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Antimicrobial pharmacokinetics and preclinical *in vitro* models to support optimized treatment approaches for uncomplicated lower urinary tract infections

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Abstract

Introduction: Urinary tract infections (UTIs) are extremely common. Millions of people, particularly healthy women, are affected worldwide every year. One-in-two women will have a recurrence within 12-months of an initial UTI. Inadequate treatment risks worsening infection leading to acute pyelonephritis, bacteremia and sepsis. In an era of increasing antimicrobial resistance, it is critical to provide optimized antimicrobial treatment.

Areas covered: Literature was searched using PubMed and Google Scholar (up to 06/2020), examining the etiology, diagnosis and oral antimicrobial therapy for uncomplicated UTIs, with emphasis on urinary antimicrobial pharmacokinetics (PK) and the application of dynamic *in vitro* models for the pharmacodynamic (PD) profiling of pathogen response.

Expert opinion: The majority of antimicrobial agents included in international guidelines were developed decades ago without well-described dose–response relationships. Microbiology laboratories still apply standard diagnostic methodology that has essentially remained unchanged for decades. Furthermore, it is uncertain how relevant standard *in vitro* susceptibility is for predicting antimicrobial efficacy in urine. In order to optimize UTI treatments, clinicians must exploit the urine-specific PK of antimicrobial agents. Dynamic *in vitro* models are valuable tools to examine the PK/PD and urodynamic variables associated with UTIs, while informing uropathogen susceptibility reporting, optimized dosing schedules, clinical trials and treatment guidelines.

Keywords: Antimicrobial resistance, Drug development, *In vitro* infection models, Pharmacokinetics/pharmacodynamics, Urinary tract infection

Article highlights

- Urinary tract infections (UTIs) affect millions of people every year and are a common indication of antimicrobial use in the community and a potential driver for emergence of resistance.
- Yet, how we diagnose UTIs, report antimicrobial susceptibility and provide treatment recommendation are based on practices unchanged for decades and old pharmacokinetic (PK) and pharmacodynamic (PD) data.
- Greater understanding of the specific urinary PK characteristics of recommended oral antimicrobial agents and the interaction between the host and the uropathogen, can inform optimized selection and dosing when tackling multidrug resistant (MDR) phenotypes.
- The use of dynamic *in vitro* PK/PD models allows us to explore antimicrobial spectrum of activity, dosing and duration of therapy, and the drivers of emergence of resistance in a site-specific infection model.
- This robust preclinical data can promote the rational design of antimicrobial dosing, guide laboratory susceptibility testing and translate findings into clinical trials to inform treatment guidelines.

1. Introduction

Urinary tract infections (UTIs) annually affect 150 million people, with significant medical and financial implications [1-4]. More than 1-in-10 women report a UTI within the past year [5]. The incidence in premenopausal sexually active women is 0.5-0.7 cases/person-year [6]. For postmenopausal women, important risk factors are mechanical and physiological changes affecting bladder emptying [7]. Other risk factors include voiding abnormalities, diabetes, neurogenic bladder, pregnancy, obesity, renal tract calculi, prostate hypertrophy, urethral stents and indwelling catheters [8]. This review examines urinary pharmacokinetics (PK) of oral antimicrobial agents recommended for the treatment of uncomplicated UTIs in adults. We discuss how *in vitro* PK/pharmacodynamic (PD) models can be designed to inform optimized therapy (Fig. 1) [9,10].

2. UTI pathogenesis

Uropathogenic *Escherichia coli* (UPEC) is the causative pathogen of UTIs in approximately 70-80% of cases [2,11]. In a retrospective study examining urinary samples collected in emergency departments in Europe (2010-2016), isolate characteristics were: *E. coli* 67.6%, *Klebsiella* spp. 8.4%, *E. faecalis* 4.5%, *Proteus* spp. 3.8%, *Pseudomonas* spp. 2.4%, *Enterobacter* spp. 2.1% and *S. saprophyticus* 1.9% [12]. Urinary pathogens often originate in the gastrointestinal tract, migrate to the periurethral area and colonize the urethra. The proximity of the urethral opening to the vaginal cavity and rectum in women allows uropathogens to reach the bladder before removal by micturition [13]. Migration relies on bacterial expression of pili, flagella and adhesins recognizing uroepithelium, and metabolic adaptations allow for replication in the harsh urinary environment. Local invasion occurs by toxin and protease production [14]. A small proportion of *E. coli* are internalized into host cells, some can go onto form intracellular bacterial communities (IBCs) [15,16]. Invasion into deeper layers of the bladder wall can also occur, forming quiescent intracellular reservoirs [17]. Uropathogen proliferation can lead to ascending infection into the ureters and renal parenchyma, with bacteremia occurring by crossing the tubular epithelial barrier into the renal vasculature.

Natural protection from UTI relies upon host-factors of the bladder, innate immunity, urine composition and urodynamics. In 1961, Cox and Hinman [18] published a series of *in vitro* and induced human bacteriuria experiments, demonstrating the bladder's defense to infection. Increased fluid intake dilutes bacteria in the bladder and high-volume frequent urination can assist bacterial clearance. Under these dynamics, bacterial growth rate in urine is a critical factor. Urine, however, is depleted of nutrients and the low pH, high nitrates and high urea make it naturally antimicrobial. Moreover, it is an incredibly

complex biological waste product, containing over 2000 different metabolites/chemicals [19]. Specific alterations in urinary composition in different patient populations (e.g. trauma patients, elderly, diabetes) can promote uropathogen growth [20-22]. Urinary antimicrobial peptides are additional defenses to bacterial infection [23,24].

3. Initial assessment

The classification of UTIs into uncomplicated and complicated, although well established in clinical practice, may represent an over-simplification of the clinical syndrome [25,26]. In general, an uncomplicated UTI presumes infection is either confined to the bladder (uncomplicated cystitis) or an ascending infection (uncomplicated pyelonephritis) in a non-pregnant woman without factors that compromise normal host defenses [27]. A UTI in a male patient is commonly associated with anatomic/functional changes, or prostate involvement, and is often considered complicated.

UTIs are often empirically managed in the community without laboratory diagnostics. A urine culture can, however, provide confirmation of the diagnosis, organism identification and antimicrobial susceptibility [8,28]. Cultures are commonly requested only when the diagnosis is unclear or following a second UTI. An alternative approach has been to defer antimicrobials until culture and susceptibility are available, with or without the use of simple analgesics [29-33]. Studies examining such antimicrobial-sparing approaches have, however, reported increased rates of ascending infections in those not receiving antibiotics upfront [34-36].

When considering enrolment in epidemiological and interventional studies, the six symptoms of the Acute Cystitis Symptom Score (ACSS) have been shown to be strongly associated with UTI diagnosis (Table 1) [37]. European Medicines Agency (EMA) recommend that females enrolled into UTI studies should have frequency, urgency, dysuria and pyuria (≥10 WBCs/mm^3) in a midstream specimen [38]. Similarly, the US Food and Drug Administration (FDA) state that females should have evidence of pyuria and at least two of dysuria, urinary frequency, urinary urgency and suprapubic pain [39]. In contrast, pyelonephritis is commonly associated with fever, chills, rigors and flank pain.

4. Uropathogens and susceptibility testing

The urinary bladder is not sterile and contains its own diverse microbiome [40-42]. Asymptomatic bacteriuria can play a protective role in preventing UTI recurrences [43], and is only treated in specific situations (pregnancy, <1 month after kidney transplant, prior to invasive urological procedures) [44].

An optimally collected urine sample from a symptomatic patient is paramount for the clinical relevance of a culture result. An instructed collection of midstream urine, with prior skin cleansing preparation, can limit normal flora contamination. Samples should be collected prior to antimicrobials and should remain at room temperature for <30 minutes.

Standard urinary culture techniques have important limitations: failure to detect slow-growing, fastidious and non-aerobic microorganisms, inability to reliably detect microorganisms $<10^3$ cfu/mL, and difficulty differentiating pathogenic Gram-positive bacteria from normal flora [45]. Technological advancements have not been widely incorporated into practice, such as: next-generation urine point-of-care tests; urine biomarkers (differentiate between infection and colonization); flow cytometry; application of MALDI-TOF MS and molecular methods directly on urine, including Next-Generation-Sequencing [46].

The traditional urinary bacterial density threshold of $\geq 10^5$ cfu/mL to differentiate between infection and colonization is likely to be fundamentally flawed and may falsely exclude around 50% of patients with a probable diagnosis of an acute infection [37]. Lowering this threshold ($\geq 10^2$ cfu/mL) demonstrates higher sensitivity but risks over-diagnosis and unnecessary treatment [47]. Low levels of *E. coli* (10^1-10^2 cfu/mL) can represent an accurate diagnosis in symptomatic women [48]. Similarly, molecular techniques have identified *E. coli* where cultures were negative [49]. In contrast, significant quantities of *Enterococcus* spp. or Group B *Streptococcus* may still represent contaminating normal flora, highlighted where invasively collected cultures do not yield the same result as midstream collection, with the exception of *E. coli* that was consistently found in both samples [48]. It is also not infrequent to recover yeast in urine, even at high densities, but these patients seldom have a yeast UTI. An important caveat is where bacteriuria may reflect passive filtration from a hematogenous source, for example *Staphylococcus aureus* [50], *Candida* spp. [51] and *Cryptococcus* spp. [52], or represents renal parenchymal infection, as seen in *Burkholderia pseudomallei* [53,54], or evident of acute infection, or chronic carriage, with invasive *Salmonella* infections [55].

European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) report UTI breakpoints for some antimicrobials (e.g. nitrofurantoin, fosfomycin, trimethoprim, amoxicillin-clavulanate) [56,57]. In these instances, antimicrobial susceptibility results, determined by MIC or disk diffusion, relate only to uncomplicated UTIs and/or infections originating from the urinary tract. There are, however, inherent challenges in relating

susceptibility testing results in a nutrient-rich *in vitro* environment to the antimicrobial activity at the site of infection [58,59]. Furthermore, individual results have variability, both biological and technical, and do not directly relate to *in vivo* antimicrobial concentrations [60,61].

5. Antimicrobial resistance

In 2018, the European Antimicrobial Resistance Surveillance Network (EARS-Net) reported population-weighted mean resistance percentages in invasive *E. coli*, finding resistance to aminopenicillins in 57.4%, followed by fluoroquinolones in 25.3%, third-generation cephalosporins (3GC) in 15.1% and aminoglycosides 11.1%. Resistance to carbapenems remained rare. For invasive *K. pneumoniae*, resistance rates were higher, with resistance to 3GC in 31.7%, followed by fluoroquinolones in 31.6%, aminoglycosides in 22.7%, and carbapenems in 7.5%. There was significant variability between countries [62]. Increasing resistance overtime has also been observed. In the US, from 2003 to 2012, ciprofloxacin-resistance in urinary *E. coli* isolates rose from 3.6% to 11.8%, and trimethoprim-sulfamethoxazole resistance from 17.2% to 22.2% [63]. Interestingly, resistance to nitrofurantoin changed only slightly (0.7% to 0.9%). Similarly, in Belgium, multidrug resistant (MDR) *E. coli* prevalence increased from 28.4% to 34.3% from 2005 to 2011-12, however, susceptibility to nitrofurantoin (90%) was maintained [64]. In Australia, over a 5-year period (2013-2017) there was a significant rise in fluoroquinolone-resistance (*E. coli*: 6.5-9.0% to 10.0-12.3%; *K. pneumoniae*: 5.1-5.3% to 6.0-7.0%) despite no increase in use [65]. A progressive rise in antimicrobial resistance among enterococcal urinary isolates has also been observed. Vancomycin-resistant *Enterococcus* (VRE) now accounts for up to 80% of *E. faecium* isolates in some hospitals [66,67].

6. Treatment guidelines

The primary goals of treatment are to ameliorate UTI symptoms and reduce the risk of progressing to severe disease. Unnecessary antimicrobials should be avoided. When indicated, antimicrobials should ideally be administered as a single dose or short course therapy (3-5 days). Prolonged courses can be poorly tolerated, promote emergence of resistance [10] and increase the risk of recurrence due to alterations in normal flora [68-72]. Longer treatment durations are recommended for ascending infections, although this assertion has been recently challenged [73-76].

Although treatment guidelines optimize care on a population level, many variations exist between different countries, societies and jurisdictions (Table 2) [27,77-101]. In a European study, 13 different antimicrobials were recommended as first-line therapy across 15 national guidelines [100,102]. Similar

findings were found across different medical societies in the US [103]. The 2010 Infectious Diseases Society of America (IDSA)/European Society for Microbiology and Infectious Diseases (ESCMID) Uncomplicated Cystitis and Pyelonephritis guidelines are being updated, with an expected publication in 2022 [101]. A systematic review of randomized controlled trials of UTI treatment has challenged the durations of therapy adopted in clinical guidelines, suggesting that for some agents, shorter courses of therapy could recommended [104].

