Healthcare-Associated Pneumonia: Approach to Management

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KEYWORDS

• Pneumonia • Healthcare-associated • Community-acquired
• Risk factors • Antibiotic therapy

Recently, a new classification of pneumonia, healthcare-associated pneumonia (HCAP), was introduced.[1] HCAP was created to identify patients with community-acquired pneumonia (CAP) at risk for developing infections from multidrug-resistant (MDR) pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* who need empiric treatment modification based on specific risk factors.[2–5] The 2005 American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) nosocomial pneumonia guidelines[1] recognized HCAP as a distinct clinical entity and defined HCAP risk factors as: (1) hospitalization for 2 or more days in an acute care facility within 90 days of infection, (2) presentation from a nursing home or long-term care facility (LTCF), (3) attending a hospital or hemodialysis clinic, and (4) receiving intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection.[1] The 2007 ATS-IDSA CAP guidelines[6] also recognized HCAP as a clinical entity but cautioned that some overlap still occurs between CAP and HCAP.

Healthcare-associated bloodstream infections were first described in a 2002 study by Friedman and colleagues.[7] The microbiology differed between patients with healthcare-associated infections and those with community-acquired infections. The predominant organism isolated from patients with a HCAI was MRSA, and *Escherichia coli* and *Streptococcus pneumoniae* were the predominant organisms isolated in community-acquired infections. In 2005, Kollef and colleagues[3] first described HCAP using a large, retrospectively collected administrative database of 4,543 patients in 59 hospitals in the United States. All of the patients identified had positive cultures, and the infections were classified as CAP, HCAP, hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP). Patients with HCAP had a mortality (19.8%) similar to patients with HAP (18.8%) but higher than those with CAP (10.0%, $P<0.0001$). Subsequent cohort studies of culture-positive HCAP and CAP patients from St Louis, MO, USA[4] Spain,[8] Italy,[9] and Japan[10] have confirmed the higher mortality associated with HCAP. In an analysis of long-term outcomes of patients with HCAP and CAP in Seattle, WA, USA, those with CAP had a better survival 8 years after their pneumonia (78.8% CAP vs 44.5% HCAP, $P<0.001$).[11] Finally, patients without a positive respiratory culture have a lower severity of illness and better survival than those with a positive culture (7.4% mortality culture negative vs 24.6% culture positive, $P<0.001$).[12]

MICROBIOLOGY

The 2005 analysis by Kollef and colleagues[3] showed that the microbiology of HCAP was similar to HAP and VAP but distinct from CAP. The most common organism isolated in all pneumonia subtypes was *S aureus*, found in 25.5% of those with CAP and 46.7% of those with HCAP ($P<0.001$) (**Table 1**). MRSA and *P aeruginosa* were more common in patients with HCAP while

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Table 1
Pathogen distribution according to geographic region

	United States						Europe				Japan	
	Kollef et al,[3] 2005		Micek et al,[4] 2007		Schreiber et al,[13] 2010		Carratala et al,[8] 2007		Venditti et al,[14] 2009		Shindo et al,[10] 2009	
Study	CAP	HCAP	CAP	HCAP	CAP	HCAP	CAP	HCAP	CAP	HCAP	CAP	HCAP
Gram-positive Pathogens (%)												
Streptococcus pneumoniae	16.6	5.5	40.9	10.4	21.9	6.4	33.9	27.8	43.9	7.1	19.1	13.5
Staphylococcus aureus	25.5	46.7	25.5	49.9	29.2	32.9	2.4	0	17.1	39.3	6.1	9.9
MRSA	8.9	26.5	12.0	36.0	14.6	22.3	—	—	6.4	25.0	0.9	3.5
MSSA	17.2	21.1	13.5	13.9	14.6	10.6	—	—	10.7	14.3	5.2	6.4
Gram-negative Pathogens (%)												
Pseudomonas aeruginosa	17.1	25.3	4.8	25.5	3.1	23.4	0.5	1.6	9.7	7.1	1.7	5.7
Haemophilus spp	16.6	5.8	17.3	4.2	—	—	6.0	11.9	—	—	7.4	2.8
Klebsiella spp	9.5	7.6	3.4	6.5	4.2	10.6	0.2	0	—	—	1.7	7.1
Escherichia coli	4.8	5.2	5.8	4.2	4.2	12.8	0.3	2.4	—	—	0.4	3.5
Other Nonfermenting GNB[a]	1.6	2.6	1.9	10	—	—	—	—	—	—	0	2.1
Other Enterobacteriaceae[b]	7.0	13.0	2.4	9.0	—	—	—	—	—	—	1.3	2.8

Abbreviations: GNB, gram-negative bacteria; MSSA, methicillin-susceptible *Staphylococcus aureus*.
[a] *Acinetobacter* species, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Burkholderia* species.
[b] *Enterobacter* species, *Citrobacter* species, *Serratia marcescens, Proteus* species, *Morganella* species.

