Original Article

Appropriate Use of Antimicrobial Agents in Urinary Tract Infections: Perception of Physicians and Resident Doctors

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Abstract

Appropriate and rational use of antibiotics in common infection syndrome such as urinary tract infection (UTI) is the need of the day to prevent bacterial resistance and side effects. Various protocols and guidelines are available for its use; however, perception as well as practices of clinicians may play an important role in their implementations. **Methodology:** To find problems as well as dilemma in regard to "when," "what," and "how long" to use antibiotics in UTI, a questionnaire and opinion-based study was conducted. Sixty clinicians engaged in adult internal medicine practice in Gujarat participated in the study. Many of the participants were resident doctors engaged in serving patients in the outpatient department, teaching hospitals, and medical intensive care units. **Results:** UTI was the second most common condition where the use of antibiotics is warranted in their practice. All of them had dilemma in the use of antibiotics because of various reasons. Majority did not ask for urine culture examination before giving antibiotics in uncomplicated UTI, but they demanded it in cases of recurrent UTIs, hospitalized patients, and pregnant patients. Their practice was akin to guidelines as far as treatment for asymptomatic bacteriuria was concerned. Fluoroquinolones and beta-lactam antibiotics were the choice of antibiotics in uncomplicated UTIs when urine culture was not ordered and was satisfied with clinical cure. Beta-lactam antibiotics were the choice in pregnant women having UTIs. Fifty-six percent responses favored 5–7-day treatment, whereas 17.86% favored 3-day treatment with fluoroquinolones or beta-lactam antibiotics. Although they were conscious and vigilant about antibiotic resistance problems, limitations did exit in their management plan which bothered them. **Conclusions:** Gaining insight from perceptions, knowledge, and practices of clinicians regarding the use of antibiotics in common situations such as UTI may be necessary to formulate a plan for local protocol and strategy. Antibiotic stewardship is an essential step. Shortening duration of antibiotics and use of appropriate antibiotics in different clinical situations of UTI may help to prevent antibiotic resistance. This topic needs priority in medical and paramedical education curriculum.

Keywords: Antibiotic stewardship, appropriate use of antimicrobials, asymptomatic bacteriuria, hospital-acquired urinary tract infections

Introduction

Clinicians are expected to use antimicrobials appropriately. However, they may be worried about antimicrobial resistance and their side effects. Stewardship, a theological belief, that we ourselves are responsible for the world and we should take care of her creation with utmost diligence is very important as far as antibiotics are concerned. One of the domains of stewardship program is the rational use of antibiotics by "prescribers." The National Institute for Health and Care Excellence (NICE) has given "pathways" as well as "guidelines" for prescribing antibiotics. Clinical assessment, recording of patient's symptoms as well as diagnosis and deciding management plan, is important for a prescriber.[1]

There are various issues faced by clinicians. First and foremost will be: Is this clinical situation warrants antibiotic treatment? If "yes" then which one and how long?, What is presumed etiological micro-organisms?, Is this infection community-acquired or is it health-care-associated infection?, Which microbiological investigations are needed before starting antimicrobial agents?, Which are likely resistant organisms or pattern present in this situation?, and last but not the least is: How review and reassessment of therapy will be advocated; once report of offending organism with sensitivity pattern are available from microbiology laboratory? To get perception and views of prescribers in relation to the above

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questions as well as issues, one of the common infection problems of "urinary tract infections" was undertaken for the study.

Urinary tract infection (UTI) can be uncomplicated or complicated and it can be recurrent or catheter-associated (CA) UTI (hospital-acquired [HA]) and may complicate into serious condition of urosepsis.[2] It is important to differentiate various types of UTIs, as etiological micro-organisms and antimicrobial management may be different. In view of recent evidence, the newer concept has emerged in antimicrobial therapy of UTIs. Thus, the topic of this study, "rational and appropriate antibiotic therapy," is geared to one of the common prescribers' domain, UTI.

