Pharmacotherapy 2

Lower Respiratory Tract Infections

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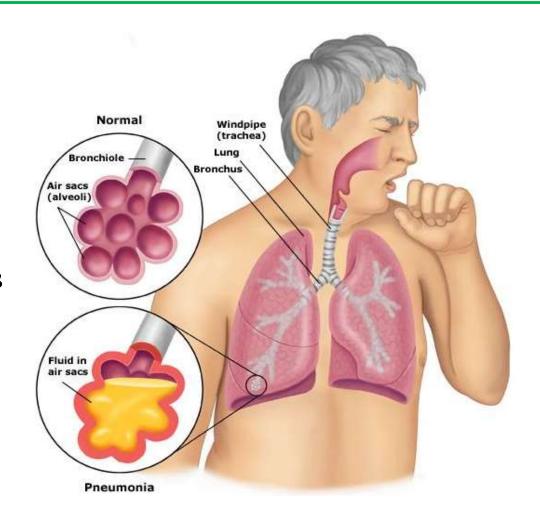
Community-Acquired Pneumonia (CAP)

General Principles

- ✓ Predominant organism: S. pneumoniae; other bacterial etiologies: H. influenzae & M. catarrhalis.
- ✓ In Jordan, S. pneumoniae and atypical microorganisms are the most common cause of CAP in previously healthy adults; while in those with associated co morbid illness, gram negative organisms are the likely cause. In children, atypical microorganisms are the most common.

 Ref: Al-Ali MK, Batchoun RG, Al-Nour TM. Etiology of community-acquired pneumonia in hospitalized patients

in Jordan. Saudi Med J. 2006 Jun; 27(6):813-6. PMID: 16758041.



✓ According to the latest WHO data published in 2018 Influenza and Pneumonia Deaths in Jordan reached 1,253 or 3.78% of total deaths.

- ✓ Pneumonia caused by atypical agents, such as Legionella pneumophila, C. pneumoniae, or M. pneumoniae, cannot be reliably distinguished clinically.
 ✓ Community-acquired MRSA is an important cause of severe, necrotizing pneumonia.
- ✓ Patients aged 65 or older, and those with certain medical conditions, should receive the pneumococcal vaccination.
- ✓ Influenza and other respiratory viruses may also cause pneumonia in adults.

TABLE 125-5 Pneumonia Classifications and Risk Factors

Type of Pneumonia	Definition	Risk Factors
Community-acquired pneumonia (CAP)	Pneumonia developing outside the hospital or < 48 hours after hospital admission	 Age >65 years Diabetes mellitus Asplenia Chronic cardiovascular, pulmonary, renal, and/or liver disease Smoking and/or alcohol abuse
Hospital-acquired pneumonia (HAP)	Pneumonia developing >48 hours after hospital admission	 Witnessed aspiration COPD, ARDS, or coma Administration of antacids, H₂-antagonists, or proton pump inhibitor Supine position Enteral nutrition, nasogastric tube Reintubation, tracheostomy, or patient transport Head trauma, ICP monitoring Age >60 years MDR risk (eg, MRSA, MDR <i>Pseudomonas</i>) if IV antibiotic use within 90 days
Ventilator-associated pneumonia (VAP)	Pneumonia developing >48 hours after endotracheal intubation	 Same as hospital acquired MDR risk with IV antibiotics in past 90 days, septic shock, ARDS preceding VAP, acute renal replacement therapy preceding VAP, or 5 + days of hospitalization preceding VAP

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; ICP, intracranial pressure; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; VAP, ventilator-associated pneumonia.

Diagnosis

- ✓ Clinical Presentation:
 - The presentation of CAP is extremely variable.
 - Fever and respiratory symptoms, including cough with sputum production, dyspnea, and pleuritic chest pain, are common in immunocompetent patients.
 - Signs include tachypnea, rales, or evidence of consolidation on auscultation.
 - CAP presents acutely, over a matter of hours to days.
 - The clinical manifestations are most severe in the very young, the elderly & the chronically ill.

