CHEST Online Supplement

Treatment of Community-Acquired Pneumonia in Immunocompromised Adults

A Consensus Statement Regarding Initial Strategies

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CHEST 2020; 158(5):1896-1911

 DOI: 10.1016/j.chest.2020.05.598

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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

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.

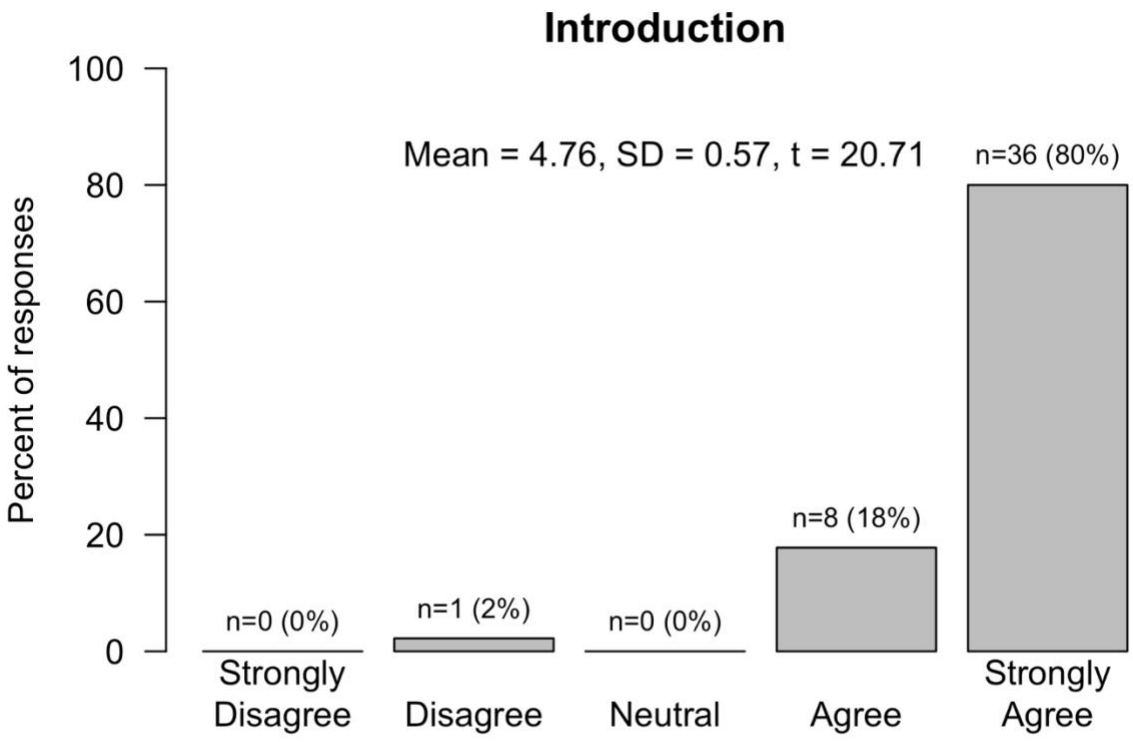
Statistical analysis

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

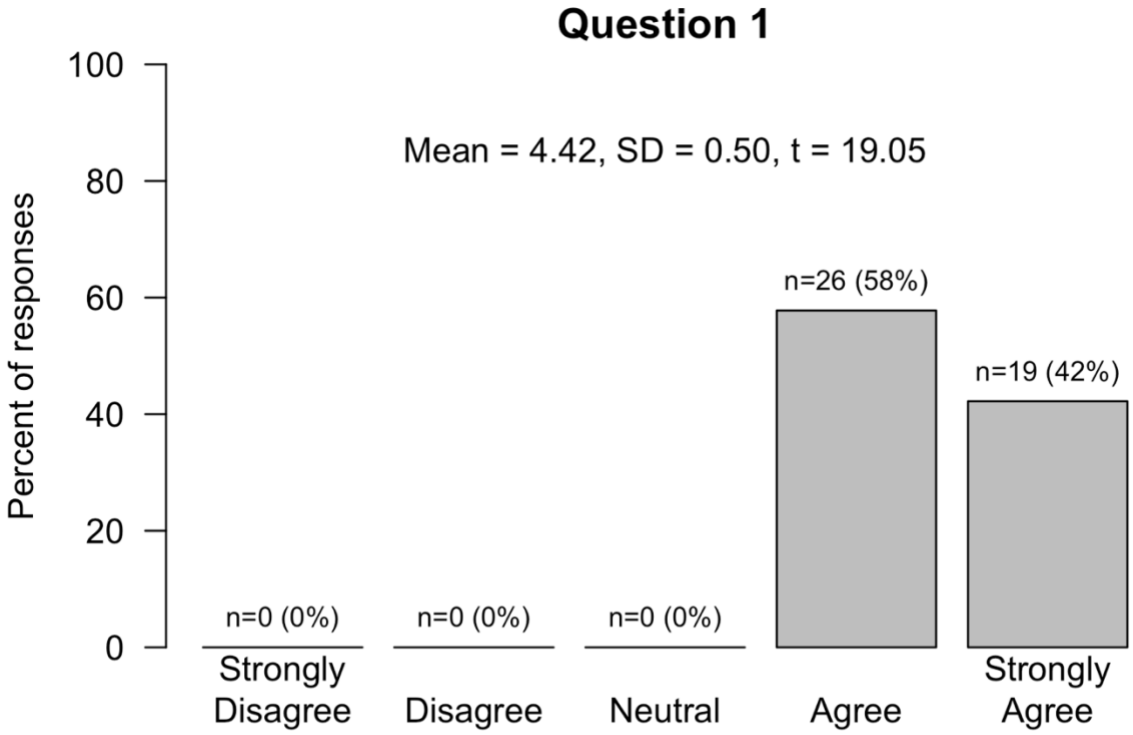
Level of agreement with the Introduction

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.



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.

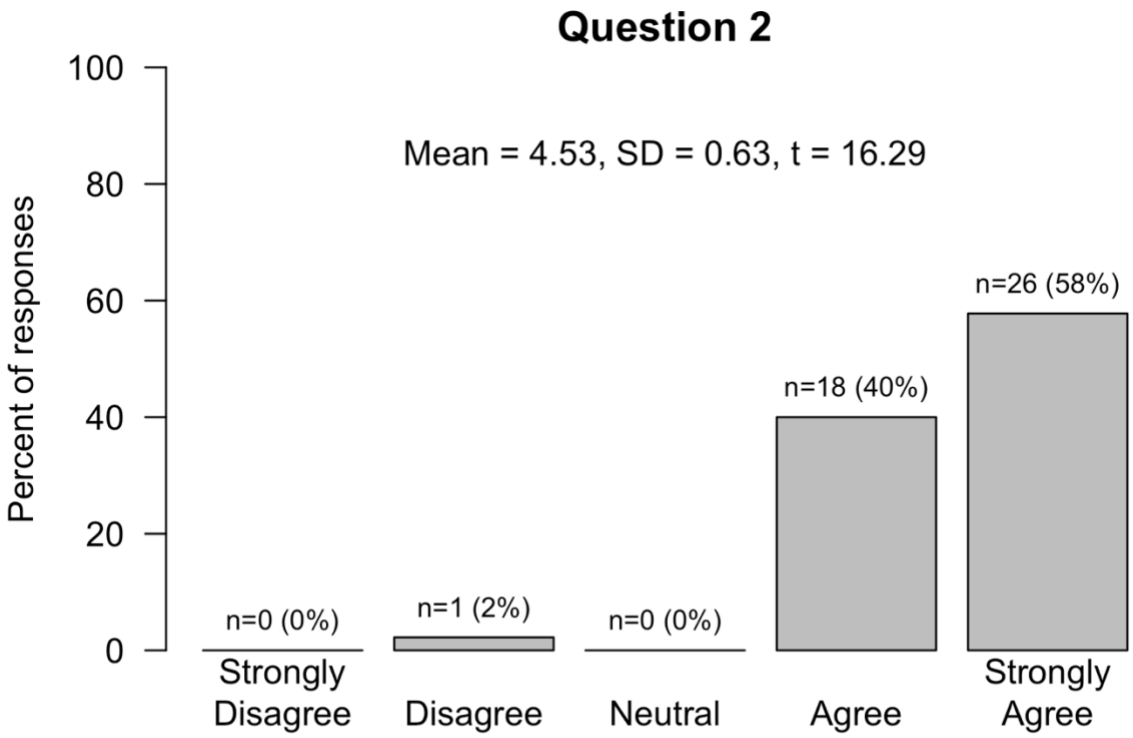


Additional comments for Question 1:

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.