METHODOLOGY

To find whether the clinicians face dilemma in appropriate use of antimicrobial agents in their practice of adult patients (above 18 years), this study was undertaken. The analysis of qualitative as well as quantitative data obtained from a questionnaire consisting of 15 questions in the form of "yes/no" or having multiple choices and also opinion-based open-ended questions was used as a study tool. Questions in relation to various problems encountered during antimicrobial usage in clinical practice, especially UTI, were prepared, validated, and finally used for this study. Questions pertained to UTIs of different types such as community-acquired uncomplicated UTI, CAUTI, and complicated UTI, UTI during pregnancy, were asked. Questions pertaining to which group of antibiotic was preferred in UTI, in what duration, were asked. They were also asked which agent was preferred (personal: P-drug) in particular group of antibiotic, e.g., if they preferred quinolone or beta-lactam group, which particular antibiotic of that group was preferred (e.g. ciprofloxacin, levofloxacin, or others in quinolone group). There were also asked "why?" for the preference. Practice of treating asymptomatic bacteriuria (ASB) in particular situations was solicited. This was especially to know about local resistance problem. There practices and problems encountered in relation to ordering relevant investigations before giving antibiotic were asked. Microbiological investigations, especially ordering "urine culture" in different types of UTIs, were inquired. Certain questions were to find their views regarding antibiotic stewardship program. The study was carried out at venue site of annual conference where physicians from all of Gujarat as well as resident doctors of medical colleges gathered. Sixty delegates participated in this study.

The analysis was done in relation to a particular question and also as per number of participants responded to a particular question. If answers to questions were >1, all answers were counted in the analysis.

RESULTS

Of the 60 participants, only 40 (66.67%) gave answers to all the questions. Responders also gave situation-based different

answers when multiple choices were given, which were analyzed quantitatively, and certain utterance, statements, and opinions were analyzed qualitatively also. All answers to study questionnaire were not going to come as integer number was one of the conclusions which we forecasted from our validation pilot work. Although precise questions would have given more clear results and we did feel that it was one of the limitations of this study, we deliberately framed some opinion-based questions. This was to get a better insight of local level which is very important in appropriate use of antibiotics. Again, infrastructural facility may not be the same at participant's local level. It is more so in relation to the facility of microbiology laboratory. We did the analysis of all statements made by participants barring some incoherence.

UTI was the second most common condition where they were using antibiotics in their practice of serving adult patients (respiratory tract infection was the first common condition). Eighty-six percent of participants responded that they have to use antibiotics in UTI in their daily practice and it was one of the common problems in their practice.

They were asked about antibiotic of their preference in uncomplicated UTI. Fifty-four responded to this question. There were total 130 responses. It included two, three, or four choices of antibiotics with some answers mentioning reasons such as in pregnancy preferring beta-lactam antibiotics [Table 1 and Figure 1].

When they were asked about the practice of ordering "urine culture" in patients with UTI before giving antibiotics in their clinic/outpatient, majority (55%) (30 of 55 responders) said "no." About 45% (25 of 55) said "yes," of which 15 responders mentioned that they will order urine culture in complicated UTI, recurrent UTI, and also pregnant women. Table 2 deals with results obtained on the duration of antibiotics in uncomplicated UTI.

A three day antibiotic regimen was preferred by 14%, 3 as well as 5-7 days course was preferred by 3% (depending on choice and use of antibiotics), 5-7 days of antibiotics was preferred by 54% responders and 11% preferred >10 days treatment [Figure 2].

A question related to ASB was answered by 46, of which 24 responded that it should not be treated (in most of the situations) whereas 12 opined that it should be treated. Four said that they were not sure whereas six said that it should be treated as per guideline. Antibiotic of choice in a pregnant woman with UTI was beta-lactams by almost all responders. One responder mentioned of nitrofurantoin (NF) and fosfomycin.

