

Treatment of Community-Acquired Pneumonia in Immunocompromised Adults

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Infectious Diseases in Immunocompromised Hosts & Transplantation fellowship

Question 1:

Which patients with CAP should be considered immunocompromised?

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- We suggest that patients with CAP should be considered to be immunocompromised if they have an underlying disease or medical treatment that alters the immune system to the point that they are at elevated risk of pneumonia not only by common organisms but also by uncommon avirulent or opportunistic organisms.

Question 1:

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- No consensus exists regarding which patients should be formally considered immunocompromised.

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TABLE 2] Patient Conditions Qualifying Patients as Immunocompromised

| Patient Condition |
|---|
| Primary immune deficiency diseases |
| Active malignancy or malignancy within 1 y of CAP, excluding patients with localized skin cancers or early-stage cancers (eg, stage 1 lung cancer) |
| Receiving cancer chemotherapy |
| HIV infection with a CD4 T-lymphocyte count < 200 cells/ μ L or percentage < 14% ^a |
| Solid organ transplantation |
| Hematopoietic stem cell transplantation |
| Receiving corticosteroid therapy with a dose \geq 20 mg prednisone or equivalent daily for \geq 14 d or a cumulative dose > 600 mg of prednisone ^b |
| Receiving biological immune modulators ^c |
| Receiving disease-modifying antirheumatic drugs or other immunosuppressive drugs (eg, cyclosporin, cyclophosphamide, hydroxychloroquine, methotrexate) |

Question 1:

Which patients with CAP should be considered immunocompromised?

- The association of HIV disease and CAP can be categorized in three levels:
- Level 1: Patients with a CD4 T-lymphocyte count > 500 cells/mL. These patients are not at increased risk of CAP.
- Level 2: Patients with a CD4 T-lymphocyte count between 500 and 200 cells/mL. These patients are at increased risk of CAP, but are not considered immunocompromised because the etiologic agents are the core CAP pathogens such as *Streptococcus pneumoniae*.
- Level 3: Patients with a CD4 T-lymphocyte count < 200 cells/mL. These patients are at risk for CAP due to opportunistic pathogens such as *Pneumocystis jirovecii*. They are considered immunocompromised patients with CAP.

Question 1:

Which patients with CAP should be considered immunocompromised?

- Most patients who develop CAP have one or more comorbid condition(s) that increase their susceptibility to infection.
- From this perspective, patients with common comorbid conditions such as **diabetes**, chronic lung disease, **liver disease**, kidney disease, or **even those who are elderly and frail**, can be considered relatively immunocompromised.
- However, patients with this degree of immune dysfunction are typically infected with the same spectrum of organisms that cause CAP in younger or healthier adults, and their treatment is covered in the current CAP guidelines.

Question 1:

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- In the case of patients taking steroid and who have CAP, both the daily dose and the cumulative dose of steroids should be considered. The association with CAP can be define in three levels:
- **Level 1: Doses ≤ 10 mg of prednisone per day and a cumulative dose of less than 600 mg of prednisone or equivalent.** These patients are not at increased risk of CAP.
- **Level 2: Doses 10 to ≤ 20 mg of prednisone per day with a cumulative dose greater than 600 mg of prednisone or equivalent** at the time of the CAP episode. These patients are at increased risk of CAP, but are not considered immunocompromised because the etiologic agents are the core CAP pathogens such as *Streptococcus pneumoniae*.
- **Level 3: Dosses ≥ 20 mg or more of prednisone per day with a cumulative dose greater than 600 mg of prednisone or equivalent** at the time of the CAP episode. These patients are at risk for CAP due to opportunistic pathogens such as *Pneumocystis jirovecii*. They are considered immunocompromised patients with CAP. Because of the cumulative dose of at least 600 mg, these patients need to have received steroid therapy for at least 3 to 4 wk to be considered as fulfilling this condition.

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Which patients with CAP should be considered immunocompromised?

- Receiving biological immune modulators : These drugs are used to treat a wide array of inflammatory conditions and have multiple immunologic targets.
- The diverse effects of these drugs include **interfering with cell signaling**, inhibiting cytokine function, **interrupting innate immunity**, depleting B cells, or **inhibiting T-cell activation**.
- However, nearly all immunomodulators carry some risk of infection.
- Because these immunomodulating agents affect different components of the immune system, the risk for specific infections varies with the target of the immunomodulator.

