Treatment of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults

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INTRODUCTION — Hospital-acquired (or nosocomial) pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) are important causes of morbidity and mortality despite improved antimicrobial therapy, supportive care, and prevention [1] .

The treatment of HAP, VAP, and HCAP will be reviewed here. The diagnosis, epidemiology, pathogenesis, microbiology, risk factors, and prevention of HAP, VAP, and HCAP are discussed separately. (See "Clinical presentation and diagnosis of ventilator-associated pneumonia" and see "Epidemiology; pathogenesis; and microbiology of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults" and see "Risk factors and prevention of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults").

DEFINITIONS

Pneumonia types — The 2005 ATS/IDSA guidelines distinguish the following types of pneumonia [2] :

- Hospital-acquired (or nosocomial) pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.
- Ventilator-associated pneumonia (VAP) is a type of HAP that develops more than 48 to 72 hours after endotracheal intubation.
- Healthcare-associated pneumonia (HCAP) is defined as pneumonia that occurs in a non-hospitalized patient with extensive healthcare contact, as defined by one or more of the following:

- Intravenous therapy, wound care, or intravenous chemotherapy within the prior 30 days
- Residence in a nursing home or other long-term care facility
- Hospitalization in an acute care hospital for two or more days within the prior 90 days
- Attendance at a hospital or hemodialysis clinic within the prior 30 days

The guidelines can be accessed through the ATS web site at

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www.thoracic.org/sections/publications/statements/index.html .

Multidrug resistance — The definition of multidrug resistance (MDR) in gram-negative bacilli, which are an important cause of HAP, VAP, and HCAP is variably defined as resistance to at least two, three, four, or eight of the antibiotics typically used to treat infections with these organisms [3] .

Panresistance refers to those gram-negative organisms with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of VAP, including, cefepime , ceftazidime , imipenem, meropenem , piperacillin-tazobactam , ciprofloxacin , and levofloxacin . (See "Empiric treatment" below).

TREATMENT — Establishing the diagnosis of HAP, VAP, and HCAP may be difficult, especially in patients on mechanical ventilation, in whom clinical, radiologic, and microbiologic findings can be due to numerous etiologies besides pneumonia. This often leads to overtreatment with its attendant risks of superinfection and antibiotic toxicity. On the other hand, appropriate antibiotic therapy significantly improves survival for patients with HAP, VAP, or HCAP [2,4] . (See "Clinical presentation and diagnosis of ventilator-associated pneumonia")

The implementation of recommendations to assess a patient's status 72 hours after the initiation of therapy and to discontinue antibiotics or narrow the regimen (deescalate therapy) based on appropriate culture results will potentially reduce the selective pressure for antimicrobial resistance. In addition, a general recommendation to reduce the duration of therapy should also be beneficial.

A prospective observational study of 398 intensive care unit (ICU) patients with suspected VAP found that mortality was lower among patients in whom therapy was deescalated as compared to those patients whose therapy was escalated or was neither escalated nor deescalated (17 versus 43 and 24 percent, respectively) [5] . The study was limited because of its observational nature; confirmation of these results awaits a randomized controlled study.

When indicated, antimicrobial selection for each patient should be based on risk factors for MDR pathogens. The choice of antibiotic is influenced by the patient's recent antibiotic therapy (if any), the resident flora in the hospital or ICU, the presence of underlying diseases, and available culture data (interpreted with care). For patients with risk factors for MDR pathogens, empiric broad-spectrum, multidrug therapy is recommended in order to provide the best chance of effective therapy. Once the results of pretherapy cultures are available, therapy should be narrowed based on the susceptibility pattern of the pathogens identified.

