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Prevalence of microbial urinary tract infection associated with COVID-19 in hospitalized patients: An example from Biskra, Algeria

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ABSTRACT

Objective: To explore and contribute to the understanding of urinary tract infections (UTIs) associated with COVID-19, a frequent yet underreported complication.

Methods: This was a retrospective study carried out on 1,620 patients suspected to have a UTI, who consulted at Hakim Saadane Hospital of Biskra (Algeria) during the year 2021. Our attention was on the refined population with a positive cytobacteriological examination of urine and COVID-19 admission, where an examination of microbial prevalence was done.

Findings: Statistical analysis of our data showed three main detected groups: Gram-negative bacteria, represented mainly by Enterobacteriales and *Pseudomonas aeruginosa*; Gram-positive bacteria, including *Staphylococcus aureus*; and a Candida group, mostly constituted by *Candida albicans* and *Candida spp.* UTI in COVID-19 patients was characterized by a significant decrease ($p<0.05$) in Gram-positive bacterial prevalence and a clear increase in Candida prevalence.

Conclusions: More studies must be conducted on UTI superinfections with COVID-19 to prevent severe outcomes and establish the ideal treatment.

KEYWORDS: COVID-19; Microbes; Urinary Tract Infection

1. INTRODUCTION

Urinary tract infection (UTI) is one the most frequent bacterial infections and it engenders commonly the need of hospitalization [1].

The COVID-19 infection extension all over the world, and the very heavy outcomes on the health sector and on communities that succeed it, needed to take strict measures to reduce its consequences and control it. The main measurement followed by hospitals was the decline in hospitalization admissions [2]. Despite that, urinary tract infections prevalence was not diminish by applying these preventative measures [3], in addition to that, the need of hospitalization and medical care was required in many cases. On one hand, infections caused by bacteria can aggravate COVID-19 expectations and viral infections are usually discerned as risk factors for attendant bacterial infections [4]. On the other hand, among cells infected by SARS-CoV-2, the renal cells, and kidneys may be an essential target organs for infection [5].

However, there are two kinds of bacterial infections related to COVID-19 or other viral infections; first, co-infections are the result of harmed immune systems, the respiratory tract mucosa damage, and elevated colonization in the nasopharyngeal, and second, super-infections, which are usually healthcare-associated infections [4]. In this regard, all UTIs were categorized as urinary tract co-infection (community-acquired UTI) or urinary tract super-infection (hospital-acquired UTI) [6], which are one of the most frequent types of infections remarked among patients with COVID-19 [07].

Urinary tract infection in patients stricken with COVID-19 has not been inspected accurately. A larger number of the actual studies have focused on pneumatological infection, while more attention should be directed to UTIs superinfected with COVID-19.

In this work, we presented a retrospective study on UTIs associated with viral infection (SARS-CoV-2) to survey the impact of the incidence on microbe’s prevalence.

2. METHODS

2.1. Participants

The present work is a retrospective study established on data collected from the bacteriology laboratory at Hakim Saâdane Hospital of Biskra city (Algeria). The study was approved by the Institutional Review Board.

The study involved patients suspected of having a urinary tract infection. Confirmed cases, with a positive cytobacteriological examination of urine: CBEU, were chosen and split into associated or not with various health cases: diabetes, cardiovascular disease, kidney stones, high blood pressure, pregnancy, and patients with COVID-19 infection, who have consulted the bacteriology laboratory (external and internal) in the period extended from January 2021 to December 2021. Cases with COVID-19 infection were retained in the internal service of the hospital to be treated according to the COVID-19 protocol. We were interested in examining the identified microbes prevalence found in cases with or without infection with the coronavirus. Prevalence with or without COVID-19 infection was analyzed, to see if a super-infection with COVID-19 can influence and affect it.

2.2. Data collection

According to the WHO report about the pandemic situation in Algeria, which is based on the Algerian Ministry of Health reports, Biskra was among the most affected cities by COVID-19, and it was concerned of the total and partial lock down many times. The number of confirmed cases during the period extending from February 2020 to October 2021 was about 4000 cases. That's why makes Biskra's city an interesting study center. Hospital Hakim Saadane was the main hospital for receiving, checking, and treating COVID-19 patients in the City, during this pandemic.

All the necessary data over the year 2021 were collected from the bacteriology laboratory, in both internal and external services, where informations on patients' medical conditions are registered on a database.

2.3. Statistical analysis

The significance of differences between percentages was analyzed by using the two samples Z-test. Percent change was also calculated. For these purposes, Excel 2010 and SPSS Statistics program version 25 were used. The difference was considered significant at $p < 0.05$.

