Antimicrobial prescribing of Lower respiratory tract infections for primary care physicians: A consensus statement of Egyptian Scientific Society of Bronchology

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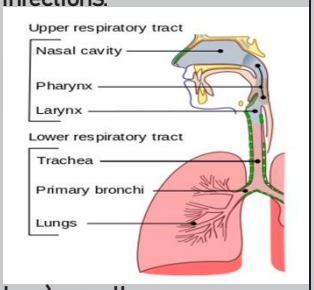
1. Objective: To write consensus statement for management of adult Lower Respiratory Tract Infections (LRTIs) in Egypt for primary care physicians in the view of the following:

- Adult LRTIs are common and increasing problem globally including Egypt.
- Widely varying standards of management of these infections.
- Increasing and emerging antimicrobial resistance among commonly isolated pathogens.
- The significant economic burden and the impact of these infections on patients' morbidity and mortality.

2. Aim: the aim of this consensus is to optimize the antibiotics use, reduce antibiotics resistance, decrease morbidity and mortality of lower respiratory tract infections, and decrease complications of lower respiratory tract infections.

3. Scope: The following items of LRTIs are discussed in this consensus:

1. Acute bronchitis and Acute exacerbation of COPD (AECOPD)
2. Community acquired pneumonia (CAP)
3. Hospital acquired pneumonia (HAP)
4. Ventilator associated-pneumonia (VAP).



Definition: Lower respiratory tract infections (LRTIs) are defined as acute illnesses (present for 21 days or less), usually with cough as the main symptom, with at least one other lower respiratory tract symptom (sputum production, dyspnea, wheeze or chest discomfort/ pain) and no alternative explanation (e.g. sinusitis or asthma), and the classification of LRTIs is described in figure 1.

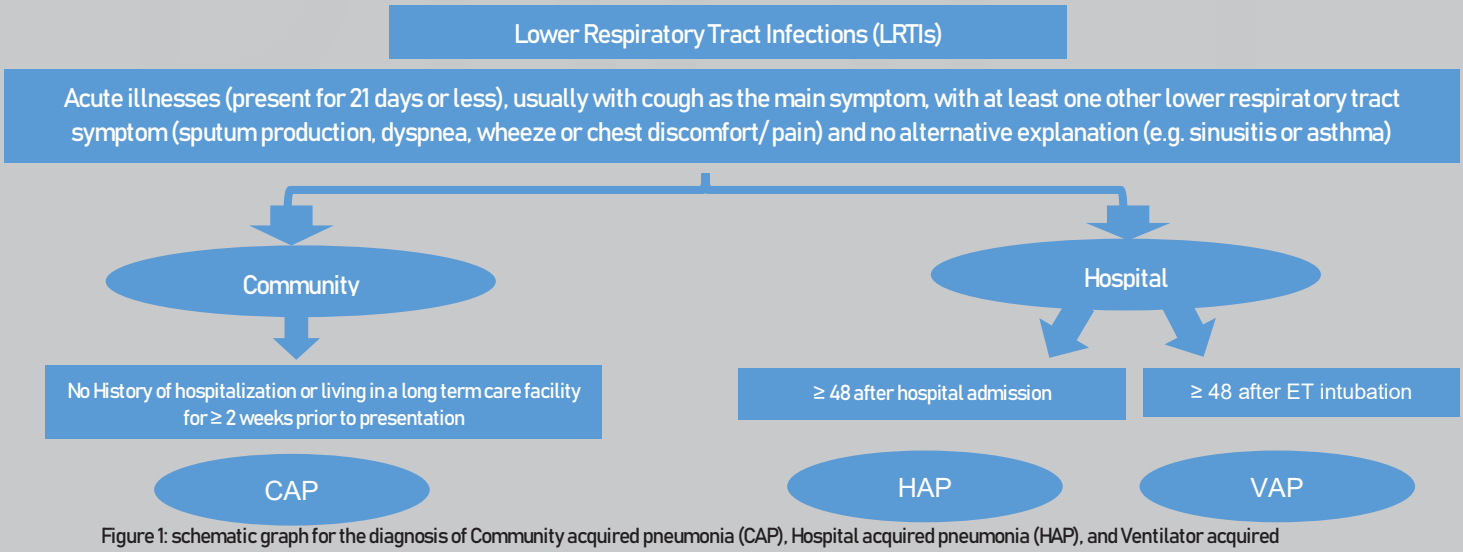


Figure 1: schematic graph for the diagnosis of Community acquired pneumonia (CAP), Hospital acquired pneumonia (HAP), and Ventilator acquired pneumonia (VAP)

Chapter 1: Management of Adults with Acute Bronchitis (AB) and Acute exacerbation of COPD (AECOPD)

