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The Role of Gram-Negative Bacteria in Urinary Tract Infections: Current Concepts and Therapeutic Options

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Abstract

Urinary tract infections (UTIs) are some of the most common infections in human medicine worldwide, recognized as an important public health concern to healthcare systems around the globe. In addition, urine specimens are one of the most frequently submitted samples for culture to the clinical microbiology laboratory, exceeding the number of most of the other sample types. The epidemiology, species-distribution and susceptibility-patterns of uropathogens vary greatly in a geographical and time-dependent manner and it also strongly correlated with the reported patient population studied. Nevertheless, many studies highlight the fact that the etiological agents in UTIs have changed considerably, both in nosocomial and community settings, with a shift towards "less common" microorganisms having more pronounced roles. There is increasing demand for further research to advance diagnostics and treatment options, and to improve care of the patients. The aim of this review paper was to summarize current developments in the global burden of UTI, the diagnostic aspects of these infectious pathologies, the possible etiological agents and their virulence determinants (with a special focus on the members of the Enterobacterales order), current guidelines and quality indicators in the therapy of UTIs and the emergence of multidrug resistance in urinary pathogens.

Keywords

Antibiotics · Clinical microbiology' virulence · Epidemiology · *Escherichia coli* · Multidrug

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resistance · Pathogenomics · Therapeutic guidelines · Urinary tract infections

Abbreviations

ACSS	Acute Cystitis Symptom Score
AP	acute pyelonephritis
ASB	asymptomatic bacteriuria
AUC	acute uncomplicated cystitis
CAUTI	catheter-associated UTI
CDC	Centers for Disease Control
CFU	colony-forming units
CRGNB	carbapenem-resistant Gram-negative bacilli
cUTI	complicated UTI
ECDC	European Centre for Disease Prevention and Control
ESBL	extended-spectrum β-lactamase
ExPEC	extra-intestinal pathogenic *Escherichia coli*
GNB	Gram-negative bacteria
ICE	integrative and conjugative element
IDSA	Infectious Diseases Society of America
InCOM	intra-intestinal commensal
InPEC	intra-intestinal pathogenic *Escherichia coli*
LPS	lipopolysaccharide
m/z	mass-to-charge
MALDI-TOF MS	matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MDR	multidrug-resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSA	methicillin-resistant *Staphylococcus epidermidis*
MRSE	methicillin-resistant *Staphylococcus epidermidis*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NACA	non-*albicans Candida*
NECE	non-*E. coli Enterobacterales*
NGS	next-generation sequencing
NICE	The National Institute for Health and Care Excellence
OMP	outer membrane proteins
OMV	outer membrane vesicles
PAI	pathogenicity islands
PCR	polymerase chain-reaction
PDR	pandrug-resistant
PROM	patient-reported outcome measures
QI	quality indicator
QoL	quality of life
rRNA	ribosomal RNA
RTX	repeats in toxin
rUTI	recurrent UTI
ShiToPInPEC	*Shigella* Toxin Producer InPEC
TMP/SMX	trimethoprim-sulfamethoxazole
UPCA	uropathogenic *Candida albicans*
UPEC	uropathogenic *Escherichia coli*
US	United States
UTI	urinary tract infections
VF	virulence factors
VRE	vankomycin-resistant *Enterococcus*
WHO	World Health Organization
XDR	extensively drug resistant

1 The Burden of Urinary Tract Infections

The global burden of diseases have shown considerable changes in the last century. In contrast to previous times of humanity, the introduction of appropriate sanitation and antibiotics has brought on an epidemiological transition, where the burden of diseases that was predominantly communicable, which has shifted towards one that is nowadays predominantly non-communicable (chronic) (Jamison et al. 2018). Nevertheless, infectious pathologies still constitute an important disease burden worldwide (Furuse 2019). Urinary tract infections (UTIs) are the second most common type of infections in human medicine (following respiratory tract infections) in the United States and Europe and the third most common infectious pathologies (following respiratory

tract infections and gastrointestinal infections) worldwide, recognized as an important public health concern to healthcare systems around the globe (Flores-Mireles et al. 2015; Sobel and Kaye 2015). In general, UTIs include infections of the urethra, bladder, ureter and the kidneys, most frequently due to bacteria originating from the alimentary tract (McLellan and Hunstad 2016). UTIs are multi-positional, multi-syndromal, multi-factorial and often multi-microbial infectious diseases occurring among different populations including men, women, adults, children, infants, aged and young people around the globe (Flores-Mireles et al. 2015; Tangdogdu and Wagenlehner 2016). UTIs should be considered as an important factor or morbidity and mortality, both among outpatients (representing 10–30% of infections) and hospitalized patients (Wiedemann et al. 2014). In fact, in the latter group, nosocomial UTIs are the most common infectious pathologies, responsible for 25–50% of infections overall (Stefaniuk et al. 2016; Wiedemann et al. 2014). The multi-positional clinical problem of UTIs is as follows: (i) UTIs cause considerable decrease in the quality of life (QoL) in the affected patients, especially in case of recurrence, complications and sequelae; (ii) the high number of patients with symptomatic UTIs will visit their primary case physicians or specialists, for which, considerable amount of human resources are required (globally, around 150–200 million people are diagnosed with UTI annually; UTIs are responsible for around 10 million GP visits, 1.5 million emergency room visits and 300,000 hospital admissions in the US alone); (iii) UTIs should be treated at the earliest convenience, as if therapy is not initiated or if the appropriate steps are not taken, it may lead to re-infection, ascending infections to the kidneys or other sequelae; (iv) the therapy of UTIs usually entails the administration of antibiotics (UTIs rank as the most common cause that leads to an antibiotic prescription after a GP visit), however, the adverse events associated with antibiotic use, *Clostridioides difficile* enterocolitis, and the emergence of antibiotic-resistant pathogens causing UTIs is a serious concern; (v) UTIs also have a substantial economic impact, including costs of pharmacotherapy, hospitalization and lost working days; the annual cost of UTIs in the US alone has been estimated to be more, than four billion US dollars, while the excess economic losses associated with UTIs to the global economy were shown to be around four billion US dollars (Bermingham and Ashe 2012; Flores-Mireles et al. 2015; Foxman 2003; McLellan and Hunstad 2016; Renald et al. 2015; Simmering et al. 2017; Stefaniuk et al. 2016; Tangdogdu and Wagenlehner 2016; Wiedemann et al. 2014). The Acute Cystitis Symptom Score (ACSS) has been recently developed for the diagnosis of acute cystitis and patient-reported outcome measures (PROMs), reporting on the typical symptoms of acute cystitis (frequency, urgency, dysuria, suprapubic pain, feeling of incomplete bladder emptying and visible blood in urine) (Alidjanov et al. 2016; Di Vico et al. 2020; Magyar et al. 2018). Recurrent UTIs (rUTI) are also frequently associated with psychiatric symptoms, such as reduced social activity, guilt (due to inability to perform various everyday tasks), anxiety (e.g., associated with incontinence in the elderly) and depression, which also major contributing factors to the QoL-decrease associated with these infections (Dason et al. 2011; Flower et al. 2014; Negus et al. 2020). As UTIs represent a major healthcare burden, there is increasing demand for further research to advance diagnostics and treatment options an to improve care of the patients (Jhang and Kuo 2017).

Under physiological conditions, urine was previously thought to be sterile; however, with the emergence of 16S rRNA PCR, metagenomics and the introduction of next-generation sequencing (NGS), the characterization of the urinary microbiome has begun and this dogma has been challenged (Bilen et al. 2018; Brubauker and Wolfe 2016; Govender et al. 2019). The threshold of microbial population for the definition of UTIs is usually reported as $\geq 10^5$ colony forming units (CFUs)/mL; however, this is subject to interpretation (going as low as 10^2 CFU/mL), depending on the studied patient population and the sample type submitted for microbial analysis (Chu and Lowder 2018; Roberts and Wald 2018; Schmiemann et al. 2010). UTIs and UTI-related