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.



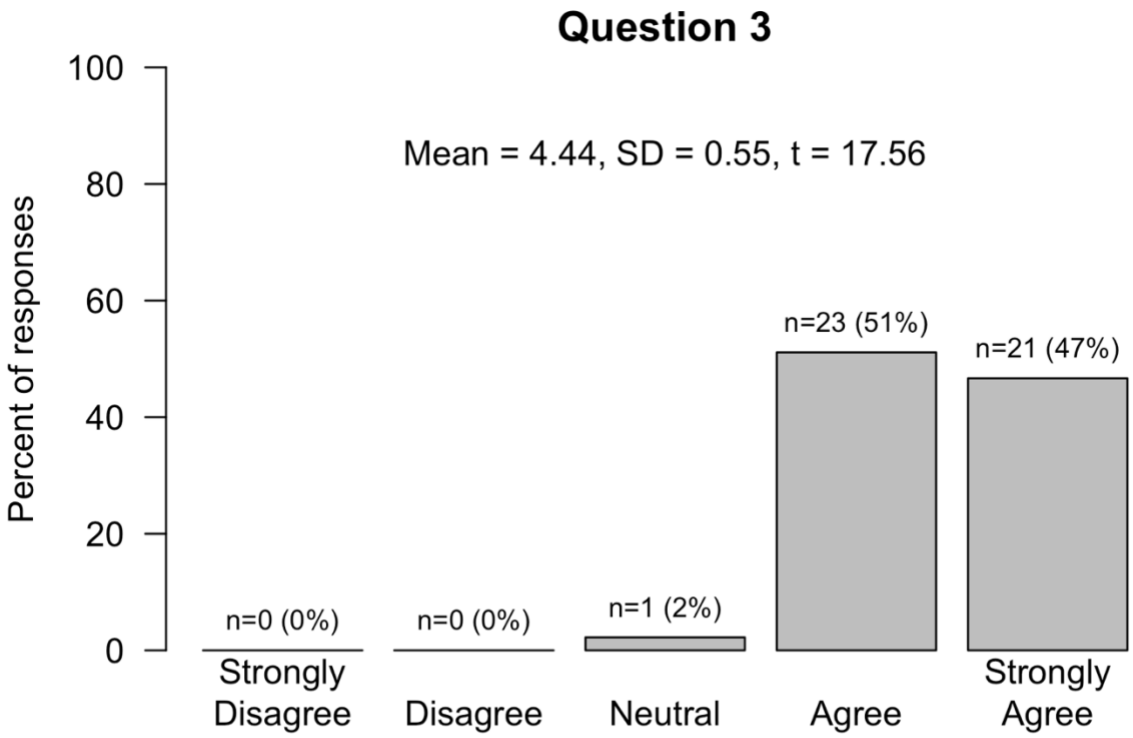
Additional comments for Question 2:

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.

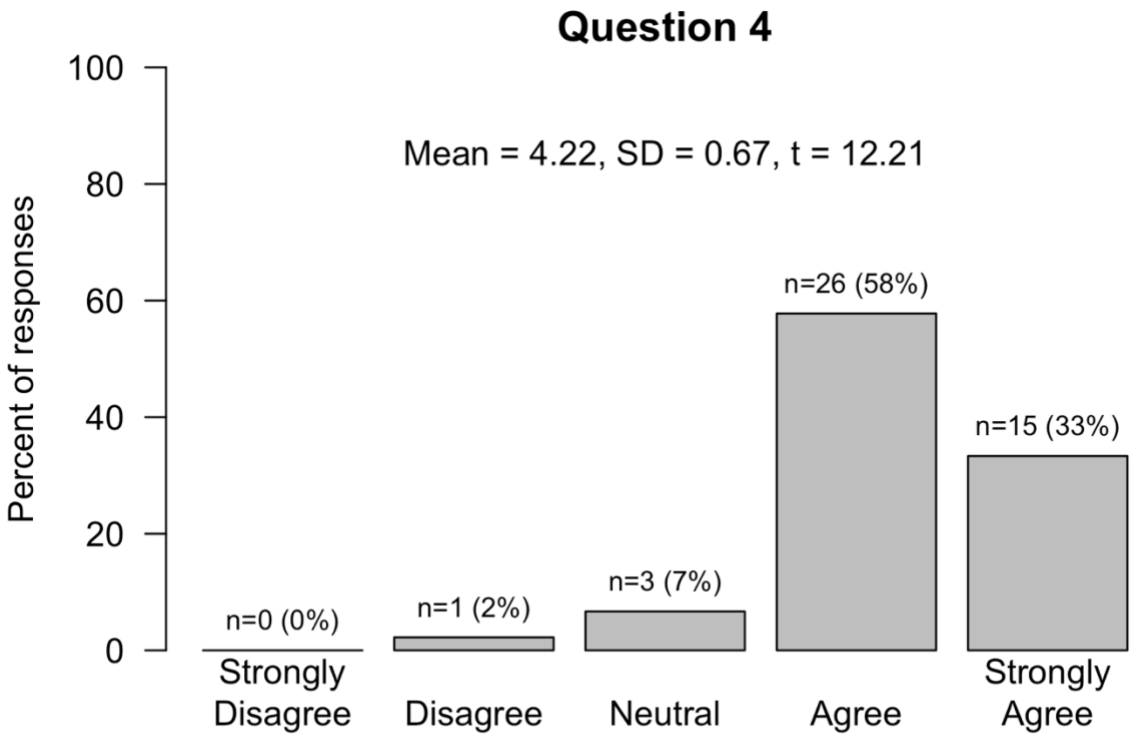
Level of agreement with Question 3: What pathogens should be considered "core respiratory pathogens" in patients with CAP who are immunocompromised?

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.