4- Acute Bronchitis (AB)

4.1 Definition:

Uncomplicated acute bronchitis is an acute illness, in a patient without chronic lung disease with symptoms including Cough with or without sputum production, dyspnea, wheeze, chest discomfort or low grade fever, no alternative explanation (e.g. sinusitis or asthma), and normal chest x-ray and it may last for up to 3 weeks
Complicated acute bronchitis should be considered if patient has a temperature ≥ 38°C, heart rate (HR) > 100, respiratory rate (RR) > 24, or persistent sputum production beyond 3 weeks

4.2 Diagnosis:

Evaluation should focus on excluding severe illness, particularly pneumonia: Pneumonia is unlikely if all of the following findings are absent, Fever ≥ 38°C, tachycardia > 100, tachypnea > 24, rales, egophony or fremitus
Chest X-Ray: isn't routinely recommended. Consider chest radiography for patients with signs of pneumonia, elderly or cough lasting beyond 3 weeks.

4.3 Management:

Recommendations of Antibiotic therapy for AB:

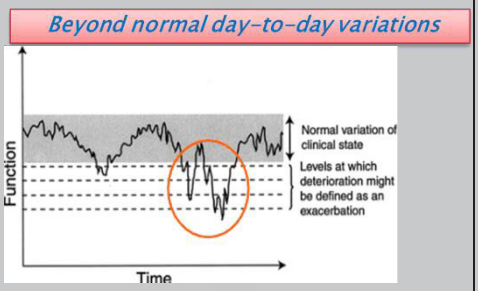
Acute Bronchitis (AB)	Uncomplicated AB	Antibiotics are not recommended
	Complicated AB (pre-existing comorbidities, or patients >65 years)	Azithromycin 500 mg daily for 5 days or Clarithromycin 500 mg/12 hours for 7 days

The following might help: smoking cessation, good hydration, analgesics/antipyretics, protussives and antitussives, bronchodilators or inhaled or oral corticosteroids

5- Acute exacerbation of COPD (AECOPD):

5.1 Definition:

An acute worsening of respiratory symptoms that result in additional therapy



5.2 Etiology:

Causes of an exacerbation in COPD patients:
Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections (infective exacerbations in 50%-70% viral or bacterial). Environmental factors also share. Up to 30% are of unknown aetiology
The most common bacteria causing AECOPD are:

Common	H.Influenza, Moraxella Catarrhalis, S.Pneumonia and S.Aureus
Common in severe Exacerbation	P.Aeruginosa and gram-negative Bacilli
Atypical	Chlamydia Pneumonia, Mycoplasma Pneumonia and Legionella spp

5.3 Diagnosis of AECOPD:

The diagnosis of exacerbation relies exclusively on the clinical presentation of patient complaining of acute change of symptoms (baseline dyspnoea, cough and/ or sputum production) that is beyond normal day-to-day variation.
Risk factors include tobacco, occupation and indoor/outdoor pollution

Symptoms and signs of an exacerbation of COPD patients:

- More breathless than usual with routine activities.
- Cough may increase in severity or frequency, or a new cough may develop.
- Change in sputum colour and amount.
- Symptoms and signs of infections in the lung, such as fever.

Sputum culture & sensitivity: Should not be routinely performed except in patients with frequent exacerbations, worsening clinical status or inadequate response after 72 hours on initial empiric antibiotic and /or exacerbation requiring mechanical ventilation.

5.4 Classification

Classification of exacerbation: absence of a universal agreed criterion

Severity of exacerbation based on symptoms

Definition elements	Severity
• Worsening dyspnoea • Increased sputum purulence • Increase in sputum volume	• Type I (Severe) – all 3 elements • Type II (Moderate) – 2 elements • Type III (Mild) – 1 element plus URI in past 5 days, fever without apparent cause, increased wheezing or cough and increased (+20%) of respiratory rate or heart rate

AECOPD are classified based on treatment received into:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

5.5 Treatment of AECOPD:

Treatment goal is to minimize the negative impact of the current exacerbation and to prevent subsequent events.

Medications:

1) Short-acting inhaled beta2-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.
2) Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.
3) Antibiotics Therapy in the management of AECOPD:
   - Selection of antibiotics therapy in AECOPD is described in table 2
   - Indications for antibiotic treatment of AECOPD
     - Severe exacerbation (Type I).
     - Moderate exacerbation (Type II) when increased purulence of sputum is one of the two cardinal symptoms.
     - Mechanical ventilation.
     - Antibiotics are generally not recommended in Moderate exacerbation (Type II) without purulence and Mild exacerbation (Type III) patients.

