Antibiotic Protocol for Empiric Therapy of Nosocomial Pneumonia:
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).

Pneumonia Diagnosis

- New or progressive radiographic infiltrate **AND**
- Signs, symptoms, and/or laboratory evidence of pneumonia
    - Fever, cough, dyspnea, increased or purulent secretions, chest pain
    - Crackles, rhonchi, egophany on exam
    - New or worsened hypoxia, elevated WBC, bandemia, elevated PCT

Pneumonia Diagnostic Testing:

- Blood cultures – Recommended before antibiotics in all patients
- Urine antigens (Pneumococcal, Legionella) – Only if lower respiratory tract specimen unavailable
- Respiratory Pathogen Panel – Not routinely recommended, may be appropriate in patients with syndromes suggestive of viral or atypical infection. Do not use if pneumonia panel ordered.
- Lower Respiratory Tract Cultures – **Recommended in all patients**
    - Sputum culture – non-intubated patients
    - Tracheal aspirate – intubated (preferred)
    - Mini-BAL and BAL – utilize if other diagnostic information is needed (fungal, AFB, biopsy, etc.) needed, but tracheal aspirate preferred for bacterial pneumonia
- Pneumonia Panel – Recommended in all HAP and VAP coupled with appropriate culture

Pneumonia Treatment:

- **Hospitalized < 5 days:**
    - Refer to CAP Guidance for all patients including those with risk factors for resistance
- **Hospitalized ≥ 5 days:**
    - Preferred: Vancomycin* plus cefepime **OR** Vancomycin plus piperacillin/tazobactam
    - Severe beta-lactam allergy: Vancomycin* plus aztreonam
    - Consider addition of the following agents based on severity of illness and likelihood of resistant pathogen isolation:
        - Tobramycin – if concern for multidrug-resistant *Pseudomonas*
        - Substitute meropenem for cefepime or P/T – **ONLY** if history of ESBL colonization or defined resistance to aztreonam
- **Aspiration pneumonitis:**
    - Antibiotics NOT recommended – Antibiotics do not decrease need for ICU care, subsequent antibiotics, or mortality

Duration of Therapy:

- 7 days adequate for all pathogens
- Patients with complications such as empyema should be treated >7 days
- Procalcitonin can be used to safely shorten duration below 7 days

* Linezolid is an acceptable alternative to vancomycin. Vancomycin/linezolid should be stopped if MRSA is not detected within 72 hours.

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 and VAP based on recent literature and guidelines.[1] 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 hours after endotracheal intubation.

Healthcare-Associated Pneumonia (HCAP) was a previously defined pneumonia category which no longer exists.[2] Patients who develop signs and symptoms of pneumonia before admission or within 5 days of admission should be managed utilizing the CAP guideline.

DIAGNOSIS:

Pneumonia Diagnosis

- New or progressive radiographic infiltrate **AND**
- Signs, symptoms, laboratory evidence of pneumonia
  - Fever, cough, dyspnea, increased or purulent secretions, chest pain
  - Crackles, rhonchi, egophany, new or worsened hypoxia,
  - Elevated WBC, bandemia, elevated PCT

The diagnosis of HAP and VAP is a clinical diagnosis based on the presence of signs or symptoms of pneumonia coupled with radiographic infiltrates. It is generally made a new or progressive radiographic infiltrate is present along with signs and symptoms of pneumonia. Signs and symptoms may include fever, cough, dyspnea, increased or purulent secretions, crackles or rhonchi on exam, new onset or worsening hypoxia, leukocytosis, and/or elevated biomarkers such as procalcitonin. While radiographic findings are generally required for a diagnosis of pneumonia the signs and symptoms are non-specific and may be due to many other conditions. A review of 231 VAP cases at a single institution found 58% were clearly not VAP resulting in >1100 days of unneeded antibiotic therapy.[3] A meta-analysis of the utility of the signs, symptoms, radiographic changes, and microbiologic results utilized to diagnose VAP found individual findings and combinations of clinical information had both low sensitivity and specificity for the diagnosis of VAP. Combinations of findings improved specificity but degraded sensitivity.[4] For example, the presence of a new infiltrate plus all three findings of fever, purulent secretions and leukocytosis had a sensitivity of 16-23% and a specificity of 91-92%. If only one clinical finding was required along with an infiltrate sensitivity improved to 65-85% but specificity degraded to

33-36%. No studies in this meta-analysis evaluated the use of biomarkers such as procalcitonin which appears to have some utility in decisions regarding antibiotic use (see discussion below).