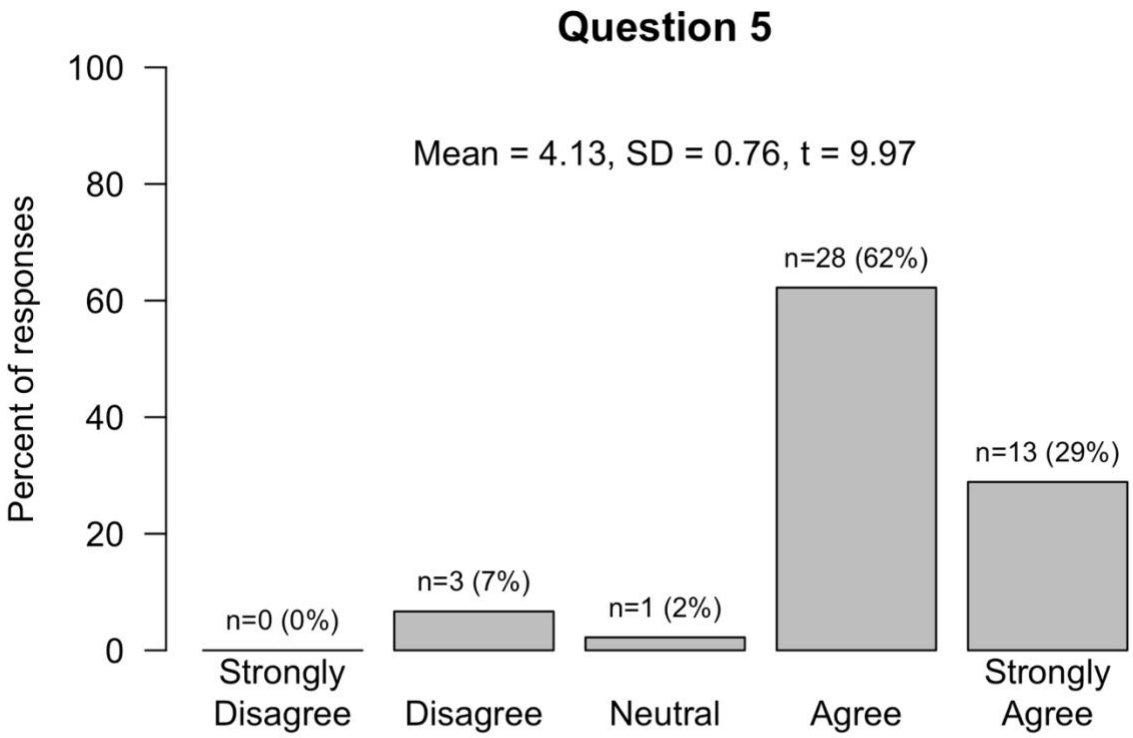
Level of agreement with Question 4: What pathogens should be considered beyond the "core respiratory pathogens" in patients with CAP who are immunocompromised?

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.



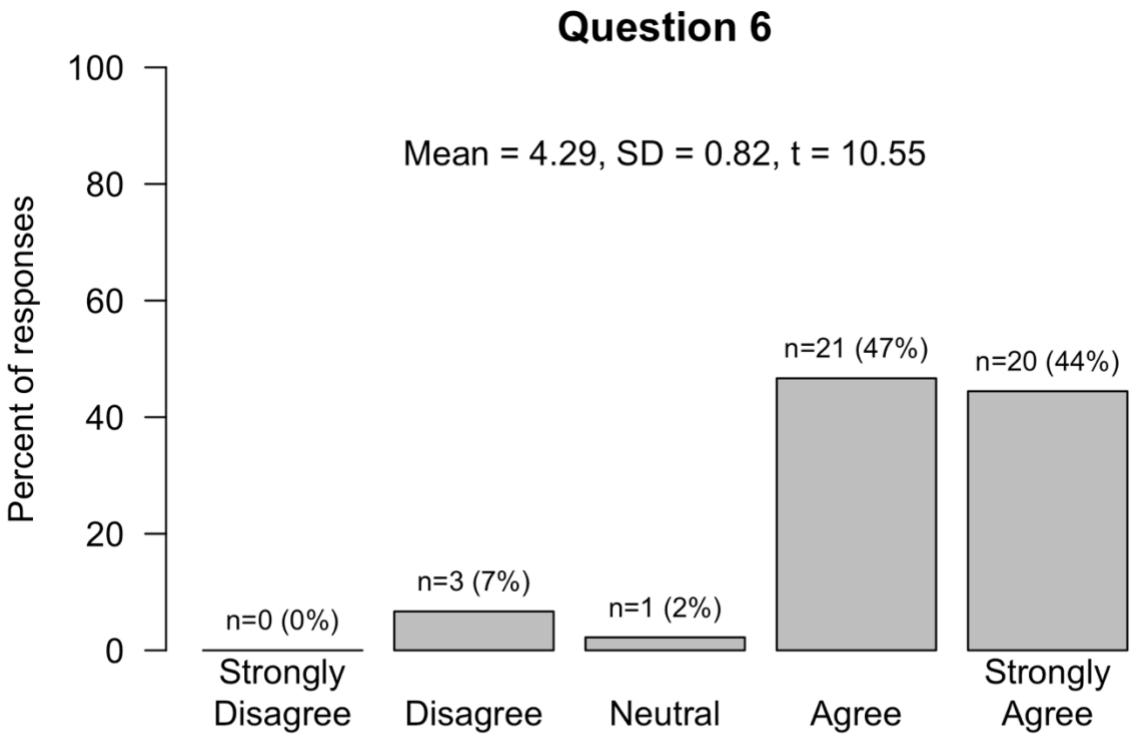
Level of agreement with Question 5: What microbiological studies should be done in hospitalized patients with CAP who are immunocompromised?

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.



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.

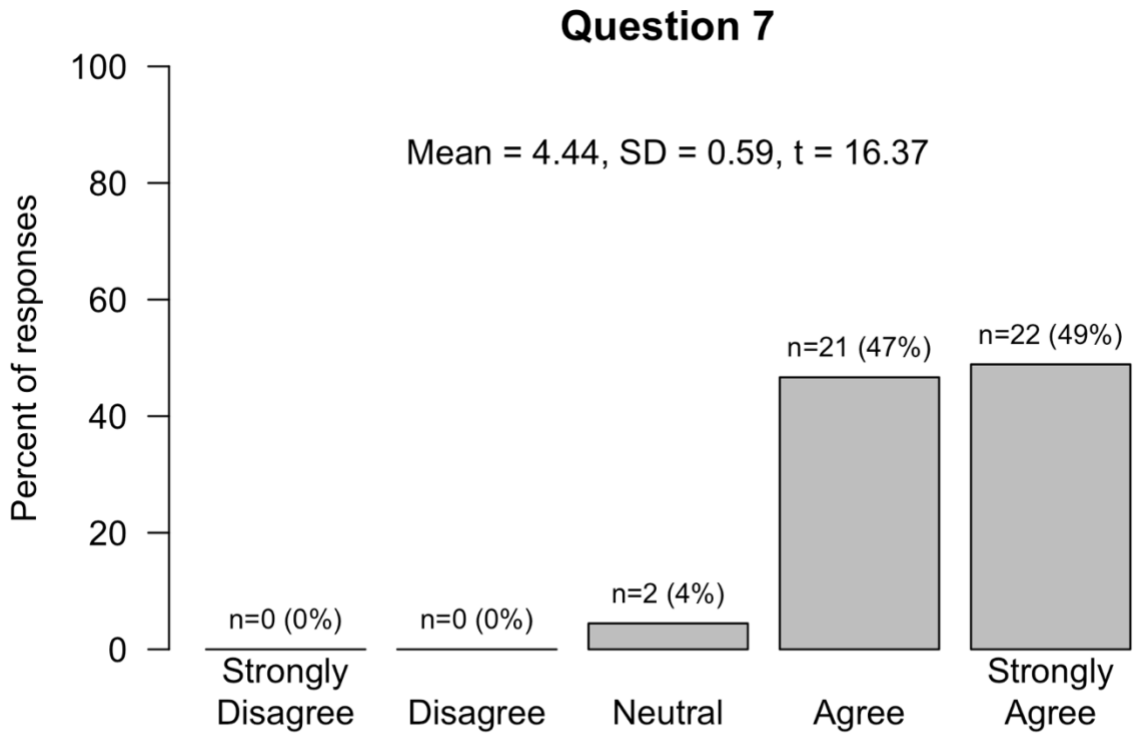
The use of next generation sequencing (NGS) in the field of pneumonia diagnosis using BAL fluid is rapidly evolving. Real-time metagenomics can be used to identify respiratory pathogens from BAL fluid in immunocompromised patients with pneumonia. This culture-independent technique for pathogen identification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

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.

