Diagnosis and management of Influenza

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NRITLD

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- Influenza is an acute viral respiratory infection that causes significant morbidity and mortality worldwide.
- Three types of influenza cause disease in humans. Influenza A is the type most responsible for causing pandemics because of its high susceptibility to antigenic variation. I
- influenza is highly contagious, and the hallmark of infection is abrupt onset of fever, cough, chills or sweats, myalgias, and malaise

- Atypical gastrointestinal symptoms such as vomiting and diarrhea can occur in children.
- A minority of patients, especially older adults, young children, and those with medical comorbidities, will experience severe disease due to viral or secondary bacterial pneumonia with respiratory and multiorgan failure

People at Increased Risk of Complications from Influenza

People with coexisting medical conditions

Any condition that may compromise the handling of respiratory secretions (e.g., neuromuscular diseases, cerebral palsy, stroke, seizure disorder, dementia)

Asthma or other chronic pulmonary disease

Chronic kidney disease

Chronic liver disease

Heart disease (acquired or congenital)

Immunosuppression (e.g., HIV infection, cancer, transplant recipients, use of immunosuppressive medications)

Long-term aspirin therapy in patients younger than 19 years

Metabolic disorders (acquired [e.g., diabetes mellitus] or inherited [e.g., mitochondrial disorders])

Morbid obesity

Sickle cell anemia and other hemoglobinopathies

Special groups

Adults 65 years and older

American Indians and Alaska Natives

Children younger than 5 years (particularly those younger than 2 years)

Institutionalized adults (e.g., residents of nursing homes or chronic care facilities)

Pregnant and postpartum women (up to 2 weeks postpartum, including pregnancy loss)

Complications of Influenza

Cardiovascular[26]

Cerebrovascular accidents

Ischemic heart disease

Myocarditis

Hematologic[26]

Hemolytic uremic syndrome

Hemophagocytic syndrome

Thrombotic thrombocytopenic purpura

Musculoskeletal[19,26]

Myositis

Rhabdomyolysis

Neurologic[26]

Acute disseminated encephalomyelitis

Encephalitis

Guillain-Barré syndrome

Postinfluenza encephalopathy (neurologic symptoms occurring after resolution but within 3 weeks of primary infection)

Reye syndrome

Ocular[26]

Conjunctivitis (most common)

Optic neuritis

Retinopathy

Uveal effusion syndrome

Pulmonary[8,25,27]

Acute respiratory distress syndrome

Diffuse alveolar hemorrhage

Hypoxic respiratory failure

Primary viral pneumonia

Secondary bacterial pneumonia

Renal[26]

Acute kidney injury (e.g., acute tubulointerstitial nephritis, glomerulonephritis, minimal change disease)

Multiorgan failure

- In outpatient and emergency department settings, testing for influenza virus is not necessary to start antiviral treatment in a patient with suspected influenza infection, especially during seasons when influenza A and B viruses are circulating in the local community.
- The diagnosis is made clinically based on presenting signs and symptoms, or if the patient has a suspected influenza-associated complication, such as exacerbation of a chronic disease, concomitant pneumonia, or rhabdomyolysis

- A symptom-only clinical prediction rule may aid clinicians in diagnosing influenza.
- It assigns 2 points for fever and cough, 2 points for myalgias, 1 point for chills or sweats, and 1 point for symptom onset within the past 48 hours.
- Patients with 2 or fewer points are at low risk of influenza, whereas those with 4 or more points are at high risk and may be considered for empiric treatment.

- According to the CDC, influenza testing can be considered when the results will modify management or when a patient with signs or symptoms of influenza is hospitalized.

- The Infectious Diseases Society of America (IDSA) suggests testing if the results will curtail the use of unnecessary antibiotics or laboratory testing, or result in prophylactic treatment of high-risk household contacts.
- A prospective study performed at a university health clinic found that rapid polymerase chain reaction testing decreased antibiotic prescriptions as well as the likelihood of the patient returning for a second visit within two weeks

Accuracy of Point-of-Care Tests for Influenza

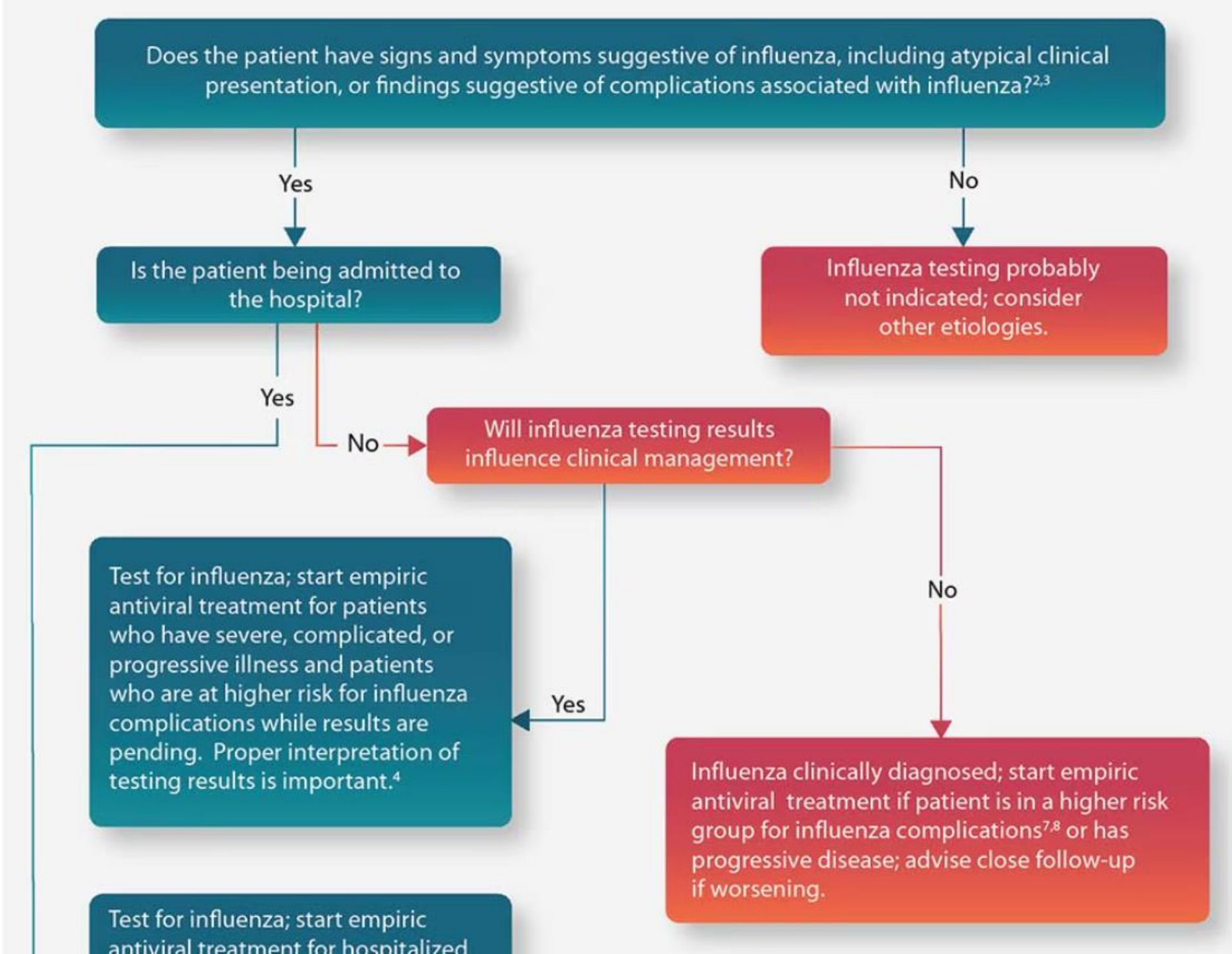
Test	Positive likelihood ratio	Negative likelihood ratio	Low prevalence (5%)		High prevalence (33%)	
			Positive predictive value (%)	Negative predictive value (%)	Positive predictive value (%)	Negative predictive value (%)
Influenza A						
Adults						
Commercially available rapid influenza tests	85	0.58	82	3	98	22
Digital immunoassays	23	0.25	55	1	92	11
Rapid nucleic acid amplification tests	44	0.13	70	1	96	6
Children						
Commercially available rapid influenza tests	76	0.39	80	2	97	16
Digital immunoassays	46	0.13	71	1	96	6
Rapid nucleic acid amplification tests	90	0.10	83	0	98	5
Influenza B						
Adults						
Commercially available rapid influenza tests	332	0.67	95	3	99	25
Digital immunoassays	47	0.44	71	2	96	18
Rapid nucleic acid amplification tests	108	0.24	85	1	98	11
Children						
Commercially available rapid influenza tests	164	0.34	90	2	99	15
Digital immunoassays	69	0.18	78	1	97	8
Rapid nucleic acid amplification tests	192	0.04	91	0	99	2