3. RESULT AND DISCUSSION

Figure 1 represented the studied population flow chart. From a population of 1620 cases suspected to have a urinary tract infection, 809 patients were declared positive after a CBEU, which represented half of the total population. This equality found between both positive and negative CBEU can be considered very important.

In the cases described as having urinary tract infection, we have found 312 (39.61%) persons with medical history recording having other diseases in the same time or health conditions, such as diabetes, high blood pressure, cardiovascular issues, kidney stones, pregnancy and infection with COVID-19. Those cases were designated as "Associated urinary tract infection (AUTI)". The "not associated urinary tract infection (NAUTI) cases represented a higher prevalence than the AUTI and which equals 60.39%. The prevalence of patients noted having a UTI associated with infection by COVID-19 was equal to 62.17% which is counted high against an inferior prevalence (37.82%) of patients having UTI associated with other diseases or health conditions (AHC). Urinary tract infections associated with COVID-19 are among the most recurrent super-infections [8]. The refine population (AUTI-COVID-19) has got the biggest interest in our study, they were in the internal service (hospitalized), Their prevalence, calculated from the initial population (194/1620), was estimated at approximately 12%, which is in accordance with results reported by Laethem et *al*. (2021) [9], where prevalence equal to 13% from a total of 622 patients. Kraba et *al*. (2021) [08] have found a prevalence less than the two mentioned and equals 3%, in their study on a total of 1016 adult patients admitted to 5 hospitals. High prevalence can be attributed to overdiagnosis.

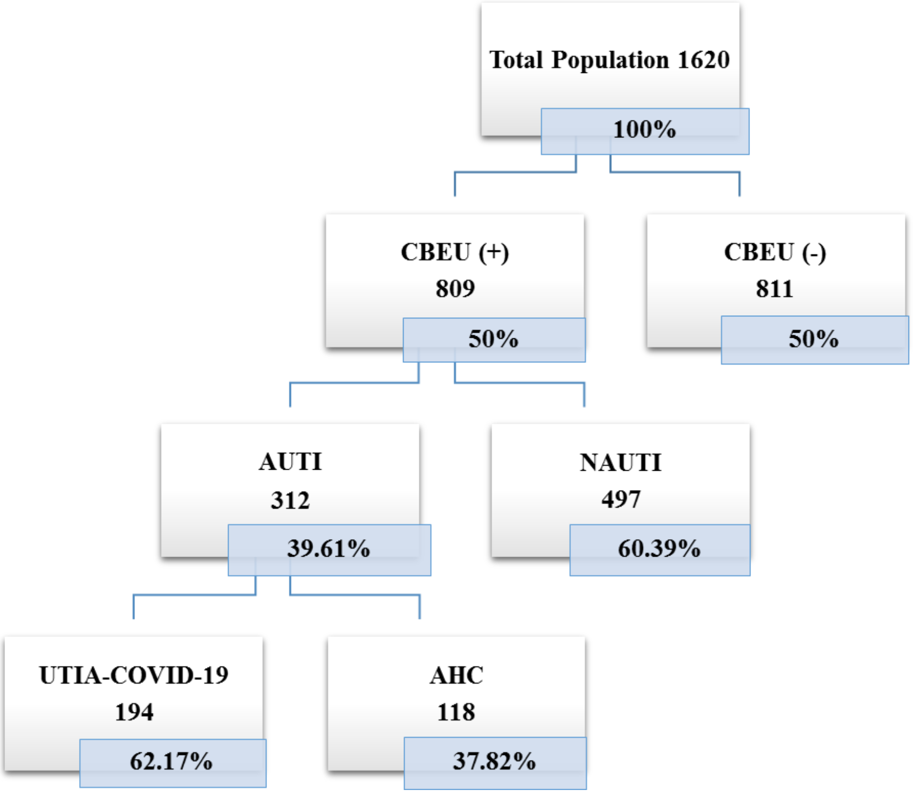

Figure 1. Study population flow chart

The urine cultures of patients having UTI, not associated with other infections or diseases, contain a variety of microorganisms, almost, resistant to antimicrobials. Microbial genera the most usual existed are *Escherichia coli*, *Proteus*, *Klebsiella*, *Pseudomonas*, *Serratia*, *Acinetobacter*, *Staphylococcus aureus*, and *Enterococci*, and many of these germs are more often related to nosocomial infections [09].

