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EDITORIAL

# Possible scenarios of the development of antibiotic resistance in patients with urinary tract infection after the COVID-19 pandemic era

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## Abstract

An outbreak of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative pathogen for COVID-19 was reported at the end of December 2019 in Wuhan, Hubei province, China, and by March 2020, it was declared a pandemic COVID-19. In hospital and critical care department settings, the majority of patients with COVID-19 receive broad-spectrum antibiotics for treatment of secondary infection complications. In patients affected by COVID-19, who had a suspected secondary bacterial superinfection, antibiotics including teicoplanin, clarithromycin, doxycycline, azithromycin, tetracyclines, levofloxacin, moxifloxacin, ciprofloxacin, and cephalosporins 3d generation were proposed as an effective treatment. In this editorial, we will consider possible scenarios of the development of antibiotic resistance after the pandemic COVID-19 in patients with urinary tract infection (UTI).

**Keywords:** COVID-19, antibiotic resistance, urinary tract infection, bacterial superinfection

## Introduction

The World Health Organization (WHO) acknowledged that the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative pathogen for COVID-19, has the potential risk to spread worldwide and by 11 March 2020, the WHO designated the disease caused by this virus, coronavirus disease 2019 (COVID-19), to be a pandemic. [1, 2]. Pathogenesis of SARS-CoV-2 is related to the recognition of the receptor on the host cell membrane, through the CoV spike (S) glycoprotein on its surface. Subsequently, this leads to various clinical manifestations, including fever, dry cough, abatement and loss of olfactory and taste senses, pneumonia, respiratory failure, lymphopenia, and thrombotic complications [3-5]. In hospital and intensive care units (ICU) settings, the majority of patients with COVID-19 routinely receive antibiotics for treatment of secondary bacterial infection complications, including teicoplanin, clarithromycin, doxycycline, tetracyclines, levofloxacin, azithromycin, moxifloxacin, ciprofloxacin, and cephalosporins 3d generation. In one meta-analysis, Langford *et al*. demonstrated that fluoroquinolones and third-generation cephalosporins comprised about 74% of all antibiotics prescribed to patients affected by COVID-19 [6, 7]. In one study, Bardi *et al*. reported that the prevalence of urinary tract infection (UTI) in patients with COVID-19 hospitalized in the ICU was only 8% and *E. faecium* and *E. faecalis* were predominant bacterial pathogens. Meanwhile, in another study, Marand *et al*. demonstrated that about 41% of patients with COVID-19 had a positive bacterial urine culture without clinical symptoms of UTI, where *E. coli, Klebsiella pneumonia*, and Proteus were the most common uropathogenic [8, 9]. Nowadays, there are several reports about COVID-19-associated cystitis, which can be related to an increased release of urinary inflammatory cytokines or the direct interaction of SARS-CoV 2 with the mucosa of the urinary bladder [10-12]. In this Editorial, we will consider possible scenarios of the development of antibiotic resistance after the pandemic COVID-19 in patients with UTI.

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## The current level of resistance to different antibiotics for UTIs caused by common uropathogens

Traditionally, microorganisms of the Enterobacteriaceae family represent the most relevant etiological factors for different UTIs [13]. Nowadays, there are many of data about the level of resistance to different antibiotics. Despite on definitive success of antibiotic therapy for the treatment of UTI, antimicrobial resistance remains a main public health problem in the world [14, 15]. Among different multidrug-resistant microorganisms (MDM), E. coli is the most common causative pathogen associated with UTI, followed by Klebsiella spp, Enterococcus spp, and other gram-negative bacteria. Antibiotic resistance develops through the following mechanisms: efflux, exclusion, target modification, sequestration, and covalent inactivation [16]. The choice of treatment for UTIs is usually based on history, laboratory findings, results of a urinalysis and urine culture, and clinical presentation. Unfortunately, the majority of patients who developed a UTI, have generally recurrent upper and lower urinary tract infections. Nevertheless, current EAU and AUA guidelines cannot always provide detailed microbiological and clinical therapy for these clinical cases. To face this problem, urologists and general practitioners have tried to elaborate therapeutical schemes based on urine culture results and rates of antibiotic resistance. The increase or decrease in resistance rates to each specific antibiotic depends on the frequency of its use as empirical therapy. Table 1 summarized the results of different studies about rates of resistance for a widely used antibiotic for UTI caused by the most prevalent uropathogens.