TABLE 125-7 Clinical Presentation of Pneumonia

Signs and symptoms

Abrupt onset of fever, chills, dyspnea, and productive cough

Rust-colored sputum or hemoptysis

Pleuritic chest pain

Dyspnea

Physical examination

Tachypnea and tachycardia

Duliness to percussion

Increased tactile fremitus, whisper pectoriloquy, and egophony

Chest wall retractions and grunting respirations

Diminished breath sounds over affected area

Inspiratory crackles during lung expansion

Chest radiograph

Dense lobar or segmental infiltrate

Laboratory tests

Leukocytosis with predominance of polymorphonuclear cells Low oxygen saturation on arterial blood gas or pulse oximetry

✓ Diagnostic Testing:

- Sputum Gram stain and culture of an adequate sputum sample and blood cultures before antibiotic therapy should be obtained in all patients who are going to be hospitalized, and, if disease is severe.
- Urinary antigen tests for S. pneumoniae and L. pneumophila
- Nasopharyngeal swab for influenza or other virus detection by PCR, and respiratory samples for atypical pathogens should be sent in selected cases.
- Chest radiography should be performed.

Treatment

- ✓ All patients should be assessed for hospitalization & evaluated for comorbid factors, oxygenation & severity of illness using validated severity scales as the Pneumonia Severity Index or CURB-65.
- ✓ For CURB-65, patients receive 1 point for each criterion present: Confusion, Uremia (BUN > 20 mg/dL [7.1 mmol/L]), Respiratory rate ≥ 30 breaths/min, Blood pressure (systolic < 90 mm Hg, diastolic ≤ 60 mm Hg), age ≥ 65 years.
- ✓ Patients with CURB-65 or CRB-65 scores < 2 are generally candidates for outpatient treatment.
- ✓ Patients with a score of 2 are typically admitted to the general ward of the hospital with ICU admission considered for patients with scores ≥ 3 .
- ✓ Empiric treatment regimens target the most likely pathogens within specific risk groups.
- ✓ Antibiotics should be given as soon as CAP is diagnosed, ideally within 4 hours of arrival to the hospital, as delays lead to higher mortality.

- ✓ Antibiotic therapy should be narrowed once a specific microbiologic etiology has been identified.
- ✓ Immunocompetent outpatients with no recent antibiotic exposure and no comorbidities should receive a macrolide, such as azithromycin 500 mg PO single dose followed by 250 mg PO every day for 4 more days, or doxycycline 100 mg every 12h for at least 5 days.
- ✓ Outpatients with recent antibiotic exposure or comorbidities should receive respiratory fluoroquinolone (e.g., moxifloxacin) monotherapy or a macrolide (azithromycin or clarithromycin) with high-dose amoxicillin 1 g PO every 8h for at least 5 days.
- ✓ Hospitalized patients should be treated with ceftriaxone 1 g IV every day or cefotaxime 1 g IV every 8h PLUS a macrolide (azithromycin or clarithromycin), OR monotherapy with a respiratory fluoroquinolone.
- ✓ Duration of therapy should be at least 5 days for low severity pneumonia, provided that the patient has been afebrile for > 48 hours and has demonstrated clinical improvement.
- ✓ For severe pneumonia, duration of therapy is 7 days (longer courses may be indicated)

- \checkmark In critically ill patients, the addition of azithromycin or a respiratory fluoroquinolone to a β-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) is necessary to provide coverage for L. pneumophila.
- ✓ MRSA coverage with vancomycin or linezolid should also be considered.
- ✓ If P. aeruginosa is a concern, an antipseudomonal β-lactam (cefepime, piperacillin-tazobactam, meropenem, imipenem) in combination with an antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin) is recommended.
- ✓ Once Pseudomonas has been isolated and antibiotic susceptibilities are available, monotherapy is an option.