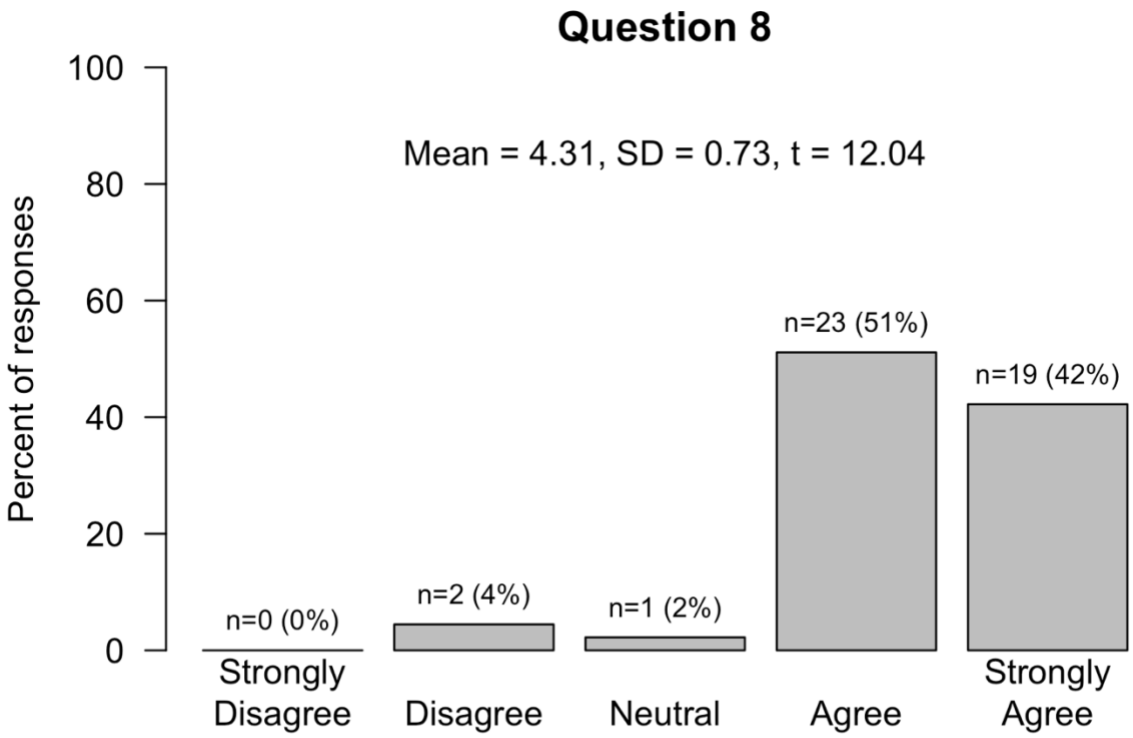
Level of agreement with Question 7: What microbiological studies can be obtained in bronchoalveolar lavage in patients with CAP who are immunocompromised?

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.



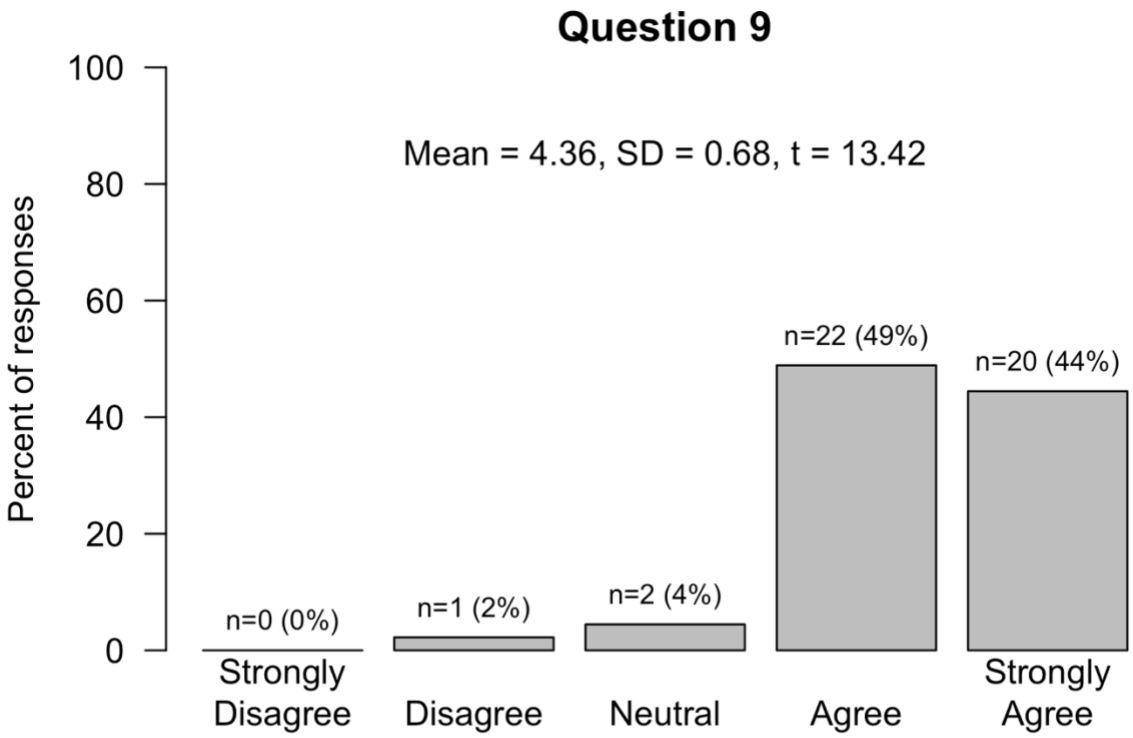
Level of agreement with Question 8: What empiric therapy should be started in hospitalized patients with CAP who are immunocompromised?

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.



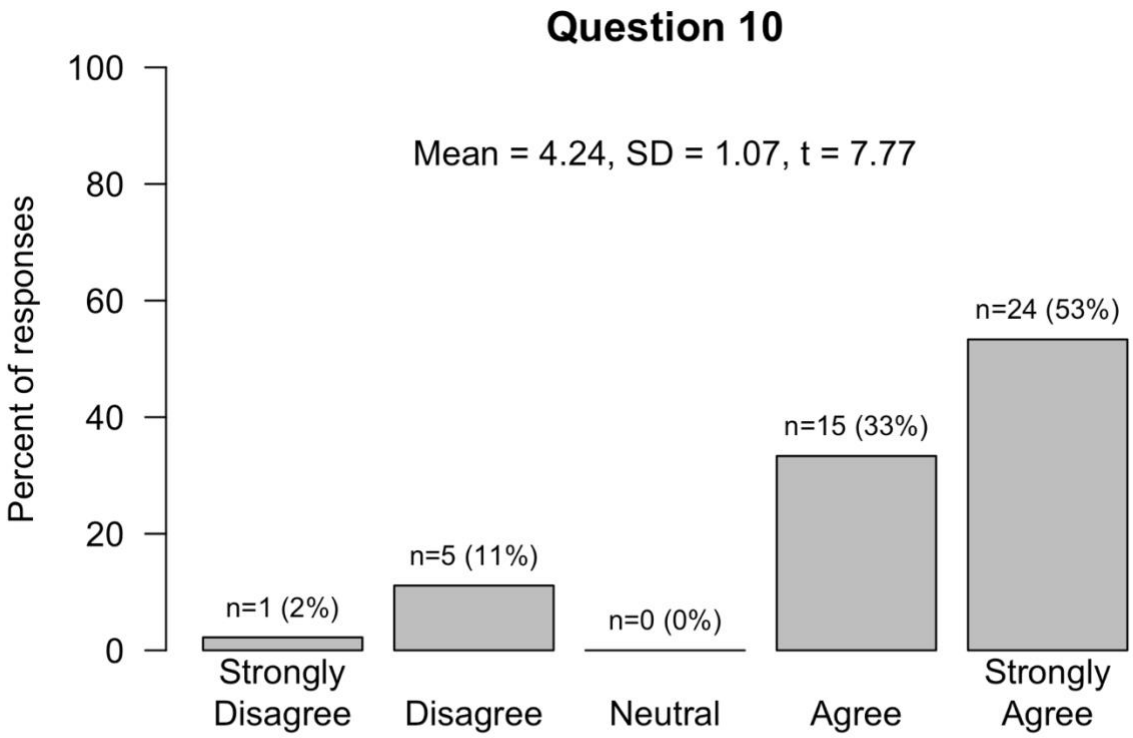
Level of agreement with Question 9: In which patients with CAP who are immunocompromised should empiric therapy be extended beyond the core respiratory pathogens?