## Potential adverse effects of COVID-19 on antibiotic therapy for UTI

Despite on implemented numerous infection control measures and prevention strategies, such as mask-wearing,

**Table 1.** The rates of resistance for widely used antibiotics for UTI caused by the most common uropathogenic.

| Reference | Pathogen | Rates of resistance (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | CIP | LEV | TMP/SMX | FM | CRO | AMC | NFT | CFX |
| Meena M *et al*. [13] | *Escherichia coli* | 72.5 | - | 78.75 | - | - | - | - | - |
| | *Klebsiella pneumonia* | 23.75 | - | 23.75 | - | - | - | - | - |
| Stapleton *et al*. [17] | *Escherichia coli* | 11.44-25.5 | - | - | - | - | 32.6-48 | - | - |
| Wong *et al*. [18] | *Escherichia coli* | 23.4 | - | 31.8 | 0.9 | - | - | - | - |
| Rossignol *et al*. [19] | *Escherichia coli* | - | - | - | - | 97.1 | - | - | - |
| Yang *et al*. [20] | *Escherichia coli* | 16.4-25.3 | 18.1-25.7 | 24.1-30.2 | 2.8-7.5 | - | - | - | - |
| | *Pseudomonas aeruginosa* | 59.4-63.3 | 56.3-61.2 | 71.4-78.1 | 3.1-4.1 | - | - | - | - |
| | *Klebsiella pneumonia* | 14.3-26.1 | 14.3-26.1 | 31.9-40.9 | 7.7-11.4 | - | - | - | - |
| | *Proteus mirabilis* | 13.8-19.5 | 12.1-14.6 | 22.4-46.3 | 0-7.3 | - | - | - | - |
| Rizwan *et al*. [21] | *Escherichia coli* | 62.16 | 51.35 | 75 | - | - | 33.33 | 10.41 | - |
| | *Klebsiella pneumonia* | 30 | 25 | 67 | - | - | 25 | 63.63 | - |
| Zilberberg *et al*. [22] | *Escherichia coli* | 43.5 | 43.5 | 36.9 | 0 | 15.1 | - | 6.7 | 5.1 |
| | *Klebsiella pneumonia* | 15.3 | 15.3 | 20.4 | 0.1 | 13.2 | - | 60.8 | 13.2 |
| | *Proteus mirabilis* | 55.6 | 55.6 | 40.7 | 0.1 | 7.9 | - | 73.7 | 7.9 |
| | *Pseudomonas aeruginosa* | 34.4 | 34.4 | 4.2 | 0 | 12 | - | 8.8 | 12 |
| Bahramian *et al*. [23] | *Escherichia coli* | 75 | 33.4 | 79.2 | 6.6 | 71.6 | - | 10.8 | - |
| Romero Palacios *et al*. [24] | *Escherichia coli* | 24.2 | - | 18.6 | - | 7.8 | - | 5.5 | - |
| | *Klebsiella pneumonia* | 6.4 | - | 8.2 | - | 6.4 | - | 63.6 | - |
| | *Proteus mirabilis* | 10 | - | 14 | - | 6 | - | 96 | - |
| Bitew *et al*. [25] | *Escherichia coli* | 50.4 | 55.6 | 70.4 | - | 34.8 | 45.2 | 20 | - |
| | *Klebsiella pneumonia* | 16.7 | 11.1 | 66.7 | - | 44.4 | 22.2 | 61.1 | - |
| | *Pseudomonas aeruginosa* | 33.3 | 0 | 100 | - | 100 | 100 | 100 | - |
| Al Wutayd *et al*. [26] | *Escherichia coli* | 56.1 | - | 49 | - | - | 72 | 14.6 | - |
| | *Klebsiella pneumonia* | 34.3 | - | 47.1 | - | - | 77.1 | 82.9 | - |
| | *Proteus mirabilis* | 58.8 | - | 58.8 | - | - | 64.7 | 94.1 | - |
| | *Pseudomonas aeruginosa* | 66.7 | - | 100 | - | - | 95.8 | 95.8 | - |
| Jalil *et al*. [27] | *Escherichia coli* | 35.4 | 82.9 | 53.7 | - | 89 | - | - | - |
| | *Klebsiella pneumonia* | - | 78.9 | 71.1 | - | - | - | - | - |

**Note:** AMC amoxicillin/clavulanic acid; CRO ceftriaxone; CIP ciprofloxacin; LEV levofloxacin; NFT nitrofurantoin; TMP/SXT trimethoprim/sulfamethoxazole; FM fosfomycin; CFX cefixime.

