Management of Adult Lower Respiratory Tract Infections

A Consensus Statement

The official Statement of the Egyptian Scientific Society of Bronchology

(ESSB), May 2012

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ABSTRACT:

This document is the executive summary of a consensus conference that was convened to review the available information and to develop a practical approach to the management of adult Lower Respiratory Tract Infections (LRTIs). The current available national and international literature was evaluated. The statement provides recommendations for the most common management questions occurring in routine clinical practice in the management of adult patients with LRTI. Topics include management outside and inside the hospital of acute bronchitis (AB), acute exacerbation of COPD (AECOPD), community acquired pneumonia (CAP), hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP), ventilator associated tracheobronchitis (VAT) and health care associated pneumonia (HCAP). The target audiences for this statement are all those whose routine practice include the management of adult LRTI. This expert consensus opinion is considered an initial step in identifying the best available clinical practices in Egyptian hospitals. Future availability of better surveillance data for different LRTIs could facilitate the development of a national evidence based treatment guidelines.

OBJECTIVE:

To write consensus statement for management of adult Lower Respiratory Tract Infections (LRTIs) in Egypt 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.

AIM OF THE CONSENSUS STATEMENT:

The ultimate goal of the present consensus statement is to provide a framework to make informed decisions regarding the diagnosis and management adult LRTIs encompassing the following conditions:

- Acute bronchitis (AB)
- Acute exacerbation of COPD (AECOPD)
- Community acquired pneumonia (CAP)
- Hospital acquired pneumonia (HAP)
- Ventilator associated pneumonia (VAP)
- Ventilator associated tracheobronchitis (VAT)
- Health care associated pneumonia (HCAP)

Process of consensus statement development:

The Egyptian Scientific Society of Bronchology (ESSB) decided to develop a consensus statement for management of adult LRTIs in Egypt as part of its continuous medical education program in the field of pulmonary medicine and bronchology. A taskforce from ESSB was responsible for consensus statement development.

Methodology:

All available national studies concerning adult LRTIs (AB, AECOPD, CAP, HAP, VAP, and HCAP) were reviewed.
International guidelines for the treatment of LRTIs including but not limited to the following organizations were identified and considered together with national and international epidemiologic data.

- American Thoracic Society and Infectious Diseases Society of America.
- European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.
- British Thoracic Society and British Society for Antimicrobial Chemotherapy.
- Association of Medical Microbiology and Infectious Diseases of Canada.
- Spanish Society of Pneumology and Thoracic Surgery.
- South African Thoracic Society.

Evidence-based recommendations specific to clinical practice in Egypt cannot be addressed currently, because of fewer data are available for supporting evidence. This situation is neither surprising nor new. This limitation is also noted that only 5 out of 11 European countries guidelines of HAP have implemented evidence grading. Also the latest ATS/IDSA and other international guidelines also acknowledge this limitation.

As a result of the difficulties inherent in evidence grading, the current statement as well as other international country-guideline recommendations were developed based on consensus/expert opinion. The expert consensus opinion achieved and reported herein is considered an initial step in identifying the best available clinical practices in Egypt hospitals.

It was agreed that the availability of better surveillance data for different LRTIs could facilitate the development of a national evidence based treatment guidelines. It is understood and expected that in the future, as more relevant data become available, these recommendations will be adapted and modified to reflect a changing evidence base.

STATEMENT

This consensus statement is published for educational purposes only. The recommendations are based on currently available scientific evidence together with the consensus opinion of the authors and available resources. The consensus statement is not meant to replace clinical judgment, but rather to give logical framework to the evaluation of patient management.

Definition of Lower respiratory tract infection:

An acute illness (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).

CHAPTER I

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

(A) DIAGNOSIS:

1. Definitions:

Acute Bronchitis (AB)

An acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI, and no alternative explanation (e.g. sinusitis or asthma) with normal chest x-ray and it may last for up to 3 weeks **(Uncomplicated acute bronchitis).**

The diagnosis of **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.

Acute exacerbation of COPD (AECOPD)

An exacerbation of COPD is an acute event in the natural course of the disease characterized by a worsening of the patient's baseline respiratory symptoms that is beyond normal day-to-day variation sufficient to warrant a change in management. If chest radiograph shadowing, consistent with infection, the patient is considered to have CAP.

2. The clinical diagnosis of AB & AECOPD

2.1- Acute Bronchitis (AB)

Acute bronchitis often develops during the course of an upper respiratory infection (URI) such as common cold or influenza. Cold like symptoms may be apparent during the first few days in the form of runny nose, sneezing & dry cough.

Symptoms and signs of acute bronchitis are of acute onset including:

- **Cough:** It is the most common symptom. Cough is deep, dry and painful with or without sputum production. Cough begins within 2 days of infection in 85% of patients. Most patients have a cough for less than 2 weeks; however, 26 % are still coughing after 2 weeks and a few cough for 6 to 8 weeks. Cough is considered to be necessary to the diagnosis of acute bronchitis.
- Each of the symptoms and signs mentioned below may be present in varying degrees or may be absent altogether.
  - **Sputum production:** Sputum may be clear, white, yellow, green, or even blood tinged. Peroxidase released by the leukocytes in sputum causes the color changes; hence, color alone should not be considered indicative of bacterial infection.
  - **Dyspnea.**
  - **Low-grade fever.**
  - **Wheezing.**
  - **Others:** chilliness, malaise, body aches, soreness & constriction behind sternum.
- **Evaluation should focus on excluding severe illness,** particularly pneumonia: Pneumonia is unlikely if all of the following findings are absent (fever ≥ 38°C, tachypnea ≥ 24 breaths/min, tachycardia ≥ 100 beats/min, rales, egophony, fremitus).
- **Chest X-ray:** Chest x-ray is not routinely recommended. Consider chest radiograph for patients with signs of pneumonia, elderly or cough lasting >3 weeks.

2.2- 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.

2.2.1- AECOPD types (Anthonisen types):

Type I - severe exacerbations with all three clinical findings (dyspnea, coughing, sputum production).

Type II - moderate exacerbations with only two clinical findings.

Type III - mild exacerbations with one finding, together with at least one of the following:

- URTI in the past five days.
- Fever without any other cause.
- Increased wheezing.
- Increased cough.
- 20% increase above baseline in the respiratory or heart rate.

3. The Microbiological diagnosis of AB & AECOPD

3.1- Microorganisms

3.1.1- Acute Bronchitis (AB):

About 90% of cases of acute bronchitis are caused by viruses, including rhinoviruses, adenoviruses, respiratory syncytial virus, corona virus influenza and parainfleunza. Bacteria in rare cases including atypical bacteria (mycoplasma pneumoniae, chlamydia pneumoniae), and bordetella pertussis, account for about 10% of cases. Pollutants (air borne chemicals or irritants) may cause acute bronchitis as well.

3.1.2- AECOPD:

Most exacerbations of COPD are caused by viral or bacterial infection. Approximately 50% of exacerbations are caused by bacterial infection. It is difficult to define precisely the proportion of exacerbations caused by viruses. A range of respiratory viruses (rhinoviruses, influenza, respiratory syncytial virus) has been shown to cause exacerbations. Potential microorganisms involved in each mild moderate and severe AECOPD are listed in table 1.

