Chapter 4
Antibiotics

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The common classes of antibiotics used to treat UTIs that clinicians should be familiar with include penicillin, cephalosporin, carbapenems, fluoroquinolones, aminoglycosides, and fosfomycin. These are explored further below and summarised in Table 4.1.

4.1 Trimethoprim

Trimethoprim is a bacteriostatic antibiotic which binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid which is an essential precursor in the thymidine synthesis pathway in bacterial DNA synthesis.

- The dosage of trimethoprim to treat UTI is usually 200 mg BD.

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Table 4.1 Summary of antibiotics used in urinary tract infections

Class of antibiotics	Type of antibiotics	Mechanism of action	Commonly used names of antibiotics	Comments
Trimethoprim	Bacteriostatic	Inhibits bacterial thymidine synthesis	N/A	Being a folate antagonist, trimethoprim should not be prescribed for pregnant ladies who are in their first trimester
Nitrofurantoin	Bacteriostatic	Believed to be inhibition of several bacterial enzymes involved in the synthesis of DNA, RNA and other bacterial metabolic enzymes	N/A	Not to be used in pregnant ladies who are in their third trimester as it may induce neonatal haemolysis. Risk of lung fibrosis and hepatotoxicity
Penicillin	Bactericidal	Interferes with bacterial cell wall synthesis	Ampicillin Amoxicillin Flucloxacillin Penicillin V Benzylpenicillin Piperacillin	Contraindicated in patients who have hypersensitivity to penicillin. Encephalopathy is also another rare but serious side of penicillin
Fluoroquinolones	Bactericidal	Inhibits DNA gyrase	Ciprofloxacin Levofloxacin Ofloxacin Moxifloxacin Norfloxacin	Contraindicated if patients have a history of tendon rupture or tendonitis

Aminoglycoside	Bactericidal	Inhibits bacterial protein synthesis	Gentamicin Neomycin Amikacin Tobramycin Streptomycin	Well known side effects of this class of medication are ototoxicity and nephrotoxicity
Fosfomycin	Bactericidal	Inhibits enzyme-catalyzed reaction in bacterial cell wall synthesis	N/A	
Cephalosporin	Bactericidal	Disrupts bacterial cell wall synthesis	First generation: cefazolin, cephalexin Second generation: cefoxitin, cefaclor, cefuroxime Third generation: ceftriaxone, cefotaxime, ceftazidime Fourth generation: cefepime	About 0.5–6.5% of penicillin-sensitive/allergic patients will also be sensitive to cephalosporins
Carbapenem	Bactericidal	Disrupts bacterial cell wall synthesis	Meropenem Ertapenem Imipenem Doripenem	

4.2 Nitrofurantoin

Nitrofurantoin is another bacteriostatic antibiotic. It has several mechanisms of antimicrobial action but none of which is properly and fully understood [1]. However, it is well established that intracellular nitroreductases produce the active form of the drug via reduction of the nitro group; and the resultant active intermediate metabolites bind to bacterial ribosomes and causes inhibition of several bacterial enzymes involved in the synthesis of DNA, RNA and other metabolic enzymes in the bacteria. Patients prescribed nitrofurantoin (especially if for a prolonged course) must be warned of the risk of lung fibrosis and hepatotoxicity. Some guidelines recommend regular liver function screening and chest X-Rays, though discussions at international meetings often feel such surveillance is excessive unless in the presence of new symptoms.

- The dosage of nitrofurantoin to treat UTI is usually 50 mg QDS or 100 mg BD.

4.3 Penicillin

First discovered incidentally in 1928, penicillin works by interfering with bacterial cell wall synthesis through inhibiting the formation of peptidoglycan cross-links in the bacterial cell wall. Without a cell wall which is essential to the survival of some bacteria, bacteria die.

- Typically penicillin based agents used in UTIs are Amoxicillin 500 mg TDS.

However, bacteria have evolved to secrete β-lactamase, an enzyme which inactivates penicillin based agents by using hydrolysis to break the β-lactam antibiotic ring, thus deactivating its bactericidal properties.

The rising incidence of amoxicillin resistance (quoted as high as 50% in certain areas of the UK) has led to the development of co-amoxiclav. This contains a β-lactam drug

called clavulanic acid which is a beta-lactamase inhibitor, thus mitigating the bacteria's ability to inactivate amoxicillin.

- The dosage of co-amoxiclav to treat UTI is usually 625 mg TDS.

4.4 Fluoroquinolones

Fluoroquinolone is a bactericidal antibiotic which works by inhibiting DNA gyrase, therefore, blocking DNA replication [2]. Commonly used fluoroquinolones include ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, and norfloxacin. Patients, in particular athletes, should be warned of the risk of tendinopathy with fluoroquinolones which can occur within hours of initiating treatment and last months after cessation. Tendon rupture is the end result, and principally the Achilles tendon is most affected.

- Commonly Ciprofloxacin 500 mg BD is utilised in the treatment of UTIs.