Based on the difficulty in diagnosing pneumonia clinicians should rigorously re-evaluate patients who have been started on antibiotics within the first 1-3 days to determine if clinical data continues to support the diagnosis of pneumonia. Patients who have an alternative explanation for respiratory issues should have antibiotic discontinued. Those who have negative respiratory tract cultures should also have antibiotics discontinued. Finally, PCT may be utilized to determine when early antibiotic discontinuation is appropriate.

ETIOLOGY:

Patients who develop pneumonia while in the hospital or on a ventilator are more likely to harbor multi-drug resistant (MDR) pathogens isolated. *Staphylococcus aureus* is a prominent pathogen detected and local data suggests 30-40% of *S. aureus* are methicillin-resistant (MRSA). Gram negative enteric pathogens such as *Klebsiella* species, *Enterobacter* species, and *E. coli* along with non-fermentive gram negative rods such as *Pseudomonas aeruginosa* and *Stenotrophomonas* can also cause HAP and VAP. As these pathogens are acquired within the hospital environment, they are more likely to harbor resistance determinants. Data regarding susceptibility to common agents utilized to treat pneumonia can be found in the pathogen specific recommendations section of the Pneumonia Panel Guideline. Nosocomial Legionella infections are unheard of at NM so testing is rarely indicated for this pathogen (consider in high-risk individuals with findings suggestive). Organisms such as enterococci, candida, coagulase-negative staphylococci, and most gram-positive rods do not cause pneumonia and can usually be disregarded when found in respiratory tract specimens.

MICROBIOLGOIC TESTING:

Blood cultures are recommended for HAP/VAP and should always be obtained before antibiotics are begun. A variety of tests exist to determine the etiology of HAP/VAP including lower respiratory tract cultures (sputum culture, tracheal aspirate, mini-BAL, and directed BAL), molecular panels (Respiratory Pathogen Panel, Pneumonia Panel), and urine antigens (Pneumococcal and Legionella). Due to the broad range of pathogens responsible for HAP/VAP and use broad spectrum antibiotics clinicians should be aggressive in defining the microbiologic etiology of all HAP and VAP so antibiotics can be subsequently narrowed. All patients with suspected HAP/VAP should have a lower respiratory tract sample sent for testing, ideally before the administration of antibiotic therapy. Patients who are not intubated should have a sputum sample obtained. Patients who are intubated should have a either a tracheal aspirate obtained as soon possible and preferably before antibiotics are started. Mini-BAL and directed BAL are also useful in determining the etiology of pneumonia but tracheal aspirate is the preferred method due to easier availability coupled with fewer complications and resources required. 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.

Recommendations for Pneumonia Diagnostic Testing:

- Blood cultures – Recommended before antibiotics in all patients
- Urine antigens (Pneumococcal, Legionella) – Use only if lower respiratory tract specimen unable to be obtained
- Respiratory Pathogen Panel – Not routinely recommended but may be appropriate in patients early in hospitalization or with syndromes suggestive of viral or atypical infection. Do not use if pneumonia panel ordered.
- Lower Respiratory Tract Cultures – **Recommended in all patients**
    - Sputum culture – non-intubated patients
    - Tracheal aspirate – intubated (preferred)
    - Mini-BAL and BAL – can be utilized if other diagnostic information is needed (fungal, AFB, biopsy, etc) needed but tracheal aspirate preferred for bacterial pneumonia
- Pneumonia Panel – Recommended in all HAP and VAP coupled with appropriate culture. Guideline available here.

