Therapy of Pneumonia

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Pneumonias

- **Pneumonia is one of the most common causes of severe sepsis, and infectious cause of death in children and adults.**
- **It affects all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill.**
- **Mortality rate is high.**

Pneumonias Causative Agents

- **The most prominent pathogen causing community-acquired pneumonia (CAP) in otherwise healthy adults is *Streptococcus pneumoniae* and accounts for up to 35% (12%-68%) of all acute cases.**
- **Other common pathogens include:**

1. ***H. influenzae* (2.5%-45%).**
2. **Atypical pathogens: *Mycoplasma pneumoniae*, *Legionella* sps, and *Chlamydia pneumoniae* (~20%).**
3. **A variety of viruses including influenza viruses.**

Pneumonia Causative Agents

- The leading causative agents in hospital-acquired pneumonia (HAP) are Gram-negative aerobic bacilli, *S. aureus*, and multidrug-resistant (MDR) pathogens.
- In pneumonia that follows the aspiration of gastric or oropharyngeal contents, anaerobic bacteria are the most common etiologic agents.
- Ventilator-associated pneumonia (VAP) is also associated with MDR pathogens.

Pneumonia Causative Agents

- **Pneumonia in infants and children is caused by a wider range of microorganisms, and viruses predominate, especially RSV, parainfluenza, and adenovirus.**
- ***M. pneumoniae* is an important pathogen in older children.**

Pneumonia Causative Agents

- Beyond the neonatal period, *S. pneumoniae* is the major bacterial pathogen in childhood pneumonia, followed by group A *Streptococcus* and *S. aureus*.
- *H. influenzae* type b, once a major childhood pathogen, has become an infrequent cause of pneumonia since the introduction of active vaccination against this organism in the late 1980s.

Pneumonia Causative Agents

- **Pneumonia in non-ambulatory residents of nursing homes and other long-term care facilities is similar to hospital-acquired pneumonia and should be treated according to the HAP guidelines.**
- **Certain other patients may be better served by management in accordance with CAP guidelines.**

Therapy of Pneumonia

Treatment:

The goals of therapy are:

1. **Eradication of the offending organism through selection of the appropriate antibiotic.**
2. **Achieving complete clinical cure, with minimal drug-induced toxicity.**

Therapy of Pneumonia

General Approach to Treatment:

Supportive care:

1) **Humidified oxygen for hypoxemia.**
2) **Bronchodilators when bronchospasm is present.**
3) **Chest physiotherapy and postural drainage with evidence of retained secretions.**
4) **Adequate hydration (IV if necessary).**
5) **Optimal nutritional support.**
6) **Control of fever.**

Therapy of Pneumonia

- **Appropriate sputum samples should be obtained to determine the microbiologic etiology.**
- **Selection of an appropriate antimicrobial must be made based on the patient's probable or documented microbiology.**

Pharmacologic Therapy:

- **Antibiotic concentrations in respiratory secretions in excess of the pathogen MIC are necessary for successful treatment of pulmonary infections.**

Therapy of Pneumonia

Selection of Antimicrobial Agents:

- **Treatment, initially involves the empirical use of a relatively broad-spectrum antibiotic(s) that is effective against probable pathogens after appropriate specimens for culture and sensitivity have been obtained.**
- **Therapy should be narrowed to cover specific pathogens after the results of cultures are known.**

Management of CAP in Adults

- **This discussion is in accordance of the "Infectious Diseases Society of America / American Thoracic Society" Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2016, Update of 2019).**

Antibiotic Treatment:

- **Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.**

Management of CAP in Adults

Recommendations depend on:

1. **The treatment setting: inpatient or outpatient.**
2. **The severity of infection.**
3. **The presence of comorbidities.**
4. **The presence of risk factors for drug-resistant pathogens.**

Management of CAP in Adults

The most common bacterial causes of CAP are:

- ***Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Staphylococcus aureus, Legionella* species, *Chlamydia pneumoniae, Moraxella catarrhalis,* Respiratory viruses.**
- **All patients with CAP should be treated empirically for bacterial infection.**