In a retrospective analysis of local microbiologic data on HAP pathogens from 111 consecutive patients in 2004, investigators developed institution-specific treatment guidelines in order to improve empiric antibiotic therapy [6] . Institution guideline-directed treatment regimens were predicted to provide adequate initial therapy for >90 percent of patients who develop HAP ≥ 10 days after hospitalization (eg, those at greatest risk of multidrug resistant pathogens). In this institution, use of a fluoroquinolone per the national guidelines, would not have provided adequate additional antimicrobial activity for the beta-lactam resistant gram-negative bacilli (ciprofloxacin was active against <10 percent of these pathogens which were also resistant to piperacillin-tazobactam and cefepime). This study illustrates the importance of using local susceptibility data to develop treatment guidelines.

There has been interest in the nonantibiotic antiinflammatory effects of macrolides. A

randomized trial of 200 patients with sepsis and VAP showed that those who received clarithromycin (in addition to standard treatment including antibiotics) had significantly faster resolution of VAP (10 versus 15.5 days) and weaning from mechanical ventilation (16 versus 22.5 days) compared to those who received placebo [7] . Among those who died of sepsis, time to death was significantly prolonged in those who received clarithromycin.

Specific antimicrobial considerations — In critically ill patients, in those receiving antibiotics prior to the onset of pneumonia, and in institutions where these pathogens are frequent, coverage of methicillin-resistant S. aureus (MRSA), P. aeruginosa, and antibiotic-resistant gram-negative bacilli, such as Acinetobacter spp, and Legionella should be considered.

MRSA — If MRSA is a frequent nosocomial pathogen in the institution, linezolid or vancomycin is a necessary first choice for anti-staphylococcal coverage [2,8] , but should be discontinued if MRSA is not isolated. An overview of the treatment of invasive MRSA infections is presented separately. (See "Treatment of invasive methicillin-resistant Staphylococcus aureus infections in adults").

Two prospective, randomized trials of nosocomial pneumonia compared linezolid with vancomycin ; each found no significant difference in outcomes for MRSA infections [9,10] . However, when the two studies were combined in a meta-analysis, linezolid was associated with significantly higher cure rates for MRSA pneumonia (59 versus 36 percent) [11] . Such an advantage may result from higher penetration of linezolid into infected lung tissue than vancomycin. The meta-analysis was later criticized because of perceived statistical flaws in the subgroup analysis [12] .

A retrospective study suggested that vancomycin failure might be related to suboptimal dosing [13] . As a result, a trough level of 15 to 20 mcg/mL is often targeted [2] . However, subsequent studies failed to confirm that higher vancomycin trough concentrations correlate with improved outcomes [14,15] . On the other hand, higher vancomycin MICs themselves may be associated with worse outcomes in patients with HAP due to MRSA.

This was suggested in a prospective cohort study of 95 patients with MRSA HCAP who were treated with vancomycin in which the targeted trough vancomycin concentration was at least four times the MIC [14] . High MIC (≥ 2 mcg/mL) strains of MRSA were detected in 54 percent of patients. Despite achieving the target trough concentration, mortality was higher among patients whose MRSA strain had a high MIC than patients whose MRSA strain had a low MIC (24 versus 10 percent).

The 2005 ATS/IDSA guidelines on HAP, VAP, and HCAP recommended either linezolid or vancomycin for infections due to MRSA [2] . It was noted that linezolid might be preferred in patients at risk for or with renal insufficiency in whom vancomycin is often underdosed and is associated with a risk of nephrotoxicity. Linezolid also may reduce toxin production, although the possible benefit of this has not been established [16,17] . Linezolid is particularly preferred in hospitals in which a substantial proportion of MRSA isolates have a vancomycin MIC ≥ 2 mcg/mL.

The usual doses are:

- Linezolid — 600 mg twice daily intravenously (or orally if or when the patient is able to receive oral medications).
- Vancomycin — 30 mg/kg intravenously in two divided doses, with a maximum dose of 2 g/day unless serum vancomycin concentrations are inappropriately low. (See "Vancomycin dosing and serum concentration monitoring in adults").