MANAGEMENT:

Antibiotic Selection

Patient who develop pneumonia while in the hospital are generally at increased risk of infection due to a resistant pathogen. HAP and VAP which occur early in the course of a hospital stay is often caused by community-acquired pathogens and therapy should be directed using the CAP guidelines. Some patients in this group may need expanded spectrum therapy but defined risk factors should be used in these decisions.

Patients who have been hospitalized for >5 days are generally considered at risk for infection due to MDRO pathogens such as *S. aureus* (including MRSA), enteric gram-negative rods, and other gram-negative pathogens including *Pseudomonas aeruginosa*. The use of this 5 day cut off is highly sensitive for inclusion of MDRO pathogens but very non-specific and will result in overtreatment of most patients.[5,6] Thus, great effort should be placed on defining the etiology of pneumonia and rapidly narrowing therapy.

The addition of a second agent active against gram-negative pathogens should be based on patient severity of illness, the likelihood of isolating resistant Gram-negative pathogens (based on microbiologic history or antibiotic exposure), and the potential adverse effects of additional therapy. Clinicians should weigh the risk versus benefit and consider addition of a second agent only in patients at particularly high risk for isolation of a resistant pathogen and those who are severely ill (e.g. septic shock). Despite the clear mortality benefit of initially active therapy in critically ill patients, combination therapy remains controversial as its use has not been associated with improved outcomes and depending on the severity of illness and patient population may be associated with worsened outcomes.[7,8] If a second agent is needed the agent with the greatest activity against *Pseudomonas aeruginosa* is tobramycin. Addition of quinolones is not recommended due to poor activity against common gram-negative pathogens such as *P. aeruginosa* and *E. coli*.

Nosocomial acquisition of *Legionella* and other atypical pathogens is exceedingly uncommon at NM. Unless there is very strong clinical suspicion treatment empiric therapy against atypical pathogens is NOT recommended for HAP or VAP. Testing for viral pathogens (influenza, coronavirus, RSV, etc.) may be appropriate in patients at risk or with findings suggestive of viral infection.

Modification of Therapy (See Figure 1)

Broad spectrum empiric antibiotic therapy should be accompanied by a commitment to de-escalate antibiotics based on microbiologic data, to limit the emergence of resistance and prevent toxicity. Microbiologic data should be reviewed daily, and antibiotics adjusted as new data becomes available. Clinical improvement usually becomes apparent after the first 48–72 hours of therapy and empiric regimens should not be escalated unless progressive deterioration is noted, or initial microbiologic studies so dictate. The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible based on culture data. In particular, anti-MRSA therapy should be stopped at 72 hours unless resistant gram-positive pathogens are detected.

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.

Aspiration Pneumonia:

Aspiration pneumonia can present in two forms: bacterial and chemical. Aspiration pneumonitis is caused by a chemical injury to the lungs and is characterized by rapid onset of dyspnea, fever, wheezing, and ARDS type findings usually after an aspiration event. Most patients with aspiration pneumonitis will recover within 36-48 hours but a portion will go on to develop bacterial pneumonia. Treatment of aspiration pneumonitis with antibiotics **DOES NOT** prevent the subsequent development of pneumonia, decrease the need for subsequent antibiotics or ICU care, or improve mortality.[9] Thus, antibiotic use is strongly discouraged in aspiration events and should be reserved for those who show persistent or progressive respiratory impairment coupled with systemic signs of inflammation. If antibiotics are started patients should be evaluated daily for the next 72 hours and if respiratory function and systemic signs return to baseline antibiotics should be stopped.[10]

If treatment for pneumonia is used in patient with suspected aspiration, the typical agents such as ceftriaxone and cefepime are active against oral anaerobic flora and metronidazole should not be added. Ampicillin/sulbactam and piperacillin/tazobactam may be appropriate choices.

