Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 26 (2020) 808–810

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

COVID-19: don't neglect antimicrobial stewardship principles!

B.D. Huttner [1, 2, *], G. Catho [2], J.R. Pano-Pardo [4], C. Pulcini [5, 6], J. Schouten [3]

[1)] Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland
[2)] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[3)] Radboud Center for Infectious Diseases; Intensive Care Department, Nijmegen, the Netherlands
[4)] Division of Infectious Diseases, Hospital Clínico Universitario, IIS Aragón, Zaragoza, Spain
[5)] Université de Lorraine, APEMAC, équipe MICS, F-54000, Nancy, France
[6)] Université de Lorraine, CHRU-Nancy, Infectious Diseases Department, F-54000 Nancy, France

ARTICLE INFO

Article history:
Received 4 April 2020
Received in revised form
17 April 2020
Accepted 21 April 2020
Available online 30 April 2020

Editor: L. Leibovici

The SARS-CoV-2 pandemic is currently dominating every aspect of health care across the globe, putting other longer-term public health issues—including the steady rise of antimicrobial resistance—in the shade. Yet, there will be a time after COVID-19, and we should not lose sight of problems that will persist and may potentially be exacerbated by this pandemic.

An important proportion of patients with COVID-19 present with fever and cough. Those requiring hospitalization because of dyspnoea usually present bilateral radiological infiltrates [1,2]. Despite the viral origin of COVID-19, a standard reflex by physicians is to start treatment with antibiotics, since cough, fever and radiological infiltrates are hallmarks of bacterial community-acquired pneumonia which requires antibiotic treatment. The anxiety and uncertainty surrounding the pandemic and the absence of antiviral treatments with proven efficacy are probably other contributors to the widespread and excessive prescription of antibiotics.

The rationale for antibiotic treatment in patients with COVID-19 seems to be based on the experience with bacterial superinfection in influenza, where most studies report initial co-infection or secondary bacterial pneumonia (11–35% of cases) in hospitalized patients caused mostly by *Streptococcus pneumoniae* and *Staphylococcus aureus* [3]. The exact incidence of bacterial superinfection in COVID-19 is unknown, and while there are anecdotal reports of documented bacterial superinfections the incidence seems to be much lower than in severe influenza [4,5]. Among 16 654 patients in Italy who died of COVID-19 (and as such the subpopulation with most severe disease) 'superinfections' were reported in 11% of cases (data as of April 09, 2020) (https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_9_aprile.pdf). In Wuhan, where the pandemic started, most patients with COVID-19 seem to have received antibiotics, mostly respiratory quinolones, although Chinese guidelines state "*inappropriate use of antibacterial drugs should be avoided, especially the broad-spectrum antibacterial drugs*" http://kjfy.meetingchina.org/msite/news/show/cn/3337.html [6]. Recommendations regarding the use of antibiotics in patients with suspected or confirmed COVID-19 vary by country, with some recommendations likely to encourage antibiotic use in a large proportion of patients (see Supplementary Material Table S1), particularly because it is unclear what 'pneumonia' means in the context of a viral infection that may cause radiological alterations even in asymptomatic patients; many guidance documents recommend antibiotic treatment for patients with COVID-19 and 'pneumonia' [7]. This scenario is worsened by the fact that health professionals involved in treating patients with COVID-19 have a high workload and show high levels of stress, and might therefore not be in a position to modulate clinical practice recommendations [8].

We acknowledge that—given the difficulty of differentiating COVID-19 from bacterial pneumonia, the uncertainty regarding bacterial superinfections, the lack of specific antiviral agents with proven efficacy, and the high mortality—antibiotics should be considered as part of the empirical treatment strategy for the most severe suspected or confirmed COVID-19 cases (e.g. patients with hypoxic respiratory failure requiring mechanical ventilation), provided their use is regularly re-evaluated. However, we believe that even during a pandemic antibiotics should be used responsibly and sparingly, given concerns about (a) the global supply chain of these valuable medicines potentially leading to antibiotics not being available for those who need them, (b) the increased nursing workload associated with parenteral administration of antibiotics,

* Corresponding author. B.D. Huttner, Division of Infectious Diseases, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205, Genève, Switzerland.
E-mail address: benedikt.huttner@hcuge.ch (B.D. Huttner).

https://doi.org/10.1016/j.cmi.2020.04.024

and (c) the many unintended negative long-term consequences associated with antibiotic overuse potentially leading to increased morbidity and mortality in the future.