adequate hand hygiene, social distancing, rapid testing on COVID-19, and avoiding the large crowd of people, the rates of antimicrobial resistance are still increasing and the increased emergence of multi-drug resistant microorganisms is representing a huge health public problem during ongoing pandemic COVID-19 [28, 29]. Above 70% of patients with COVID-19 received antibiotic therapy; however, the rates of microbiologically confirmed bacterial co-infection did not exceed 20-30% [30, 31]. It is worth noting that 57-64.3% of all bacterial coinfections in patients affected by SARS-CoV-2 are localized in the genitourinary tract [32, 33]. During the pandemic COVID-19, both in non-ICU and ICU settings, clinicians used for the treatment of secondary bacterial co-infection following antibiotics: teicoplanin, clarithromycin, doxycycline, azithromycin, tetracyclines, levofloxacin, moxifloxacin, ciprofloxacin, and cephalosporins 3d generation. In a monocenter, retrospective study, third-generation cephalosporins, and amoxiclav represented the most used antibiotics in patients with COVID-19 admitted to ICU [34]. The study conducted in Cipto Mangunkusumo Hospital showed that antibiotics were prescribed to 82.4% of the patients with SARS-CoV-2, and macrolides, cephalosporins, and quinolones were administered in 33%, 25%, and 17% of the cases, respectively. Furthermore, azithromycin, ceftriaxone, cefotaxime, cefoperazone, levofloxacin, and moxifloxacin represented the most used therapy [35]. In one study, Khurana *et al*. reported the highest resistance of amoxiclav (84%), followed by levofloxacin (83%), ciprofloxacin (79%), and trimethoprim/sulfamethoxazole (75%). However, resistance in urine samples was highest for amoxiclav (100%) and nitrofurantoin (50%). The lower rates of resistance were reported for ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole in 16.7%, 25%, and 33.3% of the cases, respectively [36]. In COVID-19 clinic settings during the hospitalization period, there was a high rate of antibiotic prescribing and many patients received more than one antibiotic [37, 38]. The prevalence of hospital-acquired UTI in hospitalized COVID-19 patients was 89.6%. Catheter-associated UTIs were the most common type (55.5%) and bacterial coinfections were predominantly determined by *E. coli* and Enterococcus faecalis [39].

Despite low rates of bacterial coinfection, antibiotic overtreatment is still high and currently, there are no unified antibiotic stewardship programs during the ongoing pandemic COVID-19 [40, 41].

## Possible scenarios development of antibiotic resistance in patients with UTI after the pandemic COVID-19

As of 23 August 2022, there have been 594,367,247 confirmed cases of COVID-19 and 6,451,016 deaths globally. At the same time, 12,409,086,286 vaccine doses have been worldwide administered [42]. Nine mRNA vaccines based on the Wuhan-Hu-1 strain showed high efficacy against symptomatic cases of COVID-19. However, despite the successful COVID-19 vaccination strategies, there is still a global threat of emerging antimicrobial resistance due to the overconsumption of antibiotics in patients affected by COVID-19 [43-45]. Therefore, all healthcare and scientific societies should share guidelines in antibiotic therapy, which have to include as following: the monitoring of antibiotic prescribing practices and external benchmarking; staff education on appropriate antibiotic administration; antibiotic restriction with approval systems for broad-spectrum drugs and adequate feedback to the antibiotic prescriber.

Considering, the abovementioned trends of antibiotic resistance in patients with UTI alone or in association with SARS-CoV-2 infection, we hypothesized the following possible scenarios for the development of antimicrobial resistance (AMR):

1) Baseless administration of fluoroquinolones, third-generation cephalosporins, amoxiclav, and other antibiotics in patients with UTIs alone or association with SARS-CoV-2 infection may significantly increase current rates of antimicrobial resistance.

2) The successful COVID-19 vaccination significantly reduces hospitalization rates; however, injudicious use of antibiotics in patients with UTI may also increase the rates of antimicrobial resistance.

3) Significant reduction of resistance to the most commonly used antibiotics in the treatment of UTIs by the development of reliable guidelines for antibiotic treatment and by increasing the number of COVID-19 vaccinations (thus decreasing the hospitalization rates).

4) Low rates of COVID-19 vaccinations and overconsumption of antibiotics in the community may significantly increase antimicrobial resistance in patients with UTIs alone or association with SARS-CoV-2 infection.

## Conclusions

The development of unified reliable guidelines for antibiotic therapy including the treatment of UTIs as a single clinical event or in association with SARS-CoV-2 infection and an increased rate of COVID-19 vaccinated patients could represent the best way to decrease the rates of antimicrobial resistance of the commonly used antibiotic for treating UTI.

## Declarations

**Authors' contributions:** Contributed to the study conception and design: Krakhotkin D.V and Chernylovskyi V.A. Critical revision of the manuscript and editing: Francesco Greco and Shuhrat M. Halilov.

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