STICHTING WERKGROEP ANTIBIOTICABELEID

The Dutch Working Party on Antibiotic Policy (SWAB) recommendations for antibacterial therapy in adults with COVID-19

This evidence-based document is a supplement to the "Management of Community-Acquired Pneumonia in Adults: 2016 Guideline Update From The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT)"

E. Sieswerda,[1] M.G.J. De Boer,[2] M.M.J. Bonten,[3] W.G. Boersma,[4] R.E. Jonkers,[5] R.M. Aleva,[6] B.J. Kullberg,[7] J.A. Schouten,[8] E.M.W. van de Garde,[9] T.J. Verheij,[10] M.M. van der Eerden,[11] J.M. Prins,[12] W.J. Wiersinga[12]

[1] Department of Medical Microbiology and Infection Control, Amsterdam UMC, University of Amsterdam, Amsterdam; [2] Department of Infectious Diseases, Leiden University Medical Center, Leiden; [3] Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht; [4] Department of Pulmonary Diseases, Northwest Hospital Group, Alkmaar; [5] Department of Respiratory Medicine, Amsterdam UMC, Amsterdam; [6] Department of Pulmonary Diseases, Máxima Medisch Centrum, Eindhoven; [7] Radboud Center for Infectious Diseases and Department of Internal Medicine, Radboud University Medical Center, Nijmegen; [8] Department of Intensive Care, Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen; [9] Department of Clinical Pharmacy, St. Antonius Hospital, Utrecht/Nieuwegein, The Netherlands; Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [10] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht; [11] Department of Pulmonology, Erasmus MC, Rotterdam; [12] Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam

Corresponding author: Elske Sieswerda, MD, PhD, Department of Medical Microbiology and Infection Control, University of Amsterdam, Amsterdam Infection and Immunity Institute, Amsterdam UMC, Amsterdam, The Netherlands. Tel: +31-6-25716442; e-mail: e.sieswerda@amsterdamumc.nl

Inhoud

Introduction and methodology

General introduction

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. An even more challenging question is how to treat patient with CAP and suspected, but not yet proven COVID-19, when bacterial CAP is still part of the differential diagnosis. This difficult differential diagnosis may be of less importance in the midst of the epidemic, but when incidence rates are slowing, differentiating COVID-19 from "regular" bacterial pneumonia will prove more challenging.

In available reports from China, the majority of hospitalized patients with COVID-19 have thus far been treated with broad-spectrum antibiotics with unknown efficacy.[3-13] As COVID-19 patients frequently need prolonged hospitalization and respiratory support, unnecessary antibiotics upon hospitalization can increase the individual risk of subsequent hospital-acquired pneumonia (HAP) by resistant bacteria or lead to other adverse events.[14,15] On a population level, universal antibiotic prescriptions for all hospitalized COVID-19 patients can lead to a steep increase in antibiotic use during a pandemic and as a result, a likely increase in antimicrobial resistance rates.[16]

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep AntibioticaBeleid) coordinates activities in the Netherlands with the aim to optimize antibiotic use, to contain the development of antimicrobial resistance, and to limit the costs of antibiotic use. For this purpose, SWAB develops evidence-based guidelines on antibiotic treatment, intended for the Dutch situation. In 2017 the SWAB, in collaboration with the Dutch Association of Chest Physicians (NVALT), the Dutch Society of Intensive Care (NVIC), and the Dutch College of General Practitioners (NHG), published a joined guideline on the management of hospitalized patients with CAP.[1,2] For the current COVID-19 pandemic, the SWAB has prepared an addendum of the CAP guideline aimed at optimizing antibacterial therapy in patients hospitalized with respiratory infection and proven or high likelihood of COVID-19. A high likelihood of COVID-19 is concluded by the treating clinician based on signs, symptoms, background prevalence of SARS-CoV-2, results of laboratory tests, imaging and available diagnostic guidelines.