Question 2:

Which immunocompromised patients with CAP should be admitted to the hospital?

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- In patients with CAP who are not immunocompromised, the admission decision is based on clinical judgment and can be supplemented by using validated severity scores such as the Pneumonia Severity Index or the CRB-65/CURB-65.
- Hospitalization of immunocompromised patients with CAP is based primarily on clinical judgment, considering that CAP severity scores have not been well validated in immunocompromised patients.
- Therefore, our suggestion is for a low threshold for hospitalization.

Question 3:

What pathogens should be considered “core respiratory pathogens” in patients with CAP who are immunocompromised?

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What pathogens should be considered “core respiratory pathogens” in patients with CAP who are immunocompromised?

- We suggest that the list of core respiratory pathogens able to cause CAP in the immunocompromised patient should be the same as those for the nonimmunocompromised.
- Immunocompromised patients are susceptible to infection with the same respiratory viruses and bacteria that cause CAP in nonimmunocompromised patients. We call these “core respiratory pathogens.” Common respiratory viral pathogens that cause mild upper respiratory tract infections in healthy adults can lead to **severe lower respiratory tract infections in immunocompromised patients.**

TABLE 3] Core Respiratory Pathogens That May Cause Community-Acquired Pneumonia in the Immunocompromised Patient

| Gram-Positive Bacteria | Gram-Negative Bacteria | "Atypical" Bacteria | Respiratory Viruses |
|-------------------------------------|--|---------------------------------|-----------------------------|
| <i>Streptococcus pneumoniae</i> | <i>Haemophilus influenzae</i> | <i>Legionella pneumophila</i> | Influenza virus |
| <i>Staphylococcus aureus</i> (MSSA) | <i>Moraxella catarrhalis</i> | <i>Chlamydophila pneumoniae</i> | Parainfluenza virus |
| <i>Streptococcus pyogenes</i> | Enterobacteriaceae (eg, <i>Klebsiella</i> species, <i>Escherichia coli</i>) | <i>Mycoplasma pneumoniae</i> | Coronavirus |
| Other streptococci | | <i>Coxiella burnetii</i> | Respiratory syncytial virus |
| | | | Rhinovirus |
| | | | Adenovirus |
| | | | Human metapneumovirus |

MSSA = methicillin-susceptible *Staphylococcus aureus*.

Question 4:

What pathogens should be considered beyond the core respiratory pathogens in patients with CAP who are immunocompromised?

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What pathogens should be considered beyond the core respiratory pathogens in patients with CAP who are immunocompromised?

- We suggest to focus attention on respiratory pathogens that may cause CAP in the immunocompromised patient and for which antimicrobial therapy is available.
- When considering likely etiologies of CAP beyond the core respiratory pathogens, it is important to focus attention on organisms that are amenable to antimicrobial treatment.

TABLE 4] Common Respiratory Pathogens in Addition to Core Respiratory Pathogens^a That Can Cause Community-Acquired Pneumonia in the Immunocompromised Patient and for Which Antimicrobial Therapy Is Available

| Bacteria | Mycobacteria | Viruses | Fungi | Parasites |
|---|-----------------------------|------------------------|-------------------------------|----------------------------------|
| Enterobacteriaceae (including those producing ESBL, and also CRE) | <i>Mycobacterium TB</i> | Cytomegalovirus | <i>Pneumocystis jirovecii</i> | <i>Toxoplasma gondii</i> |
| Nonfermenting gram-negative bacilli (eg, <i>Pseudomonas</i> or <i>Acinetobacter</i>) | Nontuberculous mycobacteria | Herpes simplex virus | <i>Aspergillus</i> species | <i>Strongyloides stercoralis</i> |
| MRSA | | Varicella-zoster virus | Mucorales species | |
| <i>Nocardia</i> species | | | <i>Histoplasma</i> species | |
| <i>Rhodococcus equi</i> | | | <i>Cryptococcus</i> species | |
| | | | <i>Blastomyces</i> species | |
| | | | <i>Coccidioides</i> species | |

CRE = carbapenemase-producing Enterobacteriaceae; ESBL = extended-spectrum β -lactamase.

Question 4:

What pathogens should be considered beyond the core respiratory pathogens in patients with CAP who are immunocompromised?

- Different types of immunocompromising conditions will predispose to different types of etiologic agents.