Adherence to guidelines is also suboptimal. In a US cohort of >600,000 healthy women with UTIs, over half were prescribed non-guideline-recommended antimicrobials, and three-quarters had treatment durations not consistent with the guidelines [105]. A 12-month review of US primary care clinics showed antimicrobials were optimally prescribed in only 29% of cases [106]. In Lebanon, appropriateness of prescriptions was only 21% (a composite of drug, dose and duration) [107]. In South Africa, 51.2% of errors were due to the incorrect treatment duration and 17.1% due to the incorrect drug [108]. In 2014, a European study revealed a range in adherence to guidelines, from 22.2% in Slovenia to 72.7% in the Netherlands [109]. In aged-care homes in Australia, antimicrobial selection, dose, frequency and duration was concordant with national recommendations in 22.3% of prescriptions [110]. Understanding why primary care providers make decisions is vital. A qualitative study identified areas for improvement, including awareness and familiarity with guidelines, attitudes to antimicrobial efficacy, impact of patient characteristics on choice of therapy and various other external barriers [111]. Antimicrobial package size has been linked to poor accordance with recommended treatment durations [112,113].

7. Antimicrobial urinary pharmacokinetics

High urinary antimicrobial concentrations are essential for efficacy in UTI treatment. In a rat model, systemically administered therapy only reaching the bladder tissue (and not the bladder lumen) was found to be insufficient for bacterial eradication [114]. In pyelonephritis, however, antimicrobial concentrations must also achieve adequate levels within the renal parenchyma, for which serum concentrations are used as a surrogate marker. Optimizing urinary antimicrobial exposures can restore the activity of narrow-spectrum agents. For example, a study of hospitalized elderly patients showed that a narrow-spectrum cephalosporin given intravenously (cefazolin) was non-inferior to fluoroquinolones [115]. This is despite many reports questioning the adequacy of β-lactam antibiotics [116,117] and surveillance studies reporting high resistance rates [12,118-120]. Where antimicrobial concentrations are high in urine, regardless of the susceptibility result, clinical efficacy has been

reported, such as amoxicillin for resistant *Enterococcus* spp. and doxycycline for *P. aeruginosa* [121-124]. Furthermore, changes in urinary pH (acidic or alkaline) can alter antimicrobial activity [125-130]. The following details the oral antimicrobials commonly recommended for UTIs (Fig. 2 [131]), highlighting the urinary drug concentrations and susceptibility testing criteria (Table 3) [56,57] and the EUCAST $MIC_{50/90}$ and epidemiological cut-off values (ECOFF) (Table 4a and 4b) [132,133].

7.1. Fosfomycin

Fosfomycin is the smallest of all antimicrobials (by molecular weight) with no cross-resistance with other classes. It acts by inhibiting cell wall synthesis by irreversibly inhibiting enolpyruvyl transferase that catalyzes the first step of peptidoglycan biosynthesis. Fosfomycin trometamol (synonym: tromethamine) is the common oral form. It has a wide spectrum against Gram-negative (especially *E. coli* isolates) and Gram-positive uropathogens (not including *S. saprophyticus*). The majority of extended-spectrum β-lactamase (ESBL)-producing *E. coli* and other MDR isolates have retained fosfomycin-susceptibility [134]. Activity against *K. pneumoniae* is less certain due to heteroresistance [135-139]. Similarly, monotherapy against *P. aeruginosa* isolates appears to be inadequate [140,141]. Fosfomycin has also been used for vancomycin-resistant *Enterococcus* (VRE) [142]. A 2016 review of fosfomycin susceptibility reported high levels of susceptibility across many uropathogens [143], although this observation is complicated by poor correlations between susceptibility methods and poor prediction of efficacy [138,144-146]. Resistance is mediated by a number of different mechanisms, including: mutations in transporter genes (*glpT* and *uhpT*) and their regulators, inactivation enzymes (*fos* genes), alteration of the active binding site (*murA*) and peptidoglycan recycling pathways [147].

Fosfomycin trometamol (Monurol®, Monuril®) is licensed as a single 3 g oral dose and rapidly achieves effective urinary concentrations for >24 h. Approximately 35-50% of the oral dose is excreted unchanged in the urine at a rate approximating creatinine clearance. There are marked variabilities in urinary concentrations after a standard dose, with an approximate average (range) peak concentration between 1000-2000 mg/L (600-3500 mg/L), occurring 4-8 h after dosing, with concentrations maintained >32 mg/L for >48 h [148-150]. Single dose therapy is beneficial for patient convenience and tolerance, limits emergence of resistance and minimizes collateral damage. Acidification increases activity (2-fold lower MIC) [128,134]. Most common side effects are nausea, vomiting and diarrhea. Several different repeat dosing regimens (daily, 48- or 72-hourly dosing for 3-7 days) have been used [151-154], although lack strong evidence and are associated with more diarrhea [149,155-157]. Although historically fosfomycin was reported with clinical success rates of >90%, more recently in a 2018

randomized controlled trial found the single 3 g dose resulted in 58% clinical resolution, compared to 70% with 5-days of nitrofurantoin [158].

7.2. Nitrofurantoin

Nitrofurans are synthetic compounds, of which nitrofurantoin is most widely used. Antimicrobial activity requires intracellular bacterial nitrofuran reductase enzymes for multiple mechanisms of action including binding to bacterial ribosomes and inhibiting synthesis of DNA, RNA and other metabolic enzymes [159]. It has activity against common uropathogens (*E. coli*, *E. faecalis* and *S. saprophyticus*), less certain activity against *Klebsiella* spp., and intrinsic resistance in *Proteus* spp., *Pseudomonas* spp. and *E. faecium*. Emergence of resistance is rare, with resistance rates commonly <5% [12,63,119,160] or <10% in MDR *E. coli* isolates [64]. Resistance is primarily due to a loss of intracellular nitroreductase activity (chromosomal *nfsA* and *nfsB*) purported to induce a fitness cost disturbing growth kinetics [161]. Plasmid encoded efflux pump, OqxAB, is an additional resistance mechanism [162].

Nitrofurantoin is available in different formulations: microcrystals (largely no longer available), macrocrystals (Macrodantin® or Furadantin®), monohydrate/macrocrystals (Macrobid® or Furabid®) and formulations marketed as "prolonged release" [163]. Dosing is dependent on the formulation. Macrocrystal formation is given 50-100 mg four-times-daily for 5-days. Long-acting formulations are given 100 mg twice-daily. Bioavailability is 20-30%, increasing to 40% when administered with food, and is rapidly excreted via the kidney, resulting in low serum concentrations and high urinary concentrations. Excretion is saturable, with equivalent urinary concentrations after 50 mg four-times-daily compared with 100 mg three-times-daily (macrocrystal formulation) [164]. Maximum urine concentrations are around 100 mg/L, but vary between 15-230 mg/L, occurring 3-10 h after dosing, but heavily dependent on formulation and fasting status [165]. Activity is enhanced under acidic conditions [166]. Nitrofurantoin is well tolerated with mild gastrointestinal side effects (in 5-16%). Severe toxicity (interstitial pneumonitis, liver toxicity, neurological reactions) appear to be extremely rare (0.001-0.0007% of courses of therapy) and mostly associated with prolonged duration of use (>6 months) [167,168]. Nitrofurantoin should be avoided in renal failure (creatinine clearance <30 mL/min) or G6P-dehydrogenase deficiency [163,169]. Clinical cure rates vary between 70% and 92% [158,159].

7.3. Pivmecillinam

Pivmecillinam is an amidinopenicillin, hydrolyzed by gut esterases to the active drug, mecillinam. It acts on the bacterial cell wall binding to penicillin-binding-protein (PBP)-2. Mecillinam is active against *E.*

coli, *Klebsiella* spp. and *P. mirabilis*, including ESBL-producing strains, without activity against *Pseudomonas* spp. or Gram-positive uropathogens [170]. Although, *in vivo* activity has been demonstrated against *S. saprophyticus* [171]. Despite 95% susceptibility in ESBL-producing urinary isolates [172], treatment failure has been reported in susceptible strains (44% treatment failure in ESBL; 14% in non-ESBL) [173]. Resistance can arise following permeability changes or β-lactamase enzymes. Pivmecillinam is not widely available outside of Scandinavia, Austria and Germany.

Dosing ranges from 200 mg twice-daily to 400 mg three-times-daily, with insufficient evidence to support the optimal combination of dose, frequency and duration [174]. Reports demonstrate similar cure rates to nitrofurantoin [175] and non-inferiority of 3-days of therapy compared to 5-days (73% versus 76% clinical success, respectively) using 400 mg three-times-daily [176]. Pivmecillinam has also been used successfully (>90%) to treat UTI in men [177]. Mecillinam is actively excreted by kidney tubules. The 12-24 h urinary recovery of unchanged mecillinam after 400 mg is 30-45% [178]. Maximum peak urinary concentration of 300 mg/L occur after 0-3 h, rapidly declines to 50 mg/L by 6 h and <5 mg beyond 12 h [179,180]. Adverse effects are commonly rash and gastrointestinal. Gastrointestinal side effects are more common (24%) at the higher dose.

7.4. Trimethoprim / Trimethoprim-sulfamethoxazole

Trimethoprim is a synthetic diaminopyrimidine agent, acting as a competitive inhibitor of dihydrofolate reductase (DHFR). Sulfamethoxazole, a sulphonamide agent, is a competitive inhibitor of dihydropteroate synthetase and enables synergistic activity by inhibiting different steps in tetrahydrofolic acid synthesis. These agents are active against *Enterobacterales* and *S. saprophyticus* isolates. There is uncertain activity against *Enterococcus* spp. and intrinsic resistance in *Pseudomonas* spp. Increasing resistance in *Enterobacterales* has limited empirical use [181,182]. Co-trimoxazole resistance in urinary isolates is around 20-40%, but can be greater in developing countries and carbapenem-resistant isolates [1,12,63,119,183-185]. Among *Enterobacterales*, the addition of sulfamethoxazole may not improve bacterial kill over trimethoprim alone, representing an unnecessary risk to many patients [186,187]. Resistance occurs by over-production or modification of target enzymes, reduced permeability and/or efflux pumps, and different *dfr*-genes encoding dihydrofolate reductase enzymes. Sulfamethoxazole-resistance is conferred by sulphonamide resistance genes (*sul*) acting as competitive inhibitors of dihydropteroate synthase. In *Enterobacterales*, resistance genes are mainly spread horizontally on integrons, commonly associated with co-resistance to β-lactams and fluoroquinolones.

Dosing of trimethoprim varies internationally from 100-200 mg twice-daily to 300 mg daily. Co-trimoxazole dosing is one 'double-strength' tablet/capsule (trimethoprim/sulfamethoxazole 160/800 mg) twice-daily. The 24 h urine excretion of trimethoprim corresponds to 61% of the total oral dose (200 mg). Of the excreted drug, around 90% is unchanged, the remainder as metabolites. Mean (±SD) urinary concentration of the unchanged drug is 36.7 mg/L (±21.9 mg/L) from 0-4 h and 38.6 mg/L (±16.9 mg/L) from 4-8 h [188]. Sulfamethoxazole is also mainly excreted in the urine, but only 30% is unchanged. The impact of pH is mixed, with trimethoprim activity enhanced in an alkaline environment, but with a concurrent reduction in urinary excretion [189]. Whereas an alkaline environment enhances sulfamethoxazole excretion. Therefore, the final ratio of trimethoprim and sulfamethoxazole can range from 1:1 in acid urine to 1:5 in alkaline urine [190]. Co-trimoxazole is associated with some severe adverse effects, including neurologic changes, decreased oxygen-carrying capacity and other hematologic effects, toxic epidermal necrolysis and other drug hypersensitivity reactions, reproductive abnormalities and hypoglycemia [191]. Hyperkalemia and acute kidney injury are seen more commonly in the elderly and in pre-existing renal impairment (creatinine clearance <60 mL/min) [192,193]. Cardiac arrythmias have been reported with concurrent use with drugs that block the renin-angiotensin system. Trimethoprim alone appears better tolerated, but acute kidney injury and hyperkalemia are still reported in patients aged >65 years [194].

7.5. Fluoroquinolones

Although highly efficacious, with reports of improved clinical outcomes compared to other agents [195,196], concerns regarding emergence of resistance and rare but serious side effects have seen fluoroquinolones commonly relegated to second-line, or reserve agents. Most treatment guidelines include norfloxacin, ciprofloxacin and levofloxacin, with newer agents less commonly available. Fluoroquinolones are derived from nalidixic acid and act by direct inhibitors of DNA synthesis, inhibiting DNA gyrase and topoisomerase IV. Emergence of resistance is primarily due to stepwise mutations in the quinolone resistance-determining region (QRDR) of chromosomal *gyr* and *par* genes, efflux pumps, Qnr proteins (protecting DNA gyrase) and inactivating enzymes. Resistance to fluoroquinolones among *Enterobacterales* has steadily increased overtime. The 2018 ECDC report showed 25.3% of invasive *E. coli* were resistant (7.2% in Iceland, up to 44.5% in Italy) and 31.3% in *K. pneumoniae* (0.3% in Iceland, up to 64.7% in Greece) [62]. A European UTI study reported resistance rates >20% [12,119] and 34% resistance among *E. coli* uropathogens in the US [185].