Daptomycin cannot be used to treat pneumonia, because it does not achieve sufficiently high concentrations in the respiratory tract. Data are limited on the use of quinupristin-dalfopristin. In a randomized trial of HAP that included 38 patients with MRSA pneumonia, there was a nonsignificant lower rate of clinical success with quinupristin-dalfopristin compared to vancomycin (31 versus 44 percent) and a higher rate of adverse effects that led to discontinuation of therapy [18]. There are no clinical studies to support the use of tigecycline for the treatment of pneumonia.

Gram-negative pathogens — Although combination antimicrobial therapy for HAP, VAP, and HCAP due to gram-negative pathogens (especially Pseudomonas) is commonly administered, there is no conclusive evidence to support this practice. The best rationale for the use of combination therapy is to provide a greater spectrum of activity when there is risk for MDR pathogens (eg, if the pathogen is resistant to one agent it may be susceptible to the other) [2]. Other commonly cited reasons for combination therapy include the potential for synergistic efficacy as well as the potential to reduce the emergence of resistance. However, it is not clear that two agents offer improved outcomes for treating gram-negative pneumonia.

A meta-analysis and a subsequent large, randomized trial suggested that monotherapy of VAP was as effective as combination therapy [19,20]. However, the percentage of MDR organisms was low in the trials reviewed in the meta-analysis and in the randomized trial. In addition, the randomized trial excluded patients known to be colonized with Pseudomonas or MRSA, and found that combination versus monotherapy was associated with improved adequacy of initial antibiotics and microbiological eradication of infecting organisms in patients who had infection due to Pseudomonas, Acinetobacter, and MDR gram-negative bacilli [20]. Thus, it is difficult to extrapolate the efficacy of monotherapy to ICUs with high incidences of these pathogens.

In ICU settings in which extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are found, cephalosporins should be avoided as monotherapy, due to the selection of resistant organisms when these agents are used [21]. The most reliable agent in this setting is a carbapenem (imipenem-cilastatin, ertapenem, meropenem, or doripenem) [22-24].

Legionella and anaerobes — Patients who have aspirated, have underlying conditions (eg, recent abdominal surgery, coma, head trauma, diabetes mellitus, renal failure, or structural lung disease), are being treated with steroids or antibiotics, or have had a prolonged ICU stay may also require coverage for Legionella and anaerobes.

Empiric treatment — We generally agree with the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines for the management of HAP, VAP, or HCAP [2]. These guidelines can be accessed through the ATS web site at www.thoracic.org/sections/publications/statements/index.html.

No known MDR risk factors — We suggest one of the following intravenous antibiotic regimens for empiric coverage of HAP, VAP, and HCAP in patients with no known risk factors for MDR pathogens:

- Ceftriaxone (2 g intravenously daily).
- Ampicillin-sulbactam (3 g intravenously every six hours) or piperacillin-tazobactam (4.5 g intravenously every six hours) if there is concern based on prevailing pathogens within an institution for gram-negative bacilli not treated by ampicillin-sulbactam (eg, Enterobacter spp, Serratia spp, Pseudomonas spp).

- Levofloxacin (750 mg intravenously daily) or moxifloxacin (400 mg intravenously daily). Both agents may be administered orally at the same doses when the patient is able to take oral medications.
- Ertapenem (1 g intravenously daily).

Choice of a specific agent for empiric therapy should be based on knowledge of the prevailing pathogens (and susceptibility patterns) within the healthcare setting.

Known MDR risk factors — We recommend empiric three-drug combination therapy including:

ONE of the following:

- Antipseudomonal cephalosporin such as cefepime (2 g intravenously every eight hours) or ceftazidime (2 g intravenously every 8 hours)
- Antipseudomonal carbapenem such as imipenem (500 mg intravenously every six hours) or meropenem (1 g intravenously every eight hours) or doripenem (500 mg intravenously every eight hours; administered over one hour for HAP or HCAP, administered over four hours for VAP) [23,24]
- Piperacillin-tazobactam (4.5 g intravenously every six hours)
- For patients who are allergic to beta-lactam antibiotics: aztreonam (2 g intravenously every six to eight hours)