Our objective was to provide an overview of the quality of available evidence and provide recommendations the **empirical antibacterial treatment of adults (≥18 years old) who present to the hospital with a respiratory infection and proven or high likelihood of COVID-19**. This guideline does not include recommendations on the diagnosis or antiviral treatment of COVID-19 nor on the antifungal treatment of patients with suspected of COVID-19 Associated Pulmonary Aspergillosis (CAPA). For recommendations on antiviral and antifungal treatment, we refer to the SWAB guidance document on treatment options for patients with COVID-19,[17] and the advice on COVID-19 associated pulmonary aspergillosis (CAPA), available at https://www.radboudumc.nl/centrum-voor-infectieziekten/onze-aandachtsgebieden/covid19/beleid-rond-covid19-geassocieerde-pulmonale-aspergillose-capa. For recommendations on the treatment of patients with COVID-19 who present to the general practitioner and patients hospitalized with CAP in whom there is a low

likelihood of COVID-19, we refer to Dutch general practitioners' (NHG) guidelines available at www.corona.nhg.org and the 2017 SWAB guideline on CAP.[1,2]

Methodology

The current addendum was based on four key questions considering population, intervention, comparison, and outcomes (PICO) relevant for the Dutch clinical setting (**Table 1**). For each key question we developed short evidence summaries after searching PubMed, which were subsequently assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as described in the draft SWAB sepsis guideline.[18,19] The PubMed search strategy included ((coronavirus and 2020) or COVID-19 or SARS-CoV-2) and (bacteria* or antibiotic* or antibacterial), and was supplemented by a screening of Twitter messages and the contents of Nederlands Tijdschrift voor Geneeskunde. Case-reports and case-series with less than ten patients were not included. Quality of evidence for clinically relevant outcomes was graded from high to very low. A multidisciplinary committee formulated recommendations after structured discussions as strong or weak. The committee anticipated on limited high quality evidence due to the recent emergence of SARS-CoV-2. When evidence could not be obtained, recommendations were provided on the basis of opinions and experiences with other viral pneumonias (good practice statements, GPS). Based on this process, we formulated ten recommendations on the antibacterial management of adults with proven or high likelihood of COVID-19 (see recommendations below).

Table 1. Key questions

1.	What is the risk of bacterial pneumonia in patients with proven or high likelihood of COVID-19?
2.	What are the causative bacterial species in patients with proven or high likelihood of COVID-19 and bacterial pneumonia?
3.	What is the optimal approach in diagnosing or refuting bacterial pneumonia in patients with proven or high likelihood of COVID-19?
4.	What is the optimal empirical antibiotic choice for patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia?

Conflicts of interest policy and funding

The Guidelines Committee would like to thank all individuals and societies who contributed to the development of these guidelines. Members of the preparatory committee reported the following potential conflicts of interest: ES: none; MGJDB: none; MJB: none; WGB: received a grant from TEVA; REJ: none; RMA: none; BJK: none; JAS: none; EMWG: grant from GSK for investigating etiology of CAP; TJV: received two grants for research and a fee for consultation from Pfizer; MMVE: none; JMP: none; WJW: performed DSMB consultancy duties for GSK.

Key questions

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

Evidence summary

At the time of writing, three reports of three single-centre Dutch cohort studies were available (**Table 2**).[20-22] All three studies reported on bacterial co-infections in COVID-19 patients, but details were limited. Overall, the percentage of patients with a potential bacterial respiratory co-infection upon admission was 8% or less. The percentage of potential bacterial co-infection was even lower in patients presenting at the emergency department cohort (less than 3%) compared to the two hospitalized COVID-19 populations (7-8%).

International studies reporting on potential bacterial co-infection early in the course of disease also reported low numbers of bacterial co-infection, although limited details were provided. A study from China reported 1% of patient with signs of bacterial co-infection upon admission.[23] Another study from China reported no bacterial co-infections in 201 hospitalized patients with COVID-19, of whom 74% had sputum culture results available.[24] One study from the US reported 0% atypical pathogens in patients with community-acquired COVID-19.[25] We found no studies reporting prevalences of bacterial CAP in patients with suspected COVID-19, i.e. in whom the diagnosis of COVID-19 was not yet confirmed.

