REVIEW

Predicting risk of drug-resistant organisms in pneumonia: Moving beyond the HCAP model

Brandon J. Webb a,b,*, Kristin Dascomb a,b, Edward Stenehjem a,b, Nathan Dean c

a Division of Infectious Diseases, University of Utah, Salt Lake City, UT, USA
b Division of Clinical Epidemiology and Infectious Diseases, Intermountain Medical Center, Salt Lake City, UT, USA
c Division of Pulmonary and Critical Care Medicine, at Intermountain Medical Center and the University of Utah, Salt Lake City, UT, USA

Received 13 June 2014; accepted 27 October 2014
Available online 13 November 2014

KEYWORDS
Pneumonia; Community-acquired; Healthcare-associated; Antibiotic; Drug-resistance; Antimicrobial stewardship

Background: Clinical management of community-acquired pneumonia (CAP) is increasingly complicated by antibiotic resistance. CAP due to pathogens resistant to guideline-recommended drugs (CAP-DRP) has increased. 2005 ATS/IDSA guidelines introduced a new category, healthcare-associated pneumonia (HCAP), and recommend extended-spectrum antibiotic treatment for patients meeting HCAP criteria. However, the predictive value of the HCAP model is limited and data suggest that outcomes are not improved using HCAP guideline-concordant therapy. Better methods to predict risk of CAP-DRP are needed.

Methods: We reviewed currently published literature on the performance status of HCAP as a predictive tool and studies describing additional risk factors for CAP-DRP. We also summarize the performance characteristics of the currently published alternative clinical prediction scores and compare them to that of the HCAP model.

Results: In addition to the five risk factors incorporated in HCAP, at least 13 other factors have been identified. The independent predictive value of any single factor is low, but accumulating factors results in increased risk of CAP-DRP. The performance characteristics of 9 clinical prediction scores are reviewed. Nearly all of the scores outperformed HCAP in their study populations. However, no single model has yet demonstrated adequate specificity to minimize unnecessary antibiotic use, while retaining sufficient sensitivity to prevent inadequate initial empiric antibiotic therapy when validated across a wide range of CAP-DRP prevalence.

Conclusions: Additional development and validation of prediction scores based upon more refined risk factors for CAP-DRP is needed. Once an accurate, adequately validated
prediction score is available, an interventional trial will be needed to determine clinical impact.
© 2014 Elsevier Ltd. All rights reserved.

Contents

Introduction .......................................................................... 2
Changing epidemiology of drug-resistant organisms . . ............................................ 2
Appropriate initial antibiotic therapy . ....................................................... 2
Healthcare-associated pneumonia . ................................................................. 3
Risk factors for CAP-DRP . ........................................................................... 3
Prediction of CAP-DRP . ........................................................................... 4
Clinical prediction models ................................................................ 7
Predicting risk of MRSA . ........................................................................ 7
Future research . ....................................................................... 8
Conclusion ............................................................................ 8
Authorship ............................................................................ 8
Financial disclosure/conflict of interest ...................................................... 8
References ........................................................................... 8

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>community-acquired pneumonia</td>
</tr>
<tr>
<td>HCAP</td>
<td>healthcare-associated pneumonia</td>
</tr>
<tr>
<td>CAP-DRP</td>
<td>CAP-drug resistant pathogens. Bacteria resistant to antibiotics recommended for treatment of CAP; i.e. beta-lactam plus macrolide or respiratory fluoroquinolone</td>
</tr>
</tbody>
</table>

Introduction

Pneumonia accounts for more than 1 million hospitalizations and 55,000 deaths per year in the United States [1,2]. Initial guidelines for inpatient management of community-acquired pneumonia (CAP) were developed in 1993 [3]. Concordance with these guidelines in hospitalized patients with CAP, i.e. a β-lactam plus macrolide or respiratory fluoroquinolone, is associated with improved outcomes [4]. Since 1993, clinical management of pneumonia has become more complex due to increasing rates of drug resistance. Revised guidelines have aimed to identify patients at risk for infection with pathogens resistant to antibiotics recommended for CAP (CAP drug-resistant pathogens or CAP-DRP). However, the HCAP model has limited predictive value and has not been shown to improve outcomes [5]. Better methods of predicting risk for CAP-DRP are needed.