Table 2: Stratification of patients with AECOPD for antibiotic treatment and potential microorganisms involved in each group and recommended antibiotic therapy

Definition	Microorganisms	Antibiotic therapy (No particular order)

Uncomplicated AECOPD: No risk factors for poor outcome	• H. influenzae • S. pneumoniae • M. catarrhalis • Chlamydia pneumoniae • Viruses	• Advanced Macrolide Azythromycin 500mg/24h (Oral) Clarithromycin 500mg/12h (Oral) • 2nd- or 3rd gneneration cephalosporins Cefditoren 200-400 mg / 12 h (Oral) Ceftriaxone 1-2 g every 12-24 h (IV)
Complicated AECOPD: Risk factor(s) for poor outcome: • Presence of comorbid diseases, • Severe COPD, • Frequent exacerbations (>3/yr) • Antimicrobial use within last 3 months.	As in Uncomplicated AECOPD plus: • Presence of resistant organisms (ß - lactamase producing,penicillin-resistant S. pneumoniae) • Enterobacteriaceae (K. pneumoniae, E. coli, Proteus, Enterobacter, etc)	• Fluoroquinolone Gemifloxacin320mg /24h (Oral) Levofloxacin 500 mg/12-24 h (Oral/IV) Moxifloxacin 400 mg/ 24 h (Oral/IV) • B-lactam/B-lactamase inhibitor Co-amoxiclav 875/125 mg every 8 h (Oral) and 1-2 g/200 mg every 6-8 h (IV),
Complicated AECOPD: Risk factor(s) for P. aeruginosa Infection: Should be considered in the presence of at least two of the following Recent hospitalization, • Frequent (>4 courses per year) • Recent administration of antibiotics (last 3 months), • Very severe disease (FEV1 < 30%), • Oral steroid use (>10 mg of prednisolone daily in the last 2 weeks)].	As in complicated AECOPD plus P. aeruginosa	• Fluoroquinolone Levofloxacin 750 mg/ 24 h (Oral/IV) Ciprofloxacin 750 mg / 12 h (Oral) and 400 mg/12 h (IV) Piperacillin-tazobactam4.5gm/6h (IV)

Principles of Antibiotics in AECOPD:

- The recommended length of antibiotic treatment is usually 5-10 days. The use of the oral or intravenous route should be guided by the stability of the clinical condition and the severity of exacerbation. Switch (intravenous to oral) should be done by day 3 of admission if the patient is clinically stable. Improvements of dyspnea and sputum purulence suggest clinical success.
- Worsening of clinical status or inadequate response in 72 hours necessitates reevaluation and sputum culture.

6. Chapter 2: Management of Adults with Community Acquired Pneumonia (CAP)

6.1 Definition

CAP is defined as an Infection of the lung parenchyma in a person who is not hospitalized or living in a long-term care facility for ≥ 2 weeks, this pneumonia develops in the outpatient setting or within 48 hours of admission to a hospital.

6.2 Diagnosis of CAP:

6.2.1 Clinical diagnosis of CAP: All patients should have full medical history and physical examination, exclude Conditions that can mimic pneumonia, define the severity of CAP and identify specific risk factors that can influence the likely etiologic pathogens and management.

6.2.2 Signs and symptoms:

a) Symptoms of CAP may be preceded by URTI:

- Respiratory: Cough dry or productive, mucopurulent sputum, sometimes rusty, dyspnea, sometimes pleuritic chest pain
- Non-respiratory: Fever, body aches, altered mental state, vomiting or diarrhea

b) Signs:
- Generally: Fever, sometimes hypothermia, tachycardia, tachypnea.
- Local: signs of consolidation (increase TVF, dullness or impaired note with percussion and bronchial breath sound with consonating crepitation).

6.2.3Diagnostic tools of CAP:

a) Radiological diagnosis:

i. 1-Chest X Ray: "No diagnosis of pneumonia without at least Chest X Ray", The pattern of infiltrates may suspect the causative organism
ii. CT scan may assist in the diagnosis of CAP severity and help in differential diagnosis.

Table 3: The pattern of infiltrates and the suspected causative organism

Pattern	Possible Diagnosis
Lobar	Streptococcus pneumoniae, Klebsiella pneumoniae or Haemophilus influenza
Patchy	Atypical or viral
Interstitial	Viral, PCP or legionella
Cavitary	Anerobes, Klebsiella pneumoniae, Tuberculosis or S.aureus
Large effusion	Anerobes, Klebsiella pneumoniae, or S.aureus

b) Bacteriological diagnosis

1. Microorganisms:

i. Typical bacterial pathogens that commonly cause CAP (85% of cases) include: Streptococcus pneumoniae , Haemophilus influenzae (ampicillin-sensitive and resistant strains), Moraxella catarrhalis. (table 4)
ii. Atypical pathogens as Chlamydia pneumoniae & Legionella pneumoniae and viruses can participate in CAP. (table 4)
iii. Very rarely pseudomonas aeruginosa can cause CAP.

