

TOWARDS EFFECTIVE REALIZATION OF SUSTAINABLE DEVELOPMENT GOALS WITH IMPETUS ON TACKLING THE MENACE OF DRUG-RESISTANT URINARY TRACT INFECTION

Aravinda Pai¹, H. N. Aswatha Ram², K. S. Chandrashekar², Angel Treasa Alex³, Jayashree V.⁴, Shruti Chaudhary⁴, Venkatesh Kamath B.^{3,✉}

¹Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India,

²Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India,

³Department of Pharmaceutical Biotechnology, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India,

⁴UG students, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India

✉Corresponding Author: venkatesh.kamath@manipal.edu

ABSTRACT

The United Nations General Assembly (UNGA) has designed a blueprint for achieving sustainable development which is intended to be achieved by 2030. The Sustainable Development Goals (SDGs) are interlinked with 17 goals that have been set up for a better and more sustainable future for all. To achieve these goals, the practices and principles associated with Chemistry, Biotechnology, Microbiology, and such related fields could play a pivotal role in achieving the set targets by 2030. Antimicrobial resistance is one of the present-day concerns that could act as a barrier in the quest for achieving many of these goals. One of the major goals includes goal 3 which caters to Health and well-being. Antimicrobial resistance could directly have a deleterious effect which could turn into a roadblock in attaining health and well-being for all. Drug resistance, in particular, antibiotic resistance to urinary tract infections has gained utmost attention over the past decade, which has led to ineffective therapeutic management and increased recurrence of the infection. The rising antimicrobial resistance also affects goal 8 which speaks about work and economic growth. Several families could face financial as well as social inequality due to added burden of time away from home, and loss of pay during absence from work to name a few. The present paper highlights various aspects of drug-resistant UTI including the major causative agents involved, female gender-specific prevalence, socio-economic consequences, treatment strategies, and future directions to attain sustainable development with health, well-being, and economic growth in mind.

Keywords: Sustainable Development Goal, Health, and well-being, UTI, Resistance, *Escherichia Coli*, Systemic Review, Socio-Economic Impact.

RASĀYAN J. Chem., Special Issue, 2022

This manuscript is focusing **SDG-3: Good Health and Well-being**

INTRODUCTION

Health, well-being, and economic growth of all are some of the major goals in the quest to reach the Sustainable Development Goals set by UNGA. Antimicrobial resistance (AMR) could be one of the key factors that could hinder the set goals especially goals 3 and 8 which cater towards health and wellbeing as well as work and economic impact respectively. It is in this context that there is an urgent need to address the risk associated with AMR not just at the national level but at the global setup. It has been observed that excessive, inappropriate use of various antibiotics has turned them increasingly ineffective leading to serious consequences on human and animal health, the environment as well as on the global economy. As *Escherichia coli* (*E. coli*) is highly prevalent in humans, the environment, and animals and keeping in mind one health approach, it becomes an ideal indicator in monitoring AMR across sectors. Urinary Tract Infections (UTIs) remain to be one of the most frequently observed infectious conditions in clinical setups

Rasayan J. Chem., Special Issue, 19-28(2022)

<http://doi.org/10.31788/RJC.2022.1558069>



This work is licensed under a CC BY 4.0 license.

and are known to affect all people irrespective of their age. It accounts to be among the chief cause of morbidity with an incidence of 150 million infections annually worldwide and signifies a severe public health problem with far-reaching implications on individuals as well as society.¹ The prevalence of UTIs is higher in females as compared to males due to various risk factors. Approximately 50–60% of women in the world encounter UTI at least once in their life with a peak observed between 16 and 64 years.^{2,3,4} UTIs can be either complicated or uncomplicated based on the clinical scenario. Complicated UTIs occur among individuals accompanied by a heightened risk of complications during the infection including pregnant females, any functional or structural anomalies of the urinary tract, renal diseases including diabetes, indwelling catheter, and any other immunosuppressive disorder. Meanwhile, uncomplicated UTIs are acute, sporadic, or recurrent that may be manifested as lower uncomplicated cystitis or upper uncomplicated pyelonephritis. Uncomplicated UTIs are mostly confined to non-pregnant females without anatomical dysfunction. Recurrent UTIs are defined as recurrent episodes of uncomplicated or complicated UTIs with the incidence of at least three UTIs annually or two episodes in the prior six months. *E. coli* is the commonest causative uropathogen among all types of UTIs. Antibiotic resistance in UTI has impacted the clinical as well as socio-economic events associated with the infection. Drug resistance attributed to *E. coli* ranks the top among all other bacterial strains followed by *Klebsiella pneumonia* and a few other Gram-negative bacteria. Treatment in cases of drug resistance must be dealt with proper caution by optimizing antibiotic therapy with an understanding of commonly isolated pathogens and local antibiotic sensitivity patterns. Various drug molecules and alternative therapeutic choices are under investigation for the effective and prospective management of drug-resistant UTIs.^{5,6,7} The present paper highlights various aspects of drug-resistant UTI including the major causative agents involved, female gender-specific prevalence, socio-economic consequences, treatment strategies, and future directions.