syndromes may be classified based on several characteristics: (i) based on the presence of symptoms: asymptomatic bacteriuria or symptomatic UTIs (mild/moderate/severe); (ii) based on the onset of the infections: acute or chronic/recurrent infections (or rUTIs are defined as UTIs occurring more, than three times in a year), community-acquired and nosocomial infections; (iii) based on the anatomical region affected: lower urinary tract infections (i.e. cystitis), upper urinary tract infections (i.e. nephritis) or systemic (i.e. urosepsis); this terminology is more often used as uncomplicated and complicated urinary tract infections (cUTI) (Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010; Renald et al. 2015; Rizwan et al. 2018; Simmering et al. 2017; Stefaniuk et al. 2016; Tangdogdu and Wagenlehner 2016; Wiedemann et al. 2014). The emergence, symptomatology and outcome of these infections is highly dependent on the microbial composition of the microbiota of the surrounding anatomical regions (i.e., gut, genitalia), the pathogenic potential of the microorganisms in question, the duration of the infection and other attributes of the host (e.g., hygiene practices, immune status) (Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010; Wiedemann et al. 2014). In healthy individuals, physical and immunological barriers provide protection from urinary infections, and urothelial cells play a pivotal role in producing pro-inflammatory cytokines and other immunological responses (Abraham and Miao 2015; Hayes and Abraham 2017). Many predisposing factors have been described for the development of UTIs, including age, female gender (and corresponding anatomical characteristics), pregnancy, sexual intercourse (or multiple sexual partners), personal hygiene, disturbances in the vaginal microbiota (i.e. absence of vaginal lactobacilli, decreases in estrogen-levels, introduction of a diaphragm), use of spermicidal formulations, nutritional aspects and obesity, Type II diabetes, immunosuppression (caused by disease or pharmacotherapy), non-circumcision in males, introduction of urinary catheters, hospitalization, urinary retention, renal failure, paraplegia or other neurological disorders, developmental abnormalities of the urinary system (vesicoureteral reflux, obstruction), pelvic prolapse, surgeries in the genitourinary tract or genetic predisposition (e.g., blood group and stone formation) (Emiru et al. 2013; Hu et al. 2004; Scholes et al. 2000; Storme et al. 2019). Urinary catheterization (associated with hospitalization) is the main risk factor for nosocomial UTIs and subsequent secondary bacteremia; insertion of urinary catheters may lead to mucosal damage, which disrupts the natural barrier of the urinary tract, allowing for colonization and the aggregation of microbial pathogens in the form of a biofilm (extracellular matrix of polysaccharides and proteins) (Clarke et al. 2019; Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010; Nicolle 2014). This may facilitate the recurrence of UTIs in the host and the biofilm also provides protection for these pathogens against external noxa, such as the lethal effects of antibiotics (Clarke et al. 2019; Trautner and Darouiche 2004; Sabir et al. 2017). The catheter-associated pathogen may enter through the extra-luminal route (moving across the outer lumen of catheter) or the intra-luminal route (by directly entering the interior of catheter) (Clarke et al. 2019; Flores-Mireles et al. 2015; Trautner and Darouiche 2004; Sabir et al. 2017). It must also be noted that these pathogens may spread to the bloodstream from the urinary tract (if the pathogens cross the tubular epithelial barrier in the kidneys) causing secondary bacteremia and sepsis, which may occur in 30% of cases (Clarke et al. 2019; Conway et al. 2015; Flores-Mireles et al. 2015; Trautner and Darouiche 2004; Sabir et al. 2017).

UTIs have been described as an important infectious pathology in patient of both sexes and in all age groups (infants, children, adults and the elderly) (Stefaniuk et al. 2016; Wiedemann et al. 2014). Nevertheless, uncomplicated UTIs are most common between females over 18 years of age, with around two-thirds of women in the ages of 20–40 years experiencing a UTI at least once during their lifetime; in addition, rUTIs in adult females is present in 20–30% of cases, within 3–4 months of the initial infection (Clarke et al. 2019; Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010; Nicolle 2014).

Management of rUTI is of paramount importance as repeat courses of antibiotics to treat these infections often results in bacteria developing resistance to the mechanism of action of previously effective antibiotics (Negus et al. 2020; Wiedemann et al. 2014). UTI occurs in 25% of kidney transplant recipients within 1 year of their transplant, and this constitutes around half of infectious complications (Giessing 2012). UTIs in men occur significantly less frequently than in women, mainly in patients with structural abnormalities in the urinary system and in men with advanced age (with a lifetime prevalence of around 2–7%) (Harper and Fowlis 2007; Schaeffer and Nicolle 2016; Tan and Chlebicki 2016). In developed countries, 3–8% of girls and 0.2–1% of boys under 18 years of age are clinically diagnosed with a UTI (Clarke et al. 2019; Flores-Mireles et al. 2015; Hellerstein 1998; White 2011). As a general rule, the rate of asymptomatic or symptomatic bacteriuria increases in both men and women with advanced age (Clarke et al. 2019; Flores-Mireles et al. 2015; Harper and Fowlis 2007; Schaeffer and Nicolle 2016). In addition to advanced age, immunosuppression and catheterization, the occurrence of hospital-associated UTIs has several non-patient-specific risk factors, including poor hospital infrastructure (insufficient equipment, understaffing, inadequate training or poor knowledge/application of basic procedure, hygienic conditions), overcrowded healthcare-institutions and lack of local and national guidelines (Clarke et al. 2019; Flores-Mireles et al. 2015; Hooton et al. 2010). Asymptomatic bacteriuria (ASB; the presence of high numbers of bacteria without clinical symptoms) is usually not treated with antibiotics in any patient group, except for pregnant women. The definition of ASB varies based on methods of sample collection and the patient population in question (Cormican and Murphy 2011; Henderson et al. 2019; Imade et al. 2010; Nicolle et al. 2005; Wingert et al. 2019). However, in pregnant women (due to their altered immune status), untreated ASB may lead to manifest and usually severe UTIs, pyelonephritis, urosepsis and preterm delivery; therefore treating ASB in this patient population is a must (Cormican and Murphy 2011; Henderson et al. 2019; Imade et al. 2010; Nicolle et al. 2005; Wingert et al. 2019).

2 Diagnosis and Etiological Agents in Urinary Tract Infections

Main clinical signs and symptoms associated with UTIs include the strong and persistent urge to urinate, burning sensations, frequent urination with a small voided volume; in addition, voided urine may be cloudy, red, bright pink, bloody, and foul-smelling in character (Alidjanov et al. 2016; Chu and Lowder 2018; Di Vico et al. 2020; Magyar et al. 2018; Tan and Chlebicki 2016). Based on the severity of the infection, urinary incontinence, pelvic pain, fever, and nausea/vomiting may also occur (Alidjanov et al. 2016; Chu and Lowder 2018; Di Vico et al. 2020; Magyar et al. 2018; Tan and Chlebicki 2016). Urine specimens are one of the most frequently submitted samples for culture to the clinical microbiology laboratory, exceeding the number of most of the other sample types; therefore, the interpretation of culture results from urine samples provide little or no challenge to clinical microbiologists (Flores-Mireles et al. 2015; Gajdács 2020). The most common urine sample type submitted from adults is voided (midstream, clean-catch) urine, which mainly originates from outpatient settings (Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010). Clean-catch urine samples are inexpensive and non-invasive without the risk of complications. Contamination of the sample with bacteria from the normal flora or the distal urethrae is a risk, however, if the patients are instructed appropriately before sample collection and some hygienic considerations are complied with (Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010; Morris 2018). In contrast, collection of urine by the use of a single catheter („straight catheter technique") is a more appropriate method to use to avoid contamination, which is most frequently used in inpatient settings. In fact, one of the main indication for catheter-specimen urine is the monitoring of urinary catheters (Flores-Mireles et al.

2015; Gupta et al. 2011; Grahn et al. 1985; Hooton et al. 2010). However, it is not indicated for most patients, as it is not labour-intensive for non-inpatients, and the insertion of a catheter through the urethra is an invasive method, may also introduce bacteria into the bladder (Flores-Mireles et al. 2015; Hooton et al. 2010). To avoid contamination with bacteria from the distal urethra, subrapubic bladder aspiration (or "bladder tap") is the best method to use; in addition, urine collected through this methods is appropriate to be cultured anaerobically (Gajdács et al. 2019a, b, c, d; Guze and Beeson 1956; Rozenfeld et al. 2018). Nevertheless, subrapubic bladder aspiration is infrequently used (in special clinical circumstances), as it is invasive (leading to discomfort and bleeding), time and resource-dependent method (Guze and Beeson 1956; Ponka and Baddar 2013; Rozenfeld et al. 2018).

Urine samples are usually cultured on either non-selective culture media (mainly blood agar) or selective media for Gram-negative bacteria (eosin methylene blue, MacConkey etc.); however, nowadays, most laboratories use chromogenic media, which allow for the rapid, phenotypic differentiation of most urinary pathogens, which may be further verified by the use of biochemical tests, automated identification systems or other, more advanced identification methods (Chaux et al. 2002; Flores-Mireles et al. 2015; Gupta et al. 2011; Grahn et al. 1985; Hooton et al. 2010). The inoculation of selective media for Gram-positive bacteria is not necessary, especially from outpatient samples; however several reports highlighted enterococci as significant pathogens in nosocomial infections (Gupta et al. 2011; Grahn et al. 1985; Hooton et al. 2010). Introduction of molecular biological methods (e.g., polymerase chain reaction; PCR) and microarray technologies into clinical microbiology have definitely paved the way for more sharper identification, however, these non-cultures-based technologies are not widely used in the diagnosis of UTIs due to their price (Davenport et al. 2017; Zee et al. 2016). On the other hand, the introduction of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has revolutionized bacteriological diagnostics, allowing for rapid, reliable and easy identification for most common urinary pathogens, directly from the cultures of urine specimens; this technology allows for protein-based identification of microorganisms, based on the separation and measurement of smaller to larger fragments of highly conserved ribosomal proteins (which are small and basic in character) by their mass to charge (m/z) ratio (Gajdács et al. 2020a, b; Hou et al. 2019; Schubert and Kostrzewa 2017). In the MALDI-TOF MS measurements, the protein spectrum of the clinical isolate is compared with the protein spectrum of strains in the device-linked database and expressed as a log score (microFlex; Bruker Daltonics) or as a percentage (VITEK MS; bioMérieux), which provides information on the level of match and security of identification (Schubert and Kostrzewa 2017). Although the initial price of the mass spectrometer was a burden to diagnostic institutions, nowadays, more and more laboratories opt into purchasing such a machine.

