Management of Acute Cystitis in the Era of COVID-19

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Abstract
Purpose of Review No specific guidelines have been developed for acute cystitis management during the COVID-19 pandemic. This review aims to provide up-to-date information about treatment and follow-up in patients with symptoms suggesting lower urinary tract infection.

Recent Findings Uncomplicated cystitis does not need microbiological confirmation; thus, clinical diagnosis via telephone interview or questionnaires may be done. When complicated infections are suspected, in-person evaluation or close follow-up is mandatory. Antibiotic treatment is still the gold standard for treatment, although non-pharmacological strategies have also been suggested and further investigations are warranted.

Summary Urinary tract infections are still a frequent reason for consultation that needs to be addressed in both primary care and specialized levels. Their management during the pandemic is similar than in precedent years, but telehealth options have emerged which can facilitate diagnosis and treatment.

Keywords COVID-19 · Urinary tract infection · Cystitis · Diagnosis · Treatment

Introduction
Urinary tract infections (UTI) account for different syndromes caused by the colonization of the urinary tract by uropathogenic bacteria leading to inflammation and subsequently appearing urinary symptoms. Acute cystitis and pyelonephritis in non-pregnant women without anatomical or functional urinary tract abnormalities are defined as uncomplicated UTI, while the rest are classified as complicated UTI [1]. Up to 80% of women will suffer at least one UTI episode during their lifetime, and around 40% will be affected by recurrent UTIs (three episodes per year or two in the last 6 months) with an average rate of 2.6 UTIs per year [2–4]. These uncomplicated UTIs generate more than 10 million ambulatory visits per year in the USA; therefore, its impact in primary care setting is remarkable.

Since the beginning of 2020, more than 504 million COVID-19 cases have been documented worldwide, including 6.2 million deaths [5]. COVID has had an enormous impact at all levels of health care systems worldwide. Human and economic resources have been deviated to fight the pandemic in primary care, emergency departments, and intensive care units, while non-COVID cases were downscaled and even completely halted in the worst pandemic peaks [5].

However, common infectious pathologies such as urinary tract infections (UTI) are supposed to maintain a high prevalence during pandemic, and probably many of the uncomplicated UTI episodes during the COVID-19 pandemic may have

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received a suboptimal or virtually no treatment. But the effects of this exceptional situation could go far beyond the lack of access to adequate health care. Theoretically, this reduction in ambulatory antibiotic prescription and reinforcement of hygiene and infectious control measures should have reduced the rise in antibiotic resistances and the spread of multidrug-resistance bacteria. Nonetheless, during the first months of COVID-19 pandemic, general antibiotic consumption fell according to data from the USA and UK [6, 7].

However, some studies have revealed an over prescription of broad-spectrum antibiotics in both outpatients and hospitalized patients with COVID-19 [8, 9••], even when the presence of bacterial coinfection is infrequent (<10%) [10, 11]. Furthermore, adherence to antimicrobial stewardship programs diminished drastically during the first wave, especially in the hospital setting, and antibiotic prescription prevalence of quinolones, cephalosporins, macrolides, and betalactamases associated with beta lactamase inhibitors has been as high as 74% in COVID-19 patients [12••]. This practice is very likely to facilitate the development of multidrug-resistant bacteria, as previous antibiotic exposure is a well-established risk factor for antimicrobial resistance increase in uropathogenic bacteria [13, 14]. Moreover, there are reports of increasing numbers of carbapenemase-producing enterobacteria in patients hospitalized with severe COVID-19 [15].

The implementation of telemedicine as the main source of access to primary health has increased tremendously, being rapidly incorporated into day-to-day practice. Within urological diseases, efficacy and safety of telemedical management of UTIs has been specifically addressed, showing good results with almost 80% of patients showing complete resolution of symptoms and only 8% requiring face-to-face consultation because of symptoms persistence and/or suspected bacterial resistance [16]. However, telemedical management of UTIs could have also some essential drawbacks. According to the results from the University of Pittsburg Medical Center, urinalysis and urine culture were less likely to be ordered in electronic vs office visits (8% vs 51%), while physicians were much more likely to prescribe antibiotics (99% in teleconsultations vs 49% in in-office consultations) [17••]. We could consider this as a “suboptimal management” of UTIs, especially in complicated or recurrent cases.

With the aim of improving antimicrobial stewardship interventions, we must reduce inappropriate antibiotic prescriptions. It is also needed to evaluate community urine culture data and antibiograms to understand antimicrobial resistance patterns to provide the best possible treatments. Although urine culture is not mandatory in the case of uncomplicated sporadic acute cystitis, it is always recommended in the case of recurrent and complicated UTI [1]. Optimizing diagnosis and thus management of UTIs, especially acute cystitis which is the most prevalent, is of paramount importance taking into account that around 25% of all antibiotic prescriptions are made to deal with UTIs [18].