Management of CAP in Adults

- **Any patient with CAP who was recently exposed to one class of antibiotics should be treated using a different class.**
- **Local epidemiology and risk factors should provide the basis for the need to cover for drug-resistant pathogens, such as methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa*.**

Management of CAP in Adults

Risk factors for MRSA and *P. aeruginosa* include:

1. **Prior respiratory isolation of the pathogen.**
2. **Hospitalization with administration of parenteral antibiotics within the last 3 months.**
3. **<u>Locally validated</u> risk factors for these pathogens, and the prevalence of MRSA or *P. aeruginosa* in CAP patients.**

Management of CAP in Adults

Outpatient setting:

1. **For patients without comorbid conditions or risk factors for drug-resistant pathogens:**
   Monotherapy with amoxicillin, doxycycline, or a macrolide (azithromycin or clarithromycin) is recommended.

- **Macrolide monotherapy has shown resistance and should not be used if the local rate of resistance of *Pneumococcus* is greater than 25%.**

Management of CAP in Adults

2. Presence of comorbidities: (chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppression; use of antimicrobials within the previous 3 months, etc):

- **Monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin), or**
- **Combination therapy with (amoxicillin-clavulanate or a cephalosporin) plus (a macrolide or doxycycline).**

Management of CAP in Adults

Inpatient setting:

Recommendations are different based on:

1. **Severity of pneumonia.**
2. **Prior respiratory isolation of MRSA or *P. aeruginosa***
3. **The presence of risk factors for these pathogens.**

Management of CAP in Adults

A. For inpatients with non-severe pneumonia use:

1. **A beta-lactam plus a macrolide or**
2. **a respiratory fluoroquinolone alone.**

- **Alternative: a beta-lactam in combination with doxycycline.**

Management of CAP in Adults

B. **For patients with severe pneumonia:**
   Combination therapy with a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) + a macrolide (azithromycin) or a fluoroquinolone.
C. **An empirical antimicrobial agent with activity against:**

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Management of CAP in Adults

- **MRSA (vancomycin or linezolid)**
- ***P. aeruginosa* (antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) + either ciprofloxacin or levofloxacin; should be added in all inpatients With prior respiratory isolation of the pathogen.**

Management of CAP in Adults

Pathogen-directed therapy:

- **Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at the specific pathogen.**

Time to first antibiotic dose:

- **For patients admitted through the emergency department (ED), the first antibiotic dose should be administered while still in the ED.**

Management of CAP in Adults

Switch from intravenous to oral therapy:

1. **Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract.**
2. **Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is NOT necessary.**

Management of CAP in Adults

Duration of antibiotic therapy:

1. **Patients with CAP should be treated for a minimum of 5 days, and should be afebrile for 2-3 days.**
2. **A longer duration of therapy may be needed if initial therapy was NOT active against the identified pathogen, or if it was complicated by extra-pulmonary infection such as meningitis or endocarditis.**

Management of CAP in Adults

Remember the importance of:

1. **The local pattern of causative pathogens.**
2. **The local pattern of antibiotic sensitivity and/or resistance.**

Management of Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)

This discussion is in accordance of the "Infectious Diseases Society of America / American Thoracic Society" Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2016, Update of 2021, 2022).

Management of HAP/VAP

- **It is advised that each hospital generate its specific antibiogram.**
- **It is suggested that patients with suspected HAP (non-VAP) be treated according to the results of microbiological studies rather than being treated empirically.**
- **In patients with suspected VAP, cover for *S. aureus, Pseudomonas aeruginosa*, and other gram-negative bacilli in all empiric regimens.**

Management of HAP/VAP

- **In empiric coverage for MRSA, either vancomycin or linezolid is recommended.**
- **In empiric coverage for MSSA (not-MRSA), piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem is recommended.**
- **With proven MSSA, oxacillin, nafcillin and cefazolin are preferred (these agents are not necessary for empiric treatment of VAP if one of the above agents is used).**