- Treatment with an anti-influenza drug is an option, with the decision to prescribe based on balancing potential benefits, harms, cost, and patient preferences

- In otherwise healthy adults and children, the clinical benefit is greatest when treatment is initiated within 24 hours of symptom onset.
- The primary benefit of treatment is a decrease in symptom duration by approximately 24 hours when treatment is initiated within 36 hours, and a reduction in disease severity

- Among adults and children with influenza in the outpatient setting who are treated with an NA inhibitor, systematic reviews of published and unpublished randomized trials found no decrease in hospitalizations or death

- However, in hospitalized adults and children, three observational studies found an association between the use of NA inhibitors and mortality benefit


Does the patient have signs and symptoms suggestive of influenza, including atypical clinical presentation, or findings suggestive of complications associated with influenza?[2,3]
Yes
No
Is the patient being admitted to the hospital?
Influenza testing probably not indicated; consider other etiologies.
Yes
No
Will influenza testing results influence clinical management?
Test for influenza; start empiric antiviral treatment for patients who have severe, complicated, or progressive illness and patients who are at higher risk for influenza complications while results are pending. Proper interpretation of testing results is important.[4]
Yes
No
Influenza clinically diagnosed; start empiric antiviral treatment if patient is in a higher risk group for influenza complications[7,8] or has progressive disease; advise close follow-up if worsening.
Test for influenza; start empiric

if worsening.

Test for influenza; start empiric antiviral treatment for hospitalized patients as soon as possible while results are pending.[4,5,6,7,8] Proper interpretation of testing results is important.[4]

- **Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who :**
- **is hospitalized**
- **has severe, complicated, or progressive illness**
- **is at higher risk for influenza complications**

- When indicated**, antiviral treatment should be started as soon as possible after illness onset**, ideally within 48 hours of symptom onset for the greatest clinical benefit
- Observational studies have reported that antiviral treatment of influenza can have clinical benefit in patients with severe, complicated or progressive illness, and in hospitalized patients when started after 48 hours of illness onset.

- **Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza**
- Clinical benefit is greatest when antiviral treatment is started as close to illness onset as possible.

- Antiviral treatment with oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir also can be considered for any previously healthy, symptomatic outpatient not at higher risk for influenza complications, who is diagnosed with confirmed or suspected influenza, on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.

- The optimal duration and dosing of antiviral treatment are uncertain for severe or complicated influenza. Treatment regimens might need to be altered to fit the clinical circumstances.
- Decisions about **extended (longer) duration of treatment** should be guided by clinical judgment in patients whose illness is prolonged.

- Critically ill patients with respiratory failure can have prolonged influenza viral replication in the lower respiratory tract and might benefit from longer duration of treatment.
- Longer treatment regimens might be necessary in immunocompromised patients who may have prolonged influenza viral replication.
- Such patients are at risk of emergence of influenza viruses with reduced susceptibility or antiviral resistance during or after antiviral

- A higher dose of oral or enterically administered oseltamivir has been recommended by some experts (e.g., 150 mg twice daily in adults with normal renal function) for treatment of influenza in **immunocompromised patients and in severely ill hospitalized patients**.

Drug/formulation	Cost*	Dosages	FDA-approved indications	Contraindications and precautions
Oseltamivir (Tamiflu), available as oral capsules or suspension	$50 to $100 ($160 to $310) depending on dosage	Adults and children 13 years and older: 75 mg 2 times per day for 5 days Children: 2 weeks to < 12 months of age (any weight): 3 mg per kg 2 times per day for 5 days < 33 lb (15 kg): 30 mg 2 times per day for 5 days 33 to 50 lb (15 to 23 kg): 45 mg 2 times per day for 5 days > 50 to 88 lb (23 to 40 kg): 60 mg orally 2 times per day for 5 days > 88 lb (40 kg): adult dosage	Prevention of influenza A and B in patients 12 months and older Treatment of uncomplicated acute influenza A and B in patients 2 weeks and older who have been symptomatic for no more than 48 hours	Contraindicated in people with serious hypersensitivity to oseltamivir or any component of the product Potential adverse effects include nausea, vomiting, and allergic reactions (e.g., rash, facial swelling) May use during pregnancy; preferred drug for influenza treatment; consider increased dose in pregnant women who are hospitalized with influenza complications; risk of embryo-fetal toxicity not expected based on human data
Zanamivir (Relenza), available as powder for inhalation Intravenous formulation available only as an emergency investigative new drug	NA ($65)	Adults and children 7 years and older: 10 mg 2 times per day for 5 days (2 doses should be taken on the first day of treatment, provided there is at least 2 hours between doses; on subsequent days, doses should be about 12 hours apart at approximately the same time each day)	Prevention of influenza A and B in patients 5 years and older Treatment of uncomplicated acute influenza A and B in patients 7 years and older who have been symptomatic for no more than 48 hours	Contraindicated in people with milk allergy, underlying reactive airway disease (e.g., asthma, chronic obstructive pulmonary disease), or history of allergic reaction to zanamivir or any component of the product Potential adverse effects include headaches, diarrhea, nausea, vomiting, allergic reaction, nasal symptoms, bronchitis, cough, sinusitis, dizziness, fever, chills, arthralgia, and articular rheumatism; serious and sometimes fatal cases of bronchospasm have occurred May use during pregnancy; risk of embryo-fetal toxicity not expected based on human data