Two studies from Wuhan in China reported on hospital-acquired bacterial infections in COVID-19 patients.[4,26] One small prospective cohort study of confirmed COVID-19 patients reported 10% nosocomial, microbiologically-confirmed bacterial pneumonia and bacteraemia.[26] The authors did not separate data for pneumonia from bacteraemia. A larger retrospective multicentre study reported secondary infections (HAP; or bacteraemia) and ventilator-associated pneumonia (VAP) in 191 COVID-19 patients who had been discharged or had died at the end of the study.[4] The authors reported an overall incidence of 15% secondary bacterial infections; this number was lower in those who survived (<1%) compared to non-survivors (50%). In the overall cohort, 5% developed VAP during hospitalization. In this series, among those who received mechanical ventilation VAP was diagnosed in 31%. In contrast, a small cohort study of ICU-admitted COVID-19 patients in the US reported not a single bacterial co-infection found in respiratory and blood cultures during first 14 days of hospitalization.[27]

In accordance with these previous reports, a systematic review on bacterial and fungal co-infections in coronaviruses similarly reported an overall percentage of 8% co-infections in COVID-19 patients at any time during hospitalization.[13] The authors did not make a distinction between co-infections upon admission and co-infections that occurred during hospitalization (HAP, VAP and other infections). Many of the reported infections were bacteraemia, suggesting the presence of bacterial infections other than pneumonia.

Conclusions

- Observational studies on community-acquired bacterial co-infection in patients with proven COVID-19 reported percentages up to ~8% in hospitalized and ~3% in emergency department patients (very low quality evidence)
- There are currently no data available on the percentage of bacterial infections at the moment of hospital presentation in patients with suspected but not yet proven COVID-19
- Observational studies on hospital-acquired bacterial co-infection (including other infections than HAP and VAP) in patients with proven COVID-19 reported overall percentages of ~15% or less, but 31 to 50% for ventilated patients and patients who did not survive (very low quality evidence)

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

Evidence summary

Reported bacterial pathogens in available studies of patients with COVID-19 are shown in **Table 2**. In eight studies, three of which Dutch, results of microbiological tests were reported.[20-23] Three studies reported no pathogens. 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 bacteria were reported in two patients. In one patient in the Netherlands, *Pseudomonas aeruginosa* was cultured from blood, but it was not described if the bacteraemia was related to a suspected respiratory or other infection.[22] In one patient in China, both *Klebsiella pneumoniae* and *Acinetobacter baumannii* were isolated from respiratory material.[23] One positive PCR for *Mycoplasma pneumoniae* and no positive *Legionella* tests were reported.[21] 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.

In two studies on hospital-acquired infections, pathogens were not reported.[4,26] In one small study from China in which the timing (i.e. community-acquired or hospital-acquired) of sputum cultures was not reported, three gram-negative bacteria were reported: 2/29 (7%) *Enterobacter cloacae* and 1/29 (3%) *A. baumannii*.[12]

Conclusions

- The most common bacterial pathogens associated with community-acquired bacterial co-infection in patients hospitalized with COVID-19 seem to be *S. aureus, S. pneumoniae and H. influenzae* (very low quality evidence)
- There are currently no data available on the spectrum of causative pathogens involved in hospital-acquired bacterial co-infection in patients with COVID-19

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

Evidence summary

We found one meta-analysis summarizing 18 studies on prediction models for the diagnosis of COVID-19.[28] Within five general prediction models, most common predictors were clinical predictors 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.

Conclusion

- There is currently not enough evidence to draw any definite conclusion on the optimal approach in diagnosing or refuting bacterial pulmonary infection in patients with proven or high likelihood of COVID-19

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

Evidence summary

There were no reports evaluating the efficacy and safety of specific antibiotic regimens in patients with proven or high likelihood of COVID-19.