TABLE 5] Specific Immune Deficiencies and Associated Respiratory Pathogens

| Specific Immune Deficiency | Unique Respiratory Pathogen Associations |
|----------------------------|--|
| Neutropenia | <i>Pseudomonas aeruginosa</i> , <i>Stenotrophomonas maltophilia</i> , Enterobacteriaceae, <i>Streptococcus mitis</i> , <i>Staphylococcus aureus</i> , <i>Nocardia</i> species, <i>Aspergillus</i> and other hyaline molds (<i>Scedosporium</i> , <i>Fusarium</i>), yeast-like fungi (<i>Trichosporon</i>), Mucorales species, dimorphic fungi |
| AIDS | <i>Pneumocystis jirovecii</i> , <i>Streptococcus pneumoniae</i> , <i>Mycobacterium TB</i> , <i>M. avium-intracellulare</i> complex, and other nontuberculous mycobacteria, <i>Histoplasma capsulatum</i> , <i>Coccidioides</i> , <i>Bartonella</i> , <i>Rhodococcus</i> , <i>Toxoplasma gondii</i> , <i>Cryptococcus neoformans</i> , <i>Cryptosporidium</i> , <i>Nocardia</i> , <i>Talaromyces marneffeii</i> , <i>Paracoccidioides</i> , <i>Burkholderia</i> , cytomegalovirus, <i>Strongyloides</i> |

TABLE 5] Specific Immune Deficiencies and Associated Respiratory Pathogens

| Specific Immune Deficiency | Unique Respiratory Pathogen Associations |
|--|--|
| T-cell depletion (anti-thymocyte globulin, alemtuzumab) | <i>Pneumocystis jirovecii</i> , <i>Streptococcus pneumoniae</i> , <i>Mycobacterium TB</i> , <i>M. avium-intracellulare</i> complex, and other nontuberculous mycobacteria, <i>Aspergillus</i> and other hyaline molds, Mucorales species, varicella-zoster, herpes simplex, cytomegalovirus, <i>Histoplasma capsulatum</i> , <i>Coccidioides</i> , <i>Bartonella</i> species, <i>Toxoplasma gondii</i> , <i>Cryptococcus neoformans</i> , <i>Nocardia</i> , <i>Legionella</i> , <i>Strongyloides</i> |
| Hypogammaglobulinemia (common variable immunodeficiency, multiple myeloma, therapies that target CD19/20, eg, rituximab) | Respiratory viruses (influenza, respiratory syncytial virus, human metapneumovirus, parainfluenza, adenovirus, enterovirus), encapsulated bacteria (<i>S pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Haemophilus influenzae</i> , <i>S aureus</i> , <i>Capnocytophaga</i> , <i>Pasteurella multocida</i>), cytomegalovirus, <i>Pneumocystis</i> |

TABLE 5] Specific Immune Deficiencies and Associated Respiratory Pathogens

| Specific Immune Deficiency | Unique Respiratory Pathogen Associations |
|--|---|
| Calcineurin inhibitors (cyclosporine and tacrolimus) | <i>Legionella</i> , <i>Nocardia</i> , <i>Aspergillus</i> and other hyaline molds, Mucorales species, cytomegalovirus, endemic fungi |
| Antimetabolites (mycophenolate mofetil, azathioprine, 6-MP, fludarabine) | Cytomegalovirus, varicella, respiratory viruses (if B-cell impairment), <i>Legionella</i> , <i>Nocardia</i> , <i>Aspergillus</i> and other hyaline molds, Mucorales species, endemic fungi (<i>Pneumocystis post-fludarabine</i>) |
| Mammalian target of rapamycin inhibitors (sirolimus, everolimus) | <i>Cryptococcus</i> , <i>Pneumocystis</i> |
| Tumor necrosis factor inhibitors | Endemic fungi, <i>Aspergillus</i> , <i>Mycobacterium</i> (tuberculous and nontuberculous), varicella-zoster, <i>Nocardia</i> , <i>Pneumocystis</i> |
| Janus kinase signaling inhibitors (eg, ibrutinib, dasatinib) | <i>Pneumocystis</i> , mold, cytomegalovirus |
| Corticosteroids | Bacteria, esp. <i>Pseudomonas aeruginosa</i> , <i>Pneumocystis jirovecii</i> , <i>Staphylococcus aureus</i> , mycobacteria, <i>Aspergillus</i> and other hyaline molds, Mucorales species, cytomegalovirus, varicella-zoster, herpes simplex, <i>Histoplasma capsulatum</i> , <i>Coccidioides</i> , <i>Cryptococcus neoformans</i> , <i>Nocardia</i> , <i>Legionella</i> , <i>Strongyloides</i> |