Changing epidemiology of drug-resistant organisms

*Streptococcus pneumoniae* is the predominant pathogen in CAP, followed by *Haemophilus influenzae*, *Moraxella catarrhalis* and atypical bacteria such as *Mycoplasma pneumoniae* and *Legionella pneumophila* [6]. Since the 1990’s, the incidence of CAP-DRP has increased, notably in patients with co-morbidities and frequent healthcare exposure. This trend was originally described in patients transferred from nursing homes and other long-term facilities, in whom Enterobacteriaceae, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) were more frequently recovered [7,8]. In 2005, Kollef et al. reported data from a commercial healthcare database of 3209 patients admitted from the community with culture-positive pneumonia in 59 U.S. hospitals [9]. In contrast to previous cross-sectional studies, this study reported a high overall prevalence of CAP-DRP (34%), of which MRSA and *P. aeruginosa* comprised the large majority [9]. Although the accuracy of the microbiology data has been criticized because *S. aureus* and *P. aeruginosa* were more prevalent than *S. pneumoniae* even in CAP patients [10], this study raised concerns that a growing number of patients are at risk for pneumonia due to CAP-DRP and may not receive effective antibiotic therapy with CAP-concordant regimens.

Appropriate initial antibiotic therapy

Initial selection of empiric antibiotics with activity against the infecting organism improves outcomes in serious bacterial infections. This has been demonstrated in multiple clinical settings, including infections in the critically ill [11], bacteremia [12], and for treatment of MRSA [13], *P. aeruginosa* [14], and extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae [15]. In pneumonia populations with elevated CAP-DRP prevalence, inadequate initial antibiotic therapy is associated with poor outcomes, including mortality [16,17].
Predicting drug resistance in pneumonia

Healthcare-associated pneumonia

In 2005, pneumonia guideline classifications were subdivided to add a novel entity, healthcare-associated pneumonia (HCAP), to the existing paradigm [18]. This new category comprises a patient population with frequent healthcare exposure in whom the risk of CAP-DRP is increased. The criteria used for HCAP classification were based upon risk factors for drug-resistant bacteremia identified by Friedman et al. [19] and subsequently applied to the large U.S. cohort described by Kollef et al. [9] HCAP criteria include: patients hospitalized within the last 90 days, those receiving chemotherapy, wound care or intravenous antibiotics, residents of nursing homes or long-term facilities, and patients requiring hemodialysis. The guidelines recommend that HCAP patients be treated with an anti-pseudomonal beta-lactam plus either an aminoglycoside or an anti-pseudomonal fluoroquinolone, plus an agent active against MRSA if risk factors for MRSA are present [18].

Subsequent studies have confirmed that the HCAP designation effectively identifies a population with multiple co-morbidities and increased mortality [16,20–27]. However, unlike CAP, for which guideline-concordant therapy has been repeatedly shown to improve mortality [4,28,29], HCAP guideline-concordant therapy has not been shown to improve outcomes [20–22,27,30–37], and may in fact be associated with increased mortality. Although this remains incompletely understood, there are several potential explanations for these results. First, poor outcomes in the HCAP population appear to be more closely associated with comorbid disease than to resistant organisms. This was demonstrated by Rello et al., [39] who showed that even in a population limited only to patients with confirmed pneumococcal pneumonia, outcomes were poorer in those meeting HCAP criteria. This was confirmed in a meta-analysis by Chalmers et al. who showed no difference in mortality between CAP and HCAP when adjusted for age and co-morbidity [5,38]. Second, unnecessary extended-spectrum antibiotic therapy increases cost [20,32], drug toxicity [39–41], *Clostridium difficile* infection [42], and antibiotic resistance [43], which may affect outcomes.