Drug/formulation	Cost*	Dosages	FDA-approved indications	Contraindications and precautions
Peramivir (Rapivab), available as solution for injection	$1,000	Adults and children 13 years and older: single dose of 600 mg Children 2 to 12 years of age: single dose of 12 mg per kg (up to 600 mg)	Treatment of uncomplicated acute influenza A and B in patients 2 years and older who have been symptomatic for no more than 48 hours	Contraindicated in people with serious hypersensitivity or anaphylaxis to peramivir or any component of the product Potential adverse effects include diarrhea, nausea, vomiting, and neutropenia Weigh risks and benefits during pregnancy; no human data available; no known risk of embryo-fetal toxicity based on animal data at 8 times the recommended human dose; possible risk of embryo-fetal toxicity with continuous intravenous infusion based on limited animal data
Baloxavir (Xofluza), available as oral tablets	NA ($160)	Adults and children 12 years and older: 88 to 174 lb (40 to 79 kg): single dose of 40 mg ≥ 175 lb (80 kg): single dose of 80 mg	Treatment of uncomplicated acute influenza in patients 12 years and older who have been symptomatic for no more than 48 hours	Contraindicated in people with a history of hypersensitivity to baloxavir or any component of the product Potential adverse effects include diarrhea, bronchitis, nasopharyngitis, headache, and nausea Avoid use during pregnancy; no human data available; no known risk of fetal harm based on animal data at 5 and 7 times the maximum recommended human dose

Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended for Use in	Adverse Events
Oral Oseltamivir	Influenza A and B	Treatment	Any age[1]	N/A	**Adverse events:** nausea, vomiting, headache. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events[2]
		Chemo-prophylaxis	3 months and older[1]	N/A	

- The CDC and the IDSA recommend antiviral therapy for patients with severe or progressive illness, who are at high risk of influenza-associated complications, or who are hospitalized.
- Although early treatment is most beneficial, treatment should be initiated in these patients regardless of symptom duration

- The IDSA also recommends that treatment be considered for household contacts of people at high risk of influenza-associated complication

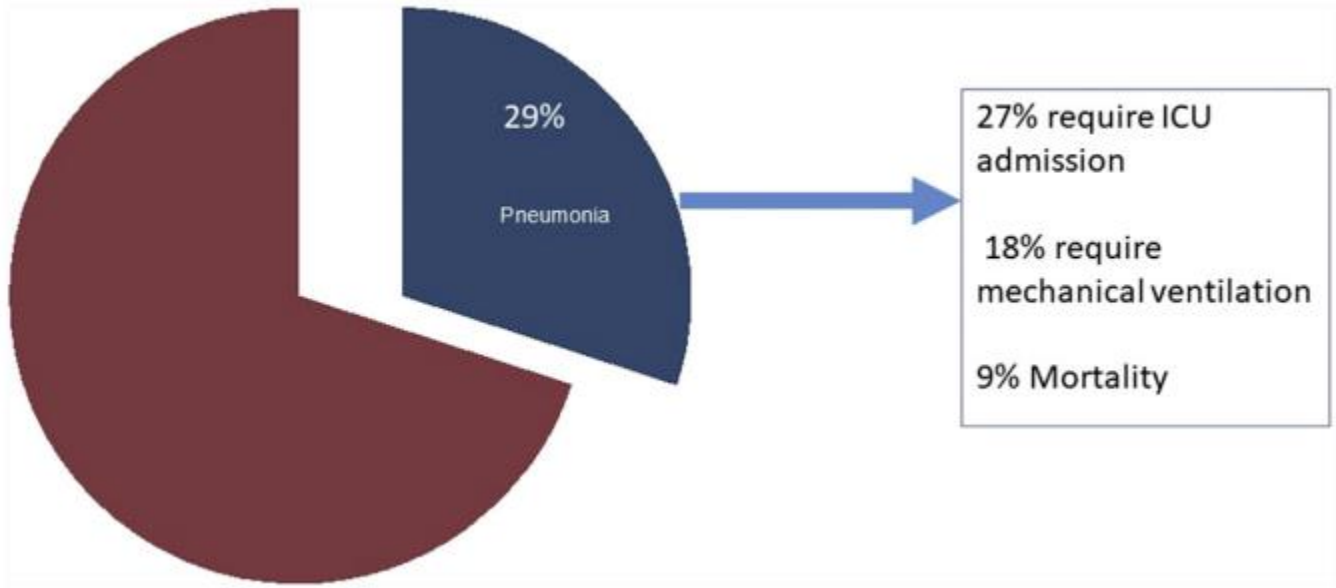
- Oseltamivir is the preferred treatment for patients with severe influenza.
- Intravenous peramivir is an option for these patients if there are contraindications to or concerns about reduced bioavailability of oral oseltamivir.
- Inhaled zanamivir is not recommended for patients with severe disease because it has not been well studied.
- It is contraindicated in patients requiring mechanical ventilation and in those with underlying lung disease because of the risk of bronchospasm

- Adamantanes (amantadine and rimantadine [Flumadine]) are approved for influenza treatment but are not currently recommended.
- These medications are not active against influenza B, and most influenza A strains have shown adamantane resistance for the past 10 years

- There is no demonstrated benefit to treating patients with more than one antiviral agent or using higher than recommended dosages
- However, extended treatment courses may be indicated in critically ill patients.
- Supportive treatment and management of complications, including potential secondary bacterial pneumonia, are paramount

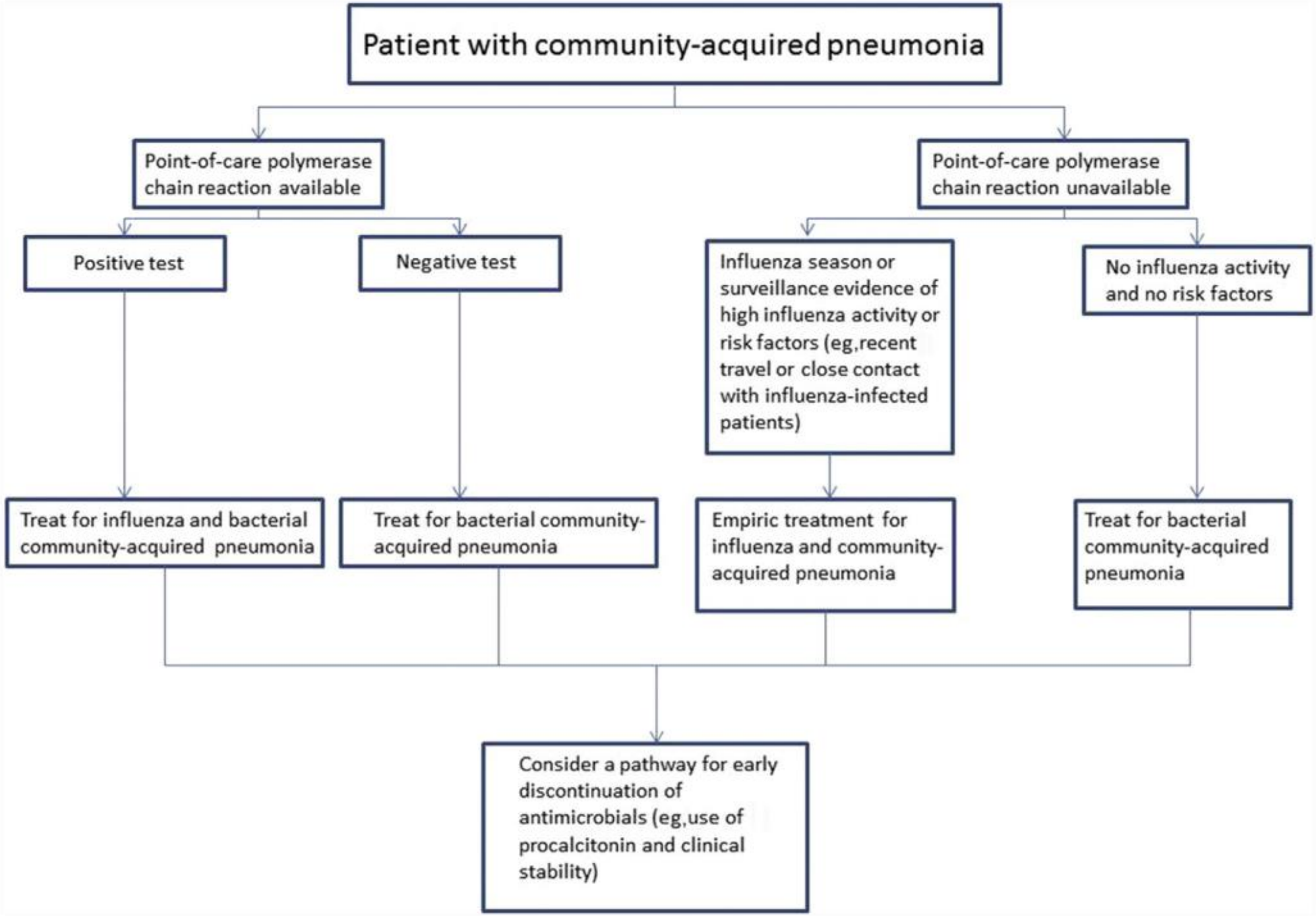
- Corticosteroids are not recommended unless the patient has another approved indication for their use.
- Treatment resistance should be considered in patients who take antivirals and develop lower respiratory tract disease, although this is less likely than natural disease progression and more common in immunosuppressed patients