S pneumoniae and *Hemophilus* species were more common in patients with CAP. In 2007, Micek and colleagues[4] confirmed these findings in a cohort of 639 patients from a single United States institution. The most common organisms were MRSA (30.6%) and *P aeruginosa* (25.5%), and the most common CAP organisms were *S pneumoniae* (40.9%) and *Hemophilus* species (17.3%). Finally, in a separate United States cohort, Schreiber and colleagues[13] confirmed the finding that MRSA and *P aeruginosa* were the most common organisms isolated from HCAP patients.

P aeruginosa and MRSA are the most common organisms causing HCAP in the United States, but cohorts from Europe and Japan have found differing results. In a prospective analysis of 727 patients presenting with pneumonia in Spain,[8] CAP was more common than HCAP (82.7% CAP vs 17.3% HCAP). In patients with HCAP, the most prevalent organism was *S pneumoniae* (27.8%) followed by *H influenzae* (11.9%). *P aeruginosa* (1.6%) and *S aureus* (2.4%) were more common in those with HCAP but were not frequently isolated. In a multicenter cohort study from Italy, *S aureus* was the most common HCAP organism (39.3%), but *P aeruginosa* was not frequently isolated (5.7%).[14] In a cohort of patients from Japan,[10] *S pneumoniae* was the most common organism in HCAP patients (13.5%), but gram-negative bacteria (24.1%), *P aeruginosa* (5.7%), and MRSA (3.5%) were more common in HCAP than CAP.

HCAP RISK FACTORS

The HCAP definition varies between the published clinical studies and the ATS-IDSA guidelines. All of the published studies include hemodialysis and residence in a LTCF as HCAP risk factors. Hospitalization for 2 or more days in the prior 90 days is used in the ATS-IDSA guidelines[1] and is the most commonly used definition[8,10,11,13,15,16] for prior hospitalization. However, time intervals as short as 30 days[3,17] and as long as 180 to 360[4,9] days have been used. Although not included in the ATS-IDSA guidelines, immunosuppression is

frequently listed as an additional HCAP risk factor.[4,8,9,11,13,15–17] In addition, the individual risk factors do not carry an equivalent risk of infection with MDR pathogens. The lack of a consistent definition and the different weight each risk factor carries for infection with resistant organisms have lead some to question whether the HCAP definition is too broad and results in over-treatment.[18]

Hospitalization places patients at risk for colonization of the upper respiratory and gastrointestinal tract with pathogens that are not commonly found in the community. Microaspiration of these organisms has been proposed as a mechanism for development of HCAP. Admission to an ICU room where the previous patient was colonized with MRSA or vancomycin-resistant *Enterococcus* (VRE) increases one's odds (odds ratio [OR] 1.4, $P = 0.04$) of becoming colonized with MRSA or VRE.[19] Hospitalization also increases the risk of colonization by resistant gram-negative organisms. In a cohort of 167 patients in at single institution, 21% of the patients became new rectal carriers of extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and 7% became nasal carriers of MRSA.[20] In a multivariate analysis of this cohort, age older than 65 and treatment with broad spectrum antibiotic therapy were risk factors for acquisition of ESBL-producing Enterobacteriaceae. Patients colonized with MDR pathogens are at risk for prolonged carriage. Of those who acquire MRSA during a hospitalization, 40% develop prolonged colonization for an average duration of 8.5 months.[21] Prolonged colonization was confirmed in subsequent studies showing an average MRSA colonization time of 7.4 months[22] and median colonization time of 132 days for ESBL-producing Enterobacteriaceae.[23]