Lastly, accumulating evidence suggests that the HCAP model is poorly predictive of pneumonia due to CAP-DRP [5,25,44]. The predictive value of the HCAP criteria varies directly with the local incidence of CAP-DRP (Table 1). The positive predictive value (PPV) of the HCAP classification is only satisfactory in areas with very high rates of CAP-DRP, at the expense of an unacceptable negative predictive value (NPV) [9]. Conversely, in areas of low-moderate CAP-DRP incidence, the HCAP-CAP distinction is effective in identifying patients at low risk of drug resistant disease, but results in over-treatment in many patients [25,30]. In a recent meta-analysis of 24 studies, Chalmers et al. confirmed the relatively poor performance of HCAP as a predictor of CAP-DRP, reporting an overall sensitivity of 53.7, specificity of 71.2 and AUROC of 0.70 [5]. Alternative strategies are needed to accurately discriminate patients at risk for CAP-DRP pneumonia from patients for whom CAP therapy is most appropriate.

### Risk factors for CAP-DRP

Data from HCAP studies reproducibly identify risk factors associated with pneumonia caused by CAP-DRP (Table 2) [16,20,21,23–27,30,31,34,36,37,44–47]. Risk factors fall into several categories: extrinsic (environmental), intrinsic (host), and factors selective specifically for CAP-DRP (Fig. 1). For example, environmental exposures such as recent hospitalization or residence in a long term care facility contribute to oropharyngeal colonization with potentially drug-resistant organisms [48,49]. Additional extrinsic factors favoring colonization with CAP-DRP include wound care [27], tube feeding [50], presence of an indwelling catheter [48], and invasive healthcare intervention in general [51]. Many of these extrinsic risk factors are collinear, and are often present in combination in debilitated patients.

Intrinsic risk factors alter host physiology to non-specifically increase risk of developing pneumonia caused by any microorganism, including CAP-DRP if present in the oropharynx. Intrinsic factors include age, aspiration risk, chronic lung disease, gastric acid suppression, immunosuppression, diabetes and cognitive impairment. Some host factors such as poor functional status [8,48,51], corticosteroid use [24] and bronchiectasis tend to foster colonization more specifically with CAP-DRP.

Prior antibiotic use is a well-established risk factor for both colonization and infection with multi-drug resistant organisms. In pneumonia specifically, antibiotic usage

<table>
<thead>
<tr>
<th>Table 1</th>
<th>HCAP criteria diagnostic performance by prevalence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author (location)</td>
<td>Prevalence (%)</td>
</tr>
<tr>
<td>Micek (St. Louis)</td>
<td>50.7</td>
</tr>
<tr>
<td>Shorr (St. Louis)</td>
<td>45.2</td>
</tr>
<tr>
<td>Kollef (US Database)</td>
<td>34</td>
</tr>
<tr>
<td>Schreiber (Washington D.C.)</td>
<td>31.6</td>
</tr>
<tr>
<td>Jung (Korea)</td>
<td>26.5</td>
</tr>
<tr>
<td>Shindo (Japan)</td>
<td>15.8</td>
</tr>
<tr>
<td>Shindo (Japan)</td>
<td>12.9</td>
</tr>
<tr>
<td>Grenier (Canada)</td>
<td>5.3</td>
</tr>
<tr>
<td>Chalmers (UK)</td>
<td>4.9</td>
</tr>
<tr>
<td>Carratala (Spain)</td>
<td>1.4</td>
</tr>
</tbody>
</table>
exerts selective pressure favoring CAP-DRP in the oropharyngeal microcosm [43,44,51].