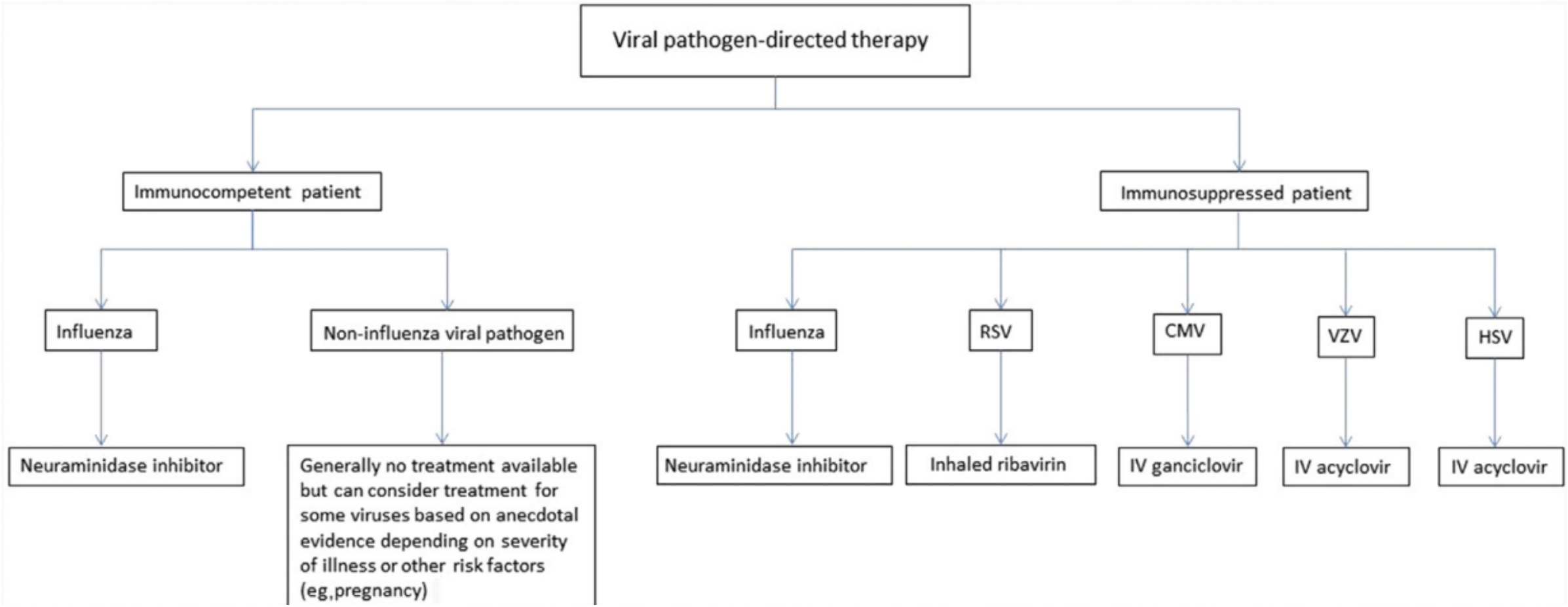
- Pregnancy is an independent risk factor for complicated influenza. The risk of maternal death increases with each trimester and continues for four weeks postpartum.
- Oseltamivir has good safety data in pregnancy, and the CDC recommends it as first-line treatment for pregnant women. No change in dosing is necessary.

