Guidelines

Recommendations for antibacterial therapy in adults with COVID-19 – an evidence-based guideline

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ABSTRACT

Scope: The Dutch Working Party on Antibiotic Policy constituted a multidisciplinary expert committee to provide evidence-based recommendation for the use of antibacterial therapy in hospitalized adults with a respiratory infection and suspected or proven 2019 Coronavirus disease (COVID-19).

Methods: We performed a literature search to answer four key questions. The committee graded the evidence and developed recommendations by using Grading of Recommendations Assessment, Development, and Evaluation methodology.

Questions addressed by the guideline and Recommendations: We assessed evidence on the risk of bacterial infections in hospitalized COVID-19 patients, how to diagnose bacterial infections and how to treat bacterial infections. Bacterial co-infection upon admission was reported in 3.5% of COVID-19 patients, while bacterial secondary infections during hospitalization occurred up to 15%. No or very low quality evidence was found to answer the other key clinical questions. Although the evidence base on bacterial infections in COVID-19 is currently limited, available evidence supports restrictive antibiotic use from an antibiotic stewardship perspective, especially upon admission. To support restrictive antibiotic use, maximum efforts should be undertaken to obtain sputum and blood culture samples as well as pneumococcal urinary antigen testing. We suggest to stop antibiotics in patients who started antibiotic treatment upon admission when representative cultures as well as urinary antigen tests show no signs of involvement of bacterial pathogens after 48 hours. For patients with secondary bacterial respiratory infection we recommend to follow other guideline recommendations on antibacterial treatment for patients with hospital-acquired and ventilator-associated pneumonia. An antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial respiratory infection is recommended upon improvement of signs, symptoms and inflammatory markers. Larger, prospective studies about the epidemiology of bacterial infections in COVID-19 are urgently needed to

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confirm our conclusions and ultimately prevent unnecessary antibiotic use during the COVID-19 pandemic. Elske Sieswerda, Clin Microbiol Infect 2021;27:61 © 2020 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Scope

The 2019 Coronavirus (COVID-19) pandemic due to the novel SARS Coronavirus (SARS-CoV-2) has resulted in a sudden, large and prolonged increase in hospitalizations of patients fulfilling the criteria for community-acquired pneumonia (CAP). SARS-CoV-2 can lead to a wide spectrum of disease, ranging from very mild symptoms of upper respiratory tract infection to life-threatening pneumonia. Severe disease is frequently associated with high inflammation marker levels. It is therefore challenging to define if a patient fulfilling criteria for CAP who is positive for SARS-CoV-2 has a bacterial co-infection upon admission. During hospitalization it may be difficult to distinguish between severe COVID-19 and bacterial secondary infections.

In several reports the majority of hospitalized patients with COVID-19 were treated with broad-spectrum antibiotics with unknown efficacy [1–11]. As COVID-19 patients frequently need prolonged hospitalization and respiratory support, unnecessary antibiotics upon hospitalization may increase the individual risk of prolonged hospitalization and respiratory support, unnecessary tests, imaging and other diagnostic tests, while awaiting the results of a SARS-CoV-2 test. The full guidelines text, literature review and rebuttal of the received commentaries are available in the supplementary material.

We constituted a committee of experts of several disciplines, including experts in guideline development and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. We aimed to answer four key questions relevant for the clinical setting (Table 1). A high likelihood of COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician based on signs, symptoms, background prevalence of SARS-CoV-2, an epidemiological link, results of laboratory tests, imaging and other diagnostic tests, while awaiting the confirmatory SARS-CoV-2 test. Proven COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician and confirmed with a SARS-CoV-2 test.

Methods

We constituted a committee of experts of several disciplines, including experts in guideline development and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. We aimed to answer four key questions relevant for the clinical setting (Table 1). A high likelihood of COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician based on signs, symptoms, background prevalence of SARS-CoV-2, an epidemiological link, results of laboratory tests, imaging and other diagnostic tests, while awaiting the confirmatory SARS-CoV-2 test. Proven COVID-19 was defined as an illness most likely COVID-19 as concluded by the treating clinician and confirmed with a SARS-CoV-2 test.