2. Recommendations for diagnostic testing remain controversial

i. Diagnostic testing in outpatient setting is optional
ii. Diagnostic testing in inpatient setting is offered in Critically ill / Severe CAP, Sputum and blood culture are recommended not only for patients with severe CAP but also for all CAP inpatients receiving empirical treatment for methicillin-resistant Staphylococcus aureus or Pseudomonas aeruginosa, and specific pathogens (suspected)
    a. Diagnostic testing for CAP etiology may include:
    b. sputum gram stain, sputum culture and sensitivity, sputum for AFB by Z.N stain, blood culture, acute phase serologic testing (e.g. Chlamydophila, Mycoplasma & Legionella), urinary antigen testing (e.g. Legionella and Pneumococcal) and PCR.
    c. Use of procalcitonin is not recommended to determine need for initial antibacterial therapy
iii. Other diagnostic testing for CAP may be indicated in special situations may include: Bronchoscopic bronchoalveolar lavage, endotracheal tube aspirate, thoracocentesis and transthoracic needle aspiration biopsy.

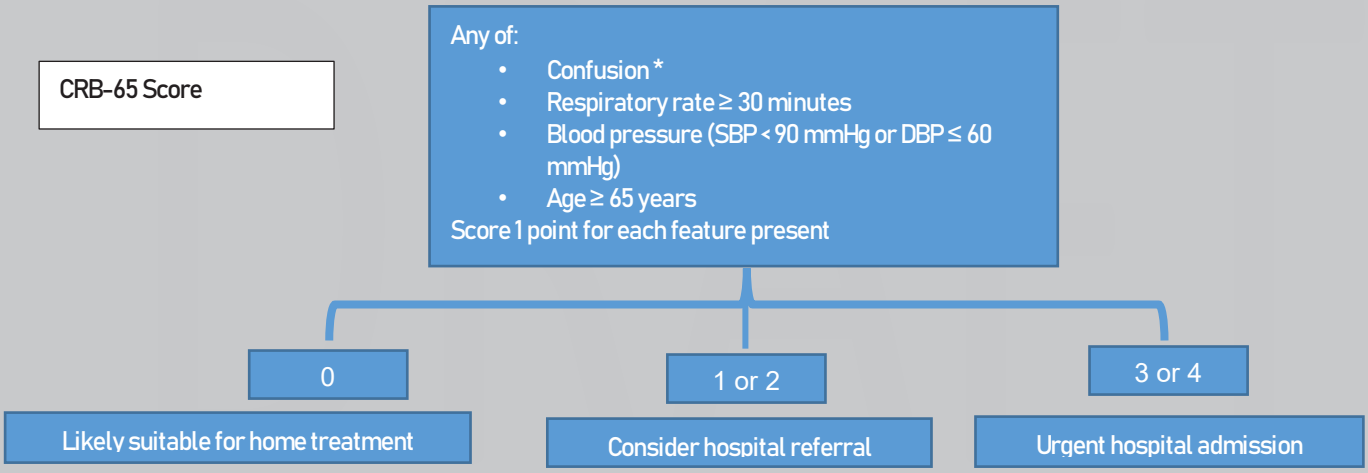
Table 4: Comparison between typical and atypical CAP

CAP	Typical	Atypical
Causative organism	Streptococcus pneumoniae, Hemophilus influenza or Moraxella catarrhalis	Mycoplasma pneumoniae, chlamydia pneumoniae or legionella pneumoniae
Site	Alveolar space: exudates	Interstitial space: swelling and collapsed alveoli

Onset	Sudden	Gradual
Non-pulmonary symptoms (headache and myalgia)	Rare and mild	Common and prominent
Cough	Productive: purulent	Dry or scanty mucoid
Fever	High grade	Low grade
Pleuritic pain	Common	Rare
Physical signs	Evident	Often minimal

c) Differential Diagnosis from other diseases like pulmonary infarction, pulmonary edema with another infection site, pulmonary hemorrhage, vasculitis, malignancy, drug toxicity, radiation pneumonitis, or preexisting lung disease (e.g. fibrosing alveolitis) should be considered

d) Severity of CAP:
Assess the severity of pneumonia and site of receiving care through an objective tool for risk assessment using CRB 65 scoring system for pneumonia.
Use CRB65 Assessment for CAP as shown in figure.2



DBP: Diastolic blood pressure, SBP: Systolic blood pressure,
*defined as a mental test score of ≤ 8, or new disorientation in person, place or time, predicted 30 days mortality: CRB-65 score 0=1.2%, CRB-65 score 1 or 2= 8.2% CRB-65 score 3 or 4= 31.3%

e) Severity-criteria for ICU admission:

- Minor Criteria:
  1) Respiratory rate ≥30 breaths/min
  2) PaO2/FiO2 ≤250
  3) Multilobar infiltrates
  4) Confusions/ disorientation
  5) Uremia (BUN level ≥ 20 mg/dl)
  6) Leukopenia (WBC count <4000 cells/mm3)
  7) Thrombocytopenia (platelets count <100,000 cells/mm3)
  8) Hypothermia (core temperature <36°C)
  9) Hypotension requiring aggressive fluid resuscitation

  } >2 = high risk for ICU admission

- Major Criteria:
  1) Invasive mechanical ventilation
  2) Septic shock with the need for vasopressors

  } (1/2 sufficient)

6.3 Management of CAP:

6.3.1 Site of care:

- Outpatient care: able to take oral medications and have adequate outpatient care
- Inpatient care: based on severity-of-illness scores.
  - If inpatient treatment required, determine if patient should be admitted to ICU or general ward
  - ICU admission required: 1 major criteria or 3 minor criteria are present

6.3.2 Antibiotic Therapy for the management of CAP:

6.3.2.1 Initial treatment for outpatients:

- Prompt initiation of appropriate antibiotic therapy is crucial for favorable outcomes
- Empiric antimicrobial therapy as soon as diagnosis of pneumonia is made remains a challenge despite the availability of treatment guidelines
- Factors related to organism, patient and antibiotic to be considered
- Start antibiotics as soon as possible in emergency department, delay to start antibiotics for more than 4 hours after arrival leads to increased mortality and increased length of hospital stay
- Selection of initial treatment for outpatients with CAP should be as follow:

initial treatment for outpatients with CAP		
No comorbidities or risk factors for MRSA or P. Aeruginosa*	Amoxicillin or Macrolide#	Amoxicillin 1 g three times daily or Azithromycin 500 mg daily or Clarithromycin 500 mg twice daily or Clarithromycin extended release 1000 mg daily
With comorbidities^	Combination therapy with Amoxicillin/Clavulanate acids or Cephalosporin And Macrolide or Respiratory Fluoroquinolone	Amoxicillin/ Clavulanate 875/125 twice daily, Cefixime 400 mg daily or Cefditoren 400 mg twice daily And Azithromycin 500 mg daily or Clarithromycin 500 mg twice daily or Clarithromycin extended release 1000 mg daily Levofloxacin 750 mg daily or Moxifloxacin 400 mg daily or Gemifloxacin 320 daily
In survived outpatient CRB-65-Score 1 or 2 if the patient refused or couldn't hospitalized	IM 3rd generation Cephalosporin And Macrolide	Ceftriaxone 1 to 2 g IM once (or in equally divided doses twice a day) Azithromycin 500 mg daily or Clarithromycin 500 mg twice daily or Clarithromycin extended release 1000 mg daily

*Risk factors include prior respiratory isolation of MRSA or P. Aeruginosa or recent hospitalization and receipt of parenteral antibiotic (in the last 90 days)
^Comorbidities include chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia
#the recommendation for macrolide monotherapy for outpatients is conditional one, based on local resistance level

6.3.2.2 Initial treatment for inpatients:

- b-lactam+ macrolide: IV Cefotaxime 1-2 g every 8 hours, Ceftriaxone 1-2 g daily, and Azithromycin 500 mg daily or Clarithromycin 500 mg twice daily
- Respiratory fluoroquinolones: IV Levofloxacin 750 mg daily or MOxifloxacin 400 mg daily
- MRSA coverage: IV vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h)
- P. Aeruginosa coverage: IV piperacillin-tazobactam (4.5 g every 6 h), cefepime (2g every 8h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), or meropenem (1 g every 8 h), doesn't include extended-spectrum b-lactamase-producing Enterobacteriaceae, which should be considered only on the basis of patient or local microbiological data

Initial treatment for inpatients with CAP			
	Standard regimen	Prior respiratory isolation of MRSA or P. Aeuginosa	recent hospitalization and receipt of parenteral antibiotic and locally validated risk factors for MRSA or P. Aeruginosa
Non-severe inpatient pneumonia	IV-B-Lactam + Macrolide or IV Respiratory fluoroquinolone	Add MRSA coverage or P. Aeruginosa coverage and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Obtain culture but initiate coverage for MRSA or P. Aeuginosa only if culture results are positive
Severe inpatient pneumonia	IV-B-Lactam + Macrolide or IV-B-Lactam + Respiratory fluoroquinolone	Add MRSA coverage or P. Aeruginosa coverage and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Obtain culture but initiate coverage for MRSA or P. Aeuginosa and obtain cultures to allow de-escalation or confirmation of need for continued therapy

IV: Intravenous *as defined by CAP severity criteria
^ Beta-lactam/macrolide and beta-lactam/fluoroquinolone therapies are both still acceptable for severe CAP, but the evidence is stronger for beta-lactam/macrolide.