Conclusion

- There is currently not enough evidence to draw any definite conclusion on the optimal empirical antibiotic treatment strategy for patients with proven or high likelihood of COVID-19 and suspected bacterial co-infection

Final considerations

The committee concluded that based on the limited evidence available, the vast majority of patients with proven COVID-19 respiratory illness presenting at the hospital will not have a bacterial co-infection (key question 1). Reported percentages of potential bacterial co-infections upon admission were 0 to 8% in eight cohorts reporting on cultured bacterial co-infections, but the quality of evidence and therefore the accuracy of these percentages is very low. Several studies did not report details on the total number of patients in which cultures were done. In patients with a positive bacterial culture or PCR from respiratory material it was not reported how this result related to a clinically or otherwise confirmed diagnosis of bacterial co-infection. A substantial part 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.

Based on the currently available evidence and antibiotic stewardship principles,[29] the committee consented on 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 clinically

mild and moderately-severe respiratory disease according to the severity categories used in the SWAB CAP guideline.[1,2]

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, as previously discussed in the SWAB CAP guideline.[1,2] 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.[30] 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.[14] 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 can 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 endorses 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 empiric antibiotic therapy while awaiting test results.[31]

As the evidence base for our recommendations is currently very 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 in order to support or refute the diagnosis of bacterial infection. In contrast to the SWAB CAP guideline, we recommend urinary pneumococcal antigen testing in all patients, as for COVID-19 patients we recommend to withhold antibiotic therapy in the group who do fulfil the formal criteria of mild or moderately-severe CAP.[1,2] A positive urinary pneumococcal antigen testing might support the diagnosis of bacterial co-infection, and thus lead to empiric antibiotic therapy. We recommend *Legionella* antigen testing in concordance with the SWAB CAP guideline.

The reported bacterial pathogens in patients with community-acquired respiratory infection and COVID-19 seemed similar to those in regular bacterial CAP, as reported in the SWAB CAP guideline (key question 2).[1,2] As there is no evidence for a specific superior empirical treatment strategy in patients with COVID-19 and bacterial pneumonia, we recommend to follow the SWAB CAP guideline recommendations on antibacterial treatment in the Dutch setting.[1,2] In this guideline, preferred

regimens depend on the severity of disease: for mild and moderately-severe CAP amoxicillin is recommended, for patients with severe CAP at the general ward a second or third generation cephalosporin. Pneumonia due to atypical pathogens in addition COVID-19 are rarely reported form the literature. As a result, the committee suggest that routine empirical treatment of atypical pathogens such as *Legionella* and *Mycoplasma* spp. is not necessary in patients with proven or high likelihood of COVID-19 hospitalized at the general ward, and to perform *Legionella* urinary antigen testing according to the criteria mentioned in the SWAB CAP guideline.[13,14] For patients admitted to the ICU, we suggest to start empirical therapy also directed at atypical pathogens, but to stop atypical pathogen coverage as soon as COVID-19 is proven and the *Legionella* urinary antigen test has returned negative.

The currently available evidence suggests a risk of bacterial HAP and VAP in COVID-19 patients, especially in severely ill patients. There is no available evidence on the additional risk of HAP and VAP 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 HAP and VAP in COVID-19 patients as well as the causative pathogens are similar to those in hospitalized patients without COVID-19. It should be noted that in the Netherlands the prevalence of VAP is thought to be lower compared to other countries due to the frequent use of selective digestive tract decontamination (SDD) in ICU patients.[32] In addition, in most patients with VAP the most likely pathogen and its resistance pattern are known because of the frequent surveillance cultures of the respiratory tract in patients on SDD in the Netherlands. The number of patients that need empirical therapy due to VAP will therefore be low. As a result we recommend to start empirical treatment, after obtaining cultures, in COVID-19 patients with suspected severe HAP or VAP in accordance with current practice and the recommendations in the draft SWAB sepsis guideline.[19] For patients without recent surveillance cultures, the SWAB sepsis guideline committee concluded that in these cases the antibacterial spectrum should include *S. aureus*, Enterobacterales, *P. aeruginosa* and *H. influenzae*.[19]

Invasive Aspergillosis in patients admitted for COVID-19 has also been described.[33,34] This topic is outside the scope of this guideline addendum and we refer to the advice on COVID-19 associated pulmonary aspergillosis (CAPA), available at https://www.radboudumc.nl/centrum-voor-infectieziekten/onze-aandachtsgebieden/covid19/beleid-rond-covid19-geassocieerde-pulmonale-aspergillose-capa.