Clinical Setting and/or Patient Characteristics	Usual Pathogens	Empirical Therapy
Outpatient/Community-Acquired		
No at-risk comorbidity (diabetes, heart/lung/liver/ renal disease, alcoholism, malignancy, asplenia) AND no antimicrobial use in past 3 months	S. pneumoniae, M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis	Macrolide ^b OR doxycycline
At-risk comorbidity (diabetes, heart/lung/liver/ renal disease, alcoholism, malignancy, aspelnia) OR immunosuppressive condition/drugs OR antimicrobial use in past 3 months	S. pneumoniae (Including drug-resistant), M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis	Antipneumococcal fluoroquinolone ^c OR β-lactam ^d + EITHER macrolide ^b OR doxycycline
Regions with more than 25% rate of macrolide- resistant <i>S. pneumoniae</i>	S. pneumoniae (including drug-resistant), M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis	Antipneumococcal fluoroquinolone c OR β -lactam $^d+$ EITHER macrolide b OR doxycyline
Inpatient/Community-Acquired		
Non-ICU	S. pneumoniae (including drug-resistant), H. influenzae, M. pneumoniae, C. pneumoniae, Legionella spp.	Antipneumococcal fluoroquinolone ^c OR β-lactam ^e + EITHER macrolide ^b OR doxycyline
ICU	S. pneumoniae (including drug-resistant), S. aureus, Legionella spp., gram-negative bacilli, H. Influenzae	$\beta \text{-lactam}^e + \text{EITHER azithromycin OR Antipneumococcal} \\ fluoroquinolone^c$
	If MRSA suspected	Add vancomycin or linezolid to above regimen
	If P. aeruginosa suspected	Antipseudomonal, antipneumococcal β-lactam ^f + EITHER (1) ciprofloxacin OR (2) levofloxacin OR (3) aminoglycoside + azithromycin OR (4) aminoglycoside + moxifloxacin
	If influenza suspected	Add oral oseltamivir or intravenous peramivir (when oral medications not possible)

Table 125-8

- **b:** Macrolide: erythromycin, clarithromycin, and azithromycin.
- **<u>c:</u>** Antipneumococcal fluoroquinolone: levofloxacin and moxifloxacin.
- <u>**d**</u>: Infectious Diseases Society of America recommended outpatient β-lactams: high-dose amoxicillin or amoxicillin/clavulanate preferred, cefpodoxime, cefuroxime, ceftriaxone (IM) alternatives.
- <u>e</u>: Infectious Diseases Society of America recommended inpatient β-lactams: ceftriaxone (IV), cefotaxime, ampicillin.
- <u>**f**</u>: Infectious Diseases Society of America recommended antipneumococcal, antipseudomonal β-lactams: piperacillin/tazobactam, cefepime, meropenem, imipenem..

TABLE 125-9	Empirical Antimicrobial Therapy for Pneumonia in Pediatric Patients ^a
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Clinical Setting and/or Patient Characteristics	Usual Pathogen(s)	Empirical Therapy
Outpatient/Community-Acquired		
<1 month	Group B Streptococcus, H. influenzae (nontypable), E. coli, S. aureus, Listeria CMV, RSV, adenovirus	Ampicillin-sulbactam, cephalosporin, ^b carbapenem ^c Ribavirin for RSV ^d
1–3 months	C. pneumoniae, possibly Ureaplasma, CMV, Pneumocystis carinii (afebrile pneumonia syndrome) S. pneumoniae, S. aureus	Macrolide/azalide, ^e trimethoprim–sulfamethoxazole Semisynthetic penicillin ^f OR cephalosporin ^g
Preschool-aged children	Viral (rhinovirus, RSV, influenza A and B, parainfluenzae, adenovirus, human metapneumovirus, coronavirus)	Antimicrobial therapy not routinely required
Previously healthy, fully immunized infants and preschool children with suspected mild– moderate bacterial CAP	S. pneumonia M. pneumoniae, other atypical	Amoxicillin, cephalosporin ^{b,g} Macrolide/azalide or fluoroquinolone
Previously healthy, fully immunized school-aged children and adolescents with mild–moderate CAP	S. pneumonia M. pneumoniae, other atypical	Amoxicillin, cephalosporin, bg or fluoroquinolone Macrolide/azalide, fluoroquinolone, or tetracycline
Moderate–severe CAP during influenza virus outbreak	Influenza A and B, other viruses	Oseltamivir or zanamivir
Inpatient/Community-Acquired		
Fully immunized infants and school-aged children	S. pneumonia CA-MRSA M. pneumoniae, C. pneumoniae	Ampicillin, penicillin G, cephalosporin ^b β-Lactam + vancomycin/clindamycin β-Lactam + macrolide/fluoroquinolone/ doxycycline

Table 125-9 continued

Not fully immunized infants and children; regions with invasive penicillin-resistant pneumococcal strains; patients with life-threatening infections

S. pneumoniae, PCN-resistant MRSA M. pneumoniae, other atypical pathogens Cephalosporin^b
Add vancomycin/clindamycin
Macrolide/azalide^e + β-lactam/doxycycline/
fluoroquinolone

- <u>a</u> See the section Selection of Antimicrobial Agents.
- **<u>b</u>** Third-generation cephalosporin: ceftriaxone and cefotaxime. Note that cephalosporins are not active against Listeria .
- **c** Carbapenem: imipenem—cilastatin and meropenem.
- **<u>d</u>** See text for details regarding possible ribavirin treatment for RSV infection.
- e Macrolide/azalide: erythromycin and clarithromycin/azithromycin.
- **<u>f</u>** Semisynthetic penicillin: nafcillin and oxacillin.
- **g** Second-generation cephalosporin: cefuroxime and cefprozil.