Recommended dosing of norfloxacin is 400 mg twice-daily. For ciprofloxacin and levofloxacin dosing varies from 250-750 mg twice-daily, with lower doses tended to be relied upon for UTI treatment, and higher doses for complicated infections or treatment of *Pseudomonas* spp. Three-day duration of therapy is commonly recommended, although for third- and fourth-generation agents, single dose therapy has been reported to be as equally effective [104]. Fluoroquinolones are predominately renally excreted by glomerular filtration and tubular secretion. For norfloxacin, 30% is excreted unchanged in the urine, with average peak urine concentrations of 30 mg/L occurring 1-2 h after administration. For ciprofloxacin, 50-75% is excreted unchanged in urine (15% as metabolites of limited activity), with >50% occurring in the first 4 h, and urinary concentrations at 6-12 hours following 250 mg of around 45-69 mg/L, and after 500 mg peak urine concentration of 200 mg/L. For levofloxacin, 80% of dose is recovered in urine after 24 h (metabolites <5%) and mean urinary concentrations after a 250 mg dose were 108 mg/L (0-12 h) and 63 mg/L (12-24 h). After a single 500 mg dose peak urine concentrations were 521-771 mg/L [192,197]. Most adverse events are mild and reversible, such as diarrhea, nausea and headaches, but serious adverse events and their low barrier to resistance, have promoted a Black Box warning [198] of collagen-associated adverse effects include aortic rupture, tendinitis and tendon rupture and retinal detachment (odds ratio: 2.2, 1.89 and 1.3, respectively) [199]. Other serious adverse events are seizures, depression, hallucinations, dysglycemia, hepatic toxicity, phototoxicity, renal impairment and QT prolongation [200].

7.6. Oral aminopenicillins

Ampicillin and amoxicillin are narrow-spectrum penicillins. Amoxicillin is preferred due to its better absorption. The addition of the β-lactamase inhibitor (BLI), clavulanate, increases the spectrum of activity by inhibiting some intrinsic and acquired narrow-spectrum β-lactamase enzymes. *E. faecalis* are commonly susceptible, whereas *E. faecium* are considered intrinsically resistant, with or without the addition of clavulanate, due to the production of PBP-5. *Pseudomonas* spp. are also intrinsically resistant. Acquired resistance among *Enterobacterales* is commonly due to β-lactamase enzymes. Although amoxicillin resistance is higher than amoxicillin-clavulanate, the fraction of amoxicillin-clavulanate susceptible strains that remain susceptible to amoxicillin alone can be >50% in *E. coli* urinary isolates, thereby limiting the need for clavulanate [201].

The usual adult oral dosage of amoxicillin is 250-500 mg, given three- to four-times daily, although PK/PD data would suggest that 500 mg given 8-hourly for 4-days would be the optimal dose for UTIs [202]. Amoxicillin-clavulanate is often dosed as a 4:1 ratio (500/125 mg), given twice or three-times

daily for UTI treatment. An alternate oral formulation contains a greater amount of amoxicillin, at a 7:1 ratio (875/125 mg). A recent review suggested that using the formulation with a narrower ratio (e.g. 4:1) and with more frequent dosing (three or four-times daily) is preferable, although the clavulanate component is dose-limiting due to intolerance [201]. Following oral administration, high amoxicillin urinary levels are found, with 60% of the dose excreted unchanged in urine in the first 6 h. Absorption is saturable, supporting more frequent dosing schedules, with no additional benefit of doses >750 mg per administration [201,203]. In healthy adults, peak urinary concentrations are 306-856 mg/L after 250 mg, and after 500 mg between 115-1850 mg/L [204,205]. Clavulanate has highly variable absorption. Only 28% (18-38%) of the dose is excreted unchanged in urine by 6 h, with hepatic clearance accounting for 50% of the absorbed dose and 30% protein-binding in serum [206,207]. Therefore, the ratio of amoxicillin to clavulanate in urine is different to that found systemically. Amoxicillin activity is largely unchanged in acidic conditions [208]. Side effects are mostly nausea, vomiting and diarrhea (2-5%) and eosinophilia (2%). Greater rates of side effects are found with the addition of clavulanate, especially diarrhea (9%) and increased hepatotoxicity. There is also greater microbiome impact with amoxicillin-clavulanate and higher risk of *C. difficile* [201].

7.7. Oral cephalosporins

Multiple different oral agents exist, although activity is increasingly limited due to resistance. Acquired resistance is essentially the same as the aminopenicillins, and all are hydrolyzed by broad-spectrum ESBLs (e.g. SHV-2 and CTX-M) and AmpC hyperproducers. All agents have no activity against *Enterococcus* spp. and *Pseudomonas* spp.. Assessment of clinical activity has demonstrated variable treatment responses when compared to comparator agents, although in older trials, clinical cure rates have been reported >70% [117,209-211]. Activity is enhanced under acidic conditions [208] and gastrointestinal disturbances are the most common adverse events.

Cephalexin is a limited-spectrum agent (first-generation cephalosporin, 1GC) and are more readily inactivated by narrow-spectrum TEM-1 β-lactamases. Cephalexin is commonly dosed at 500 mg twice-daily for UTI, however more frequent dosing would be more efficacious. Cephalexin is not metabolized and excreted in the urine unchanged by glomerular filtration and tubular secretion, such that 70-100% of the dose is found in the urine by 6-8 h. Urine concentrations are 500-1000 mg/L following 250-500 mg dose [212].

Second-generation cephalosporins (2GC), such as cefaclor, have increased activity against wild-type Gram-negative bacteria and are structurally similar to cephalexin with a chlorine atom replacing the methyl group. Cefaclor, commonly dosed 250 mg 8-hourly [213-215], or as a 2 g single-dose [216], achieves a mean peak urinary concentration of 482-684 mg/L after a 250 mg dose, and 1174-1533 mg/L after 500 mg, with 50-70% of the dose recovered in the urine by 4-6 h [217,218]. More recently, a 'modified release' formulation has been marketed [219].

Cefpodoxime, an oral 3GC, primarily targets PBP-3 and is characterized by stability against some acquired β-lactamase enzymes (including TEM-2 and SHV-1 enzymes). Reported resistance in urinary isolates is dependent on location (commonly 5-16%) [12,65,119,185]. In a EU-wide surveillance of invasive isolates, resistance in *E. coli* was 15.2% (range 5.7-35.5%) and in *K. pneumoniae* 31.2% (range 3.6-69.8%) [62]. Cefpodoxime is given as the pro-drug cefpodoxime proxetil and is commonly dosed between 100-200 mg twice-daily and has been found to be non-inferior to ciprofloxacin [117]. It is de-esterified by the intestinal mucosa, with 50% bioavailability and around 80% of the absorbed dose excreted unchanged in the urine [220]. Peak urine concentration range from 49 mg/L (50 mg dose) to 196 mg/L (800 mg dose) [221]. Following 200 mg, the mean (±SD) urine concentration was 19.8 mg/L (± 11.5 mg/L) in the 8-12 h time period and 3.9 mg/L after 12-24 h [222].

7.8. Nitroxoline

Nitroxoline is an old oral antimicrobial, although not widely available. It has broad activity against MDR uropathogens [223]. With a structurally distinct chemical structure, it is unrelated to other antimicrobial classes. Activity is mediated via multiple targets inducing chelation of metallic bivalent cations required for bacterial RNA polymerase and adhesion to bladder epithelial cells. Spectrum covers *Enterobacterales*, including MDR strains, and atypical uropathogens including *Mycoplasma hominis* and *Ureaplasma urealyticum*. Nitroxoline also has activity against *Candida* spp., while *Pseudomonas* spp. are intrinsically resistant. There is limited effect on the fecal flora [224]. Antibacterial activity appears to be static, and concerns about the inability to eradicate bacteriuria in a geriatric patient population has been reported [225]. Susceptibility of >3000 clinical UTI isolates from Germany between 2009-2012 showed >90% susceptibility in *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Enterobacter* spp., *S. saprophyticus* and *Enterococcus* spp. [226].

Standard dosing of nitroxoline is 250 mg three-times per day for 5-days. Approximately 60% of the administered dose is eliminated in the urine, 99% as conjugated metabolites (mainly nitroxoline sulfate

and nitroxoline glucuronide), which are considered to have antimicrobial activity [188]. After a single 250 mg dose, mean (± SD) peak urinary concentrations (at 0-4 h) of nitroxoline are 0.5 mg/L (± 0.37 mg/L) and of nitroxoline sulfate are 27.8 (± 7.4 mg/L) [188]. In a geriatric population, urinary concentrations of nitroxoline and nitroxoline sulfate were 0.1-5.4 mg/L and 0.8-210.6 mg/L, respectively [225]. Activity is enhanced in an acidic environment. Side effects are reported in 9.4% of patients, mainly mild gastrointestinal [224]. Efficacy in a meta-analysis of clinical data is reported at >90% and non-inferiority to co-trimoxazole and norfloxacin [224].

7.9. Tetracyclines

Although not included in most treatment guidelines, doxycycline is a therapeutic option for MDR uropathogens. The same is not true for other tetracycline agents, such as oral minocycline, oral eravacycline and intravenous tigecycline, all of which have minimal urinary excretion. Eravacycline was found to be inferior to levofloxacin in complicated UTIs, attributed to low bioavailability (28%) and a significant food effect limiting absorption [227]. Slightly more promising is oral omadacycline, a semisynthetic tetracycline derivative [228]. Tetracyclines inhibit microbial protein synthesis through interaction with 30S ribosomal subunit. Tetracyclines have a broad-spectrum of activity, including intracellular bacteria. Resistance is commonly associated with the acquisition of *tet* and *otr* genes encoding for efflux pumps or ribosomal protection proteins. Clinical and urinary *in vitro* activity has been reported against tetracycline-resistance bacteria, including *Pseudomonas* spp. that are considered intrinsically resistant [122,229].

Doxycycline is classically given as a loading dose of 100 mg twice-daily, then continued 100 mg daily. Limited guidance is provided for UTI treatment, but has been given for a duration of 4-days [230], or as a single 300 mg dose [231]. Concentration in serum is 4 mg/L, compared to >150 mg/L in urine [122]. Renal excretion accounts for 30-65% of the oral dose, which is reduced in renal impairment. Doxycycline has a prolonged serum half-life and activity is enhanced in acidic urine. Side-effects include gastrointestinal (including esophagitis) and photosensitivity. Omadacycline is given as a loading dose (300 mg or 450 mg twice-daily) and then continued daily (300 mg or 450 mg, respectively) for 5-days. Bioavailability is 35%. The fraction excreted in urine over 24 h is 34% of the absorbed dose [228]. Urinary concentrations (18-48 mg/L) may cover the omadacycline MIC_{90} for common uropathogens.

8. *In vitro* PK/PD bladder infection models

Translating PK/PD data from the bench to the bedside to optimize patient outcomes is now an established pathway for antimicrobial research and development [232-237]. PK/PD analyses can inform antimicrobial targets, susceptibility breakpoints, optimized dosing regimens and describe exposures associated with emergence of resistance [238-241]. Guidance is now provided on the approach for generating robust PK/PD data [242]. *In vitro* models have the advantage of directly mimicking human PK exposures to directly elucidate exposure-response relationships [243]. In contrast, animal models require sophisticated scaling in relation to dosing, PK and elimination [244,245].

In vitro PK/PD models can be classified according to whether antimicrobial concentrations change over time ("static" versus "dynamic") and whether there is bacterial loss in the system (Fig. 3) [243]. Usually, bacterial loss is unintended, or a source of bias. This was overcome by the hollow-fiber infection model (HFIM), which uses a separating capillary membrane to allow media and antibiotics to flow through central fibers and diffuse into the extra-capillary space where the microorganisms are trapped [242]. When investigating UTIs, however, normal urodynamics must be also considered. The dilution of bacteria during bladder filling and loss through voiding are important experimental elements unique to UTIs.

The first dynamic UTI *in vitro* model, designed in 1966 by O'Grady and Pennington (Fig. 4A) [246], used a vertical glass vessel, with a bacterial culture diluted over time with inflowing broth at a rate of 1 mL/min during the day and slowed overnight. At pre-set intervals, the vessel was emptied, leaving a residual volume. Turbidity measurements were taken to reflect bacterial density. The media used contained casitone pancreatic digest, yeast extract, glucose, K_2HPO_4, KH_2PO_4 and NaCl. Subsequently, the phosphate buffer was replaced with Tris buffer, while in later experiments Eugon broth was used. This model was updated (Fig. 4B) and used through to the 1990s, enabling the study of β-lactams, trimethoprim, co-trimoxazole, fluoroquinolones and fosfomycin [187,247-258].

In 1969, Rowe and Morozowich [259], applied drug distribution equations with consecutive first-order processes, in order to simulate dynamic drug concentration changes. The variables were the starting drug dose, *in vitro* flow rates and compartment volumes. This principle was used by Grasso *et al.* in 1978 (Fig. 4C) [260], with an open one compartment model simulating plasma cephalosporin concentrations after both intravenous and oral (or intramuscular) administration. A decade later, Satta *et al.* (Fig. 4D)

[261] used a similar model with human urine as the test medium, examining the activity of ampicillin, ceftriaxone, aztreonam and gentamicin against *E. coli*. Around the same time, urine was used in a one compartment model examining the activity of ampicillin, ciprofloxacin and co-trimoxazole compared to laboratory media [262]. Two decades later, the same model set-up was used again to examine fosfomycin activity against *E. coli* in standard laboratory media [263]. These models, however, all lacked the bladder emptying kinetics integral to earlier models.

In the late 1990s and early 2000s, a Japanese research group used a multicompartment dilution model of a "complicated" bladder infection (Fig. 4E) [264,265]. This design incorporated intermittent bladder voiding every 2 h during the day and a 10 h "night phase" without voiding. A relatively large post-void residual volume (10 mL) remained after each void. The activity of levofloxacin and gatifloxacin against *P. aeruginosa* and *E. faecalis* was investigated. Their model ran at 0.5 mL/min with Antibiotic Medium #3. In other iterations, glass beads were included within the bladder compartment to assess activity against biofilms (ofloxacin against *E. coli*; clarithromycin and fluoroquinolones against *P. aeruginosa*; clarithromycin against methicillin-resistant S. *aureus*) [266-269].