The committee emphasizes the need for appropriate de-escalation in COVID-19 patients, in order to reduce unnecessary antibiotic use as much as possible.[29,35] As a good practice statement, we therefore suggest that, if antibiotics have been started, to stop those when adequate sputum and blood culture and urinary antigen tests taken before start of empirical therapy in patients with proven or high likelihood of COVID-19 show no pathogens after 48 hours of incubation. In line with the SWAB CAP and draft SWAB sepsis guidelines, we suggest 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.[1,2,19] 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, as suggested by the SWAB antibiotic stewardship and draft sepsis guidelines.[19,29]

Recommendations

Recommendation	Strength	Quality of evidence
1. For patients hospitalized with CAP in whom there is a low likelihood of COVID-19 we refer to the SWAB guideline for CAP[1,2]	n/a	n/a
2. We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients who are mildly to moderately ill	Weak	Very low
3. 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 potential exceptions are patients who are severely ill or immunocompromised*	Weak	GPS
4. 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	Strong	GPS
5. In patients hospitalized at the general ward with proven or high likelihood of COVID-19 and suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens. *Legionella* urinary antigen testing should be performed according to the criteria mentioned in the SWAB CAP guideline[1,2]	Weak	Very low
6. We recommend that the empirical antibiotic regimens in case of suspected bacterial co-infection depends on the severity of disease: for those fulfilling criteria of mild and moderate-severe CAP we suggest amoxicillin, for severe CAP (non-ICU) a second or third generation cephalosporin and for severe CAP (ICU) moxifloxacin or a second or third generation cephalosporin plus ciprofloxacin, with the same considerations for specific antibiotic choices as mentioned in the CAP guideline	Weak	Very low
7. We recommend to follow the draft SWAB sepsis guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial HAP or VAP	Strong	GPS
8. We suggest to stop antibiotics when adequate 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
9. We suggest to stop antibiotic coverage of atypical pathogens in ICU patients with proven COVID-19 when the *Legionella* urinary antigen test is negative	Weak	GPS
10. We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial co-infection upon	Weak	GPS

improvement of signs, symptoms and inflammatory markers, unless recommended otherwise for specific pathogens in the CAP guidelines		

*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

Evidence summary of studies reporting on bacterial co-infections in patients with proven or high likelihood of COVID-19

Table 2.

Netherlands						
Study	**Study design**	**Population**	**Diagnostic modality**	**Results**	**Quality**	**Comments**
Van der Moeren et al.[20]	Retrospective cohort study	N=29 Culture results in first 29 hospitalized COVID-19 patients, Amphia hospital Breda	Bacterial culture respiratory tract materials Total number of patients with bacterial culture of respiratory tract not described	2/29 (7%): *S. aureus* in respiratory tract	Very low	Percentage potential community-acquired bacterial respiratory co-infection: 7%
Murk et al.[21]	Retrospective cohort study	N=100 Retrospective description of co-infections in the first 100 newly hospitalized COVID-19 patients in ETZ hospital Tilburg 31% patients pre-treated with antibiotics	Standard bacterial culture, PCR for respiratory viruses, PCR for *M. pneumoniae* on respiratory tract materials; pneumococcal antigen testing on urine. Total number of patients in whom mentioned diagnostic tests were done was not described	4/100 (4%): positive pneumococcal antigen test 1/100 (1%): *S. pneumoniae* in sputum 2/100 (2%): *H. influenzae* in sputum 1/100 (1%): *M. pneumoniae* PCR positive in respiratory tract	Very low	Percentage potential community-acquired bacterial respiratory co-infection: 8%
Buenen et al.[22]	Prospective cohort study	N=107 Prospective registration of co-infections in COVID-19 patients presenting between 4 and 16 March at the emergency department	Co-infections were registered if microbiological test (culture, PCR) was positive, if there was clear bacteriuria or if there was a clinical diagnosis of a co-infection.	2/107 (1,9%) bacteraemia (*P. aeruginosa*, *S. pneumoniae*) 1/107 (0,9%) *H. influenzae* in sputum	Very low	Percentage potential community-acquired bacterial respiratory co-infection: 2.8%