Besides, the most commonly isolated microorganisms in urinary tract infections associated with COVID-19 were *P. aeruginosa*, *E. coli*, *Klebsiella spp*., *S. aureus*, and *C. albicans* [10]. In this study, urine cultures of patients had shown the presence of various uropathogens, from negative Gram (Enterobacteriales and others) as well to positive Gram (Table 01). Negative gram bacteria, almost belong to Enterobacteria (*E. coli*, *E. cloacae*, *P. aeruginosa*, *P. spp*., *P. mirabilis, K. pneumonia*, *M. morganii*, *S. marcescens*, *A. baumannii*, *A. pneumonia*, and *A. spp.), were detected with very close percentages that equal to* 49.09 *% and 47.94% in NAUTI and AUTI*-COVID-19 *respectively. A no significant difference was confirmed statically with a p-value > 0.05 (Table 01). E*nterobacteria's prevalence was higher (74%) in isolated microorganisms from urine samples, in a study realized by Laethem et *al*. (2021) [09], on a total of 79 patients having COVID-19 admissions and UTI.

P. aeruginosa, as it is mentioned previously, is a very common isolated bacteria in both UTI and COVID-19*. In this study, we did not find a notable change in the prevalence of this species when UTI is associated with* COVID-19 *(Table 1). It was clinically proven that* patients with COVID-19, can develop a *P. aeruginosa* UTI as a result of renal calcification and obstruction [11], in addition, *P. aeruginosa* is considered extremely drug-resistant [12].

The ability of Gram-negative bacteria to develop UTI pathogenesis can be attributed to their Pili, which are extracellular appendages located on the outer membrane, one of their role is to mediate colonization of the bladder epithelium and eases the biofilm elaboration, formed all over and inside the infectious stone, and as consequence, the biofilm inhibits antibiotics penetration [13].

In addition, urine samples shown containing positive gram bacteria (*E. faecium*, *E. faecalis*, *Staphylococcus aureus*, *Streptococcus viridians*, *Sreptococcus* group *B, and Eubacterium aerofaciens*) (Table 01) with a clear difference between NAUTI (14.28%) and AUTI-Covid 19 (4.12%), the significance of this difference was important (p= 0.00002) where positive Gram bacteria percentages in urine samples of positive COVID-19 patients was lower than that found in NAUTI. In general, all bacteria groups, found in this study, have experienced a decrease in their percentages. This can be explained by the follow-up of preventive procedures, like the wearing of facemasks and the use of handwashing, after the pandemic diffusion, which has reduced the spreading of bacteria. Despite that, urinary tract infection prevalence was not diminished, even after the commitment of preventive measures [3].

Fungi, notably from *Candida*'s genius, were identified in urine samples (*C. albicans, C. spp, C. tropicalis*, and *C. lipolitica*) with high proportions as it's about an associated or not associated urinary tract infection, but a distinct and significant difference was observed between NAUTI (30.18%) and AUTI-COVID-19 (39.69%) where p= 0.0178 (Table 01). It is well known that *Candida* species occupy the mucosal surfaces of the body, especially the skin, in addition to the respiratory, digestive, and urinary tracts [14]. Moreover, opportunistic fungal super-infections are recurrent in COVID-19 patients, it may be the consequence of immunosuppression status, central venous catheters, prolonged stays in intensive care units, and broad-spectrum antibiotics [15, 16].

Table 1. Microbe's prevalence by groups in NAUTI and AUTI-COVID-19

Microbes group	**NAUTI % n=497**	**AUTI-COVID-19 % n=194**	**Percent change %**
Enterobacteriales	49.09 (244)	47.94 (93)	-2.34 (p*=0.802)
Other negative gram bacteria	6.44 (32)	5.67 (11)	-11.95 (p*=0.701)
Positive gram bacteria	14.28 (71)	4.12 (8)	-71.15 (p=0.00002)
Candida	30.18 (150)	39.69 (77)	+31.51 (p=0.0178)

E. coli had the highest percentage in both NAUTI (35.61%) and AUTI-COVID-19 (33.5%), without any statistical significance (p > 0.05) (Table 02). The multidrug-resistant *E. coli* was the most common bacteria found in COVID-19 super-infection (54%) [09].

K. pneumonia, *C. albicans*, and *C. spp*. were also marked by elevated percentages in associated and not associated cases, their values equal to 10.86%, 17.9%, and 12.07% respectively in NAUTI, while they equal to 7.53%, 20.62%, and 18.55% successively in AUTI-COVID-19, without any significant statistical difference marked (p > 0.05) in *K. pneumonia*, *C. albicans* prevalences (Table 02). Urinary and respiratory tract infections produced by the multidrug-resistant *K. pneumoniae* have occurred a great interest and have become a highly charged by many public health structure, specifically in hospitals [17].

It was reported that, after *Escherichia coli* and *Enterococcus* species, *Candida*'s species were to be the third most frequent microbe identified in urine [18].