Nursing-home–associated pneumonia (NHAP) is a clinical entity that was described prior to HCAP and was reported in the 2001 ATS-CAP guidelines as a risk factor for infection with MDR pathogens.[24] Originally published 20 years ago, MRSA colonization rates ranged from 13% to 35% among nursing home residents in the Veterans Administration medical system.[25,26] MDR gram-negative bacteria are also prevalent in nursing home residents. In a 648 bed facility, 51% of the residents were colonized with MDR gram-negative bacteria and 28% were colonized with MRSA.[27] In 2001, El-Solh and colleagues[28] examined a cohort of 104 elderly patients (≥75 years old) requiring mechanical ventilation for pneumonia admitted from both the community and nursing homes. The most prevalent organisms in those admitted from the community were *S pneumoniae* (14%), *Legionella* sp (9%), *H influenza* (7%), and *S aureus* (7%). *S aureus* (29%), enteric gram-negative bacilli (15%), *S pneumoniae* (9%), and *P aeruginosa* (4%) were the predominant organisms in those admitted from a LTCF. In a multicenter prospective study from Germany of patients admitted to the hospital with pneumonia, those from a nursing home had an increased risk of infection with gram-negative bacilli (18.8% from nursing home vs 5.5% from community, $P = 0.02$) and worse mortality (OR 2.38, 95%, CI 1.36–4.15).[29] Among nursing home patients, the presence of foreign bodies, chronic wounds, and recent hospitalization are risk factors for colonization with MDR bacteria.[30] In a further analysis of NHAP, El-Solh and colleagues[31] found functional dependence and receipt of antibiotics in the past 6 months to be predictors of infection with MDR bacteria.

Nursing home residents are at risk for colonization and infection with multidrug-resistant organism, but not all patients carry the same risk. El-Solh and colleagues[32] studied a cohort of 334 patients admitted to a general medical ward in a single institution from a nursing home. Patients who had been hospitalized within the previous 30 days, admitted to the ICU, or immunosuppressed were excluded from the analysis, and most of the patients were culture negative. The investigators found no difference in outcomes between those treated with an HCAP regimen targeting MDR organisms and those that received a treatment regimen targeting typical CAP organisms (77% of total patients).

Colonization and infection with MDR bacteria is frequent in hemodialysis (HD) and immunosuppressed patients. In a multicenter prospective study, patient receiving inpatient HD had a MRSA colonization rate of 15%, and those receiving HD as an outpatient had a colonization rate of 14%.[33] Despite the high incidence of colonization with MDR bacteria, limited evidence is available regarding pneumonia in HD patients. In a cohort of all HD patients who developed a microbiologically confirmed infection at a single institution, 13% of the infections were pneumonia. Gram-negative bacilli were isolated in 55% of the cases of CAP, *Pseudomonas* in 21%, MRSA in 12%, and *S pneumoniae* in 6%.[34] In immunosuppressed patients, especially those with a hematologic malignancy, atypical organisms such as fungi or viruses are frequent causes of pneumonia. In a study of immunosuppressed patients with clinical pneumonia, defined as hematologic malignancy, receipt of solid organ or bone marrow transplant, and chronic prednisone use, bacterial pneumonia accounted for 24% of the cases. The most commonly isolated organisms were *S aureus*, *P aeruginosa*, and *E coli*.[35]

The individual HCAP risk factors do not carry an equivalent risk for infection with an MDR organism. Shorr and colleagues[15] analyzed a cohort of 289 HCAP patients, and MDR pathogens were identified in 45.2%. The HCAP definition was not specific in identifying an infection with a resistant organism (48.9% specificity). In a multivariate analysis, long-term HD (OR 2.11), nursing home residence (OR 2.75), admission to an ICU (OR 1.62), and hospitalization in the previous 90 days (OR 4.21) were significantly associated with infection by an MDR pathogen. A separate cohort of 190 HCAP patients with 32.6% MDR pathogens was analyzed. The HCAP criteria had a negative predictive value of 84.9% and a positive predictive value of 45.2%. A multivariate model identified immunosuppression (OR 4.85), nursing home residence (OR 2.36), and prior antibiotic use (OR 2.12) as independent predictors of infection with a resistant organism. The investigators created a scoring system to predict MDR bacteria based on this analysis, but 17% of the patients with a score of zero were infected with resistant bacteria.[13]