CAP, community-acquired pneumonia; CMV, cytomegalovirus; MRSA, methicillin resistant Staphylococcus aureus; RSV, respiratory syncytial virus.

Data from Reference 5

TABLE 125-10 Antibiotic Doses for Treatment of Bacterial Pneumonia

		Antibiotic Dose ^a		
Antibiotic Class	Antibiotic	Pediatric	Usual Adult Dose	
Penicillin	Ampicillin ± sulbactam Amoxicillin ± clavulanate ^b Piperacillin-tazobactam Penicillin	150–200 mg/kg/day IV 45–100 mg/kg/day orally 200–300 mg/kg/day IV 100,000–250,000 units/kg/day IV	2 g IV every 4–6 h (6 h if ampicillin/sulbactam) 875–2,000 mg orally twice daily 3.375–4.5 g IV every 6–8 h 12–24 million units/day in divided doses IV every 4–6 h	
Extended-spectrum cephalosporins	Ceftriaxone Cefotaxime Ceftazidime Cefepime Ceftolozane-tazobactam Ceftazidime-avibactam	50–75 mg/kg/day IV 150 mg/kg/day IV 90–150 mg/kg/day IV 100–150 mg/kg/day IV –	1–2 g IV daily 1–2 g IV every 8 h 1–2 g IV every 8 h 1–2 g IV every 6–8 h 3 g IV every 8 h 2.5 g IV every 8 h	
Monobactam	Aztreonam	90–120 mg/kg/day IV	1–2 g IV every 8 h	
Macrolide/azalide	Clarithromycin Erythromycin Azithromycin	15 orally mg/kg/day 30–50 IV or orally mg/kg/day 10 mg/kg × 1 day (× 2 days if parenteral), and then 5 mg/kg days 2–5 IV or orally	0.5–1 g orally once or twice daily 500 mg IV or orally every 6 to 8 h 500 mg × 1 day (× 2 days if parenteral), and then 250 mg days 2–5 IV or orally	
Fluoroquinolones ^c	Moxifloxacin Levofloxacin Ciprofloxacin	- 8–20 mg/kg/day IV or orally 30 mg/kg/day IV or orally	400 mg IV or orally daily 750 mg IV or orally daily 400 mg IV every 8 h / 750 mg orally twice daily	
Tetracycline ^d	Doxycycline Tetracycline HCl	2–5 mg/kg/day IV or orally 25–50 mg/kg/day orally	100 mg IV or orally twice daily –	
Aminoglycosides	Gentamicin Tobramycin Amikacin	7.5–10 mg/kg/day IV 7.5–10 mg/kg/day IV 15–20 mg/kg/day IV	7.5 mg/kg IV daily 7.5 mg/kg IV daily 15–20 mg/kg IV daily	

Table 125-10 continued

Carbapenems	Imipenem	60–100 mg/kg/day IV	500–1000 mg IV every 6 to 8 h
	Meropenem Meropenem-vaborbactam	30–60 mg/kg/day IV	500–2000 mg IV every 6 to 8 h 2 g/2 g IV every 8 h
Polymyxins	Colistin Polymyxin B	2.5–5 mg/kg/day IV 15,000–30,000 units/kg/day IV	IV: 300 mg × 1, then 150 mg daily/ Neb: 150 mg every 8 h IV: 2–2.5 mg/kg × 1, then 1.25–1.5 mg/kg every 12 h
Other	Vancomycin Linezolid Clindamycin	45–60 mg/kg/day IV 20–30 mg/kg/day IV or orally 30–40 mg/kg/day IV or orally	15–20 mg/kg IV every 8–12 h 600 mg IV or orally every 12 h 600 mg IV or orally every 8 h or 450 mg orally every 6 h

<u>a</u> Doses can be increased for more severe disease and may require modification for patients with organ dysfunction.

