

## Editorial | Uvodnik

**COVID-19 treatment: High time for Antimicrobial Stewardship Program****Liječenje COVID-19: pravo vrijeme za program upravljanja antimikrobnom terapijom**Nenad Pandak<sup>1</sup>, Vladimir Krajinović<sup>2</sup><sup>1</sup> Medicine Department, Infectious Disease Unit, Royal Hospital, Muscat, Oman<sup>2</sup> Department of Intensive Care Medicine and Neuroinfectology, University Hospital for Infectious Diseases „Dr. Fran Mihaljević“, Zagreb, Croatia**Keywords:**

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**Summary**

Last several months, the World is witnessing Coronavirus disease 2019 (COVID-19) pandemic caused by the newly identified Coronavirus. Due to the fast and easy disease spread as well as its severity, currently this pandemic is dominating every aspect of the global healthcare systems but also it outstandingly influences every side of our lives including the global economy. Almost all COVID-19 treatment guidelines advocate the rational use of antibiotics, but if we analyse the reports published so far, it is evident that about 70% up to even 100% of patients are treated with antibiotics. This antibiotic misuse highlights the urgent need for launching the Antimicrobial Stewardship Program in order to monitor the appropriate use of antibiotics. In this article, the authors suggest the postulates for implementing the antibiotic stewardship in COVID-19 patients.

**Sažetak**

Posljednjih nekoliko mjeseci svijet je svjedok pandemije COVID-19 izazvane novootkrivenim koronavirusom. Zbog brzog i lakog širenja bolesti, kao i njezine ozbiljnosti, trenutno ova pandemija dominira svim aspektima globalnih zdravstvenih sustava, ali također iznimno utječe na sve aspekte našeg života, uključujući globalno gospodarstvo. Gotovo sve smjernice liječenja COVID-19 zagovaraju racionalnu uporabu antibiotika, ali ako analiziramo do sada objavljena izvješća, očito je da se oko 70% pa čak i do 100% bolesnika liječi antibioticima. Ova zloraba antibiotika naglašava hitnu potrebu za pokretanjem programa upravljanja antimikrobnim lijekovima radi praćenja odgovarajuće uporabe antibiotika. U ovom članku autori predlažu postulate za primjenu programa upravljanja antibioticima u bolesnika s COVID-19.

Last several months the World is witnessing Coronavirus disease 2019 (COVID-19) pandemic caused by the newly identified coronavirus, severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The outbreak started in China at the end of 2019 but it spread worldwide within just few months. Until the middle of September 2020, more than 29 million people were infected and more than 900.000 people died<sup>[1]</sup>. COVID-19 clinical presentation varies from asymptomatic infections to a severe life-threatening disease. The majority of symptomatic patients present with fever and cough, but those requiring hospital admission, mostly due to dyspnea, usually have bilateral radiological chest infiltrates. Severe COVID-19 cases can present with acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS) and even death. The studies published so far reported that the case fatality rate of COVID-19 varies from 1.4% up to 4.3%<sup>[2]</sup>.

Due to the fast and easy spread of the disease as well as its severity, this pandemic is currently dominating every aspect of the global healthcare systems but also it outstandingly influences every side of our lives including the global economy. These are some of the reasons why physicians and scientists are so intensively struggling to find the efficient treatment to alleviate this disease, but so far none of the used medications are undoubtedly effective. The recommended treatment includes different antiviral drugs, corticosteroids, immunomodulatory drugs, low molecular weight heparin, as well as antibiotics.

The rationale for antibiotic treatment of COVID-19, which obviously is a viral disease, seems to be based on three different postulates. The first postulate is based on the previous experience with influenza caused by different influenza viruses, but also the experience with other Coronavirus respiratory diseases such as SARS and MERS. According to the previous

reports, in these viral pneumonias the bacterial infection was present as co-infection or superinfection in 11 – 35% of cases so the conclusion was that the similar proportion of bacterial infections is to be expected in COVID-19 too<sup>[3,4]</sup>. Although the knowledge gap about the bacterial infection during COVID-19 does exist, there are some published studies showing that the overall proportion of these infections during SARS-CoV-2 infection is low, especially in the disease early phase<sup>[5]</sup>. The majority of confirmed COVID-19 cases do not have bacterial coinfection at the patient's presentation to the hospital. As per the current limited knowledge, at the admission, bacterial coinfection is seen in approximately 3.5% COVID-19 patients, and usually it is caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae*. At the same time, coinfections with atypical bacteria (e.g. *Mycoplasma* spp, *Legionella* spp) are rarely reported<sup>[6]</sup>.

