Treatment of Community-Acquired Pneumonia in Immunocompromised Adults

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"Management of Community-Acquired Pneumonia in Immunocompromised Adults: A Consensus Statement Regarding Initial Strategies"

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ABBREVIATION LIST

BAL:	bronchoalveolar lavage
CAP:	community-acquired pneumonia
CMV:	Cytomegalovirus
CRE:	carbapenemase-producing *Enterobacteriaceae*
DMARDs:	disease-modifying anti-rheumatic drugs
ESBL:	extended spectrum beta-lactamase
HIV:	human immunodeficiency virus
MDR:	multiple drug resistant
NTM:	non-tuberculous Mycobacteria
PCP:	*Pneumocystis jirovecii*
PCR:	polymerase chain reaction
PSI:	Pneumonia Severity Index
TMP-SMX:	trimethoprim-sulfamethoxazole
TNF:	tumor necrosis factor

ABSTRACT

Background

Community-acquired pneumonia (CAP) guidelines have improved the management and outcomes of patients with CAP, primarily by standardization of initial empiric therapy. But current society-published guidelines exclude immunocompromised patients.

Research Question

There is no concensus regarding the initial management of immunocompromised patients with suspected CAP.

Study Design and Methods

This consensus document was created by a multidisciplinary panel of 45 physicians with experience in the management of CAP in immunocompromised patients. The Delphi survey methodology was used to reach consensus.

Results

The panel focused on 21 questions addressing initial management strategies. The panel achieved consensus in defining the population, site of care, likely pathogens, microbiological work-up, general principles of empiric therapy, and empiric therapy for specific pathogens.

Interpretation

This document offer general suggestions for the initial management of the immunocompromised patient who arrives at the hospital with pneumonia.

INTRODUCTION

Guidelines for the management of patients with community-acquired pneumonia (CAP) have been published by medical societies from several countries. These guidelines have improved the management and outcomes of patients with CAP, primarily by standardization of initial empiric therapy. But current society-published CAP guidelines exclude immunocompromised patients[1-3]. Immunocompromised patients have been excluded from guidelines because of their need for complex, often individualized, treatment, the expanded spectrum of potential pathogens, and their exclusion from the large prospective studies of antibiotic efficacy used to support guideline recommendations.

The number of immunocompromised persons at risk for CAP is increasing due to: (i) longer survival of patients with cancer, and recipients of organ transplants; (ii) better recognition of immunocompromising conditions; (iii) additional risk groups, such as those receiving novel immune-modulating therapies for non-malignant diseases, and (iv) approval of newer immunomodulatory agents. It is estimated that 3% of the adult population of the United States is immunosuppressed[4]. Immunocompromising conditions are present in approximately 20 to 30% of hospitalized patients with CAP[5-7].

Frequently, the initial management of pneumonia in immuncompromised patients may not occur in specialized tertiary care centers with advanced expertise in their care. Rather, immunocompromised patients with symptoms of lower respiratory tract infection often present first to general hospitals to be managed by emergency room physicians, internists, or hospitalists. These general conditions are identical to those motivating the initial impetus for guidelines to treat CAP; namely, the frequency of the condition and the presentation of patients in many different health care settings throughout the community.

Early and adequate empiric treatment of CAP in the general population is associated with decreased morbidity and mortality, and the authors attempt here to facilitate application of these same principles to patients at high risk of CAP-related complications due to pre-existing immune dysfunction. The approaches suggested in this document are based on an extensive review of the literature and on the collective experience of the authors. A challenge of reviewing the CAP literature in the immunocompromised host is that most publications evaluate outcomes of antimicrobial therapy for patients in whom the pathogen causing CAP has been identified. No

large, prospective clinical studies comparing different empiric therapies in immunocompromised patients exist.

Susceptibility to specific infections varies widely in immunocompromised patients and depends both on the degree of immune suppression and the components of the immune system which are affected by the underlying disease and/or medical therapy. In this document we attempt to develop a unifying approach to simplify a very complex topic, involving a heterogenous population. The objective of this document is to suggest an approach to the initial management of immunocompromised patients with suspected CAP.

METHODS

The Delphi survey methodology used to reach consensus. After a full review of the English literature in the topic of management of CAP in the ICP, the Delphi questions used in the survey were developed (Table 1). The following 5-point Likert scale was used to evaluate agreement or disagreement with each proposed answer: *Strongly Disagree (1), Disagree (2), Neutral (3), Agree (4), Strongly Agree (5).* It was considered that a consensus was reached once more than 75% of participants agreed or strongly agreed with a particular suggestion.

In each round of the Delphi survey, questions regarding the management of CAP in the ICP were submitted to all 45 participants of the consensus. To anonymously record participant responses and comments, a survey was developed using Research Electronic Data Capture (REDCap) that allowed participants to answer with their level of agreement with the suggestion and to write specific comments regarding the management suggested by the group. After each round, all responses were summarized and an anonymized summary of all the comments was produced and sent to each participant. Participants have the opportunity to revise the earlier answers considering the anonymized replies of other members of the panel.

After the participants answered the third round of all questions, the range of the answers decreased significantly and it was considered that group had reached consensus. At that point, a pre-final manuscript was created and submitted to all participants for final comments and agreement ratings. After the final comments were incorporated, the manuscript was produced.

Further details regarding the Delphi survey methodology and rounds are in the supplementary material.

Statistical analysis

At each round of the survey, the mean and standard deviation of agreement based on the Likert scale for each question was calculated. To evaluate the level of agreement or disagreement for each question in a manner that incorporated both mean and standard deviation, a t-statistic for each question was calculated. The t-statistic was used to identify which questions had the least amount agreement or most controversy. Agreement was visualized by bar charts, and final agreement was reported as percentage of participants who responded as *Agree* or *Strongly Agree.*

RESULTS

A. Definition of Population

Question 1: Which patients with CAP should be considered immunocompromised?
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.

No consensus exists regarding which patients should be formally considered immunocompromised. Our pragmatic approach is to consider patients to be immunocompromised if they are at elevated risk of pneumonia not only by common organisms but also by uncommon avirulent or opportunistic organisms. Several practical aspects of meeting this definition include the need for comprehensive microbiological testing, the need to alter empirical antimicrobial therapy, and the need for adjunctive therapy. Even using this more restrictive definition, medical advances supporting longer survival of patients with serious conditions and an expanding armamentarium of biological agents results in expanding populations of at-risk individuals. Using this approach, the most common acquired conditions that qualify a patient as being immunocompromised are a malignancy that suppresses immune

responses (such as lymphoma or leukemia) and advanced HIV infection (CD4 T-lymphocyte count <200 cells/µl). The most frequent treatments that qualify a patient as being immunocompromised include glucocorticoids, therapies that suppresses B-cell or T-cell responses, chemotherapy for malignancy that causes neutropenia, conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents used to treat a broad range of rheumatological, dermatological, gastrointestinal, and autoimmune diseases. Notably, some agents (e.g., ibrutinib, alemtuzumab or fludarabine) have persistent immunosuppressive effects, long after active treatments is discontinued. A list of patients who should be considered immunocompromised is depicted in Table 2[8-13].

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 management is covered in the current CAP guidelines.

B. Site of Care

Question 2: Which immunocompromised patients with CAP should be admitted to the hospital? We suggest that the decision for hospitalization should be based on clinical judgement having a low threshold for hospital admission.

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 (PSI) 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[14-16]. Because immunosuppressive drugs are known to modulate the inflammatory response, the typical signs and symptoms of CAP may be attenuated in these patients. The blunted inflammatory response may not produce a clear infiltrate at chest x-ray. A CT scan of the chest will allow a better definition of the extent of pulmonary infiltrate as well as better recognition of complications of pneumonia such abscesses, or pleural effusions. This information, gained with

CT scan of the chest, may help in the decision regarding hospitalization. Hypoxia is a particularly useful criterion to define site of care. In non-immunocompromised patients with CAP, a blood oxygen saturation <92 percent is considered an appropriate threshold for hospital admission[17]. Immunocompromised patients may appear stable at the time of the initial evaluation but may deteriorate rapidly, progressing in a few hours from a moderately severe pneumonia to a severe pneumonia in need of intensive care. Also, the increased range of potential infecting agents renders selection of any empiric regimen much more challenging, often requiring parenteral agents. Therefore, our suggestion is for a low threshold for hospitalization. If the patient is considered sufficiently stable for outpatient care, mechanisms for close follow up and rapid re-entry to inpatient healthcare should be available.

C. Likely Pathogens

Question 3: 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 non-immunocompromised.

Immunocompromised patients are susceptible to infection by the same respiratory viruses and bacteria that cause CAP in the non-immunocompromised patient. 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 lists the primary groups of "core respiratory pathogens" that can cause CAP in immunocompromised patients[5,6,18].

Question 4: 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. Common respiratory pathogens that: 1) may cause CAP in the immunocompromised host and 2) for which antimicrobial therapy is available, are listed in Table 4. Different types of

immunocompromise conditions will predispose to different types of etiologic agents. A description of specific immune deficiencies and the associated respiratory pathogens are depicted in Table 5.

Initial empiric therapy active against these respiratory pathogens may only be necessary in selected patients presenting with specific epidemiological, clinical or immunological risk factors for infection due to a particular pathogen. These risk factors and the specific pathogens that are involved will be discussed below.

D. Microbiological Work-up

Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?
We suggest a comprehensive microbiological work-up with the goal to perform pathogen-directed therapy and de-escalation of therapy.

A critical aspect of the management of these patients is initial microbiological work-up coupled with empiric therapy, followed by a de-escalation to therapy directed to the causative pathogen. De-escalation of therapy is important since continuing a broad-spectrum therapy for the full duration of therapy is associated with selection of multi-resistant organisms, increased risk of toxicity, drug-drug interactions and impaired antimicrobial stewardship for the entire community. As the primary way to perform de-escalation therapy is knowing the pathogen that causes pneumonia, a comprehensive microbiological work-up is critically important. Another reason to obtain broad microbiological studies is that treatment of opportunistic pathogens is complex and often complicated by toxicities and drug-drug interactions.

The extent of the microbiological work-up should be individualized considering the presence of risk factors and likely organisms, as well as local capabilities. During recent years the field of diagnostic microbiological techniques has experienced a significant progress. Development of rapid diagnostic tests using new molecular techniques and sophisticated new laboratory methods such as the matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry are reshaping the clinical microbiology laboratory as well as our ability to identify etiologic agents of CAP in immunocompromised patients[19]. A list of common microbiological studies with relevant clinical considerations is depicted in Table 6[20-29].

Question 6: When should a bronchoscopy with bronchoalveolar lavage be performed in hospitalized patients with CAP who are immunocompromised?
We suggest that the decision to perform a bronchoscopy or bronchoalveolar lavage should be individualized.

A 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. Preferably, a bronchoscopy with BAL should be done early so that initial empiric therapy does not alter the culture results. If the bronchoscopy can be obtained promptly, a short delay before initiating antibiotic therapy may be acceptable, given improved culture yield. In general, the more immunocompromised the host, the greater the potential benefit of performing a bronchoscopy with BAL.

If the etiology of CAP may be defined based on initial x-rays and point of care diagnostic testing, the small, but nevertheless clear risk associated with bronchoscopy with BAL may outweigh the benefit[30].

Question 7: What microbiological studies can be obtained in bronchoalveolar lavage fluid in 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 in BAL from immunocompromised patients with CAP. In other institutions, the tests are ordered considering the presence of clinical, radiographic and immunological risk factors for specific organisms. Table 7[31-35] lists microbiological studies that can be done on BAL or tissue from a transbronchial lung biopsy together with relevant clinical considerations.

E. Empiric Therapy: General Principles

Question 8: What empiric 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 empiric therapy targeting only the core respiratory pathogens.

Although immunocompromised hosts may have unique immunological risk and often more frequent nosocomial contact and antibiotic exposure, many immunocompromised patients admitted with CAP do not have any additional risk factors for drug resistant bacteria (e.g. MRSA, Pseudomonas). For these patients, we suggest initial empiric antimicrobial therapy targeting the "core respiratory pathogens" described in Table 3. In these group of patients, the initial empiric anti-bacterial therapy would be the same as the initial empiric therapy for hospitalized patients with CAP who are not immunocompromised[1]. Additional empiric treatment beyond the core respiratory pathogens should be considered according to the presence of risk factors for drug-resistance or opportunistic pathogens and will be discussed in sections below.

Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?
We suggest to extend empiric therapy beyond core respiratory pathogens when 1) risk factors for drug resistant organisms or opportunistic pathogens are present and 2) the delay in empiric antimicrobial therapy will place the patient at increased risk of mortality.

In addition to initial empiric treatment for core respiratory pathogens, we suggest broader initial coverage when the following factors are met: 1) A resistant bacterium or an opportunistic pathogen is suspected based on the presence of risk factors from findings on history or physical examination, laboratory results and/or imaging patterns; AND 2) waiting for microbiological identification of the suspected pathogen will significantly delay initiation of antimicrobial therapy and may increase the risk of mortality. Other considerations for extending initial empiric therapy beyond core pathogens include availability of point of care tests, severity of disease at presentation, and use of prophylactic therapy for a particular opportunistic pathogen.

The need for empiric therapy of opportunistic pathogens will continue to evolve as more point-of-care tests are developed for rapid diagnosis. Empiric therapy beyond core respiratory pathogens may not be necessary if the patient is clinically stable and the local setting allows for rapid microbiological diagnostic tests.

Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?
We suggest that the presence of severe pneumonia can be used as an indication to start empiric therapy for resistant gram positive and gram negative organisms, followed by rapid de-escalation if no multi-drug resistant pathogen is identified.

Severity of illness is not by itself an accurate predictor of drug-resistance or opportunistic infection in pneumonia. For example, *Streptococcus pneumoniae* is capable of causing life-threatening septic shock, whereas invasive pulmonary aspergillosis may present with an indolent, progressive course.

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

F. Empiric Therapy: Specific Pathogens

Question 11: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to MRSA?
We suggest that initial empiric therapy to cover for MRSA should be started in patients with a history of colonization or infection with MRSA in the previous twelve months.

In patients with a history of colonization or infection with MRSA in the previous 12 months initial empiric therapy should cover the possibility of infection due to MRSA. There are other risk factors reported in the literature for MRSA infection such as prior antibiotic use, recent hospitalization, hemodialysis or wound care, but if the local prevalence of MRSA is low, these risk factors will each have a low positive predictive value and should not be used to trigger empiric anti-MRSA therapy[36-40]. On the other hand, a single patient who accumulate many of these risk factors may have a high likelihood of CAP due to MRSA. Vancomycin or linezolid are the first line for initial empiric therapy. In regions with high prevalence of MRSA, some members of the panel will start empiric anti-MRSA therapy in patients requiring ICU admission.

A negative MRSA nasal PCR, absence of Gram-positive cocci in clusters on Gram's stain, and a negative MRSA respiratory culture can be used to de-escalate anti-MRSA therapy.

Question 12: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of drug-resistant Gram-negative bacilli, including Pseudomonas aeruginosa?
We suggest that initial empiric 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 twelve months, previous hospitalization with exposure to broad-spectrum antibiotics, presence of a tracheostomy, neutropenia, or history of pulmonary comorbidity.

History of colonization or infection with a drug resistant Gram-negative bacilus in the previous 12 months, previous hospitalization with exposure to broad spectrum antibiotics, presence of a tracheostomy, neutropenia, history of pulmonary comorbidity (e.g. cystic fibrosis, bronchiectasis, or recurrent exacerbations of COPD requiring glucocorticoid and antibiotic use) have been reported in literature to increase risk of resistant Gram-negative bacili[37-42]. Patients with any of these risk factors should be considered for initial empiric therapy against resistant Gram-negative bacilli including *P. aeruginosa*. Beta-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[43].

Question 13: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to multi-drug 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 empiric therapy should cover the possibility of infection due to the colonizing MDR Gram-negative bacilli.

In patients with a recent history of colonization or infection with MDR Gram-negative bacilli such as extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceaea*, carbapenemase-producing *Enterobacteriaceae* (CRE), MDR *Pseudomonas*, or MDR *Acinetobacter*, the initial empiric therapy should cover the possibility of infection due to the

colonizing MDR Gram-negative bacilli. A knowledge of 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 empiric therapy for these organisms with difficult-to-treat resistance. For empiric therapy of MDR Gram-negative bacilli, beta-lactam antibiotics such as piperacillin-tazobactam or imipenem, may have to be changed to newer beta-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 beta-lactam is a possibility when other agents are not available. In patients treated empirically with these broad spectrum agents, we strongly emphasize an extended microbiological workup and prompt de-escalation of therapy if appropriate.

Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Pneumocystis jirovecii pneumonia (PCP)?
We suggest initial empiric 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 either (1) an HIV host who is newly diagnosed, or not on antiretroviral therapy, or with CD4 counts less than 200 cells/µl (or a percentage lower than 14%) or (2) a non-HIV host with severely impaired cell-mediated immunity (e.g., glucocorticoids with cytotoxic agents).

In these patients we suggest the addition of TMP-SMX to the initial regimen. The recommended dose for TMP-SMX is 15 to 20 mg/kg/day of the trimethoprim component orally or IV given in three or four divided doses[44]. The dose of TMP-SMX is the same for PCP in the HIV patient and PCP in the immunocompromised non-HIV patient. Adjunctive glucocorticoids are recommended for HIV patients with a room air PaO2 <70 mmHg and/or an alveolar-arterial (A-a) oxygen gradient of ≥35 mmHg[44]. Corticosteroids are not beneficial in HIV-negative patients with PCP[45].

Question 15: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Aspergillus?
We suggest that empiric 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 radiographic nodular pattern surrounded by a halo of ground-glass attenuation and/or cavitation.

Voriconazole is considered the first line treatment for patients with documented invasive aspergillosis, but we do not suggest empiric voriconazole because these patients are also at risk for other filamentous fungi resistant to voriconazole (e.g. mucormycosis)[46]. In these patients we suggest empiric therapy with liposomal amphotericin at doses of 5 to 7.5 mg/kg daily. In patients intolerant to amphotericin, empiric therapy with isavuconazole with an initial dose of 200 mg every 8 hours can be used as an alternative[47].

Patients treated with tumor necrosis factor (TNF) inhibitors, such as etanercept, infliximab, or adalimumab, are also at risk of fungal pneumonia[11,12]. In these patients we suggest an aggressive diagnostic work-up and treat if a fungus is identified. In the management 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 empiric therapy be extended to cover the possibility of CAP due to Mucorales?
We suggest that empiric 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 radiographic nodular pattern, or a reverse halo sign, or pleural effusion.

Empiric therapy for *Mucorales* is especially important when fungal infection is suspected in a patient on voriconazole antifungal prophylaxis. In these patients we suggest liposomal amphotericin as part of the initial empiric regimen at doses of 5 to 7.5 mg/kg daily[48]. In patients intolerant to amphotericin, empiric therapy with isavuconazole with an initial dose of 200 mg every 8 hours can be used as an alternative[47]. Voriconazole does not cover Mucormycosis and therefore it is not suggested as initial empiric therapy.

