Antibiotic Protocol for Empiric Therapy of Nosocomial Pneumonia:
Health-Care Associated Pneumonia (HCAP), Hospital-Acquired Pneumonia (HAP), and Ventilator-Associated Pneumonia (VAP)

This pathway is to be used in adult (age > 18 years) patients only. An Infectious Diseases consult is recommended when dealing with complicated or immunocompromised patients (e.g., hematopoetic stem cell or solid organ transplant). All dosages are based on normal renal and hepatic function.

RISK FACTORS FOR MULTIDRUG-RESISTANT ORGANISMS (MDROS)

Based upon study of local epidemiology of community-acquired pneumonia (CAP) and HCAP

- Late hospital-onset or ventilator-associated pneumonia (current hospitalization ≥ 5 days)
- Hospitalized ≥ 5 days in the past 90 days
- Broad spectrum antimicrobial therapy for ≥ 5 days in the past 90 days
- Residence in a long-term care facility (nursing home, extended care facility, etc)
- Known respiratory tract colonization with an MRDO, particularly *Pseudomonas aeruginosa*

A. No known risk factors for MDROs and hospitalized < 5 days:

a. Refer to Antibiotic Protocol for CAP

B. Risk factors for MDROs or hospitalized ≥ 5 days:

a. Preferred:

i. Vancomycin plus cefepime **OR**

ii. Vancomycin plus piperacillin/tazobactam

iii. Consider addition of the following agents based on risk factors, clinical presentation, history of resistant pathogen isolation, and severity of illness:

1. Azithromycin – if concern for *Legionella* (HCAP only, not HAP/VAP)
2. Tobramycin – if concern for multidrug-resistant *Pseudomonas*

b. Severe beta-lactam allergy:

i. Vancomycin plus aztreonam

ii. Consider addition of the following agents based on risk factors, clinical presentation, history of resistant pathogen isolation, and severity of illness:

1. Azithromycin – if concern for *Legionella* (HCAP only, do not use with HAP/VAP)
2. Levofloxacin – if high risk for *Pneumococcus* (HCAP only; do not use with azithro)
3. Tobramycin – if concern for multidrug-resistant *Pseudomonas*
4. Clindamycin – if concern for aspiration pneumonia or anaerobic infection

Antibiotic Doses:

Azithromycin 500 mg PO/IV once then 250 mg daily
Aztreonam 2 g IV q8h
Cefepime 1 g IV q6h
Clindamycin 600 mg IV q8h
Levofloxacin 750 mg PO/IV daily
Linezolid 600 mg PO/IV q12h
Piperacillin/tazobactam 4.5 g IV q8h over 4 hours
Tobramycin 7 mg/kg IV q24h
Vancomycin 15 mg/kg IV q12h

Health-Care Associated Pneumonia, Hospital-Acquired Pneumonia, and Ventilator-Associated Pneumonia Pathway

PURPOSE:
To provide a framework for the initial evaluation and management of the immunocompetent, adult patient with bacterial causes of HAP, VAP, or HCAP based on recent literature and guidelines. Delays in the initiation of appropriate antibiotic therapy can increase mortality, and therapy should not be postponed for the purpose of performing diagnostic studies in patients who are clinically unstable.

DEFINITIONS:
Hospital-Acquired Pneumonia (**HAP**) is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission.

Ventilator-Acquired Pneumonia (**VAP**) is defined as pneumonia that arises more than 48–72 hours after endotracheal intubation.

Healthcare-Associated Pneumonia (**HCAP**) includes pneumonia within 48 hours of hospital admission in any patient at an increased risk of having a resistant pathogen isolated. The clinical and epidemiologic factors which best identify this population and the subsequent need for broad spectrum antibiotics are poorly defined. A study of 521 patients admitted with CAP and HCAP to our institution found the traditional HCAP definition did not identify those who subsequently had a resistant pathogen isolated. Factors associated with MDRO isolation included:

- Duration of previous hospitalization
- Antimicrobial use in the previous 90 days
- Admission from a long-term care facility
- Recent colonization/infection with *Pseudomonas aeruginosa*.