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.



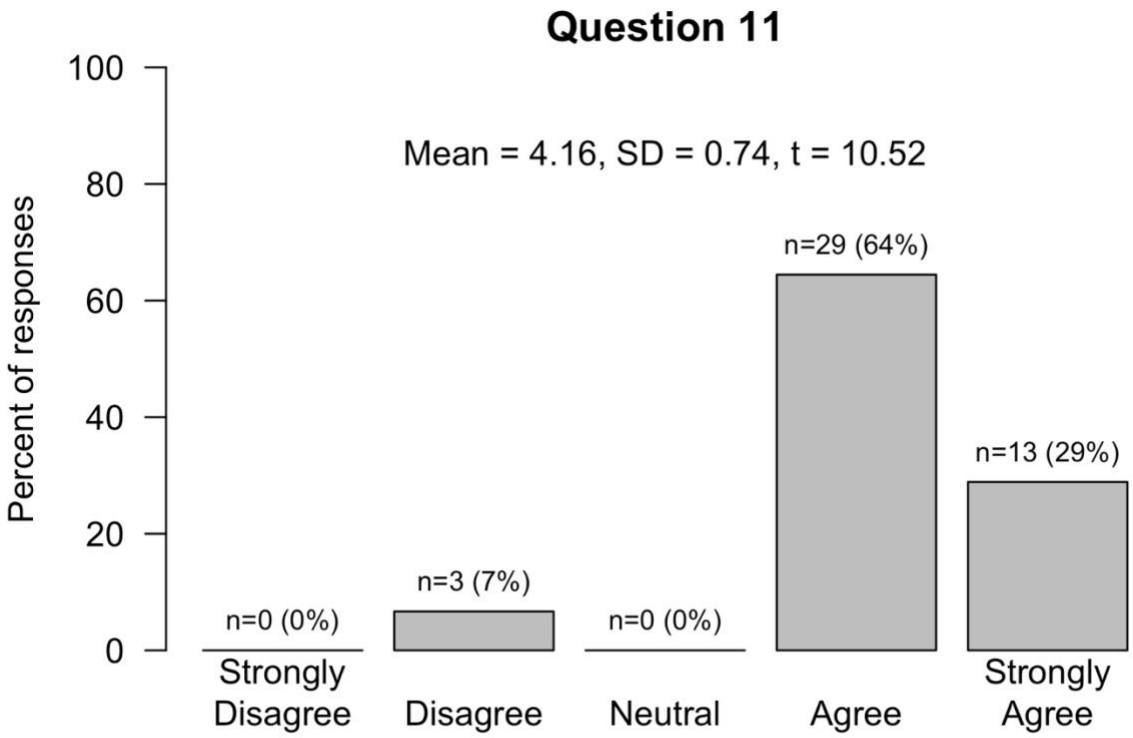
Level of agreement with Question 10: What role does the severity of pneumonia play in the selection of initial empiric therapy?

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.



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.

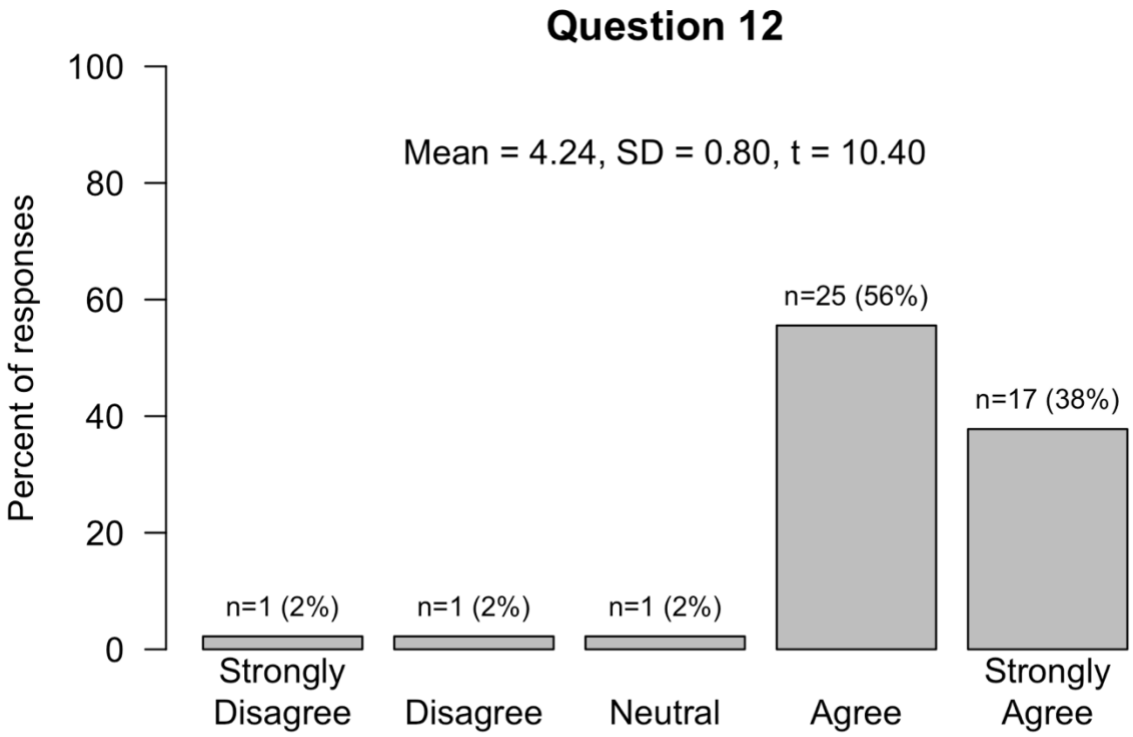


Additional comments for Question 11:

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.

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.

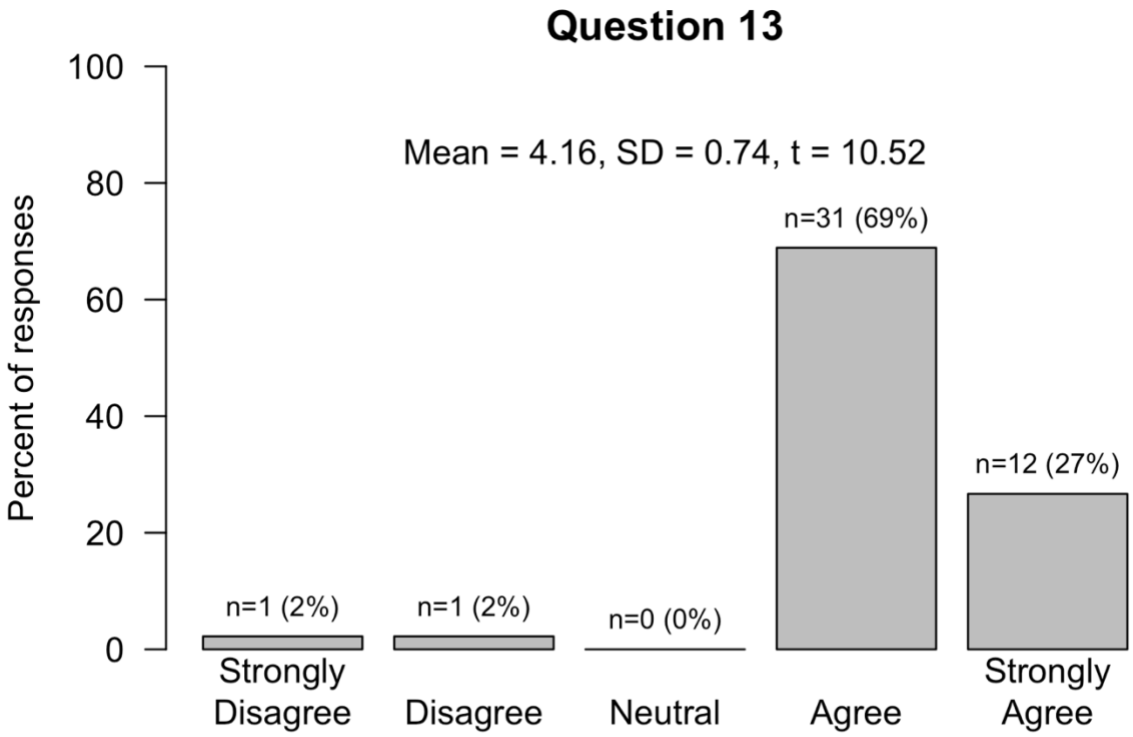


Additional comments for question 12:

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.