Question 17: In which immunocompromised patients should the initial empiric 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 dose of 15 mg/kg IV of the trimethoprim component per day in three or four divided doses[49]. Resistance of *Nocardia* spp. to TMP-SMX is a rare event[50]. If TMP-SMX is contraindicated, Linezolid also has excellent activity and can be considered for empiric therapy until susceptibilities are known[50]. If initial treatment contains already a drug with activity against Nocardia spp. (e.g. linezolid or imipenem) empiric addition of TMP-SMX is not requested. However, TMP-SMX is the drug of choice for definite treatment.

Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?
We suggest that empiric 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 intravenous acyclovir 10-15 mg/kg IV every 8 hours to the initial empiric regimen[51].

Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?
We suggest that empiric 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 dose of 5 mg/kg IV every 12 hours, with dose adjustment for renal dysfunction[52]. Elevated plasma CMV viral loads are frequent in patients with CMV pneumonitis, but this finding alone is not sufficient for diagnosis[53]. In lung transplant recipients, CMV PCR viral load in BAL is a superior diagnostic tool than plasma CMV viral load[54].

Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Mycobacterium tuberculosis?
We suggest not to start empiric therapy to cover the possibility of CAP due to Mycobacterium tuberculosis.

Pulmonary infections due to mycobacteria such as tuberculosis, are common in patients treated with TNF inhibitors and patients with long term high-dose steroids[11]. But in the case of suspected mycobacterial pneumonia we do not suggest treating the patient with empiric therapy. We suggest carrying out the indicated microbiological studies and begining treatment once the pathogen has been identified. We think that in these patients the risk-benefit of expanding empiric therapy with multiple mycobacterial drugs versus waiting to define which patients have a mycobacterial infection, is in favor of waiting for microbiological 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 tuberculosis infection, and present with severe CAP. In this patients we will start empiric therapy for tuberculosis pending microbiologic work-up[44].

Question 21: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to parasites?
We suggest not to start empiric therapy to cover CAP due to parasites.

Parasites that can produce CAP in the immunocompromised host include *Strongyloides stercoralis* and *Toxoplasma gondii*[55,56].

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 gastrointestinal tract. Patients at risk of *Strongyloides* hyperinfection syndrome include those with solid organ transplantation, hematopoietic stem cell transplantation, or patients with high and prolonged doses of corticosteroids (e.g. prednisone $\geq$20 mg per day, or its equivalent, for longer than 1 month) in combination with cytotoxic agents. Patients on this type of immune suppressing therapy, and also those with secondary bacteremias, may not have an elevated eosinophil count to raise suspicion of a parasitic infection. Therapy with ivermectin is recommended for patients with hyperinfection syndrome[55].

Toxoplasma pneumonia occurs due to reactivation of latent infection in (1) patients with HIV infection that is newly diagnosed, and not on antiretroviral therapy or with CD4 counts less than 100 cells/µl; 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[44].

We think that in these patients the risk benefit of expanding empiric therapy for parasitic infections or waiting to define which patients have a parasitic infection favors waiting for microbiological results and treat only the patients with a proven parasitic infection.

DISCUSSION

In this document we have developed general suggestions for the initial management of the immunocompromised patient who arrives at the hospital with pneumonia. Despite our suggestions of empirical therapy for specific pathogens in specific situations, we stress the importance of making a concerted effort to establish a rapid and accurate etiologic diagnosis and to de-escalate complex therapies once a presumptive pathogen is properly ruled out. It is also important to consider local susceptibility patterns when selecting empiric therapy. The participants do suggest that, if evidence supports the presence of infections that require highly specialized management (e.g. cytomegalovirus or Mucorales), after initial therapy is begun, prompt transfer to a tertiary care facility should be strongly considered. Transfer to a specialized center may not be necessary if experienced pulmonary and infectious disease specialists are available to participate in management.

An important weakness of this document is the simplification of heterogenous conditions that affect different arms of the immune system into a single group of immunocompromised patients with CAP. Another limitation is that we were not able to provide references that appropriately support several of our suggestions, hence we need to emphasize the suggestions offered in this consensus are based primarily on expert opinion.

In conclusion, we have developed general suggestions for the initial management of immunocompromised patients hospitalized with pneumonia. When possible, the care of these patients should be carried out by a multidisciplinary group of specialists. Because immunocompromised patients have been excluded from prospective randomized studies of CAP treatment, there is an urgent need to generate scientific evidence in this field.

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TABLES

Table 1. Questions addressing initial management strategies for community-acquired pneumonia (CAP) in immunocompromised adults.

A. Definition of Population
Question 1: Which patients with CAP should be considered immunocompromised?
B. Site of Care
Question 2: Which immunocompromised patients with CAP should be admitted to the hospital?
C. Likely Pathogens
Question 3: What pathogens should be considered "core respiratory pathogens" in patients with CAP who are immunocompromised?
Question 4: What pathogens should be considered beyond the "core respiratory pathogens" in patients with CAP who are immunocompromised?
D. Microbiological Work-up
Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?
Question 6: When should a bronchoscopy with bronchoalveolar lavage be performed in patients with CAP who are immunocompromised?
Question 7: What microbiological studies can be obtained in bronchoalveolar lavage in patients with CAP who are immunocompromised?
E. Empiric Therapy: General Principles
Question 8: What empiric therapy should be started in hospitalized patients with CAP who are immunocompromised?
Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?
Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?
F. Empiric Therapy: Specific Pathogens
Question 11: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to MRSA?
Question 12: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of drug-resistant Gram-negative bacilli, including *Pseudomonas aeruginosa*?
Question 13: In which immunocompromised patients should the initial empiric therapy be

extended to cover the possibility of CAP due to multi-drug resistant (MDR) Gram-negative bacilli?
Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?
Question 15: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Aspergillus*?
Question 16: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mucorales*?
Question 17: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Nocardia*?
Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?
Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?
Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?
Question 21: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to parasites?

Table 2. Patients with the following conditions should be considered immunocompromised

Primary immune deficiency diseases
Active malignancy or malignancy within one year prior to CAP, excluding patients with localized skin cancers or early stage cancers (e.g. stage 1 lung cancer)
Receiving cancer chemotherapy
HIV infection with a CD4 T-lymphocyte count <200 cells/µl or percentage <14%*[8]
Solid organ transplantation
Hematopoietic stem cell transplantation
Receiving corticosteroid therapy with a dose ≥ 20 mg prednisone or equivalent daily for ≥14 days or a cumulative dose > 700 mg of prednisone**[9,10]
Receiving biologic immune modulators***[11,12]
Receiving disease-modifying anti-rheumatic drugs[13] or other immunosuppressive drugs (e.g. cyclosporin, cyclophosphamide, hydroxychloroquine, methotrexate)

*The association of HIV disease and CAP can be categorized in 3 levels.

Level 1: Patients with a CD4 T-lymphocyte count >500 cells/µl. These patients are not at increased risk of CAP.

Level 2: Patients with a CD4 T-lymphocyte count between 500 to 200 cells/µl. 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/µl. These patients are at risk for CAP due to opportunistic pathogens such as PCP. They are considered immunocompromised patients with CAP.

**In the case of patients taking steroid and CAP, both the daily dose and the cumulative dose of steroids should be considered. The association with CAP can be define in 3 levels.

Level 1: Doses ≤10 mg of prednisone a 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 mg to ≤ 20 mg of prednisone a 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: Doses ≥20 mg or more of prednisone a 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 PCP. They are considered immunocompromised patients with CAP. Due to the cumulative dose of at least 600 mg, this patients need to be on steroid therapy for at least 3 to 4 weeks to be consider fulfilling this condition.

***These drugs are used to treat a wide array of inflammatory conditions and have multiple immunological 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. Specific discussion of these drugs in detail is beyond the scope of this paper. 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.

Table 3: List of "Core Respiratory Pathogens" that may cause CAP in the immunocompromised patient

Gram positive bacteria	**Gram negative bacteria**	**"Atypical" bacteria**	**Respiratory Viruses**
Streptococcus pneumoniae	*Haemophilus influenzae*	*Legionella pneumophila*	Influenza
Staphylococcus aureus (MSSA)	*Moraxella catarrhalis*	*Chlamydophila pneumoniae*	Parainfluenza
Streptococcus pyogenes	Enterobacteriaceae *(*e.g. *Klebsiella* spp*. Escherichia coli)*	*Mycoplasma pneumoniae*	Coronavirus
Other streptococci		*Coxiella burnetii*	Respiratory syncytial virus
			Rhinovirus
			Adenovirus
			Human metapneumovirus

Table 4: List of common respiratory pathogens in addition to core respiratory pathogens (as described in Table 3) that can cause CAP in the immunocompromised patient and for which antimicrobial therapy is available.

Bacteria	**Mycobacteria**	**Viruses**	**Fungi**	**Parasites**
Enterobacteriaceae (Including those producing ESBL and also CRE)	*Mycobacterium tuberculosis*	Cytomegalovirus (CMV)	*Pneumocystis jirovecii* (PCP)	*Toxoplasma gondii*
Non-fermenting Gram negative bacilli (e.g. *Pseudomonas* or *Acinetobacter*)	Non-tuberculous Mycobacteria (NTM)	Herpes simplex	*Aspergillus* spp.	*Strongyloides stercoralis*
MRSA		Varicella-zoster	*Mucorales* spp.	
Nocardia spp.			*Histoplasma* spp.	
Rhodococcus equi			*Cryptococcus* spp.	
			Blastomyces spp.	
			Coccidioides spp.	

Table 5. Specific immune deficiencies and associated respiratory pathogens

Specific Immune Deficiency	**Unique Respiratory Pathogen Associations**
Neutropenia	*Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, other *Enterobacteriaceae*, *Streptococcus mitis, Staphylococcus aureus, Nocardia* spp, *Aspergillus* and other hyaline molds (*Scedosporium, Fusarium*), yeast-like fungi (*Trichosporon*), *Mucorales*, dimorphic fungi
AIDS	*Pneumocystis jiroveci, Streptococcus pneumoniae, Mycobacterium tuberculosis, M. avium-intracellulare* complex and other non-tuberculous mycobacteria, *Histoplasma capsulatum, Coccidioides, Bartonella*, *Rhodococcus, Toxoplasma gondii, Cryptococcus neoformans, Cryptosporidium, Nocardia, Talaromycosis marneffei, Paracoccidioides, Burkholderia, Cytomegalovirus, Strongyloides*
T-cell depletion (Antithymocyte globulin, Alemtuzumab)	*Pneumocystis jiroveci, Streptococcus pneumoniae, Mycobacterium tuberculosis, M. avium-intracellulare* complex and other non-tuberculous mycobacteria, *Aspergillus* and other hyaline molds, *Mucorales* spp, Varicella, Herpes simplex, Cytomegalovirus, *Histoplasma capsulatum*, *Coccidioides, Bartonella* spp., *Toxoplasma gondii, Cryptococcus neoformans, Nocardia, Legionella, Strongyloides*
Hypogammaglobulinemia (Common variable immunodeficiency, Multiple Myeloma, Therapies that target CD19/20, e.g. rituximab)	Respiratory viruses (Influenza, RSV, HMPV, Parainfluenza, Adenovirus, Enterovirus), Encapsulated bacteria (*S. pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, S. aureus, Capnocytophaga, Pasteurella multocida*), Cytomegalovirus, *Pneumocystis*
Calcineurin Inhibitors (cyclosporine and tacrolimus)	*Legionella, Nocardia, Aspergillus* and other hyaline mold, *Mucorales* spp, Cytomegalovirus, endemic fungi
Antimetabolites (mycophenolate mofetil, azathioprine, 6-MP, fludarabine)	Cytomegalovirus, Varicella, Respiratory viruses (if B-cell impairment), *Legionella, Nocardia, Aspergillus* and other hyaline mold, *Mucorales* spp, endemic fungi, (*Pneumocystis*– fludarabine)
Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, evirolimus)	*Cryptococcus, Pneumocystis*
Tumor Necrosis Factor (TNF)	Endemic fungi, *Aspergillus*, *Mycobacteria* (tuberculous and non-

Inhibitors	tuberculous), Varicella, *Nocardia*, *Pneumocystis*
Janus kinase (JAK) Signaling Inhibitors (e.g. Ibrutinib, Dasatinib)	*Pneumocystis*, mold, Cytomegalovirus
Corticosteroids	Bacteria, esp. *Pseudomonas aeruginosa, Pneumocystis jiroveci, Staphylococcus aureus, Mycobacteria*, *Aspergillus* and other hyaline molds, *Mucorales* spp, Cytomegalovirus , Varicella, Herpes simplex, Cytomegalovirus, *Histoplasma capsulatum, Coccidioides, Cryptococcus neoformans, Nocardia, Legionella, Strongyloides*
Other	Natalizumab (*Cryptococcus*), vedolizumab (*M. tuberculosis*), Tocilizumab (unknown), Ustekinumab (theoretical CMV), Secukinumab (theoretical mold), eculizumab (*Pseudomonas*, mold), bortezemib (Varicella zoster)

Table 6. Microbiological studies that can be obtained in immunocompromised patients hospitalized with CAP

Sputum samples for bacterial, mycobacterial, and fungal stains and cultures
Comments: Sputum can be induced using inhaled isotonic or preferably hypertonic saline for certain pathogens (e.g., MTB, PCP) in order to avoid invasive procedures. Sputum samples can be tested using PCR for detection of MTB or PCP[20,21].
Nasopharyngeal swab with PCR multiplex for respiratory viruses
Comments: A negative nasopharyngeal PCR does not rule out viral pneumonia. If the suspicion is high, perform the PCR on bronchoscopic samples[22,23]. The finding of a virus by PCR does not rule out bacterial infection.
Nasopharyngeal swab with PCR multiplex for atypical bacteria
Comments: Atypical pathogens such as *Legionella*, *Chlamydophila*, or *Mycoplasma*, can also be identified in oropharyngeal samples.
Nasal PCR for MRSA
Comments: Use in conjunction with a respiratory sample. A negative MRSA nasal PCR, the absence of Gram-positive cocci in clusters on Gram's stain, and a negative MRSA respiratory culture make MRSA pneumonia extremely unlikely.
Blood cultures times two (at least) 30 minutes apart
Comments: 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"[24]. The separation of samples over time improve bacterial detection in case of intermittent bacteremia[25].
Urinary antigen for *Streptococcus pneumoniae*
Comments: The recent administration of pneumococcal vaccine (within days) will produce a positive urinary antigen for *Streptococcus pneumoniae.*
Urinary antigen for Legionella
Comments: Detects only *Legionella pneumophila* serotype 1. Other Gram-negative bacteria may generate a false positive test[26]. Obtain respiratory samples for culture and PCR to detect other species of Legionella or serotypes if clinically indicated.
Urinary antigen for *Histoplasma capsulatum*
Comments: Very useful for disseminated disease. Cross reaction with blastomycosis.
Serum antigen for *Cryptococcus neoformans*
Comments: A serum cryptococcal antigen test may be negative in a patient with documented cryptococcal pneumonia.
Serum galactomannan antigen
Comments: Aspergillus cell wall contains the polysaccharide galactomannan. Also elevated in *Fusarium*, *Penicillium*, blastomycosis, and histoplasmosis. False positives may occur with IVIG, transfusions and some beta-lactam antibiotics[27].
Serum 1,3-Beta-D-glucan
Comments: Beta-D-glucan is a cell component of several fungi. It screens for *Aspergillus* spp., *Candida* spp., PCP, and other fungi. It does not detect mucormycosis. False positives may occur with IVIG, hemodialysis with cellulose, albumin, infections by *Pseudomonas*, and some beta-lactam antibiotics[27].
Swabs of vesicular or ulcerated skin lesions for viral PCR and cultures
Comments: A positive PCR for HSV or VZV from skin lesions is highly correlated with herpes or varicella pneumonia.
Biopsy of skin lesion for microbiology & pathology
Comments: Sample must be sent to microbiology and pathology for stains and cultures for viruses, bacteria, mycobacteria, fungi and parasites.

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[28].
Viral load for Adenovirus
Comments: Obtain only if clinical suspicion is high[29].
Serology for Histoplasmosis, Coccidioidomycosis and Blastomycosis
Comments: Fungal serology is not generally recommended in immunosuppressed patients since they fail to generate an adequate antibody response to infection[27].

Table 7. Microbiological studies in BAL fluid or tranbronchial lung biopsy

Bacteria Gram's stain and culture
Comments: A negative stain and culture of MDR pathogens (e.g. MRSA) can be used for de-escalation of therapy unless antibiotics have been given for >48 hours.
MRSA PCR
Comments: A negative PCR for MRSA can be used for de-escalation of anti-MRSA therapy unless antibiotics have been given for >48 hours[31].
AFB stains and culture for tuberculous and non-tuberculous mycobacteria
Comments: 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[20].
Nocardia stains and culture
Comments: AFB stain may be weakly positive.
Fungal stains and culture
Comments: Since *Aspergillus* can colonize the airways, positive stains or culture of *Aspergillus* species from respiratory samples do not necessarily indicate disease[27].
PCP stains and PCR
Comments: In patients with PCP, the sensitivity of staining is higher in HIV-infected patients when compared to HIV-uninfected patients. A positive PCR may occur in patients colonized with PCP. In non-HIV patients, a negative PCR can be use to discontinue anti-PCP therapy[32].
Respiratory Viral Panel with multiplex PCR
Comments: Viruses can be detected in BAL by PCR in a patient with a negative nasopharyngeal swab PCR for the same virus[22,23].
Atypical pathogens panel with multiplex PCR
Comments: A positive PCR is considered diagnostic for atypical pneumonia since pathogens such as *Legionella*, *Chlamydophila*, or *Mycoplasma* rarely colonize the airway.
Galactomannan Antigen
Comments: The cell wall of *Aspergillus* contain 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 beta-lactam antibiotics[27].
Aspergillus PCR
Comments: The high sensitivity of PCR produce a high negative predictive value, making the diagnosis unlikely with a negative test[27].
(1,3)-Beta-D-glucan
Comments: It is considered a poor screening tool for the diagnosis of invasive fungal infections due to its low positive predictive value[27].
CMV PCR
Comments: Quantitative PCR analysis in BAL fluid may help to differentiate between CMV pneumonia (high viral load) versus CMV pulmonary shedding without pneumonia (low viral load) but cut-off levels are not defined[33].
Cellular analysis
Comments: A predominantly inflammatory cellular pattern in the BAL with neutrophil pleocytosis can be used as a predictor of bacterial etiology[34,35].
Histopathology
Comments: Routine hematoxylin and eosin (H&E) staining, special stains, and culture for viruses, bacteria, mycobacteria, fungi and parasites.