There were some noteworthy comments in connection to the cost of antibiotics and investigations in relation to UTI: nonavailability of microbiology facility, nonavailability of data on local resistance pattern, patients not willing for culture sensitivity tests even when having recurrent UTIs, patients not coming for follow-ups, coexisting comorbidities resulting in varied clinical picture such as elderly women having diabetes

Table 1: Choice of antibiotic in uncomplicated urinary tract infection

Number	Antibiotic	Responses (percentage of 130 responses) (percentage of 54 responders)*	Preferred agent in the group
1	Fosfomycin: 3 g PO as a single dose	14 (10.77) (25.93)	
2	Quinolones (PO)	46 (35.38) (85.19)	Norfloxacin: 8 responses, ciprofloxacin: 18, levofloxacin: 10, ofloxacin: 4, no specific quinolone mentioned/others: 6
3	Nitrofurantoin 100 mg	18 (13.85) (33.33)	
4	Beta-lactam	36 (27.69) (66.67)	Amoxicillin-clavulanate: 8, cefixime (third-generation cephalosporin): 10, cefdinir: 2, cefalexin: 2, ampicillin: 2, amoxicillin: 2, cefpodoxime: 2, cefuroxime: 2, parenteral ceftriaxone: 2, no specific beta-lactam mentioned and others: 4
5	Trimethoprim/sulfamethoxazole 160 mg/800 mg, PO, BID	12 (9.23) (22.22)	
6	Others including fixed-dose combination	4 (3.08) (7.41)	Beta-lactam and quinolone, injectable aminoglycoside

* Percentage in first bracket (*n*=130 responses; which includes two or three choices of antibiotic by one responder) (*n*=54 responders and percentage)

Table 2: Duration of antibiotic in uncomplicated urinary tract infection

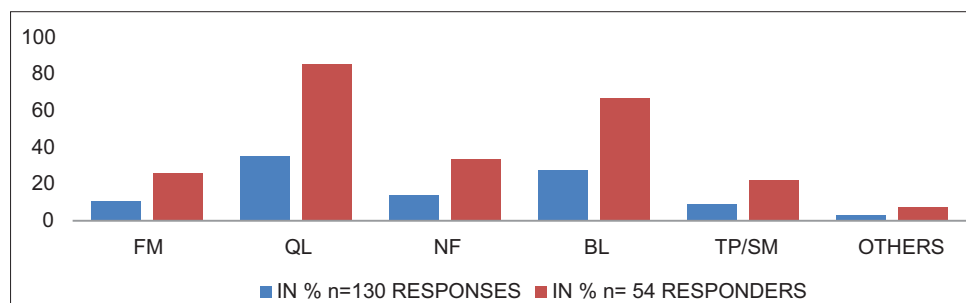| Number	Days of antibiotic therapy	Number of responses (*n*=56)	Remarks
1	3 days	8	1 had written that 1-day therapy also if fosfomycin therapy is given
2	3 days therapy and also 5-7 days therapy	2	3-day therapy with beta-lactam antibiotics and quinolones and 5-7-day therapy with nitrofurantoin
3	5-7 days	30	
4	7-10 days	10	
5	>10 days	6	

Figure 1: Choice of antibiotic in uncomplicated urinary tract infection. FM: Fosfomycin, QL: Quinolones, NF: Nitrofurantoin, BL: Beta-lactam, TP/SM: Trimethoprim/sulfamethoxazole. Others including fixed-dose combination

mellitus with vulvovaginitis and UTI, demand of immediate relief and demand of parental preparations, variation in different guideline recommendations, etc., Two responders specifically named "recurrent UTIs" when an open-ended question was asked about the prophylactic use of antibiotics.

DISCUSSION

Dilemma is a situation where choice has to be made between two or more alternatives. All responders of this study had this predicament in choosing appropriate antibiotic in their clinical practice. It was in relation to "Which antibiotic?" "Why this?" "How long?" and "Where-what." The rational

use of antimicrobial is warranted in proven and symptomatic infections.[3] Treatment with antibiotics is also warranted in some conditions where there is ASB and in prevention of infections in certain situations.[4] They also had a dilemma in regard to "where not" to use antibiotics in clinical situations.