TREATMENT

Appropriate Therapy

Therapy for any serious infection requires early, effective treatment. Inappropriate initial antimicrobial therapy, defined as in vitro resistance to an antimicrobial agent used to treat the infection, has been implicated as an independent predictor of poor outcomes in serious hospital infections and bloodstream infections.[36–41] In an international cohort of 5,715 patients with septic shock, inappropriate therapy was associated with an increased mortality in the entire cohort and within all subgroups studied, including all major infection sites and organisms.[42] In a multivariate analysis, inappropriate therapy was strongly associated with mortality (OR 8.99). Appropriate therapy is also a cornerstone of effective therapy in VAP.[43–46] The bacteria most commonly associated with inappropriate treatment in VAP are frequently MDR and include *P aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, *Enterobacter* species, and MRSA.[5]

Initial inappropriate therapy is frequent in healthcare-associated infections. In 2005, McDonald and colleagues[2] analyzed a cohort of patients with bloodstream infections and found that, compared to community-acquired infections, healthcare-associated infections were associated with an increased risk of inappropriate therapy (adjusted odds ratio [AOR] 3.1, 95% CI 1.6–6.1). Until recently, HCAP was classified and treated as CAP,[47] but it has distinct microbiologic characteristics and requires different therapy. Patients with HCAP have been shown to receive inappropriate antibiotic therapy in multiple studies,[4,9,10,48] and some have postulated that the increased mortality associated with HCAP is secondary to inappropriate initial therapy. Micek and colleagues[4] found that 28.3% of HCAP patients received inappropriate initial antibiotic therapy compared to 13.0% of CAP patients ($P<0.001$). In a multivariate analysis, inappropriate initial antibiotic therapy was an independent risk factor for hospital mortality (AOR 2.19, 95%, CI 1.27–3.78). The pathogens most associated with inappropriate therapy were *S aureus*, *P aeruginosa*, other nonfermenting gram-negative bacilli, and other Enterobacteriaceae.[4]

Early Therapy

Early antimicrobial therapy in serious infections, including CAP,[49] VAP,[50] and bacteremia,[51,52] is associated with improved mortality. Kumar and colleagues[53] analyzed a cohort of 2,731 critically ill patients with septic shock from multiple causes. The survival for patients who received appropriate therapy in the first hour of hypotension was 79.9%. In the first 6 hours of shock, each hour delay in therapy was associated with a decrease in survival of 7.6%, and in a multivariate analysis early therapy was the strongest predictor of survival. Early therapy is also important in HCAP. A retrospective analysis was performed in patients with HCAP to determine if escalation of therapy in those who received initial inappropriate therapy would improve patient outcomes.[48] Of the patients who received initial inappropriate therapy, 40.2% had therapy escalated based on in vitro culture data. The in-hospital mortality was the same for those who received therapy escalation compared to those who continued to receive inappropriate therapy (27.9% escalation and 30.2% no change, $P = 0.802$).

De-Escalation of Therapy

After a patient has received appropriate initial antibiotics, the next step in HCAP treatment is tailoring antibiotic therapy to the specific isolated organism.[54] This involves switching therapy to an antibiotic that is active against the isolated organism in vitro and frequently involves changing to monotherapy. The elimination of redundant therapy enables more effective targeting of the causative organism while avoiding increased antibiotic exposure and subsequent selection pressure for the development of antibiotic resistance. An important aspect of de-escalation is obtaining adequate respiratory cultures. Cultures can be

obtained from a bronchoalveolar lavage, protected specimen brushes, tracheal aspirate, or adequate sputum cultures.[55] In intubated patients, one should consider performing a bronchoalveolar lavage or protected specimen brushing if there is a strong clinical concern for MRSA or *P aeruginosa*.[56]

In a clinically stable patient, the decision to de-escalate therapy should be made on day 2 to 3 as this is when culture data usually returns.[1] In a prospective study of patients with severe CAP, 31% of the patients did not initially respond to therapy. Variables associated with a poor response included respiratory rate less than 25, oxygen saturation less than 90%, and confusion.[57] Patients who are not responding should be evaluated for unsuspected or resistant organisms, noninfectious mimics of pneumonia, or extrapulmonary manifestations of pneumonia.[5] In a retrospective study by Schlueter and colleagues,[58] HCAP patients whose therapy was de-escalated had a shorter length of stay in the hospital and lower mortality. Approximately half of the patients admitted with HCAP have negative respiratory cultures.[12] Culture-negative patients have a lower severity of illness and mortality than culture-positive patients, and because of this, one can consider limiting the course of antibiotics. Schlueter and colleagues[58] also found that 70% of the culture-negative patients were successfully de-escalated to a fluoroquinolone, implying that culture-negative HCAP patients may have a different microbiology than culture-positive patients.