3.2- Diagnostic Testing:

3.2.1- Acute Bronchitis:

Viral cultures, serologic assays and sputum analyses should not be routinely performed except during influenza outbreak in the community or when Pertussis is suspected (Contact with suspected pertussis, or persistent paroxysms whooping cough or post-tussive vomiting). Polymerase-chain-reaction (PCR) testing of nasopharyngeal swabs or aspirates is now standard for Influenza or Pertussis diagnosis.

3.2.2- AECOPD:

Sputum cultures should not be routinely performed expect in patients with frequent exacerbations, worsening clinical status or inadequate response after 72 hours on initial empiric antibiotic, and /or exacerbation requiring mechanical ventilation.

(B) TREATMENT:

1. Acute Bronchitis:

Because acute bronchitis is most often caused by a viral infection, usually only symptomatic treatment is required. The following might help: smoking cessation, good hydration, analgesics/antipyretics, protussives and antitussives, bronchodilators or inhaled or oral corticosteroids.

- **Antibiotics**
  - Uncomplicated acute bronchitis:

    Antibiotics are not recommended in cases of uncomplicated acute bronchitis.
  - Pertussis suspects

    If pertussis is suspected, empiric antibiotic therapy (e.g. azithromycin 500 mg daily for 5 days or clarithromycin 500mg/12hours for 7 days) may be initiated while obtaining a diagnostic test for confirmation. Antibiotic treatment decreases transmission, but has little effect on symptom resolution.
  - Complicated acute bronchitis:

    Antibiotics are recommended in cases of complicated acute bronchitis. Empiric oral antibiotic therapy (Azithromycin 500 mg daily for 5 days or clarithromycin 500mg/12hours for 7 days). Patients with acute bronchitis who are likely to be at risk of developing complications include:
    - Symptoms and signs suggesting pneumonia.
    - Those at high risk of serious complications because of pre-existing comorbidities (including patients with heart, lung, renal, liver, or neuromuscular disease, immunosuppression, or cystic fibrosis).
    - Patients >65 years, if they had:
      - Hospitalization in the past year.

- Diabetes mellitus.
- Congestive heart failure.
- On steroids.

- **Antiviral therapy:**

If influenza therapy is considered according to the local guidelines during influenza outbreak in the community, it should be initiated within 48 hours of symptom onset for clinical benefit. Antiviral therapy (including oseltamivir and zanamivir) decrease the duration of symptoms by approximately 1 day and result in an earlier return to normal activity (by 0.5 day) among patients with infections caused by susceptible viruses.

2. AECOPD:

Antibiotics

- Indications for antibiotic treatment of AECOPD
  - Patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence (type I Anthonisen exacerbation).
  - Patients with only two of the above three symptoms (type II Anthonisen exacerbation) when increased purulence of sputum is one of the two cardinal symptoms.
  - Patients with a severe exacerbation that requires invasive or non-invasive mechanical ventilation.
  - Antibiotics are generally not recommended in Anthonisen type II without purulence and type III patients.

Patients with moderate or severe exacerbation of COPD (having 2 or 3 cardinal symptoms in which increased purulence of sputum is one of them) is further sub classified into uncomplicated AECOPD, complicated AECOPD or complicated AECOPD at risk for P. aeruginosa infection are illustrated in table 1.

The stratification of patients with AECOPD for antibiotic treatment and potential microorganisms involved in each group and recommended antibiotic therapy are shown in table 1.

Table 1: 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, clarithromycin) • **Cephalosporins** 2nd or 3rd generation
Complicated AECOPD: Risk factor(s) for poor outcome #	As in Uncomplicated AECOPD **plus** presence of resistant organisms (ß - lactamase producing, penicillin-resistant S. pneumoniae), Enterobacteriaceae (K. pneumoniae, E. coli, Proteus, Enterobacter, etc)	• **ß-lactam/ß-lactamase inhibitor** (Co-amoxiclav, ampicillin/ sulbactam) • **Fluoroquinolone** (Gemifloxacin, Levofloxacin, Moxifloxacin)
Complicated AECOPD: Risk factor(s) for P. aeruginosa infection*	As in complicated AECOPD plus P. aeruginosa	• **Fluoroquinolone** (Ciprofloxacin, Levofloxacin – high dose^) • **Piperacillin-tazobactam**

#Risk factors for poor outcome in patients with AECOPD: presence of comorbid diseases, severe COPD, frequent exacerbations (>3/yr), and antimicrobial use within last 3 months. P. aeruginosa should be considered in the presence of at least two of the following [recent hospitalization, frequent (>4 courses per year) or 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)].

Classes of antibiotics are provided (with specific agents in parentheses). Choice should be based on local bacteria resistance patterns. ^ Dose 750 mg/24 h effective against P. aeruginosa.

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.

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CHAPTER II

Management of Adults with Community Acquired Pneumonia (CAP)

(A) Diagnosis:

1. Definition of Community Acquired Pneumonia:

- 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.

2. The 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.
- Identify specific risk factors that can influence the likely etiologic pathogens and management.

2.1- Symptoms:

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.

2.2- Signs:

Generally: Fever, sometimes hypothermia, tachycardia, tachypnea.
Local: signs of consolidation

2.3- Exclude conditions that can mimic pneumonia:

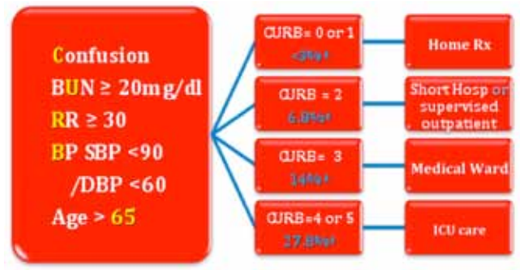
- Pulmonary infarction
- Pulmonary edema with another infection site
- Pulmonary hemorrhage
- Vasculitis
- Malignancy
- Drug toxicity
- Radiation pneumonitis
- Preexisting lung disease (e.g. fibrosing alveolitis)

2.4- Define the severity of CAP :

Assess the severity of pneumonia and site of receiving care through an objective tool for risk assessment using CURB 65 scoring system for pneumonia which consists of 5 risk factors each scores one point, for a maximum score of 5.

CURB 65 scoring system for pneumonia:

- Confusion.
- Blood urea nitrogen > 19 mg per dL.
- Respiratory rate ≥ 30 breaths per minute.
- Systolic blood pressure < 90 mm Hg or Diastolic blood pressure ≤60 mm Hg.
- Age: ≥ 65 Years.



***Risk of mortality**

Figure 1: CURB 65 scoring system for pneumonia

2.4.1- When to decide to admit CAP patient to ICU?