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|----------------------------|--|
| Other | Natalizumab (<i>Cryptococcus</i>), vedolizumab (<i>Mycobacterium TB</i>), tocilizumab (unknown), ustekinumab (theoretical cytomegalovirus), secukinumab (theoretical mold), eculizumab (<i>Pseudomonas</i> , mold), bortezomib (varicella-zoster) |

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- ✓ We suggest a comprehensive microbiological workup with the goal to perform pathogen-directed therapy and deescalation of therapy.
- ✓ Another reason to perform broad microbiologic studies is that treatment of opportunistic pathogens is complex and often complicated by toxicities and drug-drug interactions.

TABLE 6] Microbiologic Studies That Can Be Done in Immunocompromised Patients Hospitalized With Community-Acquired Pneumonia

| Studies |
|---|
| <p>Sputum samples for bacterial, mycobacterial, and fungal stains and cultures</p> <p><i>Comments:</i> Sputum can be induced with inhaled isotonic or preferably hypertonic saline for certain pathogens (eg, MTB, PCP) to avoid invasive procedures. Sputum samples can be tested by PCR for detection of MTB or PCP</p> |
| <p>Nasopharyngeal swab with multiplex PCR for respiratory viruses</p> <p><i>Comments:</i> A negative nasopharyngeal PCR result does not rule out viral pneumonia. If the suspicion is high, perform the PCR on bronchoscopic samples. The finding of a virus by PCR does not rule out bacterial infection</p> |
| <p>Nasopharyngeal swab with multiplex PCR for atypical bacteria</p> <p><i>Comments:</i> Atypical pathogens such as <i>Legionella</i>, <i>Chlamydophila</i>, or <i>Mycoplasma</i> can also be identified in oropharyngeal samples</p> |
| <p>Nasal PCR for MRSA</p> <p><i>Comments:</i> Use in conjunction with a respiratory sample. A negative MRSA nasal PCR result, the absence of gram-positive cocci in clusters on Gram stain, and a negative MRSA respiratory culture make MRSA pneumonia extremely unlikely</p> |

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| Studies |
|---|
| <p>Blood cultures times two (at least), 30 min apart</p> |
| <p><i>Comments:</i> If there is a port or central line or PICC line, to define the presence of line infection, perform blood cultures from a peripheral vein and from the catheter lumens at the same time to calculate “time to positivity.” The separation of samples over time improves bacterial detection in the case of intermittent bacteremia</p> |
| <p>Urinary antigen for <i>Streptococcus pneumoniae</i></p> |
| <p><i>Comments:</i> The recent administration of pneumococcal vaccine (within days) will produce a positive urinary antigen result for <i>Streptococcus pneumoniae</i></p> |
| <p>Urinary antigen for <i>Legionella</i></p> |
| <p><i>Comments:</i> Detects only <i>Legionella pneumophila</i> serotype 1. Other gram-negative bacteria may generate a false positive test result. Obtain respiratory samples for culture and PCR to detect other species of <i>Legionella</i> or serotypes if clinically indicated</p> |
| <p>Urinary antigen for <i>Histoplasma capsulatum</i></p> |
| <p><i>Comments:</i> Very useful for disseminated disease. Cross-reaction with blastomycosis</p> |
| <p>Serum antigen for <i>Cryptococcus neoformans</i></p> |
| <p><i>Comments:</i> A serum cryptococcal antigen test may produce a negative result for a patient with documented cryptococcal pneumonia</p> |

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| Studies |
|---|
| Serum galactomannan antigen |
| <i>Comments:</i> <i>Aspergillus</i> cell wall contains the polysaccharide galactomannan. Also elevated in <i>Fusarium</i> , <i>Penicillium</i> , blastomycosis, and histoplasmosis. False positive results may occur with IVIG, transfusions, and some β -lactam antibiotics |
| Serum 1,3- β -D-glucan |
| <i>Comments:</i> β -D-Glucan is a cell wall component of several fungi. It screens for <i>Aspergillus</i> species, <i>Candida</i> species, PCP, and other fungi. It does not detect mucormycosis. False positive results may occur with IVIG, hemodialysis with cellulose, albumin, infections with <i>Pseudomonas</i> , and some β -lactam antibiotics |
| Swabs of vesicular or ulcerated skin lesions for viral PCR and cultures |
| <i>Comments:</i> A positive PCR result for HSV or VZV from skin lesions is highly correlated with herpes or varicella-zoster pneumonia |
| Biopsy of skin lesion for microbiology and pathology |
| <i>Comments:</i> Sample must be sent to microbiology and pathology for stains and cultures for viruses, bacteria, mycobacteria, fungi, and parasites |