Overall, the independent predictive value for CAP-DRP for most risk factors is low. However, the cumulative risk of infection due to CAP-DRP increases with the presence of multiple risk factors [20,27,30]. A confluence of extrinsic and intrinsic risk factors with selective antibiotic pressure leads to the highest risk for disease due to CAP-DRP.

**Prediction of CAP-DRP**

A viable alternative to the HCAP model should accurately distinguish patients at low risk for CAP-DRP from those at high risk for whom extended-spectrum therapy is warranted. An ideal predictive model would be derived from risk factors specifically associated with CAP-DRP, validated across demographically- and microbiologically-distinct populations, be easily calculated, and able to distinguish risk of MRSA from other CAP-DRP. Current scoring models are either cumulative, in which risk factors are weighted equally and probability of CAP-DRP increases with the number of factors, or probabilistic, in which risk factors are weighted from results of regression analysis in the derivation group. Electronic decision support might ease the burden of calculation if a complex model performs better than simple models such as HCAP [52].

Methodology used to evaluate the clinical utility of a predictive model must be carefully considered. Ideally, a prediction tool establishes a threshold below which the risk of CAP-DRP is acceptably low in order to avoid inadequate treatment in most cases, but above which the probability of CAP-DRP is high enough to justify extended-spectrum antibiotics. Although a predictive model may demonstrate good overall accuracy by area under the receiver-operator curve (AUROC), it may be unable to clearly dichotomize high and low risk. This is due in part to the bell-shaped rather than binary curve of probability distribution. Also, the lack of specificity among risk factors contributes to a see-saw effect in which specificity is augmented at the expense of sensitivity as the threshold is raised.

**Table 2  Risk factors for CAP-DRP by publication.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior antibiotics</td>
<td>[16,23—25,30,36,37,44—46,51]</td>
</tr>
<tr>
<td>Prior hospitalization</td>
<td>[23,25,26,31,34,36,37,44—47]</td>
</tr>
<tr>
<td>Resident of long term care</td>
<td>[24,25,30,31,34,36,44,45,47]</td>
</tr>
<tr>
<td>Tube feeding</td>
<td>[16,23,36,37]</td>
</tr>
<tr>
<td>Multiple HCAP risk factors</td>
<td>[20,27,30,34—37,47]</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>[21,24,30,34,36,46,47]</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>[25,30,36,37,46]</td>
</tr>
<tr>
<td>Chronic kidney disease/</td>
<td>hemodialysis [25,31,34,47]</td>
</tr>
<tr>
<td>Wound care</td>
<td>[27,36]</td>
</tr>
<tr>
<td>Infusion therapy</td>
<td>[24]</td>
</tr>
<tr>
<td>Poor functional status</td>
<td>[16,37,51]</td>
</tr>
<tr>
<td>Aspiration risk</td>
<td>[21]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>[24,45]</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>[46]</td>
</tr>
<tr>
<td>Severity of pneumonia</td>
<td>[24,31,35,45]</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>[45,47]</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>[45]</td>
</tr>
<tr>
<td>Prior CAP-DRP or MRSA colonization</td>
<td>[24,37,54]</td>
</tr>
<tr>
<td>Gastric acid suppression</td>
<td>[37]</td>
</tr>
<tr>
<td>Indwelling catheter</td>
<td>[48]</td>
</tr>
</tbody>
</table>

