition: Poor Predictor of Infection with MDRO

Several recent studies have shown the poor predictive value of the ATS/IDSA HCAP definition in identifying patients with multi-drug resistant (MDR) pneumonias. Chalmers et al.'s systematic review and meta-analysis was a comprehensive evaluation of the HCAP criteria's ability to predict infection with MDRO [9•]. It should be noted that only five of 24 studies utilized the complete HCAP definition by ATS/IDSA. The authors concluded that meeting HCAP criteria was not a clinically useful test in predicting MDRO given the area under the receiver operating characteristic (AUROC) curve was 0.70 (95 % CI 0.69–0.71) and did not exceed the pre-specified value of

0.75. No geographic region (Europe, North America, or Asia) had an AUROC that exceeded 0.75, though European studies had a significantly lower AUC of 0.63 (95 % CI 0.61–0.65) compared to North American and Asian studies ($p < 0.05$).

Only four of the 24 studies were considered good quality studies by the modified Hayden's criteria with the remaining evenly split between moderate and poor quality studies. In sum, the authors concluded that the quality of evidence was overall poor to support the use of HCAP criteria in identifying patients infected with MDRO [9••].

Proposed Risk Stratification Schemes

There is increasing interest in identifying risk factors that more accurately predict MDR pneumonias than the current HCAP designation and, thereby, lead to better antibiotic stewardship. To date, at least six studies have proposed risk stratification schemes to more accurately predict those likely to be infected with MDRO [14•, 15–18] (see Table 1).

Shorr et al. proposed a graded scoring system [15] that was then validated in a different cohort than the initial population from which the risk factors were derived [17]. The scoring system assigned four points for hospitalization in the prior 90 days, three points for nursing home residence, two points for long-term hemodialysis, and one point for needing care in the intensive care unit (ICU) [15]. Using a score of one or greater as the cutoff for when to employ broad spectrum antibiotics resulted in 24.3 % of patients being categorized as potentially infected with an MDRO when they did not have an MDRO, implying broad antibiotic use when it was not warranted [17]. This scoring system had slightly improved performance compared with the HCAP criteria, which misidentified one third of patients.

Alberti et al. had a similar graded risk stratification scheme in which five points were given to patients with chronic renal failure defined as creatinine greater than 1.2 mg/dL; four points for hospitalization in the prior 90 days; three points for residence in a nursing home or extended care facility; and 0.5 points for any one of the following: cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, antimicrobial therapy in the prior 90 days, immunosuppression, home wound care, or home infusion therapy. The authors found that using a cutoff score of greater than 0.5 was associated with the best sensitivity and specificity (0.75 and 0.71, respectively) [16].

Rather than differentially weighing risk factors, Shindo et al. devised a scoring system based solely on the number of risk factors for MDRO infection, which they identified as hospitalization in the prior 90 days, immunosuppression,

antibiotic use in the prior 90 days, use of gastric acid suppression agents, tube feeding, and non-ambulatory status [18]. A subanalysis of MRSA risk factors identified previous MRSA history in the prior 90 days, chronic dialysis in the prior 30 days, and congestive heart failure to be unique risk factors for MRSA infection. The authors recommended broad spectrum antibiotics are to be considered when three or more risk factors were present for MDRO. In the case of MRSA antibiotic coverage, the authors recommended consideration of empiric broad coverage when two risk factors were present if one of the risk factors was a MRSA-specific risk factor. However, given the greater than 25 % prevalence of MDRO in patients in the study with two more or risk factors, in a community with similar MDRO prevalence rates as the study population, it would be reasonable to consider broad spectrum antibiotics with a cutoff of two risk factors for any MDRO, regardless of the presence of a MRSA-specific risk factor.

Maruyama et al. conducted a prospective, multicenter trial that employed a risk stratification scheme to guide antibiotic therapy in patients presenting with pneumonia [14•]. Risk factors for MDRO infection were defined as immunosuppression, hospitalization in the prior 90 days, poor functional status as defined by Barthel Index score less than 50, and antibiotic use in the prior 6 months. Patients at low risk for MDRO were defined as having zero to one risk factors with non-severe pneumonia or zero risk factors with severe pneumonia, defined as requiring ICU care or mechanical ventilation. Patients at high risk for infection with MDRO were defined as having 2 or more risk factors with non-severe pneumonia or 1 or more risk factors with severe pneumonia. 47 % of patients who would have traditionally been categorized as HCAP patients were re-categorized as low risk for MDRO and, thus, received CAP antibiotic coverage. A similar rate of inappropriate therapy was given to HCAP patients who were re-categorized as low risk for MDRO infection compared to CAP patients who grew resistant organisms (0.9 % vs. 1.2 %). In the 0.9 % ($n = 3$) of HCAP patients who received inappropriate antibiotics, *P. aeruginosa* was the organism isolated. This study showed a viable alternative to empiric treatment of all HCAP patients with antibiotics targeted toward MDRO, essentially sparing nearly half of patients ($n = 151$) who would have normally received treatment for MDRO based on the HCAP definition alone. However, given the relatively low overall prevalence of MDRO in the study (11.2 %), this method of risk stratification may be only applicable to geographic areas with similar prevalence of MDRO.