A systemic literature review was performed by one author (ES) on 5 May 2020 in PubMed and LitCovid and references from relevant articles. The search strategy was: ((coronavirus and 2020) or COVID-19 or SARS-CoV-2) and (bacteria* or antibiotic* or antibacterial). Two authors (JMP, WJW) checked the original literature search. The panel anticipated on limited high quality evidence due to the recent emergence of SARS-CoV-2 and reports on adults were therefore included irrespective of the study design and outcomes studied. We defined co-infections as (suspected) bacterial pneumonia in addition to COVID-19 in patients within 48 to 72 hours of admission for (suspected) COVID-19. Secondary infections were defined as (suspected) bacterial pneumonia beyond 48 to 72 hours of hospitalization for COVID-19. We did not include evidence on the diagnosis of COVID-19, the antiviral treatment of SARS-CoV-2 nor on the antifungal treatment of patients with a suspicion of COVID-19.

Questions addressed by the guidelines and recommendations

A summary of all recommendations including final grading of evidence is provided in Table 2. Our GRADE table is presented in Supplementary table 1.

1. What is the risk of bacterial pneumonia in patients with proven or high likelihood of COVID-19?

Supplementary table 2 provides an evidence summary of studies reporting on bacterial infections in patients with proven or
high likelihood of COVID-19. A study from China reported signs of bacterial co-infection upon hospital admission in 1 of 99 patients [19]. Another study from China reported no bacterial co-infections in respiratory and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission [18]. A systematic review and meta-analysis on bacterial infections in COVID-19 patients reported an overall proportion of bacterial infections of 7.1% (95% confidence interval [CI]: 4.6 – 9.6%) in 28 eligible studies [18]. The authors additionally assessed proportion of bacterial co-infections upon presentation, which was found in 3.5% (95% CI: 0.6 – 6.1%) of patients; and proportion of bacterial secondary infections after initial presentation, which was 15.5% (95% CI: 10.9 – 20.1).

2. What are the causative bacterial species in patients with proven or high likelihood of COVID-19 and bacterial pneumonia?

Reported bacterial pathogens in available studies of patients with COVID-19 are shown in Supplementary table 2. In eight studies information on bacterial pathogens was reported [19–26]. Three studies reported no bacterial pathogens [20,21,26]. The pathogens reported in COVID-19 patients with possible bacterial co-infection were mainly Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumoniae. Only three gram-negative bacterial species were reported in two patients. In one patient in China, both Klebsiella pneumoniae and Acinetobacter baumannii were isolated from respiratory material [19]. In one patient in the Netherlands, Pseudomonas aeruginosa was cultured from blood, but it was not described whether the bacteriaemia was related to a suspected respiratory or other infection [24]. One positive PCR for Mycoplasma pneumoniae and no positive Legionella tests were reported [23]. The clinical severity of pneumonia was not reported in the available studies. As a consequence, it is unknown whether the cultured S. aureus in respiratory material was associated with severe pneumonia, as can be seen after an influenza virus infection, or with colonization of the respiratory tract.

Among two studies on secondary infections, one reported on bacterial pathogens [2,25]. In this small study from China, three gram-negative species were reported: 2/29 (7%) Enterobacter cloacae and 1/29 (3%) A. baumannii [10]. The reported identified bacteria in 188 studies on bacterial infections in COVID-19 patients [18], Mycoplasma species were identified in n = 12, Enterobacteriales spp in n = 11, H. influenzae in n = 8, P. aeruginosa in n = 5, S. aureus in n = 2, A. baumannii in n = 2 and

**Table 2**

Summary of recommendations

| Recommendation                                                                 | Strength | Quality of evidence |
|-------------------------------------------------------------------------------|---------|---------------------|
| 1. We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill | Weak    | Very low            |
| 2. We suggest that exceptions for the restrictive use of antibacterial drugs can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other exceptions are patients who are severely ill or immunocompromised. | Weak    | GPS                |
| 3. We recommend maximum efforts to obtain sputum and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission | Strong  | GPS                |
| 4. In case of suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens in patients with proven or high likelihood of COVID-19 hospitalized at the general ward. Legionella urinary antigen testing should be performed according to local and/or national guidelines for CAP | Weak    | Very low           |
| 5. We recommend that the empirical antibiotic regimen in case of suspected bacterial co-infection depends on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate-severe CAP, we recommend to follow local and/or national guideline recommendations on antibacterial treatment in CAP | Weak    | Very low           |
| 6. We recommend to follow local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection | Strong  | GPS                |
| 7. We suggest to stop antibiotics when representative sputum and blood culture as well as urinary antigen tests taken before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 show no bacterial pathogens after 48 hours of incubation | Weak    | GPS                |
| 8. We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms and inflammatory markers | Weak    | GPS                |

*immunocompromised is defined as the use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications; GPS: good practice statement.
Enterococcus faecium in \( n = 1 \). Here no distinction was made between bacterial co-infection upon presentation and secondary infection after initial presentation. For 26 of 41 reported bacteria the source of identification was respiratory material, in the remainder this was unspecified.