**Figure 1  Interplay of CAP-DRP risk factors.**
<table>
<thead>
<tr>
<th>Model</th>
<th>Original reference(s)</th>
<th>Validation reference(s)</th>
<th>Population(s), ((n = \text{culture-positive cases}))</th>
<th>Risk factors</th>
<th>Points</th>
<th>Design</th>
<th>Prediction cut-off (points)</th>
<th>CAP-DRP prevalence (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niederman, 2009</td>
<td>[53] [35]</td>
<td>Japan, ((n = 195)), prospective multicenter cohort; HCAP patients only; stratified by severity</td>
<td>Hospitalization (90 d) Poor functional status Antibiotic use (180 d) Immunosuppression</td>
<td>1 Cumulative decision tree Severe PNA (\geq 1) Non-severe PNA (\geq 2)</td>
<td></td>
<td></td>
<td>Overall: 25.1</td>
<td>93.9 55.5 41.4 94.6 N/A</td>
<td>96.5 50.0 53.8 96.0</td>
<td>90.0 58.2 30.5 96.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shorr, 2008</td>
<td>[31] [25] [34] [56]</td>
<td>USA - St. Louis, ((n = 977)), retrospective single center Spain - Barcelona ((n = 493)) Italy—Milan ((n = 180)), prospective multicenter</td>
<td>Hospitalization (90 d) Resident of LTC Hemodialysis Severe PNA (ICU)</td>
<td>4 Probabilistic (\geq 1) 3 2 1</td>
<td></td>
<td></td>
<td>Overall: 46.7 46.7 7.7 60.6 86.8 75.4 22.8 98.6 0.89</td>
<td>88.6 54.5 63.0 84.5 89.7 0.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schreiber, 2010</td>
<td>[30] N/A</td>
<td>USA—Washington DC, ((n = 190)), retrospective single center; only ICU patients</td>
<td>Immunosuppression Resident of LTC Antibiotic use</td>
<td>3 Probabilistic (\geq 2) 2</td>
<td></td>
<td></td>
<td>Overall: 31.5 31.5 7.7 60.6 74.0 86.2 32.3 98.0 0.89</td>
<td>63.3 70.0 49.4 80.5 89.7 0.70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliberti, 2012</td>
<td>[47] [47]</td>
<td>Italy—Milan ((n = 180)), prospective multicenter</td>
<td>CVA, DM, COPD, Antibiotic use (90 d), wound care Immunosuppression Resident of LTC</td>
<td>0.5 Probabilistic (&gt;0.5)</td>
<td></td>
<td></td>
<td>Overall: 18.3 18.3 7.7 74.0 78.9 86.2 32.3 98.0 0.89</td>
<td>78.8 70.0 37.1 93.6 89.7 0.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shindo, 2013</td>
<td>[37] N/A</td>
<td>Japan ((n = 746)), prospective multicenter</td>
<td>MRSA Risk Factors: Hospitalization (90 d) Antibiotic use (90 d) Hemodialysis (30 d) Prior MRSA colonization Congestive heart failure Gastric acid suppression Other CAP-DRP risk factors: Hospitalization (90 d) Antibiotic use (90 d) Immunosuppression Gastric acid suppression Tube feeding Poor functional status</td>
<td>Cumulative (\geq 2) (\geq 3) (\geq 2 + 1) MRSA RF (\geq 3 + 1) MRSA RF</td>
<td></td>
<td></td>
<td>Overall: 22.4 22.4 8.9 39.3 42.9 81.0 0.76</td>
<td>74.0 70.4 22.4 95.9 92.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Model (author, year)</th>
<th>Original reference</th>
<th>Validation reference(s)</th>
<th>Population(s), ((n = \text{culture-positive cases}))</th>
<th>Risk factors</th>
<th>Points</th>
<th>Design</th>
<th>Prediction cut-off (points)</th>
<th>CAP-DRP prevalence (%)</th>
<th>Sens ((%))</th>
<th>Spec ((%))</th>
<th>PPV ((%))</th>
<th>NPV ((%))</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, 2012</td>
<td>[50]</td>
<td>[36]</td>
<td>Korea ((n = 580)), retrospective single center</td>
<td>Tube Feeding Hospitalization (90 d) Intravenous antibiotics (30 d) Resident of LTC Chemotherapy (30 d) Wound care (30 d) Hemodialysis</td>
<td>5 3 2 1 1</td>
<td>Probabilistic</td>
<td>(\geq 3)</td>
<td>39.1</td>
<td>63.9</td>
<td>74.2</td>
<td>61.4</td>
<td>76.2</td>
<td>0.73</td>
</tr>
<tr>
<td>El Solh, 2004</td>
<td>[51]</td>
<td>[51]</td>
<td>USA—Buffalo, NY ((n = 86 -\text{derivation}; n = 47-\text{validation})). Prospective, single center, Patients with severe NHAP</td>
<td>Antibiotic use (180 d) Functional status</td>
<td>1</td>
<td>Cumulative decision tree</td>
<td>(\geq 2)</td>
<td>19.8</td>
<td>52.9</td>
<td>98.6</td>
<td>90.0</td>
<td>89.7</td>
<td>0.90</td>
</tr>
<tr>
<td>Shorr MRSA, 2013</td>
<td>[45]</td>
<td>[45]</td>
<td>USA, ((n = 3993 -\text{derivation}, n = 1982 -\text{validation})) retrospective, multi-center database cohort</td>
<td>Hospitalization (90 d) Severity (ICU) Resident of LTC Extremes of age ((&lt;30, &gt;79)) Intravenous antibiotics (30 d) Cerebrovascular disease Dementia Diabetic female</td>
<td>2 2 1 1 1 1 1 1</td>
<td>Probabilistic</td>
<td>(\geq 2)</td>
<td>14.1</td>
<td>59.1</td>
<td>60.0</td>
<td>19.2</td>
<td>90.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Madaras-Kelly, 2012</td>
<td>N/A</td>
<td></td>
<td>USA ((n = 375)), retrospective multicenter VA. Only included HCAP patients</td>
<td>MRSA colonization ((&lt;90 \text{d})) MRSA colonization ((&gt;90 \text{d})) Resident of LTC Infusion Therapy (30 d) Cephalosporin use ((&lt;365 \text{d})) Diabetes Severe PNA (ICU)</td>
<td>100 45 45 35 30 30 25</td>
<td>Probabilistic</td>
<td>Score %</td>
<td>31.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Clinical prediction models