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Studies

Viral load for CMV (PCR)

Comments: Obtain only if clinical suspicion is high. CMV reactivation is common in acute illness, and the presence of copies of CMV in plasma does not necessarily indicate invasive disease. On the other hand, the absence of viremia makes CMV pneumonitis less likely

Viral load for adenovirus

Comments: Obtain only if clinical suspicion is high.

Serology for histoplasmosis, coccidioidomycosis, and blastomycosis

Comments: Fungal serology is not generally recommended in immunosuppressed patients because they fail to generate an adequate antibody response to infection

Question 6:

When should bronchoscopy with bronchoalveolar lavage be performed in hospitalized patients with CAP who are immunocompromised?

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- We suggest that the decision to perform a bronchoscopy or bronchoalveolar lavage should be **individualized**. Bronchoscopy with BAL will be useful even in a clinically unstable patient if the patient is at risk for infection with multiple opportunistic pathogens and an experienced team is available to perform the procedure.
- In general, the more immunocompromised the host, the greater the potential benefit of performing bronchoscopy with BAL.

Question 7:

What microbiologic studies can be done with BAL fluid from hospitalized patients with CAP who are immunocompromised?

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What microbiologic studies can be done with BAL fluid from hospitalized patients with CAP who are immunocompromised?

- We suggest that microbiological studies in bronchoalveolar lavage should be ordered according to the presence of risk factors for particular pathogens.
- In some institutions a fixed panel of tests is routinely performed on BAL from immunocompromised patients with CAP.
- In other institutions, the tests are ordered considering the presence of clinical, radiographic, and immunologic risk factors for specific organisms.

TABLE 7] Microbiologic Studies in BAL Fluid or Tranbronchial Lung Biopsy

| Study |
|--|
| Bacterial Gram stain and culture |
| <i>Comments:</i> A negative stain and culture of MDR pathogens (eg, MRSA) can be used for deescalation of therapy unless antibiotics have been given for > 48 h |
| MRSA PCR |
| <i>Comments:</i> A negative PCR for MRSA can be used for deescalation of anti-MRSA therapy unless antibiotics have been given for > 48 h |
| AFB stains and culture for tuberculous and nontuberculous mycobacteria |
| <i>Comments:</i> If positive AFB stain, nucleic acid amplification (NAA) tests allows for rapid diagnosis. NAA test can be performed if the AFB stain is negative and the suspicion of disease is high |
| Nocardia stains and culture |
| <i>Comments:</i> AFB stain may be weakly positive |
| Fungal stains and culture |
| <i>Comments:</i> Because <i>Aspergillus</i> can colonize the airways, positive stains or culture of <i>Aspergillus</i> species from respiratory samples do not necessarily indicate disease |
| PCP stains and PCR |
| <i>Comments:</i> In patients with PCP, the sensitivity of staining is higher in HIV-infected patients when compared with HIV-uninfected patients. A positive PCR may occur in patients colonized with PCP. In non-HIV patients, a negative PCR can be used to discontinue anti-PCP therapy |
| Respiratory viral panel with multiplex PCR |
| <i>Comments:</i> Viruses can be detected in BAL by PCR in a patient with a negative nasopharyngeal swab PCR for the same virus |

Atypical pathogens panel with multiplex PCR

Comments: A positive PCR is considered diagnostic for atypical pneumonia because pathogens such as *Legionella*, *Chlamydothila*, or *Mycoplasma* rarely colonize the airway

Galactomannan antigen

Comments: The cell wall of *Aspergillus* contains the polysaccharide galactomannan. Other fungi that contain galactomannan include *Histoplasma capsulatum*, *Penicillium* species, and *Fusarium* species. False positive levels may occur in BAL samples with some β -lactam antibiotics

Aspergillus PCR

Comments: The high sensitivity of PCR produces a high negative predictive value, making the diagnosis unlikely with a negative test