Duration of Therapy

Limiting antibiotic exposure in patients who are improving clinically is one strategy to reduce the incidence of antibiotic resistance. There are no current studies examining antibiotic treatment duration for HCAP, and recommendations are taken from studies of VAP and CAP. In a 2003 randomized, controlled trial comparing 8 versus 15 days of antibiotics for microbiologically confirmed VAP, there was no difference in recurrent pneumonia, time on the ventilator, ICU length of stay, or mortality between the groups, and patients in the 8-day group had a lower incidence of subsequent development of resistant organisms. Patients infected with *P aeruginosa* had a higher infection-recurrence rate when treated for 8 days but did not have a difference in length of mechanical ventilation, ICU length of stay, or mortality.[59] Based on the results of the above study, the latest ATS-IDSA guidelines recommend a 7 to 8 day course of antibiotics for VAP, HAP, and HCAP with consideration of a longer course for patients infected with *P aeruginosa*.[1] In several studies investigating a procalcitonin based antibiotic discontinuation protocol, antibiotic courses have been successfully shortened to 7.2 days for VAP and 5.5 to 7.2 days for CAP.[60,61]

Treatment Recommendations

The initial goal of HCAP treatment is to provide an early, appropriate empiric treatment regimen that targets the most commonly isolated organisms. As shown above, the organisms isolated from HCAP patients vary by region and hospital.[4,8,10] Not all HCAP patients carry the same risk for infection with MDR organisms. Nursing home patients without other HCAP risk factors and not admitted to the ICU have been successfully treated with a CAP regimen. In addition, culture negative patients appear to have a lower risk of infection with MDR organisms,[12,32,58] have better outcomes, and can be de-escalated to a CAP treatment regimen. Treatment should be tailored to a specific patient, and hospitals should keep updated antibiograms to assist clinicians in treating infections. However, MDR organisms, including MRSA and *P aeruginosa* are more prevalent in HCAP than CAP in all regions. Unlike CAP, the organisms isolated in those with HCAP do not appear to depend on severity of illness.[10] In the absence of initial culture data, an empiric regimen should be selected that is active against MRSA and *P aeruginosa*. One should also consider a regimen that covers *Acinetobacter* species and ESBL-positive strains of Enterobacteriaceae if these organisms are prevalent in a specific region or hospital **Fig. 1** describes a management strategy for HCAP.

The 2005 IDSA-ATS guidelines for VAP, HAP, and HCAP provided recommendations for treatment of HCAP,[1] which include empiric broad spectrum antibiotics and tailoring of therapy once a specific organism is isolated. All patients should be treated with a β-lactam that is active against *Pseudomonas*. The initial choices are an antipseudomonal cephalosporin (cefepime), carbapenem (imipenem or meropenem), or penicillin–β-lactamase inhibitor (pipercillin-tazobactam). In addition, one can consider including in the treatment regimen a second agent active against *Pseudomonas*, such as an antipseudomonal fluoroquinolone or an aminoglycoside, especially in hemodynamically unstable patients. The rational for double coverage of *Pseudomonas* is to improve the odds that the initial empiric regimen will be appropriate.[41] Thus, the second agent can be discontinued if the chosen β-lactam is active against the isolated organism. Finally, either vancomycin or linezolid should be added for coverage against