 $[\]underline{\textbf{b}} \text{ Higher-dose amoxicillin and amoxicillin/clavulanate (eg, 90 \text{ mg/kg/day}) are used for penicillin-resistant S. pneumoniae} \; .$

c Fluoroquinolones have been avoided for pediatric patients because of the potential for cartilage damage; however, they have been used for MDR bacterial infection safely and effectively in infants and children.

<u>d</u> Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years because of tetracycline-induced permanent tooth discoloration.

TABLE 125-11 Directed Antimicrobial Therapy for Common Pneumonia Pathogens in Adult Patients

Pathogen	Preferred Antibiotic Therapy	Alternative Antibiotic Therapy
Penicillin-susceptible S. pneumoniae (MIC \leq 2 mg/L)	Ampicillin, amoxicillin, penicillin G	Ceftriaxone, cefotaxime, macrolide, levofloxacin, moxifloxacin, doxycycline, clindamycin, vancomycin
Penicillin-resistant <i>S. pneumoniae</i> (MIC > 2 mg/L)	Ceftriaxone, cefotaxime, levofloxacin, moxifloxacin	High-dose amoxicillin (3 g/day), linezolid, clindamycin, vancomycin
Non-β-lactamase-producing H. Influenzae	Ampicillin (IV), amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
β-Lactamase-producing <i>H. influenzae</i>	Ceftriaxone, cefotaxime, ampicillin-sulbactam, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Chlamydophila pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Legionella pneumophila	Fluoroquinolone or azithromycin	Doxycycline
MSSA	Cefazolin, antistaphylococcal penicillin	Clindamycin, vancomycin
MRSA	Vancomycin, linezolid	Telavancin, ceftaroline, quinupristin/dalfopristin, clindamycin, sulfamethoxazole/trimethoprim
P. aeruginosa	Antipseudomonal β-lactam ^a or fluoroquinolone ^b based on antimicrobial susceptibility testing results. Can consider adding aminoglycoside if patient in septic shock or at high mortality risk	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Acinetobacter spp.	Carbapenem OR ampicillin-sulbactam based on antimicrobial susceptibility testing results	IV colistin or polymyxin B + Inhaled colistin for isolates resistant to all preferred therapies
Extended-spectrum β-lactamase- producing gram-negative bacilli	Carbapenem	Piperacillin-tazobactam or cefepime potential options depending on susceptibility/adequate dosing

Table 125-11 continued

Carbapenem-resistant organisms

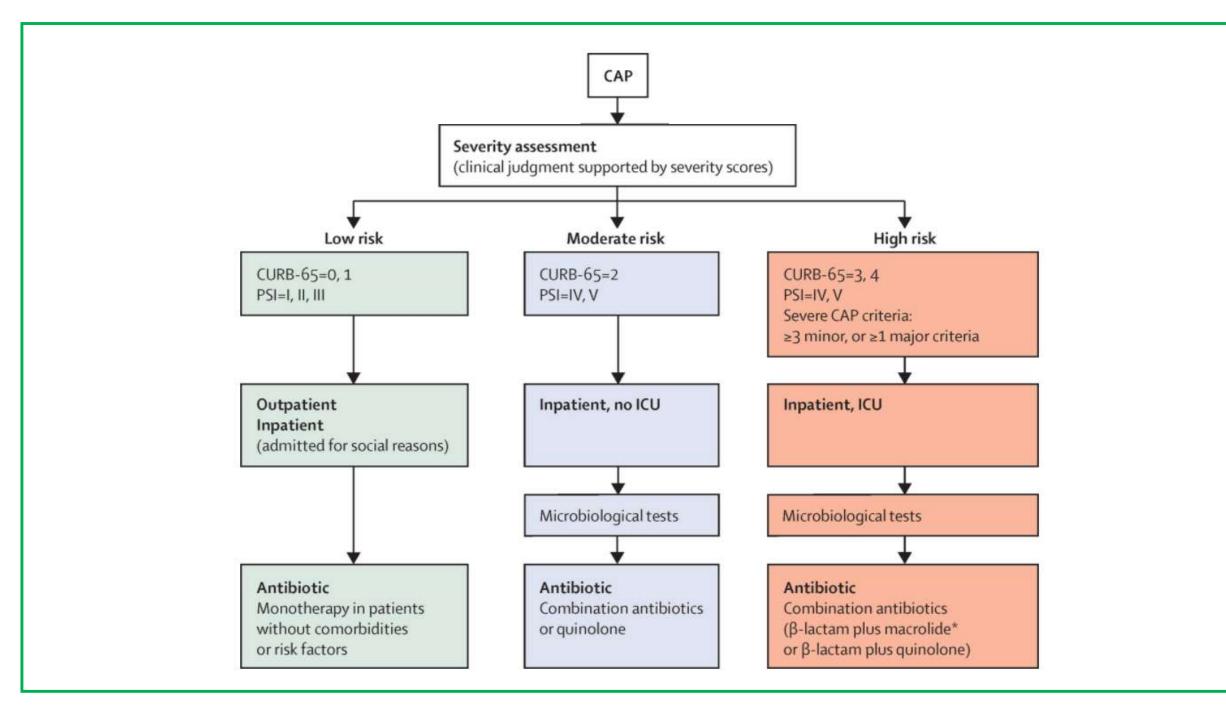
New β-lactam/β-lactamase inhibitors^c based on antimicrobial susceptibility testing OR IV colistin or polymyxin B + inhaled colistin