Most pathogenic yeasts also grow well on agar plates, therefore it is not necessary to use selective media for the fungal culture (except if the pathogenic role of some fungi with fastidious growth requirements is suspected) (Behzadi et al. 2015; Dias 2020; Gajdács et al. 2019a, b, c, d). Cultivation of *Mycobacterium* spp. requires special media and preparation from the laboratory's side, therefore clinicians should always give notice is there is clinical suspicion of a mycobacterial infection of the urinary tract (Kulchavenya and Cherednichenko 2018). As mentioned previously, suprapubic bladder aspiration is the only suitable specimen type for anaerobic processing: these culture are usually limited to patients with anatomical abnormalities (e.g., in case of an enterovesicular fistula) or when sings on infection caused by anaerobes (e.g., due to foul smell) is suspected (Guze and Beeson 1956; Ponka and Baddar 2013; Rozenfeld et al. 2018). In addition to the culture of the samples on microbiological culture media, additional methods may taken into consideration for assessing the presence of clinical infection. The native microscopic analysis and/or Gram-staining of the urine samples

(looking for polymorphonuclear leukocytes with or without bacteria) is usually a good indicator of infections, however, this method is time-consuming and tedious, therefore it is not routinely used (Cantey et al. 2015). In laboratory medicine, the use of nitrite and leukocyte-esterase tests or a hemocytometer is also common in the diagnostics of UTIs (Young and Soper 2001; Alshareef et al. 2020).

Based on literature data, 50–70% of urine cultures are culture-negative, and out of the positive urine cultures, 40–50% of isolated bacteria are relevant urinary pathogens (the rest are contaminants and members of the normal flora) (Cantey et al. 2015; Flores-Mireles et al. 2015; Gupta et al. 2011; Hooton et al. 2010). A wide range of etiological agents have been described in UTIs: the predominant group constitutes the members of the Enterobacterales order (i.e. gut bacteria), noted as the group with having the most pathogenic potential in the urinary tract; however, there is substantial heterogeneity even among the members of this order (Adelou et al. 2016; Calzi et al. 2016; Sobel and Kaye 2015). *Escherichia coli* is the most common causative agent in both community-acquired and nosocomial UTIs (Gajdács et al. 2019a, b, c, d; Rizwan et al. 2018). Pathogenic strains of *E. coli* may be differentiated into distinct pathotypes, including intestinal pathogenic an extraintestinal pathogenic *E. coli* (ExPEC) (Miri et al. 2017). Enteric *E. coli* include seven major pathotypes (responsible for gastroenteritis and blood diarrhea), while among ExPEC strains, so-called uropathogenic *E. coli* (UPEC) are the most common (Bekal et al. 2003); UPEC strains are causative agents in 50–90% of community-acquired and 30–60% of nosocomial UTIs (Terlizzi et al. 2017). Other members of the Enterobacterales order are also represented (although to a lesser extent) in UTIs, namely uropathogenic *Klebsiella pneumoniae* (UPKP; outpatients: 5–10%, inpatients: 7–15%) (Anğ-Küçüker et al. 2002; Gajdács et al. 2019a, b, c, d; Rizwan et al. 2018), members of the Proteae tribe (i.e. *Proteus-Providencia-Morganella*; outpatients: 0.5–6%, inpatients: 2–10%) and the CES-group (i.e. *Citrobacter-Enterobacter-Serratia*; outpatients: 0.2–3%, inpatients: 0.5–5%) of pathogens (Barabás et al. 2015; Gajdács and Urbán 2019a, b; Jacobsen et al. 2008; Metri et al. 2013; Samonis et al. 2009; Stefaniuk et al. 2016; Yang et al. 2018). Generally speaking, the prevalence of so-called non-*E. coli Enterobacterales* (NECE) strains grows in proportion with the age of the patients; in addition, their relevance is much higher in hospitalized patients, they are more frequently isolated in complicated UTIs, pyelonephritis, from catheter-associated infections; they are also more often associated with recurrence and prolonged treatment (Amaretti et al. 2020; Jacobsen et al. 2008; Laupland et al. 2007; Maharjan et al. 2018; Mazzariol et al. 2017).

The potential pathogenic role of non-fermenting Gram-negative bacteria (*Pseudomonas aeruginosa* [outpatients: 1–5%, inpatients: 3–8%], *Acinetobacter* spp. [outpatients: 0.3–1%, inpatients: 0.5–3%] and *Stenotrophomonas maltophilia* [outpatients: 0.05–0.1%, inpatients: 0.05–0.8%]), Gram-positive cocci (*Enterococcus* spp. (including vancomycin-resistant [VRE] strains, *Staphylococcus aureus* (including methicillin-sensitive [MSSA] and methicillin-resistant [MRSA] strains), *S. epidermidis* (including methicillin-sensitive [MSSE] and methicillin-resistant [MRSE] strains), *S. saprophyticus* [also termed „honeymoon cystitis"] and *Streptococcus agalactiae* [or Group B streptococci]) or rods (*Corynebacterium urealyticum, C. pseudogenitalium, C. striatum*) and pathogenic yeasts (0.1–2% in outpatients and 1–7% in inpatients; including uropathogenic *Candida albicans* [UPCA] and non-*albicans Candida* [NACA] species) should also be taken into consideration (Adeghate et al. 2016; Baraboutis et al. 2010; Behzadi et al. 2015; Eriksson et al. 2012; Ferreiro et al. 2017; Dias 2020; Gajdács et al. 2019a, b, c, d; Gajdács 2019; Hegstad et al., 2010; Mittal et al. 2009; Nitzan et al. 2015; Shrestha et al. 2019; Swaminathan and Alangaden 2010; Ulett et al. 2009). The prevalence of Gram-positive cocci in UTIs ranges between 2–15% in outpatients and 5–25% in inpatient samples; the occurrence of *S. saprophyticus* is overwhelmingly seen in young, sexually-active females, while over time, the

epidemiology shift towards enterococci Adeghate et al. 2016; Eriksson et al. 2012; Ferreiro et al. 2017; Hegstad et al. 2010; Nitzan et al. 2015)

Other–although much more rarely occurring (<0.1%)–urinary pathogens include strict anaerobic bacteria (e.g., *Actinotignum schaali, A. urinale, Lactobacillus delbrueckii*), *Aerococcus* spp. (e.g., *A. urinae*), *Mycobacterium* spp., *Mycoplasma hominis, Ureaplasma urealyticum, Chlamydia trachomatis,* and *Trichomonas vaginalis* (Christofolini et al. 2012; Combaz-Söhnchen and Kuhn 2017; Darbro et al. 2009; Higgins and Garg 2017; Kulchavenya and Cherednichenko 2018; Lotte et al. 2016; Masha et al. 2018). The latter group of pathogens have a common characteristic in that they are usually found in specific, narrow patient populations, and their isolation and identification usually entails the use of some kind of specialized media, long incubation times, use of cell cultures or strict anaerobic conditions. For example, *Aerococcus* spp. are predominantly isolated from elderly males with benign prostatic hypertrophy, while *L. delbrueckii* has been reported as a urinary pathogen in elderly women (>70 years of age) (Darbro et al. 2009; Higgins and Garg 2017). Similarly, mycoplasmae and ureaplasmae are more frequently found in postmenopausal women as a causative agent in UTIs (Christofolini et al. 2012; Combaz-Söhnchen and Kuhn 2017; Masha et al. 2018).

The epidemiology and species-distribution of uropathogens varies greatly in a geographical and time-dependent manner and it also strongly correlated with the reported patient population studied (Gajdács et al. 2019a, b, c, d; Köves et al. 2017; Stefaniuk et al. 2016). Nevertheless, many studies highlight the fact that the etiological agents in UTIs have changed considerably, both in nosocomial and community settings, with a shift towards "less common" microorganisms having more pronounced roles. Similarly (as presented previously), in the elderly (and in immunocompromised persons), uncommon urinary pathogens are seen more often (Kumar et al. 2001). The local epidemiological characteristics and resistance trends of UTIs should be regularly surveyed to allow for appropriate choice of therapy (Abbo and Hooton 2014).