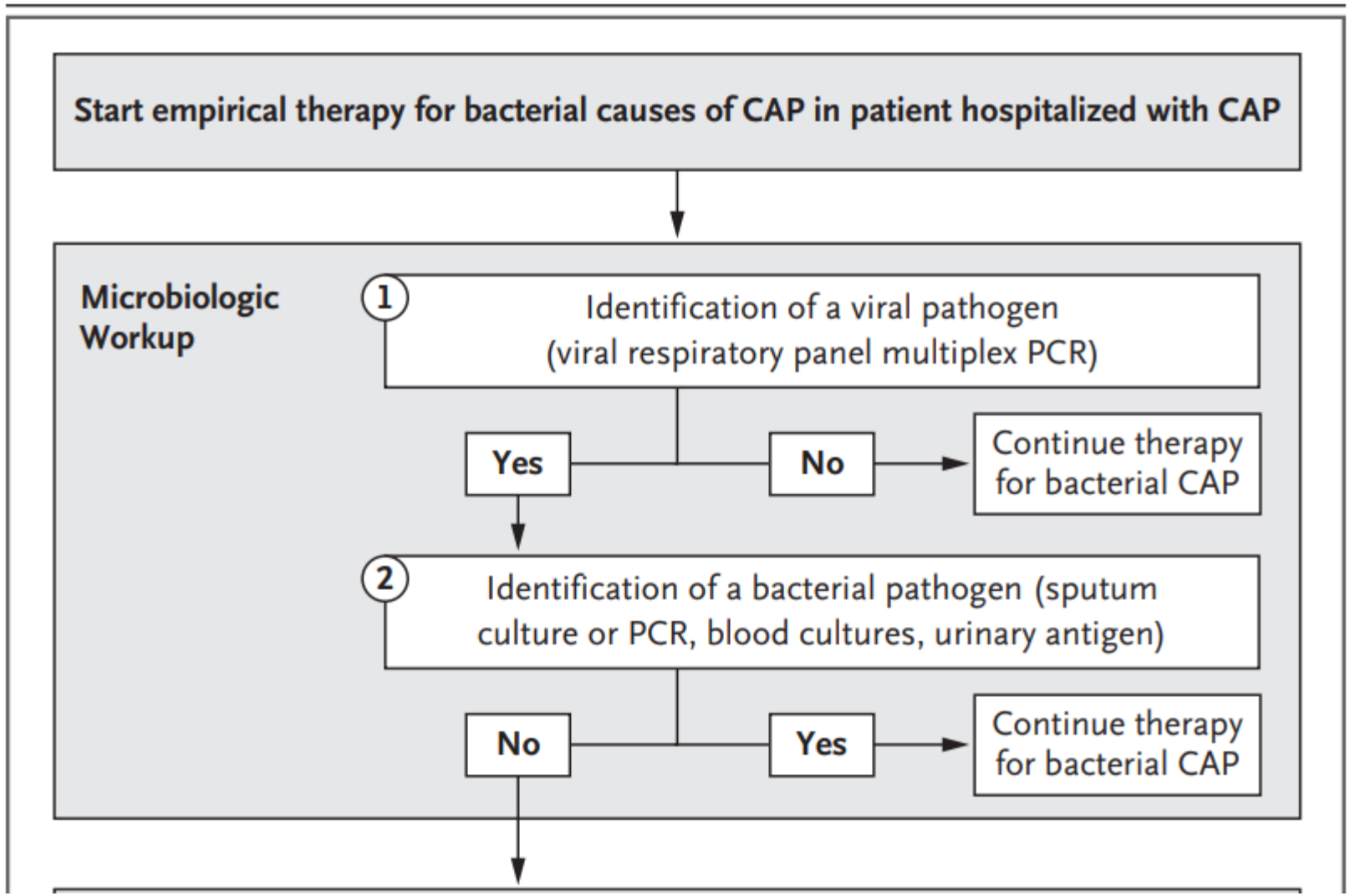

29%
Pneumonia
27% require ICU admission
18% require mechanical ventilation
9% Mortality

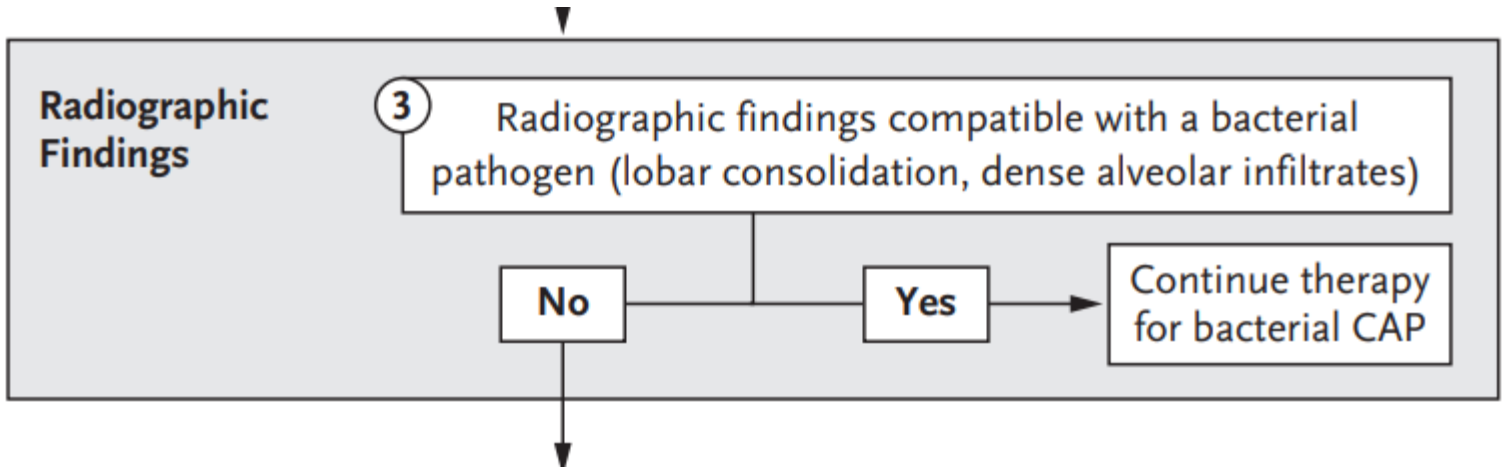
Pathogen Group	Pathogen
Common or core	
Gram-positive bacteria	*Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, *Strep. pyogenes*, other streptococci
Gram-negative bacteria	*Hemophilus influenzae*, *Moraxella catarrhalis*, Enterobacteriaceae (e.g., *Klebsiella pneumoniae*)
Atypical bacteria	*Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*
Respiratory viruses	Influenza virus, SARS-CoV-2, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, rhinoviruses, common human coronaviruses

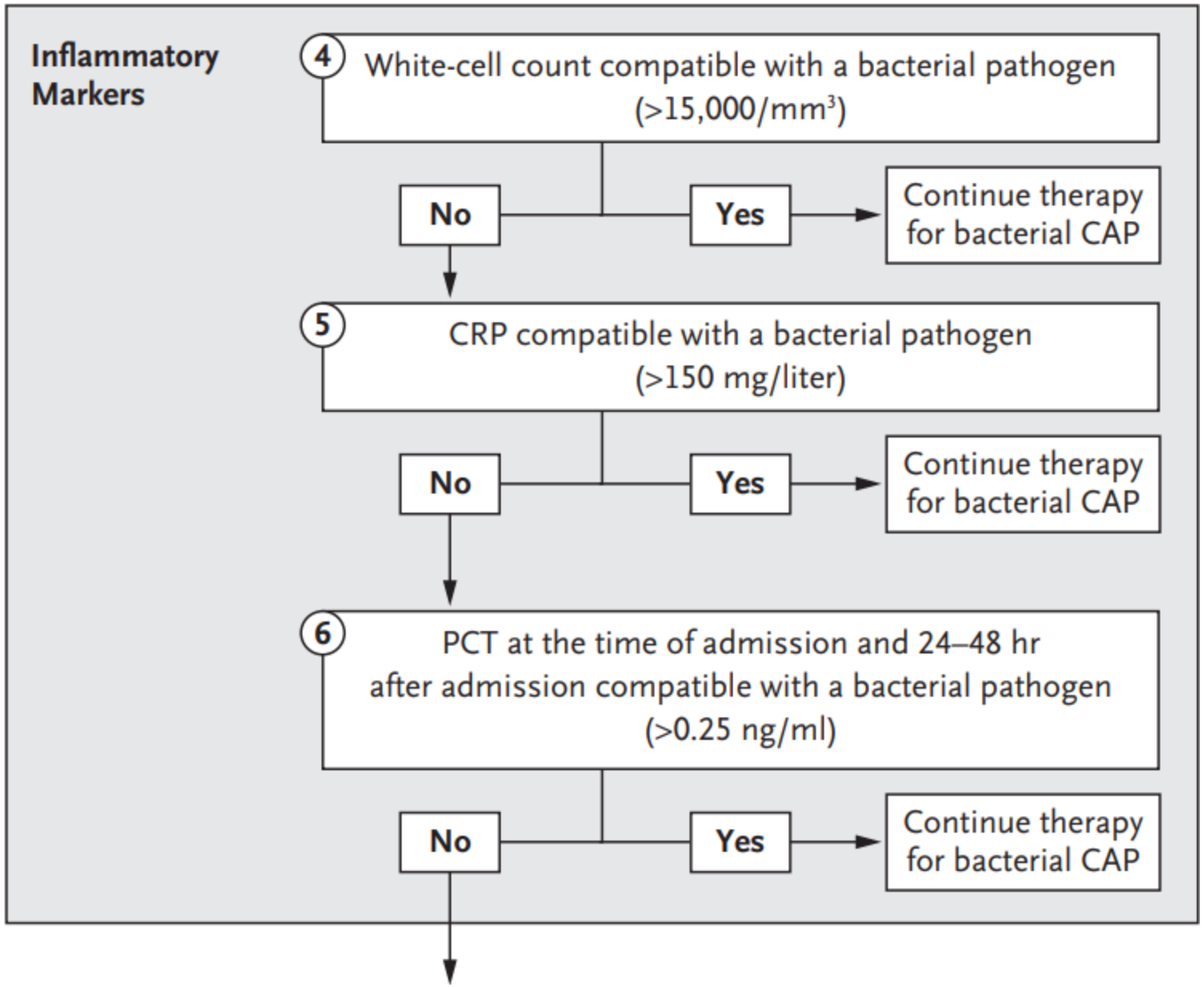
Uncommon or infrequent	
Gram-positive bacteria	Methicillin-resistant *Staph. aureus*, nocardia species, *Rhodococcus equi*
Gram-negative bacteria	Enterobacteriaceae, including extended-spectrum beta-lactamases or carbapenem-resistant enterobacteriaceae; nonfermenting bacilli (e.g., pseudomonas or acinetobacter); *Francisella tularensis*
Atypical bacteria	*Chlamydia psittaci, Coxiella burnetii*
Mycobacteria	*Mycobacterium tuberculosis*, nontuberculous mycobacteria
Viruses	Cytomegalovirus, herpes simplex, varicella zoster, MERS-CoV
Fungi	*Pneumocystis jirovecii*, aspergillus species, mucorales species, histoplasma species, cryptococcus species, blastomyces species, coccidioides species
Parasites	*Strongyloides stercoralis*, *Toxoplasma gondii*