 $\underline{\mathbf{a}}$ Antipseudomonal β-lactam: piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem/cilastatin, doripenem, aztreonam.

<u>b</u> Antipseudomonal fluoroquinolone: ciprofloxacin and levofloxacin

 $\underline{\mathbf{c}}$ New β -lactam/ β -lactamase inhibitors: ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam.

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; PCN, penicillin.



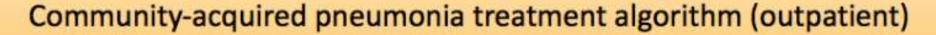
Severe pneumonia = one major criterion or 3+ minor criteria

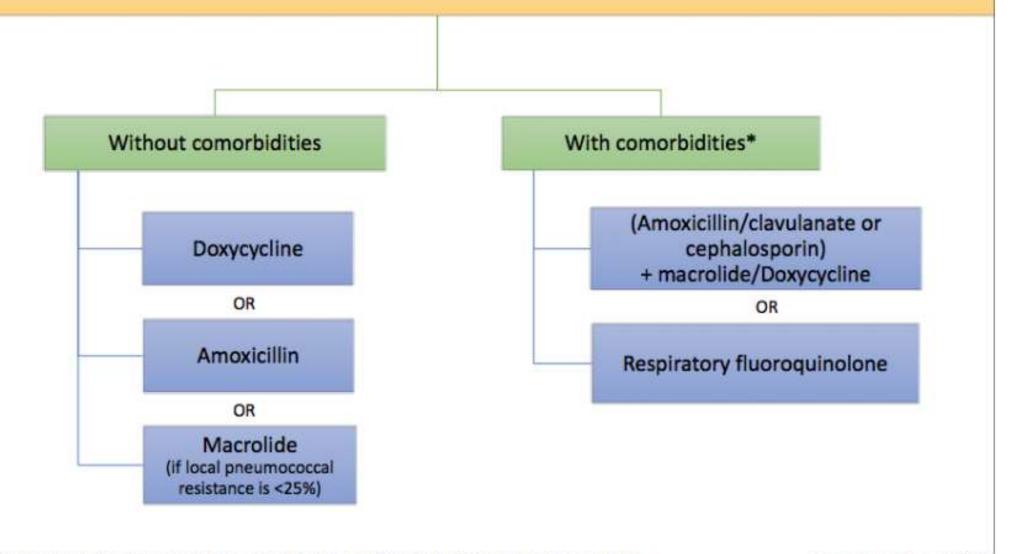
Major criteria

- Septic shock, with need for vasopressors
- · Respiratory failure requiring mechanical ventilation

Minor criteria

- Respiratory rate ≥ 30 breaths/min
- PaO2/FiO2 ratio ≤250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN≥20mg/dL)
- Leukopenia (WBC < 4,000 cells/microL)
- Thrombocytopenia (platelet <100,000/microL)
- Hypothermia (T<36C)
- · Hypotension that requires aggressive fluid resuscitation





*Comorbidities: chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcoholism; malignancy; or asplenia

Adapted from Metlay et al. 2019