(1,3)- β -D-Glucan

Comments: It is considered a poor screening tool for the diagnosis of invasive fungal infections because of its low positive predictive value

CMV PCR

Comments: Quantitative PCR analysis in BAL fluid may help to differentiate between CMV pneumonia (high viral load) vs CMV pulmonary shedding without pneumonia (low viral load), but cutoff levels are not defined

Cellular analysis

Comments: A predominantly inflammatory cellular pattern in the BAL with neutrophil pleocytosis can be used as a predictor of bacterial etiology

Histopathology

Comments: Routine hematoxylin and eosin staining, special stains, and culture for viruses, bacteria, mycobacteria, fungi, and parasites

Question 8:

What empirical therapy should be started in hospitalized patients with CAP who are immunocompromised?

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What empirical therapy should be started in hospitalized patients with CAP who are immunocompromised?

- We suggest that immunocompromised patients without any additional risk factors for drug-resistant bacteria can receive initial empirical therapy targeting only the core respiratory pathogens.
- Additional empirical treatment beyond the core respiratory pathogens should be considered according to the presence of risk factors for drug-resistant or opportunistic pathogens

Question 9:

In which patients with CAP who are immunocompromised should empirical therapy be extended beyond the core respiratory pathogens?

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In which patients with CAP who are immunocompromised should empirical therapy be extended beyond the core respiratory pathogens?

- We suggest to extend empirical therapy beyond core respiratory pathogens when (1) risk factors for drugresistant organisms or opportunistic pathogens are present and (2) the delay in empirical antimicrobial therapy will place the patient at increased risk of mortality.
- Empirical therapy beyond core respiratory pathogens may not be necessary if the patient is clinically stable and the local setting allows for rapid microbiologic diagnostic tests.

Question 10:

What role does the severity of pneumonia play in the selection of initial empirical therapy?

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What role does the severity of pneumonia play in the selection of initial empirical therapy?

- We suggest that the presence of severe pneumonia can be used as an indication to start empirical therapy for resistant gram-positive and gram-negative organisms, followed by rapid deescalation if no multidrug-resistant pathogen is identified.

Question 10:

What role does the severity of pneumonia play in the selection of initial empirical therapy?

- The impact of severe pneumonia on empirical therapy is the critical need to start early with an appropriate antimicrobial therapy, because an initial inadequate antibiotic spectrum has been identified as an independent risk factor for mortality in CAP.
- The presence of severe pneumonia or pneumonia requiring ICU care can be used as a threshold to start empirical therapy for resistant gram positive organisms (eg, MRSA) and resistant gram negative organisms (eg, Pseudomonas).

Question 11:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to MRSA?

Question 11:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to MRSA?

- We suggest that initial empirical therapy to cover for MRSA should be started in patients with a history of colonization or infection with MRSA in the previous 12 months.
- Vancomycin or linezolid are the first line for initial empirical therapy.

Question 11:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to MRSA?

- In regions with a high prevalence of MRSA, some members of the panel will start empirical anti-MRSA therapy in patients requiring ICU admission.
- A negative MRSA result by nasal polymerase chain reaction (PCR), absence of gram-positive cocci in clusters on Gram's staining, and a negative MRSA respiratory culture can be used to deescalate anti-MRSA therapy.

Question 12:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to drug-resistant gram negative bacilli, including *Pseudomonas aeruginosa*?

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In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to drug-resistant gram negative bacilli, including *Pseudomonas aeruginosa*?

- We suggest that initial empirical therapy for immunocompromised patients should cover resistant gram-negative bacilli, including *Pseudomonas aeruginosa*, **if there is a history of colonization or infection with a resistant gram-negative bacilli in the prior 12 months, previous hospitalization with exposure to broad-spectrum antibiotics, the presence of a tracheostomy, neutropenia, or a history of pulmonary comorbidity.**

Question 12:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to drug-resistant gram negative bacilli, including *Pseudomonas aeruginosa*?

- Patients with any of these risk factors should be considered for initial empirical therapy against resistant gram-negative bacilli including *P.aeruginosa*.
- **b-Lactam antibiotics with activity against *P aeruginosa*, such as piperacillin/tazobactam or a carbapenem, should be used as core therapy.**
- However, ceftazidime, which has no reliable activity against *S.pneumoniae*, should **not** be used as monotherapy.

Question 13:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to multidrug-resistant (MDR) gram-negative bacilli?

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In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to multidrug-resistant (MDR) gram-negative bacilli?

