Severe Community-Acquired Pneumonia

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A 58-years-old male, smoker (8 pack-years) and having Diabetes mellitus and Hypertension for 8 years, presented to the ED with fever and acute dyspnoea for the last 48 h. On examination, respiratory rate was 34 breaths/min, blood pressure-150/96 mm Hg, heart rate-112/min, regular, and Oxygen saturation of 86% on 4L of oxygen by mask. He was conscious and oriented. His chest X-ray showed left lower zone consolidation.

Community Acquired Pneumonia (CAP) is one of the leading causes of hospitalization and morbidity and mortality. Of all patients presenting with CAP, only about 18% require hospitalization, of which 2–24% require intensive care unit (ICU) care. Mortality in hospitalized patients is 17–49%.

Step 1: Initiate Resuscitation

1. Airway patency is ensured.
2. If $SpO_2 < 90\%$ or $PaO_2 < 60$ mmHg, Oxygen therapy or HFNC is started. If hypoxemia persists despite maximal O_2 therapy, hypercapnea progresses, or if there is severe acidosis, the patient is transferred immediately to the ICU.

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3. Assess the volume status (invasive and/or non-invasive hemodynamic monitoring) and administer IV fluids and/or vasopressors as needed.

Step 2: Assess Severity of CAP and Risk Stratification

1. **Severity assessment:** The severity of CAP is assessed according to the various severity scores e.g. Pneumonia severity index (PSI), CURB-65, CRB-65, 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for ICU admission for CAP
   (a) Pneumonia severity index (PSI): It has moderate to good accuracy in predicting the 30 day mortality in patients with CAP. Points are given for age, gender, co-morbid illness, physical examination findings, ABG analysis, blood chemistry, hematocrit and chest X-ray findings and score is calculated. Patients are classified as PSI I to V according to their final score with mortality ranging from 0.1% to 27% respectively. It has superior ability to detect low risk patients. PSI I & II can be managed as an outpatient whereas IV and V needs hospitalisation
   (b) CURB-65: It consists of 5 core elements (new onset **C**onfusion, **U**rea > 20 mg/dl, **R**R > 30 bpm, S**B**P < 90 mmHg or DBP < 60 mmHg, Age **65** years or older, 1 point each for a total of 5). CURB 65 of 0 can be managed as outpatient, CURB 65 1&2 generally require ward treatment and a score of 3 or more warrants inpatient and aggressive treatment, usually in the ICU. It has superior ability to detect high risk patients. A simpler version of this score the CRB-65, does away with urea measurement without losing it effectiveness to detect high risk patients. Some studies have suggested an age group of ≥ 80 years (CRB-80) to have better predictability for mortality.
   (c) 2007 ATS/IDSA criteria for ICU admission for CAP: It consists of 2 major (invasive mechanical ventilation, septic shock requiring vasopressors) and 9 minor criteria (confusion, RR > 30 bpm, PaO_2/FiO_2 ratio < 249, multilobar infiltrates, BUN>20 mg/dL, WBC < 4000/mm^3, platelet count<1,000,000/mm^3, temperature < 36 °C, hypotension requiring fluid resuscitation). Presence of 1 major or 3 minor criterion requires admission to ICU. It has the ability to predict ICU admission with 84% sensitivity and 78% specificity.

Step 3: Start Empiric Antibiotics

The principles of therapy for severe CAP are:

1. Early initiation of antibiotic therapy even as the initial resuscitative measures are ongoing should be the aim as it improves mortality. Those patients of severe CAP admitted through the emergency department (ED) should receive the first dose of antibiotic in the ED itself.
2. Blood and sputum cultures should be sent for antibiotic sensitivity testing before starting antibiotics but this should not delay the initiation of antibiotic therapy.

3. The initial choice of antibiotic will depend on a detailed and in-depth history with particular emphasis on identifying etiology of CAP (see Table 12.1) and whether the patient is at risk for infection with drug resistant organisms (see Table 12.2).
4. The initial choices of antibiotics in patient with no risk factors are:
   (a) A Beta-lactam/Beta lactamase inhibitor (Amoxicillin-clavulanate, Ampicillin-sulbactum, OR a cephalosporin (Cefuroxime, Cefotaxime, Ceftriaxone) plus a Macrolide (Azithromycin, Clarithromycin)/Doxycycline/respiratory Fluoroquinolone (Levofloxacin, Moxifloxacin).
   OR
   (b) A Beta-lactam (Amoxicillin-clavulanate, Ampicillin-sulbactum, Cefuroxime, Cefotaxime, Ceftriaxone) plus Aztreonam (for patients with penicillin allergy).