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ABBREVIATION LIST

BAL:	bronchoalveolar lavage
CAP:	community-acquired pneumonia
CMV:	Cytomegalovirus
CRE:	carbapenemase-producing *Enterobacteriaceae*
DMARDs:	disease-modifying anti-rheumatic drugs
ESBL:	extended spectrum beta-lactamase
HIV:	human immunodeficiency virus
MDR:	multiple drug resistant
NTM:	non-tuberculous Mycobacteria
PCP:	*Pneumocystis jirovecii*
PCR:	polymerase chain reaction
PSI:	Pneumonia Severity Index
TMP-SMX:	trimethoprim-sulfamethoxazole
TNF:	tumor necrosis factor

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ABBREVIATION LIST

BAL:	bronchoalveolar lavage
CAP:	community-acquired pneumonia
CMV:	Cytomegalovirus
CRE:	carbapenemase-producing *Enterobacteriaceae*
DMARDs:	disease-modifying anti-rheumatic drugs
ESBL:	extended spectrum beta-lactamase
HIV:	human immunodeficiency virus
MDR:	multiple drug resistant
NTM:	non-tuberculous Mycobacteria
PCP:	*Pneumocystis jirovecii*
PCR:	polymerase chain reaction
PSI:	Pneumonia Severity Index
TMP-SMX:	trimethoprim-sulfamethoxazole
TNF:	tumor necrosis factor

ABSTRACT

Background

Community-acquired pneumonia (CAP) guidelines have improved the management and outcomes of patients with CAP, primarily by standardization of initial empiric therapy. But current society-published guidelines exclude immunocompromised patients.

Research Question

There is no concensus regarding the initial management of immunocompromised patients with suspected CAP.

Study Design and Methods

This consensus document was created by a multidisciplinary panel of 45 physicians with experience in the management of CAP in immunocompromised patients. The Delphi survey methodology was used to reach consensus.

Results

The panel focused on 21 questions addressing initial management strategies. The panel achieved consensus in defining the population, site of care, likely pathogens, microbiological work-up, general principles of empiric therapy, and empiric therapy for specific pathogens.

Interpretation

This document offer general suggestions for the initial management of the immunocompromised patient who arrives at the hospital with pneumonia.

INTRODUCTION

Guidelines for the management of patients with community-acquired pneumonia (CAP) have been published by medical societies from several countries. These guidelines have improved the management and outcomes of patients with CAP, primarily by standardization of initial empiric therapy. But current society-published CAP guidelines exclude immunocompromised patients[1-3]. Immunocompromised patients have been excluded from guidelines because of their need for complex, often individualized, treatment, the expanded spectrum of potential pathogens, and their exclusion from the large prospective studies of antibiotic efficacy used to support guideline recommendations.

The number of immunocompromised persons at risk for CAP is increasing due to: (i) longer survival of patients with cancer, and recipients of organ transplants; (ii) better recognition of immunocompromising conditions; (iii) additional risk groups, such as those receiving novel immune-modulating therapies for non-malignant diseases, and (iv) approval of newer immunomodulatory agents. It is estimated that 3% of the adult population of the United States is immunosuppressed[4]. Immunocompromising conditions are present in approximately 20 to 30% of hospitalized patients with CAP[5-7].

Frequently, the initial management of pneumonia in immuncompromised patients may not occur in specialized tertiary care centers with advanced expertise in their care. Rather, immunocompromised patients with symptoms of lower respiratory tract infection often present first to general hospitals to be managed by emergency room physicians, internists, or hospitalists. These general conditions are identical to those motivating the initial impetus for guidelines to treat CAP; namely, the frequency of the condition and the presentation of patients in many different health care settings throughout the community.

Early and adequate empiric treatment of CAP in the general population is associated with decreased morbidity and mortality, and the authors attempt here to facilitate application of these same principles to patients at high risk of CAP-related complications due to pre-existing immune dysfunction. The approaches suggested in this document are based on an extensive review of the literature and on the collective experience of the authors. A challenge of reviewing the CAP literature in the immunocompromised host is that most publications evaluate outcomes of antimicrobial therapy for patients in whom the pathogen causing CAP has been identified. No

large, prospective clinical studies comparing different empiric therapies in immunocompromised patients exist.

Susceptibility to specific infections varies widely in immunocompromised patients and depends both on the degree of immune suppression and the components of the immune system which are affected by the underlying disease and/or medical therapy. In this document we attempt to develop a unifying approach to simplify a very complex topic, involving a heterogenous population. The objective of this document is to suggest an approach to the initial management of immunocompromised patients with suspected CAP.

METHODS

The Delphi survey methodology used to reach consensus. After a full review of the English literature in the topic of management of CAP in the ICP, the Delphi questions used in the survey were developed (Table 1). The following 5-point Likert scale was used to evaluate agreement or disagreement with each proposed answer: *Strongly Disagree (1), Disagree (2), Neutral (3), Agree (4), Strongly Agree (5).* It was considered that a consensus was reached once more than 75% of participants agreed or strongly agreed with a particular suggestion.

In each round of the Delphi survey, questions regarding the management of CAP in the ICP were submitted to all 45 participants of the consensus. To anonymously record participant responses and comments, a survey was developed using Research Electronic Data Capture (REDCap) that allowed participants to answer with their level of agreement with the suggestion and to write specific comments regarding the management suggested by the group. After each round, all responses were summarized and an anonymized summary of all the comments was produced and sent to each participant. Participants have the opportunity to revise the earlier answers considering the anonymized replies of other members of the panel.

After the participants answered the third round of all questions, the range of the answers decreased significantly and it was considered that group had reached consensus. At that point, a pre-final manuscript was created and submitted to all participants for final comments and agreement ratings. After the final comments were incorporated, the manuscript was produced.

Further details regarding the Delphi survey methodology and rounds are in the supplementary material.

Statistical analysis

At each round of the survey, the mean and standard deviation of agreement based on the Likert scale for each question was calculated. To evaluate the level of agreement or disagreement for each question in a manner that incorporated both mean and standard deviation, a t-statistic for each question was calculated. The t-statistic was used to identify which questions had the least amount agreement or most controversy. Agreement was visualized by bar charts, and final agreement was reported as percentage of participants who responded as *Agree* or *Strongly Agree.*

RESULTS

A. Definition of Population

Question 1: Which patients with CAP should be considered immunocompromised?
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.

No consensus exists regarding which patients should be formally considered immunocompromised. Our pragmatic approach is to consider patients to be immunocompromised if they are at elevated risk of pneumonia not only by common organisms but also by uncommon avirulent or opportunistic organisms. Several practical aspects of meeting this definition include the need for comprehensive microbiological testing, the need to alter empirical antimicrobial therapy, and the need for adjunctive therapy. Even using this more restrictive definition, medical advances supporting longer survival of patients with serious conditions and an expanding armamentarium of biological agents results in expanding populations of at-risk individuals. Using this approach, the most common acquired conditions that qualify a patient as being immunocompromised are a malignancy that suppresses immune

responses (such as lymphoma or leukemia) and advanced HIV infection (CD4 T-lymphocyte count <200 cells/μl). The most frequent treatments that qualify a patient as being immunocompromised include glucocorticoids, therapies that suppresses B-cell or T-cell responses, chemotherapy for malignancy that causes neutropenia, conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents used to treat a broad range of rheumatological, dermatological, gastrointestinal, and autoimmune diseases. Notably, some agents (e.g., ibrutinib, alemtuzumab or fludarabine) have persistent immunosuppressive effects, long after active treatments is discontinued. A list of patients who should be considered immunocompromised is depicted in Table 2[8-13].

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 management is covered in the current CAP guidelines.

B. Site of Care

Question 2: Which immunocompromised patients with CAP should be admitted to the hospital? We suggest that the decision for hospitalization should be based on clinical judgement having a low threshold for hospital admission.

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 (PSI) 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[14-16]. Because immunosuppressive drugs are known to modulate the inflammatory response, the typical signs and symptoms of CAP may be attenuated in these patients. The blunted inflammatory response may not produce a clear infiltrate at chest x-ray. A CT scan of the chest will allow a better definition of the extent of pulmonary infiltrate as well as better recognition of complications of pneumonia such abscesses, or pleural effusions. This information, gained with

CT scan of the chest, may help in the decision regarding hospitalization. Hypoxia is a particularly useful criterion to define site of care. In non-immunocompromised patients with CAP, a blood oxygen saturation <92 percent is considered an appropriate threshold for hospital admission[17]. Immunocompromised patients may appear stable at the time of the initial evaluation but may deteriorate rapidly, progressing in a few hours from a moderately severe pneumonia to a severe pneumonia in need of intensive care. Also, the increased range of potential infecting agents renders selection of any empiric regimen much more challenging, often requiring parenteral agents. Therefore, our suggestion is for a low threshold for hospitalization. If the patient is considered sufficiently stable for outpatient care, mechanisms for close follow up and rapid re-entry to inpatient healthcare should be available.

C. Likely Pathogens

Question 3: 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 non-immunocompromised.

Immunocompromised patients are susceptible to infection by the same respiratory viruses and bacteria that cause CAP in the non-immunocompromised patient. 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 lists the primary groups of "core respiratory pathogens" that can cause CAP in immunocompromised patients[5,6,18].

Question 4: 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. Common respiratory pathogens that: 1) may cause CAP in the immunocompromised host and 2) for which antimicrobial therapy is available, are listed in Table 4. Different types of

immunocompromise conditions will predispose to different types of etiologic agents. A description of specific immune deficiencies and the associated respiratory pathogens are depicted in Table 5.

Initial empiric therapy active against these respiratory pathogens may only be necessary in selected patients presenting with specific epidemiological, clinical or immunological risk factors for infection due to a particular pathogen. These risk factors and the specific pathogens that are involved will be discussed below.

D. Microbiological Work-up

Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?
We suggest a comprehensive microbiological work-up with the goal to perform pathogen-directed therapy and de-escalation of therapy.

A critical aspect of the management of these patients is initial microbiological work-up coupled with empiric therapy, followed by a de-escalation to therapy directed to the causative pathogen. De-escalation of therapy is important since continuing a broad-spectrum therapy for the full duration of therapy is associated with selection of multi-resistant organisms, increased risk of toxicity, drug-drug interactions and impaired antimicrobial stewardship for the entire community. As the primary way to perform de-escalation therapy is knowing the pathogen that causes pneumonia, a comprehensive microbiological work-up is critically important. Another reason to obtain broad microbiological studies is that treatment of opportunistic pathogens is complex and often complicated by toxicities and drug-drug interactions.

The extent of the microbiological work-up should be individualized considering the presence of risk factors and likely organisms, as well as local capabilities. During recent years the field of diagnostic microbiological techniques has experienced a significant progress. Development of rapid diagnostic tests using new molecular techniques and sophisticated new laboratory methods such as the matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry are reshaping the clinical microbiology laboratory as well as our ability to identify etiologic agents of CAP in immunocompromised patients[19]. A list of common microbiological studies with relevant clinical considerations is depicted in Table 6[20-29].

Question 6: When should a bronchoscopy with bronchoalveolar lavage be performed in hospitalized patients with CAP who are immunocompromised?
We suggest that the decision to perform a bronchoscopy or bronchoalveolar lavage should be individualized.

A 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. Preferably, a bronchoscopy with BAL should be done early so that initial empiric therapy does not alter the culture results. If the bronchoscopy can be obtained promptly, a short delay before initiating antibiotic therapy may be acceptable, given improved culture yield. In general, the more immunocompromised the host, the greater the potential benefit of performing a bronchoscopy with BAL.

If the etiology of CAP may be defined based on initial x-rays and point of care diagnostic testing, the small, but nevertheless clear risk associated with bronchoscopy with BAL may outweigh the benefit[30].

Question 7: What microbiological studies can be obtained in bronchoalveolar lavage fluid in 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 in BAL from immunocompromised patients with CAP. In other institutions, the tests are ordered considering the presence of clinical, radiographic and immunological risk factors for specific organisms. Table 7[31-35] lists microbiological studies that can be done on BAL or tissue from a transbronchial lung biopsy together with relevant clinical considerations.

E. Empiric Therapy: General Principles

Question 8: What empiric 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 empiric therapy targeting only the core respiratory pathogens.

Although immunocompromised hosts may have unique immunological risk and often more frequent nosocomial contact and antibiotic exposure, many immunocompromised patients admitted with CAP do not have any additional risk factors for drug resistant bacteria (e.g. MRSA, Pseudomonas). For these patients, we suggest initial empiric antimicrobial therapy targeting the "core respiratory pathogens" described in Table 3. In these group of patients, the initial empiric anti-bacterial therapy would be the same as the initial empiric therapy for hospitalized patients with CAP who are not immunocompromised[1]. Additional empiric treatment beyond the core respiratory pathogens should be considered according to the presence of risk factors for drug-resistance or opportunistic pathogens and will be discussed in sections below.

Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?
We suggest to extend empiric therapy beyond core respiratory pathogens when 1) risk factors for drug resistant organisms or opportunistic pathogens are present and 2) the delay in empiric antimicrobial therapy will place the patient at increased risk of mortality.

In addition to initial empiric treatment for core respiratory pathogens, we suggest broader initial coverage when the following factors are met: 1) A resistant bacterium or an opportunistic pathogen is suspected based on the presence of risk factors from findings on history or physical examination, laboratory results and/or imaging patterns; AND 2) waiting for microbiological identification of the suspected pathogen will significantly delay initiation of antimicrobial therapy and may increase the risk of mortality. Other considerations for extending initial empiric therapy beyond core pathogens include availability of point of care tests, severity of disease at presentation, and use of prophylactic therapy for a particular opportunistic pathogen.

The need for empiric therapy of opportunistic pathogens will continue to evolve as more point-of-care tests are developed for rapid diagnosis. Empiric therapy beyond core respiratory pathogens may not be necessary if the patient is clinically stable and the local setting allows for rapid microbiological diagnostic tests.

Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?
We suggest that the presence of severe pneumonia can be used as an indication to start empiric therapy for resistant gram positive and gram negative organisms, followed by rapid de-escalation if no multi-drug resistant pathogen is identified.

Severity of illness is not by itself an accurate predictor of drug-resistance or opportunistic infection in pneumonia. For example, *Streptococcus pneumoniae* is capable of causing life-threatening septic shock, whereas invasive pulmonary aspergillosis may present with an indolent, progressive course.

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

F. Empiric Therapy: Specific Pathogens

Question 11: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to MRSA?
We suggest that initial empiric therapy to cover for MRSA should be started in patients with a history of colonization or infection with MRSA in the previous twelve months.

In patients with a history of colonization or infection with MRSA in the previous 12 months initial empiric therapy should cover the possibility of infection due to MRSA. There are other risk factors reported in the literature for MRSA infection such as prior antibiotic use, recent hospitalization, hemodialysis or wound care, but if the local prevalence of MRSA is low, these risk factors will each have a low positive predictive value and should not be used to trigger empiric anti-MRSA therapy[36-40]. On the other hand, a single patient who accumulate many of these risk factors may have a high likelihood of CAP due to MRSA. Vancomycin or linezolid are the first line for initial empiric therapy. In regions with high prevalence of MRSA, some members of the panel will start empiric anti-MRSA therapy in patients requiring ICU admission.

A negative MRSA nasal PCR, absence of Gram-positive cocci in clusters on Gram's stain, and a negative MRSA respiratory culture can be used to de-escalate anti-MRSA therapy.

Question 12: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of drug-resistant Gram-negative bacilli, including Pseudomonas aeruginosa?
We suggest that initial empiric 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 twelve months, previous hospitalization with exposure to broad-spectrum antibiotics, presence of a tracheostomy, neutropenia, or history of pulmonary comorbidity.

History of colonization or infection with a drug resistant Gram-negative bacilus in the previous 12 months, previous hospitalization with exposure to broad spectrum antibiotics, presence of a tracheostomy, neutropenia, history of pulmonary comorbidity (e.g. cystic fibrosis, bronchiectasis, or recurrent exacerbations of COPD requiring glucocorticoid and antibiotic use) have been reported in literature to increase risk of resistant Gram-negative bacili[37-42]. Patients with any of these risk factors should be considered for initial empiric therapy against resistant Gram-negative bacilli including *P. aeruginosa*. Beta-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[43].

Question 13: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to multi-drug 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 empiric therapy should cover the possibility of infection due to the colonizing MDR Gram-negative bacilli.

In patients with a recent history of colonization or infection with MDR Gram-negative bacilli such as extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceaea*, carbapenemase-producing *Enterobacteriaceae* (CRE), MDR *Pseudomonas*, or MDR *Acinetobacter*, the initial empiric therapy should cover the possibility of infection due to the

colonizing MDR Gram-negative bacilli. A knowledge of 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 empiric therapy for these organisms with difficult-to-treat resistance. For empiric therapy of MDR Gram-negative bacilli, beta-lactam antibiotics such as piperacillin-tazobactam or imipenem, may have to be changed to newer beta-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 beta-lactam is a possibility when other agents are not available. In patients treated empirically with these broad spectrum agents, we strongly emphasize an extended microbiological workup and prompt de-escalation of therapy if appropriate.

Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Pneumocystis jirovecii pneumonia (PCP)?
We suggest initial empiric 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 either (1) an HIV host who is newly diagnosed, or not on antiretroviral therapy, or with CD4 counts less than 200 cells/μl (or a percentage lower than 14%) or (2) a non-HIV host with severely impaired cell-mediated immunity (e.g., glucocorticoids with cytotoxic agents).

In these patients we suggest the addition of TMP-SMX to the initial regimen. The recommended dose for TMP-SMX is 15 to 20 mg/kg/day of the trimethoprim component orally or IV given in three or four divided doses[44]. The dose of TMP-SMX is the same for PCP in the HIV patient and PCP in the immunocompromised non-HIV patient. Adjunctive glucocorticoids are recommended for HIV patients with a room air PaO2 <70 mmHg and/or an alveolar-arterial (A-a) oxygen gradient of ≥35 mmHg[44]. Corticosteroids are not beneficial in HIV-negative patients with PCP[45].

Question 15: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Aspergillus?
We suggest that empiric 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 radiographic nodular pattern surrounded by a halo of ground-glass attenuation and/or cavitation.

Voriconazole is considered the first line treatment for patients with documented invasive aspergillosis, but we do not suggest empiric voriconazole because these patients are also at risk for other filamentous fungi resistant to voriconazole (e.g. mucormycosis)[46]. In these patients we suggest empiric therapy with liposomal amphotericin at doses of 5 to 7.5 mg/kg daily. In patients intolerant to amphotericin, empiric therapy with isavuconazole with an initial dose of 200 mg every 8 hours can be used as an alternative[47].

Patients treated with tumor necrosis factor (TNF) inhibitors, such as etanercept, infliximab, or adalimumab, are also at risk of fungal pneumonia[11,12]. In these patients we suggest an aggressive diagnostic work-up and treat if a fungus is identified. In the management 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 empiric therapy be extended to cover the possibility of CAP due to Mucorales?
We suggest that empiric 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 radiographic nodular pattern, or a reverse halo sign, or pleural effusion.

Empiric therapy for *Mucorales* is especially important when fungal infection is suspected in a patient on voriconazole antifungal prophylaxis. In these patients we suggest liposomal amphotericin as part of the initial empiric regimen at doses of 5 to 7.5 mg/kg daily[48]. In patients intolerant to amphotericin, empiric therapy with isavuconazole with an initial dose of 200 mg every 8 hours can be used as an alternative[47]. Voriconazole does not cover Mucormycosis and therefore it is not suggested as initial empiric therapy.

