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.
- Ventilator-associated pneumonia (VAP) is also associated with MDR pathogens.
- In pneumonia that follows the aspiration of gastric or oropharyngeal contents, anaerobic bacteria are the most common etiologic agents.

Pneumonia Causative Agents

- **Pneumonia in infants and children is caused by a wider range of microorganisms, and viruses predominate, especially RSV, parainfluenza, and adenovirus. *Mycoplasma 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.

Management of CAP in Adults

C. An empirical antimicrobial agent with activity against:

- **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.**

Management of CAP in Adults

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 Hospital-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 should be converted to more narrow and specific coverage.**
- **[Cefiderocol (5th GCS) 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 and 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), except for *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.