Several clinical prediction models have been developed to improve upon the performance of the HCAP criteria (Table 3) \cite{24,25,30,31,34-37,45,47,51,53}. While most scores demonstrate better test performance when compared to HCAP, a model able to sensitively predict CAP-DRP while minimizing unnecessary antibiotic coverage has yet to be validated.

The first predictive model was proposed by El-Solh et al. prior to HCAP guideline publication \cite{51}. This cumulative decision tree model was prospectively derived and validated in a small cohort of nursing home patients admitted with severe pneumonia. Using functional status and recent antibiotic use (within 180 days), the El Solh model yielded positive and negative predictive values of 90% and an AUROC of 0.90. However, a significant decrease in test performance would be expected if applied beyond this narrow population with elevated risk of CAP-DRP.

The first of several probabilistic clinical prediction scores was derived and validated \cite{25} in large, single-center, retrospective cohorts with CAP-DRP prevalence >45% using risk factors weighted according to strength of correlation in logistic regression analysis. Using hospitalization, long-term care, hemodialysis and severity as risk factors, the Shorr model significantly improved upon the specificity of the HCAP criteria (54.5% vs 34.3%) with only a marginal decrease in sensitivity. Unnecessary extended-spectrum antibiotic therapy would have been reduced from 30% to 24.3% compared to HCAP in this observational study in a high-prevalence population \cite{25}. In subsequent evaluations in four distinct populations with lower rates of CAP-DRP \cite{34,37,47}, the score outperformed HCAP, recommending inadequate therapy in 1–7% and overtreatment in 19–23% of cases.