One limitation of several of the studies on improved MDRO risk stratification schemes is the use of varying definitions of immunosuppression [14•, 16, 18], making it

Table 1 Proposed risk stratification schemes to more accurately identify patients infected with multi-drug resistant organisms in pneumonias presenting from the community

Study	Risk factors	Scoring	Score interpretation	Scoring system performance	Scoring system performance compared to HCAP criteria
Manyama et al. [14]	<i>All patients met HCAP criteria and were assessed for the following risk factors:</i> Hospitalization in prior 90 days Antibiotic use in prior 6 months Immunosuppression Poor functional status Severe pneumonia	Non-severe, 0–1 risk factors Severe, 0 risk factors Non-severe, ≥ 2 risk factors Severe ≥ 1 risk factors	Treated as CAP Treated as CAP Treated as HCAP Treated as HCAP	0.9 % of all HCAP patients ($n = 3$) received inappropriate antibiotics	47 % ($n = 151$) were spared broad spectrum antibiotics they would have received given HCAP designation
Shindo et al. [20]	<i>Risk stratification for organisms resistant to CAP therapy. 1 point each for:</i> Hospitalization in prior 90 days Antibiotic use in prior 90 days Immunosuppression Use of gastric acid suppressive agents Tube feeding Non-ambulatory status	Score ≤ 1 Score ≥ 2 Score ≥ 3	<i>Prevalence of organisms resistant to CAP therapy</i> <10 % >25 % (25 % in CAP, 37 % in HCAP) ~ 50 % (67 % in CAP, 48 % in HCAP)	AUROC = 0.79 (95 % CI 0.74–0.84)	Not assessed
	<i>Risk stratification for MRSA. 1 point each for:</i> Hospitalization in prior 90 days Antibiotic use in prior 90s days Use of gastric acid suppressive agents Previous MRSA history in prior 90 days ⁱ Chronic HD in prior 30 days ⁱ CHF ⁱ	Score ≤ 1 Score ≥ 2 Score ≥ 3	<i>Prevalence of MRSA:</i> 4 % 22 % (39 % if one of risk factors was MRSA specific ^j) 28.3 % (42.9 % if one of risk factors was MRSA specific ^j)	<i>For MRSA detection:</i> AUROC = 0.76 (95 % CI 0.70–0.81)	Not assessed
Shorr et al. [17]	4 points: hospitalization in prior 90 days 3 points: nursing home resident 2 points: chronic HD 1 point: need for ICU care	Score 0 Score 1–5 Score >5	<i>Prevalence of MDRO</i> 15 % 55 % 75 %	AUROC = 0.71 (95 % CI 0.66–0.73)	AUROC = 0.62 (95 % CI 0.58–0.65)
Aliberti et al. [16]	5 points: chronic renal failure 4 points: hospitalization in prior 90 days 3 points: nursing home resident 0.5 points: any one of the following: cerebrovascular disease, diabetes, COPD, antibiotics in prior 90 days, immunosuppression, home wound care, or home infusion therapy	0–0.5 3–12.5	<i>Prevalence of MDRO</i> 8 % 38 %	AUROC = 0.79 (95 % CI 0.71–0.87) Score >0.5 : sensitivity 0.75, specificity 0.71	Not assessed

Table 1 continued

Study	Risk factors	Scoring	Score interpretation	Scoring system performance	Scoring system performance compared to HCAP criteria
Shorr et al. [15]	4 points: hospitalization in prior 90 days 3 points = nursing home resident 2 points = chronic HD 1 point = need for ICU care	Score <3 Score 3–5 Score >5	Prevalence of MDRO <20 % 55 % >75 %	AUROC = 0.74 (95 % CI 0.65–0.80)	Not assessed
HCAP healthcare-associated pneumonia, CAP community-acquired pneumonia, MRSA methicillin-resistant <i>Staphylococcus aureus</i> , HD hemodialysis, CHF congestive heart failure, AUROC area under receiver operating characteristic, CI confidence interval, ICU intensive care unit, MDRO multi-drug resistant organism, COPD chronic obstruction pulmonary disease					
i MRSA specific risk factors: Previous MRSA history in prior 90 days, chronic dialysis in prior 30 days, congestive heart failure					

difficult to compare results and reach definitive conclusions regarding which types of immunosuppression warrant empiric antibiotic coverage. Another limitation of all studies is that the predictive value of each system is highly dependent on the prevalence of MDRO in the population studied. All but Shorr's risk stratification scheme [15, 17] were evaluated only in the derivation cohort without additional validation. Thus, additional prospective studies, ideally in diverse populations, must be done to evaluate the clinical utility of the various scoring systems before recommending implementation.