An alternative multicompartment infection model (Fig. 4F), applies a continuous dilution system that simulates oral antimicrobial absorption and elimination into 16 bladder compartments. This design enabled a higher throughput of bacterial strains to provide PK/PD data examining the efficacy of oral fosfomycin against different uropathogens (*E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, *E. faecalis, E. faecium*) [135,136,270,271] and following single and multiple doses [272]. The model was run with standard laboratory media, human urine and synthetic urine alternatives [273].

Most recently, a dynamic UTI "micromodel" has been used to analyze the impact of urinary flow on persistence of *E. coli* colonization [274]. This model uses transitional epithelial cells and type IV collagen. By simulating urinary tract shear stresses and flow velocities, they have examined the dynamics of *E. coli* cell adhesion, reporting a phenomenon of epithelial cell "rolling-shedding" that promotes bacterial attachment into deeper layers of epithelial cells.

Although *in vitro* UTI models mimic, as closely as possible, the conditions at the site of infection, important limitations apply to the translation of results to humans [58,275-277]. Immunological factors, host-pathogen interactions, pathological reactions to infection, tissue architecture, bacterial gene expression, virulence and metabolic changes are not easily simulated [11,24,278-280]. Equally, despite

urinary bladder containing a relatively low oxygen content (urinary PO_2 approximately 40 mmHg) [281-285], *in vitro* models are commonly held at normal atmospheric conditions.

8.1. Media

The environment in which bacteria are challenged with an antimicrobial is critical when considering their response. In a nutrient-rich environment, there is an evolutionary drive for bacteria to develop resistance. In contrast, in a nutrient-deficit environment, such as urine, there is greater propensity to alter metabolic pathways leading to persistence [286,287]. Collecting and using human urine in *in vitro* models is logistically challenging. Considerations include: collection method (midstream versus 24 h urine-collection); source (gender, age, dietary and fluid intake, number of volunteers, exclusion criteria); sterilization (autoclave, filtration, gamma-irradiation); storage (uncertain shelf life refrigerated or frozen); and reproducibility (variability between collections). Different chemical recipes for artificial alternatives have been suggested [288-295]. These media provide a reproducible way to examine growth kinetics and antimicrobial activity. Synthetic human urine (SHU) is the most recently developed medium [14].

8.2. Antimicrobial exposure

In humans, urinary antimicrobial concentrations are greatly impacted upon behavioral factors, such as fluid intake, urine output and voiding pattern. As such, most PK studies demonstrate marked inter-/intrapersonal variation. Considerations should be made to simulate high and low extremes. The free, unchanged, active drug present in urine should be simulated. Where active metabolites are also excreted, their contribution to the overall bacterial killing should be evaluated. Dose fractionation studies can be performed to examine the PK/PD index important for bacterial clearance. Studies performed over only 24 h may provide insufficient time for the amplification of a resistance subpopulation. Ideally, simulated treatment durations should mimic the therapy intended in the clinical indication.

8.3. Quantification of antimicrobial concentrations

In vitro antimicrobial concentrations should be measured to confirm that observed values match the simulation, while also providing data for analysis. Drug concentrations should be quantified multiple times during each dosing interval to detail the peak concentration, rate of decline and trough measurements. The method of quantification will depend on availability of resources. Direct quantification using a HPLC or LCMS method is preferable [296]. Biological assays using inhibition

zones of an indicator organism on solid agar may also be used [297,298]. Drug stability should be confirmed within the conditions of the *in vitro* model, or appropriate dose adjustments made.

8.4. Strain selection and starting inoculum

The selection of test isolates is paramount for analyzing experimental data to answer clinically relevant research questions. Multiple strains of the same, or different species, should be selected, based on the full range of susceptibility profiles to the test antimicrobial, including fully susceptible, low-level and high-level resistant isolates. Inclusion of clinical UTI strains in preferable, together with a reference control strain. To test resistance suppression, the number of bacteria added to the *in vitro* model is required to be 1 $\log_{10}$ CFU higher than the inverse of the mutant frequency [299,300]. The starting inoculum should be in log-growth phase prior to exposure to antimicrobials, therefore an initial period of drug-free incubation within the *in vitro* model should be observed.

8.5. Quantifying bacterial density and emergence of resistance

The bacterial response to antimicrobial exposure should be assessed at multiple timepoints. The standard method is quantitative cultures on antibiotic-free agar. Antibiotic carry-over should be addressed by serial dilution [263], repeat washing and centrifuge steps [301] and/or antimicrobial inactivation [302]. Other methods of bacterial density quantification for growth curve analysis include: turbidimetry, impedance, bioluminescence, phase-contrast microscopy, fluorimetric assays, microcalorimetry and flow cytometry [243,303-305]. Molecular techniques include, quantitative PCR (qPCR) using primers and probes targeting *hlyD* [306], bacterial growth assessments measuring plasmid segregation (pGTR902) and measuring chromosomal replication [307,308]. Emergence of resistance can be assessed by quantitative growth on agar supplemented with critical antimicrobial concentrations, incubated for 48-72 h [242]. Re-assessment of antimicrobial susceptibility can also be performed on the re-growth of bacteria over time. Whole genome sequencing of paired isolates (pre and post-exposure), quantitative gene expression and assessment of changes in metabolic pathways can also provide insights into the drivers of antimicrobial failure. Bacterial persistence and tolerance are other important factors to consider in the re-growth population [309,310].

9. Conclusions

To optimize UTI treatment, the correct antimicrobial, given at the right dose and for the shortest effective duration, should be individualized to the patient and the infecting uropathogen. Future advances could incorporate the presence of macrophages and bladder epithelial cell lines into existing *in*

vitro models [311-315]. With a greater appreciation of antimicrobial urinary PK and uropathogen susceptibility, bladder infection models can help establish robust drug-bug targets, inform UTI-specific breakpoints, define PK/PD targets for bactericidal activity and support dose-optimization in patients. Furthermore, the adequacy of current antimicrobial dosing and reported clinical success rates should be re-assessed, applying modern laboratory diagnostics and detailing activity in antimicrobial-resistant uropathogens.

10. Expert opinion

Understanding the exposure-response relationship at the site of infection, and the drivers that promote emergence of resistance, is crucial to prevent modern medicine slipping into a 'post-antibiotic' era. UTIs are a common indication for an antimicrobial. By optimizing therapy in this setting, we can benefit a large number of patients and reduce a major driver for the emergence of resistance. However, our understanding of the relationship between the host, urine composition, uropathogen growth, metabolism and virulence remains limited.

Novel antimicrobial agents hold some promise for the future, although clinical trials are needed. In 2020, the WHO published a target product profile to guide the urgent development of new oral antimicrobial agents for UTIs, which, in turn, would benefit from assessment within a dynamic bladder infection PK/PD *in vitro* model [316]. Novel oral β-lactamase inhibitor combinations can expand the antimicrobial activity against ESBL-producing uropathogens [209]. 3GC agents (cefpodoxime and ceftibuten) have been paired with β-lactamase inhibitors such as QPX7728, ETX0282 and VNRX7145, while ceftibuten has been paired with clavulanate [317-320]. In addition, an orally absorbed derivative of avibactam has been developed [321], and oral carbapenems, sulopenem and tebipenem, are under investigation [322,323].

The management of recurrent UTIs has attracted novel therapeutic approaches, such as behavior and dietary interventions, probiotics, phytotherapy, D-mannose, methenamine hippurate, vaginal estrogens and intravesical glycosaminoglycans [324]. Of particular interest are the studies into immunotherapies that stimulate the host's immune response (e.g. bacterial lysates, oral immunostimulants and vaccines) [325,326], bacterial interference by the deliberate colonization of the bladder with an asymptomatic bacteriuria strain [327,328], fecal microbiota transplantation [329-332] and bacteriophage therapy [333-335].

More robust and contemporary bladder infection *in vitro* models will continue to inform antimicrobial PD profiling and the setting of urine-specific susceptibility breakpoints. In the future, a symptomatic patient will have access to a rapid diagnosis that differentiates infection from colonization and provides a risk profile for ascending infection. Uropathogens will have an antimicrobial susceptibility profile specific to the urinary tract. Updated international guidelines will provide antimicrobial dosing and duration recommendations that consider urinary PK, while minimizing emergence of resistance and microbiome disruption. With AMR forcing reliance on broad-spectrum antimicrobials, novel approaches targeting the host–pathogen interface, such as bacterial virulence, antimetabolites and alterations to urine composition, will be valuable antimicrobial-sparing tools.

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REFERENCE ANNOTATIONS

[11] ** In-depth and informative basic science review of UTIs pathogenesis and the host-pathogen interface.

[14] * Review of urinary biochemical make-up and development of a new synthetic alternative medium.

[15] ** Comprehensive review on uropathogenic *Escherichia coli* and the metabolic factors integral for rapid growth and success as a pathogen in humans.

[18] * An old *in vitro* and *in vivo* study demonstrating the protective aspects of the bladder and urodynamics in preventing UTIs. Interestingly, this study included the direct bacterial inoculation of the bladders of healthy male volunteers.

[27] * A very informative, practical and evidence-based web-resource detailing UTI treatment recommendation and narrative.

[42] * An in-depth review article examining the microbiome of the urinary tract, the role in maintaining urinary health and interaction with the host.

[45] ** Highlights the major limitations in contemporary UTI description: the language of UTI, UTI diagnostic testing, the *Escherichia coli*-centric view of UTI, and the CFU threshold-based diagnosis.

[104] * A large systematic review that challenges the evidence for treatment durations adopted in clinical management guidelines.

[208] * An interesting article offering an alternative perspective on UTI treatment based on urinary PK characteristics of antimicrobial agents, with therapeutic success regardless of *in vitro* susceptibility result.

[209] * Informative and practical review on UTI treatment with oral cephalosporins and their enhanced activity when combined with novel oral beta-lactamase inhibitors.

[238] * Insightful article putting into perspective how each component of PK/PD research relates to each other in the process of setting clinical susceptibility breakpoints.

[242] ** Fantastic resource for *in vitro* and *in vivo* PK/PD experiment work that outlines important considerations for the design and analysis of research in this area.

[243] ** A thorough, clear and explanatory review of the different pharmacodynamic *in vitro* models, their design aspects and perspectives on *in vitro* investigations in drug discovery and clinical research.

[246] * The “original” UTI *in vitro* PK/PD model.

[259] ** Provides the mathematical foundation for simulating dynamic *in vitro* antimicrobial exposures.

[274] * “Next-generation” dynamic *in vitro* model that incorporates both the immune system and human cells.

[276] * Antimicrobial susceptibility testing performed in media mimicking host environments to better identifying specific antimicrobials effective in bacterial clearance.

[309] ** A consensus statement on the definitions of bacterial persistence and the impact upon antimicrobial therapy.

[310] ** A comprehensive overview on bacterial persistence including the eco-evolutionary aspects relating to how persistence evolves in the face of treatment with antibiotics.

TABLES

Table 1. Acute Cystitis Symptom Score (ACSS) Questionnaire

Domain 1: Typical
Urinary frequency
Urgency
Dysuria
Incomplete bladder emptying
Suprapubic pain
Hematuria
Domain 2: Differential
Flank pain
Vaginal discharge
Urethral discharge
Fever
Domain 3: Quality of life
Level of discomfort
Impact on work/everyday activities
Impact on social life
Domain 4: Additional
Menstruation
Premenstrual symptoms
Menopausal symptoms
Pregnancy
Diabetes mellitus
Follow-up: Dynamics
Changes in symptoms

The ACSS contains 18 questions divided into 4 domains used at the first visit: typical acute cystitis symptoms, differential diagnosis symptoms, impact on quality of life and additional relevant questions. The first 3 domains are scored on a severity scale and totaled (0 = no, 1 = mild, 2 = moderate, 3 = severe), while the remaining are 'Yes/No' answers. The same questionnaire can also be used on follow-up. The follow-up dynamics domain details the overall impression of any changes in symptoms (0 = all symptoms resolved, 1 = majority of symptoms resolved, 2 = majority of symptoms still present, 3 = no change in symptoms, 4 = worsening of symptoms). The questionnaire has been translated into multiple different languages. Adapted from http://www.acss.world/index.html [37].