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.

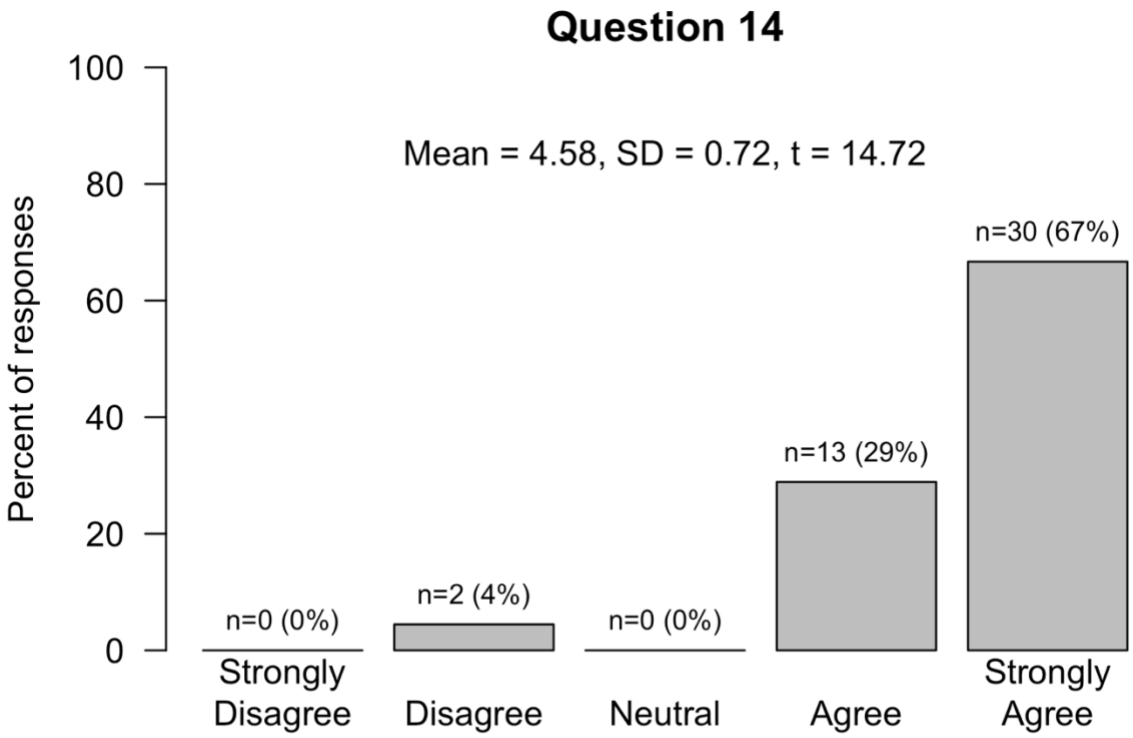


Additional comments for question 13:

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.

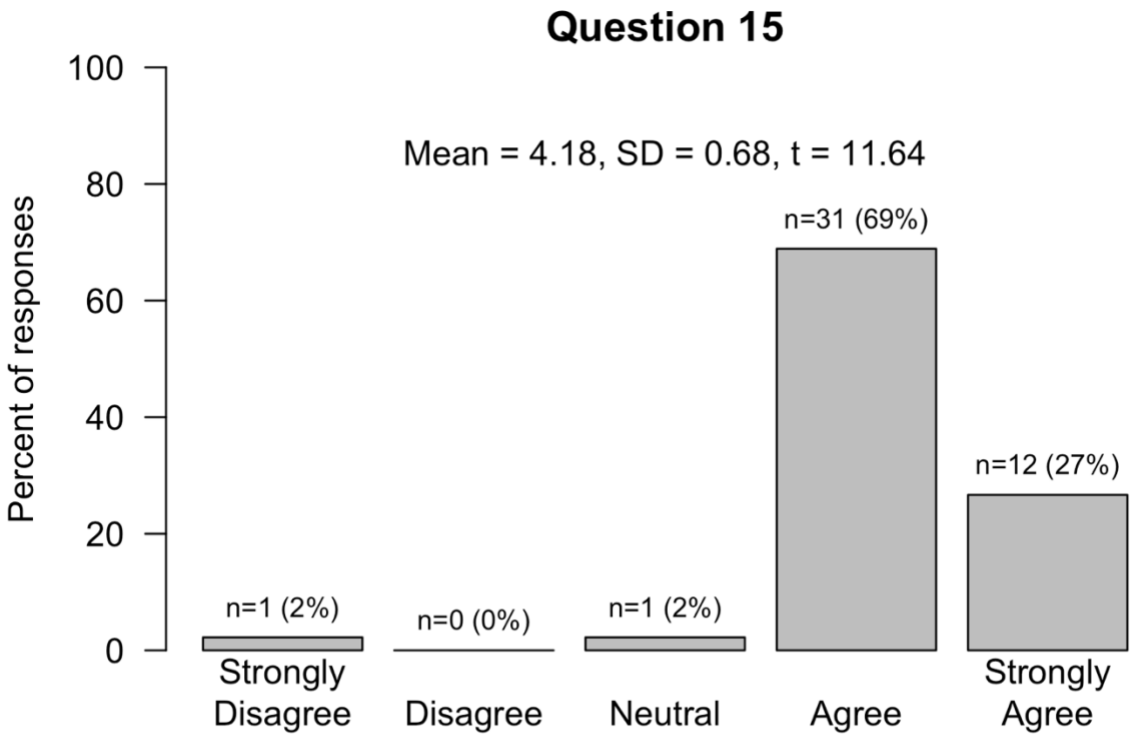
Level of agreement with Question 14: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Pneumocystis jirovecii* pneumonia (PCP)?

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.



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.