Question 17: In which immunocompromised patients should the initial empiric 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 dose of 15 mg/kg IV of the trimethoprim component per day in three or four divided doses[49]. Resistance of *Nocardia* spp. to TMP-SMX is a rare event[50]. If TMP-SMX is contraindicated, Linezolid also has excellent activity and can be considered for empiric therapy until susceptibilities are known[50]. If initial treatment contains already a drug with activity against Nocardia spp. (e.g. linezolid or imipenem) empiric addition of TMP-SMX is not requested. However, TMP-SMX is the drug of choice for definite treatment.

Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?
We suggest that empiric 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 intravenous acyclovir 10-15 mg/kg IV every 8 hours to the initial empiric regimen[51].

Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?
We suggest that empiric 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 dose of 5 mg/kg IV every 12 hours, with dose adjustment for renal dysfunction[52]. Elevated plasma CMV viral loads are frequent in patients with CMV pneumonitis, but this finding alone is not sufficient for diagnosis[53]. In lung transplant recipients, CMV PCR viral load in BAL is a superior diagnostic tool than plasma CMV viral load[54].

Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Mycobacterium tuberculosis?
We suggest not to start empiric therapy to cover the possibility of CAP due to Mycobacterium tuberculosis.

Pulmonary infections due to mycobacteria such as tuberculosis, are common in patients treated with TNF inhibitors and patients with long term high-dose steroids[11]. But in the case of suspected mycobacterial pneumonia we do not suggest treating the patient with empiric therapy. We suggest carrying out the indicated microbiological studies and begining treatment once the pathogen has been identified. We think that in these patients the risk-benefit of expanding empiric therapy with multiple mycobacterial drugs versus waiting to define which patients have a mycobacterial infection, is in favor of waiting for microbiological 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 tuberculosis infection, and present with severe CAP. In this patients we will start empiric therapy for tuberculosis pending microbiologic work-up[44].

Question 21: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to parasites?
We suggest not to start empiric therapy to cover CAP due to parasites.

Parasites that can produce CAP in the immunocompromised host include *Strongyloides stercoralis* and *Toxoplasma gondii*[55,56].

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 gastrointestinal tract. Patients at risk of *Strongyloides* hyperinfection syndrome include those with solid organ transplantation, hematopoietic stem cell transplantation, or patients with high and prolonged doses of corticosteroids (e.g. prednisone ≥20 mg per day, or its equivalent, for longer than 1 month) in combination with cytotoxic agents. Patients on this type of immune suppressing therapy, and also those with secondary bacteremias, may not have an elevated eosinophil count to raise suspicion of a parasitic infection. Therapy with ivermectin is recommended for patients with hyperinfection syndrome[55].

Toxoplasma pneumonia occurs due to reactivation of latent infection in (1) patients with HIV infection that is newly diagnosed, and not on antiretroviral therapy or with CD4 counts less than 100 cells/μl; 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[44].

We think that in these patients the risk benefit of expanding empiric therapy for parasitic infections or waiting to define which patients have a parasitic infection favors waiting for microbiological results and treat only the patients with a proven parasitic infection.

DISCUSSION

In this document we have developed general suggestions for the initial management of the immunocompromised patient who arrives at the hospital with pneumonia. Despite our suggestions of empirical therapy for specific pathogens in specific situations, we stress the importance of making a concerted effort to establish a rapid and accurate etiologic diagnosis and to de-escalate complex therapies once a presumptive pathogen is properly ruled out. It is also important to consider local susceptibility patterns when selecting empiric therapy. The participants do suggest that, if evidence supports the presence of infections that require highly specialized management (e.g. cytomegalovirus or Mucorales), after initial therapy is begun, prompt transfer to a tertiary care facility should be strongly considered. Transfer to a specialized center may not be necessary if experienced pulmonary and infectious disease specialists are available to participate in management.

An important weakness of this document is the simplification of heterogenous conditions that affect different arms of the immune system into a single group of immunocompromised patients with CAP. Another limitation is that we were not able to provide references that appropriately support several of our suggestions, hence we need to emphasize the suggestions offered in this consensus are based primarily on expert opinion.

In conclusion, we have developed general suggestions for the initial management of immunocompromised patients hospitalized with pneumonia. When possible, the care of these patients should be carried out by a multidisciplinary group of specialists. Because immunocompromised patients have been excluded from prospective randomized studies of CAP treatment, there is an urgent need to generate scientific evidence in this field.

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TABLES

Table 1. Questions addressing initial management strategies for community-acquired pneumonia (CAP) in immunocompromised adults.

A. Definition of Population
Question 1: Which patients with CAP should be considered immunocompromised?
B. Site of Care
Question 2: Which immunocompromised patients with CAP should be admitted to the hospital?
C. Likely Pathogens
Question 3: What pathogens should be considered "core respiratory pathogens" in patients with CAP who are immunocompromised?
Question 4: What pathogens should be considered beyond the "core respiratory pathogens" in patients with CAP who are immunocompromised?
D. Microbiological Work-up
Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?
Question 6: When should a bronchoscopy with bronchoalveolar lavage be performed in patients with CAP who are immunocompromised?
Question 7: What microbiological studies can be obtained in bronchoalveolar lavage in patients with CAP who are immunocompromised?
E. Empiric Therapy: General Principles
Question 8: What empiric therapy should be started in hospitalized patients with CAP who are immunocompromised?
Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?
Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?
F. Empiric Therapy: Specific Pathogens
Question 11: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to MRSA?
Question 12: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of drug-resistant Gram-negative bacilli, including *Pseudomonas aeruginosa*?

Question 13: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to multi-drug resistant (MDR) Gram-negative bacilli?
Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?
Question 15: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Aspergillus*?
Question 16: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mucorales*?
Question 17: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Nocardia*?
Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?
Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?
Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?
Question 21: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to parasites?

Table 2. Patients with the following conditions should be considered immunocompromised

Primary immune deficiency diseases
Active malignancy or malignancy within one year prior to CAP, excluding patients with localized skin cancers or early stage cancers (e.g. stage 1 lung cancer)
Receiving cancer chemotherapy
HIV infection with a CD4 T-lymphocyte count <200 cells/μl or percentage <14%*[8]
Solid organ transplantation
Hematopoietic stem cell transplantation
Receiving corticosteroid therapy with a dose ≥ 20 mg prednisone or equivalent daily for ≥14 days or a cumulative dose > 700 mg of prednisone**[9,10]
Receiving biologic immune modulators***[11,12]
Receiving disease-modifying anti-rheumatic drugs[13] or other immunosuppressive drugs (e.g. cyclosporin, cyclophosphamide, hydroxychloroquine, methotrexate)

*The association of HIV disease and CAP can be categorized in 3 levels.

Level 1: Patients with a CD4 T-lymphocyte count >500 cells/μl. These patients are not at increased risk of CAP.

Level 2: Patients with a CD4 T-lymphocyte count between 500 to 200 cells/μl. 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/μl. These patients are at risk for CAP due to opportunistic pathogens such as PCP. They are considered immunocompromised patients with CAP.

**In the case of patients taking steroid and CAP, both the daily dose and the cumulative dose of steroids should be considered. The association with CAP can be define in 3 levels.

Level 1: Doses ≤10 mg of prednisone a 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 mg to ≤ 20 mg of prednisone a 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: Doses ≥20 mg or more of prednisone a 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 PCP. They are considered immunocompromised patients with CAP. Due to the cumulative dose of at least 600 mg, this patients need to be on steroid therapy for at least 3 to 4 weeks to be consider fulfilling this condition.

***These drugs are used to treat a wide array of inflammatory conditions and have multiple immunological 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. Specific discussion of these drugs in detail is beyond the scope of this paper. 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.

Table 3: List of "Core Respiratory Pathogens" that may cause CAP in the immunocompromised patient

Gram positive bacteria	**Gram negative bacteria**	**"Atypical" bacteria**	**Respiratory Viruses**
Streptococcus pneumoniae	*Haemophilus influenzae*	*Legionella pneumophila*	Influenza
Staphylococcus aureus (MSSA)	*Moraxella catarrhalis*	*Chlamydophila pneumoniae*	Parainfluenza
Streptococcus pyogenes	Enterobacteriaceae *(*e.g. *Klebsiella* spp. *Escherichia coli)*	*Mycoplasma pneumoniae*	Coronavirus
Other streptococci		*Coxiella burnetii*	Respiratory syncytial virus
			Rhinovirus
			Adenovirus
			Human metapneumovirus

Table 4: List of common respiratory pathogens in addition to core respiratory pathogens (as described in Table 3) that can cause CAP in the immunocompromised patient and for which antimicrobial therapy is available.

Bacteria	**Mycobacteria**	**Viruses**	**Fungi**	**Parasites**
Enterobacteriaceae (Including those producing ESBL and also CRE)	*Mycobacterium tuberculosis*	Cytomegalovirus (CMV)	*Pneumocystis jirovecii* (PCP)	*Toxoplasma gondii*
Non-fermenting Gram negative bacilli (e.g. *Pseudomonas* or *Acinetobacter*)	Non-tuberculous Mycobacteria (NTM)	Herpes simplex	*Aspergillus* spp.	*Strongyloides stercoralis*
MRSA		Varicella-zoster	*Mucorales* spp.	
Nocardia spp.			*Histoplasma* spp.	
Rhodococcus equi			*Cryptococcus* spp.	
			Blastomyces spp.	
			Coccidioides spp.	

Table 5. Specific immune deficiencies and associated respiratory pathogens

Specific Immune Deficiency	Unique Respiratory Pathogen Associations
Neutropenia	*Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, other *Enterobacteriaceae*, *Streptococcus mitis, Staphylococcus aureus, Nocardia* spp, *Aspergillus* and other hyaline molds (*Scedosporium, Fusarium*), yeast-like fungi (*Trichosporon*), *Mucorales*, dimorphic fungi
AIDS	*Pneumocystis jiroveci, Streptococcus pneumoniae, Mycobacterium tuberculosis, M. avium-intracellulare* complex and other non-tuberculous mycobacteria, *Histoplasma capsulatum, Coccidioides, Bartonella*, *Rhodococcus, Toxoplasma gondii, Cryptococcus neoformans, Cryptosporidium, Nocardia, Talaromycosis marneffei, Paracoccidioides, Burkholderia, Cytomegalovirus, Strongyloides*
T-cell depletion (Antithymocyte globulin, Alemtuzumab)	*Pneumocystis jiroveci, Streptococcus pneumoniae, Mycobacterium tuberculosis, M. avium-intracellulare* complex and other non-tuberculous mycobacteria, *Aspergillus* and other hyaline molds, *Mucorales* spp, Varicella, Herpes simplex, Cytomegalovirus, *Histoplasma capsulatum*, *Coccidioides, Bartonella* spp., *Toxoplasma gondii, Cryptococcus neoformans, Nocardia, Legionella, Strongyloides*
Hypogammaglobulinemia (Common variable immunodeficiency, Multiple Myeloma, Therapies that target CD19/20, e.g. rituximab)	Respiratory viruses (Influenza, RSV, HMPV, Parainfluenza, Adenovirus, Enterovirus), Encapsulated bacteria (*S. pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, S. aureus, Capnocytophaga, Pasteurella multocida*), Cytomegalovirus, *Pneumocystis*
Calcineurin Inhibitors (cyclosporine and tacrolimus)	*Legionella, Nocardia, Aspergillus* and other hyaline mold, *Mucorales* spp, Cytomegalovirus, endemic fungi
Antimetabolites (mycophenolate mofetil, azathioprine, 6-MP, fludarabine)	Cytomegalovirus, Varicella, Respiratory viruses (if B-cell impairment), *Legionella, Nocardia, Aspergillus* and other hyaline mold, *Mucorales* spp, endemic fungi, (*Pneumocystis*– fludarabine)
Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, evirolimus)	*Cryptococcus, Pneumocystis*

Tumor Necrosis Factor (TNF) Inhibitors	Endemic fungi, *Aspergillus*, *Mycobacteria* (tuberculous and non-tuberculous), Varicella, *Nocardia*, *Pneumocystis*
Janus kinase (JAK) Signaling Inhibitors (e.g. Ibrutinib, Dasatinib)	*Pneumocystis*, mold, Cytomegalovirus
Corticosteroids	Bacteria, esp. *Pseudomonas aeruginosa, Pneumocystis jiroveci, Staphylococcus aureus, Mycobacteria*, *Aspergillus* and other hyaline molds, *Mucorales* spp, Cytomegalovirus , Varicella, Herpes simplex, Cytomegalovirus, *Histoplasma capsulatum, Coccidioides, Cryptococcus neoformans, Nocardia, Legionella, Strongyloides*
Other	Natalizumab (*Cryptococcus*), vedolizumab (*M. tuberculosis*), Tocilizumab (unknown), Ustekinumab (theoretical CMV), Secukinumab (theoretical mold), eculizumab (*Pseudomonas*, mold), bortezemib (Varicella zoster)

Table 6. Microbiological studies that can be obtained in immunocompromised patients hospitalized with CAP

Sputum samples for bacterial, mycobacterial, and fungal stains and cultures
Comments: Sputum can be induced using inhaled isotonic or preferably hypertonic saline for certain pathogens (e.g., MTB, PCP) in order to avoid invasive procedures. Sputum samples can be tested using PCR for detection of MTB or PCP[20,21].
Nasopharyngeal swab with PCR multiplex for respiratory viruses
Comments: A negative nasopharyngeal PCR does not rule out viral pneumonia. If the suspicion is high, perform the PCR on bronchoscopic samples[22,23]. The finding of a virus by PCR does not rule out bacterial infection.
Nasopharyngeal swab with PCR multiplex for atypical bacteria
Comments: Atypical pathogens such as *Legionella*, *Chlamydophila*, or *Mycoplasma*, can also be identified in oropharyngeal samples.
Nasal PCR for MRSA
Comments: Use in conjunction with a respiratory sample. A negative MRSA nasal PCR, the absence of Gram-positive cocci in clusters on Gram's stain, and a negative MRSA respiratory culture make MRSA pneumonia extremely unlikely.
Blood cultures times two (at least) 30 minutes apart
Comments: 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"[24]. The separation of samples over time improve bacterial detection in case of intermittent bacteremia[25].
Urinary antigen for *Streptococcus pneumoniae*
Comments: The recent administration of pneumococcal vaccine (within days) will produce a positive urinary antigen for *Streptococcus pneumoniae.*
Urinary antigen for Legionella
Comments: Detects only *Legionella pneumophila* serotype 1. Other Gram-negative bacteria may generate a false positive test[26]. Obtain respiratory samples for culture and PCR to detect other species of Legionella or serotypes if clinically indicated.
Urinary antigen for *Histoplasma capsulatum*
Comments: Very useful for disseminated disease. Cross reaction with blastomycosis.
Serum antigen for *Cryptococcus neoformans*
Comments: A *s*erum cryptococcal antigen test may be negative in a patient with documented cryptococcal pneumonia.
Serum galactomannan antigen
Comments: Aspergillus cell wall contains the polysaccharide galactomannan. Also elevated in *Fusarium*, *Penicillium*, blastomycosis, and histoplasmosis. False positives may occur with IVIG, transfusions and some beta-lactam antibiotics[27].
Serum 1,3-Beta-D-glucan
Comments: Beta-D-glucan is a cell component of several fungi. It screens for *Aspergillus* spp., *Candida* spp., PCP, and other fungi. It does not detect mucormycosis. False positives may occur with IVIG, hemodialysis with cellulose, albumin, infections by *Pseudomonas*, and some beta-lactam antibiotics[27].
Swabs of vesicular or ulcerated skin lesions for viral PCR and cultures
Comments: A positive PCR for HSV or VZV from skin lesions is highly correlated with herpes or varicella pneumonia.
Biopsy of skin lesion for microbiology & pathology
Comments: Sample must be sent to microbiology and pathology for stains and cultures for viruses, bacteria, mycobacteria, fungi and parasites.

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[28].
Viral load for Adenovirus
Comments: Obtain only if clinical suspicion is high[29].
Serology for Histoplasmosis, Coccidioidomycosis and Blastomycosis
Comments: Fungal serology is not generally recommended in immunosuppressed patients since they fail to generate an adequate antibody response to infection[27].

Table 7. Microbiological studies in BAL fluid or tranbronchial lung biopsy

Bacteria Gram's stain and culture
Comments: A negative stain and culture of MDR pathogens (e.g. MRSA) can be used for de-escalation of therapy unless antibiotics have been given for >48 hours.
MRSA PCR
Comments: A negative PCR for MRSA can be used for de-escalation of anti-MRSA therapy unless antibiotics have been given for >48 hours[31].
AFB stains and culture for tuberculous and non-tuberculous mycobacteria
Comments: 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[20].
Nocardia stains and culture
Comments: AFB stain may be weakly positive.
Fungal stains and culture
Comments: Since *Aspergillus* can colonize the airways, positive stains or culture of *Aspergillus* species from respiratory samples do not necessarily indicate disease[27].
PCP stains and PCR
Comments: In patients with PCP, the sensitivity of staining is higher in HIV-infected patients when compared to HIV-uninfected patients. A positive PCR may occur in patients colonized with PCP. In non-HIV patients, a negative PCR can be use to discontinue anti-PCP therapy[32].
Respiratory Viral Panel with multiplex PCR
Comments: Viruses can be detected in BAL by PCR in a patient with a negative nasopharyngeal swab PCR for the same virus[22,23].
Atypical pathogens panel with multiplex PCR
Comments: A positive PCR is considered diagnostic for atypical pneumonia since pathogens such as *Legionella*, *Chlamydophila*, or *Mycoplasma* rarely colonize the airway.
Galactomannan Antigen
Comments: The cell wall of *Aspergillus* contain 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 beta-lactam antibiotics[27].
Aspergillus PCR
Comments: The high sensitivity of PCR produce a high negative predictive value, making the diagnosis unlikely with a negative test[27].
(1,3)-Beta-D-glucan
Comments: It is considered a poor screening tool for the diagnosis of invasive fungal infections due to its low positive predictive value[27].
CMV PCR
Comments: Quantitative PCR analysis in BAL fluid may help to differentiate between CMV pneumonia (high viral load) versus CMV pulmonary shedding without pneumonia (low viral load) but cut-off levels are not defined[33].
Cellular analysis
Comments: A predominantly inflammatory cellular pattern in the BAL with neutrophil pleocytosis can be used as a predictor of bacterial etiology[34,35].
Histopathology
Comments: Routine hematoxylin and eosin (H&E) staining, special stains, and culture for viruses, bacteria, mycobacteria, fungi and parasites.

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e-Appendix 1.

SUPPLEMENTAL MATERIAL

Introduction

The goal of this project was to generate a consensus document on the initial management of community-acquired pneumonia (CAP) in the immunocompromised patient (ICP). Consensus was reached by using the Delphi survey method. In this supplemental material, we will describe: 1) the methodology used for the Delphi survey, and 2) the level of agreement for each of the recommendations.