3 Virulence Factors of Various Urinary Pathogens in the Era of Molecular Biology and Bioinformatics

3.1 General Concepts

To understand the pathomechanisms of developing a UTI, one first need to establish the presence and relevance of various cell- and non-cell-associated virulence-determinants of individual pathogens. The sciences of molecular biology, immunology and bioinformatics are great supporters for detection, recognition and interpretation of molecular mechanisms belonging to both pathogenic bacteria and the hosts (Behzadi et al. 2016; Behzadi and Behzadi 2016, 2017; Behzadi 2020; Hozzari et al. 2020; Jahandeh et al. 2015). In this regard, this section focuses on microbial molecular treasures of virulence factors (microbial virulome) and the importance of bioinformatics in this regard. The microbial pathogenome and virulome are important factors in determining the severity of UTIs; some of these microbial virulence genes are located on plasmids, while others are integral part of the bacterial chromosomes (Behzadi et al. 2016; Behzadi and Behzadi 2016, 2017; Behzadi 2020; Hozzari et al. 2020; Jahandeh et al. 2015). Generally, adherence is a key step initiating UTI pathogenesis is adherence: initially, a urinary pathogen (most often residing in the gut) colonizes the periurethral region, followed by migration of these microorganisms upstream to the bladder (Flores-Mireles et al. 2015; Terlizzi et al. 2017). These bacteria need to withstand the strong hydrodynamic shear forces and the removal by the flow of urine. For these steps to occur, the presence of molecular appendages, such as flagella and pili are required. Bacterial adhesins bind to receptors (e.g., Type I fimbriae mediate binding to uroplanktins, which are D-mannosylated proteins) on the uroepithelium, mediating colonization and subsequent invasion (Issakhanian and Behzadi 2019; Behzadi et al. 2019). If these pathogens are present in sufficient amounts, they may overcome the host immune

response and ascend to the bladder and the kidneys. Uropathogens produce several tissue-damaging toxins and proteases (IgA protease, elastase, phospholipase, hemolysin, cytotoxins) to obtain nutrients from host cells, and siderophores to acquire iron, necessary for maintaining their biochemical processes (Behzadi et al. 2011; Behzadi et al. 2015; Behzadi and Behzadi 2008). In addition, urease-production (characteristic for *Proteus* spp., *S. saprophyticus, K. pneumoniae* and *P. aeruginosa* among others) is also important for colonization and persistence. Urease-production results in a shift in pH, leading to tissue destruction, scarring and stone formation, through the composition of struvite and apatite crystals via precipitation of Ca^{2+} and Mg^{2+} ions). Several species also produce pigments (pyoverdine, pyocyanine in case of *P. aeruginosa*, prodigiosin in case of *Serratia marcescens*), which may further cause tissue destruction (Behzadi 2018; Behzadi et al. 2011; Behzadi et al. 2015; Behzadi and Behzadi 2008).

3.2 Uropathogenic Escherichia coli (UPEC)

E. coli pathotypes are divided into three groups of Intra-intestinal pathogenic *E.coli* (InPEC), *Shigella* Toxin Producer InPEC (ShiToPInPEC) and Extra-intestinal pathogenic *E. coli* (Behzadi 2018; Jahandeh et al. 2015). The pangenomic studies indicate two genomic pools of flexible (movable genes for the cells' environmental adaption) and core (key genes, e.g., housekeeping genes) for the cells' survival) among commensal and pathogenic strains of *E. coli*. In accordance with pangenomic investigations, the *E. coli* strains encompass a high plasticity in their genomes. Due to this fact, the estimated genomic load of *E. coli* strains is from 4.5 Mb up to 5.5 Mb. In this regard, the lowest level of genomic volume belongs to Intra-intestinal commensal (InCOM) strains of *E. coli* while the highest level of genomic content (5.5 Mb) belongs to drug resistant ExPEC strains including UPEC. The InPEC and ExPEC (e.g., UPEC) drug-sensitive strains bear genomic contents more than 4.5 and lesser than 5.5 Mb. These properties make UPEC a pathogen with a strong virulome (Behzadi and Behzadi 2016, 2017; Behzadi et al. 2016; Behzadi 2018; Behzadi 2020; Hozzari et al. 2020; Jahandeh et al. 2015).

As mentioned, the flexible (or Supplementary, Accessory or Adaptive) genomic pool is consisted of different genes, gene clusters and gene cassettes belonging to plasmids, transposons, retrotransposons, pathogenicity islands (PAIs), integrons and phages. These mobile genes determine the virulencity and pathogenicity of *E.coli* pathogenic strains including UPEC (Behzadi and Behzadi 2017; Brockhurst et al. 2019; Jahandeh et al. 2015; Ranjbar et al. 2017). The presence of a wide range of genes and in particular those which constitute the supplementary genomic pools among *E. coli* strains, gives us a proper opportunity to have a phylogenetic classification with eight phylogroups of *Escherichia* cryptic clade I (*arpA*-, *chuA*-, *yjaA*+, TspE4.C2-)/(*arpA*+, *chuA*+, *yjaA*+, TspE4.C2-), A (*arpA*+, *chuA*-, *yjaA*-, TspE4.C2-)/(*arpA*+, *chuA*-, *yjaA*+, TspE4.C2-), B1 (*arpA*+, *chuA*-, *yjaA*-, TspE4.C2+), B2 (*arpA*-, *chuA*+, *yjaA*+, TspE4.C2-)/(*arpA*-, *chuA*+, *yjaA*-, TspE4.C2+)/(*arpA*-, *chuA*+, *yjaA*+, TspE4.C2+), C (*arpA*+, *chuA*-, *yjaA*+, TspE4.C2-), D (*arpA*+, *chuA*+, *yjaA*-, TspE4.C2-)/(*arpA*+, *chuA*+, *yjaA*-, TspE4.C2+), E (*arpA*+, *chuA*+, *yjaA*-, TspE4.C2-)/(*arpA*+, *chuA*+, *yjaA*-, TspE4.C2+)/(*arpA*+, *chuA*+, *yjaA*+, TspE4.C2-) and F (*arpA*-, *chuA*+, *yjaA*-, TspE4.C2-) (Clermont et al. 2000; Clermont et al. 2013). This phylogenetic categorization is based on PAIs markers (Clermont et al. 2000, 2013; Najafi et al. 2018). The PAIs genes and other virulence genes (e.g., fimbrial and afimbrial adhesins, chaperone-usher (CU) and non-chaperone-usher adhesins, capsule, LPS, flagella, toxins, outer membrane proteins (OMPs) and vesicles (OMVs), metal (mostly iron and zinc) acquisition systems and autotransporter proteins) which are located within the adaptive genomic pool for the most (Behzadi 2020; Bien et al. 2012; Jahandeh et al. 2015; Ko et al. 2019a, b; Subashchandrabose and Mobley 2017; Walters and Mobley 2009). Hence, *in toto* the virulence factors (VFs) of UPEC can be

divided into superficial virulome and secretome st (Behzadi 2020; Bien et al. 2012; Jahandeh et al. 2015; Ko et al. 2019a, b; Subashchandrabose and Mobley 2017). The virulome elements belonging to UPEC surface contribute in attachment, colonization and biofilm formation while the secretome including secreted VFs (mostly toxins), secretion machineries and the related receptors and components are not only involved in colonization and biofilm formation but also they contribute in bacterial invasion, bacterial internalization, the host immunologic responses etc. which directly are associated with bacterial survival (Behzadi 2020; Bien et al. 2012; Jahandeh et al. 2015; Ko et al. 2019a, b; Subashchandrabose and Mobley 2017; Walters and Mobley 2009).

The secretome is consisted of secreted toxins such as Cytotoxic Necrotising Factor-1 (Cnf-1), Autotransporter Toxin (AT/Secreted Autotransporter Toxin (Sat), α-Haemolysin (HlyA) known as a member of Repeats in Toxin (RTX) toxins family, and Cytolethal Distending Toxin (Cdt) (Behzadi 2020; Bien et al. 2012; Jahandeh et al. 2015; Ko et al. 2019a, b; Subashchandrabose and Mobley 2017; Walters and Mobley 2009); metal acquisition systems (such as autotransporter proteins), metal receptors and chelators (e.g. siderophores), OMPs, OMVs (Bien et al. 2012; Jahandeh et al. 2015; Ko et al. 2019a, b; Subashchandrabose and Mobley 2017); and different secretion machineries (Costa et al. 2015; Jahandeh et al. 2015; Sana et al. 2020). The secretion machineries are the main secretome components in both Gram-positive and Gram-negative bacteria. These machineries produce and secrete different types of molecules including DNA and proteins. The secreted molecules have direct effects on environmental factors and contribute in bacterial adaptation, bacterial adhesion and attachment, bacterial pathogenicity and virulency and bacterial survival. Hence, the secreted molecules may have direct or indirect effects on exterior targeted cells (Costa et al. 2015; Jahandeh et al. 2015; Sana et al. 2020). Until now, we have recognized nine types of secretion systems (TSSs) including T1SS (type I secretion system) up to T9SS (Jahandeh et al. 2015). In accordance with transport procedures, the secretion machineries are categorized into two groups of single procedure or one-step process (just spanning the OM) and double-step procedure or two-step process (spanning the inner and outer membranes simultaneously) (Costa et al. 2015; Jahandeh et al. 2015; Navarro-García et al. 2016; Sana et al. 2020). T1SS, T3SS, T4SS (common between Gram-negative and Gram-positive bacteria) and T6SS are known as one-step and T2SS, T5SS, T7SS (recognized in mycobacteria), T8SS and T9SS are recognized as two-step secretion machineries (Abby et al. 2016; Jahandeh et al. 2015; Sana et al. 2020). In addition to T1SS-T9SS secretion machineries, Curli, CU and are recognized as important components of bacterial secretome (Abby et al. 2016; Hawthorne et al. 2016; Jahandeh et al. 2015; Konovalova and Silhavy 2015; Navarro-García et al. 2016; Sana et al. 2020).