Results have indicated an increase of about +34.93% in *C. spp*. portion regarding the associated cases with SARS-COV-2 compared to those not associated, this increase was statistically considered very important (p=0.0307) (Table 02). In fact, among *candida*'s genius, *Candida albicans* is the main detected species in 17% of patients hospitalized in Intensive Care Units [14]. However, Infections by other species of the genus *Candida* are becoming recurrent [19]. Part of studies propose that more than19% of COVID-19 patients can catch fungi infections in the hospital [20]. In addition to that, treating other infections with antibiotics may empower the fungi's growth by destroying bacteria [21].

Compared to bacterial and viral co-infections, fungal co-infections appear to be imply in worsen consequences in COVID-19 patients [19]. That's why it should be taken seriously.

The presence of *P. mirabilis* has increased by about +95.69% when patients have UTIs associated with COVID-19, which is found highly significant (p= 0.00006) (Table 02). Many virulence factors are used by *P. mirabilis*, to start an infection in the bladder, comprising adhesive mannose-resistant Proteus-like MR/P fimbriae and flagella [22].

M. morganii was identified in a small percent in both NAUTI and AUTI- COVID-19 cases, with a little increase in AUTI- COVID-19 prevalence, without any statistical significance ($p > 0.05$) (Table 02). It was reported that *M. morganii* is a non-negligent opportunistic pathogen that mostly generates multiple infections like urinary tract infections and it was found in the Faecal samples of COVID-19 patients [23, 24].

Gram-positive bacteria *Streptococcus* group B was found in 4.83% in NAUTI, while it decreased and equals to 2.58% in AUTI-COVID-19 (Table 03). The prevalence of this bacteria detected in urine was ranging from 0.72% to 2.1%, in other studies [25, 26]. UTIs caused by *Streptococcus* group B were rare [27].

A statically significant diminish was observed in *Enterococus Faecium* prevalence, in AUTI-COVID-19 when comparing it with NAUTI (p = 0.012) (Table 02). It was demonstrated that *Enterococci* use fibrinogen, located on the urinary catheter, as a nutrient source, promoting their multiplication in urine, and making them involved in nosocomial infection [28].

We have noted the existence of *Enterobacter Cloacae*, *Enterococus Faecalis* and *Candida tropicalis* in low values (2.58%, 1.03%, 0.51% successively) just in urine samples of patients with AUTI-COVID-19, this observation was statically significant only in regards to *Enterobacter Cloacae* (p = 0.00003). *Enterobacter Cloacae* is designed as a multidrug-resistant bacteria [07]. It was one of the most common bacteria in Carbapenemase-producing Enterobacterales infections, and this type of infection was frequent in COVID-19 patients [29]. Whereas, the NAUTI cases have been characterized by microbes like *Serratia marcescens*, *Acinetobacter baumannii*, *Acinetobacter pneumonia*, *Pseudomonas spp.*, *Staphylococcus aureus*, *Eubacterium aerofaciens*, *Streptococcus viridans and Candida lipolitica*, in small amounts, which are not found in AUTI-COVID-19 cases. The statistical significance of this remark was considerable in regards to *Acinetobacter pneumonia* (p=0.0002) (Table 2).

Also, *Staphylococcus aureus* has been distinguished in an interesting percentage (5.63%) in NAUTI cases, while it was absent in AUTI- COVID-19 cases. The difference was statistically a high significant (p= 0.00004) (Table 02). The same result was announced by Laethem et *al*. (2021) [09] who have not noticed *S. aureus* in super-infection at COVID-19.