1. Delphi survey methodology

We started this process with a core group of two infectious diseases physicians and four pulmonary physicians. After a full review of the English literature in the topic of management of CAP in the ICP, the initial Delphi questions used in the survey were developed. The core group performed several initial versions of the manuscript to reach a basic level of agreement regarding the answers for each of the Delphi survey questions. The following 5-point Likert scale was used to evaluate agreement or disagreement with each proposed answer: *Strongly Disagree (1), Disagree (2), Neutral (3), Agree (4), Strongly Agree (5).* It was considered that a consensus was reached once more than 75% of participants agreed or strongly agreed with a particular recommendation.

Once the basic document was developed, the first round of the Delphi questions regarding the management of CAP in the ICP were submitted to all 45 participants of the consensus. To anonymously record participant responses and comments, a survey was developed using Research Electronic Data Capture (REDCap) that allowed participants to answer with their level of agreement with the suggested recommendations and to write specific comments regarding the management suggested by the group.

After the first round of the survey was completed, all responses were summarized and plot using a bar chart to identify patterns and to indicate the level of agreement for each section of the manuscript. An anonymized summary of all the comments was produced. Each participant received the bar chart results and a summary of the comments and suggestions. Participants have the opportunity to revise the earlier answers considering the anonymized replies of other members of the panel. Additionally, we identified two areas with a significant level of disagreement.

For the second round of the survey, we focused only in these two areas of disagreement, which allowed the group to concentrate the discussion on the two questions with the highest level of disagreement. To reach agreement, some of the original questions were divided into new, more specific

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questions. After a better level of agreement was achieved for these questions, a third round of all questions were circulated among the group.

After the participants answered the third round of all questions, the range of the answers decreased significantly and it was considered that group had reached consensus. At that point, a pre-final manuscript was created and submitted to all participants for final comments and agreement ratings. After the final comments were incorporated, the manuscript was produced.

Statistical analysis

At each round of the survey, we calculated the mean and standard deviation of agreement based on the Likert scale for each question. To evaluate the level of agreement/disagreement for each question in a manner that incorporated both mean and standard deviation, we calculated a t-statistic for each question. This way, we could identify the questions, which had the least agreement or most controversy. Agreement was visualized by bar charts, and final agreement was reported as percentage of participants who responded as *Agree* or *Strongly Agree.*

2. Level of agreement for each section of the manuscript

Level of agreement with the Introduction

Agreement with the statements mentioned in the introduction of the manuscript was achieved in 44 of the 45 participants (98%). Initial agreement was also 98%. Results of the Likert scale for the introduction of the manuscript are depicted in the bar chart below.

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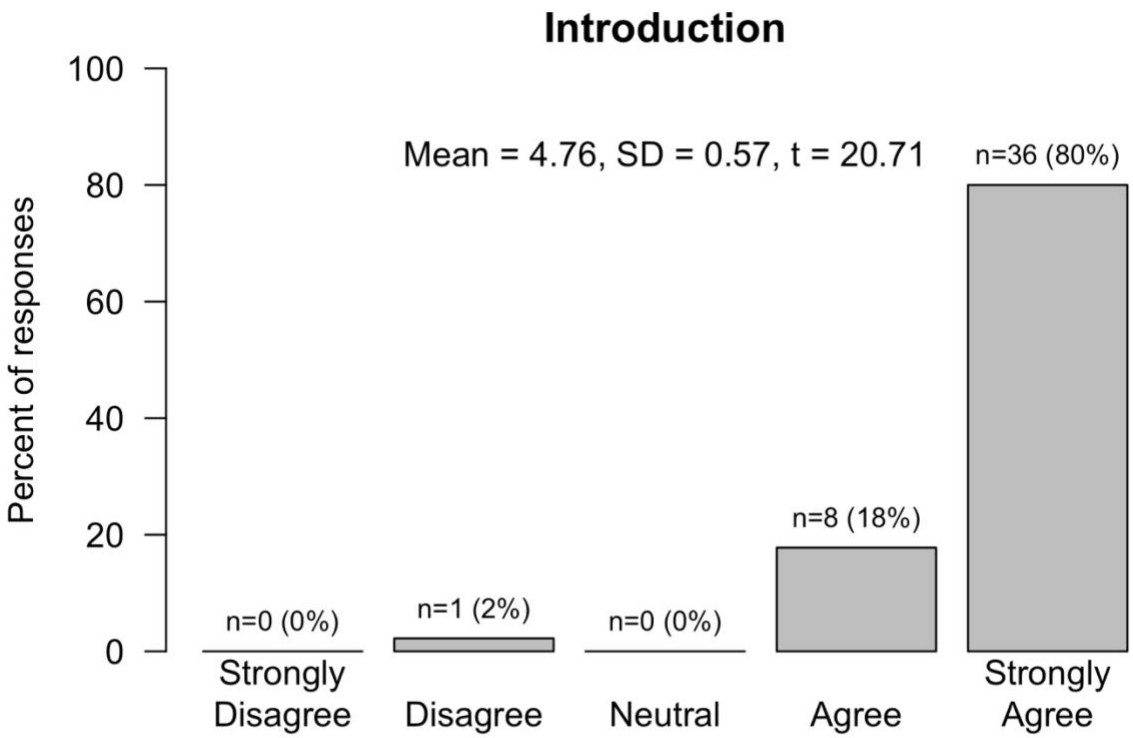

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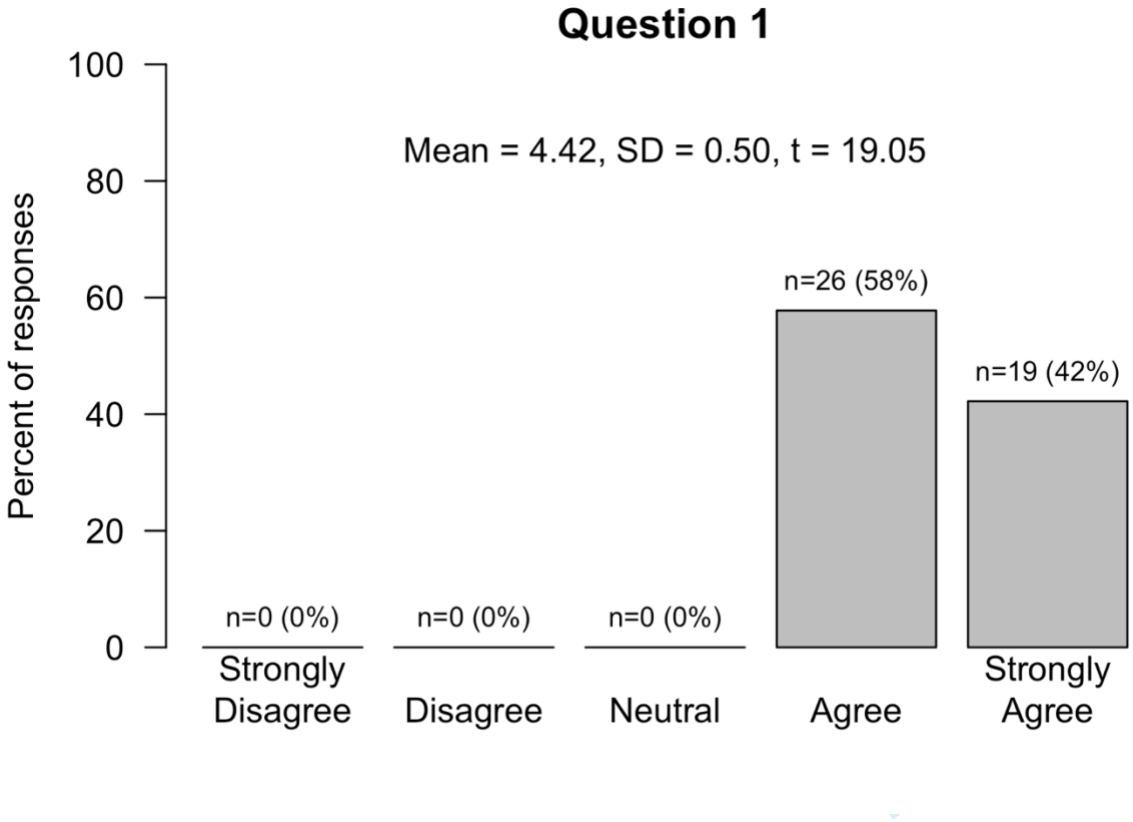
Level of agreement with Question 1: Which patients with CAP should be considered immunocompromised?

Agreement with the answer to question 1 was achieved in 45 of the 45 participants (100%). Initial agreement for the original, proposed answer to question 1 was 93%. Results of the Likert scale for question 1 are depicted in the bar chart below.



Additional comments for Question 1:

In patients without spleen, even though they are at increased risk for pneumonia, the organisms causing pneumonia are still the common organisms that cause CAP. Since patients without spleen are not at risk for opportunistic pathogens, they were not considered in this definition of immunocompromised. The same concept applies to patients on inhaled corticosteroids.

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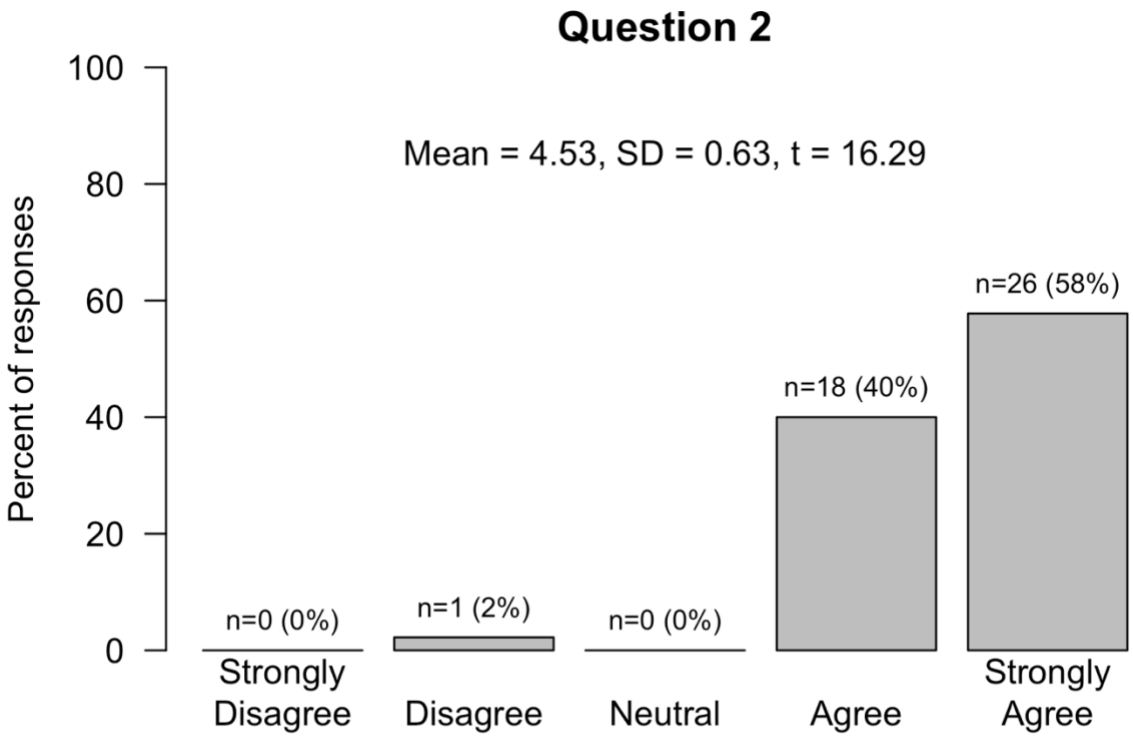
Level of agreement with Question 2: Which immunocompromised patients with CAP should be admitted to the hospital?

Agreement with the answer to question 2 was achieved in 44 of the 45 participants (98%). Initial agreement for the original, proposed answer to question 2 was 86%. Results of the Likert scale for question 2 are depicted in the bar chart below.



Additional comments for Question 2:

Immunosuppressive drugs are known to modulate the inflammatory response, thus the typical signs and symptoms of CAP may be attenuated in these patients. This blunted inflammatory response may also produce low levels of inflammatory markers. Because of this, it was considered not to use inflammatory biomarkers when determining the need for hospitalization.

Additionally, some experts considered that all immunocompromised patients with CAP should be admitted to the hospital. Few would manage some of these patients in the outpatient setting, as long as patients can have a close follow-up and rapid mechanism to be seen if clinical deterioration occurs. This clinical scenario may be possible only in specific medical centers with experience in the management of these patients.

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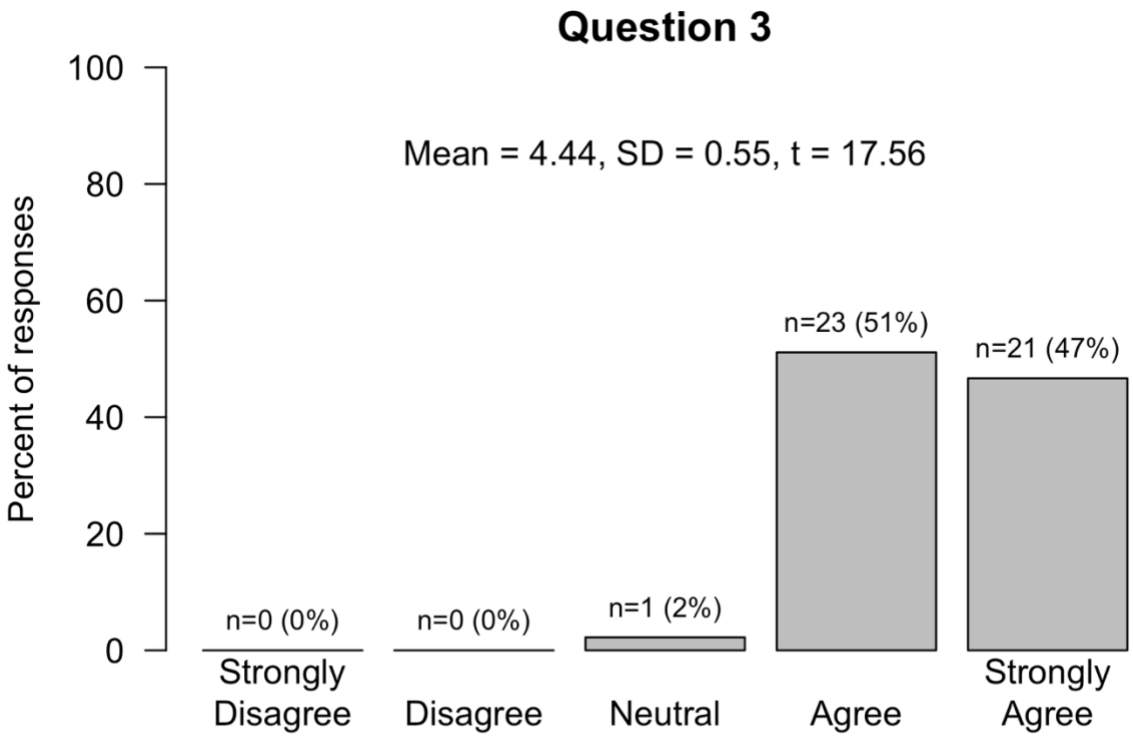
Level of agreement with Question 3: What pathogens should be considered "core respiratory pathogens" in patients with CAP who are immunocompromised?

Agreement with the answer to question 3 was achieved in 44 of the 45 participants (98%). Initial agreement for the original, proposed answer to question 3 was 77%. Results of the Likert scale for question 3 are depicted in the bar chart below.



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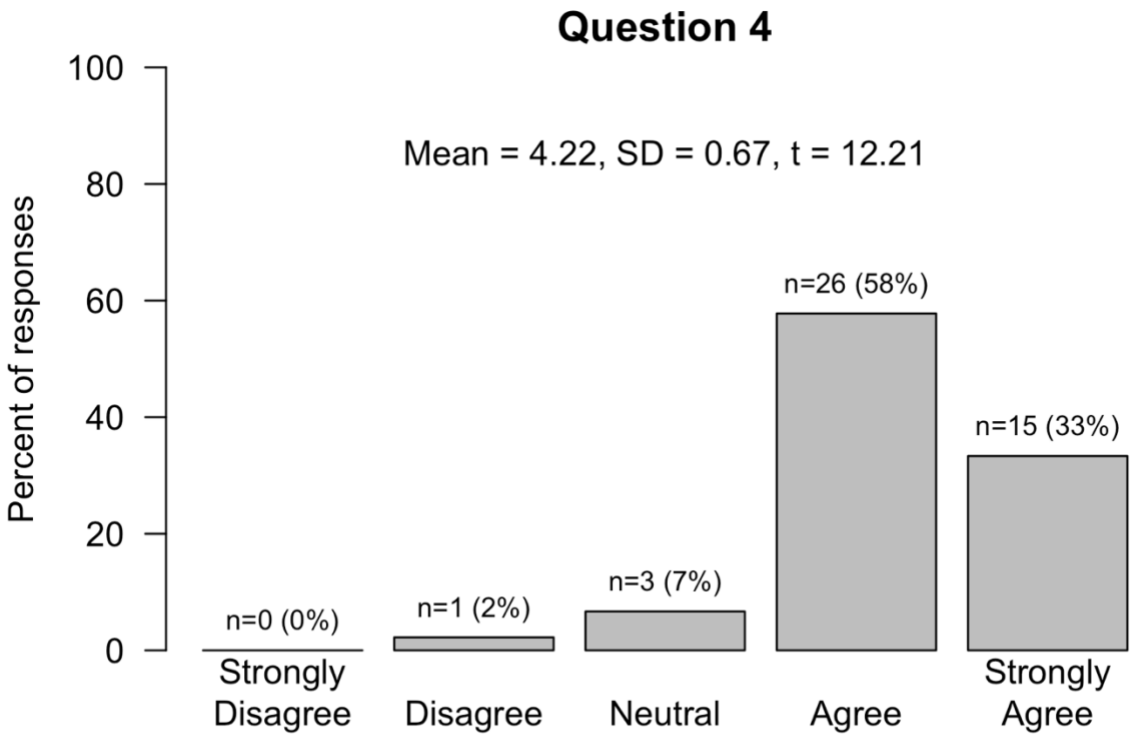
Level of agreement with Question 4: What pathogens should be considered beyond the "core respiratory pathogens" in patients with CAP who are immunocompromised?

Agreement with the answer to question 4 was achieved in 41 of the 45 participants (91%). Initial agreement for the original, proposed answer to question 4 was 84%. Results of the Likert scale for question 4 are depicted in the bar chart below.