3.3 Uropathogenic Klebsiella pneumoniae (UPKP)

UPKP is usually known as the second ranked Gram-negative bacterial agent of UTIs after UPEC (Behzadi et al. 2010; Terlizzi et al. 2017). Up to 5–10% of community-acquired and nosocomial UTIs are caused by UPKP (Paczosa and Mecsas 2016); while these percentages for UPEC are respectively, 95% and 50% (Behzadi et al. 2010; Terlizzi et al. 2017). Both of UPEC and UPKP belong to *the* Enterobacterales order and may cause community acquired and nosocomial UTIs (Behzadi et al. 2010; Paczosa and Mecsas 2016; Terlizzi et al. 2017). Besides Gram-negative bacteria such as UPEC and UPKP possess complicated cellular structure and therefore the effect of antimicrobial agents on them is tougher than Gram-positive bacteria. This property explains why the treatment procedure of UTIs caused by bacterial agents like UPEC and UPKP is harsher than UTIs caused by Gram-positive bacteria (Issakhanian and Behzadi 2019). *K. pneumoniae* resembling *E. coli* encompasses different types of strains from commensal strains to opportunistic pathogens and pathogens. The most common strains of *K. pneumoniae* belong to opportunistic pathogens

which may lead to classical (or health-care-associated) infections e.g. UTIs (Holt et al. 2015; Li et al. 2014; Paczosa and Mecsas 2016; Wyres et al. 2020). The main reservoirs for commensal strains of *K. pneumoniae* within human body are gastro-intestinal and respiratory tracts (Holt et al. 2015; Li et al. 2014; Paczosa and Mecsas 2016; Wyres et al. 2020). Those strains of *K. pneumoniae* which acquire antimicrobial resistance or hypervirulent (HV) genes are considered as serious problem regarding treatment of infectious diseases (Issakhanian and Behzadi 2019).

The pangenomic investigations confirm the presence of a genome with a size of five to six Mb in *K. pneumoniae*. It is estimated that this genome encodes about five to six thousands genes (Martin and Bachman 2018; Wyres et al. 2020). Among this number of genes, one thousand seven hundred genes belong to the core genomic pool of *K. pneumoniae* while the left belongs to supplementary (flexible/accessory/adaptive) genomic pool. The core genome is common between more than 95% of isolated strains of *K. pneumoniae* (Martin and Bachman 2018; Wyres et al. 2020). The adaptive genome usually includes a wide range of virulence and antimicrobial resistance genes which are gained from via horizontal gene transfer. They are mobile genes and genomic islands (Martin and Bachman 2018). Moreover, the total number of recognized sequences encoding proteins in different species of *Klebsiella* reaches more than hundred thousand proteins (Martin and Bachman 2018; Wyres et al. 2020). In accordance with bioinformatic and pangenomic surveys, *K. pneumoniae* involves a large number of genes with different origins of chromosomal, plasmids and phages. It seems that the diversity of recognized plasmids among *K. pneumoniae* is more than those that detected in ESKAPE members (Gajdács and Albericio 2019; Gajdács et al. 2020a, b; Wyres et al. 2020). In recent years, some bioinformatic databases have been established to determine the type and diversity of genomic elements like plasmid. The PlasmidFinder database is used for plasmid typing within *Enterobacteriaceae* pathogens (Carattoli et al. 2014; Carattoli and Hasman 2020). There is another database which can be used for molecular typing and microbial genome diversity (https://pubmlst.org/).

The VFs of UPKP are comparable with UPEC; because there is a wide range of virulence genes in UPKP and UPEC genomes. In this regard, capsule as a bacterial exopolysaccharide can be considered as an important VF in UPEC and UPKP (Holt et al. 2015; Li et al. 2014; Paczosa and Mecsas 2016; Wyres et al. 2020). Capsule is produced by *cps* gene clusters in classical UPKP (31). The HV strains possess thick capsules with significant content of mucoviscous polysaccharide increase the pathogenicity and virulencity of UPKP. The high content of capsule in HV strains can be supported by enhanced expression of plasmid borne genes of transcriptional regulators (*rmpA* and *rmpA2*). In the lack of *rmpA* and *rmpA2* genes in HV strains the *magA* gene contributes in hypercapsulation process. The *magA* gene is in association with invasion (Holt et al. 2015; Li et al. 2014; Paczosa and Mecsas 2016; Rastegar et al. 2019; Wyres et al. 2020). The lipopolysaccharide (LPS) is another VF which its genes are located on the core genome of *K. pneumoniae*. LPS is consisted of three structural sections including an O-antigen, a core oligosaccharide and the lipid A which are produced by the gene clusters of *wb*, *waa* and *lpx* (Holt et al. 2015; Paczosa and Mecsas 2016; Rastegar et al. 2019; Wyres et al. 2020). Siderophores are important metal-(iron) chelators which have significant role in UPKP infections throughout metal acquisition systems. The CU fimbrial adhesins of type 1 and type 3 fimbriae are produced by *fim* and *mrk* cluster genes, respectively which play significant role in bacterial attachment. Siderophores, type 1 and type 3 fimbriae are common between UPEC and UPKP strains (Holt et al. 2015; Li et al. 2014; Paczosa and Mecsas 2016; Rastegar et al. 2019; Wyres et al. 2020). The mentioned VFs together with efflux pumps and the secretion systems (e.g. T6SS) compose the main virulome of *K. pneumoniae* (UPKP) (Li et al. 2014; Martin and Bachman 2018).

3.4 Uropathogenic Proteus mirabilis (UPPM)

After UPEC and UPKP, Uropathogenic *P. mirabilis* (URPM) is recognized as the third bacterial causative agent of UTIs (Cestari et al. 2013). *P. mirabilis* is a well-known bacterial agent for blocking urine catheter and urolithiasis in urine bladder and kidneys by the help of its nickel metalloenzyme urease (encoded by the *ureDABCEFG* gene cluster/operon). The waste nitrogen within our urine (in the form of urea) is the main substrate for the urease which getting hydrolyzed into carbon dioxide (CO_2) and ammonia (NH_3). The released molecules of NH_3 within our urine may lead to alkalization of the pH of urine (Armbruster et al. 2018; Cestari et al. 2013; Ko et al. 2019a, b; Schaffer and Pearson 2017). The alkalized environment leads to crystallization of soluble anions and cationes and urolithiasis occurs by the mineral crystals of carbonate apatite [(pH $\geq$ 6.8) (calcium-phosphate/$Ca_{10}(PO_4)_6CO_3$)] and struvite [($\geq$7.2) (magnesium ammonium phosphate hexahydrate/$MgNH_4PO_4{\cdot}6H_2O$)]. The long-term UTIs caused by *P. mirabilis* can be lethal (Armbruster et al. 2018; Bichler et al. 2002; Cestari et al. 2013; Ko et al. 2019a, b; Prywer et al. 2012; Schaffer and Pearson 2017). *P. mirabilis* encompasses an abundance of VFs including capsule, LPS, Adhesins, fimbriae, flagellum, enzymes (urease), metal acquisition systems, different secretion systems, etc. which may lead to serious infections in patients with UTIs (Armbruster et al. 2018; Cestari et al. 2013; Ko et al. 2019a, b; Schaffer and Pearson 2017). In accordance with previous reports, up to 10% of UTIs is caused by *P. mirabilis* (Schaffer and Pearson 2017). This motile Gram-negative bacterium which is famous for its bull's-eye swarming pattern on agar, usually contributes in complicated UTIs and catheter-associated UTI (CAUTI) (Pearson et al. 2010; Schaffer and Pearson 2017). Moreover, *P. mirabilis* is a serious problem in elderly patients with CAUTI; because it can be the murderer of up to 50% of the old patients with long-term CAUTI (Schaffer and Pearson 2017).

Genomic investigations regarding *P. mirabilis* indicate a high diversity in genomic pool of this microorganism. Despite this significant diversity, a considerable part of chromosomal genome is conserved among different strains of *P. mirabilis* (Armbruster et al. 2018). All in all, *P. mirabilis* has a mosaic pangenome resembling *E. coli* which is obtained throughout horizontal gene transfer. The genomic island of integrative and conjugative element (ICE) which is known as ICEPm1 in *P. mirabilis* acts as a chromosomal transposon (Armbruster et al. 2018; Flannery et al. 2011). The ICE is common among bacterial microorganisms of *P. mirabilis*, *Morganella morganii* and *Providencia stuartii* and this PAI contains two virulence genes of *nrp* (encoding non-ribosomal peptide siderophore) and *pta* (*Proteus* Toxic Agglutinin) operons (Armbruster et al. 2018; Barker 2013; Flannery et al. 2011). The bioinformatic, molecular biological and genomic surveys have revealed a wide range of VFs in *P. mirabilis* including secretion systems (e.g. T1SS, T3SS, T4SS, T5SS and T6SS), toxins (such as hemolysin (HpmA-HpB), Pta, ZapA metalloprotease), fimbriae/fimbrial adhesins (like Mannose-resistant *Proteus*-like fimbriae (MR/P), "non-agglutinating fimbriae" (NAF/UCA), *P. mirabilis* fimbriae (PMF), Ambient temperature fimbriae (ATF), *P.mirabilis* P-like fimbriae (PMP), Fimbria 14), afimbrial adhesins (e.g. Uroepithelial cell adhesin (UCA/NAF)), metal acquisition systems (for iron, zinc, nickel and phosphate) and flagella (Armbruster et al. 2018; Barker 2013; Flannery et al. 2011).