In order to base antibiotic stewardship in the times of COVID-19 on a more evidence-based approach, several unmet research needs that could improve management of COVID-19 patients should be addressed as outlined in Table 1.

Until better evidence is available, we propose the following.

1. Antibiotics should be reserved for the patients with the most severe presentations (e.g. those with high oxygen demands and rapidly progressing respiratory failure). Biomarkers (C-reactive protein, procalcitonin) may play a role in deciding for which patients antibiotics can be withheld, but this needs further investigation. Patients without severe respiratory compromise should be managed without antibiotics. As in hospitals the diagnostic work-up often includes a thorax CT, this allows for a more exact determination of the typical infiltrate associated with bacterial lower respiratory tract infection as opposed to the typical glass ground opacities seen in COVID-19. This extra diagnostic (CT scan for conventional pneumonia patients is not common) should empower physicians to withhold empirical antibiotics in patients with characteristic images for COVID-19 on CT [9].
2. If antibiotics are started, microbiological tests should ideally be obtained beforehand (e.g. urinary antigen test for *Legionella*, blood cultures) although this has to be balanced with the potentially limited availability of these tests due to supply problems during the pandemic.
3. Antibiotic treatment should be rapidly re-evaluated and stopped as soon as possible if the probability of bacterial superinfection is considered low (e.g. persistently low inflammatory biomarkers, negative bacteriological tests, CT scan non-compatible with COVID).
4. If antibiotic treatment is continued, an oral switch should be performed rapidly if the patient is able to take oral medication, and the absence of fever should not be required as a criterion since patients with COVID-19 often show persistent fever over several days.
5. Antibiotic treatment duration should not exceed 5 days in most cases, as generally recommended in most guidelines for community-acquired pneumonia [10].
6. If antibiotics are considered, a β-lactam providing coverage for *S. pneumoniae* ± methicillin-susceptible *S. aureus* should be the first option (e.g. amoxicillin + clavulanic acid or third-generation cephalosporins). Once-a-day administration (where applicable) or continuous administration of β-lactam antibiotics should be considered to decrease the use of personal protective equipment which may be in short supply in many places. Macrolides and quinolones should be avoided because of their cardiac side effects—considering that other agents associated with cardiac side effects such as (hydroxy) chloroquine and lopinavir/ritonavir are used in many places notwithstanding the limited evidence for their efficacy—and impact on antimicrobial resistance. If atypical coverage is considered necessary (e.g. COVID-19 not yet confirmed and suspicion of *Legionella* infection) consideration should be given to doxycycline. However, routine atypical coverage does not seem warranted given the low *a priori* probability of superinfection with atypical pathogens [5,11].
7. For patients in intensive care units requiring mechanical ventilation, standard measures to prevent ventilator-associated pneumonia (VAP) and other healthcare-associated infections should be applied. Empirical treatment of VAP in these patients should be based on local and individual patient-level resistance data, and treatment should be adapted according to microbiological results (ideally from the lower respiratory tract).
8. Anecdotal data about the impact of azithromycin on SARS-CoV-2 viral load does not justify the routine administration of this antibiotic before confirmatory trials are completed.
9. Antibiotics should not be given 'prophylactically' to prevent bacterial pneumonia; use of selective digestive decontamination (SDD) may be an exception in intensive care units where this is established practice.
10. If during COVID-19 treatment a secondary respiratory worsening occurs, one should re-consider the use of antibiotics after taking adequate respiratory samples and performing radiological diagnostics. It is, however, important