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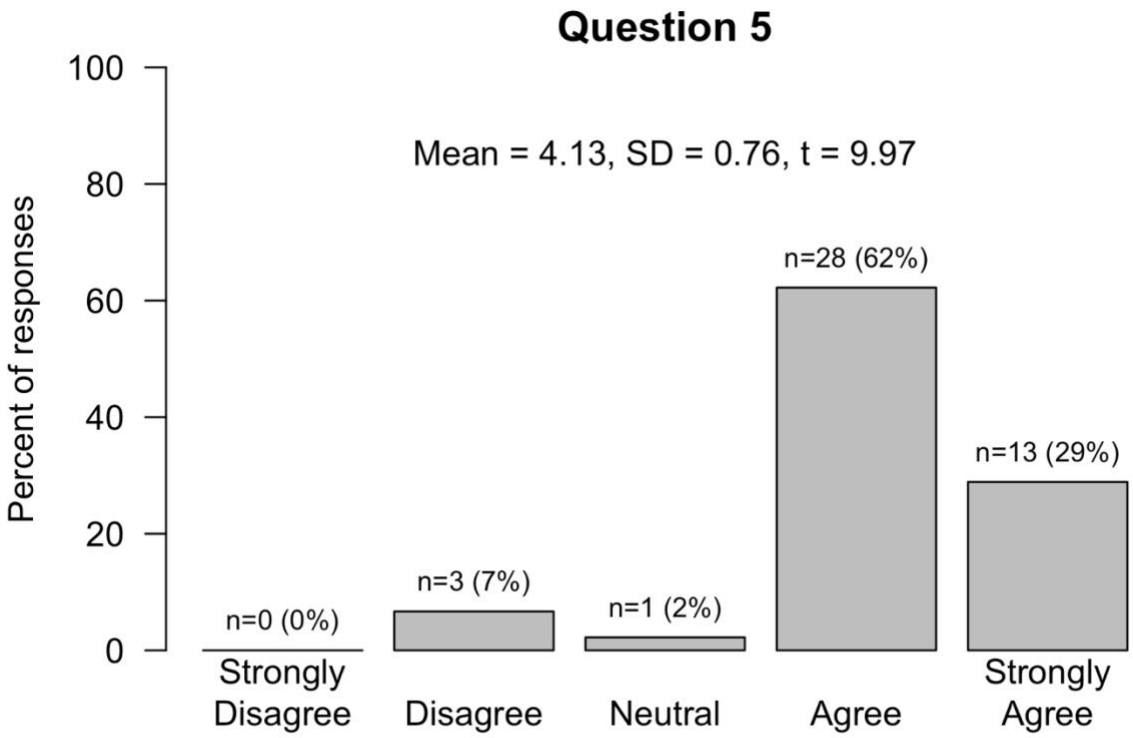
Level of agreement with Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?

Agreement with the answer to question 5 was achieved in 41 of the 45 participants (91%). Initial agreement for the original, proposed answer to question 5 was 66%. Results of the Likert scale for question 5 are depicted in the bar chart below.



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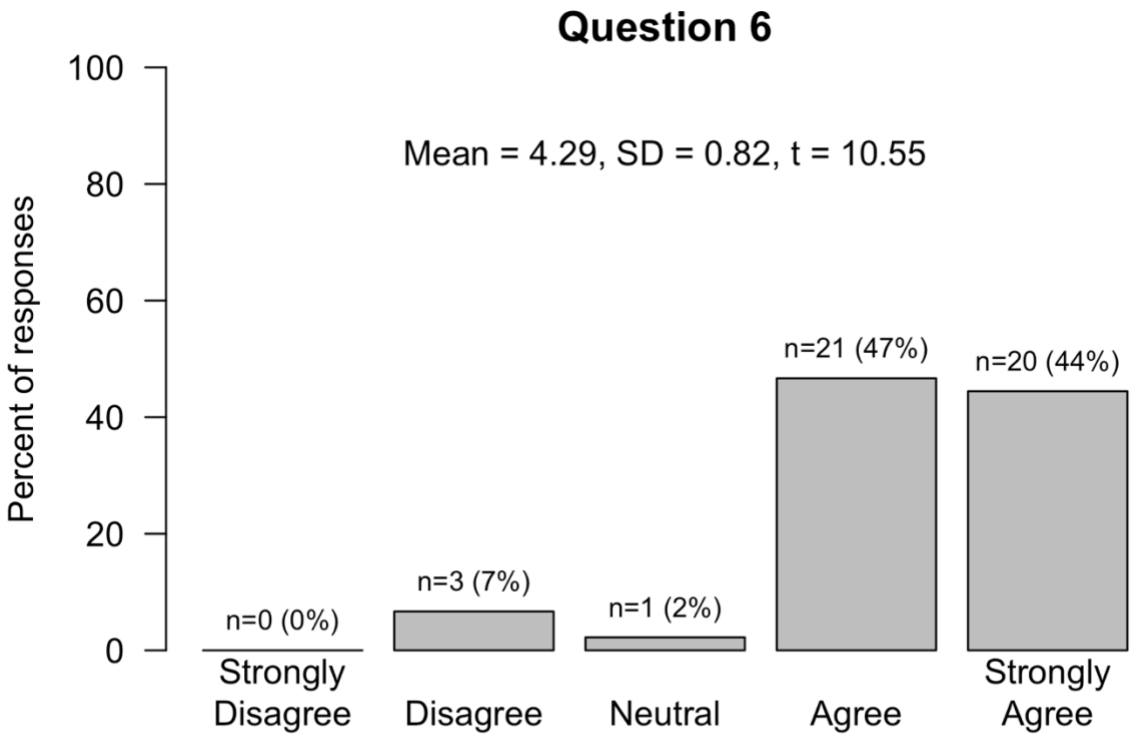
Level of agreement with Question 6: When should a bronchoscopy with bronchoalveolar lavage be performed in patients with CAP who are immunocompromised?

Agreement with the answer to question 6 was achieved in 41 of the 45 participants (91%). Initial agreement for the original, proposed answer to question 6 was 66%. Results of the Likert scale for question 6 are depicted in the bar chart below.



Additional comments for question 6:

Some experts wanted to emphasize the need for bronchoscopy in the immunocompromised population. In these patients more than one causative agent may play a role as a cause of pneumonia and there is additional value of bronchoscopy in defining non-infectious etiologies of pulmonary infiltrates. On the other hand, some experts considered that bronchoscopy was associated with significant side effects.

The use of next generation sequencing (NGS) in the field of pneumonia diagnosis using BAL fluid is rapidly evolving. Real-time metagenomics can be used to identify respiratory pathogens from BAL fluid in immunocompromised patients with pneumonia. This culture-independent technique for pathogen identification can generate results faster than the traditional culture techniques. Current challenges for

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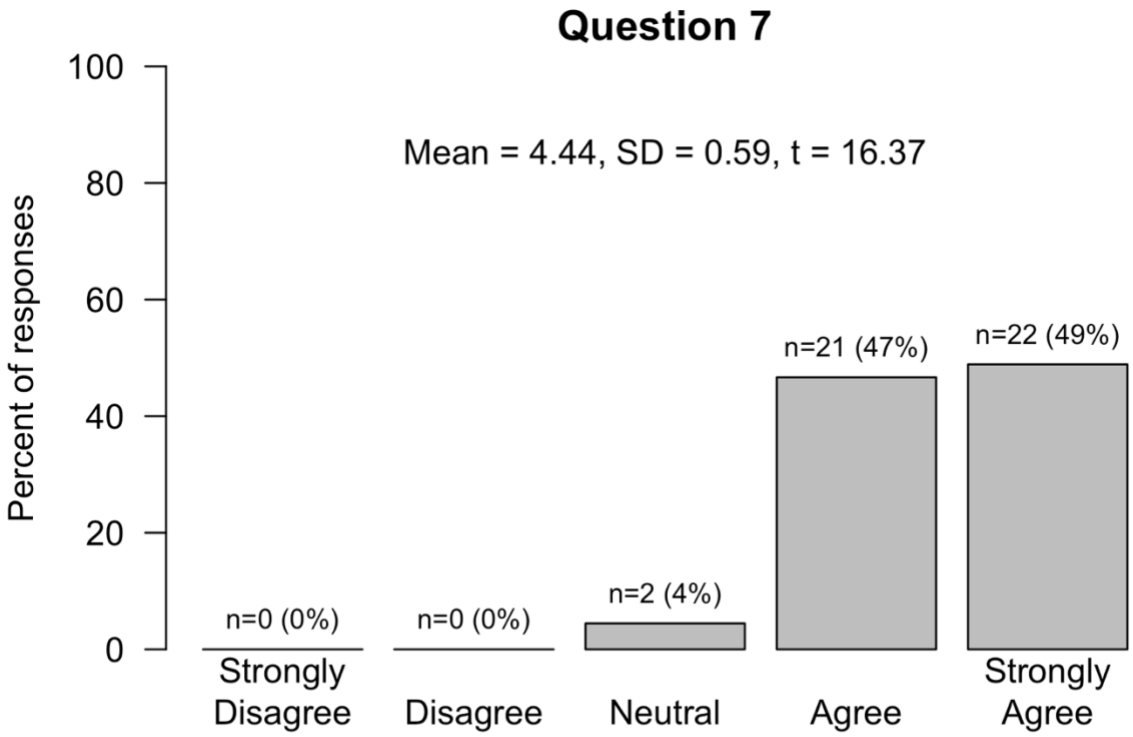
widespread application of NGS include the cost and the fact that the analysis requires substantial computational skills and resources.

BAL fluid is typically obtained after the introduction of the bronchoscope into the tracheobronchial tree and the inspection of the airway. Mini-BAL is a blind non-bronchoscopic procedure to obtain samples in patients on mechanical ventilation. Mini-BAL sampling can be obtained using telescoping catheters. These techniques have been primarily studied in patients with VAP, but may be considered in immunocompromised patients with CAP requiring mechanical ventilation.

Level of agreement with Question 7: What microbiological studies can be obtained in bronchoalveolar lavage in patients with CAP who are immunocompromised?

Agreement with the answer to question 7 was achieved in 43 of the 45 participants (96%). Initial agreement for the original, proposed answer to question 7 was 66%. Results of the Likert scale for question 7 are depicted in the bar chart below.



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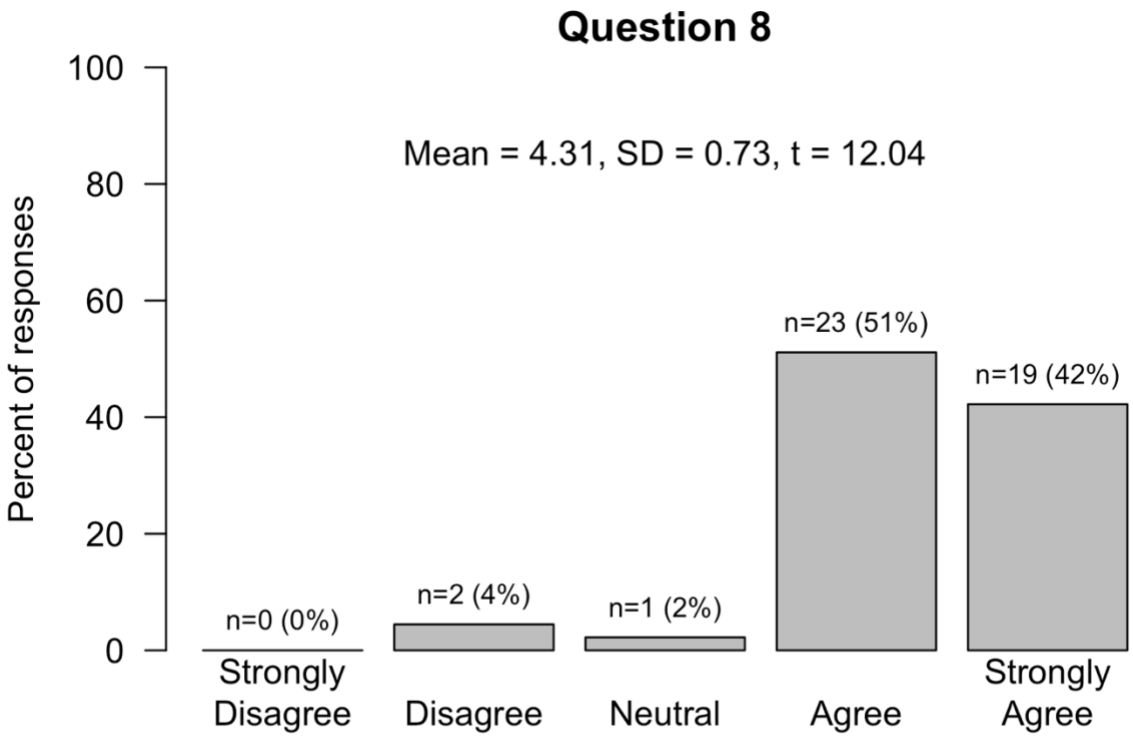
Level of agreement with Question 8: What empiric therapy should be started in hospitalized patients with CAP who are immunocompromised?

Agreement with the answer to question 8 was achieved in 42 of the 45 participants (93%). Initial agreement for the original, proposed answer to question 8 was 60%. Results of the Likert scale for question 8 are depicted in the bar chart below.



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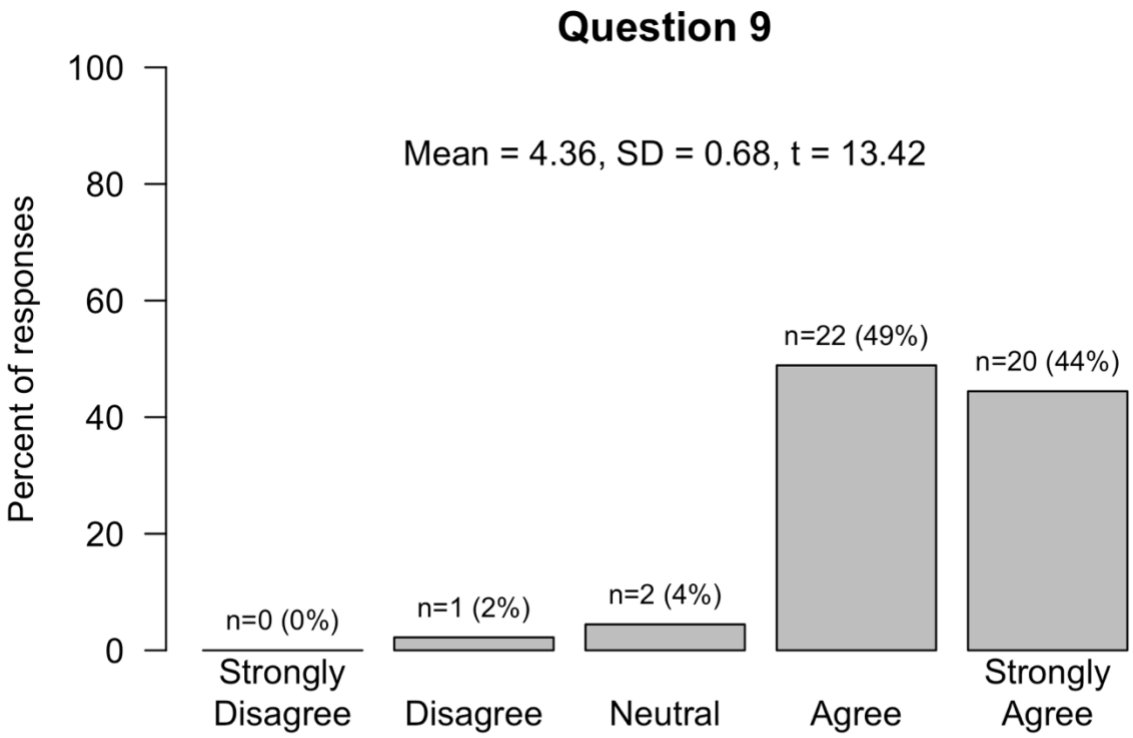
Level of agreement with Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?

Agreement with the answer to question 9 was achieved in 42 of the 45 participants (93%). Initial agreement for the original, proposed answer to question 9 was 86%. Results of the Likert scale for question 9 are depicted in the bar chart below.



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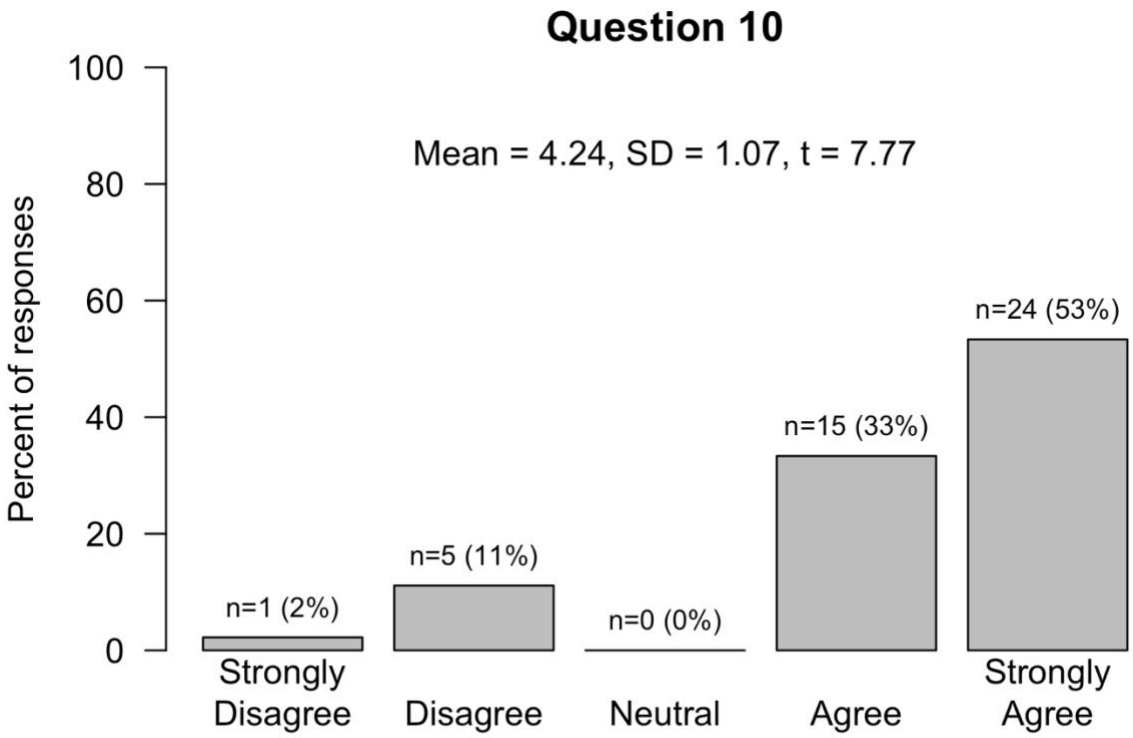
Level of agreement with Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?

Agreement with the answer to question 10 was achieved in 39 of the 45 participants (87%). Initial agreement for the original, proposed answer to question 10 was 83%. Results of the Likert scale for question 10 are depicted in the bar chart below.



