

# **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

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 culture and sensitivity 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** ).
- **See this if you like:** Am Fam Physician. 2022;105(6):625-630.  
<https://www.aafp.org/pubs/afp/issues/2022/0600/p625.pdf>

## 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. Locally validated risk factors for these pathogens, and the prevalence of MRSA or *P. aeruginosa* in CAP patients (< 3% generally).**

# 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  $\beta$ -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.
- 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 (5<sup>th</sup> 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 antibiotic 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 regimen 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  $\beta$ -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  $\beta$ -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 vaccine is important in reducing the severity of childhood pneumococcal infections.**
- **Immunization also applies for adults > 65 years of age.**

# 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.**