Table 1
Research needs regarding COVID-19 and antibiotic steward

Research need	Study design	Challenges	Comment
(1) Establish the exact incidence of bacterial co-infection and superinfection at the different phases of the disease	Observational cohort study or in the context of randomized controlled trials assessing other interventions	Adequate diagnostics of lower respiratory tract infections require bronchoalveolar lavage (BAL) which may be difficult to perform (risk of respiratory deterioration, risk of exposure for healthcare personnel, resource constraints) Limited availability of bacteriological tests in the context of the pandemic)	• Ideally combined with (2)
(2) Assess the diagnostic performance of biomarkers to rule out/rule in bacterial superinfection	Observational cohort study or in the context of randomized controlled trials assessing other interventions	The reference standard (presence or absence of bacterial super-/co-infection) may be difficult to ascertain and may have suboptimal accuracy by itself: see (1)	• Ideally combined with (1) • Ideally studies should assess more than one biomarker
(3) Better understand the contribution of infection versus immune response in the different phases of COVID (first days after start of symptoms versus second week)	Observational cohort study or in the context of randomized controlled trials (e.g. of immune-modulating interventions such as steroids or IL-6 or IL-1 inhibitors)	See (1). Obtaining BAL samples may be challenging	
(4) Assess the impact of the COVID pandemic on antibiotic use and resistance in all settings (community, nursing homes, hospitals)	National, regional, local surveillance of antibiotic use and resistance based on established networks	Many confounding factors besides antibiotic use need to be taken into account (e.g. overcrowding of hospitals)	

to realize that secondary worsening commonly seen at day 7–9 is in most cases probably attributable to the hyper-inflammatory phase (adaptive immune reaction) rather than to a bacterial superinfection [12]. Other causes of respiratory worsening—such as cardiogenic failure (myocarditis is common), pulmonary embolism (thrombotic events are commonly reported) or fluid overload—should be ruled out.

11. Finally, it should be kept in mind that even during the COVID pandemic patients will present with other infections such as urinary tract infections, skin and soft tissue infections, intra-abdominal infections etc., and these should be considered in the differential diagnosis (especially in the elderly) and be managed according to established guidelines. Importantly, the suspicion of COVID-19 should not delay the adequate management of these patients.
12. National recommendations taking into account this stewardship perspective should be promoted, as well as sharing of best practices.

The COVID-19 pandemic puts a tremendous pressure on all healthcare professionals, not least on infectious disease and infection control specialists. We advocate that antibiotic stewardship principles will continue to be applied and promoted even in these challenging times.

Author contributions

BH and J: conceptualization; BH: writing—original draft; all authors: writing—review and editing.

Transparency declaration

The authors declare no conflicts of interest. No external funding was received for this communication.

Acknowledgements

We would like to thank Lorenzo Moja for his useful comments. This manuscript has been endorsed by the ESGAP (ESCMID Study Group Antimicrobial Stewardship) executive committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.04.024.

References

[1] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, Villamizar-Pena R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020:101623.
[2] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.
[3] Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Virus. 2016;10:394–403.
[4] Bhatraju P. Covid-19 in Critically ill patients in the Seattle region. New Engl J Med 2020. https://doi.org/10.1056/NEJMoa2004500 [Epub ahead of print].
[5] Rawson TM. Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020 May 2:ciaa530. https://doi.org/10.1093/cid/ciaa530. Online ahead of print.
[6] Zhang J, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. Lancet Respir Med 2020;8:e11–2.
[7] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425–34.
[8] Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open 2020;3:e203976.
[9] Claessens YE, Debray MP, Tubach F, Brun AL, Rammaert B, Hausfater P, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. Am J Respir Crit Care Med 2015;192:974–82.
[10] Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, 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:e45–67.
[11] Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA 2020. https://doi.org/10.1001/jama.2020.6266 [Epub ahead of print].
[12] Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, et al. Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. Invest Radiol 2020;55(6):332–9. https://doi.org/10.1097/RLI.0000000000000674.