Table 2: CAP: severity assessment to guide ICU-admission

Major Criteria(1/2 sufficient)	
• Acute respiratory failure(mechanical ventilation)	
• Severe sepsis or septic shock(need of vasopressors)	
Minor Criteria (ICU admission recommended if ≥3)	
• Respiration rate	≥ 30/min
• PaO2:FiO2 ≤250	+/-SaO2 <90% with 6 L O2
• Multi lobar involvement	
• Confusion/ disorientation	
• Uremia	BUN ≥20 mg/dl
• Leukopenia	WBC < 4 x 109/L
• Thrombocytopenia	Tc < 100.000 / mm3
• Hypothermia	core temp< 36°
• Hypotension requiring aggressive fluid resuscitation	

2.5- Identify specific risk factors:

- History of altered conscious level e.g. epilepsy, coma,… etc.
- History suggestive of aspiration.
- Altered Immunity e.g. DM, malignancy, chemotherapy… etc

3. Radiological diagnosis of CAP:

3.1- Indication for Chest X Ray

In addition to a constellation of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia, i.e.

"No diagnosis of pneumonia without at least Chest X Ray"

The value of Chest x-ray in CAP is to establish the diagnosis, evaluate the severity (e.g. multilobar or bilateral disease may indicate severe pneumonia), identify co-existing conditions (e.g. bronchial obstruction or abscess) and identify pattern of infiltrates.

3.2- The pattern of infiltrates may suspect the causative organism

Table 3: Infiltrate patterns and pathogens

Pattern	Possible Diagnosis
Lobar	Streptococcus pneumoniae, Klebsiella pneumoniae, Haemophilus influenzae
Patchy	Atypical, viral
Interstitial	Viral, PCP, Legionella
Cavitary	Anaerobes, Klebsiella pneumoniae, Tuberculosis, Staphylococcus aureus, fungi
Large effusion	Staphylococcus aureus, anaerobes, Klebsiella pneumoniae

CT scan may assist in the diagnosis of CAP severity and help in differential diagnosis

4. Bacteriological diagnosis of CAP:

CAP is usually acquired via inhalation or aspiration of pulmonary pathogenic organisms into a lung segment or lobe. A number of pathogens can give rise to CAP:

4.1- Microorganisms:

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

4.2- How to suspect the causative organism:

Table 4: Comparison between typical and atypical CAP		
CAP	Typical	Atypical
Causative organisms	Streptococcus pneumoniae Haemophilus influenzae Moraxella catarrhalis	• Mycoplasma pneumoniae • Chlamydia pneumoniae • Legionella pneumophila
Site	Alveolar space: exudates	Interstitial space: swell& collapsing alveoli
Onset	Sudden	Gradual
Non-pulmonary symptoms headache, myalgia	Rare & mild	Common & prominent
Cough	Productive: purulent	Dry or scanty mucoid
Fever	High grade	Low grade
Pleuritic pain	Common	Rare
Physical signs	Evident	Often minimal

Table 5: Modifying risk factors that increase risk of infection with specific pathogens
Penicillin-resistant and drug resistant pneumococci: Age >65 years, B-lactam therapy within the past 3 months, alcoholism, immunosuppressive illness (including corticosteroids), multiple medical comorbidities
Legionella: Treatment with high doses of corticosteroids, neoplasms (especially hematologic) Elderly, Compromised host, Smokers.
Haemophilus influenzae: Elderly, COPD.
Pseudomonas aeruginosa: prolonged ICU stay, corticosteroid therapy (>10mg prednisolone therapy), previous antibiotic treatment (>7 days in past months), structural lung disease, malnutrition.
Enteric gram negatives: nursing home resident, underlying cardiopulmonary disease, multiple medical comorbidities, recent antibiotic therapy.
Anaerobes: Altered mental status, poor dentition, nursing home resident, alcoholism, airway obstruction, witnessed aspiration.

4.3- Diagnostic testing:

- **Outpatient setting:** Routine diagnostic tests to identify an etiologic diagnosis are optional for outpatients with CAP. Microbiological tests are not recommended.
- **Inpatient setting:** Routine diagnostic tests to identify an etiologic diagnosis are required in critically ill CAP and when specific pathogens are suspected (e.g. TB) that would likely change individual antibiotic management.

Diagnostic testing for CAP etiology may include: 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.

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.

4.3.1 Cultures to identify the causative organism:

Sputum cultures are not recommended in cases of CAP except in certain occasions:

- Patients admitted in hospital or ICU.
- Patients who do not respond to empirical antibiotic therapy.
- Suspect of resistant strains of S.pneumoniae.

4.3.2 Sputum Gram stain:

It is a rapid and inexpensive test that can help in differentiation between gram negative and positive bacteria. Hence broadens the initial empirical coverage for less common etiologies such as infection with S. aureus or gram-negative organisms. Gram stain can validate the subsequent sputum culture result (i.e. A positive Gram stain was highly predictive of a subsequent positive culture). Also excess pus cells without organism in gram stain suspect atypical infection.

4.3.3 Blood Culture:

Blood Culture is recommended for all patients with moderate and high severity CAP, preferably before antibiotic therapy is commenced.

4.3.4 Examination of sputum for Mycobacterium tuberculosis

Sputum for Mycobacterium tuberculosis should be considered for patients with a persistent productive cough, especially if malaise, weight loss or night sweats, or risk factors for tuberculosis (e.g. ethnic origin, social deprivation, elderly) are present.

(B) TREATMENT:

1. General Recommendations:

1.1- Empirical Treatment is recommended

- The start of empirical treatment should not be delayed.
- An **"Appropriate"** empirical treatment refers to the use of an antibiotic to which the possible etiological microorganism(s) are sensitive. **"Adequate"** treatment refers to the use of an appropriate antibiotic at the correct dosage, with good penetration at the site of the infection and, when indicated, in a combination.
- In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class.
- **Factors taken in consideration before selection of empirical antibiotic therapy:**
  - Antibiotic taken in last 3 months.
  - Ask about the history of sensitivity to any antibiotic.
  - Underlying co-morbidity to avoid or adjust dose e.g. renal impairment, liver impairment …etc.

1.2- Where to treat the patient with CAP:

- Most patients with CAP can be treated at home.
- Those who fail to improve after 48 h of treatment should be considered for hospital admission or revise diagnosis.
- Patients admitted in hospital or ICU according to assessment using CURB 65 scoring system as described before.

1.3- General management strategy for patients treated in the community

- Patients with suspected CAP should be advised to rest, to drink plenty of fluids and not to smoke.
- Patients diagnosed with CAP should be isolated and take precautions of infection control.
- Pleuritic pain & Fever should be relieved using simple analgesia such as paracetamol.

2. Recommendations for the Empirical Treatment:

- **Outpatient treatment:**
  Oral Respiratory Fluroquinolones
  OR Oral B-Lactam/ B-Lactamase + Oral New Macrolide
  OR IM 3rd Generation Cephalosporin + Oral New Macrolide
- **In-patient treatment: Non-ICU:**
  Intravenous (IV)Respiratory fluoroquinolone
  OR IV B-Lactam/ B-Lactamase + IV New Macrolide
  OR IV 3rd Generation Cephalosporin + IV New Macrolide
- **In-patient treatment: ICU: No Monotheapy.**
  IV Respiratory fluoroquinolone + 3rd or 4th generation cephalosporin OR IV Imipenem + IV New Macrolide
- **Special entities in ICU:**
  - Aspiration:
    As Before + i.v. Clindamycin OR Metronidazole
  - Risk of Pseudomonas Infection:
    Antipseudomonal beta-lactam (3rd or 4th generation cephalosporin OR Piperacillin-tazobactam OR carbapenem)
    Plus (aminoglycoside OR antipseudomonal fluoroquinolone)

- **For community-acquired methicillin-resistant Staphylococcus aureus infection (MRSA):**

  Add Teicoplanin OR linezolid

  Alternative: Vancomycin (considering its renal side effects)

- Recommended adult doses and intervals for the main oral antibiotics recommended in the treatment for CAP are shown in table 6. For intravenous route see table 7.