In toto, uropathogenic bacteria and in particular the UPEC, UPKP and UPPM are "live treasures" of VFs which have their own properties and characteristics. Each VF has its own structure and molecular mechanism which can activate different molecules of the host's immune systems. Any defect within the host's immune system may lead to leak of uropathogenic bacteria into the host's urinary tract which results in different types of UTIs from mild and asymptomatic to severe infections. Due to this fact, the bioinformatics helps us to have conscious guess regarding the immunological, molecular biological

characteristics of bacterial virulence and pathogenicity.

4 Therapeutic Aspects of Urinary Tract Infections

In the following section, the therapeutic aspects of UTIs are summarized, based on the most recent international guidelines available in the published literature in English.

4.1 Indication of Antibiotic Therapy

Urinary tract infections (UTIs) have mainly bacterial etiologies, hence the crucial role of antibacterials in the treatment of UTIs is unquestionable. Even in the case of lower urinary tract infection (cystitis), antibacterial use is recommended as clinical cure is significantly higher compared to placebo (Bonkat et al. 2019). Despite this, some national guidelines recommend the watchful waiting approach for 48 h in case of acute cystitis in women if pregnancy is not present (NICE 2018), or the urinanalysis is negative (Kranz et al. 2018a, b) to allow spontaneous recovery of symptoms.

UTIs can be classified in many ways. Based on various patient characteristics, acute cystitis can be grouped into uncomplicated form and complicated form (Bonkat et al. 2019; Chapple and Mangera 2018). In the later case, the eradication of the pathogen is more difficult (Bonkat et al. 2019) and response rate to short-course antibiotic therapy is worse (Chapple and Mangera 2018).

4.2 Treatment of Acute Uncomplicated Cystitis (AUC)

Acute uncomplicated cystitis (sporadic or recurrent) pertains to pre-menopausal, non-pregnant women without relevant co-morbidities or anatomical/functional urinary tract abnormalities (Bonkat et al. 2019). The recommended empiric antibacterial agents in different guidelines are summarized in Table 1.

Most national guidelines recommend one dose (3 grams) fosfomycin as a first line treatment in AUC (Bonkat et al. 2019; Chapple and Mangera 2018; Gilbert et al. 2019; Kranz et al. 2018a, b; Melia 2017). Some American guideline recommends to reserve fosfomycin for suspected multidrug resistant (MDR) infections or when other first-line agents cannot be used (Hooton and Gupta 2019a, b). Nitrofurantoin is recommended as first line treatment of AUC in all of the identified guidelines (Table 1), with a dose varying from 150 mg to 400 mg daily, for 3–5 days (Bonkat et al. 2019; Chapple and Mangera 2018; Gilbert et al. 2019; Hooton and Gupta 2019a, b; Kranz et al. 2018a, b; Melia 2017; Melia and DeMaio 2017; Network SIG 2012; Wuorela 2018).

Trimethoprim and its combination with a sulphonamide derivative: trimethoprim-sulfamethoxazole (TMP/SMX) are often recommended in the treatment guidelines with the proviso that it should be used only if local resistance level among *E.coli* or *Enterobacteriaceae* is below 20% (Bonkat et al. 2019; Chapple and Mangera 2018; Gilbert et al. 2019; Kranz et al. 2018a, b; Melia 2017). Except pivmecillinam which is an extended spectrum penicillin (WHO 2019), all other beta-lactam agents are considered as second line treatment (see Table 1), with a longer course (usually 5–7 days).

The role of fluoroquinolones in the treatment of AUC is limited to special cases where other agents cannot be used due to adverse drug reactions (e.g. allergy, intolerance) (Melia 2017). Certain guidelines explicitly advise against the use of fluoroquinolones in AUC (Bonkat et al. 2019; Network SIG 2012; Wuorela 2018). This is in line with recent resolution of the both the American and European Medicine Authorities which recommend against the use of fluoroquinolones in any non-complicated infections (including AUC) as associated collateral damage and risk of severe permanent adverse effect clearly outweighs the potential benefits (Hooper 2019).

The evidence supporting the add-on effect of analgesics for symptomatic relief in

Table 1 The recommended empiric antibacterial agents for acute uncomplicated cystitis (women)

	Finnish-2017 (10)	Scottish – 2012 (11)	German-2017 (4)	UK-2018 (2)	BMJ Best Practise-UK 2018 (5)	John Hopkins-2017 (7)	EUA guideline-2019 – (1)	Sanford guide-2019 (6)	UpToDate 2018 (8)
Fosfomycin			First line	Second line	First line	First line	First line	First line	Second line
Nitrofurantoin	First line	First line	First line	First line and second line	First line	First line	First line	First line	First line
Nitroxolin			First line						
Trimethoprim[a]	First line	First line		First line	First line				First line
SMX-TMP			Second line		First line	First line	Second line	First line	First line
Pivmecillinam	First line		First line	Second line	First line	First line	First line	Second line	First line
Co-amoxiclav		Avoid				Second line	Avoid	Second line	Second line
Cephalexin		Avoid			Second line			Second line	Second line
Cefdinir		Avoid						Second line	Second line
Cefpodoxime-axetil		Avoid	Second line		Second line	Second line			Second line
Cefixime		Avoid				Second line			
Cefadroxil		Avoid							Second line
Ofloxacin	Second line	Avoid	Second line			Second line	Avoid		
Norfloxacin		Avoid	Second line		Third line	Second line	Avoid		
Ciprofloxacin	Second line	Avoid	Second line		Third line	Second line	Avoid	Second line	Third line
Levofloxacin	Second line	Avoid	Second line		Third line	Second line	Avoid	Second line	Third line

Bonkat et al. (2019), Chapple and Mangera (2018), ECDC (2018), Frassetto (2018), Gagyor et al. (2012), Gagyor et al. (2015), Gilbert et al. (2019) Hooton and Gupta (2019a, b), Hooper (2019), Kranz et al. (2018a, b), Kroneberg et al. (2017), Melia (2017), Melia and DeMaio (2017), NICE (2018), Network SIG (2012), WHO (2019), Wuorela (2018)
SMX-TMP sulphamethoxazole/trimethoprim
[a]Use in empiric therapy only if local resistance in *E. coli* is lower than 20% and if not used to treat UTI in past 3 months

uncomplicated UTIs is lacking. However some studies revealed that ibuprofen can reduce the rate of antibiotic prescribing (Gagyor et al. 2012, 2015). Consequently, some guidelines recommend the use of paracetamol (Bonkat et al. 2019; Chapple and Mangera 2018; Gilbert et al. 2019; Hooton and Gupta 2019a, b; Kranz et al. 2018a, b; Melia 2017; Melia and DeMaio 2017; Network SIG 2012; Wuorela 2018) or ibuprofen (Gagyor et al. 2012, 2015) or the urinary analgesic phenazopyridine (Bonkat et al. 2019; Chapple and Mangera 2018; Hooton and Gupta 2019a, b; Kranz et al. 2018a, b; Melia 2017) to relieve the discomfort (dysuria). Symptomatic treatment is primarily important in cases where patient refuse to take antibiotics or when the watchful-waiting approach for 48 h can be considered.

4.3 Treatment of Acute Cystitis in Men

The acute cystitis in men is often accompanied by prostate involvement. The choice of antibacterial is repetitive doses of fosfomycin (3 grams on consequent 2–3 days) or TMP/SMX, which should be revised based on microbiological results (Gilbert et al. 2019; Hooton 2018; Kroneberg et al. 2017). Nitrofurantoin and pivmecillinam should be avoided in the cystitis of men, due to the limited prostate penetration (Gilbert et al. 2019; Hooton 2018; Kroneberg et al. 2017).

4.4 Treatment of Acute Pyelonephritis (AP) and Complicated Urinary Tract Infections (cUTIs)

The definitions of upper urinary tract infections (acute pyelonephritis-AP) and complicated urinary tract infection (cUTIs) are smeared. Most guidelines differentiate between acute uncomplicated pyelonephritis where causative organisms are identical with AUC and complicated urinary tract infections- cUTIs (including pyelonephritis) with broad range of possible pathogen bacteria (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b). An other approach is to define all UTI cases that extend beyond the bladder as complicated infection, and do not automatically consider urological abnormalities, immuncompromising conditions, as complicating factors (Hooton and Gupta 2019a, b). The listed complicating factors (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b) also lack consensus and generally cover a wide variety of conditions. The heterogeneity of the patient population considered to have cUTIs preclude general approach to the initial empiric antibacterial therapy. The diversity in antibiotic resistance also makes the up-to-date knowledge of local resistance patterns critical.

The need of urine culture and sensitivity analysis concurs in different guidelines to tailor initial empiric therapy in cUTIs (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b). Duration of treatment can also range widely, but generally 7–14 days are needed to achieve clinical cure. Empiric antibiotic choice is typically based on individual assessment of disease severity, local bacterial susceptibilities, personal risk factors for antibiotic resistant bacteria, drug contraindications (e.g. allergies), and may include a wide range of antibacterial agents based on local availability of active agents (see Table 2).

Those patient that have mild-moderate symptoms, (hemodinamically) stable, laboratory parameters are essentially normal and lack any risk factors which predispose them to deteriorating can be treated as outpatients (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b). The recommended empirical agents typically include oral fluoroquinolones (if local resistance is below 10% and no personal risk for resistant bacteria), oral cephalosporins (mostly third generation agents) and in few guidelines with some restrictions: TMP/SMX (see Table 2). In many guidelines oral treatment should be preceded by one dose of ceftriaxone or aminoglycoside and in some guides ertapenem.