- We suggest that in patients with a recent history of colonization or infection with MDR gram-negative bacilli, the initial empirical therapy should cover the possibility of infection due to the colonizing MDR gramnegative bacilli.
- In patients with a recent history of colonization or infection with MDR gram-negative bacilli such as extended-spectrum b-lactamase-producing Enterobacteriaceae, carbapenemase-producing Enterobacteriaceae, MDR Pseudomonas, or MDR Acinetobacter, the initial empirical therapy should cover the possibility of infection with the colonizing MDR gram-negative bacilli.

Question 13:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to multidrug-resistant (MDR) gram-negative bacilli?

- A knowledge of the local susceptibility profile for gram-negative bacilli and the most recent susceptibility profile of the colonizing MDR gram-negative bacilli will help in the selection of empirical therapy for these organisms with difficult-to-treat resistance.
- For empirical therapy of MDR gram-negative bacilli, b-lactam antibiotics such as piperacillin-tazobactam or imipenem may have to be changed to newer b-lactam antibiotics that have better activity against some of the MDR bacteria.
- In these patients, consideration should be given to the addition of ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem/vaborbactam.
- Adding a polymyxin such as colistin to a traditional b-lactam is a possibility when other agents are not available.

Question 14:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?

Question 14:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?

- We suggest initial empirical therapy should be extended to cover the possibility of PCP in patients with **diffuse, bilateral, interstitial infiltrates** or **alveolar opacities** and who are not receiving PCP prophylaxis, and those who are either
 - (1) HIV hosts who is newly diagnosed, or not on antiretroviral therapy, or with CD4 counts less than 200 cells/mL (or a percentage lower than 14%) or
 - (2) non- HIV hosts with severely impaired cell-mediated immunity (eg, taking glucocorticoids with cytotoxic agents).

Question 14:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?

- In these patients we suggest the addition of trimethoprim-sulfamethoxazole (TMP-SMX) to the initial regimen.
- The dose of TMP-SMX is the same for PCP in the HIV-infected patient and PCP in the immunocompromised non-HIV-infected patient.
- Adjunctive glucocorticoids are recommended for HIV-infected patients with room air PaO₂ < 70 mm Hg and/ or an alveolar-arterial (A-a) oxygen gradient ≥ 35 mm Hg.
- Corticosteroids are not beneficial in HIV-negative patients with PCP.

Question 15:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Aspergillus*?

Question 15:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Aspergillus*?

- We suggest that empirical therapy should cover the possibility of pneumonia due to filamentous fungi such as *Aspergillus* in patients with cancer and chemotherapy with severe and prolonged neutropenia and a **radiographic nodular pattern surrounded by a halo of ground-glass attenuation and/or cavitation.**

Question 15:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Aspergillus*?

- **Voriconazole** is considered the first-line treatment for patients with documented invasive aspergillosis, but we do not suggest empirical voriconazole because these patients are also at risk for other filamentous fungi resistant to voriconazole (eg, those causing mucormycosis).
- In these patients we suggest empirical therapy with **liposomal amphotericin** at dosages of 5 to 7.5 mg/kg daily.
- In patients intolerant to amphotericin, empirical therapy with **isavuconazole** at an initial dosage of 200 mg every 8 h can be used as an alternative.

Question 15:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Aspergillus*?

- Patients treated with tumor necrosis factor (TNF) inhibitors, such as etanercept, infliximab, or adalimumab, are also at risk of fungal pneumonia.
- In these patients we suggest an aggressive diagnostic workup, and treat if a fungus is identified.
- In the treatment of these patients it is important to discontinue the use of the anti-TNF drug at the time of diagnosis of pneumonia to improve the level of immunity of the patient.

Question 16:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to Mucorales?

Question 16:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to Mucorales?

- We suggest that empirical therapy should cover the possibility of pneumonia due to filamentous fungi such as Mucorales in patients with cancer and chemotherapy with severe and prolonged neutropenia and a radiographic nodular pattern, or a reverse halo sign, or pleural effusion.

Question 16:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to Mucorales?

- Empirical therapy for Mucorales is especially important when fungal infection is suspected in a patient receiving voriconazole antifungal prophylaxis.
- In these patients we suggest liposomal amphotericin as part of the initial empirical regimen at dosages of 5 to 7.5 mg/kg daily.⁴⁸
- In patients intolerant to amphotericin, empirical therapy with isavuconazole at an initial dosage of 200 mg every 8 h can be used as an alternative.
- Voriconazole does not cover mucormycosis, and therefore it is not suggested as initial empirical therapy.