Table 2. Comparison of international antibiotic treatment guideline recommendations for uncomplicated UTI[a]

	FOT	NIT	PIV	TMP	SXT	QIN	AMX	AMC	1/2GC	3GC	Other	Ref.
EAU (2019)	(1)	(1)	(1)	(2)[c]	(2)[c]				(2)		(2) cefadroxil	[27]
International (UpToDate 2019)	(1)[b]	(1)	(1)	(1)	(1)	(3)		(2)	(2)	(2)		[77]
International (Sanford 2019)	(1)	(1)	(2)		(1)	(2)		(2)	(2)	(2)		[78]
Australia / NZ (eTG 2019)	(3)	(1)		(1)	(2)	(3)	(2)	(2)	(1)			[79]
India (2019)	(1)[b]	(1)			(2)						(2) ertapenem, amikacin	[80]
UK (NICE 2018)	(2)	(1)	(2)	(1)								[81]
France (2018)	(1)	–[d]	(2)	–[e]	–[e]	–[f]						[82]
Asia (2018)	(1)	(1)			(1)	(2)		(1)	(1)	(2)		[83]
Korea (2018)	(1)	–[g]	–[h]		(2)[i]	(1)		(2)[i]		(1)		[84]
Germany (2017)	(1)	(1)	(1)	(2)[c]	(2)	(3)				(3)	(1) nitroxoline	[85]
Canada (2017)	(1)	(1)		(1)	(1)	(2)						[86]
Russia (2017)	(1)	(1)				(2)				(2)	(1) furazidin	[87]
Sweden (2017)		(1)	(1)	(2)[i]						(2)		[87]
Spain (2017)	(1)	(1)			–[j]	(2)	–[k]	(3)		(3)		[88]
Denmark (2016)			(1)	(1)							(1) sulfametizole	[89]
Norway (2016)		(1)	(1)	(1)		(2)						[90]
Belgium (2016)	(2)	(1)		(2)								[91]
Serbia (2016)	(1)	(1)			(1)	(2)		(2)	(2)			[92]
Japan (2015)	(2)					(1)		(2)	(2)	(2)	(2) faropenem	[93]
Sth Africa (2014/15)	(2)	(2)				(1)		(2)				[94,95]
Finland (2015)	–[l]	(1)	(1)	(1)		(2)	(2)	(2)		(2)		[87]
Poland (2015)	(1)	(1)		(1)	(1)	(2)		(2)			(1) furazidin	[87]
Croatia (2014)	(1)	(1)				(3)		(2)	(2)	(2)		[96]
Switzerland (2014)	(1)	(1)			(1)	(2)		(2)	(2)			[97]
Netherlands (2013)	(2)	(1)		(3)								[98]
Austria (2012)	(1)		(1)			(1)						[99,100]
IDSA/ESCMID (2010)	(1)	(1)	(1)		(1)	(2)		(2)	(2)	(2)		[101]

FOT, fosfomycin. NIT, nitrofurantoin. PIV, pivmecillinam. TMP, trimethoprim. SXT, trimethoprim-sulfamethoxazole. QIN, fluoroquinolone. AMX, amoxicillin. AMC, amoxicillin-clavulanate. 1GC, first-generation cephalosporin. 2GC, second-generation cephalosporin. 3GC, third-generation cephalosporin. EAU, European Association of Urology. [a], Recommended first-line (1, green), second-line alternative (2, yellow) and third-line/reserve alternative (3, grey) agents. [b], Suggest reserving use of fosfomycin for documented MDR infections, or when other first-line agents cannot be used. [c], Only if local resistance in *E. coli* is < 20%. [d], Not recommended for regulatory reasons (very rare but risk of severe toxicity). [e], Not recommended due to resistance rates close to 20%. [f], Not recommended because of their selection pressure and preference to be saved for more severe infections. [g], Not routinely available in Korea; introduction urgently recommended as a first-line agent. [h], Not routinely available in Korea; recommended for introduction but to be used with caution. [I], Recommended only after susceptibility testing. [j], Trimethoprim/sulfamethoxazole not recommended for empiric therapy because resistance rates in *E. coli* is > 20% in Spain. [k], Ampicillin and amoxicillin not recommended given the high incidence of resistance. [i], Fosfomycin not licensed in Finland.

Table 3. Uncomplicated UTI treatment: antimicrobial dosing, susceptibility interpretation and pharmacokinetics

Antimicrobial	Recommended dose	Susceptibility breakpoints[a]		Pharmacokinetics (mg/L, unless otherwise stated)	Comments
		MIC (mg/L or µg/mL)	Disk diffusion diameter (mm)		
Fosfomycin					
Fosfomycin trometamol	3 g D Duration: SD	**EUCAST:**		Plasma C_{max}: 26.1 Plasma $t_{½}$: 4.5-9h Urine C_{max}: 1000-2000 Urine AUC_{0-24}: 8000-20,000mg.h/L Urine recovery: 35-50% (unchanged)	*S. saprophyticus* intrinsically resistant. G6P enhances activity in most *Enterobacterales*. No enhancement with *Enterococcus* or *Pseudomonas* spp.. Agar dilution with 25 mg/L G6P required for MIC. Fosfomycin 200 µg disk contains 50 µg G6P. EUCAST ignore isolated colonies with inhibition zone, CLSI read inner diameter.
		Enterobacterales [UTI]: S ≤ 32; R > 32	*E. coli* [UTI]: S ≥ 24; R < 24		
		Pseudomonas: ECOFF = 128	*Pseudomonas*: ECOFF = 12		
		CLSI:			
		E. coli [UTI]: S ≤ 64; R ≥ 256	*E. coli* [UTI]: S ≥ 16; R ≤ 12		
		E. faecalis [UTI]: S ≤ 64; R ≥ 256	*E. faecalis* [UTI]: S ≥ 16; R ≤ 12		
Nitrofurans					
Nitrofurantoin - Macrocrystal - Monohydrate macrocrystal, or prolonged-release	50 - 100 mg QID 100 mg BID Duration: 5 days	**EUCAST:**		Plasma C_{max}: <2 Plasma $t_{½}$: 1.7-2.3h Urine C_{max}: 50-250 Urine recovery: 50% (unchanged) Urine AUC_{0-24}: 900mg.h/L	EUCAST consider *E. faecium* to have intrinsic resistance. *Proteus* and *Pseudomonas* spp. also intrinsically resistant. Absorption enhanced with food. Urinary excretion is saturable (50 mg QID = 100 mg TID). EUCAST nitrofurantoin disk content is 100 µg, CLSI uses 300 µg.
		E. coli [UTI]: S ≤ 64; R > 64	*E. coli* [UTI]: S ≥ 11; R < 11		
		E. faecalis [UTI]: S ≤ 64; R > 64	*E. faecalis* [UTI]: S ≥ 15; R < 15		
		S. saprophyticus [UTI]: S ≤ 64; R > 64	*S. saprophyticus* [UTI]: S ≥ 13; R < 13		
		CLSI:			
		Enterobacterales [UTI]: S ≤ 32; R ≥ 128	*Enterobacterales* [UTI]: S ≥ 17; R ≤ 14		
		Enterococcus [UTI]: S ≤ 32; R ≥ 128	*Enterococcus* [UTI]: S ≥ 17; R ≤ 14		
		Staphylococcus [UTI]: S ≤ 32; R ≥ 128	*Staphylococcus* [UTI]: S ≥ 17; R ≤ 14		
Antifolate agents					
Trimethoprim	100 - 200 mg BID (Alt: 300 mg D) Duration: 3 - 5 days	**EUCAST:**		Trimethoprim: Plasma C_{max}: 1.5-2 (46-70% protein bound) Plasma $t_{½}$: 10-12h Urine C_{max}: 100 Urine recovery: 40-60%	Activity uncertain to predict clinical outcome against *Enterococci*; CLSI report intrinsic resistance. *Pseudomonas* spp. intrinsically resistance.
		Enterobacterales [UTI]: S ≤ 4; R > 4	*Enterobacterales* [UTI]: S ≥ 15; R < 15		
		Enterococcus [UTI]: ECOFF = 1	*Enterococcus* [UTI]: ECOFF = 21		
		Staphylcoccus [UTI]: S ≤ 4; R > 4	*Staphylococcus* [UTI]: S ≥ 14; R < 14		
		CLSI:			
		Enterobacterales [UTI]: S ≤ 8; R ≥ 16	*Enterobacterales* [UTI]: S ≥ 16; R ≤ 12		

		Staphylococcus [UTI]: S ≤ 8; R ≥ 16	*Staphylococcus* [UTI]: S ≥ 16; R ≤ 10	(unchanged)	EUCAST test TMP/SMX in the ratio 1:19 and report TMP concentration.
Trimethoprim-sulphameth-oxazole	180 + 600 mg BID Duration: 3 days	**EUCAST:**		Sulphamethoxazole: Plasma C_{max}: 45-50 (66% protein bound) Plasma $t_{½}$: 10-12h Urine C_{max}: 40-320 (if high dose used) Urine recovery: 46% (only 30% unchanged)	
		Enterobacterales: S ≤ 2; R > 4	*Enterobacterales*: S ≥ 14; R < 11		
		Enterococcus: ECOFF MIC = 1	*Enterococcus*: ECOFF = 23		
		Staphylococcus: S ≤ 2; R > 4	*Staphylococcus*: S ≥ 17; R < 14		
		CLSI:			
		Enterobacterales: S ≤ 2/38; R ≥ 4/76	*Enterobacterales*: S ≥ 16; R ≤ 10		
		Staphylococcus: S ≤ 2/38; R ≥ 4/76	*Staphylococcus*: S ≥ 16; R ≤ 10		
Fluoroquinolones					
Norfloxacin	400 mg BID Duration: 3 days	**EUCAST:**		Norfloxacin: Plasma C_{max}: 1.58 Plasma $t_{½}$: 3.5-5h Urine C_{max}: 30 Urine recovery: 24-30% (unchanged)	Norfloxacin can be used as a screen for other fluoroquinolones. Note differences between EUCAST and CLSI dosing of ciprofloxacin and levofloxacin. EUCAST recommend high dose for *Pseudomonas* and *Staphylococcus* spp. CLSI recommend for levofloxacin 750 mg daily and, for *Pseudomonas* spp. ciprofloxacin 400 mg q8 intravenous
		Enterobacterales [UTI]: S ≤ 0.5; R > 0.5	*Enterobacterales* [UTI]: S ≥ 22; R < 22		
			Enterococcus (screen): S ≥ 12; R < 12		
			Staphylococcus (screen): S ≥ 17; R < 17		
		CLSI:			
		Enterobacterales [UTI]: S ≤ 4; R ≥ 16	*Enterobacterales* [UTI]: S ≥ 17; R ≤ 12		
		Pseudomonas [UTI]: S ≤ 4; R ≥ 16	*Pseudomonas* [UTI]: S ≥ 17; R ≤ 12		
		Enterococcus [UTI]: S ≤ 4; R ≥ 16	*Enterococcus* [UTI]: S ≥ 17; R ≤ 12		
		Staphylococcus [UTI]: S ≤ 4; R ≥ 16	*Staphylococcus* [UTI]: S ≥ 17; R ≤ 12		
Ciprofloxacin	250-500 mg BID (HD: 750 mg BID) Duration: 3 days	**EUCAST:**		(Dose: 250 mg) Plasma C_{max}: 0.8-1.9 Plasma $t_{½}$: 5-6h Urine C_{max}: 45-69 Urine recovery: 50-75% (15% as metabolites)	
		Enterobacterales: S ≤ 0.25; R > 0.5	*Enterobacterales*: S ≥ 25; R < 22		
		Pseudomonas: S ≤ 0.001; R > 0.5	*Pseudomonas*: S ≥ 50; R < 26		
		Enterococcus [UTI]: S ≤ 4; R > 4	*Enterococcus* [UTI]: use NOR screen		
		Coag-neg *Staph.*: S ≤ 0.001; R > 1	Coag-neg *Staph.*: S ≥ 50; R < 24		
		CLSI:			
		Enterobacterales [IE]: S ≤ 0.25; R ≥ 1	*Enterobacterales* [IE]: S ≥ 26; R ≤ 21		
		Pseudomonas [IV]: S ≤ 0.5; R ≥ 2	*Pseudomonas* [IV]: S ≥ 25; R ≤ 18		
		Enterococcus [UTI]: S ≤ 1; R ≥ 4	*Enterococcus*: S ≥ 21; R ≤ 15		
		Staphylococcus: S ≤ 1; R ≥ 4	*Staphylococcus*: S ≥ 21; R ≤ 15		
Levofloxacin	250-750 mg D (HD: 500 mg BID) Duration: 3 days	**EUCAST:**		(Dose: 250 mg) Plasma C_{max}: 2.8 Plasma $t_{½}$: 6-8h Urine C_{max}: 108 Urine recovery: 80% (unchanged, <5% as metabolites)	
		Enterobacterales: S ≤ 0.5; R > 1	*Enterobacterales*: S ≥ 23; R < 19		
		Pseudomonas: S ≤ 0.001; R > 1	*Pseudomonas* (HE): S ≥ 50; R < 22		
		Enterococcus [UTI]: S ≤ 4; R > 4	*Enterococcus* [UTI]: use NOR screen		
		Coag-neg *Staph.*: S ≤ 0.001; R > 1	Coag-neg *Staph.*: S ≥ 50; R < 24		
		CLSI:			
		Enterobacterales (IE): S ≤ 0.5; R ≥ 2	*Enterobacterales* (IE): S ≥ 21; R ≤ 16		