- Special entities in ICU: Aspiration: as Before + IV. Clindamycin 600mg /12h iv OR Metronidazole 500mg /8h iv

6.3.2.2 Duration of treatment: Minimum 5 days of treatment, should be afebrile 48–72hrs, and no more than 1 CAP associated sign of clinical instability before discontinuing therapy.

- Criteria for clinical stability:
  - Temperature ≤°C
  - Heart rate ≤ 100 beats per minute
  - Respiratory rate ≤ 24 breaths per minute
  - Systolic blood pressure ≥ 90 mmHg
  - Arterial O2 saturation ≥ 90% or pO2 ≥ 60mmHg
  - Maintain oral intake and normal mental status
- IV to oral switch Usually switch to oral form of the same antibiotic or same pharmacologic class when patient is :
  - Afebrile
  - No abnormal GIT absorption
  - Cough and respiratory distress improved
  - WBC returning to normal
- Follow-Up:
  - Criteria for Clinical Stability:
    - Temp ≤37.8°C.
    - Heart rate ≤100 beats per min.
    - Respiratory rate ≤24 breaths per min.
    - Systolic blood pressure ≥90mmHg.
    - Arterial O2 saturation ≥90% or pO2 ≥60mmHg.
    - Maintain oral intake and normal mental status.
  - Non responding pneumonia:
    Defined a situation in which an inadequate clinical response is present despite antibiotic treatment. Lack of response also varies according to the site of treatment (e.g. outpatients versus ICU) and the time of

evaluation (e.g. persistent fever after the first day of treatment differs significantly from fever persisting or recurring at day 7 of treatment).

- Failure to improve:
  - Early (<72 h of treatment): Normal response
  - Delayed: resistant microorganism; uncovered pathogen or inappropriate by sensitivity. paraneumonic effusion/ empyema. Nosocomial superinfections; nosocomial pneumonia or extra-pulmonary. noninfectious; complication of pneumonia (e.g. bronchiolitis obliterans organizing pneumonia), misdiagnosis: pulmonary embolus, congestive heart failure, vasculitis or drug fever
- Deterioration or progression:
  - Early (<72 h of treatment); severity of illness at presentation, resistant microorganism (uncovered pathogen or inappropriate by sensitivity), metastatic infection (empyema/ parapneumonic, endocarditis, meningitis or arthritis), Inaccurate diagnosis (pulmonary embolus, aspiration, acute respiratory distress syndrome) or, Vasculitis (e.g. systemic lupus erythematosis)
  - Delayed; nosocomial superinfection (nosocomial pneumonia or extra-pulmonary), exacerbation of comorbid illness or intercurrent noninfectious disease (pulmonary embolus, myocardial infarction or renal failure)

6.3.3 Common complications of CAP:

Pleural effusion and empyema and lung abscess and metastatic infection are the common complications of CAP.

6.3.4 Prevention and vaccination:

Strategies to prevent CAP include Influenza and pneumococcal Vaccination and Smoking cessation.

7. Chapter 3: Management of Adults with Hospital-acquired pneumonia (HAP) (nosocomial pneumonia) & Ventilator associated pneumonia (VAP)

7.1 Definitions:

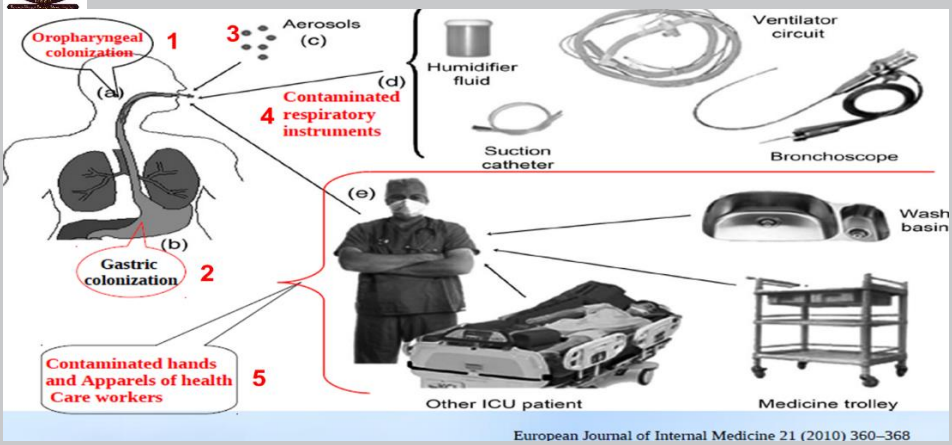
- Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs ≥ 48 h after admission that did not appear to be incubating at the time of admission.
- Ventilator associated pneumonia (VAP) is defined as a type of HAP that develops >48 h after endotracheal intubation.