Table 6: Recommended Adult Doses and Intervals for the Main Oral Antibiotics Recommended in the Treatment for CAP

Group	Antibiotic	Dose	Interval
Respiratory Fluoroquinolone	Levofloxacin	750mg	Every 24h
	Gemifloxacin	320 mg	Every 24 h
	Moxifloxacin	400 mg	Every 24 h
B-Lactam/ B-Lactamase	Amoxicillin/ Clavulanate	1g	Every 8-12 h
New Macrolide	Azithromycin	500 mg	Every 24 h
	Clarithromycin	500 mg	Every 12 h

Table 7: Recommended Adult Doses and Intervals for the Main parenteral Antibiotics Recommended in the Treatment for CAP

Antibiotic	Dose	Interval	Perfusion Time
Levofloxacin	500mg	Every12 h*	½–1 h
Amoxicillin/ Clavulanate	1200mg	Every 6-8 h	½–1 h
Ampicillin/ Sulbactam	1.5-3gm (IV)	Every 6 h	½–1 h
Ceftriaxone	1 g (IV/IM)	Every 12 h	½–1 h
Azithromycin	500 mg	Every 24 h	1-2 h
Clarithromycin	500 mg	Every 12 h	1-2 h
Ceftazidime	2 g	Every 8 h	2–3 h
Cefepime	2 g	Every 8 h	2–3 h
Imipenem	500 mg to 1 g	Every 6–8 h	2–3 h
Meropenem	500 mg to 1 g	Every 6–8 h	2–3 h
Ertapenem	1g	Every24 h	½–1 h
Piperacillin-tazobactam	4.5 g	Every 6 h	2–3 h
Amikacin	15 mg/kg	Every 24h	½–1 h
Gentamicin	7 mg/kg	Every 24h	½–1 h
Ciprofloxacin	400 mg	Every 8 h	½ h
Vancomycin	15 mg/kg	Every 12 h	1–3 h
Linezolid	600 mg	Every 12 h	1 h
Teicoplanin	Loading dose: 400 mg	Every 12 h for the first three doses	½ h
	Maintenance dose: 400 mg	Every 24 h	½ h
Clindamycin	600 mg	Every 8 h	
Metronidazole	500 mg	Every 8 h	

Dosages are based on normal renal and hepatic function.
*Administer this dose for 3 days and then continue with 500 mg every 24 h.

3. Switching from intravenous to oral:

- Patients treated initially with parenteral antibiotics should be transferred to an oral regimen when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract.
- Patients should be discharged as soon as they are clinically stable (table 8), have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is not necessary.

Table 8: Criteria for clinical stability

Temperature≤37.8_C
Heart rate ≤100 beats/min
Respiratory rate≤24 breaths/min
Systolic blood pressure ≥90 mm Hg
Arterial oxygen saturation ≥90% or pO2 ≥60 mm Hg on room air
Ability to maintain oral intake*
Normal mental status*

* Important for discharge or oral switch decision but not necessarily for determination of non response.

4. Duration of the Treatment:

- Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 8) before discontinuation of therapy.

- For patients managed in the community and for most patients admitted to hospital with low or moderate severity and uncomplicated pneumonia, 7 days of appropriate antibiotics is recommended. For those with high severity microbiologically-undefined pneumonia, 7–10 days of treatment is proposed.
- A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection.

(C) NON RESPONDING PNEUMONIA

- Non responding pneumonia is used to define 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). Table 9 shows the pattern for evaluating non response to antibiotic treatment of CAP.
- Two patterns of unacceptable response are seen in hospitalized patients. The first is progressive pneumonia or actual clinical deterioration, with acute respiratory failure requiring ventilatory support and/or septic shock, usually occurring within the first 72 h of hospital admission and it is often related to intercurrent complications, deterioration in underlying disease, or development of nosocomial superinfection. The second pattern is that of persistent or non responding pneumonia. Non response can be defined as absence of or delay in achieving clinical stability. Concern regarding non response should be tempered before 72 h of therapy. Antibiotic changes during this period should be considered only for patients with deterioration or in whom new culture data or epidemiologic clues suggest alternative etiologies.
- Non resolving or slow-resolving pneumonia has been used to refer to the conditions of patients who present with persistence of pulmonary infiltrates >30 days after initial pneumonia- like syndrome.

Table 9 : Patterns and etiologies of types of failure to respond

- **Failure to improve**
  - **Early (<72 h of treatment)**
    - Normal response
  - **Delayed(>72 h of treatment)**
    - Resistant microorganism
      - Uncovered pathogen
      - Inappropriate by sensitivity
    - Parapneumonic effusion/empyema
    - Nosocomial superinfection
      - Nosocomial pneumonia
      - Extrapulmonary
    - Noninfectious
      - Complication of pneumonia (e.g. Bronchiolitis obliterans organizing pneumonia [BOOP])
      - Misdiagnosis: pulmonary embolus, congestive heart failure, vasculitis
      - Drug fever
- **Deterioration or progression**
  - **Early <72 h of treatment)**
    - Severity of illness at presentation
    - Resistant microorganism
      - Uncovered pathogen
      - Inappropriate by sensitivity
    - Metastatic infection
      - Empyema/parapneumonic
      - Endocarditis, meningitis, arthritis
    - Inaccurate diagnosis
      - Pulmonary embolus, aspiration, acute respiratory distress syndrome
      - Vasculitis (e.g. systemic lupus erythematosis)
  - **Delayed(>72 h of treatment)**
    - Nosocomial superinfection
      - Nosocomial pneumonia
      - Extrapulmonary
    - Exacerbation of comorbid illness
    - Intercurrent noninfectious disease
      - Pulmonary embolus
      - Myocardial infarction
      - Renal failure

(D) Common complications of CAP

1. Pleural effusion and empyema:

Parapneumonic effusions develop in 36–57% of bacterial pneumonias admitted to hospital and can be the cause of persisting pyrexia despite adequate antibiotic treatment.
The presence of bilateral pleural effusions in CAP is associated with increased mortality.

- **Recommendation:**
  - -Early thoracocentesis is indicated for all patients with a parapneumonic effusion.
  - -Those found to have an empyema or clear pleural fluid with pH 7.2 should have early and effective pleural fluid drainage.

2. Lung abscess:

Lung abscess is a rare complication of CAP, being seen most commonly in the debilitated or alcoholic patient and following aspiration.
Infection with anaerobic bacteria, S. aureus, Gram negative enteric bacilli or Streptococcus milleri (in the presence of poor dental hygiene) should be considered.

- **Recommendation:**
  - A prolonged course of antibiotics may be required, and the optimum duration of antimicrobial therapy is assessed according to the clinical, radiological and lab response.
  - Early surgical intervention may occasionally be needed.