The Causative Pathogen of UTI

UTIs develop as a result of microbial invasion of the urinary tract through the urethra by several uropathogens. Although bacteria are the major culprit causing the highest incidence of infections with up to 95%, various other micro-organisms including fungi and viruses also cause the disease. *E. coli* is the common uropathogen resulting in both complicated and uncomplicated UTIs and accounts for about 80–85% of total infections. In the case of uncomplicated UTI, the causative organisms in their decreasing order of prevalence after *E. coli* are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida spp.*^{8–11} In case of complicated UTIs, the other responsible organisms include *Enterococcus spp.*, *K. pneumonia*, *Candida spp.*, *S. aureus*, *P. mirabilis*, *P. aeruginosa* and GBS.^{12,13} UTI causing bacterial pathogens are known to have a unique property of biofilm formation and adaptable morphological variations that makes it distinct enough to cause recurrent infections and increase resistance towards antibiotics. Multi-drug resistance, especially of the Enterobacteriaceae family constituting *E. coli*, and *K. pneumoniae*, pose a great threat to the management of UTI. Extended-spectrum β -lactamases (ESBLs), enzymes produced by Enterobacteriaceae, are the prime factor responsible for the increased resistance towards Penicillin and Cephalosporins. *E. coli* extends its resistance towards aminoglycosides, sulphonamides, and fluoroquinolones through their action of plasma-mediated transfer of genes encoding ESBLs, meanwhile, *K. pneumoniae* exerts its mechanism of resistance via chromosome-encoded ESBLs, which confer activity against β -lactams.¹⁴

In addition to inhibition of drug activity by ESBLs producing *E. coli* strains, several other sub-groups of ESBLs including CTX-M, OXAs, AmpC enzymes, and carbapenemase have demonstrated resistance towards specific antibiotics used in the treatment of UTI. CTX-Ms have increased resistance to Penicillin, Monobactams, and extended-spectrum cephalosporins including Cefotaxime and Ceftriaxone, but not against Ceftazidime. Originating from the chromosomes of *Kluyvera spp.*, these have gained popularity during the last decade in both hospital and community settings with *E. coli* reporting the highest frequency of this enzyme production.¹⁵ Another chromosomally encoded ESBL enzyme, AmpC is highly active against Penicillin, third-generation, and extended-spectrum Cephalosporins, and Cephamycins as a result of exposure to these drugs. It also extends its spectrum of activity to β -lactamase inhibitors, including Clavulanic acid.

Carbapenemase, ESBLs first originated in *K. pneumonia* through its swift transmission among the Enterobacteriaceae family has resulted in carbapenem-resistant Enterobacteriaceae (CRE)— an alarming crisis that targets the failure of Carbapenem (Figure 1) antibiotics left for the treatment of drug-resistant UTI.¹⁶ Studies have indicated the increasing prevalence of CRE, especially *E.coli* strains that encode genes for Carbapenemase in their plasmids and offers high resistance towards extended-spectrum Penicillin and Cephalosporins.^{17,18} OXAs are carbapenemases that have specific activity against β -lactamase inhibitors apart from resisting aminopenicillins, and penicillinase-resistant Penicillins through hydrolysis of the beta-lactam ring.

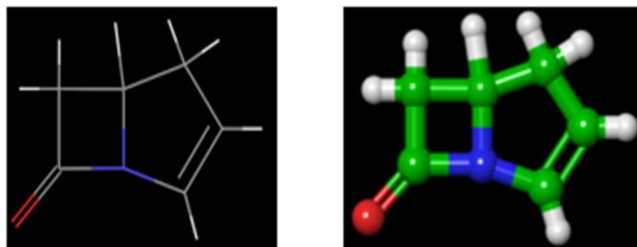


Figure 1: 2D and 3D structure of Carbapenem

OXAs were primarily produced only in *Pseudomonas aeruginosa* however, their presence has been detected recently in *E. coli* species. Data from studies indicated that *E.coli* strains were found to be the most prevalent in causing UTI and associated with resistance to multiple antibiotics.^{19,20,21} A meta-analysis showed that *E.coli* resistance was highest in Amoxicillin and least in Colistin among samples of humans, animals, food, and environment.²² Even among children, the most prevalent causative organism of UTI is *E.coli* followed by *Klebsiella pneumonia* and *E.coli* was found to be resistant to Ceftriaxone, Ampicillin, Ampicillin-Sulbactam, Amoxicillin-Clavulanate, Cefuroxime Axetil, TMP-SMX and Ciprofloxacin.^{23,24}

Prevalence Among Females

UTI is among the most frequently occurring infections in clinical practice with a significantly higher prevalence among females, approximately 8 times as in males, and recent evidence revealed that UTIs occur in 50-60% of females once in their entire life.²⁵ Recurrence of UTI and global statistics state that around 20-30% of women may suffer from re-infection within 3–4 months of the first occurrence. Several studies have reported the evolution of drug-resistant UTIs in the female population, especially among pregnant women. Factors such as age, structural changes, altered immune response, familial history, comorbid conditions, prior or current catheterization, lack of personal hygiene, and pregnancy could be some of the major factors attributing to the higher prevalence of UTI among females.²⁶ A systematic review on drug-resistant UTI among pregnant women in many developing countries in Asia and Africa over the last decade reported an overall prevalence of 13.5% in the study population. The gestational stage in women is crucial due to several predisposing factors such as physiological and hormonal alterations during pregnancy, infection route, and urinary instrumentation that could induce the incidence of infection.²⁷ In addition, history of UTI incidence, catheterization, poor socio-economic status, educational status, age between 25–34 years, frequent sexual intercourse in the pregnancy period, recent contraceptive use, gestational age, and multiparity exhibit significant association with infection.²⁸⁻³³