DIAGNOSIS:
The clinical diagnosis of HAP, VAP and HCAP can be made if the patient has a new radiographic infiltrate PLUS at least two of the following: fever > 38°C, leukocytosis or leukopenia, or purulent secretions. Etiologic diagnosis generally requires a lower respiratory tract culture, but rarely may be made from blood or pleural fluid cultures.

All patients with suspected HAP/VAP/HCAP should have a lower respiratory tract sample and blood sent for culture, and patients with HAP and HCAP should have sputum samples sent whenever possible before the administration of antibiotic therapy. Extrapulmonary infection should be excluded as part of the evaluation. Every effort should be made to obtain a microbiologic diagnosis so antibiotics can be subsequently narrowed appropriately. To facilitate etiologic diagnosis, early bronchoalveolar lavage (BAL) sampling, either by mini-BAL technique plus semi-quantitative culture or conventional bronchoscopy with lavage and semi-quantitative culture, should be strongly considered, particularly in all intubated patients. If a BAL cannot be obtained tracheal aspirates have been shown to correlate with BAL findings and should be obtained. The probability for a specimen with high yield is highest when the specimen is obtained early (before empiric antimicrobial therapy is started). Unless there is low clinical suspicion for lower respiratory tract infection, empiric antibiotics should be initiated. Procalcitonin measurement may be very useful in cases where the diagnosis is in question and is discussed subsequently.

MANAGEMENT:

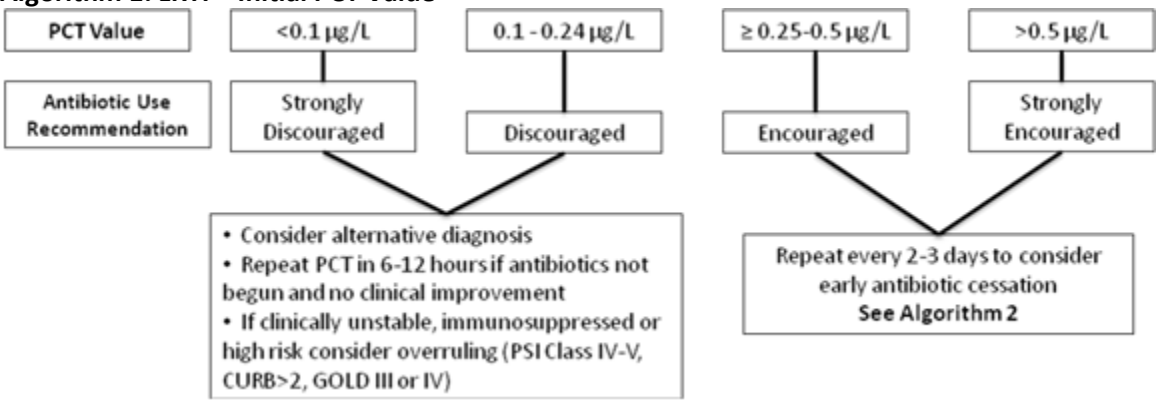
Procalcitonin:

Procalcitonin (PCT) is a highly specific biomarker for systemic bacterial infection and has been shown to have significant utility in antibiotic decision making in pneumonia. Multiple meta-analyses and randomized clinical trials support the use of PCT for assisting clinicians in antibiotic management in lower respiratory tract infection (LRTI) including pneumonia, exacerbations of chronic bronchitis, and other assorted LRTIs (bronchitis, asthma exacerbation, etc). A meta-analysis of 8 studies with 3431 patients found the use of PCT in LRTI resulted in a 31% decrease in antibiotic prescriptions and a decrease in antibiotic duration of 1.3 days without any increase in adverse outcomes. Studies specifically addressing its use in pneumonia have had similar findings of decreased antibiotic use with equivalent clinical outcomes.