3. Metastatic infection:

- -Patients with septicaemia associated with pneumonia may occasionally develop metastatic infection as Meningitis, peritonitis, endocarditis and septic arthritis.
- -Purulent pericarditis can occur, usually in direct relation to an empyema.
- -Most of such complications can be detected by careful history and examination.

(E) Prevention and vaccination:

1. Influenza and pneumococcal vaccination.

The prevention of CAP, particularly in those considered at high risk of infection, is an important issue in the overall management. All patients aged 65 years or at risk of invasive pneumococcal disease who are admitted with CAP and who have not previously received pneumococcal vaccine should receive 23-polyvalent pneumococcal polysaccharide vaccine (23-PPV). Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the fall and winter.

2. Smoking cessation

Cigarette smoking, both active and passive, is a recognized independent risk factor for CAP. Smoking cessation should be a goal for persons hospitalized with CAP who smoke.

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CHAPTER III

Management of Adults with Hospital-acquired pneumonia, Ventilator-associated pneumonia, Ventilator associated tracheobronchitis and Healthcare-associated pneumonia

(A) DIAGNOSIS:

1. Definitions:

Hospital-acquired pneumonia (HAP) (nosocomial pneumonia):
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):
VAP is defined as a type of HAP that develops >48 h after endotracheal intubation.
Ventilator-associated tracheobronchitis (VAT):
VAT is defined as the presence of all of the following in a patient endotracheally intubated and receiving mechanical ventilation for > 48 hours: body temperature > 38.3 °C or < 36.0 °C, new or increased purulent tracheal secretions, positive culture of tracheal secretions at a concentration • of ≥ 10^5 cfu/ml, and no new or progressive infiltrate on portable chest radiograph.
Health care–associated pneumonia (HCAP):
A relatively new clinical entity, is defined as pneumonia that occurs in a non hospitalized patient with extensive health care contact, as defined by 1 of the following modes:

- Intravenous therapy (including antibiotics), wound care, or intravenous chemotherapy during the prior 30 days,
- Residence in a nursing home or other long-term care facility,
- Hospitalization in an acute care hospital for 2 days or more during the prior 90 days, or
- Attendance at a hospital or hemodialysis clinic during the prior 30 days.

Time of onset:

Early-onset HAP and VAP is defined when HAP and VAP occurs within the first 4 days of hospitalization.

Late-onset HAP and VAP is defined when HAP and VAP occurs on the 5th day or more from hospitalization.

Early onset HAP and VAP tends to carry a better prognosis than does late-onset HAP and VAP; the latter tends to be associated with multidrug resistant (MDR) organisms and so is characterized by higher mortality rates.

2. The clinical diagnosis of HAP, VAP & HCAP

The clinical diagnosis of HAP and VAP is difficult and there are no universally accepted clinical criteria.

All patients should have a **full medical history** obtained and undergo physical examination in order to define the severity of HAP, to exclude other potential sources of infection, and to identify specific risk factors that can influence the likely etiologic pathogens.

Arterial oxygen saturation should be measured in all patients to determine the need for supplemental oxygen. Arterial blood gases should be determined if concern exists regarding either metabolic or respiratory acidosis, and this generally needed to manage patients who require mechanical ventilation. Other **laboratory studies** (complete blood count, serum electrolytes, renal and liver function), can point to the presence of multiple organ dysfunctions and thus help define the severity of illness.

A diagnostic **thoracentesis** to rule out a complicating empyema or parapneumonic effusion should be performed if the patient has a large pleural effusion or if the patient with a pleural effusion appears toxic.

2.1- Criteria for clinical diagnosis of pneumonia

It is recognized when there is a **new or progressive**

radiographic pulmonary infiltrate and **2 of the following signs or symptoms:** fever, leukocytosis, purulent sputum.

For patients suffering from ARDS and for whom it is difficult to demonstrate deterioration of radiological images, at least one of the three preceding may suffice to activate initial screening.

2.2- Conditions that can mimic pneumonia

HAP and/or VAP should be differentiated from other conditions that can mimic pneumonia such as pulmonary infarction, adult respiratory distress syndrome, pulmonary edema with another infection site, pulmonary hemorrhage, vasculitis, malignancy, drug toxicity, radiation pneumonitis and preexisting lung disease (e.g. fibrosing alveolitis).

2.3- Severe Pneumonia

Patients with pneumonia were further defined as having severe pneumonia by admission to the ICU and any one of the following conditions: (1) shock defined as systolic BP of < 90 mm Hg or diastolic BP of < 60 mm Hg; (2) respiratory failure (ie, mechanical ventilation or the need for a fraction of inspired oxygen of > 0.35 to maintain an oxygen saturation of > 90%; (3) requirement of vasopressor therapy for > 4 h; (4) 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; (5) acute renal failure requiring dialysis; or (6) rapid radiographic progression, multilobar pneumonia, or cavitation of a lung infiltrate.

2.4- The clinical pulmonary infection score

With the aim to improve the sensitivity and the specificity of the diagnosis of pneumonia. The modified Clinical Pulmonary Infection Score (CPIS) (Table 10) was developed as a predictor scale for diagnosis of pneumonia. It evaluates a series of parameters (temperature, leukocyte count, appearance of respiratory secretions, oxygenation, chest radiography, Gram stain and tracheal aspiration culture). Scores higher than 6 were associated with the diagnosis of pneumonia in the original series, where the sensitivity and specificity were 93% and 100%, respectively. CPIS score of <6 indicate low likelihood of pneumonia.

Table 10: THE MODIFIED CLINICAL PULMONARY INFECTION SCORE(CPIS) *

Criteria	0	1	2
Tracheal secretions	None	purulent	Abundant and purulent
Infiltrates on chest radiography	No	Diffuse	Localized
Temperature, ºC	≥36.5 and ≤38.4	≥38.5 or ≤38.9	≥39 or ≤36
Leukocytes	≥4000 and≤11 000	<4000 or >11 000	<4000 or >11 000 + bands >50% or >500
PaO2/FiO2	>240 or ARDS		≤240 without ARDS
Microbiology	Negative		Positive

CPIS is made up of 6 items with a score ranging from 0 to 12. A score of more than six is considered suggestive of pneumonia.

CPIS of 6 or less for 3 days may be an objective criterion to select patients at low risk for early discontinuation of empiric treatment. CPIS may be useful for monitoring response to treatment.

3. The radiological diagnosis of HAP, VAP & HCAP

There is little available evidence to assess the value of imaging investigations in the diagnosis of HAP and VAP.

The diagnostic value of CXR is usually greater in HAP than VAP, because of the problems of performing mobile radiographic investigations on ventilated patients who cannot be moved and because of other cardiothoracic co-morbidities often present in such patients.

CT can be useful as an additional diagnostic tool to exclude other pathology in a patient with a complex CXR.

It is recommended that when a diagnosis of HAP or VAP is being considered, a good quality CXR should be obtained and compared with previous CXRs if available. The CXR can help to define the severity of pneumonia (multilobar or not) and the presence of complications, such as effusions or cavitation.

CT scanning may assist in the differential diagnosis of HAP or VAP and may guide management in patients who are not responding to treatment and who have a complex CXR.

4. The bacteriological diagnosis of HAP, VAP & HCAP

4.1- Microorganisms

Bacteria cause most cases of HAP, VAP, and HCAP and many infections are polymicrobial; rates are especially high in patients with ARDS.