		Pseudomonas (IE): S ≤ 1; R ≥ 4	*Pseudomonas* (IE): S ≥ 22; R ≤ 14		
		Enterococcus [UTI]: S ≤ 2; R ≥ 8	*Enterococcus*: S ≥ 17; R ≤ 13		
		Staphylococcus: S ≤ 1; R ≥ 4	*Staphylococcus*: S ≥ 19; R ≤ 15		
Beta-lactams: Penicillins					
Pivmecillinam	400 mg TID Duration: 3 days	**EUCAST:**		Mecillinam: Plasma C_{max}: 2.5 Plasma $t_{½}$: 1h Urine C_{max}: 300 Urine recovery: 30-45% (unchanged)	*Pseudomonas* spp. are intrinsically resistant. All β-lactams have optimal activity by prolonged T > MIC. Pivmecillinam is a prodrug of mecillinam with activity against ESBL-producing organisms. EUCAST report mecillinam breakpoints for *E. coli*, *Citrobacter* spp., *Klebsiella* spp., *Raoultella* spp., *Enterobacter* spp. and *Proteus mirabilis*. Results for ampicillin (AMP) testing can be used to predict results for amoxicillin. Oral amoxicillin dosing considered only appropriate for UTIs. EUCAST used a fixed 2mg/L concentration for clavulanate, whereas CLSI apply a 2:1 ratio.
		Enterobacterales [UTI]: S ≤ 8; R > 8	*Enterobacterales* [UTI]: S ≥ 15; R < 15		
		CLSI:			
		E. coli [UTI]: S ≤ 8; R ≥ 32	*E. coli* [UTI]: S ≥ 15; R ≤ 11		
Amoxicillin	500 mg TID Duration: 5 days	**EUCAST:**		Plasma C_{max}: 8-10 Plasma $t_{½}$: 1h Urine C_{max}: 115-1850 Urinary excretion: 60% (unchanged)	
		Enterobacterales [UTI]: S ≤ 8; R > 8	*Enterobacterales* [UTI]: S ≥ 14; R < 14 (AMP)		
		Enterococcus [UTI]: S ≤ 4; R > 8	*Enterococcus* [UTI]: S ≥ 10; R < 8 (AMP)		
		-	*S. saprophyticus*: S ≥ 18; R < 18 (AMP)		
		CLSI:			
		Enterobacterales: S ≤ 8; R ≥ 32 (AMP)	*Enterobacterales*: S ≥ 17; R ≤ 13 (AMP)		
		Enterococcus: S ≤ 8; R ≥ 16 (AMP)	*Enterococcus*: S ≥ 17; R ≤ 16 (AMP)		
		Staphylococcus: S ≤ 0.12; R ≥ 0.25 (PEN)	*Staphylococcus*: S ≥ 29; R ≤ 28 (PEN)		
Amoxicillin-clavulanate[b]	500 + 125 mg TID Duration: 5 days	**EUCAST:**		Clavulanate: Plasma C_{max}: 3.5 Plasma $t_{½}$: 1h Urine recovery: 18-38% (unchanged) Relatively unstable at 37°C	
		Enterobacterales [UTI]: S ≤ 32; R > 32	*Enterobacterales* [UTI]: S ≥ 16; R < 16		
		Enterococcus [UTI]: S ≤ 4; R > 8	*Enterococcus* [UTI]: S ≥ 10; R < 8		
		-	*S. saprophyticus*: S ≥ 18; R < 18		
		CLSI:			
		Enterobacterales: S ≤ 8/4; R ≥ 32/16	*Enterobacterales*: S ≥ 18; R ≤ 13		
		Enterococcus: S ≤ 8; R ≥ 16 (AMP)	*Enterococcus*: S ≥ 17; R ≤ 8 (AMP)		
		-	*S. saprophyticus*: S ≥ 25; R ≤ 24 (FOX)		
Beta-lactams: Cephalosporins					
Cephalexin 1st Gen. (1GC); Limited spectrum	500 mg BID Duration: 5 days	**EUCAST:**		Plasma C_{max}: 15-18 Plasma $t_{½}$: 1h Urine C_{max}: 500-1000 Urinary recovery: 70-100% (unchanged)	*Enterococcus* and *Pseudomonas* spp. are intrinsically resistant. Cefadroxil is another 1GC. Cefuroxime axetil (2GC) offers limited benefit over 1GC agents for UTIs. Cefaclor (2GC) have some improved Gram-negative
		Enterobacterales [UTI]: S ≤ 16; R > 16	*Enterobacterales* [UTI]: S ≥ 14; R < 14		
		S. saprophyticus: R > 8	*S. saprophyticus*: S ≥ 22; R < 22 (FOX)		
		CLSI:			
		Enterobacterales [UTI]: S ≤ 16; R ≥ 32 (CFZ)	*Enterobacterales* [UTI]: S ≥ 15; R ≤ 14 (CFZ)		
		-	*S. saprophyticus:* S ≥ 25; R ≤ 24 (FOX)		
Cefaclor 2nd Gen. (2GC);	250 mg TID	**EUCAST:**		Plasma C_{max}: 10.6 Plasma $t_{½}$: 1h	
		S. saprophyticus: R > 8	*S. saprophyticus*: S ≥ 22; R < 22 (FOX)		

Improved Gram-negative cover	Duration: 5 days (Alt. 2 g SD)	**CLSI:**		Urine C_{max}: 482 Urinary recovery: 70% (unchanged)	cover. EUCAST does not provide breakpoints for Cefaclor. Susceptibility in *S. saprophyticus* is inferred from cefoxitin. CLSI use cephazolin (CFZ) to predict susceptibility oral cephalosporins; may overcall resistance for 3GC. Other oral 3GC include: ceftibuten, cefdinir.
		Enterobacterales [UTI]: S ≤ 16; R ≥ 32 (CFZ)	*Enterobacterales* [UTI]: S ≥ 15; R ≤ 14 (CFZ)		
		-	*S. saprophyticus:* S ≥ 25; R ≤ 24 (FOX)		
Cefpodoxime 3rd Gen. (3GC); Broad spectrum	200 mg BID Duration: 3 days (Alt. 100 mg BID)	**EUCAST:**		Plasma C_{max}: 2-4 Plasma $t_{½}$: 2.7h Urine C_{max}: 19.8 (200 mg) Urinary recovery: 40% (unchanged)	
		Enterobacterales [UTI]: S ≤ 1; R > 1	*Enterobacterales* [UTI]: S ≥ 21; R < 21		
		-	*S. saprophyticus*: S ≥ 22; R < 22 (FOX)		
		CLSI:			
		Enterobacterales: S ≤ 2; R ≥ 8	*Enterobacterales*: S ≥ 21; R ≤ 17		
		-	*S. saprophyticus*: (FOX) S ≥ 25; R ≤ 24		
Other agents					
Nitroxoline	250 mg TID Duration: 5 days	**EUCAST:**		Plasma C_{max}: 5-9.5 (uncj.) Plasma $t_{½}$: 2h Urine C_{max}: 0.5 (uncj.); 28 (conj. nitroxoline sulfate) Urinary recovery: 60% (99% conjugated metabolite)	*Pseudomonas* intrinsically resistant. Not widely available. CLSI do not report susceptibility.
		E. coli [UTI]: S ≤ 16; R > 16	*E. coli* [UTI]: S ≥ 15; R < 15		
		Enterococcus [UTI]: IE	*Enterococcus* [UTI]: IE		
		S. saprophyticus [UTI]: IE	*S. saprophyticus* [UTI]: IE		
Doxycycline	100 mg BID load, then 100 mg daily Duration: 4 days (Alt: 300 mg SD)	**EUCAST:**		Plasma C_{max}: 2.6-4.2 Plasma $t_{½}$: 14h Urine C_{max}: 300 Urinary recovery: 35-40% (unchanged)	May still be effective against resistant uropathogens (including. *Pseudomonas* spp.) due to high urinary concentration. Very limited guidance on dosing or duration.
		Staphylococcus: S ≤ 1; R > 2	-		
		CLSI:			
		Enterobacterales: S ≤ 4; R ≥ 16	*Enterobacterales*: S ≥ 14; R ≤ 10		
		Enterococcus: S ≤ 4; R ≥ 16	*Enterococcus*: S ≥ 16; R ≤ 12		
		Staphylococcus: S ≤ 4; R ≥ 16	*Staphylococcus*: S ≥ 16; R ≤ 12		

UTI, breakpoint related only to urinary tract infection. ECOFF, epidemiological cut-off value. MIC, minimum inhibitory concentration. SD, single dose. HD, high dose. $t_{½}$, half-life. uncj., unconjugated; conj., conjugated. 1GC, first-generation cephalosporin. 2GC, second-generation cephalosporin. 3GC, third-generation cephalosporin. AMP, ampicillin. PEN, penicillin. FOX, cefoxitin. CFZ, cefazolin. NOR, norfloxacin. TMP, trimethoprim. SMX, sulphamethoxazole. IE, insufficient evidence. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. Refer to the main text for all references. [a], The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint tables updates were used [56,57]. CLSI do not recommend routine testing of urine isolates of *S. saprophyticus* because infections respond to antimicrobial agents commonly used to treat acute, uncomplicated UTIs (e.g. nitrofurantoin, trimethoprim/sulphamethoxazole, or a fluoroquinolone). [b], Increased frequency dosing (three to four times daily, rather than twice daily) is more likely to achieve PK/PD targets but can be poorly tolerated. EUCAST breakpoints related to TID dosing.

Table 4a. Antimicrobial MIC distributions and wild-type cut-offs for common Gram-negative uropathogens

Antimicrobial	*Enterobacterales*								*Pseudomonas* spp.	
	E. coli		*K. pneumoniae*		*P. mirabilis*		*E. cloacae*		*P. aeruginosa*	
	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF
Fosfomycin trometamol	1 / 4[a]	4	16 / 64	ND	4 / 64[a]	8	16 / 256[e]	ND	64 / 128[a]	ND
Nitrofurantoin	16 / 32[a]	64	-		IR		16 / 64[b,c,e]	ND	IR	
Trimethoprim	0.5 / 64[a]	2	0.5 / 16[a]	ND	2 / 16[a]	ND	0.5 / 16[a]	ND	IR	
Trimeth.-sulphamethoxazole	0.125 / 32[a]	0.25	0.125 / 16[a]	0.5	0.25 / 16[a]	0.5	0.125 / 2[a]	0.5	IR	
Norfloxacin	0.064 / 0.125	0.25	0.125 / 0.25[d]	0.25	0.064 / 0.25[b,c]	0.25	0.064 / 8[c,e]	0.25	0.5 / 2	2
Ciprofloxacin	0.016 / 1[a]	0.064	0.032 / 2[a]	0.125	0.032 / 2[a]	0.064	0.016 / 0.5[a]	0.125	0.25 / 8[a]	0.5
Levofloxacin	0.032 / 4[a]	0.25	0.064 / 2[a]	0.25	0.064 / 1[a]	0.25	0.064 / 0.5[a,e]	0.25	0.5 / 4[a]	2
Pivmecillinam[f]	0.125 / 2[a]	1	0.25 / 128[b]	1	2 / 128[b,c]	ND	2 / 4[b,c]	ND	IR	
Amoxicillin	8 / ≥ 512[a]	8	IR		1 / ≥ 512	2	IR		IR	
Amoxicillin-clavulanate[g]	4 / 16[a]	8	2 / 16[a]	8	2 / 8[a]	2	IR		IR	
Cephalexin	4 / 8[b]	16	4 / 8[b,d]	16	8 / 16	16	IR		IR	
Cefaclor	1 / 4[b]	4	0.25 / 2[d]	ND	1 / 2[b,c]	ND	IR		IR	
Cefpodoxime	0.5 / 4[a]	2	-		-		2 / 64[a]	ND	IR	
Nitroxoline[h]	4 / 8	16	2 / 4[c]	ND	8 / 16	ND	8 / 16[c]	ND	IR	
Doxycycline	4 / 32[a]	4	2 / 16	4	IR		2 / 8	8	IR	

Table 4b. Antimicrobial MIC distributions and wild-type cut-offs for common Gram-positive uropathogens

Antimicrobial	*Enterococcus* spp.				*Staphylococcus* spp.			
	E. faecalis		*E. faecium*		*S. saprophyticus*		*S. aureus*	
	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF	MIC 50 / 90	ECOFF
Fosfomycin trometamol	32 / 64[a]	ND	64 / 128[b]	ND	IR		4 / 16[a]	32
Nitrofurantoin	8 / 16	32	64 / 256[a]	256	8 / 16[c]	32	16 / 16[a]	32
Trimethoprim	-		-		-		1 / 8	2
Trimeth.-sulphamethoxazole	-		0.25 / 16[b]	ND	-		0.064 / 0.5[a]	0.25
Norfloxacin	4 / 16	8	16 / 64[b,c]	ND	2 / 4[b,c]	ND	1 / 32	4
Ciprofloxacin	1 / 2[a]	4	2 / 4[a]	8	0.5 / 0.5[a]	1	0.5 /2[a]	1
Levofloxacin	2 / 32[a]	4	4 / 64[a]	4	16 / ≥512	0.5	0.25 / 4[a]	0.5
Pivmecillinam[f]	-		-		16 / 32[b,c]	ND	-	
Amoxicillin	-		IR		IR		IR	

Amoxicillin-clavulanate[g]	2 / 2[a]	4	32 / 32[b]	4	2 / 16[b]	-	0.5 / 8[a]	2
Cephalexin	IR		IR		4 / 8[b,c]	-	2 / 128[b]	8
Cefaclor	IR		IR		-		4 / 128[b]	8
Cefpodoxime	IR		IR		-		2 / 32[a]	4
Nitroxoline[h]	16 / 32	ND	8 / 8[c]	ND	8 / 8[c]	ND	8 / 8	ND
Doxycycline	8 / 32[a]	0.5	16 / 32[a]	0.5	0.125 / 0.25[b,c]	-	0.125 / 2[a]	0.5

Data from the EUCAST MIC distribution website http://www.eucast.org (last accessed 17 Aug 2020) [132], which define the epidemiological cut-off values (ECOFF) and give an indication of the MICs for organisms with acquired resistance mechanisms. The distributions should not infer resistance rates since the data are aggregated from many time periods and many countries. IR, intrinsic resistance. ND, not determined. -, indicates data not available. [a], >1 data source and >1000 observations. [b], Single data source only. [c], < 100 observations. [d], Refers to *Klebsiella* spp.. [e], Refers to *Enterobacter* spp.. [f], Refers to mecillinam MIC. [g], amoxicillin-clavulanate as a ratio. [h], Data from EUCAST nitroxoline rationale document (version 1.0, 2016) [133], the number of contributing data sources not documented.