		of Bernhoven hospital Uden	Total number of patients in whom mentioned diagnostic tests were done was not described			
China						
Chen et al.[23]	Retrospective, single-centre cohort study	N=99 Hospitalized adolescents (≥14 years) and adults between Jan 1 to Jan 20, 2020 diagnosed with COVID-19 according to WHO guidance and confirmed in the laboratory	Sputum or endotracheal aspirates were obtained at admission for identification of possible causative bacteria or fungi. Total number of patients with bacterial culture of respiratory tract not described	1/99 (1%) *A. baumannii, K. pneumoniae* in culture of respiratory material	Very low	Percentage potential community-acquired bacterial respiratory co-infection: 1%
Wu et al.[24]	Retrospective cohort study	N= 201 Patients with confirmed COVID-19, hospitalized in a single center in Wuhan, China between December 25, 2019, and January 26, 2020 Follow-up until February 13, 2020	Bacterial co-infection was based on sputum culture at admission in N=148 (74%)	0/148 bacterial co-infection	Very low	Percentage community-acquired bacterial respiratory co-infection: 0%
Huang et al.[26]	Prospective cohort study of hospitalized patients	N=41 Prospective registration of secondary infections in first 41 hospitalized, laboratory confirmed COVID-19 patients in a	Secondary infection: clinical symptoms or signs of nosocomial pneumonia or bacteraemia, combined with a positive culture of a new pathogen from a lower respiratory tract specimen	4/41 (10%) secondary infection. Pathogens were not reported	Very low	Percentage potential hospital-acquired bacterial respiratory co-infection during hospitalization: 10% or less

		designated hospital in Wuhan	(including the sputum, transtracheal aspirates, or bronchoalveolar lavage fluid, or from blood samples taken ≥48 h after admission)			
Zhou et al.[4]	Retrospective multicenter study of hospitalized patients	N=191 All adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 hospitalized in a single center in Wuhan, China and who had been discharged or had died by Jan 31, 2020	Secondary infection: clinical symptoms or signs of pneumonia or bacteraemia and a positive culture of a new pathogen in lower respiratory tract specimens or blood samples after admission Ventilator-associated pneumonia (VAP) was diagnosed according to the IDSA guidelines for treatment of hospital-acquired and ventilator-associated pneumonia[10]	<u>Secondary infections:</u> • 28/191 (15%) in the overall cohort • 27/54 (50%) in non-survivors • 1/137 (<1%) in survivors • Pathogens not reported <u>VAP</u> • 10/191 (5%) in the overall cohort • 10/32 (31%) in patients on mechanical ventilation • Pathogens not reported • Most patients with VAP received corticosteroids	Very low	Percentage potential hospital-acquired bacterial respiratory co-infection during hospitalization: • 10% or less in general • up to 50% in severely sick patients Percentage VAP during admission for COVID: • 5% in general • 31% in ventilated patients
Wang et al.[12]	Retrospective cohort study	N= 69 Patients with confirmed COVID-19, hospitalized in a single center in	Sputum cultures. Cultures were taken from N=29 (43%) Timing of sputum cultures not reported	2/29 (7%) *E. cloacae,* in sputum culture 1/29 (3%) *A. baumannii,* in sputum culture	Very low	Percentage potential bacterial co-infection during hospitalization: 10,3%