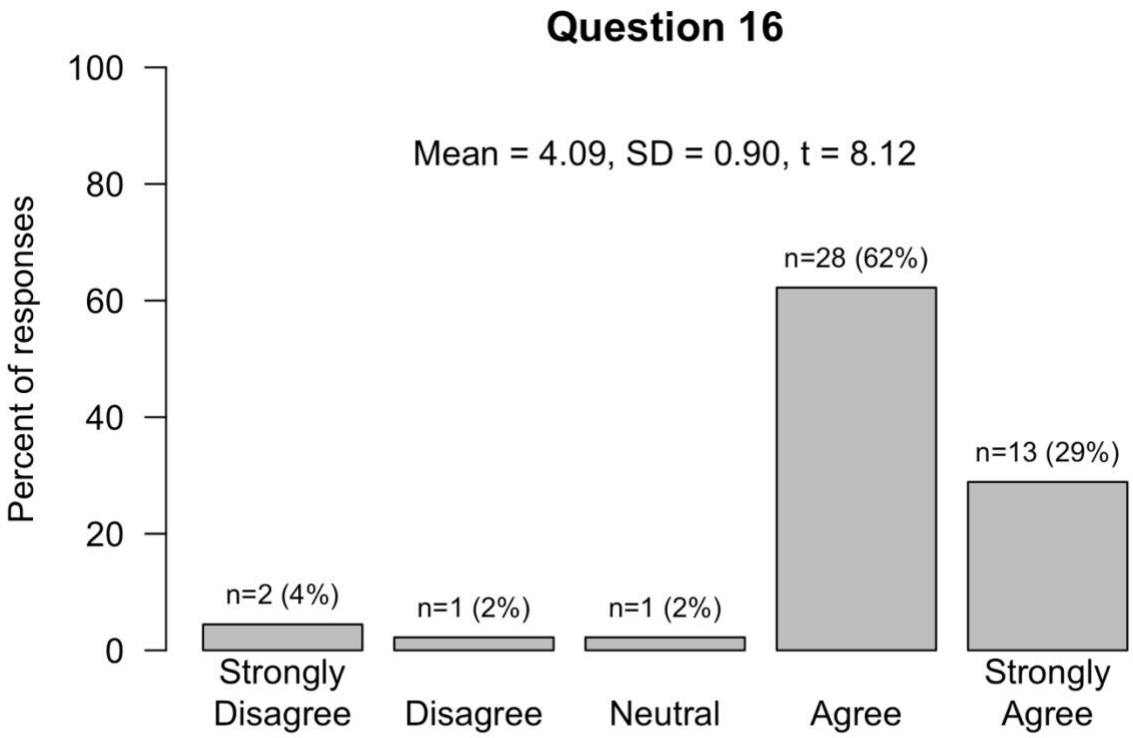


Additional comments for question 15:

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.

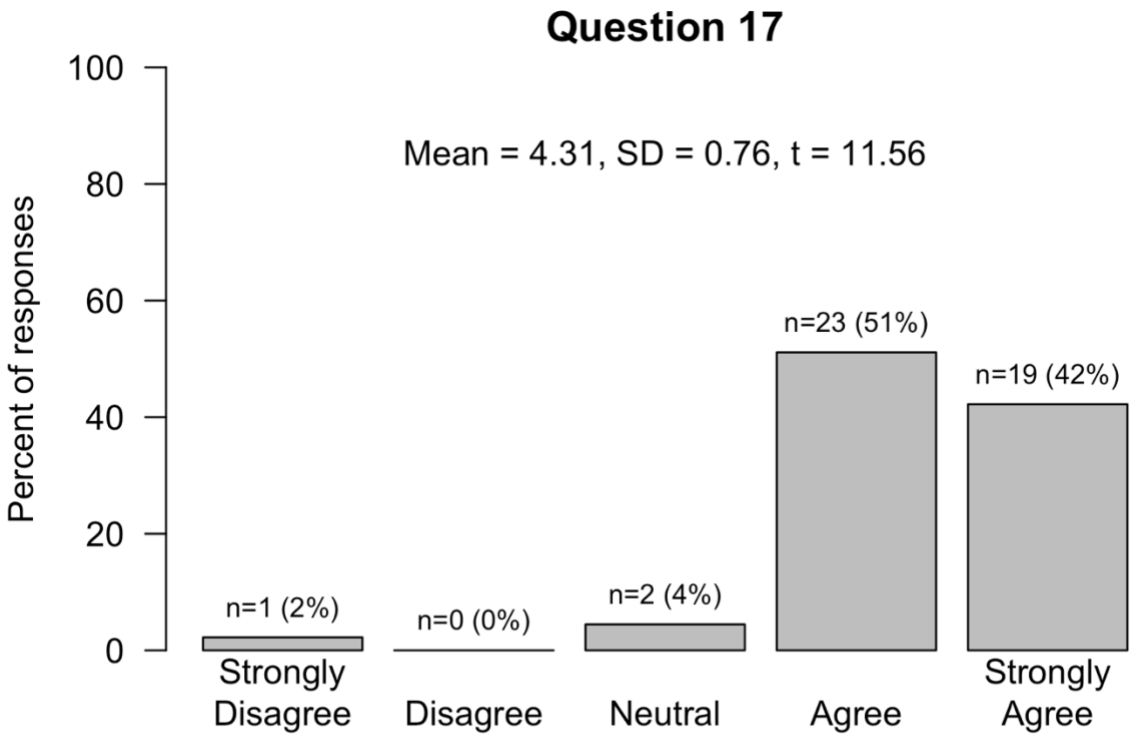
Level of agreement with Question 16: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mucorales*?

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.



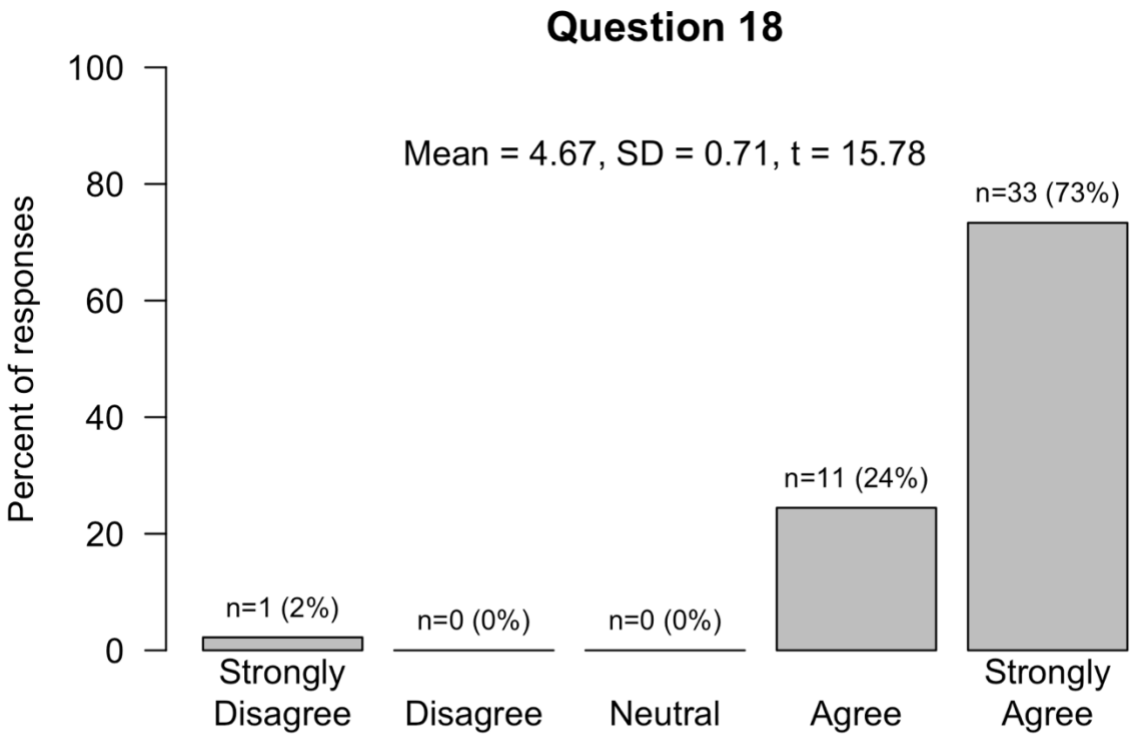
Level of agreement with Question 17: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Nocardia*?

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.