True aspiration pneumonia is most commonly a community-onset infection characterized by a subacute presentation with cough, foul-smelling and tasting sputum, and often cavitary findings on imaging. Patients with true aspiration pneumonia should be treated with agents active against Streptococci and anaerobes such as ampicillin/sulbactam, ceftriaxone plus metronidazole, piperacillin/tazobactam.

PROCALCITONIN:

Procalcitonin (PCT) is most useful in situations of diagnostic uncertainty, where bacterial infection is unclear or alternative diagnoses are possible. Additionally, it can be used to shorten the duration of therapy, although if short duration of treatment (5-7 days) is already planned, PCT is unlikely provide additional benefit. Decisions regarding antimicrobial therapy should NOT be based solely on PCT serum concentrations; test results should be placed into the clinical context of each patient scenario considering the likelihood of bacterial infection, the severity of illness, and any other pertinent clinical data. There

are non-infectious conditions which can result in elevated PCT levels (see NM PCT guidance). Finally, if PCT levels will not influence decision-making, do not order the test.

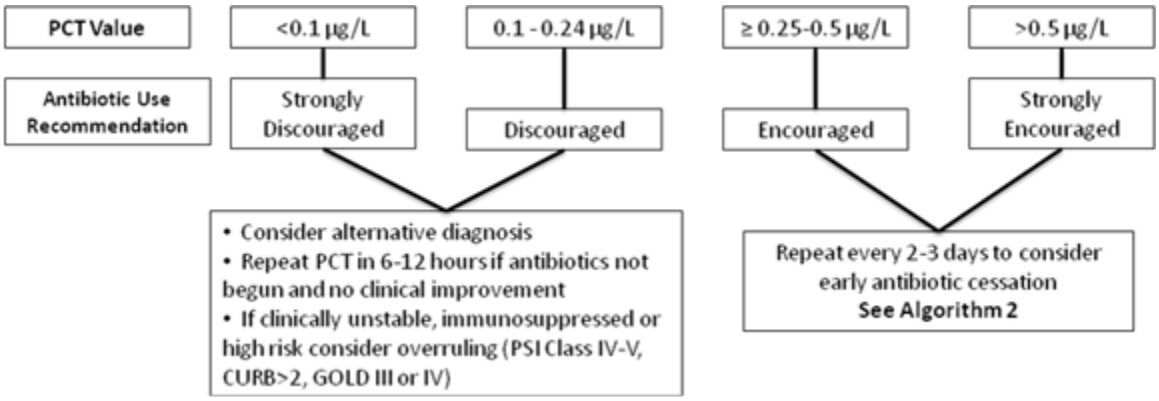
Procalcitonin (PCT) is the most specific biomarker available diagnosis of systemic bacterial infection and has been shown to have utility in antibiotic decision making in lower respiratory tract infections (LRTI). Multiple randomized clinical trials support the use of PCT for assisting clinicians in antibiotic management in LRTI presenting to the ED including pneumonia, exacerbations of chronic bronchitis, and other assorted lower respiratory tract infections (bronchitis, asthma exacerbation, etc.).[11-13] Scheutz, et al performed a patient level meta-analysis of 26 trials with 6708 patients with LRTI and found the use of PCT resulted in a significant decrease in mortality (OR 0.83 (95% CI 0.70-0.99, *p*=.037).[14] PCT use was also associated with a reduction in antibiotic exposure by 2.4 days and decreased antibiotic side effects.