Table 2. Microbe's prevalence in NAUTI and AUTI-COVID-19

Microbe Species	**NAUTI % n=497**	**AUTI-COVID-19 % n=194**	**Percent change %**
Escherichia. Coli	35.61 (177)	33.5 (65)	-6.30 p*=0.271
Klebsiella pneumonia	10.86 (54)	7.73 (15)	-40.49 p*=0.183
Proteus mirabilis	0.2 (1)	4.64 (9)	+95.69 p*=0.00006
Enterobacter cloacae	0	2.58 (5)	0 p*=0.00003
Morganella morganii	0.2 (1)	1.03 (2)	+80.58 p*=0.183
Serratia marcescens	0.4 (2)	0	-100 p*=0.741
Acinetobacter baumannii	0.2 (1)	0	-100 p*=0.441
Acinetobacter pneumonia	1.41 (7)	0	-100 p*=0.0002
Acinetobacter spp.	0.2 (1)	1.03 (2)	+80.58 p*=0.087
Pseudomonas aeruginosa	5.83 (29)	5.67 (11)	-2.82 p*=0.960
Pseudomonas spp.	0.6 (3)	0	-100 p*=0.230
Staphylococcus aureus	5.63 (28)	0	-100 p*=0.00004
Streptococcus groupB	4.83 (24)	2.58 (5)	-87.20 p*=0.211
Eubacterium aerofaciens	0.6 (3)	0	-100 p*=0.230
Streptococcus viridians	0.2 (1)	0	-100 p*=0.441
Enterococcus faecium	3.02 (15)	0.51 (1)	-492 p*=0.012
Enterococus faecalis	0	1.03 (2)	0 p*=0.087
Candida albicans	17.9 (89)	20.62 (40)	+13.19 p*=0.412
Candida spp.	12.07 (60)	18.55 (36)	+34.93 p*=0.0307
Candida tropicalis	0	0.51 (1)	0 p*=0.096
Candida lipolitica	0.2 (1)	0	-100 p*=0.441
Total	497=100%	194=100%	

Note. p: p-value for "two samples Z test"*

The involvement of *S. aureus* in developing pneumoniae has been reported in many kinds of research [30, 31]. It is one of the infectious agents, as well as *Streptococcus pneumonia*, which infected about 1.2–2.1% of COVID-19 patients [10]. The nonexistent of *S. aureus* is probably due to the use of some antimicrobials that affect this bacteria species. During the pandemic, the Algerian ministry of health urged hospitals to prevent co- or super-infections with COVID-19 by administrating Azithromycin [32]. This antibiotic was found to have the capacity to decrease the number of viable *S. aureus* bacteria [33].

Besides, Azithromycin is a broad-spectrum antibiotic that is effective against Gram-positive, Gram-negative, and atypical bacteria [34], that's, probably, the cause of disappearance or the percentages decrease of some bacteria in AUTI- COVID-19, remarked in this study.

We just can make some suggestions to explain the incidence of the apparition of some bacteria species or the increase in their percentages in AUTI-COVID-19 cases, compared to those in NAUTI. During this pandemic, the earlier prescription of antimicrobial treatments was pursued by hospitals, to decline the number of hospitalized cases and consequently avoid the dispersion of SARS-CoV-2 infection. Antibiotics with a broad spectrum have been more commonly used in patients with suspected UTIs [03]. Many studies have demonstrated that the use of antimicrobial therapy was not consistent with the real prevalence of bacterial co-/super-infection among COVID-19 patients, it was quite abused [35]. For example, data from China on SARS-COV-2 cases, indicate that approximately 70% of the patients received antimicrobial therapy, whereas, under 10% faced bacterial or fungal co/super-infection [36]. Moreover, antibiotic consumption is directly correlated with the rise in bacterial resistance levels [37]. Furthermore, studies indicate that COVID-19 can offensive the immune system, and conducts an immunosuppression [38], which could, partially, explains the patients' predisposition to infections.

Many factors can increase the occurrence of co-/super-infections, especially in hospitals, such as urinary catheters. It was demonstrated that COVID-19 patients with hospital-acquired UTIs (super-infection) represented 89.6% of the total of 87 admitted COVID-19 patients with UTIs, in study conducted by Pollan et al., (2022) [06], and 67.9% of super-infections were related to urinary catheters. The longer length of hospital stay, the administration of certain medications, such as steroids, immunomodulatory agents, and the poor infection control practice in hospitals may also increase hospital-acquired co/super-infections [39, 40] which may worsen COVID-19 disease gravity, extend the healing time of patients, and conduct to excessive mortality rates [40].

Three years have passed since the SARS-COV-2 apparition and spreading in all world's corners. Until now many parts of the pandemic are not clear, it is the case of co/super-infections, notably, the association of bacterial or fungal infections with the viral ones.

This retrospective study have revealed the predominance of negative Gram bacteria, especially *E. coli*, *K. pneumonia*, and *P. aeruginosa* in the two cases (associated and not associated). Besides, a highly significant decrease in positive Gram bacteria' prevalence when it's about super-infection. An elevation in *Candida*'s prevalence rate was remarked, also, in AUTI-COVID-19.

More attention should be aimed at UTIs associated with COVID-19, and more studies must be done to understand this incidence, for the reason to select the appropriate antimicrobial treatment, without developing a multidrug resistance and to reduce its outcomes which may in some cases lead to the enlargement of mortality rate.

4. CONCLUSIONS

Three years have passed since the SARS-COV-2 apparition and spreading in all world's corners. Until now many parts of the pandemic are not clear, it is the case of co/super-infections, notably, the association of bacterial or fungal infections with the viral ones.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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