UTI is one of the common bacterial infections which is accounted for frequent visits to doctor's clinic, emergency department and hospitalization.[5] Majority of our responders mentioned that UTI was very common in their clinical practice. They were treating such patients on outdoor basis and also in hospital who came with complicated UTI or had nosocomial UTI. About 35%–45% of the nosocomial infections are HA
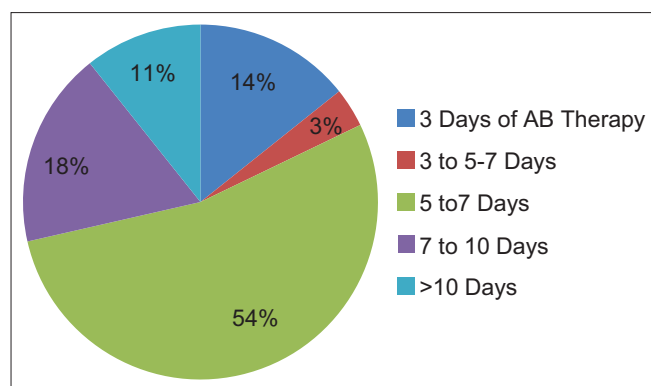
Figure 2: Preference of duration of antibiotics in uncomplicated urinary tract infection by 54 responders: In percentage

UTIs which maybe polyantimicrobial, resistant nosocomial pathogens, requiring attention to antibiotic prescription practices.[5,6] *Escherichia coli*, Pseudomonas, Klebsiella, and Candida organisms may lead to nosocomial UTI which may be resistant to most groups of antimicrobials.[6] Most clinicians were treating HAUTI and were aware of resistant organisms; however, they faced practical difficulties as mentioned in results such as poor local investigatory facility, cost, and affordability issues. "Priority of treatment was more focused by the patients than to diagnosis especially of culture report" was the response of clinicians.

UTI is a challenging clinical condition because of high incidence and also due to difficult diagnosis. One of the most important general principals of antimicrobial therapy is "proper diagnosis" and also to find microbiological etiology. Diagnosis may not be straight forward in all the cases such as in asymptomatic patients, in neutropenic patients, and also in patients who present with atypical signs and symptoms. It may cause significant burden to clinical microbiological laboratories.[7] This is more so in rural Indian situation where microbiological infrastructure facility is not there or is poor. Most clinicians ordered complete blood count and urine examination studies. Majority (55%) of our responders did not agree for urine culture to be done in uncomplicated UTI.

Urine culture examination is an important microbiological evaluation procedure, but it may not be necessary for outpatients with uncomplicated UTIs.[7] Responders of our study rightly opined that urine culture was ordered in all hospitalized patients, in CAUTIs and also in outpatients who had recurrent UTIs, treatment failure and complicated UTIs. The Centers for Disease Control and Prevention (CDC) (USA) has formulated guidelines in relation to urine culture stewardship in hospitalized patients, which strives at multifaceted approach. Recommendation of CDC is for performing urine cultures only when appropriate indications are present. A protocol also suggests proper urine culture method starting from collection, storage, and process such that contamination is avoided.[8] Colonization of urinary catheters is very common. Eradication of bacteria is difficult, as there is is a biofilm formation in

such indwelling catheters. Bacteriuria is very common with indwelling urinary catheters. If patients are asymptomatic, then CA-ASB should not be treated with antibiotics.[8]

The survey contained questions on ASB. The Infectious Diseases Society of America (IDSA) has recommended treatment for ASB in pregnant women and in patients subjected to invasive urological procedures. Screening and treatment of ASB is not justifiable in premenopausal nonpregnant women, in diabetic individuals, in the elderly living in the community, in patients with spinal cord injury, and in CA-ASB patients.[9]