Numerous studies have also been performed in patients with respiratory tract infections in the ICU and those with sepsis where LRTI typically makes up around half of infections treated. Analysis of patients cared for in the ICU from the Scheutz meta-analysis found PCT use associated with a decrease in antibiotic use of roughly 1.5 days and a non-significant decrease in mortality (OR 0.84 (95% CI 0.69-1.02, *p*=0.081)).[14] Patients with HAP and VAP made up 8% and 6% respectively of the included patients. Those with VAP managed using PCT had antibiotic duration decreased 2.22 days with a non-significant decrease in mortality when (OR 0.75 (95% CI 0.41-1.39, *p*=0.366)). A small randomized trial utilizing PCT to support antibiotic decision making in patients with VAP found PCT use associated with a 27% decrease in antibiotic duration (*p*=0.038) without any change in mortality.[15] Finally, a patient level meta-analysis of trials which randomized patients with presumed sepsis to either PCT guided therapy or usual care and with 49% of patients having respiratory tract infection found PCT use was associated with a decrease in antibiotic therapy of 1.19 days (p<0.001) and a decrease in 30-day mortality (OR 0.89 (95% CI 0.8-0.99, P=0.03).[16] Findings were similar in the sub-group of patients with respiratory tract infections although the mortality decrease was non-significant.

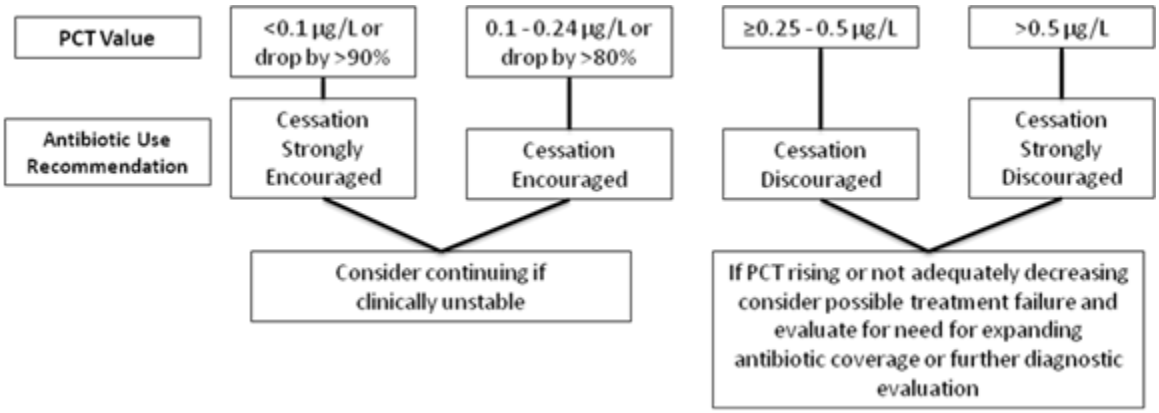
This data suggests PCT can be a useful tool in the evaluation of pneumonia and in antibiotic decision making especially in early discontinuation. PCT is particularly useful in situations where there diagnostic uncertainty exits regarding the need for antibiotics such as differentiating pneumonia from heart failure.[14] Patients with severe illness such as septic shock should be managed using the sepsis algorithm which supports more liberal antibiotic initiation with withdrawal if PCT levels remain low. RCT in sepsis support this strategy as safe and effective at decreasing antibiotic use.[17]

When PCT is used in pneumonia it is recommended it be measured when initially evaluating for pneumonia and every 2-3 days subsequently. Patients with initially low values where suspicion for bacterial infection still exists and antibiotics were not initiated should have a repeat PCT measured in the next 6-12 hours. If Interpretation of PCT values should be as listed below in Algorithms 1 and 2.