FIGURES

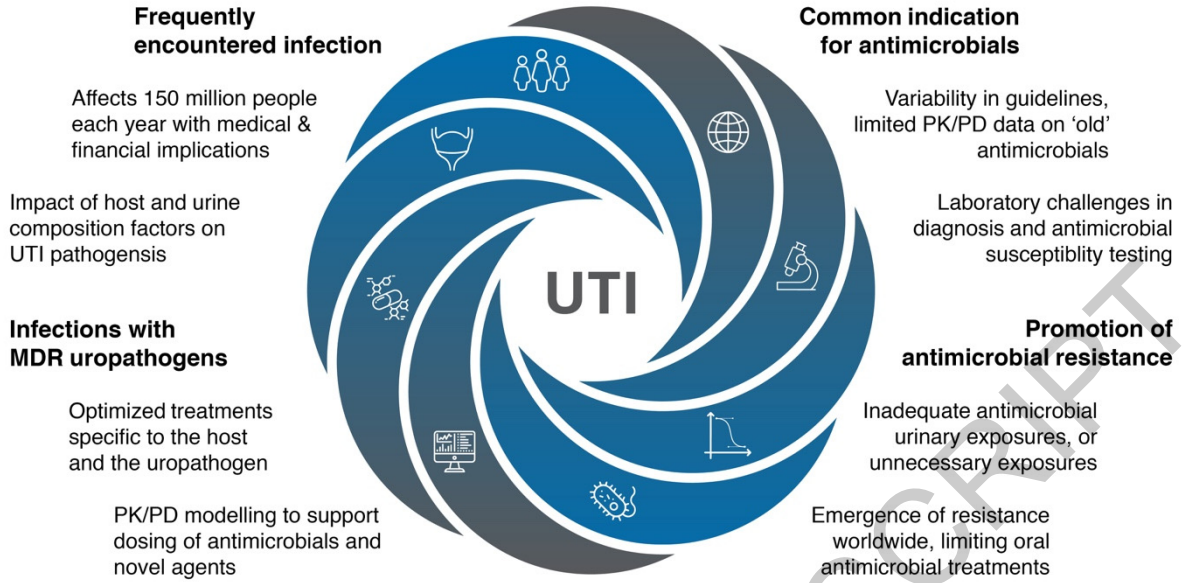


Figure 1. Overview of the challenges associated with urinary tract infections.
UTI, urinary tract infection. PK, pharmacokinetics. PD, pharmacodynamics. AMR, antimicrobial resistance. MDR, multidrug-resistant.

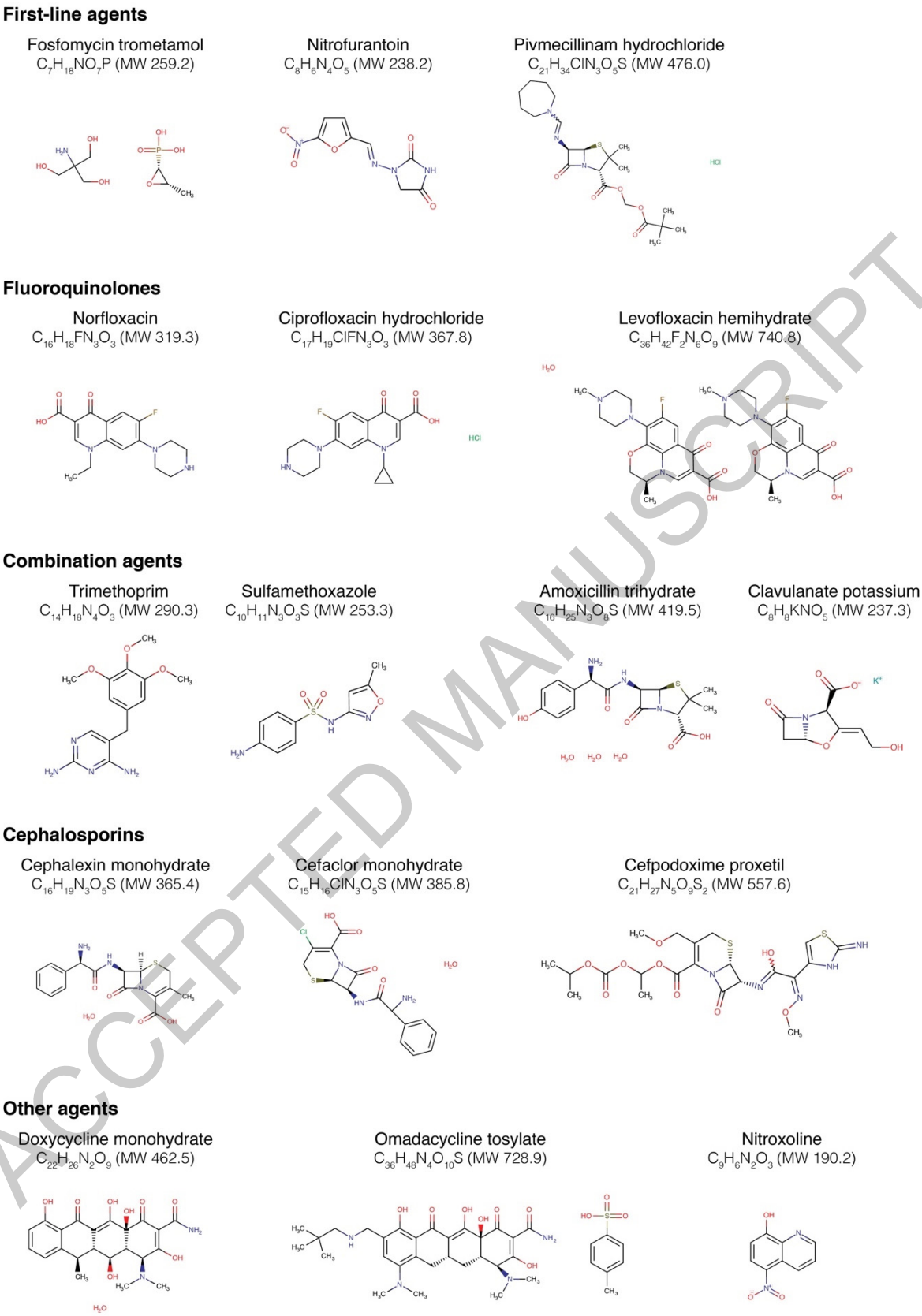


Figure 2. Oral antimicrobial agents for the treatment of urinary tract infections.
Chemical structures obtained from https://www.drugbank.ca [131]. MW, molecular weight.

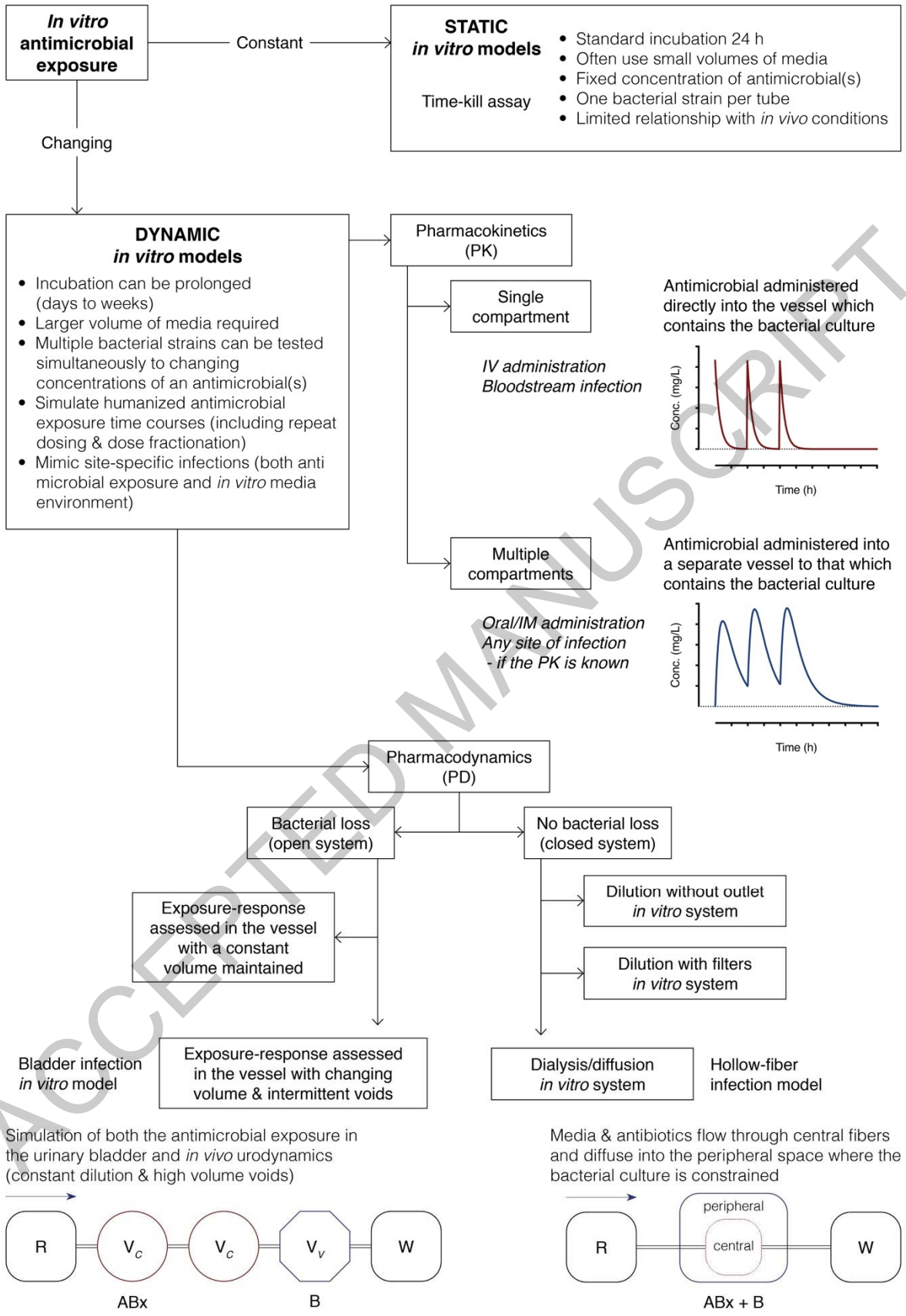


Figure 3. Generalized overview of PK/PD *in vitro* models

IV, intravenous. IM, intramuscular. R, reservoir. V_C, constant volume compartment. V_V, variable volume compartment. W, waste. ABx, antimicrobial. B, bacterial culture.

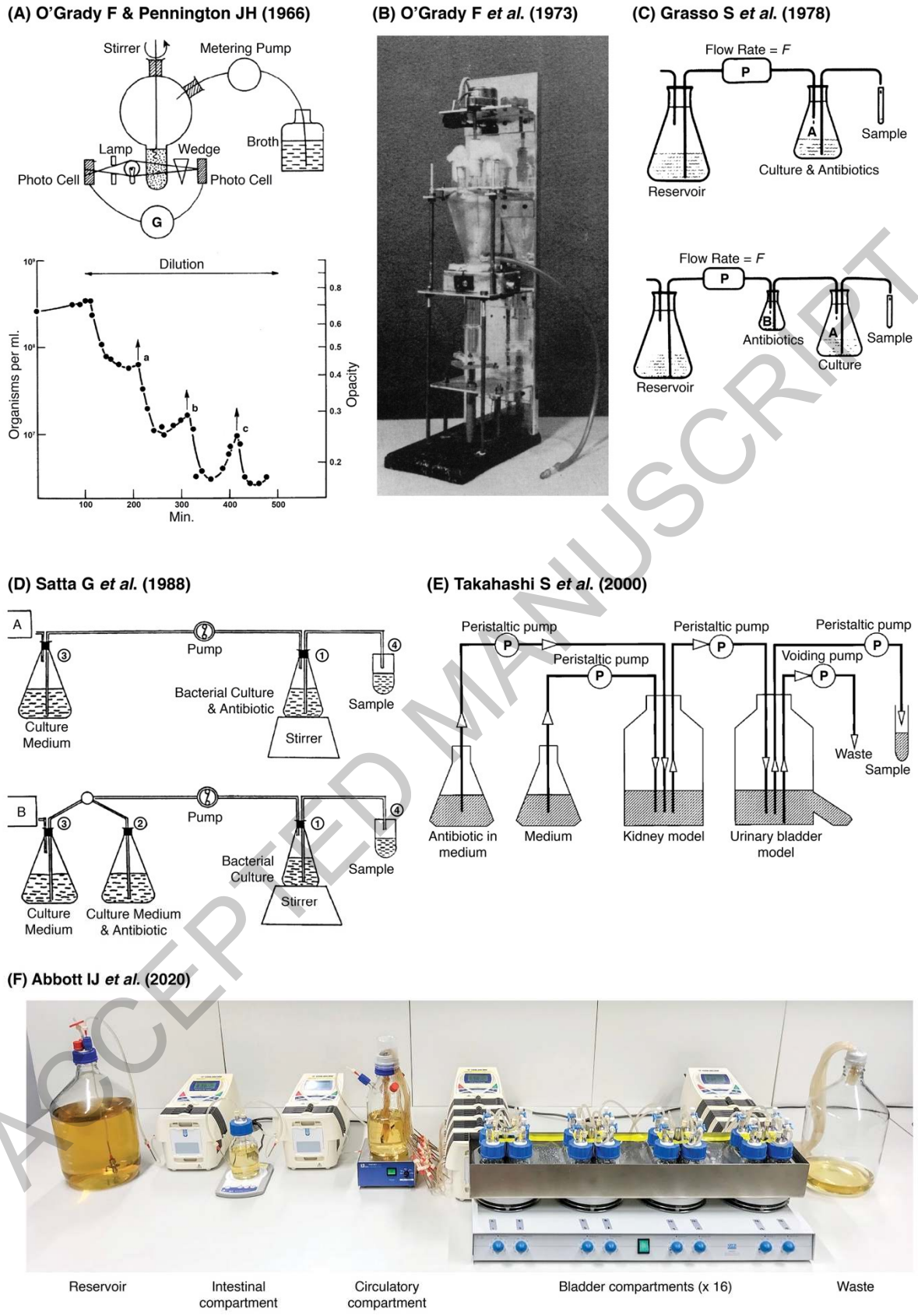


Figure 4. Bladder infection *in vitro* models

(A) A 400 mL glass vessel with a tubular prolongation at the base enclosed in a water bath maintained at 37°C, with a stirrer. The tubular base is fixed in the light path of a photometer. The graph shows the effect of