7.2 Pathogens:

Common Pathogens for HAP and VAP are shown in the below table:

HAP Pathogens	VAP Pathogens
P. aeroginosa (common)	P. aeroginosa
S. aureus including MSSA and MRSA (common)	S. aureus including MSSA and MRSA
K. pneumoniae (common)	Stentophomas maltophila
E. coli (common)	Acinobacter species
Non-Enterobacteriaceae bacteria such as S. marcescens, stentophomas maltophila, and Acinobacter species are less common	Enterobacteriaceae are less commonly seen in VAP than in HAP

Sources of microorganisms cause HAP and VAP include oropharyngeal colonization, gastric colonization, aerosols, contaminated respiratory instruments and contaminated hands and apparels of healthcare workers



7.4 Prevention, HAP and VAP could be prevented by preventing pathogenesis as shown in the below diagram

Pathogenesis		Prevention	
Germs in mouth	• Dental plaque provides microhabitat • Replicate 5X/24 hrs	Germs in mouth	• comprehensive oral care • oral care protocol that includes all patients
Aspirated	• Most common route • 45% of healthy adults micro-aspirate in sleep	Aspirated	• Swallow screens • Tube feeding protocols • Head of bed elevated
Weak host	• Poor cough • Immunosuppressed • Multiple co-morbidities	Weak host	• Lung expansion/mobilize • Adequate nutrition • Serum glucose target range

7.5 Diagnosis of HAP/VAP:

- Clinical criteria (Suspected HAP):
  Symptoms, signs, radiological findings and leukocytosis or leukopenia (figure 5)
- Microbiological criteria (Microbiologically confirmed HAP; Final diagnosis)
- No role for biomarkers to make the decision to initiate antibiotic therapy for HAP or VAP. Rely on clinical criteria alone.

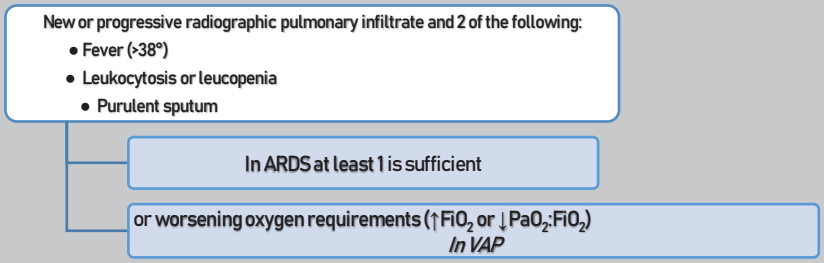


Figure 5: Criteria for Clinical diagnosis of pneumonia

- Microbiology samples:
  - Microbiology samples should be done to all patients at time of clinical diagnosis, and should be taken before initiating antibiotic treatment.
  - Microbiology examination: could be done by Gram staining, qualitative culture, semi-quantitative culture (Preferred first) or quantitative culture
  - HAP (Non-VAP)
    1. Non-invasive respiratory samples (Preferred first)
       - Sputum: spontaneous or induction
       - Nasotracheal suctioning (non cooperative patients)
       - Endotracheal aspiration
       - (HAP under mechanical ventialtion)
    2. Invasive respiratory samples
       - When respiratory sample cannot be obtained noninvasively
       - Blood culture (always)
- VAP
  1. Non-invasive respiratory samples (Preferred first)
     - Endotracheal aspiration.
  2. Invasive respiratory sampling
     - Bronchoscopic Broncho-alveolar Lavage (BAL) [>104 CFU/ml]
     - Bronchoscopic Protected specimen brush (PSB) [>103 CFU/ml]
     - Blind bronchial sampling (i.e. mini-BAL) [>104 CFU/ml]

- Pneumonia mimics:
  Exclude Pneumonia mimics such as:
  - Pulmonary infarction
  - Adult respiratory distress syndrome
  - Pulmonary hemorrhage
  - Vasculitis
  - Pulmonary edema with another infection site
  - Malignancy
  - Drug toxicity
  - Radiation pneumonitis
  - Preexisting lung disease (e.g. fibrosing alveolitis)
- Risk factors for multidrug-resistant (MDR) pathogens:
  - Risk factors for MDR HAP:
    - Ventilatory support
    - Septic shock
    - Prior IV antibiotic use within 90 days
  - Risk factors for MDR VAP:
    - Prior IV antibiotic use within 90 days
    - Septic shock at time of VAP
    - ARDS preceding VAP
    - ≥ 5 days of hospitalization prior to the occurrence of VAP
    - Acute renal replacement therapy prior to VAP onset