Socio-Economic Impact

The advent and spread of drug-resistant UTIs at an unprecedented pace is a global health concern that amplifies the clinical as well as socio-economic burden. Misutilization of antibiotics, application of antibiotics in the food industry, genetic mutations in bacterial strains, and knowledge gap leads to the incline in antimicrobial resistance over the years. A recent report on drug resistance by the World Bank suggests that it poses a serious threat to developing countries by deteriorating their economic integrity relative to other nations in the world. Few other studies forecast an approximately 1% reduction in the GDP per annum and a net loss of 5–7 % in emergent nations by the year 2050. Increasing rates of antimicrobial resistance in the modern era significantly affect the patient as manifested in clinical outcomes including extended hospitalization, increased morbidity, and mortality rate, worsening quality of life, and socio-economic outcomes like increased healthcare costs decreased productivity and unemployment. A prospective cohort

study performed in different hospital settings in Lebanon compared the economic impact of UTI caused by *E. coli* – resistant and – sensitive strains. The data revealed a higher count of resistant *E.coli* bacterial isolates that exceeded the total costs of hospitalization by 29% and one-day longer duration of hospital stay as compared to the *E.coli* sensitive strains.³⁴ Similar results of economic loss were reported among third-generation cephalosporin–non-susceptible *E.coli* and *K. pneumoniae* isolates, Carbapenem-resistant *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* in comparison to susceptible strains of these pathogens in a multicenter retrospective analysis in China.^{35,36} Recurrent UTIs affecting the patient's quality of life are also associated with significant social and economic burdens.³⁷ Ciani *et al.* demonstrated that recurrent UTIs encountered within 6 months among females ultimately lead to resignation from their workplace for appropriate symptom resolution, achieving beneficial health outcomes and improved quality of life.³⁸

Treatment of Drug-Resistant UTI

UTIs represent a major health issue among healthcare professionals as well as patients and their appropriate management is of paramount significance in current clinical practice. Older therapeutic agents such as Trimethoprim-Sulfamethoxazole, Ciprofloxacin, and Ampicillin have been excluded from the empirical therapy of UTIs due to high recurrence rates of infection and failure in therapy owing to the increasing resistance by uropathogenic strains of Enterobacteriaceae family. UTI management must be patient-directed, hence it warrants a consistent and careful approach to ascertain the presence of infection based on urine culture and sensitivities, the site and type of infection along with risk factor assessment. Furthermore, appropriate knowledge of the common UTI-associated pathogens and focus on local sensitivity patterns is crucial in deciding rational antibiotics for empirical therapy of UTIs.³⁹

Uncomplicated UTI

The Infectious Society of America (IDSA) recommends five-day therapy of Nitrofurantoin 100mg, a three-day course of double-strength Trimethoprim-Sulfamethoxazole 160/80 mg twice daily in conditions where the prevalence of *E. coli* resistance towards the drug is <20%, or a 3g single dose of Fosfomycin Trometamol as first-line agents for treating uncomplicated cystitis among healthy adult non-pregnant females. Second-line agents include fluoroquinolones and oral β -lactams including cephalosporins. However, due to the mounting rates of antimicrobial resistance, researchers have indicated that Fosfomycin, Nitrofurantoin, and Pivmecillinam are the drugs with the highest activity against multi-drug resistant ESBLs and AmpC enzyme isolates producing *E.coli* among patients having acute cystitis.⁴⁰ Fosfomycin (Figure 2), commercially available as Fosfomycin tromethamine in salt form is an approved choice single-dose oral therapy for uncomplicated UTI due to *E.coli* and *Enterococcus faecalis* in women, but not approved in *Klebsiella* associated UTIs. The extensive use of Fosfomycin in the management of multi-drug resistant or complicated UTIs remains controversial due to scarce data and rising resistance rates with the drug.^{41,42} Huttner A. *et al.* in an open-label randomized trial conducted on 513 women with uncomplicated lower UTIs found that Nitrofurantoin administered as 100mg thrice daily for 5 days, was dominant to 3g single dose of Fosfomycin in terms of symptoms resolution and cure rate after 2 weeks and 4 weeks respectively.⁴³ Nitrofurantoin (Figure 3) was also superior to fluoroquinolones owing to its primary indication in UTI, narrow spectrum of activity, and safety profile.⁴⁴ Therefore, Nitrofurantoin is indicated as the first choice of antibiotic therapy for acute cystitis and Fosfomycin should not be used unless in cases of resistance or hypersensitivity reaction to Nitrofurantoin and renal failure (Creatinine clearance <30ml/minute).