4.5 Aminoglycosides

Aminoglycosides are natural or semisynthetic antibiotics derived from actinomycetes [3]. It is a bactericidal agent which inhibits bacterial protein synthesis by binding to the 30s ribosome subunit in the bacteria, leading to the misreading of mRNA. This misreading results in the synthesis of abnormal peptides which accumulate intracellularly and eventually lead to bacteria cell death. This class of antibiotics includes gentamicin, neomycin, amikacin, tobramycin, and streptomycin. This class of medications is well known to be associated with ototoxicity and nephrotoxicity. Clinicians need to exercise caution in prescribing this class of drug to elderly patients or patients with renal failure due to nephrotoxicity and when accumulated, the risk of ototoxicity.

- Commonly gentamicin is used as first line and is given according to lean body mass. The dosage varies from 3, 5 to 7 mg/kg depending on indication, disease severity, underlying renal disease and local policies.

4.6 Fosfomycin

Fosfomycin is an old antibiotic agent which was discovered in 1969 and it is a bactericidal antibiotic agent [4–6]. It works by inhibiting an important enzyme-catalyzed reaction in the first and crucial cytoplasmic step of the synthesis of the bacterial cell wall. Due to this unique mechanism of action, cross-resistance is unlikely; and, therefore, it allows fosfomycin to retain significant in vitro activity against many Gram-positive and Gram-negative pathogens.

- The usual dosage of Fosfomycin is 3 g stat.

4.7 Cephalosporin

Cephalosporin has a similar mode of action on bacteria as penicillin, but it is less susceptible to β-lactamases which are produced by bacteria [7]. Commonly, cephalosporins are grouped into "generations" by their antimicrobial properties. Essentially, each newer generation of cephalosporin has significantly greater Gram-negative antimicrobial properties than the preceding generation. The first cephalosporins were designated as first-generation cephalosporins, i.e. cefazolin and cephalexin. The second-generation cephalosporins, i.e. cefoxitin, cefaclor and cefuroxime have more extended-spectrum activity than the first-generation cephalosporins. Third-generation cephalosporins include ceftriaxone, cefotaxime and ceftazidime; while cefepime is a fourth-generation cephalosporin which has a very broad-spectrum activity.

4.8 Carbapenems

Carbapenems is another member of β-lactam antibiotics. Similar to other antibiotics in this class of antibiotics, carbapenems work by disrupting the bacterial cell wall synthesis. Of all the different β-lactams, carbapenems possess the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacteria [8]. Therefore, it is often used as the last line of antibiotics regime. Commonly used carbapenems include meropenem, ertapenem, imipenem and doripenem.

4.9 Multidrug-Resistance Bacteria

Unsurprisingly, in recent years, we have witnessed the rise and spread of multidrug-resistance bacteria such as extended-spectrum beta-lactamases (ESBL), vancomycin-resistant enterococci (VRE) and carbapenem-resistant enterobacteriaceae (CRE) globally [9]. Without any doubt, it is a very serious concern. Therefore, knowledge of the local epidemiology of multidrug-resistant bacteria is key in determining empirical antimicrobial therapy. Furthermore, in order to combat these multidrug-resistance bacteria, clinicians and scientists worldwide are racing against time to find new antibiotics. Several new drugs or drug combinations are being studied or currently in the market include new or old cephalosporins or carbapenems combined with new or old β-lactamase inhibitors, i.e. ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam; new aminoglycosides, i.e. plazomicin; and new fluoroquinolones, i.e. finafloxacin [10, 11]. Cefiderocol, which is a siderophore cephalosporin, is currently being studied to treat complicated urinary tract infections [12, 13]. The preliminary result of this trial is promising. We anticipate the results of this promising trial with much eagerness.

4.10 Antibiotics Prophylaxis

Recurrent UTI is defined as more than two infections in 6 months or three within 12 months. Clinical guidelines from European Association of Urology (EAU) [14] and the National Institute for Health and Care Excellence (NICE) [15] recommend several methods for preventing recurrent UTIs including avoidance of risk factors, vaginal oestrogens, immunoprophylaxis or long-term low-dose antibiotic prophylaxis.

Common long-term low-dose antibiotic prophylaxis regime include **nitrofurantoin 50 or 100 mg once daily, trimethoprim 100 mg once a day,** and **fosfomycin treatment 3 g every 10 days**.

Interestingly, although meta-analyses advocate the use of continuous antimicrobial prophylaxis for 6–12 months for the treatment of recurrent UTIs [16, 17], clinical guidelines usually only recommend a treatment period of 3–6 months. Studies by Price et al. [18] and Ahmed et al. [19] show that nitrofurantoin is superior to other antibiotics; however, it carries a higher risk of adverse events. For example, long-term use of nitrofurantoin could cause lung fibrosis. Therefore, clinicians should always exercise caution and counsel patients appropriately prior to starting them on long-term prophylactic nitrofurantoin.

Alternatively, in patients who have recurrent UTIs and perceived to have good compliance, clinicians could consider this group of patients to self-diagnose and self-treat with a short course of an antimicrobial agent.

Current 2019 EAU guidelines recommend the use of continuous or post-coital antibiotic prophylaxis to prevent recurrent UTIs when non-antimicrobial interventions have failed

- In these cases, it is essential to warn patients of long term side effects.

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