Aliberti et al. employed similar methodology to derive a predictive model in a prospective Italian cohort, heavily weighting chronic renal disease, recent hospitalization and long-term care but also including minor risk factors such as cerebrovascular accident, diabetes mellitus, chronic obstructive pulmonary disease, wound care, immunosuppression and antibiotic use \cite{47}. The model was validated in an independent, prospective, multinational population with a very low CAP-DRP prevalence (7.7%) where it outperformed the HCAP criteria. In this setting, the Aliberti score would potentially reduce inappropriate therapy to <2% of all cases while limiting use of unnecessary extended-spectrum antibiotic treatment to 12.7%. The Aliberti and Shorr models demonstrated similar performance characteristics in this population \cite{34}.

Park et al. derived a probabilistic scoring model by weighting the six HCAP criteria in addition to a novel risk factor, tube feeding \cite{50}. In a retrospective validation study in a high-prevalence population, this model demonstrated marginal improvement over HCAP (PPV 61.4% vs. 56.9%). Overtreatment would have only been reduced from 50.7% to 43.7% using this model, and low sensitivity (63.9%) and high CAP-DRP prevalence in this population resulted in a NPV of only 76.2% \cite{36}.

Two additional probabilistic scores, proposed by Schreiber \cite{30} and Madaras-Kelly \cite{24}, have not yet been independently validated. The Schreiber score is comprised of weighted factors including immunosuppression, long-term care and antibiotic use. In a single center derivation cohort of patients admitted to the ICU with severe pneumonia with a CAP-DRP rate of >30%, this score demonstrated a PPV of 49.4% at the expense of a relatively low NPV of 80.5%; under- and over-treatment were recommended in 11.5% and 20% of cases using this model. The Madaras-Kelly model was retrospectively derived from HCAP patients, and included risk factors MRSA colonization, long-term care, infusions, cephalosporin use, diabetes, and severity. The authors reported an AUROC of 0.71, a similar test performance as reported for other published scores.

A decision tree algorithm previously published \cite{53} has recently been evaluated in a prospective implementation study \cite{35}. The Niederman model retains the HCAP/CAP distinction, but further stratifies HCAP patients according to CAP-DRP risk on the basis of additional risk factors including antibiotic use within 180 days of admission, hospitalization within 90 days, poor functional status and immunosuppression. This model assigns a lower threshold for extended-spectrum therapy in patients with severe disease. When implemented in a multi-center Japanese cohort comprised of 195 HCAP patients with bacterial pneumonia, the algorithm limited inadequate empiric therapy to 1.5%, but resulted in unnecessary extended-spectrum antibiotic therapy in 65/195 (33%) of cases \cite{35}.

Another recent publication describes a cumulative model derived from a large, prospective multicenter Japanese cohort \cite{37}. Shindo et al. assigned one point each to the following risk factors: hospitalization within 90 days, antibiotic use within 90 days, immunosuppression, gastric acid suppression, tube feeding and poor functional status. The risk of pneumonia due to a CAP-DRP was then calculated according to the total score. In a population with an overall CAP-DRP prevalence of 16.6%, a score threshold of ≥2 demonstrated a NPV of 93.5% and a PPV of 34.2%. Antibiotic prescribing according to this score would have resulted in inadequate initial therapy in 4% of patients, and unnecessary antibiotic coverage in 22.5%. This model has not been validated in an independent population.

Predicting risk of MRSA

Several models have attempted to differentiate risk for MRSA from other CAP-DRP such as P. aeruginosa. Shindo et al. found that in addition to risk factors common for all CAP-DRP, hemodialysis, prior MRSA colonization and congestive heart failure were uniquely associated with increased risk of MRSA. In patients with 2 or more risk factors for CAP-DRP, the presence or absence of at least one MRSA-specific risk factor resulted in a PPV for MRSA pneumonia of 39.3%, and NPV of 91.1%. Shorr et al. \cite{45} derived a MRSA-specific prediction model from a large retrospective database cohort, and found that odds of MRSA pneumonia were increased in patients with recent hospitalization, severe pneumonia, long-term care, extremes of age, recent intravenous antibiotic use, cerebrovascular disease, dementia and diabetic females. In a validation cohort, a probabilistic scoring model based on
these risk factors demonstrated a PPV of 19.2% and NPV of 90.1% in a population with 14.1% prevalence. In this cohort, the novel MRSA score did not perform better than the HCAP criteria. Given the lack of specificity of risk factors for MRSA, point of care determination of nasal MRSA colonization may prove to be a more accurate method of determining MRSA risk. A recent retrospective study found that detection of nasal MRSA colonization by polymerase chain reaction (PCR) had a PPV of nearly 40% and NPV of >98% for clinical MRSA pneumonia [54]; further study is warranted.