Patient who cannot take oral medication, volume depleted, has severe signs as early septic haemodynamic parameters or having relevant complicating factors should be admitted and

Table 2 The recommended empiric antibacterial agents for acute pyelonephritis (AP) and complicated urinary tract infections (cUTI)

	German	UK – 2018	USA BMJ-Best-2018	US – John Hopkins-2017	EUA-2019	Sanford guide-2019	UpToDate-2019
Levofloxacin	Uncomplicated pyelonephritis: First line iv/oral		Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease (if R < 10%): Second line oral	Complicated UTI, mild/moderate ill: First line: Oral/iv	Uncomplicated pyelonephritis: First line oral/iv, only if R < 10% cUTI: Only if R < 10%, not severe infection and beta-lactam anaphylaxia	Pyelonephritis in women/men, with low risk for resistant bacteria: First line cUTI with low MDR GNB risk: First line	Outpatient, if personal risk of R isolate is low (if local R is above 10%, administer 1 dose of ceftriaxone, ertapenem or aminoglycoside first): First line Outpatient, high personal MDR risk AND no prior FQ use/resistance within 3 months Use only after one dose of ertapenem: First line Hospitalized, oral/iv, No risk for MDR GNB (if no FQ resistant isolate in prior 3 months and local *E. coli* R is below 10%): First line
Ciprofloxacin	Uncomplicated pyelonephritis: First line iv/oral	Acute pyelonephritis women/men: First line oral/iv based on severity	Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease (if R < 10%): First line oral AND Acute pyelonephritis, severe symptoms/ complicated disease: first line, iv	Complicated UTI, mild/moderate ill: First line: Oral/iv	Uncomplicated pyelonephritis: First line oral/iv, only if R < 10% cUTI: Only if R < 10%, not severe infection and beta-lactam anaphylaxia	Pyelonephritis in women/men, with low risk for resistant bacteria: First line	Outpatient, if personal risk of R isolate is low (if local R is above 10%, administer 1 dose of ceftriaxone, ertapenem or aminoglycoside first): First line, Outpatient, if high personal MDR risk AND no prior FQ use/resistance within 3 months Use only after one dose

							of ertapenem: First line Hospitalized, oral/iv, No risk for MDR GNB (if no FQ resistant isolate in prior 3 months and local *E. coli* R is below 10%): First line
Ofloxacin			Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease (if R < 10%): First line oral Acute pyelonephritis, severe symptoms/ complicated disease: First line, iv				
Amikacin	Uncomplicated pyelonephritis: Severe infection: Second line	Acute pyelonephritis women/men, severe infection: First line i			Uncomplicated pyelonephritis: Second line, iv cUTI: First line, **with** amoxicillin/2nd gen cephalosporin		
Gentamycin	Uncomplicated pyelonephritis: Severe infection: Second line	Acute pyelonephritis women/men, severe infection: First line i	Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease: 1 initial dose before oral empiric treatment OR Acute pyelonephritis, severe symptoms/ complicated disease: First line (+/− ampicillin)		Uncomplicated pyelonephritis: Second line cUTI: First line, **with** amoxicillin/2nd gen cephalosporin	Pyelonephritis in women with low risk for resistant bacteria: Second line cUTI with low risk of MDR GNB: First line	Only as initial one dose before oral treatment (see above)

(continued)

Table 2 (continued)

	German	UK – 2018	USA BMJ-Best-2018	US – John Hopkins-2017	EUA-2019	Sanford guide-2019	UpToDate-2019
Plazomycin							Hospitalized: Critical illness and/or urinary tract obstruction AND selected cases of highly resistant infections (Outpatient, high MDR risk: Second line as initial one dose)
SMX/TMP			Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease: Second line oral (as many *E.coli* are resistant)		Uncomplicated pyelonephritis: First line oral, after a single dose parenteral ceftriaxone/ aminoglycoside cUTI: No indication		Outpatient, orally, if FQ is contraindicated AND low personal risk of MDR But only after 1 initial dose of ceftriaxone/ ertapenem/ aminoglycoside
Co-amoxiclav	Uncomplicated pyelonephritis: Severe infection: Second line,	Acute pyelonephritis women/men: First line, based on severity: Oral/iv, (only if sensitive on antibiogram)					Outpatient, orally, if FQ is contraindicated AND low risk of MDR But only after 1 initial dose of ceftriaxone/ ertapenem/ aminoglycoside
Ampicillin-sulbactam			Acute pyelonephritis, severe symptoms/ complicated disease: First line				

Piperacillin-tazobactam	Uncomplicated pyelonephritis: Severe infection: Second line		Acute pyelonephritis, severe symptoms/ complicated disease: Second line		Uncomplicated pyelonephritis: Second line	Acute pyelonephritis, severe: Second line only in pregnant women cUTI with low risk of MDR GNB: First line	Hospitalized, no risk for MDR GNB: First line
Cefalexin		Acute pyelonephritis women, men: Mild: First line					
Cefadroxil							Outpatient, mild if FQ is contraindicated AND low risk of MDR But only after 1 initial dose of ceftriaxone/ ertapenem/ aminoglycoside
Cefuroxim		Acute pyelonephritis women/men, severe: First line, iv			cUTI: First line in combination with aminoglycosides		
Cefixim			Acute pyelonephritis, mild/moderate symptoms & uncomplicated disease: First line as oral				
Ceftriaxone	Uncomplicated pyelonephritis: Severe infection: First line	Acute pyelonephritis women/men, severe: First line i	Acute pyelonephritis, mild/moderate: One initial dose before oral empiric treatment Acute pyelonephritis, severe symptoms or complicated disease: First line		Uncomplicated pyelonephritis: First line cUTI: First line	Pyelonephritis in women with low risk for resistant bacteria: First line cUTI with low risk of MDR GNB: First line	Hospitalized, no risk for MDR GNB: First line Outpatient: One initial dose before oral empiric treatment (see above)

(continued)

Table 2 (continued)

	German	UK – 2018	USA BMJ-Best-2018	US – John Hopkins-2017	EUA-2019	Sanford guide-2019	UpToDate-2019
Cefotaxime	Uncomplicated pyelonephritis: Severe infection: First line				Uncomplicated pyelonephritis: First line cUTI: First line		
Cefpodoxim OR cefdinir -3GEN	Uncomplicated pyelonephritis, mild-moderate: First line oral				Uncomplicated pyelonephritis: First line, after a single dose parenteral ceftriaxone/ aminoglycoside		Outpatient, mild if FQ is contraindicated AND low risk of MDR But only after 1 initial dose of ceftriaxone/ ertapenem/ aminoglycoside
Ceftibuten	Uncomplicated pyelonephritis, mild-moderate: First line oral				Uncomplicated pyelonephritis: First line, after a single dose parenteral ceftriaxone/ aminoglycoside		
Ceftazidime	Uncomplicated pyelonephritis: Severe infection: Second line			Complicated UTI, severe/ LTCF/prior FQ	cUTI: First line		
Ceftazidime/ avibactam	Uncomplicated pyelonephritis: Severe infection: Second line		Acute pyelonephritis, severe symptoms/ complicated disease: Second line	Complicated UTI, severe/ LTCF/prior FQ	Uncomplicated pyelonephritis: Second line	cUTI with high risk MDR GNB: First line	Critical illness/urinary tract obstruction OR hospitalized & MDR GNB risk AND selected cases of highly resistant infections

Ceftolozane/ tazobactam	Uncomplicated pyelonephritis: Severe infection: Second line			Complicated UTI, severe/ LTCF/prior FQ	Uncomplicated pyelonephritis: Second line	cUTI with high risk MDR GNB: First line	Critical illness/urinary tract obstruction OR hospitalized & MDR GNB risk AND selected cases of highly resistant infections
Cefepime	Uncomplicated pyelonephritis: Severe infection: Second line			Complicated UTI, severe/ LTCF/prior FQ	Uncomplicated pyelonephritis: Second line	Pyelonephritis in pregnant women: First line cUTI with low risk of MDR GNB: First line	
Ertapenem	Uncomplicated pyelonephritis: Severe infection: Second line					Pyelonephritis in women: First line if high MDR risk, second line if low MDR risk Pyelonephritis in men, high MDR GNB risk: First line	Outpatient, high risk of MDR: 1 dose followed by FQ (if no contraindication or no prior use/resistance) or continue as OPAT
Imipenem	Uncomplicated pyelonephritis: Severe infection: Second line		Acute pyelonephritis, severe symptoms/ complicated disease: Second line	Complicated UTI, severe/ LTCF/prior FQ	Uncomplicated pyelonephritis: Third line (only if early culture result indicate MDR)		Critical illness and/or urinary tract obstruction (+vancomycin) OR Hospitalized and risk for MDR GNB
Meropenem	Uncomplicated pyelonephritis: Severe infection: Second line			Complicated UTI, severe/ LTCF/prior FQ	Uncomplicated pyelonephritis: Third line (only if early culture result indicate MDR)	Acute pyelonephritis in women/men AND high risk for MDR: First line cUTI with high MDR GNB risk: First line	Critical illness and/or urinary tract obstruction (+vancomycin) OR Hospitalized and risk for MDR GNB

(continued)