3. What is the optimal approach in diagnosing or refuting bacterial pneumonia in patients with proven or high likelihood of COVID-19?

We found one meta-analysis summarizing 18 studies on prediction models for the diagnosis of COVID-19 [27]. Within five general prediction models, most common predictors were clinical or demographical factors, such as age, fever and other signs and symptoms. The other 13 studies assessed CT scan-based prediction models for the diagnosis of COVID-19. All studies were at high risk of bias and almost all were not externally validated. The studies did not report on alternative diagnoses such as bacterial pneumonia or co-infections. We found no other studies on diagnosing or refuting bacterial pneumonia in patients with COVID-19.

4. What is the optimal empirical antibiotic choice for patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia?

There were no studies yet evaluating the effectiveness and safety of specific antibiotic regimens in patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia.

Discussion

Based on current limited evidence, the vast majority of patients with proven COVID-19 respiratory illness presenting at the hospital does not have or develop a bacterial co-infection. Reported percentages of potential respiratory bacterial co-infections upon admission was 3.5% in cohort studies reporting on cultured bacterial co-infections, but the quality of evidence and therefore the accuracy of these percentages is very low. Based on the currently available evidence and antibiotic stewardship principles, the committee recommends restrictive use of antibacterial drugs in patients with community-acquired respiratory infection and proven or high likelihood of COVID-19. This especially applies to patients with mild or moderately-severe respiratory disease based on clinical assessment [16,28–30].

Several studies did not report details on the total number of patients from whom culture samples were obtained. In patients with a positive bacterial culture or PCR result from respiratory material, it was not reported how this result related to a clinically or otherwise confirmed diagnosis of bacterial co-infection. A substantial proportion of patients was already treated with antibiotics before hospitalization, decreasing the yield of bacterial cultures. Importantly, there were only data available for patients with (subsequently) proven COVID-19.

The committee agreed that clinicians should always assess the risk of a bacterial co-infection in patients with suspected COVID-19. However, in daily practice, it is difficult to distinguish viral from bacterial pneumonia [16,31]. Of note, the Infectious Disease Society of America (IDSA) guideline on CAP concluded that procalcitonin cannot be used in the decision to start or withhold antibiotics in patients with CAP [31]. The IDSA guideline on HAP and VAP performed extensive evidence summaries evaluating the additional value of using procalcitonin, CRP, or the Modified Clinical Pulmonary Infection Score plus clinical criteria for the diagnosis of HAP or VAP [12]. None of these diagnostic modalities were of additional value compared to clinical criteria alone. In current clinical practice, some hospitals do make use of procalcitonin to direct the initiation of antibiotic therapy in patients with suspected or proven COVID-19. This might be a valid strategy, however the evidence base for such a strategy is currently lacking. In daily practice, a combination of the clinical course of disease and results obtained from laboratory tests and imaging are leading in the assessment of the likelihood of bacterial co-infection in patients with COVID-19.

Therefore, as a good practice statement, the committee suggests that antibiotic therapy should be considered if the clinician has a high suspicion of bacterial co-infection in a patient with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other patients with proven or high likelihood of COVID-19 in whom it is reasonable to start empirical antibiotic therapy while awaiting diagnostic test results include those who are severely immunocompromised. These patients have a higher likelihood of deteriorating rapidly in the event of an untreated bacterial co-infection. We defined immunocompromised as use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications. In addition, the guideline committee endorsed the recommendation of the 2020 Surviving Sepsis Campaign guideline on COVID-19 to treat critically ill patients admitted to the ICU for COVID-19 with empirical antibiotic therapy while awaiting the results of diagnostic testing.