**Diagnosis and Management**

### Uncomplicated UTI

It has been shown that a symptom-based diagnosis has a high positive predictive value for uncomplicated acute cystitis. Bent and colleagues found that women in childbearing age complaining about dysuria, frequency and/or hematuria, and not complaining about vaginal discharge or vaginal irritation, have a probability of having a UTI of over 90% [19]. Furthermore, some factors can increase the probability of having a UTI, as recent sexual intercourse, a new sexual partner or the use of spermicides [20]. On the contrary, the presence of fever or back pain in a woman with dysuria points out to an upper urinary tract infection, that is, a complicated UTI, rather than an uncomplicated UTI [21].

Given the broad availability and low costs of urine dipstick, some international societies recommend it in order to increase the diagnostic accuracy [22, 23], but due to its high false positive and false negative rates, others consider it only when diagnosis is not clear [24•, 25].

Therefore, a reliable diagnosis of cystitis can be made in a woman based only on a focused investigation of her symptoms by a phone interview. In fact, several protocols have been developed in order to simplify the diagnosis of uncomplicated acute cystitis [26, 27, 28] and some have been already used for telephonic or internet diagnosis.

Telephonic diagnosis has been proven to have a high sensitivity and specificity to predict a non-complicated UTI [26, 27] and a similar capacity than office-based visits of differentially diagnosing upper urinary tract or complicated UTIs and gynecologic problems [29•]. The telephonic approach also has the same cure rates than office-managed cystitis, without increasing repeated visits or hospital admissions [16, 29•, 30].

One study assessing antibiotic prescription rates for sore throat, dysuria, or respiratory symptoms in a large private health care provider in Sweden, including 3847 electronic visits and 759 office visits, found no differences in antibiotic prescription rates between the two modes [31]. However, other studies have found a much higher antibiotic use at virtual visits for urinary symptoms as reported by Mehrrotra et al. [17••].

### Complicated UTI

Complicated UTIs occur in individuals with functional or anatomical factors that could make more difficult to eradicate infection, including men and pregnant women. These patients...
may have atypical symptoms, especially neurogenic and catheterized patients [32••, 33]. Criteria for complicated UTI can be identified through a thorough clinical history, even during a virtual visit. Studies examining the efficacy of telephone-based management of acute cystitis and involving patients with some criteria of complicated UTIs such as diabetes, pregnancy, or male gender [28, 34, 35] did not find an increased risk of upper UTI or sepsis in that cohort [34].

Patients with complicated UTI should undergo additional diagnostic tests, including at least a urine culture with antimicrobial susceptibility testing (AST) due to the high resistance rate of microorganisms causing these infections [36]. The current criteria to order these tests are (i) suspected acute pyelonephritis, (ii) symptoms that do not resolve or recur within 4 weeks after treatment, (iii) atypical symptoms, and (iv) pregnancy (1). Nowadays, these tests can be also prescribed through a telephonic visit.

Depending upon the symptoms the patient refers during the telephonic interview, an office visit appointment should be schedule in order to properly explore the patient and check for severity signs (tachycardia, tachypnea, fever, or even ill appearance). These cases should undergo at least blood test for severity signs (tachycardia, tachypnea, fever, or even ill appearance). These cases should undergo at least blood test and culture and might need to be hospitalized. Caution is therefore advised when managing complicated UTIs through telephonic visits.

**Recurrent UTI**

In women with recurrent UTI, self-diagnosis of a new episode seems to be reasonably accurate, with a positive predictive value of up to 86% [37]. As in complicated infections, patients with recurrent acute cystitis should undergo a urine culture [38] to test for antibiotic susceptibility. Antibiotic treatment has been proven to be superior to placebo in uncomplicated UTIs in women. However, a strategy based on supportive care, hydration, and analgesics until urine culture results are available has been proven to be safe in women with acute uncomplicated cystitis [39].

**Treatment**

**Non-antibiotic Therapy**

Although the current standard of therapy for uncomplicated acute cystitis includes antibiotic as first-line therapy, there is a growing trend to explore alternatives to diminish the global consumption of antibiotics in order to avoid harmful effects in the microbiome and to reduce the appearance of bacterial resistances [40]. Studies randomizing patients to oral antibiotic versus symptomatic drugs (such as NSAIDs) have shown that around two thirds of patients with uncomplicated acute cystitis can be managed without any antibiotics that could be prescribed in case of symptoms’ worsening if necessary [41••]. With regard to potential complications of the non-antibiotic approach such as pyelonephritis or febrile UTI, there is conflicting evidence with studies showing a slightly superior risk of pyelonephritis in the NSAID group [41••], and studies showing no differences between NSAID and antibiotic group [42].

D-mannose, a monosaccharide naturally produced by the body from glucose that inhibits the adhesion of pilated *Escherichia coli* to human bladder cells [43], has shown its effectiveness in the reduction of UTI recurrences [44]. Its mechanism of action, based on the competitive inhibition of FimH-mediated bacterial adhesion to urothelial mannosylated receptors, does not interfere with bacteriostatic and/or bactericidal activity of antibiotics, and it has been used as coadjuvant in cystitis treatment [45]. However, its usefulness has also been shown for this purpose in monotherapy (D-mannose alone or with other non-antibiotic substances) in prospective uncontrolled studies, retrospective case-controlled studies, and even randomized controlled trials evaluating symptomatic improvement, including suprapubic pain, urinary frequency and/or urgency, and dysuria, among others [45]. When compared to antibiotic treatment, monotherapy with D-mannose achieves very good clinical cure rates with similar symptom relief scores after 3 days of treatment [46], while not affecting antibiotic resistance.