PLUS one of the following:

- Antipseudomonal fluoroquinolone, preferred regimen if Legionella is likely, such as ciprofloxacin (400 mg intravenously every eight hours) or levofloxacin (750 mg intravenously daily). These agents may be administered orally when the patient is able to take oral medications. The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.
- Aminoglycoside such as gentamicin or tobramycin (7 mg/kg intravenously per day adjusted to a trough level <1 mcg/mL) or amikacin (20 mg/kg intravenously per day adjusted to a trough level <4-5 mcg/mL). The aminoglycoside can be stopped after five to seven days in responding patients.

PLUS ONE of the following (if MRSA is suspected, there are MRSA risk factors, or there is a high incidence of MRSA locally):

- Linezolid (600 mg intravenously every 12 hours; may be administered orally when the patient is able to take oral medications)
- Vancomycin (15 mg/kg intravenously every 12 hours, dosed so that trough levels are 15 to 20 mcg/mL)

If patients have recently received an antibiotic, empiric therapy should generally be with a drug from a different class of antibiotics since earlier treatment may have selected pathogens resistant to the initial class.

Colistin, polymyxin, or inhaled aminoglycosides may be considered as potential additional antibiotics in patients with MDR gram-negative bacilli [25,26]. Aerosolization may increase antibiotic concentrations at the site of infection, and may be particularly useful for treatment of organisms that have high MICs to systemic antimicrobial agents [27]. (See "Colistin: An

overview").

Antibiotic regimens — When the etiology of HAP, VAP, or HAP has been identified based upon reliable microbiologic methods and there is no laboratory or epidemiologic evidence of coinfection, treatment regimens should be simplified and directed to that pathogen. The choice of specific agents will be dictated by the results of susceptibility testing. It is crucial to avoid broad-spectrum therapy once a pathogen has been identified [2] .

A novel approach may determine antimicrobial susceptibility more quickly than traditional methods. In a trial, Gram stain was performed on endotracheal aspirates from 250 patients with bacteriologically confirmed VAP [28] . The endotracheal aspirates whose Gram stain identified a microbe were randomly assigned to either rapid testing — the endotracheal aspirates were directly applied to antibiotic susceptibility test strips — or standard culture. Rapid testing more quickly identified susceptibility than standard culture (1.4 versus 4.2 days). In addition, patients were more likely to receive appropriate antimicrobial therapy, have fewer days of antimicrobial therapy, and have more rapid resolution of fever. Antimicrobial selection based on this strategy has never been compared to that based on a Gram stain or local susceptibility patterns. Nor has it been compared to empiric broad spectrum therapy based on MDR risk factors. Until further clinical studies are performed, this approach cannot be recommended in the routine management of HAP.

Patients who are improving clinically, are hemodynamically stable, and able to take oral medications can be switched to oral therapy. If the pathogen has been identified, the choice of antibiotic for oral therapy is based upon the susceptibility profile for that organism. If a pathogen is not identified, the choice of antibiotic for oral therapy is either the same antibiotic as the intravenous antibiotic, or an agent in the same drug class, which achieves adequate lung penetration when administered orally.

Duration — The duration of therapy should be based upon the clinical response. The standard duration of therapy in the past was 14 to 21 days in part because of a concern for difficult to treat pathogens (eg, Pseudomonas spp). However, a shorter course could significantly reduce the amount of antimicrobial drugs used in hospitals where the emergence of resistant pathogens is a concern.

The following studies found that short course treatment is effective:

- A prospective, randomized, multicenter trial of 401 patients with VAP compared outcomes following eight versus 15 days of treatment [29] . All patients underwent bronchoscopy for quantitative cultures and were empirically treated with a combination of an antipseudomonal beta-lactam plus either an aminoglycoside or a fluoroquinolone. Investigators were encouraged to change the regimen to a pathogen-directed treatment based upon culture results.