7.6 Management:

7.6.1 Severity of Pneumonia

Defined as having severe pneumonia by admission to the ICU and any one of the following conditions:

A. Shock defined as systolic BP of < 90 mm Hg or diastolic BP of < 60 mm Hg;
B. Respiratory failure (i.e., mechanical ventilation or the need for a fraction of inspired oxygen of > 0.35 to maintain an oxygen saturation of > 90%;
C. Requirement of vasopressor therapy for > 4 h;

D. Urine output of < 20 mL/h or total urine output of < 80 mL/h for > 4 h, unless oliguria is present due to a condition other than infection/sepsis;
E. Acute renal failure requiring dialysis; or
F. Rapid radiographic progression, multilobar pneumonia, or cavitation of a lung infiltrate.

7.6.2 Empiric treatment of suspected HAP/VAP:

When HAP is suspected, it is crucial to identify risk factors for being infected with MDR pathogens, certain host and environmental factors make a patient more susceptible to MDR pathogens

7.6.2.1 Principles of empiric antimicrobial therapy in HAP and VAP:

- Selection of an empiric antibiotic regimen for HAP/VAP should be guided by local antibiotic-resistance data.
  - Targeting the specific pathogens and to assure adequate treatment
  - Determined & updated by each institution.
  - Consider: rate of change, resources, and the amount of data available for analysis.
- Empiric coverage for MRSA is indicated when:
  - Risk factor for antimicrobial resistance
  - >10–20% of S. aureus isolates MRSA
  - Unknown prevalence of MRSA
- Two antipseudomonal antibiotics from different classes are indicated when:
  - Risk factor for antimicrobial resistance
  - >10% resistant GNB to an agent being considered for monotherapy
  - Local ICU antimicrobial susceptibility not available
  - Structural lung disease
  - (One antipseudomonal antibiotic is indicated when all the above factors not present)
- Empiric coverage for MSSA (if MRSA is not covered) by:
  Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem, if MSSA confirmed→ switch to oxacillin, nafcillin, or cefazolin.
- Acinetobacter
  - Either a carbapenem or ampicillin/sulbactam → susceptible to these agents
  - If resistant to these agents inhaled & IV colistin
  - Recommend against the use of tigecycline
- When Culture and sensitivity are available:
  - De-escalation (empiric broad-spectrum regimen converted to a narrower & specific regimen)
- Duration of therapy
  - 7–8 day regimens are recommended.
  - Shorter or lengthened depends on the individual clinical response

7.6.2.1 Selection of empiric antimicrobial therapy in HAP and VAP:

A. HAP:
   1- Patients not at high risk of mortality and without risk of MRSA:
   Select one antipseudomonal activity antibiotics (Table 7)
   2- Patients not at high risk of mortality but with increased likelihood of MRSA:
   Select one antipseudomonal activity antibiotics plus Empiric coverage for MRSA (Table 7)
   3- Patients at high risk of mortality
   Select two antipseudomonal activity antibiotics from different classes plus Empiric coverage of MRSA (Table 7)

B. VAP: Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in ICUs Where Empiric Methicillin-Resistant Staphylococcus aureus Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate (table 8)
   Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C.

Table 7. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h

OR	OR	
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h	Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h	Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h	Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily Gentamicin 5–7 mg/kg IV daily Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
	If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.	

Abbreviations: HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus.
[a] Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock.
[b] Indications for MRSA coverage include intravenous antibiotic treatment during the prior 90 days, and treatment in a unit where the prevalence of MRSA among S. aureus isolates is not known or is >20%. Prior detection of MRSA by culture or non-culture screening may also increase the risk of MRSA. The 20% threshold was chosen to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use; hence, individual units can elect to adjust the threshold in accordance with local values and preferences. If MRSA coverage is omitted, the antibiotic regimen should include coverage for MSSA.
[c] If patient has factors increasing the likelihood of gram-negative infection, 2 antipseudomonal agents are recommended. If patient has structural lung disease increasing the risk of gram-negative infection (ie, bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended. A high-quality Gram stain from a respiratory specimen with numerous and predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non-glucose-fermenting microorganisms.
[d] Extended infusions may be appropriate.
[e] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant Staphylococcus aureus Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotic With MRSA Activity	B. Gram-Negative Antibiotic With Antipseudomonal Activity: β-lactamase-Based Agents	C. Gram-Negative Antibiotic With Antipseudomonal Activity: Non- β-lactamase-Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.
Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus.

a Drug levels and adjustment of doses and/or intervals required.
b Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.
c On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.
d The dose may need to be lowered in patients weighing <70 kg to prevent seizures.
e Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].
f In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137]

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