Symptomatic UTI, which is community acquired, HA and may be CAUTI, requires appropriate antibiotics. For choosing antibiotic, etiological agents in community acquired and HA should be known. Although causative agent and their antibiotic sensitivity pattern may be different in relation to time (more resistant microorganisms) and place, enteric bacteria remain most frequent. *E. coli* is the most common cause of community-acquired UTI while *Proteus* species, *Pseudomonas* species, yeasts, Group B streptococci, *Acinetobacter* species, and *Klebsiella pneumoniae* can cause HAUTI. Funguria can be due to *Candida albicans* in most cases but may be due to *Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida krusei*, and others.[7]

NF monohydrate/macrocrystals, trimethoprim alone or with sulfamethoxazole (TMP-SMX) and fosfomycin is recommended as antibiotic of choice in uncomplicated UTIs by various guidelines. Beta-lactam and fluoroquinolones are recommended for complicated cystitis.[10,11] NF and fosfomycin are not advocated in suspected early pyelonephritis. Trimethoprim/sulfamethoxazole 160 mg/800 mg is considered one of the choices of antibiotics for uncomplicated UTI when local bacterial resistance is <20%.[12] The IDSA 1999 guideline recommended TMP-SMX as a first-line therapy; however, due to bacterial resistance, it lost its place.[13] In the present study, quinolone was the choice of antibiotic by majority. This was because of ease of availability and had better clinical experience with these agents. Ciprofloxacin was the most common quinolone used. Taur and Smith had undertaken a cross-sectional study of 2339 adult women above the age of 18 years having uncomplicated UTI. TMP-SMX and ciprofloxacin were the most commonly prescribed antibiotics.[14] Evidence and consensus-based German guidelines suggest "fosfomycin-trometamol, NF, nitroxoline, pivmecillinam, and trimethoprim (depending on the local rate of resistance)" as antibiotics for uncomplicated UTI. Co-trimoxazole, fluoroquinolones, and cephalosporins are not recommended by these German guidelines.

The second most common response choice of antibiotic in the present study was beta-lactam group in UTIs. The use of β-lactic/β-lactamase inhibitor combinations was more noted in the National Health Service hospitals because of "Start Smart-Then Focus" policy. "Start Smart" guiding principle may lead to empirical treatment with broad spectral antibiotics such as β-lactam/β-lactamase inhibitor combinations,

fluoroquinolones, and others greater in common infection syndromes.[15]"Then Focus" part is related with strategies to reduce antibiotic overuse in secondary care by keeping "focus then" on decreasing the duration and breadth of spectrum of antibiotics. It may need to focus on antimicrobial prescription reviews and shortening duration of therapy which is an evolving concept.[15,16]

Many responders commented about variety of recommendations by different international guidelines, and this was also one of the causes and concerns to them.

The Indian Council Medical Research in 2017 has come up with treatment guideline which includes UTI also.[17] Common pathogen for uncomplicated UTI is *E. coli*, *Proteus* spp., and *Klebsiella* spp. Empiric antibiotics recommended are NF100 mg BD for 7 days, co-trimoxazole 500/125 mg BD for 3–5 days, and ciprofloxacin 500 mg BD for 3–5 days. This treatment is recommended when the culture report is unavailable. Cefuroxime 250 mg BD for 3–5 days and cefixime 400 mg BD for 5 days are the alternative antibiotic suggestions.[17] Beta-lactam antibiotic was the second most common choice in our responders. International guidelines recommend beta-lactam antibiotics as the second-line antibiotics.[10,11]