Algorithm 1: LRTI – Initial PCT Value



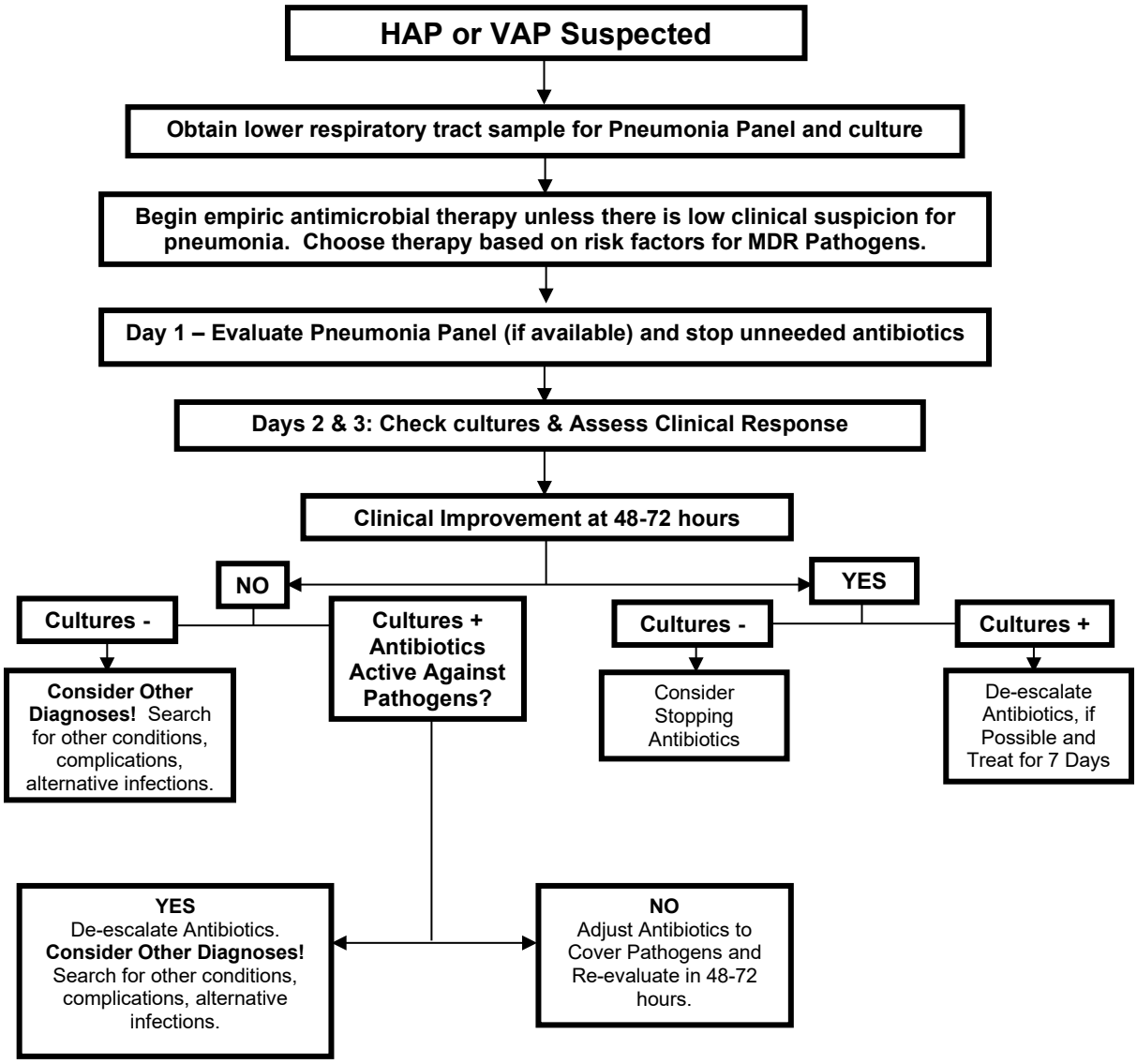
Algorithm 2: LRTI – Follow-Up PCT Value



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 patients with VAP and HAP are effectively treated with 7 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. Longer courses of therapy are not recommended in non-lactose fermenting gram-negative rods (*Pseudomonas, Acinetobacter, Stenotrophomonas*). Longer courses of therapy are indicated in patients with complications such as empyema. PCT monitoring may be useful in customizing antibiotic duration and in particular shortening antibiotic courses (see information above). In patients whose PCT values have declined to < 0.25 or 80% lower than their peak, antibiotics can generally be safely stopped even if they have not received 7 days of therapy.

Figure 1: Management of HAP and VAP



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