A different strategy for the non-antibiotic management of uncomplicated cystitis is the use of different herbal extracts that have shown clinical efficacy in well conducted studies. Canephron™ is a combination of centaury powder (*Centaurii herba*), lovage root powder (*Levistici radix*), and rosemary leaf powder (*Rosmarini folium*), commercially available in 28 countries. A randomized controlled trial using fosfomycin trometamol as active comparator was conducted in 51 centers in Europe including 659 patients with acute uncomplicated UTI. Authors demonstrated the non-inferiority of Canephron™ versus fosfomycin trometamol, with more than 80% of patients treated with this herbal combination not needing antibiotic therapy to solve their symptoms, and only one patient developing pyelonephritis during the study period of 30 days [47••]. Another open, non-comparative, prospective study was conducted in 29 non-pregnant women with acute uncomplicated cystitis. All patients received Canephron™ daily for 1 month plus ketoprofen for the first 5 days. Patients without symptoms relief in 48 h were classified as non-responders to phytotherapy and subsequently received oral antibiotics. With this approach, only 13.8% (4 patients) needed antibiotic therapy, so 86.2% were successfully managed with this strategy. No patient developed febrile UTI and no serious side effects of the therapy were noted [48].
Another combination of herbal products containing as active ingredients horseradish root (*Armoracia rusticana radix*) and nasturtium (*Tropaeoli majoris herba*) has also been tested in a randomized prospective trial versus trimethoprim sulfamethoxazole (co-trimoxazole). More than 50 patients with uncomplicated acute cystitis completed the study protocol. Response rates were similar for co-trimoxazole and the herbal combination, with 90% of patients free of symptoms in the group treated with herbal combination after 15 days and similar rates of recurrent cystitis in the optional 6-month observational period [49•].

Unfortunately, the evidence of herbal extracts is scarce, and more randomized studies controlled with standard oral antibiotic treatment are needed to recommend these options as first-line therapies. However, if these positive results are confirmed, this could greatly reduce the consumption of commonly used antibiotics and thus bring down antibiotic resistances in the medium term.

### Antibiotic Treatment

#### Uncomplicated UTIs

Empiric antibiotic treatment should be used in uncomplicated UTIs with no criteria for urine culture testing. Prescriptions can be made also through telephonic/electronic visits. The antibiotic agent should be chosen based on known antibiotic resistance rates in the community, the pharmacological distribution of the preparation and patient characteristics (allergies, renal or hepatic insufficiency) [1, 24•].

First-line antibiotics are [1, 24•, 50, 51]:

- Fosfomycin trometamol 3 g in a single dose
- Nitrofurantoin monohydrate/macrocystals 100 mg every 12 h (5 days)
- Pivmecillinam 400 mg every 8 h (3–5 days)
- Trimethoprim 200 mg every 12 h (5 days) or trimethoprim/sulfamethoxazole 160/800 mg every 12 h (3 days) when the resistance rate is lower than 20%

Although a follow-up culture is not needed, a telephonic follow-up visit might be required to assess the resolution of the infection. A drug-resistant bacteria can be suspected when symptoms do not disappear after treatment or when they recur in less than 3 months. In these cases, a urine culture and AST should be considered [1, 24•].

#### Complicated UTIs

Patients suffering from complicated UTIs should be managed through in office visits or even hospitalized [52] except for those cases in which severe infection can be certainly excluded. Treatment should be guided by the AST results given the fact that complicated UTIs are caused by a broad range of bacteria, and they are frequently multi-resistant [1, 53]. However, an initial empirical treatment selected based on patient’s characteristics, previous use of antibiotics, local susceptibility patterns, and type of complicated UTI is usually needed [24•, 53]. When AST results are available, a narrower spectrum antibiotic should be prescribed accordingly [1].

The recommended initial empirical treatment is [1, 54]:

- A second- or third-generation cephalosporin, although sometimes even fifth- or sixth-generation cephalosporin (ceftolozane or cefiderocol) are needed
- An aminoglycoside (+ amoxicillin)
- An extended-spectrum penicillin

Management of the complicating factor should be attempted if possible: if obstruction and/or residual urine are present, urinary tract drainage should be performed [55]; and if the patient has an indwelling urinary catheter, it should be changed [1].

### Conclusions

Acute cystitis can be safely managed through telemedicine, and in times when interpersonal contact should be reduced, it seems to be a good strategy. However, it should not encourage straightforward antibiotic prescription in cases that could be managed with symptomatic treatment and non-antibiotic measures, or when an AST must be performed before initiating therapy. Considering that overprescription of antibiotics is an increasing problem worldwide, there is a need for promoting antibiotic stewardship programs, as well as potentiation of non-antibiotic management strategies in patients with uncomplicated acute cystitis.

### Declarations

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- Of importance
- Of major importance

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