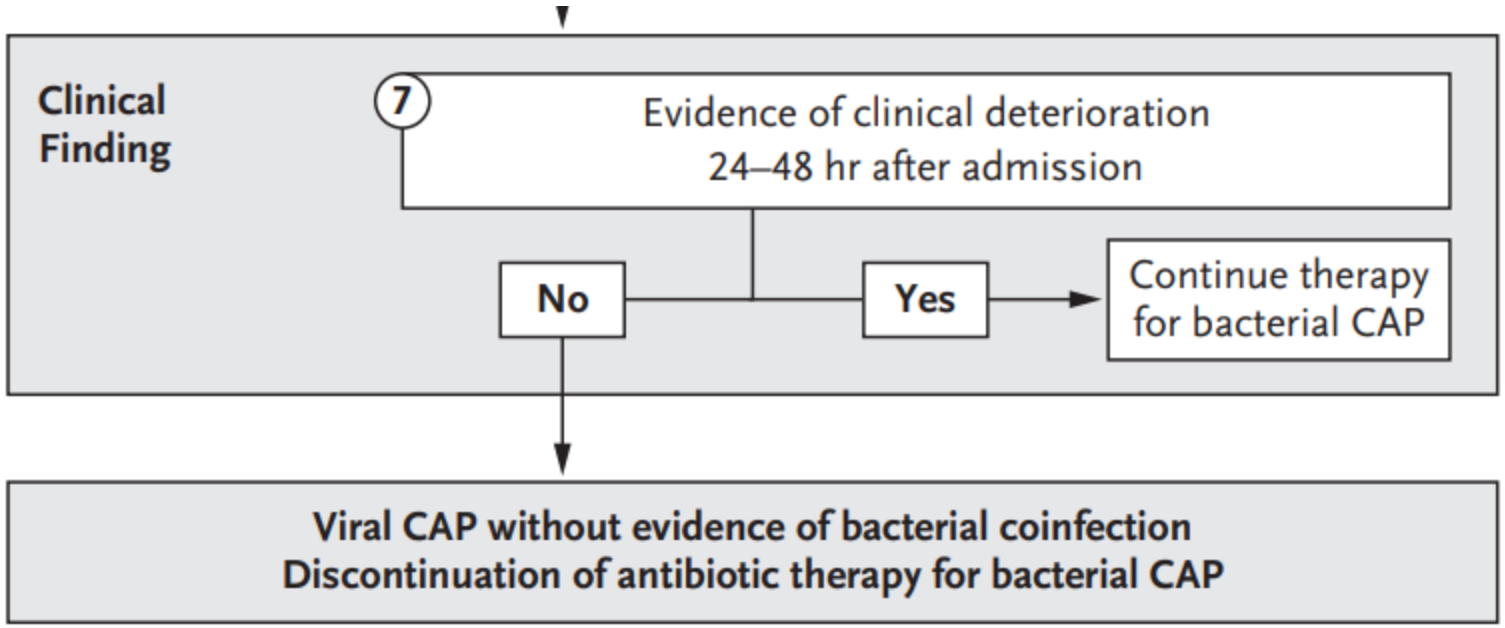

Patient with community-acquired pneumonia
Point-of-care polymerase chain reaction available
Point-of-care polymerase chain reaction unavailable
Positive test
Negative test
Influenza season or surveillance evidence of high influenza activity or risk factors (eg,recent travel or close contact with influenza-infected patients)
No influenza activity and no risk factors
Treat for influenza and bacterial community-acquired pneumonia
Treat for bacterial community-acquired pneumonia
Empiric treatment for influenza and community-acquired pneumonia
Treat for bacterial community-acquired pneumonia
Consider a pathway for early discontinuation of antimicrobials (eg,use of procalcitonin and clinical stability)