Question 17:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Nocardia*?

Question 17:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to Nocardia?

- We suggest that empirical therapy should include the possibility of Nocardia infection in patients with heart, lung, liver, or hematopoietic stem cell transplant with pneumonia and evidence for a lung or brain abscess, and who have not been receiving prophylaxis with TMP-SMX.
- In these patients we suggest the addition of TMP-SMX to the initial empirical therapy at a dosage of 15 mg/kg/ d of the trimethoprim component IV in three or four divided doses.
- If TMP-SMX is contraindicated, linezolid also has excellent activity and can be considered for empirical therapy until susceptibilities are known.

Question 18 :

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to cytomegalovirus?

Question 18 :

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to cytomegalovirus?

- We suggest that empirical therapy be extended to cover the possibility of CAP due to cytomegalovirus in patients with **bilateral interstitial pneumonia** after a recent lung transplant or hematopoietic stem cell transplant.
- **In these patients we suggest the addition of ganciclovir to the initial regimen at a dosage of 5 mg/kg IV every 12 h, with dose adjustment for renal dysfunction.**

Question 18 :

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to cytomegalovirus?

- Elevated plasma cytomegalovirus (CMV) viral loads are frequent in patients with CMV pneumonitis, but this finding alone is not sufficient for diagnosis.
- In lung transplant recipients, CMV PCR viral load in BAL is a superior diagnostic tool than plasma CMV viral load.

Question 19 :

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to varicella-zoster virus?

Question 19 :

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to varicella-zoster virus?

- We suggest that empirical therapy be extended to cover the possibility of CAP due to varicella-zoster virus in patients with bilateral reticulonodular infiltrates who also have a vesicular rash.
- In these patients we suggest the addition of IV acyclovir, 10 to 15 mg/kg IV every 8 h, to the initial empirical regimen.

Question 20:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?

Question 20:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?

- We suggest not to start empirical therapy to cover the possibility of CAP due to *Mycobacterium TB*.
- Pulmonary infections due to mycobacteria, such as TB, are common in patients treated with TNF inhibitors and patients with long-term high-dose steroids.
- But in the case of suspected mycobacterial pneumonia we do not suggest treating the patient with empirical therapy. We suggest carrying out the indicated microbiologic studies and beginning treatment once the pathogen has been identified.

Question 20:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?

- We think that in these patients the risk-to-benefit ratio of expanding empirical therapy with multiple mycobacterial drugs, vs waiting to define which patients have a mycobacterial infection, is in favor of waiting for microbiologic results and treating them specifically.
- An exception to this approach would be in patients with HIV infection with a history of recent exposure, who have other clinical findings and radiographic features compatible with TB infection, and who present with severe CAP.
- In these patients we will start empirical therapy for TB pending microbiologic workup.

Question 21:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to parasites?

Question 21:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to parasites?

- We suggest not to start empirical therapy to cover CAP due to parasites.
- Parasites that can produce CAP in the immunocompromised host include *Strongyloides stercoralis* and *Toxoplasma gondii*.

Question 21:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to parasites?

- Pneumonia in patients with Strongyloides hyperinfection syndrome may be due to invasion of lung tissue by the filariform larvae or with gram-negative bacteremia secondary to seeding of the blood from the GI tract.
- Patients at risk of Strongyloides hyperinfection syndrome include those with solid organ transplantation, hematopoietic stem cell transplantation, or patients with high and prolonged dosages of corticosteroids (eg, prednisone ≥ 20 mg/d, or its equivalent, for longer than 1 month) in combination with cytotoxic agents.
- Therapy with ivermectin is recommended for patients with hyperinfection syndrome.

Question 21:

In which immunocompromised patients should the initial empirical therapy be extended to cover the possibility of CAP due to parasites?

- **Toxoplasma pneumonia** occurs due to reactivation of latent infection in (1) patients with HIV infection that is newly diagnosed, and not undergoing antiretroviral therapy or with CD4 counts less than 100 cells/mL; or (2) patients with defects in cell-mediated immunity due to high and prolonged doses of corticosteroids in combination with cytotoxic agents.
- Therapy with pyrimethamine and sulfadiazine is recommended for patients with *Toxoplasma pneumonia*.

TANK YOU