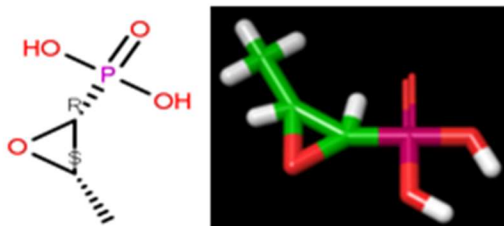


Fig.-2: 2D and 3D structure of Fosfomycin

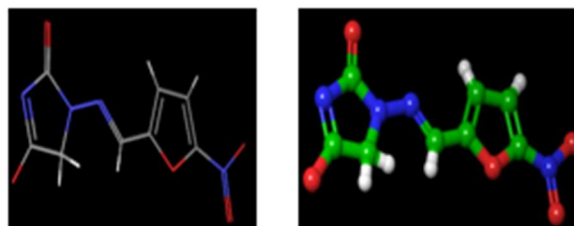


Fig.-3: 2D and 3D structure of Nitrofurantoin

Fluoroquinolones and Trimethoprim-Sulfamethoxazole (Figure 4) can be considered in the management of uncomplicated cystitis as an empirical or definitive choice of therapy only during antimicrobial resistance as well as allergy to first-line agents and UTIs caused by *Enterobacteriaceae* except for *E. coli*. Pivmecillinam, an orally administered synthetic Penicillin, is an alternative option in the treatment of ESBL producing *E. coli* and ESBL-producing *Klebsiella pneumoniae* despite few cases have reported insignificant clinical outcomes concerning MIC and failure in Mecillinam-susceptible ESBLs-*E. coli* strains.^{45,46} Oral cephalosporins occupy the last position in the list of activity against *E. coli*. Due to growing rates of antibiotic-induced adverse events and diarrhea with Cephalexin, these agents are also considered a choice after failure to Nitrofurantoin or Fosfomycin therapy.^{47,48} Amoxicillin-Clavulanic acid in drug-resistant UTI is restricted due to a dearth of data on its efficacy and safety, and booming rates of resistance, but its addition to Aztreonam can be an effective approach in the treatment of Metallo- β -lactamases (MBLs) producing Gram-negative bacteria.

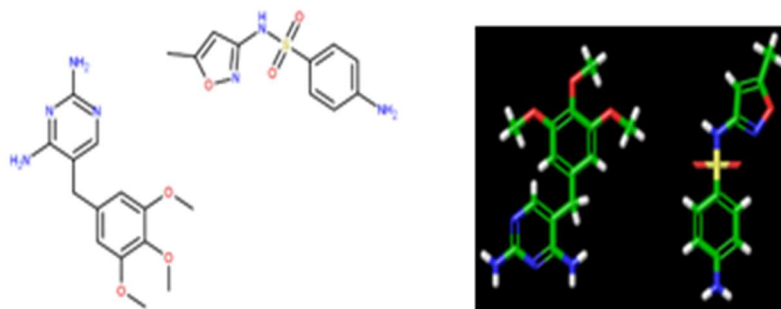


Fig.-4: 2D and 3D Structure of Trimethoprim-Sulfamethoxazole

Complicated UTI

Complicated UTIs are often associated with infection recurrences and therapeutic failure due to physiological anomalies of the urinary tract that impose practitioners to target intravenous broad-spectrum antibiotics in the empirical management of complicated UTIs including acute pyelonephritis caused by *Enterobacteriaceae*. Switching from an intravenous route to the oral agent, to which the isolated pathogen is susceptible, can be encouraged once initial therapy attains clinical response and antimicrobial sensitivity testing is available for the completion of the antibiotic course even in cases of symptomatic bacteremia. Ceftriaxone, a broad spectrum third-generation cephalosporin is the recommended first choice of empirical therapy for acute pyelonephritis when risk factors are absent for resistance-producing organisms such as ESBLs- *Enterobacteriales*, *P. aeruginosa* or *Enterococci*.⁴⁹ Cefepime and Ceftazidime possess similar antibacterial activity to Ceftriaxone, with additional benefits.^{50,51} Cefepime is comparably stable to AmpC enzyme hydrolysis, and studies have shown that 96.6% AmpC- producing *E. coli* strains are sensitive to Cefepime while Ceftazidime is active against *Pseudomonas* species, hence both these drugs are a viable option for the management of complicated UTI and pyelonephritis.⁵² Ceftazidime-Avibactam combination is approved by FDA to treat complicated UTIs as well as pyelonephritis and Gram-negative infections. Evidence suggest that Ceftazidime-Avibactam has inhibited microbial resistance >99.9% of *Enterobacterales* and 99.4% of *P. aeruginosa* which were initially resistant to Meropenem, Ceftazidime, and Piperacillin-Tazobactam and 100% of OXA-48 enzyme producing uropathogens.⁵³ Another combination of cephalosporin and β -lactamase inhibitor, Ceftolozane-Tazobactam has profound inhibitory activity against *P. aeruginosa* but not against ESBLs or MBLs. Randomized, double-blind, phase III trial revealed high infection cure rates with the drug and was found to be superior to high-dose Levofloxacin in complicated UTIs, however, an incremental rate of resistance among ESBLs-*Klebsiella pneumoniae* restricted its use as a choice to Carbapenems.^{54,55,56} Ertapenem (Figure 5) is the most preferred choice of Carbapenems in the management of moderate to severe complicated UTIs, commonly affected by ESBLs-*Enterobacteriaceae* about its clinical efficacy, narrow spectrum activity, and convenience for ambulatory therapy. Despite its inhibitory action, ertapenem is losing its glory in clinical practice due to growth in resistance rates towards *Enterobacter cloacae*, *K. pneumoniae*, ESBL-*Enterobacteriaceae*, and nosocomial infections.⁵⁷