HAP, VAP, and HCAP are commonly caused by aerobic gram-negative bacilli, such as Pseudomonas aeruginosa (P. aeruginosa), Klebsiella pneumoniae (K. pneumoniae), and Acinetobacter species, or by gram-positive cocci, such as Staphylococcus aureus (S. aureus), much of which is Methicillin-resistant Staphylococcus aureus (MRSA); anaerobes are an uncommon cause of VAP.

Early-onset HAP or VAP is often caused by Streptococcus pneumoniae, Haemophilus influenzae, Methicillin-sensitive Staphylococcus aureus, Antibiotic-sensitive enteric gram-negative bacilli (Escherichia coli, K. pneumoniae, Enterobacter species, Proteus species, Serratia marcescens).

Late-onset HAP or VAP is commonly caused by MDR pathogens [P. aeruginosa, K. pneumoniae (ESBL- Extended-spectrum beta-lactamase), Acinetobacter species, MRSA] and Legionella pneumophila (L. pneumophila).

Rates of L. pneumophila vary considerably between hospitals and disease occurs more commonly with when the water supply is colonized or there is ongoing construction.

Nosocomial virus and fungal infections are uncommon causes of HAP and VAP in immunocompetent patients. Outbreaks of influenza have occurred sporadically and risk of infection can be substantially reduced with widespread effective infection control, vaccination, and use of antiinfluenza agents.

The prevalence of MDR pathogens varies by patient population, hospital, and type of ICU, which underscores the need for local surveillance data.

MDR pathogens are more common in patients with severe, chronic underlying disease, those with risk factors for HCAP, and patients with late-onset HAP or VAP.

4.2- Blood cultures

The overall sensitivity of blood cultures is less than 25% in VAP, and when positive, organisms isolated from the blood are not necessarily those causing VAP. They may originate from an extrapulmonary source. **Blood culture should not be routinely performed to all patients, but it should be preserved to those who are unresponsive to the initial therapy.**

4.3- LRT secretions sampling:

A fresh specimen from lower respiratory tract secretions should be submitted from all patients at time of clinical diagnosis of suspected HAP, VAP or HCAP before initiating antibiotic treatment.

Samples are preferably analyzed within 2–4 h, but can be kept at 4°C up to 24 h if needed. The microbiological investigation of HAP, VAP or HCAP may include gram stain, qualitative and quantitative culture of respiratory secretions.

4.3.1- Invasive versus Non-invasive LRT secretions sampling:

Samples can be obtained through bronchoscopy-directed methods (invasive) e.g. bronchoscopy-directed bronchoalveolar lavage (BAL), bronchoscopy-directed protected specimen brush (PSB) and non-bronchoscopic 'blind' techniques (non-invasive) e.g. mini-BAL and endotracheal tube aspirate (ETA). Sputum may be used to obtain samples in non- intubated patients.

Invasive diagnostic techniques are not essential or routinely recommended. It is recommend that the least expensive, least invasive method requiring minimal expertise be used for microbiological diagnosis.

4.3.2-Quantitative microbiology:

- The use of quantitative culture techniques is more favorable over qualitative culture of respiratory secretions to guide appropriate antibiotic choices.

It is recommended to use quantitative cultures whenever possible.

4.3.3- Direct Microbiological Testing:

- A reliably performed Gram stain of tracheal aspirates is recommended as it can be used to guide initial empiric antibiotic therapy.
- Intracellular organisms in polymorphs in respiratory specimens can be visualized microscopically by a variety of staining methods. The quantification of such 'infected' cells has been proposed as a rapid method for the diagnosis of pneumonia. The determination in BAL of more than 2% of intracellular microorganisms has a positive predictive value of close to 100%. There is a need to initiate the use of this technique in our hospital practice as it is rapid and specific test and can also be used as a guide to initial therapy.

(B) Treatment:

1. General Recommendations

In patients with suspicion for HAP and VAP, the samples for microbiological studies should be collected as soon as possible. Meanwhile, however, the start of empirical treatment should not be delayed due to the need for performing diagnostic studies. Delays in the initiation of appropriate antibiotic therapy can increase the mortality of VAP.

A fundamental aspect at this moment is to ensure that initial treatment is appropriate and adequate. An **"appropriate"** empirical treatment refers to the use of an antibiotic to which the possible etiological microorganism(s) are sensitive. **"Adequate"** treatment refers to the use of an appropriate antibiotic at the correct dosage, with good penetration at the site of the infection and, when indicated, in a combination.

It is of vital importance to know the local patterns of microbiology and drug resistance that are present in the hospital where the patient is being treated.

Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay pneumonia begun.

Inappropriate therapy (failure of the etiologic pathogen to be sensitive to the administered antibiotic) is a major risk factor for excess mortality and length of stay for patients with HAP, and antibiotic-resistant organisms are the pathogens most commonly associated with inappropriate therapy.

In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.

The following factors should be taken in consideration in all patients before selection of empirical antibiotic therapy (Table 11). Identification of patients with risk factors for MDR pathogens is crucial as one of the key decisions in initial empiric therapy depends whether the patient has risk factors for MDR organisms. Table 12 shows the risk factors for MDR pathogens causing HAP, HCAP and VAP.

Empiric antibiotic therapy is not started when there is low clinical suspicious of pneumonia together with negative microscopy of LRT sample.

Algorithm for initiating empiric antibiotic therapy for HAP, VAP and HCAP is shown in figure 2.

Table 11: Factors taken in consideration before selection of empirical antibiotic therapy

- Risk factors for Multidrug-Resistant (MDR) pathogens
- Time of onset (early or late)
- Local microbiological data and resistance patterns
- Patient status
- LRT sampling gram stain
- Allergy to medication
- Underlying comorbidities
- Formulary restriction
- Cost

Table 12: Risk Factors for Multidrug-Resistant Pathogens causing HAP, HCAP and VAP

- Antimicrobial therapy in preceding 90 d.
- Current hospitalization of 5 d or more.
- High frequency of antibiotic resistance in the community or in the specific hospital unit.
- Presence of risk factors for HCAP:

  Hospitalization for 2 d or more in the preceding 90 d
  Residence in a nursing home or extended care facility
  Home infusion therapy (including antibiotics)
  Chronic dialysis within 30 d
  Home wound care
  Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy.

Specific risk factors

- Pseudomonas aeruginosa: prolonged ICU stay, corticosteroid therapy, previous antibiotic treatment, structural lung disease.
- Staphylococcus aureus: coma, craneoencephalic trauma, diabetes mellitus, renal failure.
- Methicillin-resistant Staphylococcus aureus (MRSA): previous MRSA colonization, prolonged hospital stay, previous antibiotic consumption, undergone invasive procedures (e.g. surgery, catheters, intravascular devices), weakened immune system, severe illness.
- Streptococcus pneumoniae: previous use of antibiotics in the last three months, contact with children with respiratory infections
- Legionella: treatment with high doses of corticosteroids, neoplasms (especially hematologic).
- Anaerobes: recent abdominal surgery, witnessed aspiration.