There was no significant difference between patients treated for eight compared to 15 days in mortality or recurrent infection at 28 days; as expected those patients treated for eight days had more antibiotic-free days. Among patients who developed recurrent infections, MDR pathogens were isolated less frequently in those treated for eight days (42 versus 62 percent for those treated 15 days). However, patients with VAP caused by nonfermenting gram-negative bacilli (eg, Pseudomonas spp) had a higher pulmonary infection recurrence rate when treated for eight versus 15 days (41 versus 25 percent with 15 days of treatment), although mortality was not different.

- An ICU study evaluated clinical outcomes, including duration of treatment, following implementation of a clinical guideline for the treatment of VAP compared to historical

controls (patients with VAP treated prior to implementation of the guideline) [30]. The clinical guideline group had a shorter duration of antimicrobial therapy and was less likely to have a recurrent episode of VAP.

- A prospective study evaluated the ability of the Clinical Pulmonary Infection Score (CPIS) to determine the duration of therapy for ICU patients with new pulmonary infiltrates (show table 1) [31]. Patients were included in the study if they had new-onset pulmonary infiltrates and a CPIS <6. The patients were randomized to either a control group (standard therapy) or to the experimental group (intravenous ciprofloxacin 400 mg every eight hours for three days).

The CPIS was reevaluated at three days and in patients with a CPIS <6, antibiotics were discontinued in the experimental group. If the CPIS was >6, ciprofloxacin was continued or antibiotics were changed based upon the microbiologic results. Significantly more patients in the control group received antibiotics beyond three days compared to those in the experimental group (90 compared to 28 percent in the experimental group). In addition to reduced antibiotic use, the experimental group was less likely to have colonization/infection with resistant organisms (15 compared to 35 percent of patients in the control group) and had a trend towards lower mortality [2].

In a separate prospective cohort study of 312 patients who were treated with empiric antibiotics in an ICU, investigators sought to determine if the CPIS score could be used to decrease the amount or duration of antibiotic therapy [32]. The CPIS score was compared to the assessment of a "pneumonia committee" (PC), which was comprised of investigators and clinicians experienced in the management of ICU patients. The CPIS score had a reasonable predictive value, but assessment by the PC and the CPIS score often diverged when the CPIS score was six or less. Half of the empiric antibiotic use was for patients in whom pneumonia was suspected but the PC or the CPIS score indicated that pneumonia was unlikely.

Recommendations — Based upon these data, we recommend that all patients with HAP, VAP, or HCAP should be evaluated after 72 hours of initial empiric antimicrobial therapy.

If the patient has improved after 72 hours, and a pathogen is isolated, antimicrobial therapy should be changed to a pathogen-directed regimen based upon the susceptibility pattern. Therapy should be continued to complete a total course of seven days; we would treat up to 15 days if P. aeruginosa were the etiologic agent. If the patient has improved and no pathogen is identified, we would narrow the regimen, discontinuing therapy for Pseudomonas spp and MRSA.

If the patient has not improved at 72 hours and a resistant pathogen is identified, therapy can be changed to pathogen-directed treatment based upon the susceptibility pattern. In addition, failure to improve at 72 hours should prompt a search for infectious complications, other diagnoses, or other sites of infection.

SUMMARY AND RECOMMENDATIONS

- The choice of the antibiotic treatment regimen for HAP, VAP, and HCAP should be influenced by the patient's recent antibiotic therapy (if any), the resident flora in the hospital or intensive care unit, the presence of underlying diseases, available culture data (interpreted with care), and whether the patient is at risk for MDR pathogens. (See "Treatment" above).
- For empiric coverage of HAP, VAP, and HCAP in patients with no known risk factors for

MDR pathogens, we suggest one of the following intravenous antibiotic regimens :

- Ceftriaxone (2 g intravenously daily)

- Ampicillin-sulbactam (3 g intravenously every six hours) or piperacillin-tazobactam (4.5 g intravenously every six hours) if there is concern based on prevailing pathogens within an institution for gram-negative bacilli not treated by ampicillin-sulbactam (eg, Enterobacter spp, Serratia spp, Pseudomonas spp)

- Levofloxacin (750 mg intravenously daily) or moxifloxacin (400 mg intravenously daily). Both agents may be administered orally at the same doses when the patient is able to take oral medications.