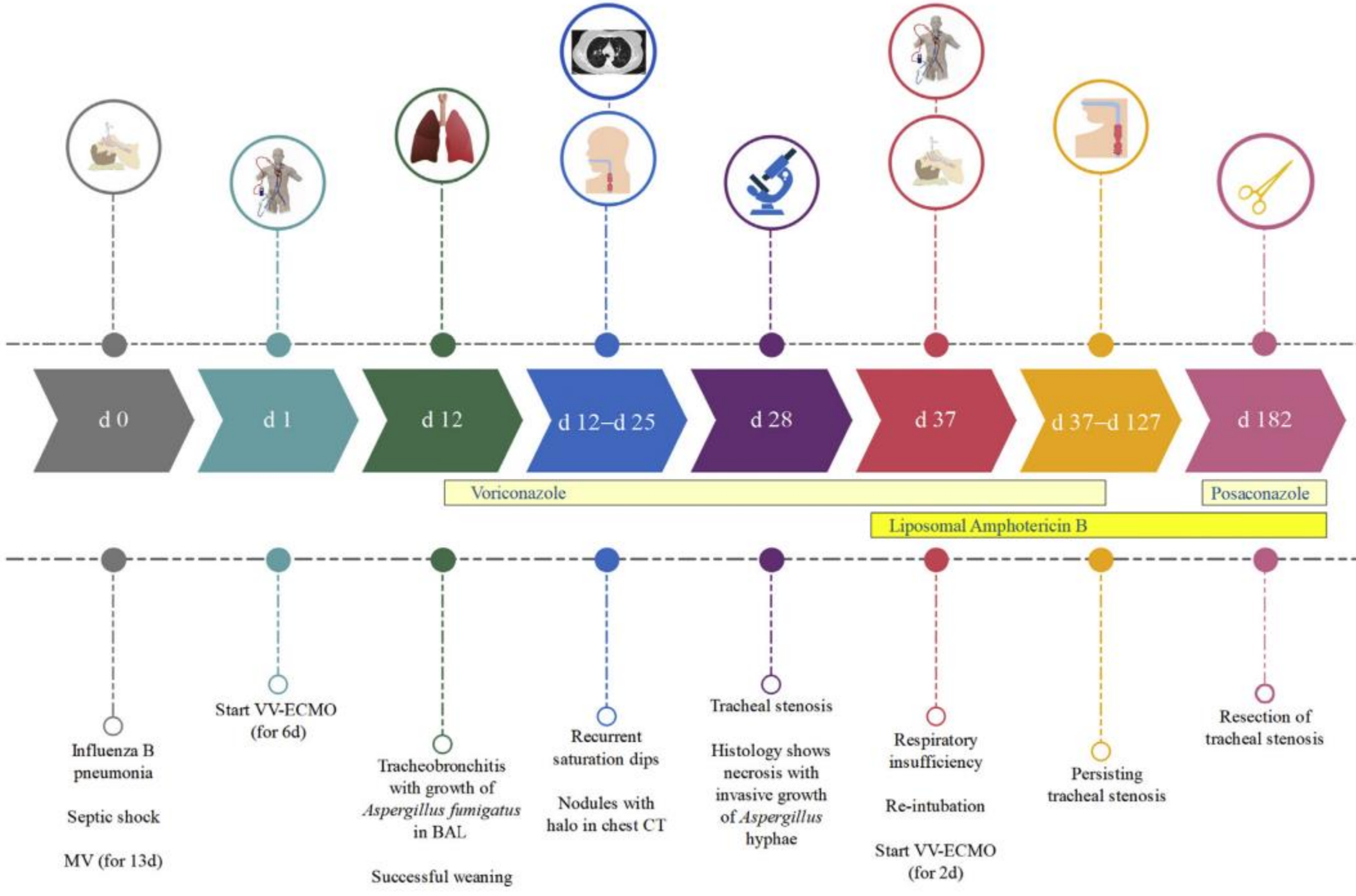

Viral pathogen-directed therapy
Immunocompetent patient
Immunosuppressed patient
Influenza
Non-influenza viral pathogen
Influenza
RSV
CMV
VZV
HSV
Neuraminidase inhibitor
Generally no treatment available but can consider treatment for some viruses based on anecdotal evidence depending on severity of illness or other risk factors (eg,pregnancy)
Neuraminidase inhibitor
Inhaled ribavirin
IV ganciclovir
IV acyclovir
IV acyclovir

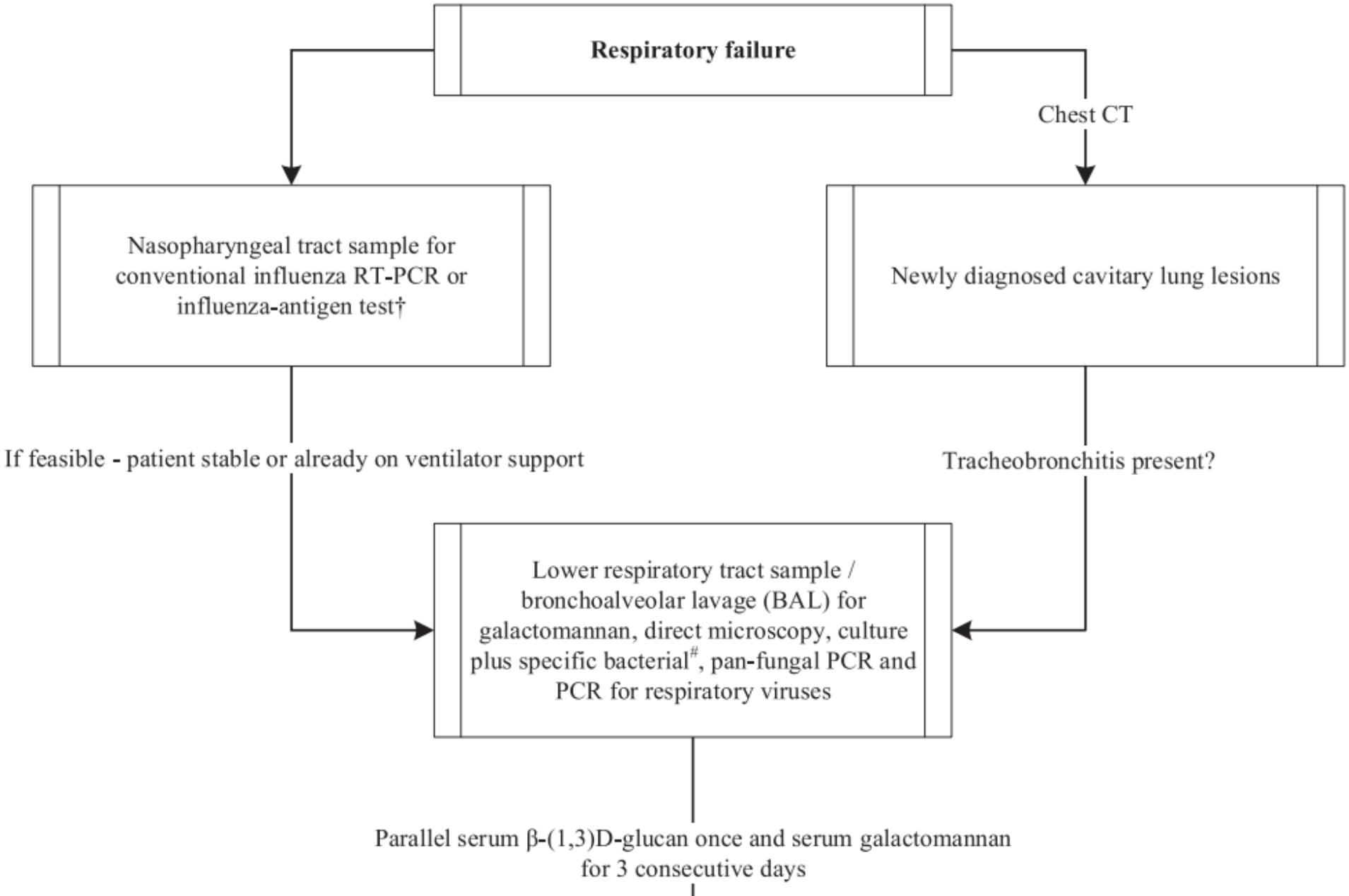

Start empirical therapy for bacterial causes of CAP in patient hospitalized with CAP
Microbiologic Workup
1
Identification of a viral pathogen (viral respiratory panel multiplex PCR)
Yes
No
Continue therapy for bacterial CAP
2
Identification of a bacterial pathogen (sputum culture or PCR, blood cultures, urinary antigen)
No
Yes
Continue therapy for bacterial CAP