Management of HAP/VAP

- **For patients being treated empirically for HAP, cover for *S. aureus.***
- **For patients with HAP/VAP due to *Pseudomonas aeruginosa,* the choice of antibiotic for definitive (not empiric) therapy should be based on the results of antimicrobial susceptibility testing.**
- **For patients with HAP/VAP, a 7-day course of antimicrobial therapy is recommended.**

  (traditionally it was 7-14 days)

Management of HAP/VAP

- ***Pseudomonas aeruginosa*** **may require > 7 days.**
- **When the final culture and sensitivity results are available, the empiric broad spectrum regimen shoul be converted to more narrow and specific coverage.**
- **[Cefiderocol has been approved for HAP/VAP due to the following microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli, Enterobactercloacae* complex, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Serratia marcescens*. It was not inferior to high dose meropenem].**

Initial and Definitive Treatment of HAP

- **MSSA should be covered unless the patient has risk factors for MRSA:**

1. **IV antibiotics within the preceding 90 days.**
2. **Exposure to a hospital unit where > 20% of S. aureus isolates are MRSA.**
3. **High risk of death (need for ventilatory support due to septic shock).**

- **Vancomycin or linezolid should be used for empiric therapy (guided by local antibiogram).**

Initial and Definitive Treatment of HAP

- **For empiric coverage of MSSA, piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem is recommended.**
- **With proven MSSA, oxacillin, nafcillin and cefazolin are favored.**
- **For empiric coverage against *Pseudomonas aeruginosa* use double coverage in patients at high risk of death (need for ventilatory support and/or septic shock).**
- **For all other cases single coverage is indicated.**

Initial and Definitive Treatment of VAP

- **Empiric treatment of VAP should cover for *S. aureus, Pseudomonas aeruginosa,* and other gram negative bacilli.**
- **MRSA should be covered empirically in patients with any risk factors for antimicrobial resistance:**

1. **Patients located in a unit where > 10-20% of *S. aureus* isolates are MRSA.**
2. **Patients in units where prevalence of MRSA is unknown.**

Initial and Definitive Treatment of VAP

- **For MRSA infection, linezolid is preferred over vancomycin in:**

1. **Patients with renal insufficiency.**
2. **Patients infected with high MIC MRSA isolates.**

- **A single antibiotc with activity against *Pseudomonas aeruginosa* should be administered except in patients with risk factors for multidrug-resistant (MDR) organisms:**

Initial and Definitive Treatment of VAP

1. **Intravenous antibiotic use within the preceding 90 days.**
2. **Septic shock or ARDS preceding VAP onset.**
3. **Five or more days of hospitalization prior to VAP onset.**
4. **Acute renal replacement therapy prior to VAP onset.**
5. **The patient is located in a unit where > 10% of gram-negative isolates are resistant'**
6. **Patients in ICU where antibiotic sensitivity rates are not available.**

Initial and Definitive Treatment of VAP

- **Double-drug coverage for *Pseudomonas aeruginosa* combine agents with high degree of antipseudomonal activity and low resistance potential: piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam + levofloxacin, ciprofloxacin or aminoglycoside (amikacin, gentamicin, tobramycin), or polymyxins (polymyxin B, colistin).**

Initial and Definitive Treatment of VAP

- **In general, aminoglycosides and colistin should be avoided in therapy of VAP, due to poor penetration of these agents in the lung tissues in addition to the potential nephrotoxicity.**
- **VAP due to *Pseudomonas aeruginosa* has a high failure rate (~40%), regardless of the antibiotic regimens.**

Initial and Definitive Treatment of VAP

- **The use of inhaled antibiotic therapy should be limited to cases of VAP produced by gram-negative bacilli that are sensitive only to aminoglycosides and polymyxins (colistin anf polymyxin B), which should also be administered intravenously.**

Initial and Definitive Treatment of VAP

- **A carbapenem or ampicillin/sulbactam should be used for *Acinetobacter* HAP/VAP**
- **If there is resistance to these agents, they should be substituted by inhaled and intravenous colistin.**
- **The guidelines are against the use of tigecycline for *Acinetobacter* VAP.**