- Ertapenem (1 g intravenously daily) (See "No known MDR risk factors" above).

- For empiric coverage of HAP, VAP, and HCAP in patients with known risk factors for MDR pathogens, we recommend empiric three-drug combination therapy including:

One of the following:

- Antipseudomonal cephalosporin such as cefepime (2 g intravenously every eight hours) or ceftazidime (2 g intravenously every 8 hours)

- Antipseudomonal carbapenem such as imipenem (500 mg intravenously every six hours) or meropenem (1 g intravenously every eight hours) or doripenem (500 mg intravenously every eight hours; administered over one hour for HAP or HCAP, administered over four hours for VAP)

- Piperacillin-tazobactam (4.5 g intravenously every six hours)

- For patients who are allergic to beta-lactam antibiotics: aztreonam (2 g intravenously every six to eight hours)

PLUS one of the following:

- Antipseudomonal fluoroquinolone, such as ciprofloxacin (400 mg intravenously every eight hours) or levofloxacin (750 mg intravenously daily).

- Aminoglycoside such as gentamicin or tobramycin (7 mg/kg intravenously per day adjusted to a trough level <1 mcg/mL) or amikacin (20 mg/kg intravenously per day adjusted to a trough level <4-5 mcg/mL). The aminoglycoside can be stopped after five to seven days in responding patients.

PLUS one of the following (if MRSA is suspected, there are MRSA risk factors, or there is a high incidence of MRSA locally):

- Linezolid (600 mg intravenously every 12 hours; may be administered orally when the patient is able to take oral medications)

- Vancomycin (15 mg/kg intravenously every 12 hours, dosed so that trough levels are 15 to 20 mcg/mL) (See "Known MDR risk factors" above).

- Critical to reducing overuse of antimicrobials, "deescalation" of therapy should be considered after 48 to 72 hours of initial therapy, and should be based upon the results of initial cultures and the clinical response of the patient. (See "Duration" above).

- The duration of therapy should be based upon the clinical response. A short duration

of therapy (eg, seven days) is sufficient for most patients with uncomplicated HAP, VAP, or HCAP who have had a good clinical response. (See "Duration" above).

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GRAPHICS

Clinical pulmonary infection score (CPIS) scoring

Temperature
≥36.5 or ≤38.4 = 0 point
≥38.5 or ≤38.9 = 1 point
≥39 or <36.5 = 2 points
Blood leukocytes, microL
≥4000 or ≤11,000 = 0 points
<4000 or >11,000 = 1 point
Band forms ≥50 percent = add 1 point
Tracheal secretions
Absence of tracheal secretions = 0 point
Presence of non-purulent tracheal secretions = 1 point
Presence of purulent tracheal secretions = 2 points
Oxygenation
PaO2/FIO2, mmHg >240 or ARDS (defined as PaO2/FIO2 ≤200, PAWP ≤18 mmHg and acute bilateral infiltrates) = 0 points
PaO2/FIO2 ≤240 and no ARDS = 2 points
Pulmonary radiography
No infiltrate = 0 point
Diffuse (patchy) infiltrate = 1 point
Localized infiltrate = 2 points
Progression of pulmonary infiltrate
No radiographic progression = 0 point
Radiographic progression (after HF and ARDS excluded) = 2 points
Culture of tracheal aspirate

Pathogenic bacteria cultured in rare or few quantities or no growth = 0 point
Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
Same pathogenic bacteria seen on Gram's stain, add 1 point
Total (a score of >6 was considered suggestive of pneumonia)

ARDS: acute respiratory distress syndrome; HF: heart failure; PAWP: pulmonary arterial wedge pressure.

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