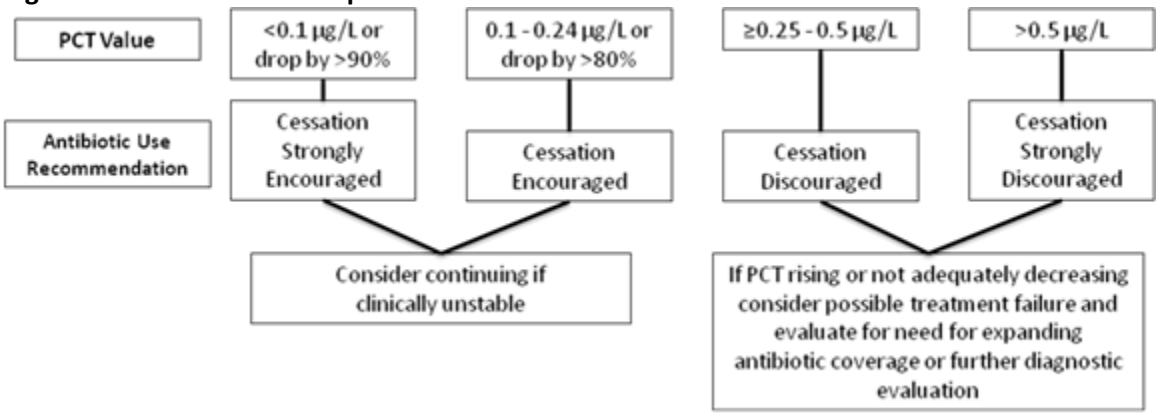
PCT can be used at Nebraska Medicine to assist clinicians in the diagnosis of infection and to support antimicrobial therapy decisions. **Decisions regarding antimicrobial therapy should NOT be based solely on PCT serum concentrations**; PCT should be placed into the clinical context of each patient scenario considering the site of possible infection, the likelihood of bacterial infection, the severity of illness, and any other pertinent clinical data.

It is strongly suggested that patients considered at risk for pneumonia or being started on antibiotics for pneumonia have a PCT value measured on admission and every 2-3 days subsequently. Recommended interpretation of PCT values is listed below in Algorithms 1 and 2.

Algorithm 1: LRTI – Initial PCT Value



Algorithm 2: LRTI – Follow-Up PCT Value



Antibiotic Selection

The key decision in initial empiric therapy is whether the patient has risk factors for MDROs. Coverage in patients at risk for MDROs should be directed at organisms such as *S. pneumoniae*, *S. aureus* (including MRSA), and gram-negative pathogens including *Pseudomonas aeruginosa*. The addition of a second antimicrobial agent may be added to expand the empiric coverage for resistant gram-negative pathogens. Combination therapy has been advocated in critically ill patients with severe sepsis or septic shock as delays to active therapy have been associated with increased mortality. Despite the clear mortality benefit of initially active therapy in critically ill patients, combination therapy remains controversial as its use has not been clearly associated with improved outcomes and depending on the severity of illness and patient population may be associated with worsened outcomes.

The addition of a second agent (e.g. tobramycin added to anti-pseudomonal beta-lactam) should be based on patient severity of illness, the likelihood of isolating resistant Gram-negative pathogens, and the potential adverse effects of additional therapy. Clinicians should weigh the risk versus benefit and consider addition of a second agent in patients at particularly high risk for isolation of a resistant pathogen and those who are severely ill (e.g. severe CAP). When there is a concern for atypical pathogens such as *Legionella*, azithromycin should be added.

De-escalation to a single active agent is **strongly** recommended when culture and susceptibility results return.

Continuation of Therapy

Broad spectrum empiric antibiotic therapy should be accompanied by a commitment to de-escalate antibiotics, on the basis of serial clinical and microbiologic data, to limit the emergence of resistance and prevent toxicity.