Implications for Antibiotic Therapy

A study by Zilberberg et al. found that initial appropriate coverage for HCAP was a predictor of reduced mortality and that changing to appropriate coverage after initial inappropriate coverage did not improve mortality [21]. Such evidence supports the current ATS/IDSA guidelines which recommend empiric coverage with an agent active against MRSA and two antibiotics with anti-pseudomonal activity (i.e., double coverage) in HCAP. However, results of subsequent studies comparing mortality rates with use of guideline-concordant therapy versus guideline discordant therapy have been mixed [4, 22, 23].

As discussed above, the prevalence of MRSA and *P. aeruginosa* in HCAP varies considerably across a number of studies from 0.7 to 30 % and 0.7 to 23 %, respectively [9•]. In populations with a relatively low prevalence of MDRO, concordance with the guidelines would lead to overtreatment for most patients. However, treating all pneumonia patients with HCAP risk factors as though they have CAP may lead to undertreatment of MDRO, especially in populations with a higher prevalence of MDRO, with possible adverse outcomes. This conundrum was illustrated in a study demonstrating that U.S. clinicians believe they treat patients according to HCAP guidelines but that, when presented with specific scenarios, they are much more likely to choose less aggressive, non-concordant therapy [24]. This disconnect may be due to clinicians' perceptions that they uncommonly encounter MDRO in conjunction with some HCAP risk factors. Chalmers et al. estimated that the number needed to treat for one patient to benefit from HCAP guideline-concordant therapy ranged from 4 to 499 for MRSA, 5 to 330 for *P. aeruginosa*, and 6 to 282 for Enterobacteriaceae [9•]. These estimates raise the concern for unnecessary use of broad spectrum antibiotics and the subsequent risk of creating more resistant strains [25], incurring higher costs associated with unnecessary broad empiric treatment [11], and increasing toxicity and adverse drug events related to antibiotic exposure.

Anti-pseudomonal Therapy: Double Coverage

Pseudomonal HCAP poses a particular management challenge, due to the virulence of *P. aeruginosa* coupled with the pathogen's intrinsic antibiotic resistance and its propensity to develop further resistance during therapy. These challenges have led to a long running debate about whether two anti-pseudomonal agents should be used when *P. aeruginosa* infection is suspected or confirmed and whether combination therapy, or double coverage, should be included in guidelines for the empiric treatment of HCAP as is currently the case [3•]. Presumably, empiric treatment with more than one agent increases the likelihood that at least one agent will be effective against the pathogen. In addition, in vitro evidence suggests that particular antibiotic combinations provide synergistic killing of *P. aeruginosa*. There was also the hope that combination therapy might prevent development of resistance [26•, 27]. In clinical studies, there are some data to support the first contention that combination therapy increases the chances of having an agent on board to which the organism is susceptible; however, there is insufficient evidence to support use of combination therapy on the basis of possible synergy or preventing development of resistance [27•]. In addition, combination therapy has been associated with increased adverse events, namely nephrotoxicity with use of aminoglycosides [28].

Ultimately, though, improved clinical outcomes are the most relevant rationale for employing combination anti-pseudomonal therapy. Unfortunately, there have been no studies to date specifically examining clinical effectiveness of combination anti-pseudomonal therapy in HCAP patients; extant studies have included patients with a variety of pseudomonal infections (including intra-abdominal, urinary tract, and wound infections) and underlying conditions (including cystic fibrosis, neutropenia, and human immunodeficiency virus infection). In most studies, patients with *P. aeruginosa* infections are analyzed as a subset of gram negative rod infections. Nevertheless, earlier evidence seemed to support improved cure rates and/or a survival benefit with combination therapy in pseudomonal infections but several of these studies included aminoglycosides as the monotherapy agent [29–31], which has since been shown to be an inferior therapy for *P. aeruginosa*.