Antimicrobial resistance is a global and local problem which poses a significant threat to community, and thus, judicious and rational use of antimicrobials is the need of the day. In Indian market, antimicrobials are available in the form of fixed-dose combination (FDC). Patel *et al.* studied total 6485 FDCs, of which 1575 were antimicrobial FDCs. Patel *et al.* studied total 6485 FDCs, of which 1575 were antimicrobial FDCs. As per authors, 70% of these FDC antimicrobials were irrational, 1% was semi-rational and 29% were irrational.[18] In our study, small number of responders (4 of 54) preferred brand containing FDC of oral beta-lactam and quinolone and other FDC antimicrobial for uncomplicated UTI which may not be considered rational. One of the studies performed in South India found 74.1% resistance rate for fluoroquinolones with also high rate of extended-spectrum beta-lactamase-positive organisms.[19]

UTIs during pregnancy need special therapy and diagnostic workup. The appropriate use of antibiotic is important such that maternal as well as fetal outcome is favorable and safety is ensured.[20] Drug of the first choice in the NICE guidelines is NF 50 mg four times a day or 100 mg of modified release twice a day for 7 days in pregnant women above 12 years. The second choice was beta-lactam antibiotic such as cephalexin or amoxicillin (for susceptible organisms).[10] In our survey, antibiotic of choice in a pregnant woman with UTI was beta-lactams. NF and fosfomycin were rare choices. Commonly accepted therapy in pregnancy is penicillin and cephalosporins. Cephalexin is preferred as it has low protein-binding ability. Majority cross the placenta and grouped as pregnancy category B drugs. Teratogenic potentials are also present.[20,21]

Most guidelines suggest a shortened duration of treatment. Three-day treatment in uncomplicated UTI is effective and is recommended.[10,15,16,22,23] Co-trimoxazole, amoxicillin/clavulanate and fluoroquinolones can eradicate organisms causing UTI in 3 days. NF, sulfonamides other than co-trimoxazole, and tetracyclines may require treatment for 5–7 days. Duration of therapy can also be shortened for 7 days instead of 10 days in acute pyelonephritis if a patient improves rapidly. Longer duration of treatment (10–14 days) can be advocated in patients having delayed response or is hospitalized. Of course, all guidelines recommend switching to oral therapy from parenteral, once clinical improvement is observed. In the present study, 15% of clinicians did opine for shortened therapy, whereas majority were treating uncomplicated UTI for > 5 days. A concept has evolved that if antibiotics are taken for longer time than necessary, chance of resistance increases. Again, it may increase cost and side effects. Patients need not be instructed to complete 5–7-day course of fixed days. Instruction now used is "antibiotics to be taken exactly as prescribed" and not as earlier "complete the course."[16]

Onakpoya *et al.* did a systematic review on advantages and disadvantages of short versus long duration antibiotic treatment for bacterial infections in secondary care. Study concluded that having limited evidence base, it weakly supports short durations of antibiotic therapy.

Proper knowledge of prescribing antimicrobials is important which requires educational efforts not only targeted at clinicians but also to trainees. Academic institutions should incorporate these topics in curriculum with emphasis on principles of prudent and rational prescribing.[24] This study incorporated responses from resident doctors doing postgraduate studies in general medicine subjects. Some of the responses from them were as per recent guidelines and evidence. Their unstructured feedback was very positive and felt sensitized to various issues in their day-to-day practice.

CONCLUSIONS

Existence of dilemma in treating patients of infective syndrome does exist among clinicians. Gaining insight from perceptions, knowledge, and practices of clinicians regarding the use of antibiotics in common situations such as UTI may be necessary to formulate a plan for local protocol and strategy. This is for rational and appropriate use of antibiotics. Antibiotic stewardship is essential at local level also and step which includes small set of interventions such as urine culture stewardship, preparing write-ups, and accepting some recent evidence-based concepts from international guidelines. Shortening duration of antibiotics in uncomplicated UTI and use of appropriate antibiotics in different clinical situation of UTI may help to prevent antibiotic resistance. This topic needs priority in medical and paramedical education curriculum. Preservation of effectiveness of antibiotics is the need of today's clinicians, and for it, more research and efforts are needed.

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Conflicts of interest

There are no conflicts of interest.

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