The other reason for antibiotic use in viral disease is a possible antiviral activity that some antibiotics showed *in vitro*. Azithromycin, a macrolide antibiotic has *in vitro* antiviral properties, such as decreased viral replication, due to blocking the viral entrance into the host cells. Another *in vitro* study demonstrated synergistic activity of the combination of hydroxychloroquine and azithromycin against SARS-CoV-2<sup>[7]</sup>. Several other clinical studies didn't confirm the benefit of azithromycin COVID-19 treatment, and because of the other possible side effects, like QT interval prolongation, this drug is not recommended to be empirically used<sup>[8]</sup>. Some authors even suggested the use of teicoplanin as the new potential anti-SARS-CoV-2 drug because it previously showed some antiviral activity against various viruses such as Ebola virus, influenza virus, flaviviruses, hepatitis C virus, HIV, and on Coronavirus such as MERS-CoV and SARS-CoV<sup>[9]</sup>. To the authors' best knowledge there are no published reports about the use of teicoplanin in COVID-19 treatment so far.

The usual differential diagnostic procedure is the third reason for the antibiotic treatment of COVID-19 patients. The majority of COVID-19 patients admitted to the hospital are significantly sick and sometimes it is extremely difficult to distinguish if the disease is of viral or bacterial origin. In everyday work, the usual inflammatory markers are used to distinguish between the two etiologies, yet, these parameters are not so helpful in COVID-19. Several studies showed that in COVID-19, without any bacterial infection, serum C-reactive protein levels can be very high, most probably as the result of intense immune response<sup>[10]</sup>. Similar to this, even serum procalcitonin levels might be high during the possible cytokine storm syndrome

(CSS) commonly seen in COVID-19, although procalcitonin is considered to be a rather specific acute phase reactant during bacterial infections<sup>[11]</sup>.

Almost all COVID-19 treatment guidelines advocate the rational use of antibiotics. If we analyse the published reports, it is evident that at least 70% of patients received antibiotics. This proportion goes even up to 100% of treated patients and highlights the urgent need for the introduction of the Antimicrobial Stewardship Program (ASP) in order to monitor the rational use of antibiotics and the adequate COVID-19 patients' treatment.

Suggested guidelines for the rational use of antibiotics in COVID-19

- 1 Antibiotics should not be routinely administered in patients with mild to moderate COVID-19 pneumonia.
- 2 Due to rather rare coinfections or superimposed bacterial complications in COVID-19 pneumonia, routine antibiotics should not be administered in patients admitted with severe COVID-19 pneumonia/ARDS. In case when the patient, who is already admitted for more than 48 hours, deteriorates and develops severe pneumonia/ARDS, empirical treatment for nosocomial infection has to be started as soon as complete sepsis workup is done. The choice of drug should be compliant to the antibiotic treatment guidelines and local bacterial resistance pattern. Daily clinical and laboratory assessment will help in deciding about the total duration of antibiotic treatment.
- 3 In cases where empirical antimicrobial therapy is prescribed in the setting of severe COVID-19 pneumonia, frequent clinical re-evaluations are mandatory in order to be able to discontinue the empirical antibiotic treatment, if the bacterial superinfection is ruled out. Generally, a total duration of empirical antimicrobial therapy should not exceed more than 5 days.
- 4 The samples for microbiological tests (blood cultures, sputum cultures, endotracheal secretion cultures, urine for legionella antigen detection) should be obtained prior to the introduction of antimicrobial therapy.
- 5 If the patient is admitted with severe COVID-19 pneumonia and empirical antibiotics are prescribed, ceftriaxone is the drug of choice due to *Streptococcus pneumoniae* coverage, and once daily administration which spares the personal protective equipment consumption. Macrolides and fluoroquinolones should be avoided due to the risk of QT interval prolongation. They

should be prescribed only if urine legionella antigen is positive. If coverage for atypical bacteria is needed, doxycycline is considered the drug of choice.

- 6 For patients who are mechanically ventilated and under ICU care, all measures should be dedicated to prevent ventilator associated pneumonia (VAP) and/or hospital acquired infection or pneumonia (HAI, HAP). In suspected cases of VAP, HAP or HAI, complete sepsis work-up should be done after which the empirical antibiotic treatment for nosocomial infections should be started immediately. Daily antibiotic treatment assessment is mandatory taking in consideration that possible CSS presentation mimics sepsis and/or septic shock. The duration of antibiotic treatment depends on clinical assessment, laboratory and microbiology test results.
- 7 Antimicrobial stewardship teams (AST) conducting the antimicrobial stewardship program (ASP) remains the integral part of the treatment decisions related to COVID-19 pandemic. The ASP activities are important for all COVID-19 patients, but especially for those hospitalized in the ICU setting. The AST work in developing the treatment protocols is essential for adequate treatment of COVID-19 patients and at the same time controlling the antibiotic consumption that influences the bacterial resistance spreading.

The only COVID-19 comprehensive solution shall be the efficient vaccine. Until it is available, we have to continue the treatment with medications that we have at present. This means that occasionally we are going to witness the antibiotic overuse and misuse, but we have to continue the hard work on implementing the ASP and appropriate antibiotic use in COVID-19 patients. Even when we succeed to prevent the SARS-CoV-2 infection with future vaccines, this pandemic should be considered as the turning point in human history as it clearly shows that only united humanity can overcome the global threat like this disease.

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