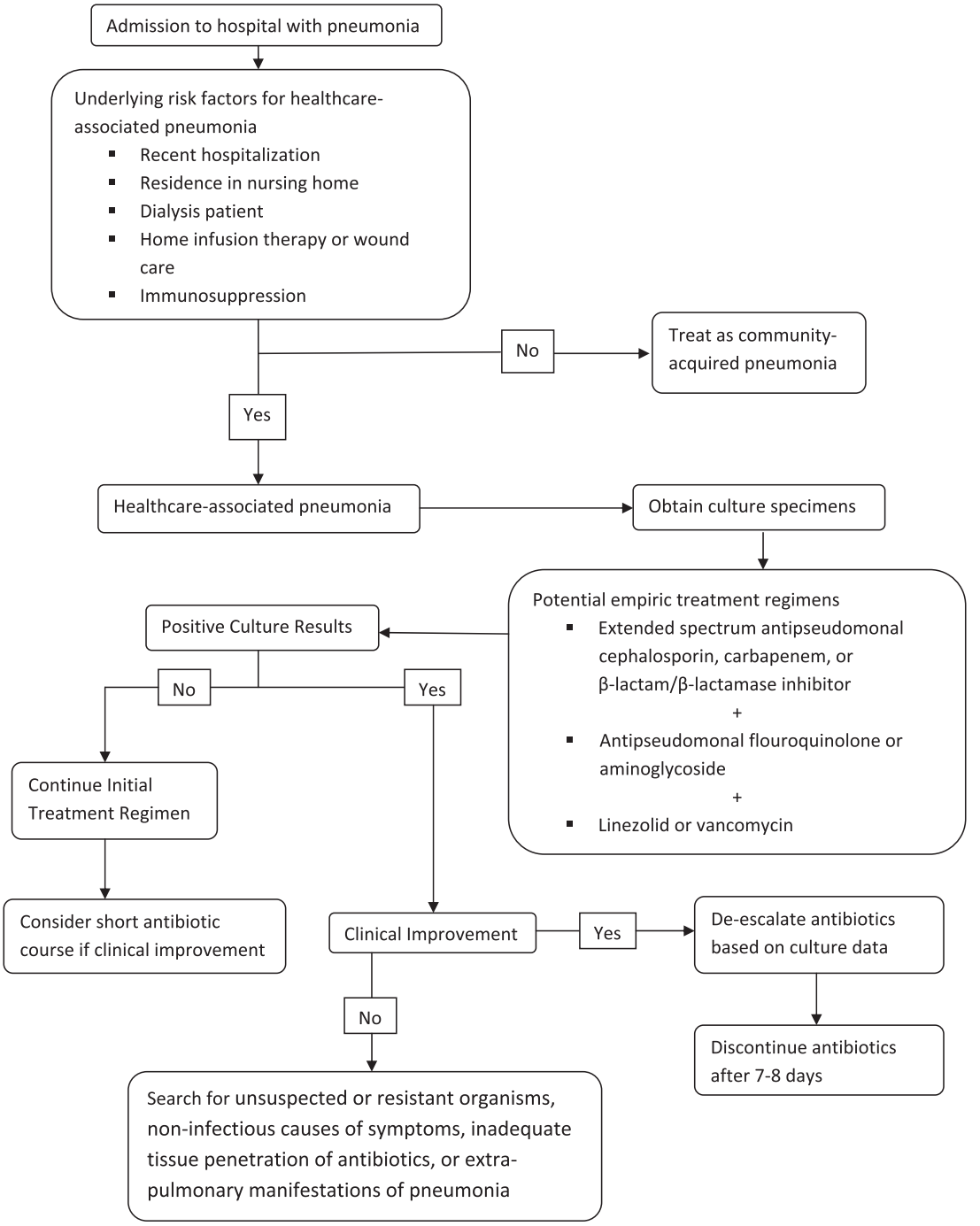

Fig. 1. Treatment strategy for patients with HCAP presenting from the Emergency Department

MRSA. For patients with MRSA pneumonia not responding to vancomycin, one should consider switching to linezolid because increasing minimal inhibitory concentrations for vancomycin still within the susceptible range has been associated with worse outcomes[62,63] and linezolid achieves better lung penetration than vancomycin.[64–66] For patients with Panton Valentine leukocidin producing strains of community-acquired MRSA, one should also consider treatment with linezolid as it has been shown to decrease toxin production in an in vitro model.[67]

SUMMARY

This article provides evidence that HCAP is a distinct clinical entity from CAP. HCAP is associated with worse outcomes and a different microbiologic cause than CAP and more closely resembles HAP. However, the incidence and microbiology of HCAP vary by region, and physicians should ensure that their local practice is similar to published studies. Although patients with HCAP risk factors are at a greater risk for infection with MDR organisms, the HCAP definition itself is not a specific marker for infection with drug-resistant bacteria. In addition, the individual risk factors themselves do not carry equal weight in predicting MDR bacteria and vary in different study populations. Further study is needed to better define which patients are at risk for MDR bacteria and which patients do not need broad-spectrum antibiotic therapy tailored for resistant infections. The goals of therapy should be to provide an early, appropriate initial antibiotic regimen based on local microbiologic data and patient risk factors. Cultures should be obtained, and in responders, antibiotic therapy should be de-escalated and antibiotic course limited. Further awareness of HCAP as a distinct clinical entity and further study of the pathogens associated with and risk factors for HCAP may help to advance and tailor therapy.

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