Table 12.1 Etiology of severe community acquired pneumonia

Bacteria
Streptococcus pneumonia, Legionella pneumophilus, Staphylococcus aureus (methicillin-sensitive S. aureus), Gram-negative bacilli (ESBL or non-ESBL), Haemophilus influenzae, Moraxella catarrhalis Pseudomonas spp., Community-acquired methicillin-resistant S. aureus (MRSA), Others-Mycoplasma pneumoniae, Coxiella burnetti, Chlamydia spp.
Viruses
Influenza A (including H1N1) and B viruses, Rhinovirus, Parainfluenza virus, Human metapneumovirus, Respiratory syncytial virus, Middle East Respiratory Syndrome corona virus (MERS CoV)
Unknown

Table 12.2 Factors present in patients at risk for infection with drug resistant organisms

Hospitalization for >48 h in previous 9 months
Antibiotics use in last 3 months
Resident of Nursing Home or long term treatment facility
Family member residing with patient diagnosed with multi-drug resistant pathogen
Home wound care or recent domiciliary infusion therapy
Acute or chronic comorbidities Hepatic failure, Renal failure or chronic dialysis, Chronic Obstructive Pulmonary Disease (Class C-D GOLD), Cardiac failure, Diabetes mellitus, Asplenia
Use of steroids and/or immunosuppressive drugs

5. The initial choices of antibiotics in patient with risk factors for infection with drug resistant organisms are mentioned below.
   (a) Pseudomonas or Extended spectrum beta- lactamase (ESBL) producing organisms are suspected—antipneumococcal, antipseudomonal Beta-lactam (Piperacillin-tazobactam, Cefepime/Ceftazidime/Avibactam /Cefoperazone sulbactam) or Carbapenem (Imipenem, Meropenem) plus antipseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin)/Doxycycline /Macrolide OR.
   Antipneumococcal, antipseudomonal Beta-lactam (Piperacillin-tazobactam, Cefepime) plus Aminoglycoside (Amikacin) plus Macrolide (Azithromycin, Clarithromycin)/antipseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin)/Doxycycline.
   [Replace beta-lactam with Aztreonam in patients with penicillin allergy].
   (b) Multi-drug resistant Pseudomonas aeruginosa is suspected- Give Colistin.
   (c) Suspicion of MRSA—Add Vancomycin or Linezolid.
   (d) In persons with risk of aspiration (CVA, seizures, dysphagia, vomiting, head or neck cancer)—Add Metronidazole or Clindamycin.
6. Antibiotics which have been started should cover common microorganisms causing pneumonia (both typical and atypical organisms covered), should be used parenterally and in adequate dose and frequency, keeping in mind pharmacokinetics and pharmacodynamics of the drug. Continuous/extended intravenous infusions of antibiotics may be used, where appropriate. Follow the antibiotic policy of the hospital, if present. The above antibiotics may be tailored according to local sensitivity pattern of the organisms.

Step 4: Investigations

The following investigations are sent simultaneously with resuscitation and empirical antibiotic initiation (see Table 12.3):

Step 5: Supportive Therapy

1. Severe CAP associated with septic shock and multi-organ dysfunction/failure should be treated according to appropriate Surviving Sepsis guidelines.
2. In patients with COPD or Bronchial asthma, aerosolised bronchodilators should be used as and when required, in adequate doses and frequency.
3. Non-invasive Ventilation (NIV): NIV is tried cautiously in patients with hypoxemia and increased work of breathing (respiratory distress), especially those with COPD or bronchial asthma. These patients are closely monitored and if no improvement is apparent after 2 h, may be intubated and mechanically ventilated. Patients with severe hypoxemia or bilateral/multilobar infiltrates and having respiratory distress should receive immediate invasive mechanical ventilation.

Table 12.3 Investigations in patients with severe CAP

General investigations	
Complete blood cell count	– Increased WBC count suggests an infective process, while neutrophilic predominance (especially in presence of immature neutrophils) suggests bacterial infection – A significantly elevated (>20,000/mm^3) WBC count or presence of leucopenia (<4000/mm^3) may suggest severe disease. – Hematocrit is used for severity scoring
Blood culture-(2-3samples from different sites)	Recommended by guidelines in all patients with severe CAP – Minimum 20 ml of blood should be sent
C-reactive protein (CRP)	– In appropriate clinical scenario, a positive CRP (>100 mg/L) on admission, is a sensitive and specific marker for pneumonia – Serial monitoring for measuring response to treatment (Failure of CRP to reduce <50% within 4 days of initiation of treatment suggests failure of treatment or onset of complications like empyema)
Procalcitonin	Similar to CRP
Renal function tests (Blood urea, serum creatinine and electrolytes)	– Used in severity scoring and to assess underlying comorbid conditions – Chronic renal failure is a significant risk factor for mortality in patients with severe CAP
Liver function test with prothrombin time and international normalised ratio (INR)	– Liver failure is a risk factor for infection with drug resistant organisms – Pulmonary complications of pneumococcal pneumonia are more common in patients with chronic liver disease
Blood glucose levels	For detecting hyperglycemia
Arterial blood gas, lactate	– Used for severity scoring and determining adequacy of tissue perfusion – Used for initiation and monitoring of mechanical ventilation
Urine for microscopy and Pneumococcal and Legionella antigen test	– Antigen testing to be done if available
Electrocardiogram	– For cardiac status
Radiology	
Chest X-ray	– To be obtained in all patients – Usually pa view and occasionally lateral view – Presence of a new infiltrate gives definitive diagnosis of pneumonia – Used for severity scoring – Single lobar consolidation (usually lower lobe) is commonly seen – Lobar consolidation in the upper lobe is commonly seen in klebsiella pneumonia – Multilobar consolidation is commonly seen is legionella, severe pneumococcal or staphylococcal pneumonia
Echocardiogram	– To be done if patient has septic shock or IHD