Modified from the ATS Guidelines, 2005, Modified from Campbell et al., 1996

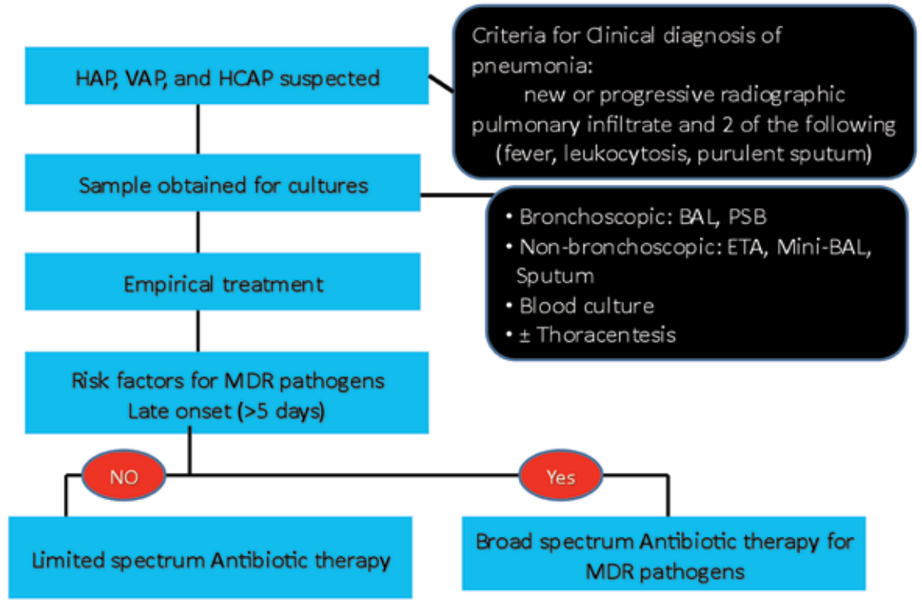

Figure 2: Algorithm for initiating empiric antibiotic therapy for HAP, VAP and HCAP

2. Stratification of the Patients and Recommendations for Empirical Treatment

Two main factors that determine the type of antibiotics to be administered are the time that the patient has been hospitalized, classifying the pneumonia as early onset (<5 days) or late onset (≥5 days), and the presence of risk factors for infection by potentially MDR pathogens (Table 13).

In patients with early-onset HAP or VAP and without risk factors for MDR pathogens, the treatment should cover pathogens that are generally found in the community and with low probability of multi-resistance (Limited spectrum antibiotic therapy) (Table 13).

On the contrary, patients with late-onset HAP or VAP or with presence of risk factors for MDR pathogens should receive a wide (Broad) -spectrum initial empirical treatment, administered in combination in order to guarantee the coverage of the majority of causal microorganisms in this group of patients (Table 14). The objective of the use of combined treatment is to find the synergy between different antibiotic groups, widening the spectrum to ensure an appropriate treatment against Gram-negative microorganisms, and avoid the development of resistance. Both the antibiotic dose and the recommended intervals are shown in Table 15.

Table 13: Initial Empiric Intravenous Antibiotic therapy for HAP or VAP in patients with no risk factors for MDR pathogens, Early-onset and Any Stage of Severity

Probable Microorganisms	Recommended Antibiotic*
Streptococcus pneumoniae Haemophilus influenzae Staphylococcus aureus sensitive to methicillin Gram-negative enteric bacilli Escherichia coli Klebsiella pneumoniae Enterobacter spp. Proteus spp. Serratia marcescens	3rd generation Cephalosporin Or Levofloxacin Or Ertapenem

* See Table 6 for proper initial doses of antibiotics.

Table 14: Initial Empiric Intravenous Antibiotic Therapy for HAP, HCAP or VAP in patients with Late-onset or risk factors for MDR pathogens and Any Stage of Severity

Probable Microorganisms	Recommended Antibiotic*
Pathogens listed in Table 13 and MDR pathogens Pseudomonas aeruginosa Klebsiella pneumoniae (ESBL⁺)# Acinetobacter species# Methicillin-resistant Staphylococcus aureus (MRSA) Legionella pneumophila#	Antipseudomonal cephalosporin (Ceftazidime or Cefepime) or Carbapenem (Imipenem, Meropenem) or β-Lactam/ β-lactamase inhibitor (Piperacillin-tazobactam) Plus Antipseudomonal fluoroquinolone# (Ciprofloxacin, Levofloxacin) or Aminoglycoside (Amikacin, Gentamicin) Plus Teicoplanin or Vancomycin or Linezolid ‡

* See Table 15 for proper initial doses of antibiotics.

If an ESBL+ strain, such as K. pneumoniae, or an Acinetobacter species is suspected, a carbapenem is a reliable choice. If L. pneumophila is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or Levofloxacin) should be used rather than an aminoglycoside.

‡ If MRSA risk factors are present or there is a high incidence locally.

Table 15: Recommended Adult Doses and Intervals for the Main Intravenous Antibiotics Recommended in the Treatment for HAP, HCAP and VAP

Antibiotic	Dose	Interval	Perfusion Time
Ceftriaxone	1 g	Every 12 h	½–1 h
Ceftazidime	2 g	Every 8 h	2–3 h
Cefepime	2 g	Every 8 h	2–3 h
Imipenem	500 mg to 1 g	Every 6–8 h	2–3 h
Meropenem	500 mg to 1 g	Every 6–8 h	2–3 h
Ertapenem	1g	Every24 h	½–1 h
Piperacillin-tazobactam	4.5 g	Every 6 h	2–3 h
Amikacin	15 mg/kg	Every 24h	½–1 h
Gentamicin	7 mg/kg	Every 24h	½–1 h
Levofloxacin	500mg	Every12 h*	½–1 h
Ciprofloxacin	400 mg	Every 8 h	½ h
Vancomycin	15 mg/kg	Every 12 h	1–3 h
Linezolid	600 mg	Every 12 h	1 h
Teicoplanin	Loading dose: 400 mg Maintenance dose: 400 mg	Every 12 h for the first three doses Every 24 h	½ h ½ h

Dosages are based on normal renal and hepatic function. *Administer this dose for 3 days and then continue with 500 mg every 24 h.

3. Duration of the Treatment:

It is recommended to limit the treatment to 7–10 days in early pneumonia provided that the patient has a good clinical response with resolution of clinical features of infection. Lengthening of therapy to a minimum of 14 days is recommended in cases of late pneumonia, especially those caused by multi-resistant bacteria, both Gram-negative (Pseudomonas aeruginosa, Acinetobacter baumanii) as well as Gram-positive (MRSA).

4. De-escalation:

De-escalation or reduction therapy consists of a reduction in the spectrum or number of antibiotics based on the results of microbiological cultures. In various studies, this strategy has achieved a decrease in the use of antibiotics, without a significant increase in the rate of recurrences or mortality.

5. Combination versus Monotherapy:

Combination therapy should be used if patients are likely to be infected with **MDR pathogens.** No data have documented the superiority of this approach compared with monotherapy, except to enhance the likelihood of initially appropriate empiric therapy.

If patients receive combination therapy with an aminoglycoside-containing regimen, the aminoglycoside can be stopped after 5–7 days in responding patients.