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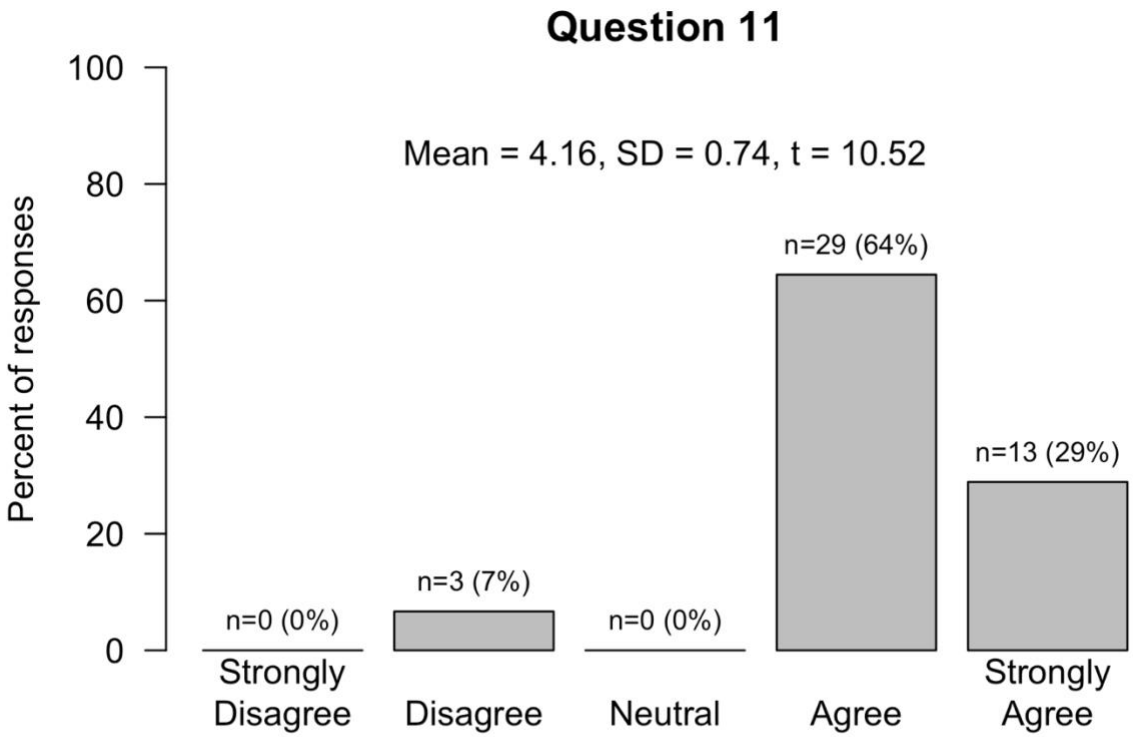
Level of agreement with Question 11: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to MRSA?

Agreement with the answer to question 11 was achieved in 42 of the 45 participants (93%). Initial agreement for the original, proposed answer to question 11 was 60%. Results of the Likert scale for question 11 are depicted in the bar chart below.



Additional comments for Question 11:

There was some debate over what would be considered a "low" MRSA prevalence. The recently published HAP and VAP guidelines from the ATS/IDSA suggest that an MRSA prevalence of 25% or above should trigger the use of anti-MRSA therapy, but the authors recognize that there is no solid epidemiological data to support this recommendation. In the guidelines document, the authors express the following: "We acknowledge that, given the lack of data to inform optimal thresholds for broadening coverage, individual units can adjust these thresholds in accordance with local values and preferences." We face a similar problem with the lack of data to inform an optimal epidemiologic threshold in patients with CAP.

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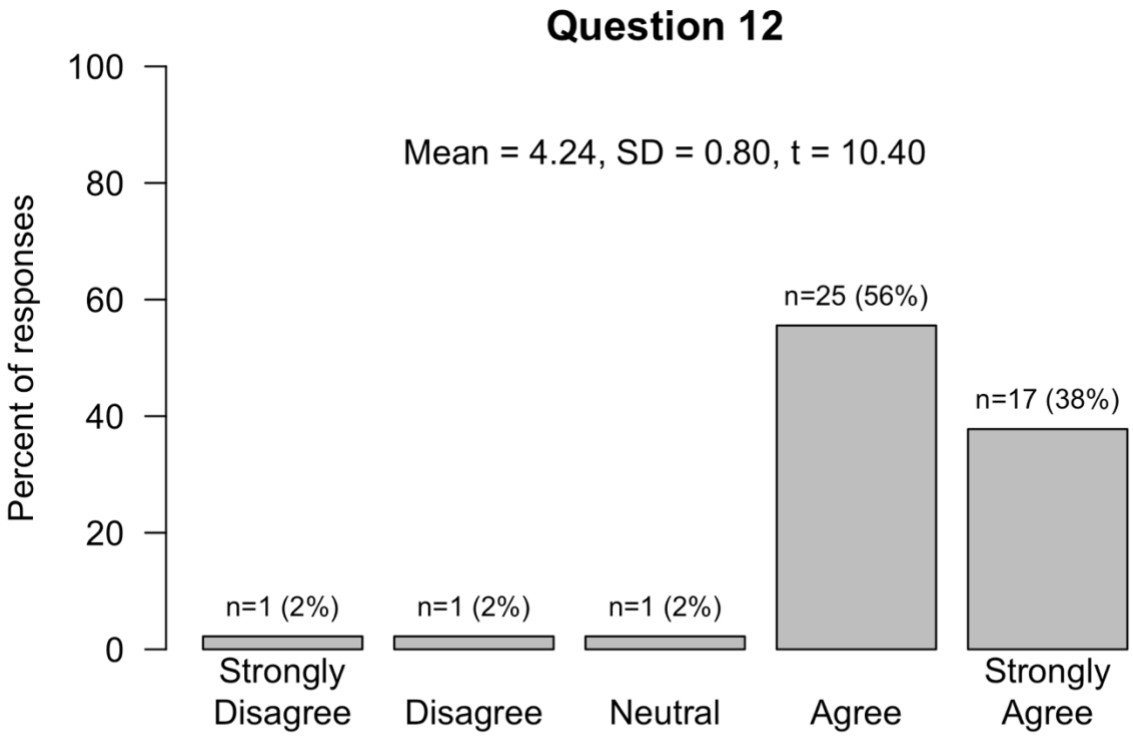
Level of agreement with Question 12: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of drug-resistant Gram-negative bacilli, including *Pseudomonas aeruginosa*?

Agreement with the answer to question 12 was achieved in 42 of the 45 participants (93%). Initial agreement for the original, proposed answer to question 12 was 60%. Results of the Likert scale for question 12 are depicted in the bar chart below.



Additional comments for question 12:

The consensus from the Delphi survey concluded that in the context of CAP treatment, drug resistant gram-negative bacilli refers to organisms that are resistant to the standard beta-lactam antibiotics used for the treatment of CAP. Using the traditional approach of empiric therapy of ceftriaxone plus azithromycin any *Pseudomonas aeruginosa* will be a drug resistant pathogen as they are routinely resistant to ceftriaxone. The implication of a drug-resistant gram negative bacilli is the need to extend the coverage of the beta-lactam antibiotic to cover *Pseudomonas aeruginosa*. Appropriate beta-lactam antibiotics in this situation may be piperacillin-tazobactam or ceftazidime.

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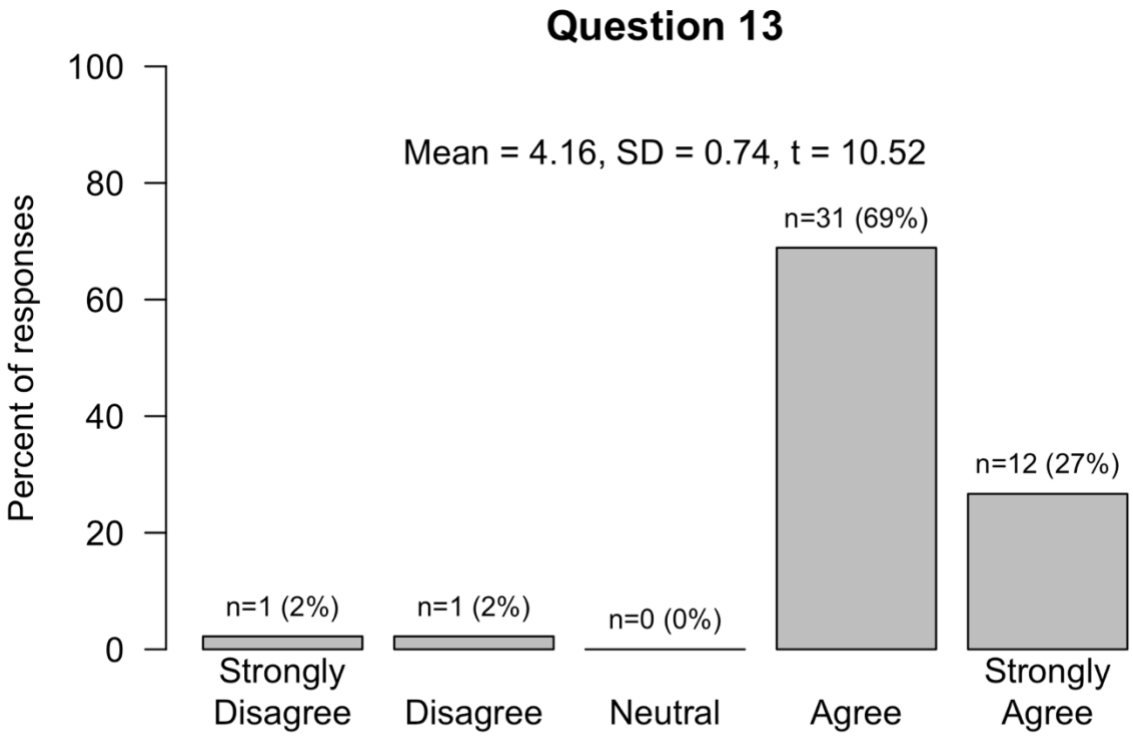
Level of agreement with Question 13: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to multi-drug resistant (MDR) Gram-negative bacilli?

Agreement with the answer to question 13 was achieved in 43 of the 45 participants (96%). Initial agreement for the original, proposed answer to question 13 was 91%. Results of the Likert scale for question 13 are depicted in the bar chart below.



Additional comments for question 13:

The consensus from the Delphi survey concluded that MDR gram-negative rods are considered organisms that would be resistant to the first line of beta-lactam antibiotics used for the treatment of *Pseudomonas aeruginosa* or other gram-negative rods. These would be gram negative rods resistant to piperacillin-tazobactam or ceftazidime or even carbapenems. In this clinical scenario, the empiric therapy would need to escalate to new beta-lactam antibiotics or new beta-lactamase inhibitors.

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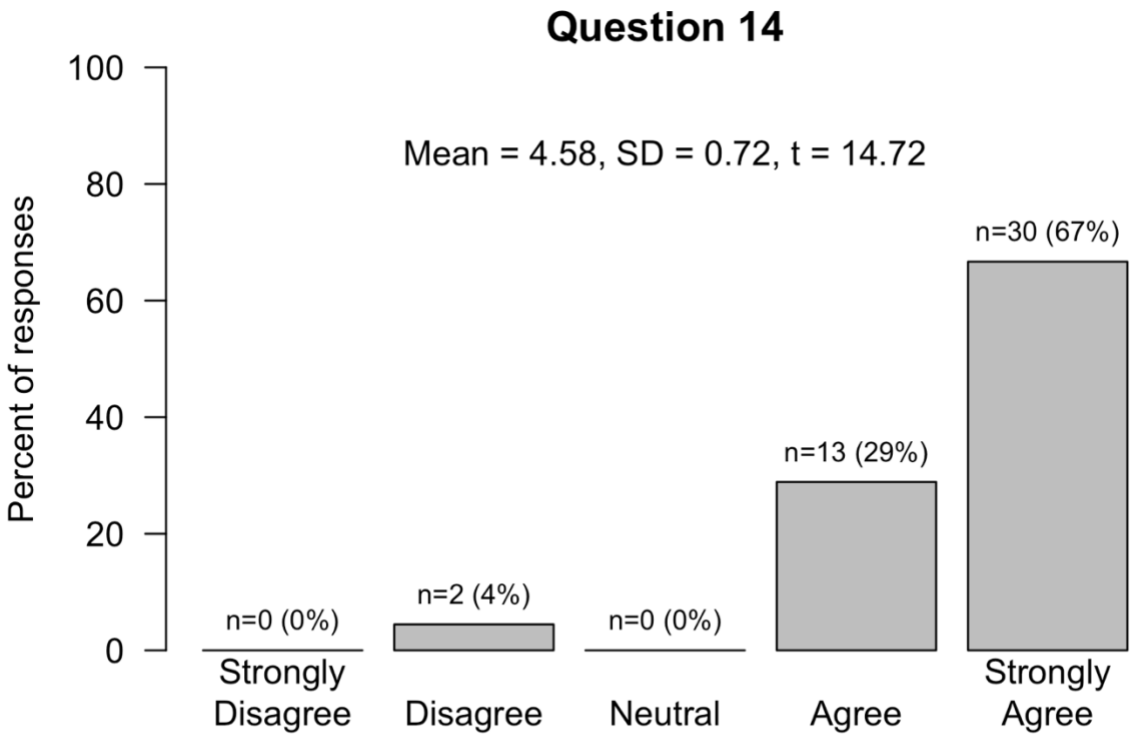
Level of agreement with Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?

Agreement with the answer to question 14 was achieved in 43 of the 45 participants (96%). Initial agreement for the original, proposed answer to question 14 was 90%. Results of the Likert scale for question 14 are depicted in the bar chart below.



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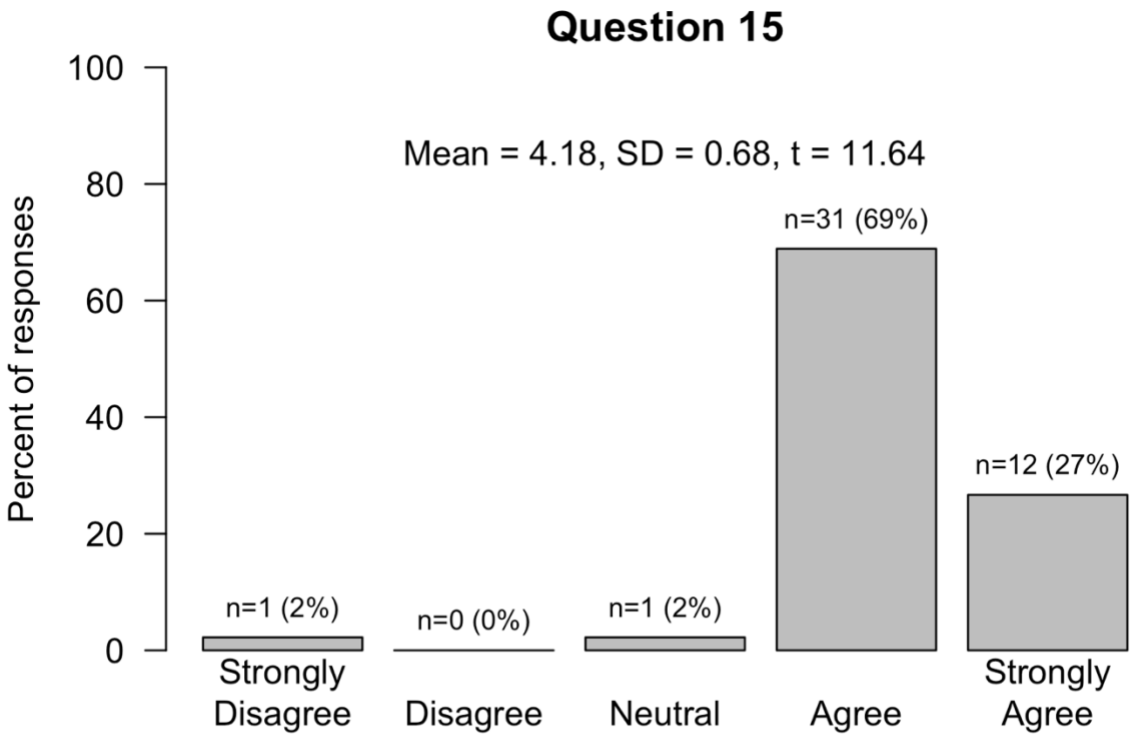
Level of agreement with Question 15: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Aspergillus*?

Agreement with the answer to question 15 was achieved in 43 of the 45 participants (96%). Initial agreement for the original, proposed answer to question 15 was 69%. Results of the Likert scale for question 15 are depicted in the bar chart below.



Additional comments for question 15:

Due to the superposition of risk factors (e.g. cancer and chemotherapy, severe and prolonged neutropenia, and radiographic nodular pattern), the initial empiric therapy should be performed with an anti-fungal that covers the possibility of both *Aspergillus* and *Mucorales*. We also strongly suggest extensive microbiological workup to allow for de-escalation of therapy and continuation of treatment of *Aspergillus* with a narrow spectrum antifungal.

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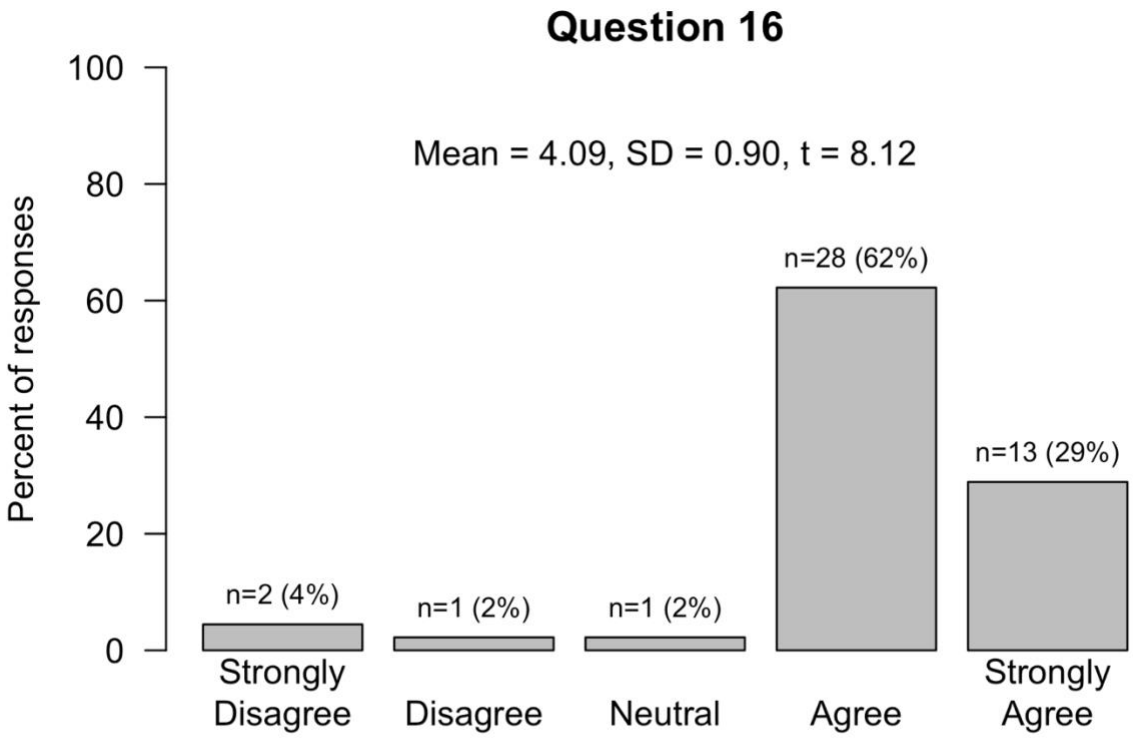
Level of agreement with Question 16: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mucorales*?