Several innovative drugs have been investigated and introduced into the market that offers an effective therapeutic approach in the management of complicated UTIs. One such antibiotic includes FDA approved combination of Vaborbactam with Meropenem which has a four-fold increased potency compared to Ceftazidime-Avibactam. It has shown superior efficacy to Piperacillin-Tazobactam in UTIs and significant improvement in clinical response against the standard treatment options for CRE infections.⁵⁸ Relebactam is a non- β -lactam β -lactamase inhibitor with a similar spectrum of activity of Vaborbactam plus *P.aeruginosa* which shows an additive effect with Amikacin or Colistin.^{59,60}

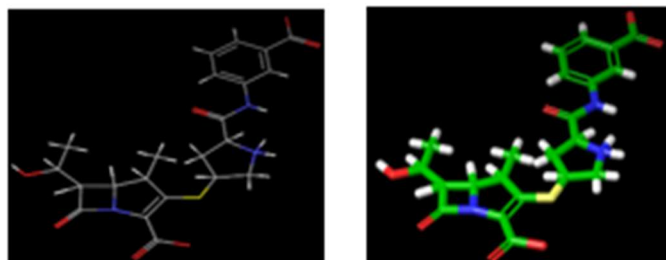


Fig.-5: 2D and 3D structure of Ertapenem

Among aminoglycosides, Plazomicin is the newly FDA-approved the choice of drug in complicated UTIs including pyelonephritis due to the *Enterobacteriaceae* family when there are only limited or no other treatment options available. Plazomicin showed non-inferiority to Meropenem in a randomized, double-blind, phase III study attaining higher clinical response detected as a clinical cure and microbiological cure rates.⁶¹ Another novel therapeutic option is Temocillin, a Ticarcillin derivative that shows in vitro activity against AmpC-, ESBLs-, and KPC-producing *Enterobacteriaceae*, Ceftriaxone-resistant *Enterobacteriaceae* with the least likelihood of Clostridium-associated infection. Currently, Temocillin is recommended at a dose of 2g either twice daily or thrice daily based on the severity of infection and sensitivity patterns although its clinical efficacy in UTI management remains questionable. In addition to the above antibiotics that have been used in ameliorating the severity of UTI attributed to resistance by various uropathogens, vaccines open an alternative platform for effective therapeutic prevention of the infection. Currently, four vaccines are commercially available that offer protection against common uropathogens and prevents the recurrence of UTI. The progressive development of several therapeutic nuances that target the UTI mechanism and pathological factors is evident since the last decade. Vaccines aimed at the protective capsule layer of the uropathogens, pathological steps of adhesion to the epithelium, toxins produced by bacterial strains, and iron metabolism relevant to the survival of bacteria have been studied with great prospects. Likewise, small compounds of bacterial substrates with inhibitory action on protein and substrate binding sites of the uropathogens are also promising candidates in disease prevention. However, further research is warranted in vaccines and other molecules in real-world settings to confirm their efficacy and safety in the management of drug-resistant UTIs.

CONCLUSION

Antibiotic resistance to extended-spectrum Carbapenems is a flashpoint in the management of UTI endangering the disease severity as well as the efficacy of existing antibiotics. Conversely, it put forward the scope of newer agents in clinical practice. Trials on various drug molecules of different categories have been found successful in the long run. Although fluoroquinolones are not recommended in the empirical antibiotic therapy of complicated UTIs due to the rising fluoroquinolone-resistant *E. coli* strains, Finafloxacin is a newer fluoroquinolone in its experimental stage which exhibits inhibitory activity against ESBLs- *Enterobacteriaceae* and *E. coli* strains resulting in resistance to conventional fluoroquinolones. Finafloxacin possesses higher potency in acidic pH relative to Levofloxacin and Ciprofloxacin and higher clinical cure rates when compared with Ciprofloxacin. Cefiderocol is a recently developed cephalosporin and a siderophore antibiotic with *Burkholderia cepacia*. A phase II trial demonstrated the superior efficacy of Cefiderocol over Imipenem/Cilastatin in achieving a clinical and microbiological response in complicated UTIs due to Gram-negative bacteria. Sulopenem is an investigational Carbapenem indicated for the treatment of both complicated and uncomplicated UTI with a similar activity profile of other Carbapenems against common uropathogens except *P.aeruginosa*. A few other promising candidates in the

treatment of UTIs include Eravacycline and Omadacycline which are still in their developmental stages. Eravacycline, a Tigecycline derivative has a broad spectrum of activity extending to CRE, *A.baumannii*, and strains resistant to Polymyxin, Methicillin-susceptible and resistant *Staphylococci*, Vancomycin-susceptible and resistant *Enterococci*. Omadacycline is a semisynthetic tetracycline antibiotic with inhibitory action towards Gram-positive, and Gram-negative aerobes, anaerobes, and atypical bacterial strains. Phage therapy has indeed come into the limelight for the treatment of severe antibiotic-resistant UTIs. Even though there are only a few animal-based studies and case reports supporting its efficacy in disease management, human trials are required to ascertain its significance. In a nutshell, drug-resistant UTI remains a matter of concern in the current healthcare settings which necessitates cautious antibiotic prescribing practices for appropriate management. Although recent reports on novel therapeutic substitutes have demonstrated positive results in animal studies as well as few human trials, extensive real-world evidence would help clinicians in the management of widespread antibiotic-resistant UTIs. A robust tracking system, a comprehensive surveillance mechanism, preparedness, and lessons learned from previous experiences along with effective management of antibiotic therapy would help in the realization of sustainable development goals for a better future for all.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the facilities provided by the Manipal College of Pharmaceutical Sciences and Manipal Academy of Higher Education in executing this review article.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the faculty authors can be verified from their ORCID ids, given below:

Aravinda Pai  <https://orcid.org/0000-0003-2010-9479>
H. N. Aswatha Ram  <https://orcid.org/0000-0003-4119-6890>
K. S. Chandrashekar  <https://orcid.org/0000-0003-3667-1781>
Angel Treasa Alex  <https://orcid.org/0000-0002-5793-6868>
Jayashree V  <https://orcid.org/0000-0002-1706-0240>
Shruti Chaudhary  <https://orcid.org/0000-0002-9791-7207>
Venkatesh Kamath B  <https://orcid.org/0000-0001-6508-782X>

Open Access: This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. A. L. Flores-Mireles, J. N. Walker, M Caparon, S. J. Hultgren, *Nature Reviews Microbiology*, **13**(5), 269(2015), <https://doi.org/10.1038/nrmicro343>
2. T. M. Hooton, *International Journal of Antimicrobial Agents*, **17**(4), 259(2001), [https://doi.org/10.1016/s0924-8579\(00\)00350-2](https://doi.org/10.1016/s0924-8579(00)00350-2)
3. A. Vyas, K. Singh, G. Kumar, *Research Journal of Pharmacy and Technology*, **10**(2), 575(2017), <https://doi.org/10.5958/0974-360X.2017.00114.7>
4. D. Minardi, G. d'Anzeo, D. Cantoro, A. Conti, G. Muzzonigro, *International Journal of General Medicine*, **4**, 333(2011), <https://doi.org/10.2147/IJGM.S11767>
5. P. Dadgostar, *Infection and drug resistance*, **12**, 3903(2019), <https://doi.org/10.2147/IDR.S234610>
6. M. S. Bader, M. Loeb, D. Leto, A. A. Brooks, *Postgraduate Medicine*, 2020 **132**(3), 234(2020), <https://doi.org/10.1080/00325481.2019.1680052>