adding fresh broth at 1 mL/min, while at a, b and c the volume of the culture was reduced to 30 mL. Copyright © Blackwell Publishing LTD. Reproduced with permission [246]. (B) Updated designed from the previous model to overcome imperfect mixing and progressive occlusion of the light path of the photometer. The bladder as an inverted conical flask with tubulures set into the base, a drainage tube at the side and a glass syringe welded to the neck. The stirrer motor sits above, the photometer box at the waist and the piston at the base. The piston is activated every 5-minutes to clear the light path of the photometer. Copyright © Blackwell Publishing LTD. Reproduced with permission [247]. (C) Apparatus for simulation of mono-exponential decreases in antibiotic concentration and for simulation of biexponential time curves of antibiotic concentrations, such as those observed in serum after oral or intramuscular administration of drug. Copyright © American Society for Microbiology. Reproduced with permission [260]. (D) *In vitro* set-up simulating antibiotic concentrations in blood (apparatus A) and urine (apparatus B). Copyright © American Society for Microbiology. Reproduced with permission [261]. (E) Model used to simulate urinary concentrations of fluoroquinolones. Changing urinary antimicrobial concentrations simulated by a flow of media at 0.5 mL/min into the bladder, that was voided every 2 h during the day, withdrawing the entire volume except for 10 ml in the side arm. Overnight the bladder was not voided for 10 h. Copyright © Karger Publishers. Reproduced with permission [265]. (F) Media continuously pumped through three sequentially arranged peristaltic pumps from the fresh medium reservoir. Fosfomycin was administered into the intestinal compartment, simulating absorption, distribution and elimination into the 16 bladder compartments run in parallel. Automated and timed bladder voiding was controlled by a fourth peristaltic pump. Copyright © American Society for Microbiology. Reproduced with permission [272].

Figure 1

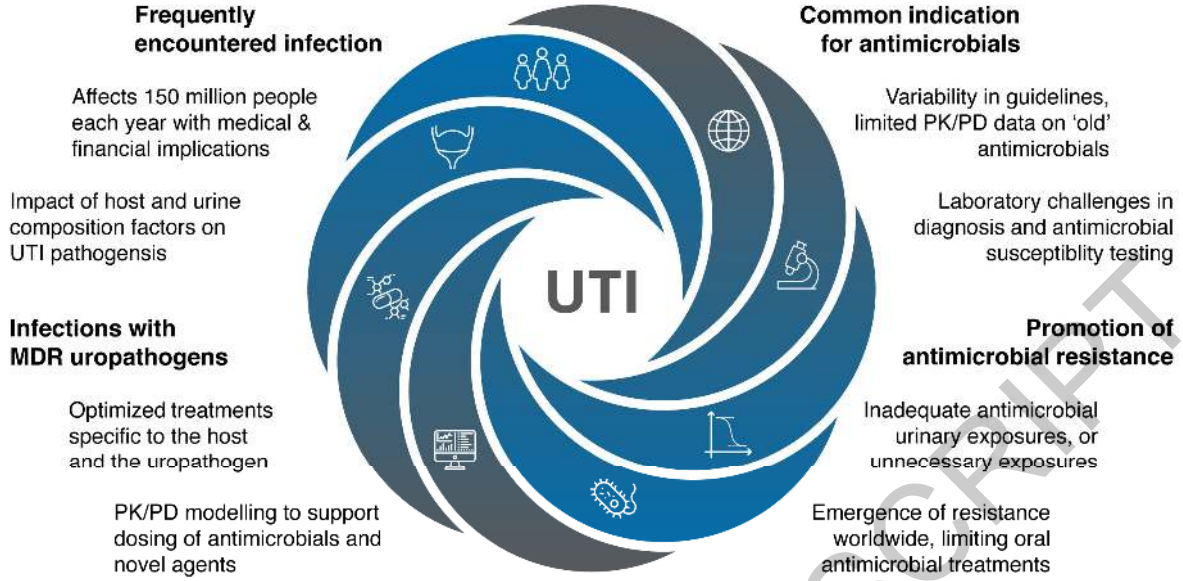
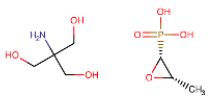


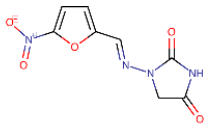
Figure 2

First-line agents

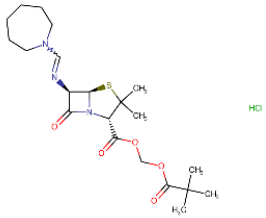
Fosfomycin trometamol
$C_7H_{18}NO_7P$ (MW 259.2)



Nitrofurantoin
$C_8H_6N_4O_5$ (MW 238.2)

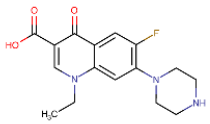


Pivmecillinam hydrochloride
$C_{21}H_{34}ClN_3O_5S$ (MW 476.0)

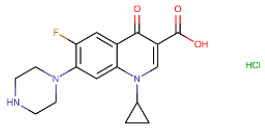


Fluoroquinolones

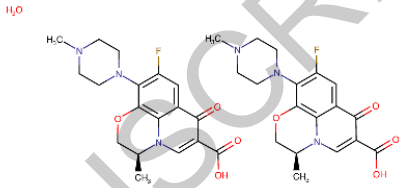
Norfloxacin
$C_{16}H_{18}FN_3O_3$ (MW 319.3)



Ciprofloxacin hydrochloride
$C_{17}H_{19}ClFN_3O_3$ (MW 367.8)

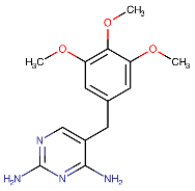


Levofloxacin hemihydrate
$C_{36}H_{42}F_2N_6O_9$ (MW 740.8)

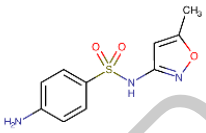


Combination agents

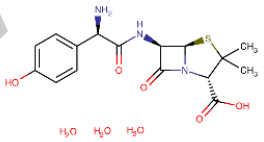
Trimethoprim
$C_{14}H_{18}N_4O_3$ (MW 290.3)



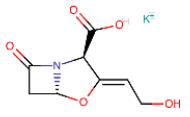
Sulfamethoxazole
$C_{10}H_{11}N_3O_3S$ (MW 253.3)



Amoxicillin trihydrate
$C_{16}H_{25}N_3O_8S$ (MW 419.5)

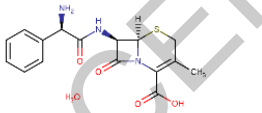


Clavulanate potassium
$C_8H_8KNO_5$ (MW 237.3)

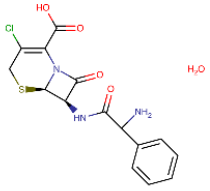


Cephalosporins

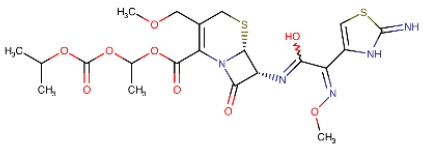
Cephalexin monohydrate
$C_{16}H_{19}N_3O_5S$ (MW 365.4)



Cefaclor monohydrate
$C_{15}H_{16}ClN_3O_5S$ (MW 385.8)

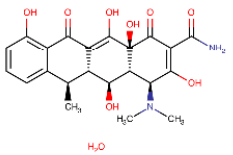


Cefpodoxime proxetil
$C_{21}H_{27}N_5O_9S_2$ (MW 557.6)

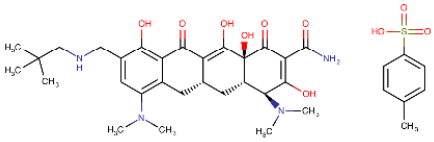


Other agents

Doxycycline monohydrate
$C_{22}H_{26}N_2O_9$ (MW 462.5)



Omadacycline tosylate
$C_{36}H_{48}N_4O_{10}S$ (MW 728.9)



Nitroxoline
$C_9H_6N_2O_3$ (MW 190.2)

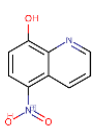


Figure 3

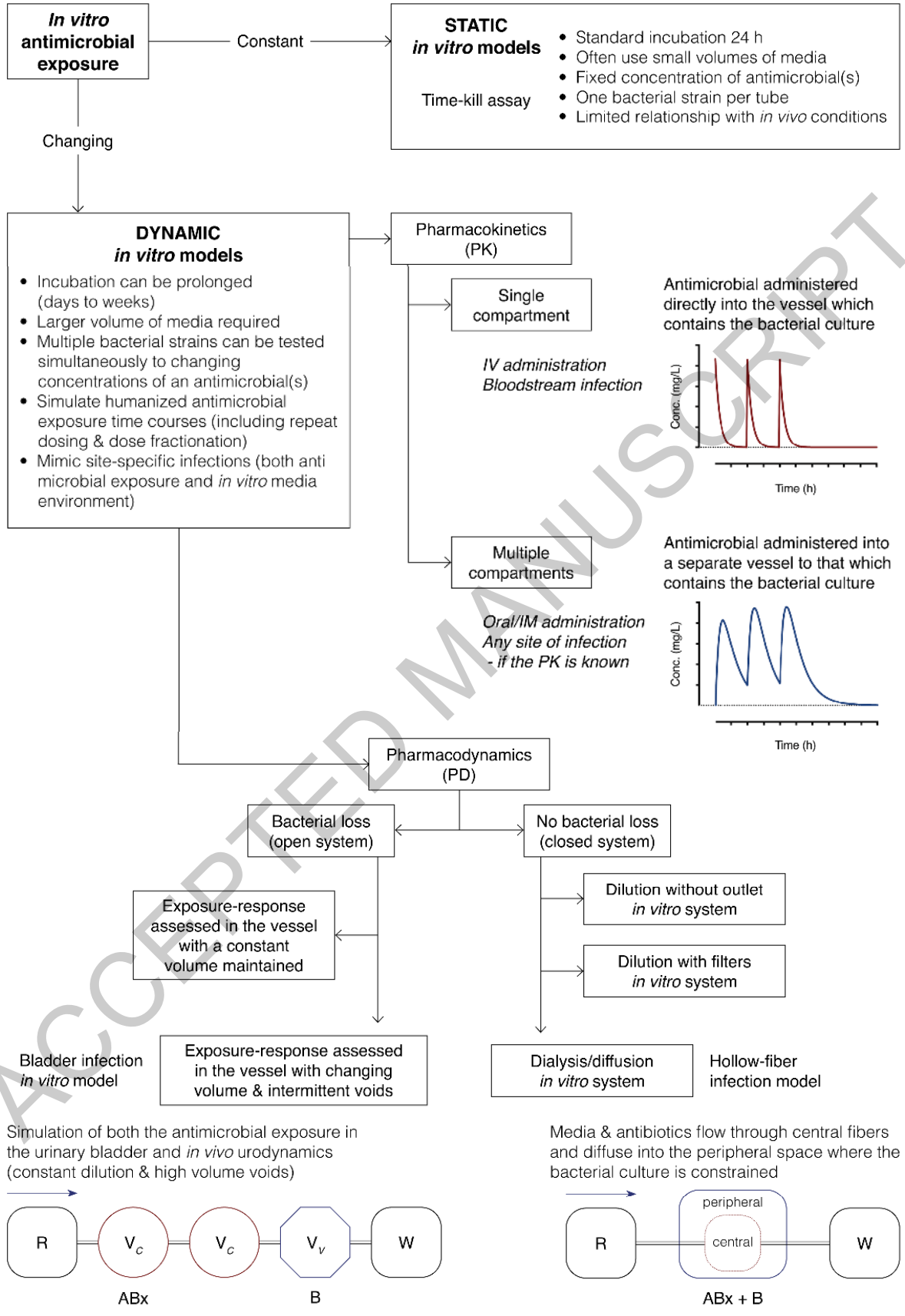


Figure 4