Monotherapy with selected agents can be used for patients with severe HAP and VAP in the absence of resistant pathogens. Patients in this risk group should initially receive combination therapy until the results of lower respiratory tract cultures are known and confirm that a single agent can be used.

6. Switching from intravenous to oral:

Initial therapy should be administered to all patients intravenously, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable agents, such as the quinolones and linezolid, may be easily switched to oral therapy in such patients.

7. Local Instillation and Aerosolized Antibiotics:

Aerosolized antibiotics have not been proven to have value in the therapy of VAP. However, they may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy.

If antibiotics are to be given by the endotracheal (ET) route, instillation through an ET tube, as opposed to nebulization, is the preferred route of administration.

8. Specific Antibiotic Regimens

The recommended treatments against specific antibiotic resistant pathogens are outlined in Table 16.

8.1- P. aeruginosa pneumonia:

If P. aeruginosa pneumonia is documented, combination therapy is recommended. The principal justification is the high frequency of development of resistance on monotherapy. Although combination therapy will not necessarily prevent the development of resistance, combination therapy is more likely to avoid inappropriate and ineffective treatment of patients.

8.2- Acinetobacter species:

If Acinetobacter species are documented to be present, the most active agents are the sulbactam, carbapenem, colistin, and polymyxin. There are no data documenting an improved outcome if these organisms are treated with a combination regimen. Tigecycline is a new treatment choice against antimicrobial activity against MDR (including carbapenem-resistant) Acinetobacter species. Tigecycline is administered via intravenous infusions over 30-60 minutes. The initial dose is 100 mg followed by 50 mg every 12 hours. The most common side effects of tigecycline are diarrhea, nausea and vomiting.

8.3- ESBL+ Escherichia coli and Klebsiella pneumoniae

If ESBL+ Enterobacteriaceae (e.g. ESBL+ Escherichia coli and K. pneumoniae) are isolated, then monotherapy with a third-generation cephalosporin should be avoided. The most active agents are the carbapenems. Piperacillin-tazobactam could be an alternative choice.

8.4- MRSA

Teicoplanin or vancomycin is recommended as first-line treatment for MRSA. Vancomycin therapy requires careful monitoring of blood levels; side effects include nephrotoxicity and ototoxicity. Teicoplanin has fewer side effects and does not require monitoring of serum levels.

Linezolid should be reserved as a second-stage agent (after vancomycin and teicoplanin), to avoid the selection of resistant strains, which would lead to loss of this valuable agent.

9. Antibiotic Heterogeneity and Antibiotic Cycling

Antibiotic restriction can limit epidemics of infection with specific resistant pathogens. Heterogeneity of antibiotic prescriptions, including formal antibiotic cycling, may be able to reduce the overall frequency of antibiotic resistance. However, the long-term impact of this practice is unknown.

10. Response to Empirical Treatment

10.1- Modification of Empiric Antibiotic Regimens

Empiric antibiotics may need modification once the results of blood or respiratory tract cultures become available in conjunction with serial assessment of clinical parameters (Figure 3).

Table 16: Antibiotic regimen against specific antibiotic resistant pathogens

Probable Microorganisms	Recommended Antibiotic*
Pseudomonas aeruginosa	Antipseudomonal beta-lactam (third or fourth generation cephalosporin or Piperacillin-tazobactam or carbapenem) plus (aminoglycoside or antipseudomonal fluoroquinolone)
Acinetobacter*	Cefoperazone-sulbactam or carbapenem or Tigecycline^
ESBL⁺ Escherichia coli and K. pneumoniae*	Carbapenem or Piperacillin-tazobactam
Methicillin-resistant Staphylococcus aureus (MRSA)	Teicoplanin or Vancomycin or Linezolid

* There are no data documenting an improved outcome if this organism are treated with a combination regimen
ESBL+ Extended-spectrum beta-lactamase. ^Tigecycline: for more details see text

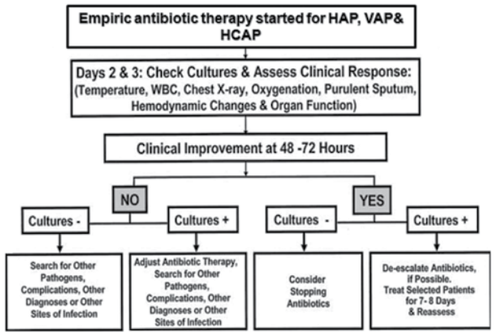

Figure 3: Modification of Empiric Antibiotic Regimens

10.2- Normal Pattern of Resolution

Resolution of HAP can be defined either clinically or microbiologically. The **clinical improvement** generally becomes evident in the first 48–72 h of treatment; therefore, the antimicrobial treatment should not be changed during this period, unless progressive deterioration is observed or the initial cultures indicate it. Serial cultures of respiratory samples can establish the **microbiological response.** These can define microbial eradication, superinfection, recurrent infection and persistence. It is recommendable to repeat the microbiological cultures 72 h after initiating treatment, as there is a good correlation between clinical failure and isolation of pathogens at significant concentrations in the follow-up. Together with microbiology, the **most reliable parameters for defining the resolution of HAP are leukocyte count, oxygenation and central temperature**. In patients with adequate initial treatment, these parameters improve during the first week of treatment. There is also a good correlation between the evolution of the Clinical Pulmonary Infection Score (CPIS) (Table 1) in the first 3 days of treatment with regards to the adequacy of the empirical treatment and survival.

The **radiological resolution** has limited value. An initial radiological deterioration is common, especially in patients with bacteriemia or highly virulent organisms. Furthermore, the radiological improvement is usually slower than the clinical parameters. Nevertheless, an increase higher than 50% of the size of the infiltrate after 48 h, with multi-lobar affectation, cavitation or significant pleural effusion, should be considered a sign of alarm.

It has been proposed to define the **lack of response to empirical treatment** according to one of the following criteria in the first 72 h of treatment: (1) no improvement in oxygenation or need for tracheal intubation; (2) persistence of fever or hypothermia together with purulent secretions; (3) increase in radiological lung infiltrates ≥50%; or (4) appearance of septic shock or multi-organ dysfunction.

10.3- Causes of Deterioration or Lack of Response to Empirical Treatment

There are many possible causes of a rapid deterioration or absence of improvement (Table 17). For patients who are deteriorating rapidly or not responding to initial therapy. Diagnostic testing should be directed to whichever of these causes is likely.

Table 17 : Possible Causes for the Lack of Clinical Response to Initial Antibiotic Treatment

Microorganisms or Antibiotics	Other Infections	Non-infectious	Host Factors
Inadequate antibiotic choice or combination	Sinusitis	Acute respiratory distress syndrome	Prolonged mechanical ventilation
Low dose or levels of antibiotics	Sepsis associated with the catheter	Atelectasis	Severe respiratory insufficiency
Resistance to antibiotics	Abdominal sepsis	Cryptogenic organizing pneumonia	Chronic pulmonary disease
Microorganisms outside the usual spectrum	Lung abscesses	Pulmonary hemorrhage	Advanced age
Superinfection	Pleural effusion/ empyema	Pulmonary embolism–infarction	Increased systemic inflammatory response
	Urinary sepsis	Heart failure Lung contusion Edema after lung resection Fever due to drugs	

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