7. M. S. Bader, M. Loeb, A. A. Brooks, *Postgraduate Medicine*, **129(2)**, 333(2017), <https://doi.org/10.1080/00325481.2017.1246055>
8. M. Medina, E. Castillo-Pino, *Therapeutic Advances in Urology*, **11**, 3(2019)
9. B. Foxman, *Infectious Disease Clinics of North America*, **28(1)**, 1(2014), <https://doi.org/10.1016/j.idc.2013.09.003>
10. K. A. Kline, D. J. Schwartz, W. G. Lewis, S. J. Hultgren, A. L. Lewis, *Infection and Immunity*, **79(9)**, 3588(2011)
11. A. Ronald, *The American Journal of Medicine*, **113(1)**, 14(2002), [https://doi.org/10.1016/s0002-9343\(02\)01055-0](https://doi.org/10.1016/s0002-9343(02)01055-0)
12. V. Dias, *Future Microbiology*, **15(2)**, 81(2020), <https://doi.org/10.2217/fmb-2019-0262>
13. S. M. Jacobsen, D. J. Stickler, H. L. Mobley, M. E. Shirtliff, *Clinical Microbiology Reviews*, **21**, 26(2008)
14. D. S. Lee, S. J. Lee, H. S. Choe, *BioMed Research International*, **2018**, 1(2018), <https://doi.org/10.1155/2018/7656752>
15. R. Cantón, T. M. Coque, *Current Opinion in Microbiology*, **9(5)**, 466(2006), <https://doi.org/10.1016/j.mib.2006.08.011>
16. S. H. Kim, G. R. Kim, J. Jeong, S. Kim, J. H. Shin, *Japanese Journal of Infectious Diseases*, **73(6)**, 431(2020), <https://doi.org/10.7883/yoken.JJID.2020.043>
17. A. Govindaswamy, V. Bajpai, S. Khurana, P. Batra, P. Mathur, R. Malhotra, *Journal of Global Infectious Diseases*, **11(3)**, 123(2019), https://doi.org/10.4103/jgid.jgid_68_18
18. G. Peirano, P. A. Bradford, K. M. Kazmierczak, R. E. Badal, M. Hackel, D. J. Hoban, J. D. Pitout, *Emerging Infectious Diseases*, **20(11)**, 1928(2014), <https://doi.org/10.3201/eid2011.141388>
19. G. Córdoba, A. Holm, F. Hansen, A. M. Hammerum, L. Bjerrum, *BMC Infectious Diseases*, **17(670)**, 1(2017), <https://doi.org/10.1186/s12879-017-2785-y>
20. R. Thapa, P. Lamichhane, M. R. Banjara, G. P. Acharya, *Asian Journal of Pharmaceutical and Clinical Research*, **8(1)**, 207(2015)
21. S. Ny, P. Edquist, U. Dumpis, K. Gröndahl-Yli-Hannuksela, J. Hermes, A. M. Kling, A. Klingeberg, R. Kozlov, O. Källman, D. O. Lis, M. Pomorska-Wesołowska, M. Saule, K. T. Wisell, J. Vuopio, I. Palagin, NoDARS UTI Study Group, *Journal of Global Antimicrobial Resistance*, **17**, 25(2019), <https://doi.org/10.1016/j.jgar.2018.11.004>
22. A. Pormohammad, M. J. Nasiri, T. Azimi, *Infection and Drug Resistance*, **12**, 1181(2019), <https://doi.org/10.2147/IDR.S201324>
23. R. S. Abdul Raheem, M. A. Hussein, N. I. Al-Din, *The Journal of Pakistan Medical Association*, **3(8)**, 59(2019)
24. S. Samancı, M. Çelik, M. Köşker, *Turkish Archives of Pediatrics*, **55**, 4(2020), <https://doi.org/10.14744/TurkPediatriArs.2020.22309>
25. A. Al-Badr, G. Al-Shaikh, *Sultan Qaboos University Medical Journal*, **13**, 3(2013), <https://doi.org/10.12816/0003256>
26. L. Paudel, N. Manandhar, S. Sah, S. Khadka, S. Neupane, S. K. Joshi, *International Journal Of Community Medicine And Public Health*, **5(7)**, 2714(2018)
27. M. A. Belete, M. Saravanan, *Infection and Drug Resistance*, **13**, 1465(2020), <https://doi.org/10.2147/IDR.S250654>
28. B. Derese, H. Kedir, Z. Teklemariam, F. Weldegebreal, S. Balakrishnan, *Therapeutics and Clinical Risk Management*, **12**, 251(2016), <https://doi.org/10.2147/TCRM.S99831>
29. A. K. Labi, A. E. Yawson, G. Y. Ganyaglo, M. J. Newman, *Ghana Medical Journal*, **49(3)**, 154(2015), <https://doi.org/10.4314/gmj.v49i3.5>
30. G. Sibi, P. Kumari, N. Kabungulundabungi, *Asian Pacific Journal of Tropical Medicine*, **7(S1)**, 116(2014), [https://doi.org/10.1016/S1995-7645\(14\)60216-9](https://doi.org/10.1016/S1995-7645(14)60216-9)
31. C. G. Math, S. Patil, S. Gaddad, C. Shivannavar, *Advances in Microbiology*, **3(6)**, 473(2013), <https://doi.org/10.4236/aim.2013.36063>
32. C. Turpin, B. Minkah, K. Danso, E. Frimpong, *Ghana Medical Journal*, **41(1)**, 26(2007)