		Wuhan, China between January 16 and January 29 2020				
United States						
Kim et al.[25]	Retrospective cohort study	N=115 patients positive for SARS-CoV-2 Analysis on respiratory samples of 1092 patients submitted to CDC for SARS-CoV-2 testing and in which the analysis included broad PCR testing for respiratory pathogens The majority of patients was tested in an outpatient clinic or at the emergency department. None of the SARS-CoV-2 positive patients were admitted	Nasopharyngeal swabs tested on *C. pneumoniae and M. pneumoniae* (PCR)	0/115 (0%)	Very low	Percentage community-acquired respiratory co-infection due to atypical bacteria: 0%
Bhatraju et al.[27]	Retrospective cohort study	N=24 laboratory confirmed COVID-19 patients admitted to ICU in 9 hospitals in Seattle-area. Patients had at least 14 days of follow-up until March 23 2020	Chart review of microbiological diagnostics: bacterial culture of sputum (N=15), bronchial secretions (N=2) and blood (N=20) Timing of microbiological diagnostics not reported	Growth in bacterial culture: 0/15 (0%) from sputum 0/2 (0%) from bronchial secretions 0/20 (0%) from blood	Very low	Percentage of bacterial co-infections during first 14 days of hospitalization in ICU: 0%

References

1. Wiersinga WJ, Bonten MJ, Boersma WG, et al. Management of Community-Acquired Pneumonia in Adults: 2016 Guideline Update From The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). https://www.swab.nl/swab/cms3.nsf/uploads/6A6E127F9A2C1168C125816F004A013A/$FILE/CAP_SWAB_2017-DEF_R5.pdf.
2. Wiersinga WJ, Bonten MJ, Boersma WG, et al. Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). Neth J Med 2018;76:4-13.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
5. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest 2020.
6. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. Bmj 2020;368:m1091.
7. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol 2020.
8. Du Y, Tu L, Zhu P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. Am J Respir Crit Care Med 2020.
9. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.
11. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020.
12. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020.
13. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020.
14. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61-e111.
15. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. Clin Infect Dis 2011;53:42-8.
16. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis 2014;14:13.
17. Vollaard AG, E.; van der Linden, P.; Sinha, B.; de Boer, M. Medicamenteuze behandelopties bij patiënten met COVID-19 (infecties met SARS-CoV-2). https://swab.nl/nl/covid-192020.
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336:924-6.
19. Sieswerda E, Bax HI, Hoogerwerf JJ, et al. The Dutch Working Party on Antibiotic Policy (SWAB) guideline for empirical antibacterial therapy of sepsis in adults (draft). http://swab.nl/exec/file/download/1302020.
20. Van der Moeren N, Talman S, Van den Bijllaardt W, et al. The first 29 COVID-19-patients in a clinic: early experiences from a Dutch hospital. Ned Tijdschr Geneeskd 2020;164:D4981.
21. Murk J, Van de Biggelaar R, Stohr J, et al. The first 100 COVID-19 patients admitted to the Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands. Ned Tijdschr Geneeskd 2020;164:D5002.

22. Buenen AG, Wever PC, Borst DP, Slieker KA. COVID-19 in the Emergency Department of Bernhoven hospital. Ned Tijdschr Geneeskd 2020;164:D5001. .
23. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
24. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.
25. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. Jama 2020.
26. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
27. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020.
28. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. Bmj 2020;369:m1328.
29. Schuts EC, Hulscher ME, Mouton JW, et al. SWAB Guidelines for Antimicrobial Stewardship 2016.
30. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200:e45-e67.
31. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020:1-34.
32. Oostdijk EAN, De Jonge E, Kullberg BJ, et al. SWAB-Richtlijn: selectieve decontaminatie bij patienten op de intensive care. https://swab.nl/nl/selectieve-decontaminatie-sdd2012.
33. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19 Associated Pulmonary Aspergillosis. Am J Respir Crit Care Med 2020.
34. Verweij PE, Gangneux J, Bassetti M, et al. Diagnosing COVID-19-associated pulmonary aspergillosis. Lancet Microbe 2020;0.
35. Huttner B, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect 2020.