(continued)

Table 12.3 (continued)

Microbiology	
Sputum-gram stain	– Aids in identification of the causative agent – May help to broaden initial antibiotic coverage for less common micro-organisms – Validates results of sputum culture
Sputum-aerobic culture and sensitivity (C&S)	– Aids in treatment – Therapy may be de-escalated accordingly
Urine for Legionella antigen, pneumococcal antigen (if available)	– Aids in identification of the causative agent
PCR or serology for Mycoplasma, Respiratory syncytial virus and Legionella	– Done, where appropriate, to identify causative organism and direct therapy

4. Steroids: Patients with vasopressor resistant shock are given low dose intravenous steroids. Patients with COPD or Bronchial asthma on oral steroids are continued on equivalent intravenous doses of steroids. The routine use of corticosteroids as an adjunctive therapy for severe CAP with brisk inflammatory response has been suggested by some RCTs and meta-analyses but as per the latest guidelines, it is not recommended. Steroids should be used only in the presence of septic shock not responding to vasopressor therapy, as per the surviving sepsis guidelines.

   Avoid steroid in patients with Viral and Aspergillus pneumonia, Immunosuppressed host and Uncontrolled diabetic.
5. Patients with severe CAP should receive routine supportive ICU measures.

Step 6: Non-Responders

On institution of appropriate antibiotic therapy, improvement in clinical course of the patient is apparent within 3 days, as assessed clinically by Halm's clinical stability criteria [temperature ≤ 37.8 °C, heart rate ≤ 100 bpm, respiratory rate ≤ 24 bpm, SBP ≥90 mmHg, O_2 saturation ≥ 90%, or arterial O_2 tension ≥60 (on room air), normal mental status, and normal oral intake) or simplified ATS criteria [improvement in cough and dyspnea, absence of fever (>37.8 °C) for >8 h, normalisation of total leukocyte count by 10% from the previous day, and adequate oral intake]. An associated improvement in biomarkers (CRP reduction <50%, reduction in procalcitonin) will also act as a guide to response.

Patients who do not show the expected clinical response within the expected timeline are labelled as non-responders. The reasons for non-response may be:

1. Infection related causes:
   (a) Treatment failure: It is defined as persistence /progression of pneumonia resulting in need for mechanical ventilation or development of septic shock. This may be early (within 72 h) or late (after 72 h). It may be due to various reasons as mentioned below:

- Infection by pathogens not covered by initial empiric therapy,
- Infection with atypical pathogens (tuberculosis, strongyloidosis, influenza H1N1 virus),
- Nosocomial secondary infections, iv) infectious complications (parapneumonic effusions, empyema, lung abscess, bronchial obstruction).

(b) Slow responders: These patients are improving with therapy, but at a rate slower than expected. Old Age, presence of co-morbidities, severe infections (with organisms like Gram negative bacilli, Legionella, Staphylococcus aureus) are predictors of slow response. Eight or nine days of treatment may be needed before clinical improvement is noted .

2. Non infectious causes:
   (a) Malignancy (lung cancer or metastatic),
   (b) Interstitial lung disease [Cryptogenic organising pneumonia, Diffuse alveolar damage, Hypersensitivity pneumonia, Eosinophilic pneumonia, Alveolar hemorrhage, Drug fever, Vasculitis (Churg-Strauss, Wegener's)],
   (c) Foreign body,
   (d) Pulmonary embolism Pulmonary infarct,
   (e) Pulmonary edema,
   (f) Lipoid pneumonia.

Step 7: Further Workup for Non-Responders

1. Fibreoptic Bronchoscopy with analysis of BAL.
2. Endotracheal aspirate culture (preferably quantitative) and sensitivity.
3. Serology for HIV, Influenza A virus (H1N1), Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody.
4. BNP and pro-BNP levels.
5. D-dimer levels, Venous Doppler of lower limbs.
6. Ultrasonography of the Chest/Computed tomography of the Chest-demonstrates presence of effusion, empyema or abscess and their localisation.

Step 8: Duration of Antibiotics

1. The duration of therapy depends on the clinical response, organism involved, co-morbidities present, biomarker response and presence of complications.
2. Patients with severe CAP should be treated for a minimum of 5 days and generally for 7–10 days. Patient should be afebrile for 48–72 h, and should be clinically stable before discontinuation of therapy.
3. The duration of antibiotics may be prolonged (upto 14 days) in slow responders, infections with Pseudomonas, Gram negative bacilli or Staphylococcus, presence of complications like lung abscess or empyema and presence of extra- pulmonary and metastatic infections (meningitis, endocarditis) secondary to the severe CAP.

Step 9: Key Preventive Measures

Smoking cessation, Influenza and Pneumococcal Vaccination.

Suggested Reading

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Websites

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