Future research

Additional research is needed in order determine the optimal method of identifying patients with pneumonia at highest risk for CAP-DRP. Rapid molecular-based diagnostic testing holds promise as a means both for guiding appropriate therapy and deescalating from broad spectrum therapy [54]. Assays employing multiplex PCR or 16s RNA amplification techniques to detect respiratory pathogens or genetic determinants of resistance directly from respiratory specimens are under investigation [55]. The diversity of gram-negative resistance mechanisms and the number of potential CAP-DRP implicated in pneumonia are a significant challenge for novel diagnostic testing development. The majority of these techniques have yet to be validated and remain several years from routine clinical practice.

Until then, improving the accuracy of clinical prediction models should remain the focus of clinical research as a means of optimizing pneumonia management while reducing antibiotic over-utilization. Additional refinement of CAP-DRP risk factors is necessary. For example, although recent hospitalization and antibiotic use are both associated with risk for CAP-DRP, the time elapsed from exposure to pneumonia admission may be an important contributor, perhaps to be integrated as a continuous variable in scoring algorithms. Likewise, the class of prior antibiotic exposure or type of hospitalization (ICU versus medical/surgical ward) may also impact magnitude of risk and specificity of the risk factor.

Antibiotic overtreatment will always be favored over inadequate empiric therapy given the evidence of poor outcomes with the latter. In order to reduce cost, prevent resistance and limit adverse effects, additional research is needed to guide safe and timely antibiotic de-escalation in culture-negative patients with intermediate to high CAP-DRP risk.

Nearly all of the recently published predictive models have outperformed HCAP in their respective study populations. However, no single model has yet demonstrated adequate specificity to minimize unnecessary antibiotic use, while retaining sufficient sensitivity to prevent inadequate initial empiric antibiotic therapy when validated across a wide range of CAP-DRP prevalence. Head-to-head validation studies will be necessary in order to evaluate these models’ generalizability and performance. With some refinement, development of a score capable of differentiating high and low CAP-DRP risk in diverse validation populations is conceivable. Prospective implementation studies of scores with acceptable performance in validation studies will then be key to determine whether patients benefit.

Conclusion

Clinicians are increasingly faced with the difficult decision of which patients to treat with CAP antibiotic regimens, and which patients might benefit from empiric extended-spectrum therapy. Although the HCAP model correctly identifies a population prone to poor outcomes, it does not adequately predict risk for CAP-DRP. Novel methods are needed in order to avoid unnecessary broad spectrum antibiotic use while minimizing empiric therapy lacking activity against drug-resistant pathogens. Although multiple prediction models have been proposed that improve upon HCAP criteria, none has yet been validated across broad microbiological and demographic populations. Additional research is necessary in order to refine scoring models and identify alternatives to HCAP with wide clinical generalizability. Once validated, interventional trials will be needed to evaluate safety and performance.

Authorship

All authors (BW, KD, ES & ND) contributed significantly to manuscript preparation. All authors have approved the final draft.

Financial disclosure/conflict of interest

None of the authors have any sources of financial support or conflicts of interest to disclose.

References


Brito V, Niederman MS. Healthcare-associated pneumonia is a heterogeneous disease, and all patients do not need the same broad-spectrum antibiotic therapy as complex nosocomial pneumonia. Curr Opin Infect Dis 2009;22(3):316–25.