Several meta-analyses have examined clinical outcomes in trials comparing monotherapy with combination therapy for various infections, with subanalyses looking specifically at *P. aeruginosa* [26•, 28, 30, 32, 33]. All but one meta-analysis found no mortality difference between monotherapy and combination therapy in patients with *P. aeruginosa* infections. Of note, the meta-analysis that found a survival benefit included studies of patients with

febrile neutropenia, and the relevance of outcomes in this at-risk patient population compared to those with HCAP is unclear. Additionally, many of the studies included in that analysis evaluated large numbers of patients with *P. aeruginosa* urinary tract infections, which, again, may have limited applicability to the HCAP population, as high cure rates would be expected [30].

The most recent meta-analysis was the first to systematically examine the clinical benefit of combination therapy specifically in patients with *P. aeruginosa* infections, whereas the prior meta-analyses examined *P. aeruginosa* infections as subanalyses. It included 19 studies, of which 8 were randomized clinical trials, and, again, found no difference in mortality (RR = 0.97; 95 % CI 0.77–1.22) or clinical cure rates (RR 1.36; 95 % CI 0.99–1.86) between definitive monotherapy and combination therapy with B-lactam–aminoglycoside or B-lactam–fluoroquinolone combinations [26•]. This study suggested no increased benefit with combination therapy as long as one agent was effective against *P. aeruginosa*. There was also no difference in mortality between the two therapies given as empiric treatment (RR = 1.02; 95 % CI 0.78–1.34), and none of the included studies that had performed multivariate analyses found a mortality difference. However, there was a higher clinical cure rate for patients receiving empiric combination therapy over monotherapy (RR 1.23; CI 1.05–1.43).

A limitation of all the current meta-analyses is that the majority of studies included were conducted prior to 2000 [26•, 28, 30, 32, 33], and antibiotic resistance may now be more prevalent. In addition, all meta-analyses included studies looking at a variety of *P. aeruginosa* infections other than pneumonia. There have not been individual trials or observational studies examining combination anti-pseudomonal therapy in exclusively HCAP. Perhaps the closest approximation of an HCAP trial was conducted by Park et al. who retrospectively compared monotherapy to combination therapy in bacteremic *P. aeruginosa* pneumonias of all types, of which 22 % were HCAP ($n = 14$) [34•]. Of those who received appropriate empiric therapy, as determined by in vitro susceptibility of the organism to the initial therapy, there was a mortality benefit to empiric combination therapy over monotherapy (AOR 0.05; 95 % CI 0.01–0.34) and a higher clinical cure rate (54.5 % vs. 28.1 %, $p = 0.04$). One strength of this study was that it included only *P. aeruginosa* pneumonias with concurrent bacteremia which nearly eliminates the chance that a positive *P. aeruginosa* respiratory culture was due to colonization as opposed to true pathogenic etiology. Its retrospective design is a limitation that may have introduced bias in terms of which patients were selected to receive combination therapy rather than monotherapy.

The pseudomonal VAP literature may also provide evidence that is more directly applicable to HCAP than the

meta-analyses that reviewed outcomes associated with various types of infections. Garnacho-Montero et al. found that monotherapy was associated with 13.6 % excess mortality but this difference was not seen in patients who had received definitive monotherapy versus combination therapy, suggesting that double coverage is not necessary if at least one agent is effective against the pathogen [35].

The current body of evidence is lacking in both quantity and quality to definitively advise for or against empiric combination therapy. Some experts recommend use of empiric double coverage in areas where rates of resistance to commonly used anti-pseudomonal therapies is high [36] or in instances of critically ill patients with risk factors for pseudomonas infection [28]. We believe this is a reasonable approach until further data accrue. Ideally, randomized controlled trials of patients with HCAP due to *P. aeruginosa* would be conducted to further clarify the benefit of combination therapy. However, given the relatively low prevalence of culture proven pseudomonal HCAP, the cost and time involved for such a trial pose significant barriers. Further work to better define the groups at high risk for *P. aeruginosa* HCAP could also help to target empiric combination therapy to a smaller group most likely to benefit. Once *P. aeruginosa* antibiotic susceptibilities are obtained, therapy should be narrowed to a single effective agent.

Conclusion

There is growing consensus that the HCAP designation, while it does help identify patients who are more likely to have MDRO compared to CAP patients, is an insufficient predictor of which patients are at highest risk of being infected with an MDRO and, thus, warrant empiric broad spectrum therapy. Validated risk stratification schemes are needed to more accurately predict patients at highest risk for infection with an MDRO. Such algorithms must account for local MDRO prevalence rates. In settings where *P. aeruginosa* resistance to anti-pseudomonal therapies is high or in patients who are critically ill, empiric combination therapy for *P. aeruginosa* may be considered. However, therapy should be narrowed to a single agent once an effective agent has been identified from culture and susceptibility data.

Compliance with Ethics Guidelines

Conflict of Interest Rita Nguyen and Lisa G. Winston have both reported no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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