Clinical Caveats in Selecting an Empiric Antibiotic Regimen

1. **The administration of the antibiotics should not be delayed for the sole purpose of performing diagnostic tests.**
2. **If the patient received antibiotics in the recent past, the new antibiotic should be from a different class.**
3. **When an appropriate and adequate initial antibiotic regiment is started, the duration of therapy should be shortened (from the traditional 14-21 days to 7 days), for except *P. aeruginosa.***

Clinical Caveats in Selecting an Empiric Antibiotic Regimen

4. **False negative cultures occurs in patients who have been taking antibiotics for 24-72 hours before collection of respiratory specimens.**
5. **Aerosolized antibiotics may be used as adjunct to systemic antibiotics. They are not effective as sole therapy.**
6. **Certain organisms (*E. coli*, *Klebsiella* spp, *Enterobacter* spp) produce extended-spectrum β-lactamase. These are usually susceptible to carbapenems.**

Neonatal Pneumonia

Onset:

1) **May be within hours of birth, and as part of a generalized sepsis syndrome.**
2) **After 7 days (most commonly in neonatal ICUs among infants who require prolonged endotracheal intubation because of lung disease).**

Neonatal Pneumonia

Organisms are acquired from the maternal genital tract or the nursery, and include:

a) **Gram-positive cocci (groups A and B streptococci, both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*)**
b) **Gram-negative bacilli (*E. coli, Klebsiella* sp, *Proteus* sp).**
c) ***Pseudomonas, Citrobacter, Bacillus,* and *Serratia* in infants who have received broad-spectrum antibiotics.**

Neonatal Pneumonia

Treatment:

- **Antimicrobial therapy in early-onset disease is similar to that for neonatal sepsis: Vancomycin and a broad-spectrum β-lactam drug such as meropenem, piperacillin/tazobactam, or cefepime are the initial treatment of choice.**
- **This regimen treats sepsis as well as pneumonia with typical hospital-acquired pathogens including *P. aeruginosa* and MRSA.**

Neonatal Pneumonia

- **Local patterns of infection and bacterial resistance should always be used to help guide empiric choices of antimicrobials.**
- **More specific antibiotics are substituted after sensitivity results are available.**

Neonatal Pneumonia

Chlamydial pneumonia:

- **Exposure to chlamydial organisms (*Chlamydia trachomatis*) occurs during delivery.**
- **May result in development of chlamydial pneumonia at 2 to 18 wk.**

Treatment:

- **Erythromycin or azithromycin lead to rapid resolution.**
- **Erythromycin may cause hypertrophic pyloric stenosis in neonates.**
- **The mother and father should also be treated for chlamydia.**

Community-Acquired Pneumonia in Children

- **The most likely etiology depends on the age of the child.**
- **Viral and *Streptococcus pneumoniae* infections are most common in preschool-aged children, whereas *Mycoplasma pneumoniae* is common in older children.**

Community-Acquired Pneumonia in Children

- **Preschool-aged children with uncomplicated bacterial pneumonia should be treated with amoxicillin.**
- **Macrolides are first-line agents in older children.**
- **Immunization with the 13-valent pneumococcal conjugate vaccine is important in reducing the severity of childhood pneumococcal infections.**

Recommended Empiric Outpatient Treatment of Childhood CAP

60 days to 5 years of age:

- **Preferred regimens: Amoxicillin for 7-10 days.**
- **Alternative regimens for patients allergic to penicillin or beta-lactam antibiotics: Azithromycin (5 days), clarithromycin (7-10 days), or erythromycin (7-10 days).**

5 to 16 years of age: Azithromycin (5 days).

Recommended Empiric Inpatient Treatment of Childhood CAP

60 days to 5 years of age:

- **Cefuroxime for 10-14 days.**
- **In critically ill patients: Cefuroxime + erythromycin 10-14 days, or cefotaxime + cloxacillin for 10-14 days**

5 to 16 years of age: Cefuroxime + erythromycin 10-14 days, or azithromycin for 5 days.