Agreement with the answer to question 16 was achieved in 41 of the 45 participants (91%). Initial agreement for the original, proposed answer to question 16 was 70%. Results of the Likert scale for question 16 are depicted in the bar chart below.



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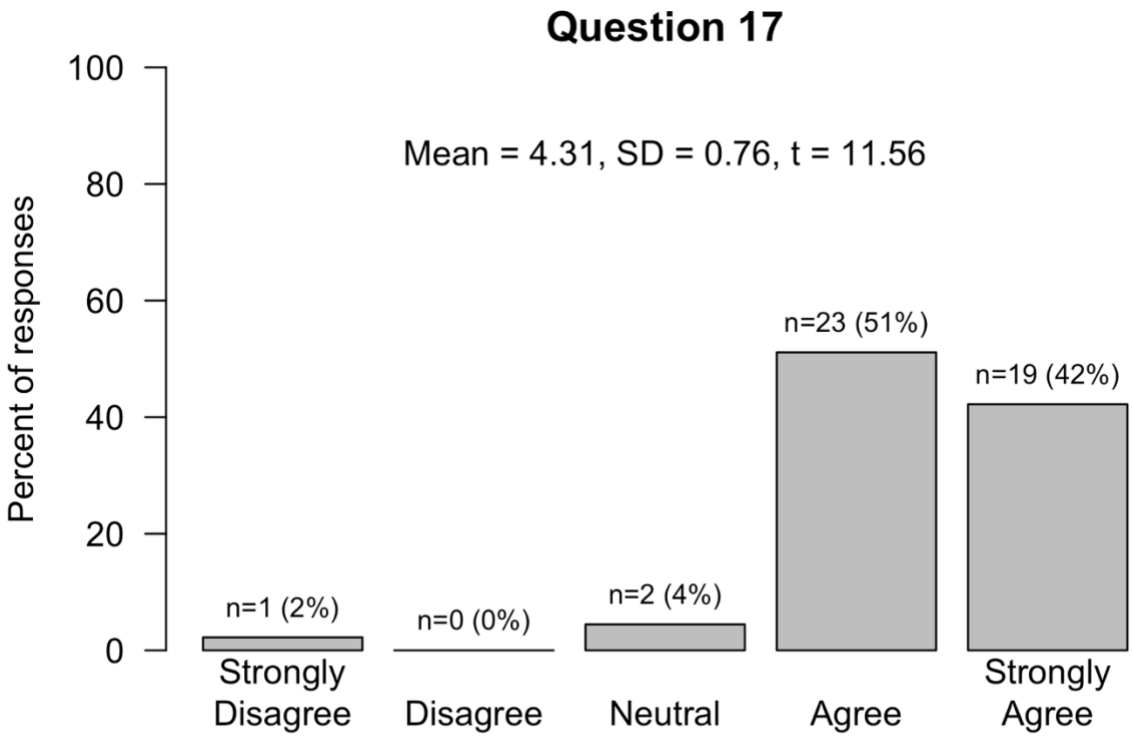
Level of agreement with Question 17: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Nocardia*?

Agreement with the answer to question 17 was achieved in 42 of the 45 participants (93%). Initial agreement for the original, proposed answer to question 17 was 71%. Results of the Likert scale for question 17 are depicted in the bar chart below.



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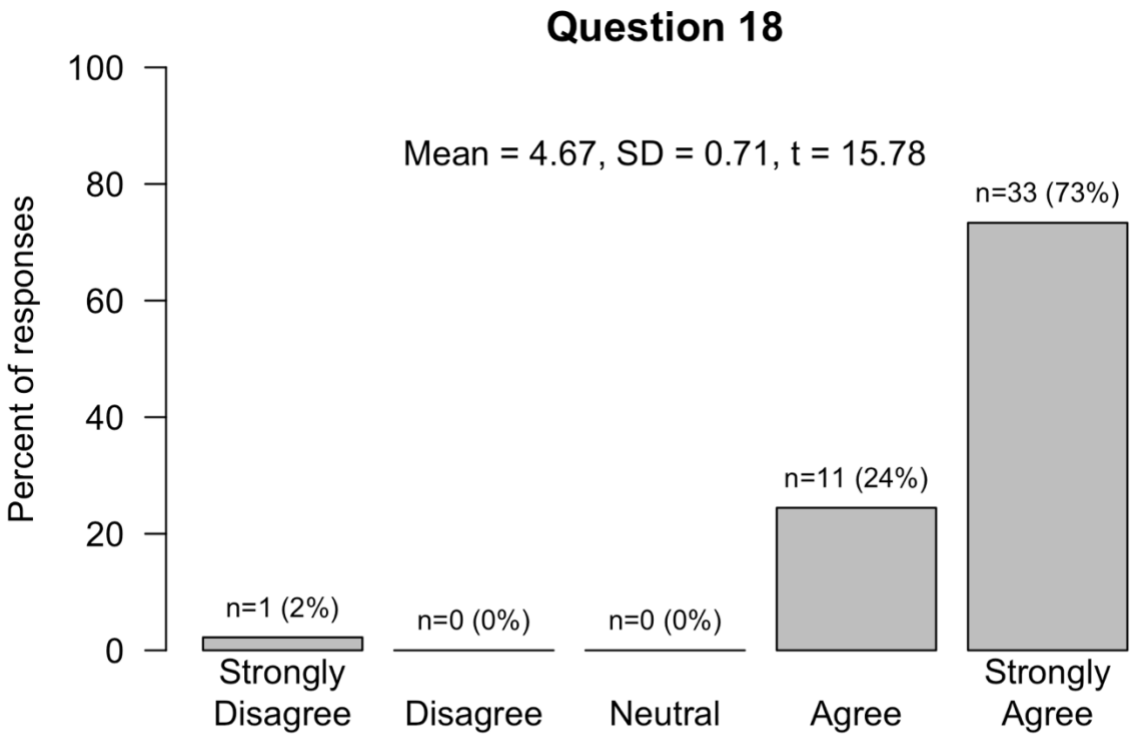
Level of agreement with Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?

Agreement with the answer to question 18 was achieved in 44 of the 45 participants (98%). Initial agreement for the original, proposed answer to question 18 was 95%. Results of the Likert scale for question 18 are depicted in the bar chart below.



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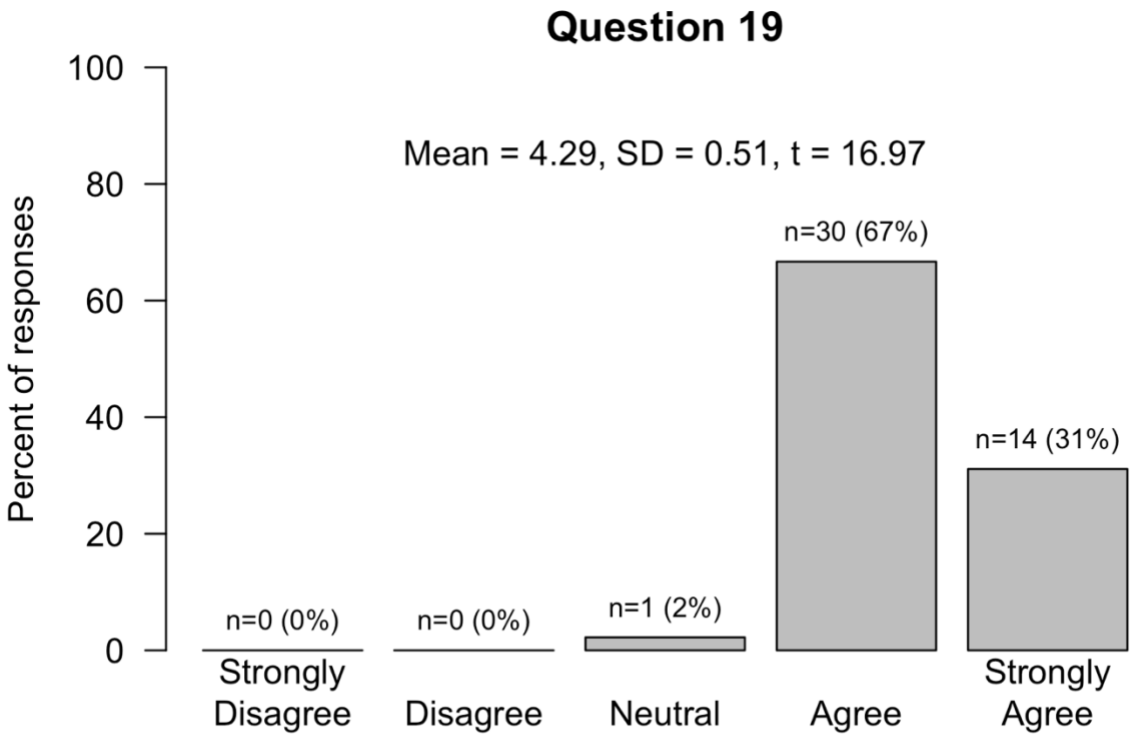
Level of agreement with Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?

Agreement with the answer to question 19 was achieved in 44 of the 45 participants (98%). Initial agreement for the original, proposed answer to question 19 was 85%. Results of the Likert scale for question 19 are depicted in the bar chart below.



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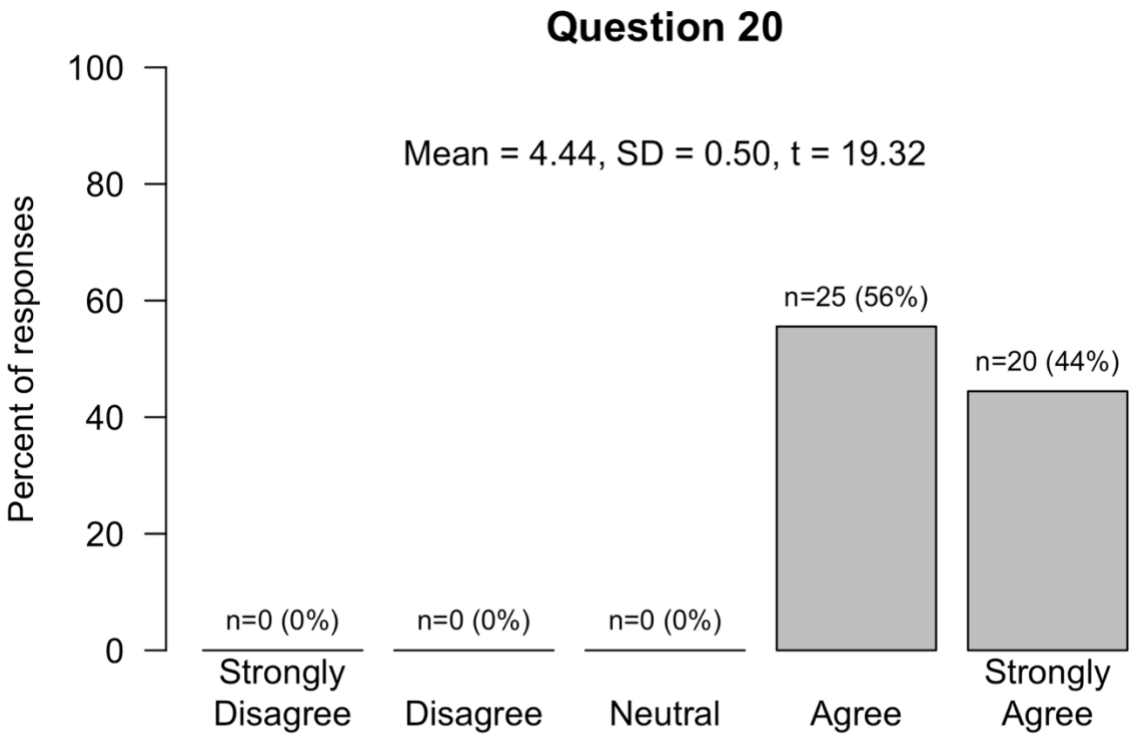
Level of agreement with Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?

Agreement with the answer to question 20 was achieved in 45 of the 45 participants (100%). Initial agreement for the original, proposed answer to question 20 was 68%. Results of the Likert scale for question 20 are depicted in the bar chart below.



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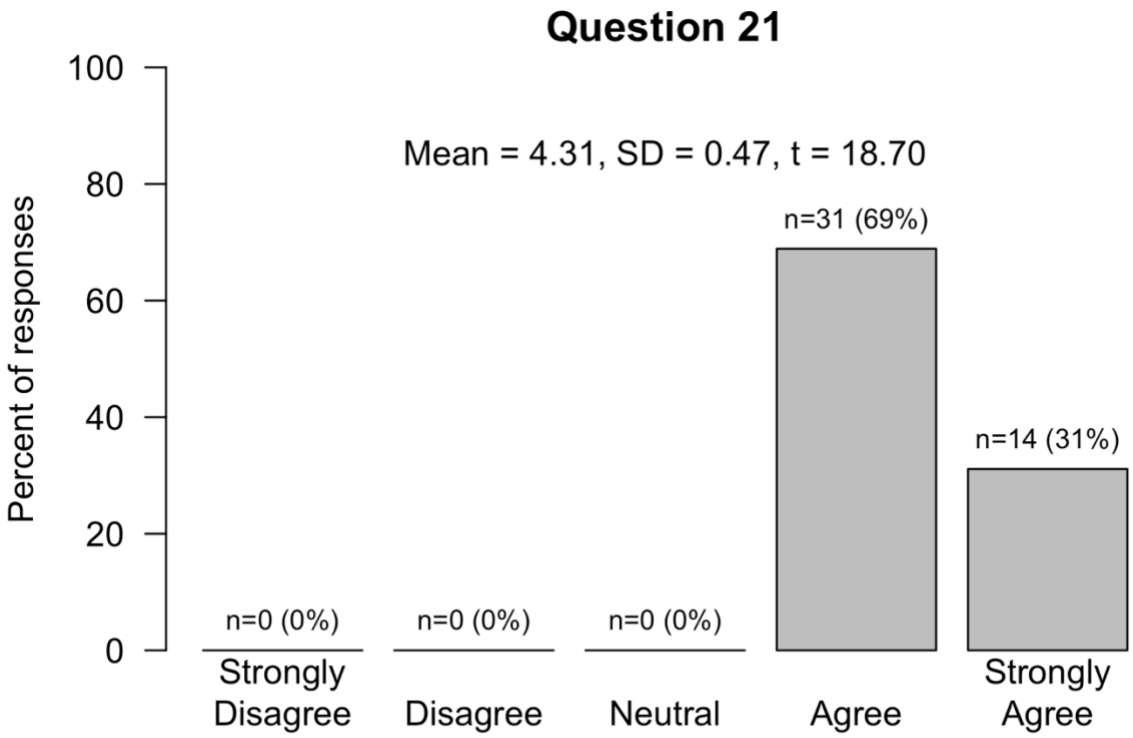
Level of agreement with Question 21: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to parasites?

Agreement with the answer to question 21 was achieved in 45 of the 45 participants (100%). Initial agreement for the original, proposed answer to question 21 was 82%. Results of the Likert scale for question 21 are depicted in the bar chart below.



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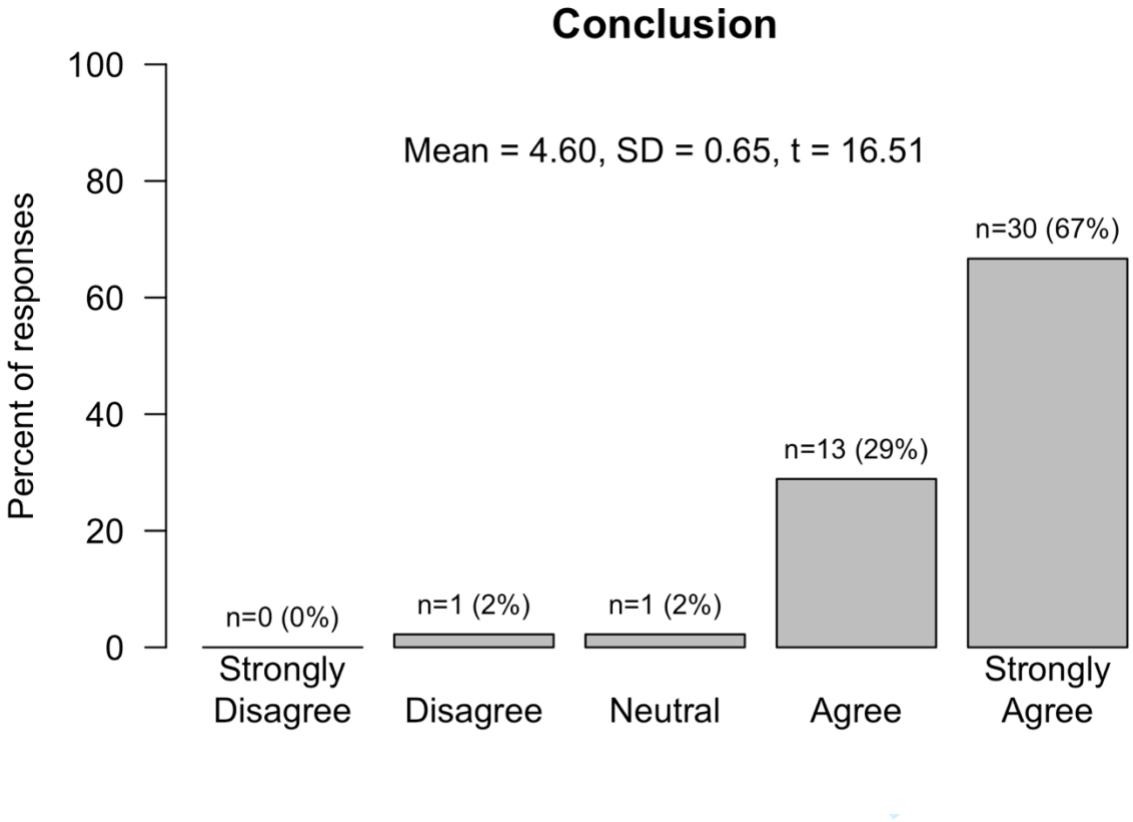
Level of agreement with the Conclusion

Agreement with the statements mentioned in the conclusion of the manuscript was achieved in 43 of the 45 participants (96%). Initial agreement with the concluding statements was 87%. Results of the Likert scale for the introduction of the manuscript are depicted in the bar chart below.



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ABBREVIATION LIST

BAL:	bronchoalveolar lavage
CAP:	community-acquired pneumonia
CMV:	Cytomegalovirus
CRE:	carbapenemase-producing *Enterobacteriaceae*
DMARDs:	disease-modifying anti-rheumatic drugs
ESBL:	extended spectrum beta-lactamase
HIV:	human immunodeficiency virus
MDR:	multiple drug resistant
NTM:	non-tuberculous Mycobacteria
PCP:	*Pneumocystis jirovecii*
PCR:	polymerase chain reaction
PSI:	Pneumonia Severity Index
TMP-SMX:	trimethoprim-sulfamethoxazole
TNF:	tumor necrosis factor