Review Article

An Overview of Antibiotics Used in Lower Respiratory Tract Infections (LRTIs)

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ABSTRACT

Lower Respiratory Tract Infections (LRTIs) refers to infection of the bronchi and lung parenchyma. It is a broad terminology which includes Acute Bronchitis, Pneumonia, Acute Exacerbations of Chronic Obstructive Pulmonary Disease/Chronic Bronchitis (AECB) and Acute Exacerbation of Bronchiectasis. Early symptoms appear in nose and upper lungs like congestion. Smoking, chronic medical illness and long-term bedridden condition increase the risk of mortality. Various Gram-positive bacteria (Staphylococcus Aureus, Staphylococcus Pneumonia etc) and Gram-negative bacteria (Haemophilus Influenza, Pseudomonas etc) are recovered from LRTIs. Beta-lactam antibiotics, Macrolides and Fluoroquinolones are routinely prescribed medicines for the management of ALRTIs. Change in antibiotic resistance patterns are a threat to its effective treatment. Hence there is increasing concern about antibiotic prescription in the community. The final goal is to promote the most appropriate use of antibiotics to maximize therapeutic outcome with minimize the development of antibiotic resistance.

Key words: Antibiotics, Bronchitis, Pneumonia

INTRODUCTION

Acute respiratory infection is a serious infection which prevents the person to breathe properly. It is particularly dangerous for children, older adults and people with immune system disorders. These infections account for 20 to 40% of outpatient and 12 to 35% of inpatient attendance in general hospital[1]. According to WHO 2004 report, respiratory infections generated 94.6 disability- adjusted life years (DALY) lost worldwide and were the fourth major cause of mortality[2]. According to the Global Burden of Disease 2015 (GBD 2015) COPD and lower respiratory infection represent the 3rd and 4th most common cause of death, respectively.[3]

Types of Respiratory Tract Infections (RTIs):

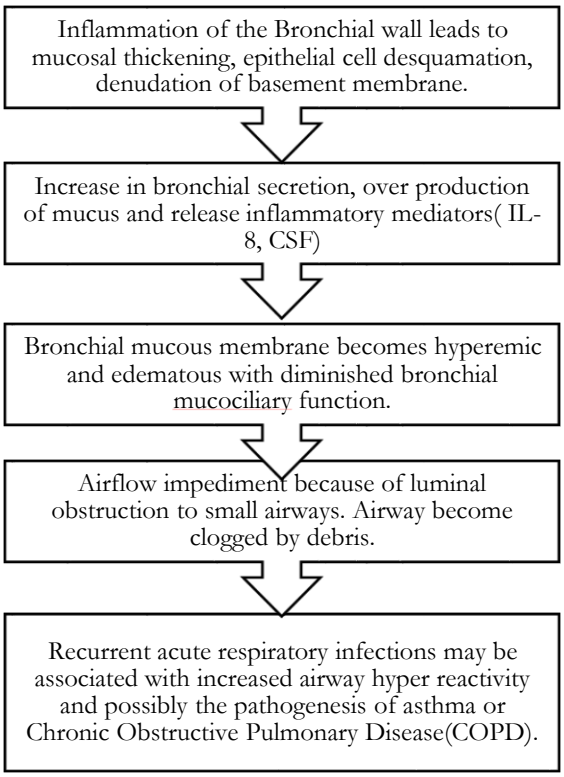
They are traditionally divided into upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs).[4] LRTIs are generally more serious than URTIs.[5] Three major types of LRTIs are Bronchitis, Bronchiolitis and Pneumonia

(1) Bronchitis

Bronchitis is an inflammation of the bronchial tubes. They are classified as (a) Acute Bronchitis (b) Chronic Bronchitis or COPD[6].

Pathophysiology[7,8] : Common defense mechanisms that are compromised in the pathogenesis of Bronchitis include:

(A) Acute Bronchitis[6]: Acute Bronchitis is a transient inflammation of the trachea and major bronchi. It happens once and then person recovers. About 5 % of adults have an episode of acute bronchitis each year.



Etiology[9]: Acute bronchitis is most often caused by a viral infection. The most commonly identified viruses are, Rhinovirus, Enterovirus, Influenza A and B, Corona virus and Respiratory syncytial virus.

Clinical Features[10,11]: The most common clinical features of acute bronchitis are fever, cough with sputum (yellow or green), dyspnea (breathlessness), wheezing and chest pain.

Diagnosis[12]:

1. History and Physical examination.
2. Viral antigen detection test.
3. Culture or serological diagnosis
4. Culture or Fluorescent antibody test

Treatment

1. OTC/Antihistaminic drugs[9]: Antihistamines in combination with decongestants are first line treatment for acute cough.

