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

Krakhotkin D.V1, Chernylovskyi V.A2, Greco F3, Halilov S.M4

1Central District Hospital, Outpatient Department, Kamenolomni, Rostov Region 346480, Russia.

2Department of Urology 1, City Clinical Hospital No. 4, Dnipro 49102, Ukraine.

3 Urology Unit, Centro Salute Uomo, Bergamo, Italy

4Department of Urology, City Clinical Hospital № 1, Tashkent, Uzbekistan.

**Corresponding author:** Volodymyr A. Chernylovskyi City Clinical Hospital No. 4 31 Blizhnya St., 49102 Dnipro, Ukraine tel: +380973695672 e-mail: chernylovskyi@gmail.com

**Abstract**

An outbreak of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the causative pathogen for the 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’s settings, majority patients with COVID-19 receive broad-spectrum antibiotics for treatment 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 effective treatment. In this editorial, we will consider possible scenarios of the development antibiotic resistance after pandemic COVID-19 in patients with urinary tract infection (UTI).

**Key words:** 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 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 losing of olfactory and taste senses, pneumonia, respiratory failure, lymphopenia, thrombotic complications [3-5]. In hospital and intensive care units (ICU) settings, majority 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 the all antibiotics prescribed in patients affected by COVID-19 [6,7]. In one study, Bardi et al. reported that prevalence of 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% patients with COVID-19 had a positive bacterial urine culture without clinical symptoms of UTI, where E. coli, Klebsiella pneumoniae and Proteus were the most common uropathogenes [8,9]. Nowadays, there are several reports about COVID-19 associated cystitis, which can be related with an increased release of the urinary inflammatory cytokines or the direct interaction of SARS-CoV 2 with mucosa of the urinary bladder [10-12]. In this Editorial, we will consider possible scenarios of the development of antibiotic resistance after pandemic COVID-19 in patients with urinary tract infection (UTI).

**Current level of resistance to different antibiotics for UTIs caused by common uropathogens**

Traditionally, microorganisms of Enterobacteriaceae family represent the most relevant etiological factors for different UTIs [13]. Nowadays, there are many data about the level of resistance to different antibiotics. Despite on definitive success of antibiotic therapy for treatment of UTI, antimicrobial resistance still 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 to 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 urinalysis and urine culture, and clinical presentation. Unfortunately, the majority of patients who developed an UTI, have generally recurrent upper and lower urinary tract infections. Nevertheless, current EAU and AUA guidelines cannot always provide a detailed microbiological and clinical therapy for these clinical cases. In order 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. The table 1 summarized results of different studies about rates of resistance for 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 measure and prevention strategies, such as mask wearing, adequate hand hygiene, social distance, rapid testing on COVID-19, 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 worthy to note that 57-64.3% of all bacterial coinfections in patients affected by SARS-CoV-2 are localized in the genitourinary tract [32,33]. During 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 the 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 not unified antibiotic stewardship programs during ongoing pandemic COVID-19 [40, 41].

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

As of 23.08.2022 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 vaccine 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 of antimicrobial resistance due to 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 an 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 following possible scenarios of development of the antimicrobial resistance (AMR):

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

2) The successful COVID-19 vaccination significantly reduce the 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 an overconsumption of antibiotics in the community may significantly increase of antimicrobial resistance in patients with UTIs alone or in association with SARS-CoV-2 infection.

**Conclusions**

The development of unified reliable guidelines for antibiotic therapy including the treatment of UTIs as 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 treatment UTI.

**Declarations**

**Authors’ contributions:** Made a contribution to the study conception and design : Krakhotkin D.V and Chernylovskyi V.A.

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**Conflicts of interest:**

Krakhotkin D.V, Chernylovskyi V.A and Francesco Greco are members of the Editorial Board of Uro-Technology Journal. All authors declare they have no conflict of interest.

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