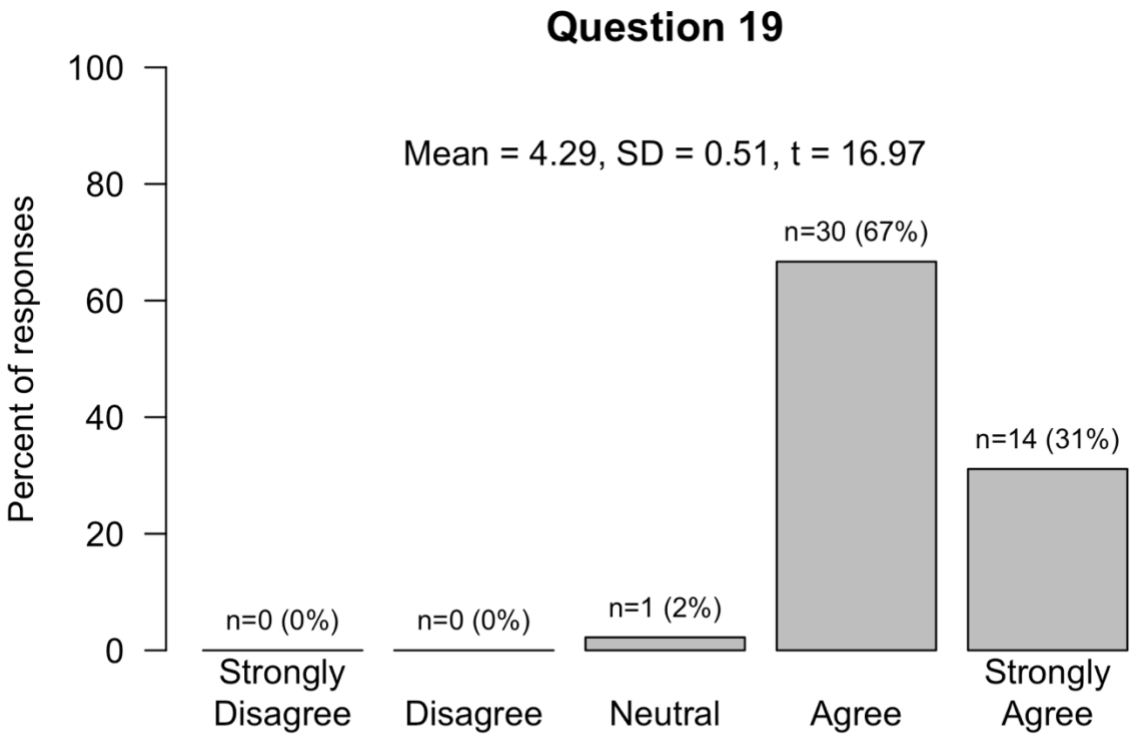
Level of agreement with Question 18: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Varicella-zoster virus?

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.



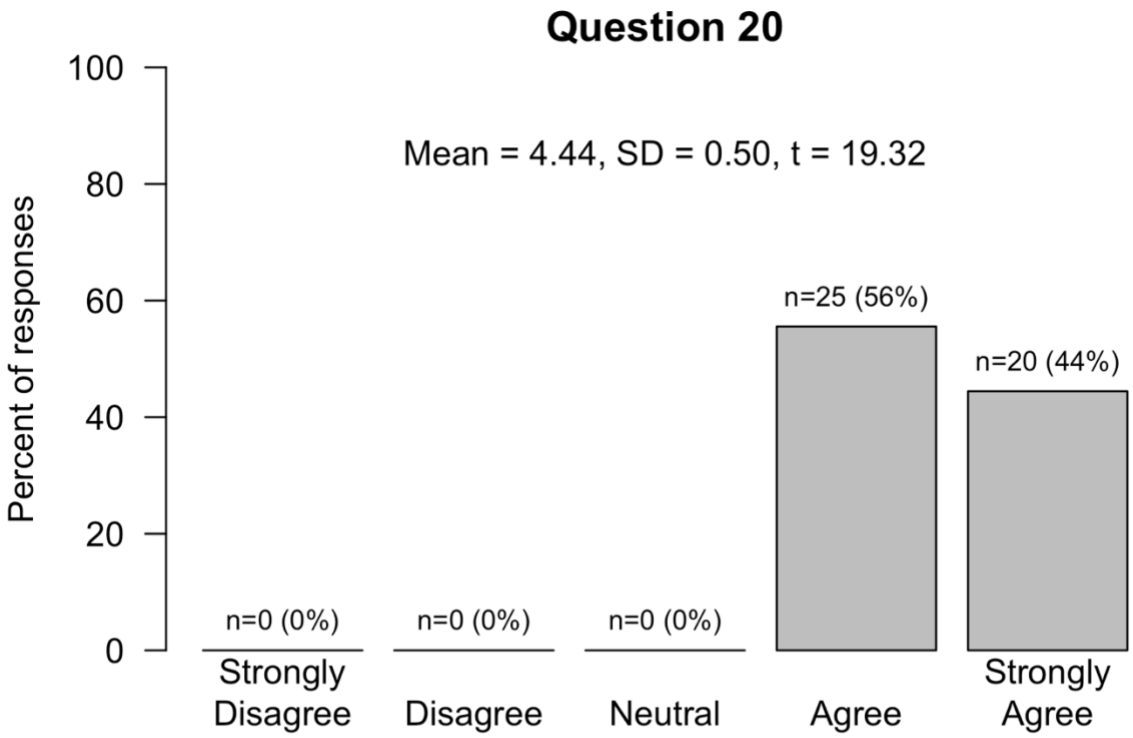
Level of agreement with Question 19: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to Cytomegalovirus?

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.



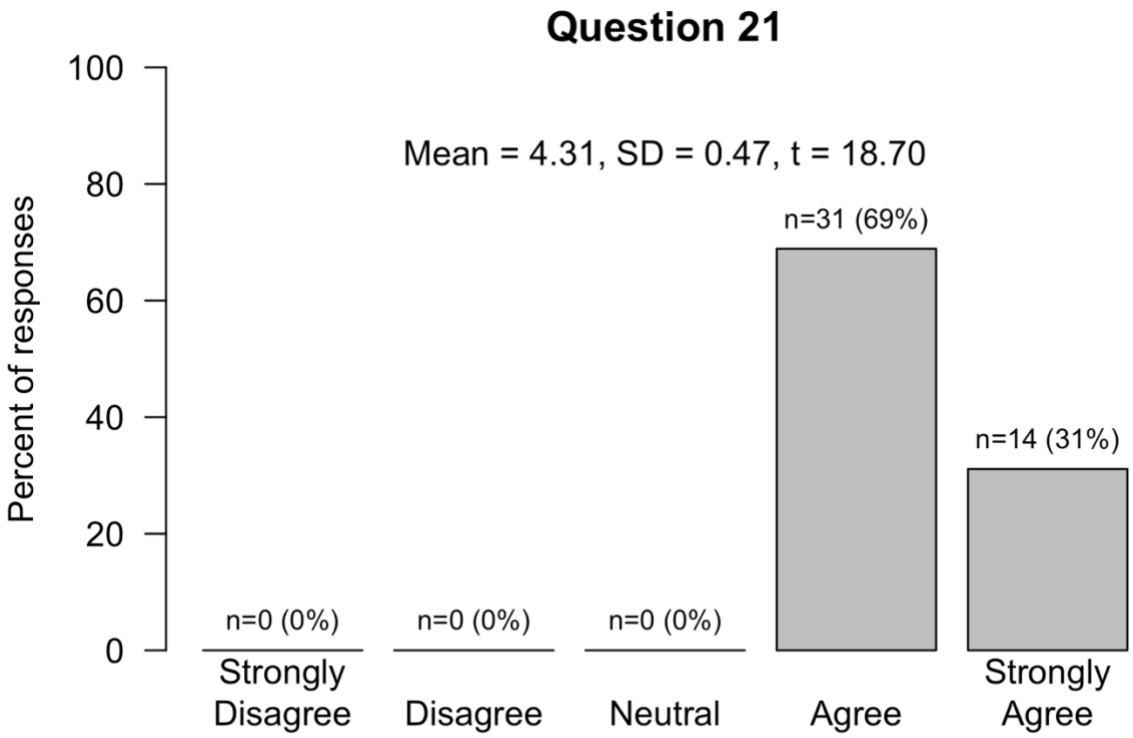
Level of agreement with Question 20: In which immunocompromised patients should the initial empiric therapy be extended to cover the possibility of CAP due to *Mycobacterium tuberculosis*?

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.



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.



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.