33. G. Haider, N. Zehra, A. A. Munir, A. Haider, *Journal of Pakistan Medical Association*, **60(3)**, 213(2010)
34. K. Iskandar, R. Rizk, R. Matta, R. Husni-Samaha, H. Sacre, E. Bouraad, N. Dirani, P. Salameh, L. Molinier, C. Roques, *Value Health Reg Issues*, **25**, 90(2021), <https://doi.org/10.1016/j.vhri.2021.03.001>
35. X. Zhen, C. Stålsby Lundborg, X. Sun, N. Zhu, S. Gu, H. Dong, *Antimicrobial Resistance and Infection Control*, **6(10)**, 1(2021), <https://doi.org/10.1186/s13756-020-00872-w>
36. X. Zhen, C. Stålsby Lundborg, X. Sun, S. Gu, H. Dong, *Antibiotics (Basel)*, **9(8)**, (2020), <https://doi.org/10.3390/antibiotics9080514>
37. F. Wagenlehner, B. Wullt, S. Ballarini, D. Zingg, K. G. Naber, *Expert Review of Pharmacoeconomics & Outcomes Research*, **18(1)**, 107(2018), <https://doi.org/10.1080/14737167.2017.1359543>
38. O. Ciani, D. Grassi, R. Tarricone, *Clinical Drug Investigation*, **33(4)**, 255(2013), <https://doi.org/10.1007/s40261-013-0069-x>
39. K. Gupta, T. M. Hooton, K. G. Naber, B. Wullt, R. Colgan, L. G. Miller, G. J. Moran, L. E. Nicolle, R. Raz, A. J. Schaeffer, D. E. Soper, *Clinical Infectious Diseases*, **52(5)**, e103(2011)
40. H. J. Morrill, J. B. Morton, A. R. Caffrey, L. Jiang, D. Dosa, L. A. Mermel, K. L. LaPlante, *Antimicrobial Agents and Chemotherapy*, **61(5)**, e02236(2017)
41. A. Peretz, B. Naamneh, L. Tkhawkho, O. Nitzan, *Microbial Drug Resistance*, **25(3)**, 408(2019), <https://doi.org/10.1089/mdr.2018.0393>
42. W. M. Quek, C. B. Teng, Y. Z. Tan, K. Chong, D. C. Lye, T. M. Ng, *International Journal of Antimicrobial Agents*, **53(2)**, 195(2019), <https://doi.org/10.1016/j.ijantimicag.2018.10.008>
43. A. Huttner, A. Kowalczyk, A. Turjeman, T. Babich, C. Brossier, N. Eliakim-Raz, K. Kosiek, B. Martinez de Tejada, X. Roux, S. Shiber, U. Theuretzbacher, E. von Dach, D. Yahav, L. Leibovici, M. Godycki-Cwirko, J. W. Mouton, S. Harbarth, *The Journal of American Medical Association*, **319(17)**, 1781(2018), <https://doi.org/10.1001/jama.2018.3627>
44. H. Ahmed, D. Farewell, N. A. Francis, S. Paranjothy, C.C. Butler, *PLoS Medicine*, **15(9)**, e1002652(2018), <https://doi.org/10.1371/journal.pmed.1002652>
45. T. J. Monsen, S. E. Holm, B. M. Ferry, S. A. Ferry, *APMIS*, **122(4)**, 317(2014), <https://doi.org/10.1111/apm.12147>
46. A. Søråas, A. Sundsfjord, S. B. Jørgensen, K. Liestøl, P. A. Jenum, *PLoS One*, **9(1)**, e85889(2014), <https://doi.org/10.1371/journal.pone.0085889>
47. D. Kavatha, H. Giamarellou, Z. Alexiou, N. Vlachogiannis, S. Pentea, T. Gozadinos, G. Poulakou, A. Hatzipapas, G. Koratzanis, *Antimicrobial Agents and Chemotherapy*, **47(3)**, 897(2003)
48. K. L. Bunnell, E. Wenzler, A. T. Harrington, L. H. Danziger, *Diagnostic Microbiology and Infectious Diseases*, **90(4)**, 335(2018), <https://doi.org/10.1016/j.diagmicrobio.2017.12.007>
49. S. S. Wang, P. D. Ratliff, W. R. Judd, *International Journal of Clinical Pharmacy*, **40(1)**, 143(2018), <https://doi.org/10.1007/s11096-017-0560-1>
50. L. M. Blanchette, J. L. Kuti, D. P. Nicolau, M. D. Nailor, *Scandinavian Journal of Infectious Diseases*, **46(11)**, 803(2014), <https://doi.org/10.3109/00365548.2014.954262>
51. L. S. Briongos-Figuero, T. Gómez-Traveso, P. Bachiller-Luque, M. Domínguez-Gil González, A. Gómez-Nieto, T. Palacios-Martín, M. González-Sagrado, A. Dueñas-Laita, J. L. Pérez-Castrillón, *International Journal of Clinical Practice*, **66(9)**, 891(2012), <https://doi.org/10.1111/j.1742-1241.2012.02991.x>
52. D. J. Hoban, C. Lascols, L. E. Nicolle, R. Badal, S. Bouchillon, M. Hackel, S. Hawser, *Diagnostic Microbiology and Infectious Disease*, **74(1)**, 62(2012), <https://doi.org/10.1016/j.diagmicrobio.2012.05.024>
53. M. Castanheira, R. E. Mendes, H. S. Sader, *Antimicrobial Agents and Chemotherapy*, **61(3)**, e02252(2017)
54. H. Bouxom, D. Fournier, K. Bouiller, D. Hocquet, X. Bertrand, *International Journal of Antimicrobial Agents*, **52(1)**, 100(2018), <https://doi.org/10.1016/j.ijantimicag.2018.03.014>
55. S. García-Fernández, M. García-Castillo, G. Bou, J. Calvo, E. Cercenado, M. Delgado, C. Pitart, X. Mulet, N. Tormo, D. L. Mendoza, J. Díaz-Regañón, R. Cantón, SUPERIOR Study Group, *International Journal of Antimicrobial Agents*, **53(5)**, 682(2019), <https://doi.org/10.1016/j.ijantimicag.2019.02.004>

56. M. A. Pfaller, D. Shortridge, H. S. Sader, A. Gales, M. Castanheira, R. K. Flamm, *Brazilian Journal of Infectious Disease*, **21(6)**, 627(2017), <https://doi.org/10.1016/j.bjid.2017.06.008>
57. Rattanaumpawan P, Werarak P, Jitmuang A, Kiratisin P, Thamlikitkul V. *BMC Infectious Diseases*, **17(1)**, Article Number183(2017), <https://doi.org/10.1186/s12879-017-2284-1>
58. L. A. Petty, O. Henig, T. S. Patel, J. M. Pogue, K. S. Kaye, *Infection and Drug Resistance*, **11**, 1461(2018), <https://doi.org/10.2147/IDR.S150447>
59. J. A. Karlowsky, S. H. Lob, K. Young, M. R. Motyl, D. F. Sahm, *Journal of Pediatric Infectious Disease Society*, **10(3)**, 274(2021)
60. T. E. Asempa, D. P. Nicolau, J. L. Kuti, *Antimicrobial Agents and Chemotherapy*, **63(9)**, e00997(2019)
61. J. A. McKinnell, J. P. Dwyer, G. H. Talbot, L. E. Connolly, I. Friedland, A. Smith, A. M. Jubb, A. . Serio, K. M. Krause, G. L. Daikos, CARE Study Group, *New England Journal of Medicine*, **380(8)**, 791(2019), <https://doi.org/10.1056/NEJMc1807634>

[RJC-8069/2022]