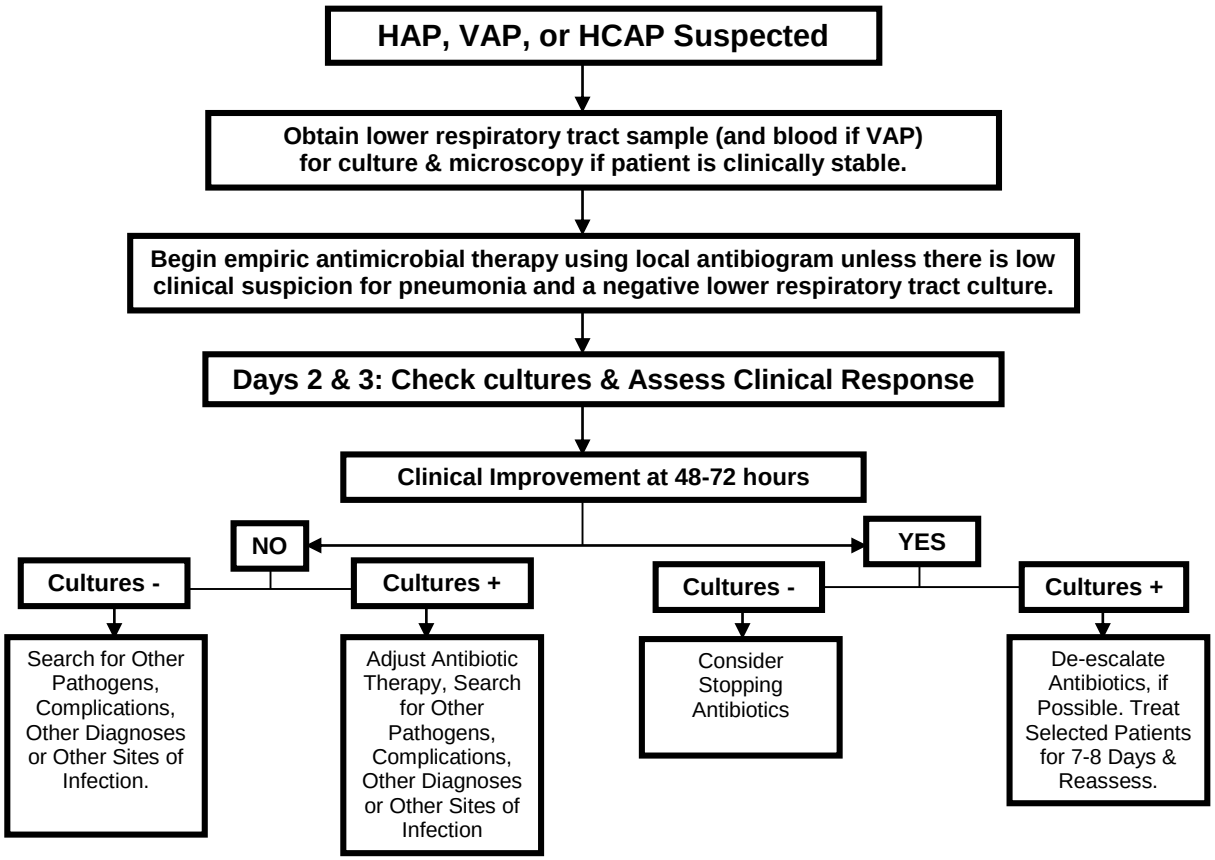
All patients with HAP, VAP and HCAP should initially receive therapy intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients. Clinical improvement usually becomes apparent after the first 48–72 hours of therapy, and therefore, the selected antimicrobial regimen should not generally be changed during this time unless progressive deterioration is noted or initial microbiologic studies so dictate. Clinical parameters including the white blood cell count, PCT, and measures of oxygenation and core temperature have been used in several studies to define the normal pattern of resolution of pneumonia. The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible on the basis of culture data.

The non-responding patient should be evaluated for noninfectious mimics of pneumonia, unsuspected or drug-resistant organisms, extrapulmonary sites of infection, and complications of pneumonia and its therapy. Diagnostic testing should be directed to whichever of these causes is likely.

Duration of Therapy

Efforts to reduce the duration of therapy are justified by studies of the natural history of the response to therapy. Data strongly support the premise that most patients with VAP, who receive appropriate antimicrobial therapy and have a good clinical response, can be treated with 7-8 days of antibiotics. Prolonged therapy leads to colonization with antibiotic resistant bacteria, which may precede a recurrent episode of VAP, increased toxicity, and increased cost. The exception to short courses of antibiotics is pneumonia due to non-lactose fermenting gram-negative rods (*Pseudomonas, Acinetobacter, Stenotrophomonas*) where a longer duration of treatment is recommended (10-14 days). PCT monitoring may also be useful in determining treatment duration. Patients whose PCT values return to normal (< 0.25) are candidates for stopping antimicrobials.

Algorithm 3: Management of HAP, VAP, and HCAP



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