As the evidence base for our recommendations is limited, we recommend maximum efforts of to obtain sputum and blood cultures before start of empirical therapy in patients fulfilling criteria of CAP and proven or high likelihood of COVID-19 to support or refute the diagnosis of bacterial infection. An urinary pneumococcal antigen testing is recommended in all patients, as for COVID-19 patients we recommend to withhold antibiotic therapy in the group who do fulfill the formal criteria of mildly or moderately severe CAP [16,28–30]. A positive urinary pneumococcal antigen testing might support the diagnosis of bacterial co-infection, and thus lead to empiric antibiotic therapy.

The reported bacterial pathogens in patients with a co-infection seemed similar to those in regular bacterial CAP [16,31]. As there is no evidence for a specific superior empirical treatment strategy in patients with COVID-19 and bacterial pneumonia, we recommend to follow local and/or national guidelines for the antibacterial treatment of CAP [16,31,33]. As an example, in the Dutch SWAB guideline on CAP, preferred regimens depend on the severity of disease: for mildly and moderately severe CAP amoxicillin is recommended, for patients with severe CAP at the general ward a second or third generation cephalosporin is recommended [16]. Pneumonia due to atypical pathogens as a co-infection to COVID-19 are rarely reported in the literature. As a result, the committee suggests that routine empirical treatment of atypical pathogens such as Legionella and Mycoplasma spp. is not started in patients with proven or high likelihood of COVID-19 hospitalized. Again, it is recommended to perform Legionella urinary antigen testing according to the criteria mentioned in local and/or national guidelines [16,31,33].

The available evidence suggests a risk of up to 20% secondary infections in COVID-19 patients, especially in severely ill patients. There is no available evidence on the additional risk of such secondary infections in COVID-19 patients compared to other severely ill patients, and neither on causative pathogens. The committee thought it currently reasonable to assume that the risk of secondary infections in COVID-19 patients as well as the causative pathogens are similar secondary infections in hospitalized patients without COVID-19. It is currently unknown what the effect of antibacterial strategies is on outcomes of secondary infections in COVID-19 patients, including selective decontamination of the digestive tract. We therefore recommend to start empirical treatment, after obtaining cultures, in COVID-19 patients with suspected secondary
bacterial respiratory infection in accordance with local and/or national guideline recommendations on antibacterial treatment for patients with HAP and VAP. For patients without recent surveillance culture results, the antibacterial spectrum is suggested to include *S. aureus*, Enterobacteriales, *P. aeruginosa*, *A. baumannii* and *H. influenzae*, depending on local prevalences.

The committee emphasizes the need for appropriate de-escalation in COVID-19 patients, in order to reduce unnecessary antibiotic use as much as possible [34,35]. As a good practice statement, we therefore suggest that, if antibiotics have been started, to stop those when representative sputum and blood culture and urinary antigen tests obtained before start of empirical therapy in patients with proven or high likelihood of COVID-19 show no pathogens after 48 hours of incubation. The guideline committee suggests that an antibiotic treatment duration of five days is likely sufficient in patients with COVID-19 and suspected bacterial co-infection upon improvement of signs, symptoms and inflammatory markers [16,31]. Procalcitonin levels could be used to support shortening the duration of antibacterial therapy in patients with sepsis if the optimal duration of antibiotic therapy is unclear [31,36].

In conclusion, this is an executive summary of a multidisciplinary guideline with recommendations for the empirical antibiotic treatment of hospitalized adults with a respiratory infection and proven or high likelihood of COVID-19. Such recommendations on treatment in COVID-19 patients need to be updated regularly, as the evidence on bacterial co-infections, secondary infections and the optimal management of COVID-19 patients expands. Although the evidence base on bacterial infections in COVID-19 is currently limited, available studies support restrictive antibiotic use from an antibiotic stewardship perspective upon admission. Larger, prospective studies on the epidemiology of bacterial co-infections and secondary infections in COVID-19, adjusted for antibiotic use and other confounders, are warranted to confirm our conclusions and ultimately prevent unnecessary antibiotic use during the COVID-19 pandemic.

Transparency declaration

Members of the preparatory committee reported the following potential conflicts of interest: ES: none; MGJDB: none; MJB: none; WGB: none; REJ: none; RMA: none; BJK: reports personal fees from Pfizer, outside the submitted work; JAS: none; EMWG: none; TJV: none; MMVE: none; JMP: none; WJW: reports support by the Netherlands Organization of Scientific Research (VIDI grant). No conflict of interest to disclose.

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Author contributions

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Appendix A. Supplementary data

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