2. **Aspirin/Acetaminophen[7]:** Aspirin works by blocking the production of prostaglandins and reduce inflammation. In children, Aspirin should be avoided and Acetaminophen used as the preferred agents because of the possible association between Aspirin use and the development of Reye's syndrome.

3. **Ibuprofen[7]:** It relieves cold related symptoms and lowers fever. Aspirin and Ibuprofen inhibit prostaglandin synthesis in predisposed population like pediatric and geriatric.

4. **Antitussives[13]**: Antitussive therapy (prevent/control cough) is indicated if cough is creating significant discomfort and is suppressing body's protective mechanism for airway clearance. Non specific antitussives (Hydrocodone, Dextromethorphan, Codeine, Benzonatate) suppress cough.

5. Antibiotics[7,9]: Clinicians are more likely to prescribe antibiotics in patients with purulent sputum. Smokers are also more likely to receive antibiotic prescription. Commonly used antibiotics are, Erythromycin, Clarithromycin and Azithromycin (Active against M. Pneumonia) Fluoroquinolone (e.g; Gatifloxacin or Levofloxacin)

6. **Antiviral[7]:** Amantadine or Rimantadine (Active against Influenza A virus)

Neuraminidase inhibitors (Zanamivir and Oseltamivir) (active against both influenza A and B viral infections).

(**b) Chronic Bronchitis or COPD** : Chronic Bronchitis and Emphysema are the 2 conditions that commonly comprise Chronic Obstructive Pulmonary Disease(COPD)[14].

Chronic bronchitis is inflammation and irritation of the bronchial tube. The irritation of the tubes causes mucus to build up. This mucus and swelling of the tubes make it harder for the lungs to move oxygen in and carbon dioxide out of the body.[15] Emphysema refers to chronic dyspnea, resulting from enlarged air spaces and destruction of lung tissue. COPD is a slowly progressing disease with a long asymptomatic phase, during which lung function continues to decline. Symptoms do not usually occur until forced expiratory volume in 1 second (FEV1) is approximately 50% of the predicted normal value[16].

Etiology[17,18]

1. Active cigarrate smoking or passive inhalation
2. Smog, industrial pollutants
3. Most common bacteria are Haemophilus Influenza, S. Pneumonia, Klebsiella Pneumonia etc.

Clinical Features[15,16] :

Common symptoms includes persistent cough with mucus production, cough, whistling sound on breathing, shortness of breath, tightness in the chest. In severe cases, weight loss**,** weakness in lower muscle, swelling can also occur.

Diagnosis[19]:

1. **Spirometry Test:** This is breathing test to assess lung work.
2. **Chest x-ray**: This can give an indication of severity and progression of the obstruction.
3. **Blood Test:** This is to see if a symptoms could be due to anemia or due to the genetic marker alpha-1-antitrypsin deficiency.
4. **Phlegm sample**: This is to check to see if there is an infection that is causing the symptoms.

Treatment

1. Inhaled Bronchodilators[17] : Short acting inhaled β_2 agonists (SABA) and anticholinergic agents (short acting muscarinic antagonists, SAMAs) remain the mainstay in the treatment of symptoms and airflow obstruction. Formoterol, a rapid long acting inhaled β2 agonist has also been use for the management of exacerbation.[20]

2. Corticosteroids[21]: The inhaled steroids have been shown to improve symptoms, and reduce the frequency of exacerbations in COPD patients with FEV1<50 % predicted.

3.Phosphodiesterase-4-Inhibitors[21]: Phosphodiesterase-4(PDE-4) inhibitors decrease inflammation and promote airway smooth muscle relaxation by preventing the hydrolysis of cyclic adenosine monophosphate to its inactive metabolite. Cilomilast and Roflumilast are highly specific second generation oral PDE-4 inhibitors.[22]

4. Antibiotics

Macrolides have anti-inflammatory properties and may play a role in the treatment of CB. They have been shown to inhibit pro inflammatory cytokines, decreases neutrophil burst, inhibit migration and increase apoptosis, decreases Eosinophilic inflammation, increase mucociliary transport, reduce goblet cell secretion and decrease bronchoconstriction.[22]

Other agents, such as the Cephalosporins, Cefuroxime or Cefpodoxime, may be appropriate as they are active against H.influenzae and higher doses would also be effective against the pneumococcus. For hospitalized patients with risk for pseudomonas or other more resistant organisms, anti pseudomonal agents such as Piperacillin-Tazobactam, Cefepime or Ciprofloxacin may be considered.[18]

As such, initial antibiotic of choice would be Amoxycillin or Fluoroquinolone. However, the US Food and Drug Administration has recommended that the later should be used only as a last resort agent and be reserved for use in patients who have no other treatment options because of both side effects and potential collateral damage.