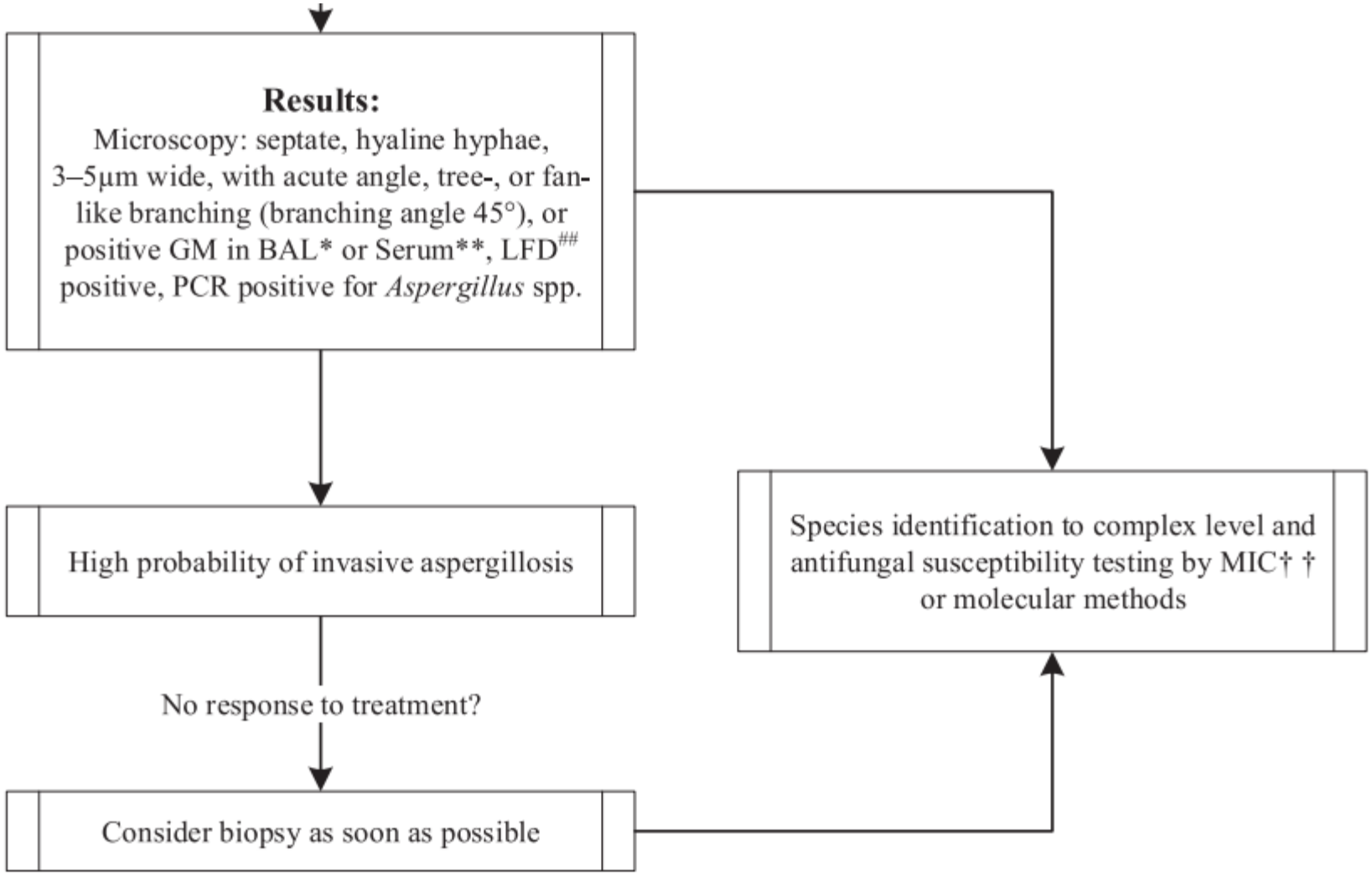

Radiographic Findings
3
Radiographic findings compatible with a bacterial pathogen (lobar consolidation, dense alveolar infiltrates)
No
Yes
Continue therapy for bacterial CAP


Inflammatory Markers
4
White-cell count compatible with a bacterial pathogen (>15,000/mm³)
No
Yes
Continue therapy for bacterial CAP
5
CRP compatible with a bacterial pathogen (>150 mg/liter)
No
Yes
Continue therapy for bacterial CAP
6
PCT at the time of admission and 24–48 hr after admission compatible with a bacterial pathogen (>0.25 ng/ml)
No
Yes
Continue therapy for bacterial CAP


Clinical Finding
7
Evidence of clinical deterioration 24–48 hr after admission
No
Yes
Continue therapy for bacterial CAP
Viral CAP without evidence of bacterial coinfection
Discontinuation of antibiotic therapy for bacterial CAP


d 0
d 1
d 12
d 12–d 25
d 28
d 37
d 37–d 127
d 182
Voriconazole
Posaconazole
Liposomal Amphotericin B
Influenza B pneumonia
Septic shock
MV (for 13d)
Start VV-ECMO (for 6d)
Tracheobronchitis with growth of *Aspergillus fumigatus* in BAL
Successful weaning
Recurrent saturation dips
Nodules with halo in chest CT
Tracheal stenosis
Histology shows necrosis with invasive growth of *Aspergillus* hyphae
Respiratory insufficiency
Re-intubation
Start VV-ECMO (for 2d)
Persisting tracheal stenosis
Resection of tracheal stenosis


Respiratory failure
Chest CT
Nasopharyngeal tract sample for conventional influenza RT-PCR or influenza-antigen test†
Newly diagnosed cavitary lung lesions
If feasible - patient stable or already on ventilator support
Tracheobronchitis present?
Lower respiratory tract sample / bronchoalveolar lavage (BAL) for galactomannan, direct microscopy, culture plus specific bacterial#, pan-fungal PCR and PCR for respiratory viruses
Parallel serum β-(1,3)D-glucan once and serum galactomannan for 3 consecutive days


Results:
Microscopy: septate, hyaline hyphae, 3–5µm wide, with acute angle, tree-, or fan-like branching (branching angle 45°), or positive GM in BAL* or Serum**, LFD## positive, PCR positive for *Aspergillus* spp.
High probability of invasive aspergillosis
No response to treatment?
Consider biopsy as soon as possible
Species identification to complex level and antifungal susceptibility testing by MIC† † or molecular methods

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
Annual influenza vaccination is recommended for all people 6 months and older.[15,16]	A	Reports of expert committees
The decision to begin antiviral treatment should be based on the clinical diagnosis of influenza, not on test results. Laboratory diagnosis should be obtained when results will change clinical management and for patients with severe illness.[19,28]	C	Reports of expert committees
Patients with severe illness or who are at high risk of complications from influenza should receive antiviral treatment regardless of symptom duration, although early treatment is most beneficial.[18,28]	B	Observational studies and a meta-analysis of observational studies
Oseltamivir (Tamiflu), peramivir (Rapivab), baloxavir (Xofluza), or zanamivir (Relenza) may be considered to reduce symptom duration in patients with influenza or influenza-like illness, but only if administered within 48 hours—and ideally 24 hours—of symptom onset.[18,28]	A	Systematic review of randomized trials
Oral oseltamivir is the preferred treatment for influenza during pregnancy.[18,28]	B	Pharmacokinetic studies and cohort studies