(2). Bronchiolitis

Definition[23]: Broncholitis is characterized by inflammatory changes in the small bronchi and bronchioles and commonly seen in young individuals.

Etiology[23]: The most common identified viruses are, Respiratory syncytial virus, Human Rhinovirus, Corona Virus, Adenovirus, Parainfluenza virus and Human boca virus

Pathophysiology[23]: The clinical features of bronchiolitis are primarily due to airway obstruction and diminished lung compliance. The virus infects the epithelial cells in the airways and induces an inflammatory reaction that leads to ciliary dysfunction and cell death. The accumulated debris, edema of the airways and narrowing of the airways due to release of cytokines eventually lead to symptoms and lowered lung compliance. Typical features includes, Air trapping, Increased mucus production, Atelectasis, Labored breathing, Decreased ventilation.

Clinical presentation[24]: Most common symptoms are runny and stuffy nose, cough, fever, dyspnea, wheezing etc.

Diagnosis[7]:

1. History and clinical findings.
2. Viral antigen detection test. Eg., ELISA, Fluorescent antibody detection test.
3. Identification of RSV by PCR.

Treatment[7]:

(a) General Approach: Oxygen therapy, i.v fluids.
(b) Pharmacologic therapy:

1. Bronchodilators therapy e.g., Theophyline
2. Aerosolized β2 adrenergic therapy e.g., Salbutamol

3. Pneumonia

Definition[16]: Pneumonia is defined as inflammation of the lung parenchyma and is characterized by consolidation.

Classification:

(1) Community acquired pneumonia (CAP)[22] :

Any pneumonia acquired outside of a hospital in a community setting.

(2) Hospital acquired pneumonia/ Nosocomial Pneumonia (HAP):

Any pneumonia acquired 48 hours after being admitted in an inpatient setting such as hospital and not incubating at the time of admission is considered as HAP[25] and pneumonia that develops more than 48 hours after incubation and mechanical ventilation is considered as ventilator associated pneumonia (VAP). It is a type of HAP[18].

Etiology[3]: The most common identified pathogens for CAP are Streptococcus pneumonia, Staphylococcus aureus, Klebsiella pneumon**,** Legionella pneumophila, Mycoplasma pneumonia etc and pathogen causing HAP are gram negative bacilli like Enterobacteriaceae, Pseudomonas species, Staph. Aureus (including MRSA) etc.

Pathophysiology[26]: Systemic defense mechanisms like humoral and complement mediated immunity is compromised. Impaired cell mediated immunity predisposes individuals to infection by intracellular organisms like viruses and organisms of low virulence like pneumocystis pneumonia, fungal causes, among others.

The inflammatory response is the main reason for the clinical manifestation of bacterial pneumonia. Cytokines are released in response to inflammatory reaction and cause the constitutional symptoms, for example; IL-1 (interleukin-1) and TNF (Tumor necrosis factor) cause fever. Chemokine like IL-8 and colony stimulating factors like G-CSF (granulocyte colony stimulating factor) promote chemotaxis and neutrophils maturation respectively, resulting in leukocytosis on serological lab and purulent secretion. These cytokines are responsible for the leakage of the alveolar capillary membrane at the site of inflammation, causing a decrease in compliance and shortness of breath. Sometimes even erythrocytes cross this barrier and result in hemolysis.

Clinical features[3]: Common symptoms are sore throat, cough with greenish phlegm, fever and chills hoarseness of voice, headache, pharyngitis and wheezing, leukocytosis >10,000 cells/μ liter, uneasiness, malaise, loss of appetite, nausea and vomiting, sharp chest pain that gets worse with deep breathing or coughing, shortness of breath, decreased blood pressure and fast heart rate. In elderly person, mental changes or confusion.

Diagnosis[27]:

1. Sputum culture test
2. Bronchoscopy and Broncho alveolar lavage
3. Serum antibody test

Treatment: Pneumonia is commonly treated using antibiotics like,

(a) Community Acquired Pneumonia[8,18] ,

- Macrolide, Doxycycline, Fluoroquinolones and Ketolides
- Amoxycilin or Tetracycline(for outpatient)
- Intravenous β lactam (Cefuroxime, Ceftriaxone, Amoxycillin Ampicillin/ Salbactam) plus Macrolide or Doxycyclin is recommended.

(b) Hospital Acquired Pneumonia[23] ,

- Ceftriaxone, Levofloxacin, Moxifloxacin, Ciprofloxacin, Ampicillin-Sulbactam and Ertapenem.
- Elderly patients with pronounced clinical symptoms, are often treated with second generation Cephalosporins in conjunction with aminoglycosides or Ureidopenicillins(Piperacillin,Azlocillin, Mezocillin) in combination with Aminoglycosides or with third generation Cephalasporins, with or without addition of Macrolides.

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