Table 2 (continued)

	German	UK – 2018	USA BMJ-Best-2018	US – John Hopkins-2017	EUA-2019	Sanford guide-2019	UpToDate-2019
Doripenem				Complicated UTI, severe/ LTCF/prior FQ			Critical illness and/or urinary tract obstruction (+vancomycin) OR Hospitalized and risk for MDR GNB
Meropenem-avorbactam						cUTI with high risk MDR GNB: First line	Critical illness/urinary tract obstruction OR hospitalized & MDR GNB risk AND selected cases of highly resistant infections
Aztreonam						Pyelonephritis in pregnant women, moderately ill: Second line (if penicillin allergic) cUTI with low risk of MDR GNB: Second line (if penicillin allergic)	

Bonkat et al. (2019), Chapple and Mangera (2018), ECDC (2018), Frassetto (2018), Gagyor et al. (2012), Gagyor et al. (2015), Gilbert et al. (2019), Hooton and Gupta (2019a, b), Hooper (2019), Kranz et al. (2018a, b), Kroneberg et al. (2017), Melia (2017), Melia and DeMaio (2017), NICE (2018), Network SIG (2012), WHO (2019), Wuorela (2018)

treated with parenteral regimen (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b). Possible regimens include extended-spectrum cephalosporins, aminoglycosides with or without ampicillin (if enterococcus is being considered), fluoroquinolones, aminopenicillins with beta-lactamase inhibitors, antipseudomonal penicillins, and in special cases carbapenems. With clinical improvement, the patient can be switched to an oral antimicrobial to which the organism is susceptive to complete the course of therapy (Bonkat et al. 2019; Frassetto 2018; Hooton and Gupta 2019a, b).

The recommended therapeutic agents of AUC: fosfomycin, nitrofurantoin, pivmecillinam cannot be used in infections involving the kidneys, due to the low tissue penetration (Bonkat et al. 2019; Hooton and Gupta 2019a, b).

Despite the broad spectrum of antimicrobial activity against most uropathogen and achievement of high drug levels in the urinary tract, fluoroquinolones losted importance due to high resistance level (ECDC 2018) and can be recommended as first choice agent only in uncomplicated acute pyelonephritis (see Table 2). According to the guideline of the European Association of Urology fluoroquinolones can only be used in cUTIs if local resistance levels are below 10%, the patient is not severely ill and initial therapy cannot be started with a beta-lactam due to anaphylactic reaction (Bonkat et al. 2019). Other guidelines also make restrictions on the use of fluoroquinolones in cUTIs and even in uncomplicated pyelonephritis (see Table 2).

Aminoglycosides have a reinassance in treating UTIs: they can be used as an initial one dose before switching to oral regimen in mild/moderate cases, and is used widely in severe infections, usually in combination with amoxicillin or second generation cephalosporins.

The parenteral form of second generation cephalosporins has indication in AP (NICE 2018) or cUTIs in combination with aminoglycosides (Bonkat et al. 2019). Third generation parenteral cephalosporins, most often ceftriaxon, are the gold standard in the treatment of cUTIs and AP. Ceftriaxone is also recommended as an initial first dose before starting oral treatment in mild/moderate AP. Carbapenems have limited indications in UTIs: in uncomplicated AP they are used only if early results indicate MDR bacteria (so basically used only as targeted therapy), while in other guides they are used in severely ill patients or who are hospitalized and have a high risk of infections due to MDR gram negative bacteria (GNB) (i.e. extended spectrum β-lactamase-producing Enterobacterales), for example nursing home residents, or who had prior antibiotic exposure, etc. Aminopenicillins with beta-lactamase inhibitors have indications in few guidelines, while the antipseudomonal piperacilin-tazobactam is widely recommended, usually as second line agent in severe infection or in complicated disease, when there is low risk for MDR GNB.

4.5 Assessing the Quality of Antibiotic Use

The utilisation of antibiotics are often appraised by the so-called quality indicators (QIs). QIs are defined as a specific and measurable elements of practice performance for which there is evidence or consensus that can be used to assess and hence, change the quality of care (Campbell et al. 2003; Donabedian 1998). Most often, QIs are categorised as structure (reflecting the organizational issues), process (reflecting diagnostic and treatment related decisions) or outcome indicators (focusing on the consequences) (Donabedian 1998).

Recently two systematic reviews followed by an international, multidisciplinary consensus procedure have been published on quality indicators of antibiotic use: one on ambulatory care and one on hospital care (Le Marechal et al. 2018; Monnier et al. 2018). These internationally developed quality indicators are purposely generic (i.e. not specific to certain infections), can be applied worldwide by different stakeholders and provide a comprehensive evaluation of antibiotic use. The existence and elements of antibiotic stewardship programme, regular audits,

availability of antibiotic treatment guidelines, essential antibiotic list/antibiotic formulary and the continuous availability of essential antibacterial agents are examples of structure QIs that can be generally applied (Le Marechal et al. 2018; Monnier et al. 2018; Pollack et al. 2016). Nosocomial *C. difficile* infection rate is typical example for outcome indicator, but due to its limitations (potentially influenced by many concurrent factors) it provide only indirect evidence of the provided care (Monnier et al. 2018). The prescribing of antibiotics for acute bacterial infections, the compliance with different elements of treatment guidelines, rare prescription of certain antibiotics and acknowledgement of contraindications are some of those generic process QI that can be applied for urinary tract infections (Le Marechal et al. 2018; Monnier et al. 2018; Pollack et al. 2016).

Process indicators enable a direct evaluation of the provided treatment hence their use is widespread. In Table 3 we summarized those quality indicators that pertain specifically to urinary tract infections. No validated indicator exist for the diagnostic process of urinary tract infection, except the need for urine culture in complicated UTIs (Pollack et al. 2016). As urinary tract infections –with few exceptions- have bacterial aetiology, the use of antibiotics is acceptable in every case (quality indicator 1.). The European quality indicator and those from Norway and Sweden target to use the first line agents in minimum 80% or 90% of women with afebrile urinary tract infection (quality indicator 3 and 4). Moreover, the avoidance of fluoroquinolones in the ambulatory care treatment of UTI is evident, the most permissive target is that maximum 10% of women below the age of 80 years should be treated with fluoroquinolones (quality indicator 5,6,7) (Hermanides et al. 2008; Adriaenssens et al. 2011; Pollack et al. 2016). Due to the higher rate of trimethoprim resistance in the elderly population, in UK, they try to reduce its prescribing in the elderly (quality indicator 8, 9) (D'Atri et al. 2019; Norwegian Ministries 2015).

It is important to note that quality indicators cannot provide a definitive judgement of quality, but they generate reflection, debate and allow benchmarking across different practices and such comparison has been proven to be an important stimulus for quality improvement (D'Atri et al. 2019; Drivsholm 2014; Norwegian Ministries 2015). In summary, the assessment of the quality of antibiotic use in frequent infections like UTIs is essential to evaluate the impact of antibiotic stewardship activities and to help health care providers and policy makers to set priorities for interventions to rationalise antibiotic use (Le Marechal et al. 2018; Saust et al. 2016).

4.6 Treatment of Urinary Tract Infections in the Context of the Emerging Multidrug Resistance

Although uncomplicated UTIs are often a self-resolving infections (with cure rates of 15–45%), almost all UTIs are treated with the administration of antibiotics (both as self-medication or doctor-prescribed) (Bonkat et al. 2019). In many primary care/outpatient settings, most patients experiencing UTIs are treated empirically, without establishing the exact etiological agents or their antibiotic susceptibilities (Bischoff et al. 2018). Current therapeutic recommendations emphasize the role of nitrofurantoin, fosfomycin, pivmecillinam and trimethoprim-sulfamethoxazole (TMP/SMX) as first-line treatments in (uncomplicated) UTIs as safe and effective therapeutic alternatives; in general, β-lactam antibiotics [extended-spectrum cephalosporins and carbapenems], aminoglycosides and fluoroquinolones should only be considered in complicated UTIs (e.g., pyelonephritis), in inpatients and in patients with an unmodifiable drug interaction, intolerance, hypersensitivity (-β-lactam-allergy, prolonged QT interval or other risk factors for torsades de pointes) to the abovementioned agents (see previous subsections). The chosen antimicrobial drug should achieve adequate concentrations in the urine or in the respective anatomical region and should be effective in shorter courses. Additionally, the adverse events associated with inappropriate antibiotic use, the overuse of fluoroquinolones and the concept of

Table 3 Use of quality indicators related to urinary tract infections

No	Quality indicator	Acceptable range (%)	QI type
1	Percentage of female patients older than 18 years with cystitis/other urinary infection (ICPC-2-R: U71) prescribed antibacterials for systemic use (ATC: J01) (European indicator)	80–100	Decision to prescribe
2	Female patients older than 18 years with cystitis/other urinary infection receiving the recommended antibacterials (ATC: J01XE or J01EA or J01XX) (European indicator)	80–100	Decision on antibiotic choice: (preferring first line agents)
3	More than 80% of women and more than 50% of men with afebrile urinary tract infection should receive first-line treatment. (Sweden, ambulatory care)	80–100 (female) 50–100 (male)	Decision on antibiotic choice: (preferring first line agents)
4	More than 90% of patients with afebrile urinary tract infection should receive first-line treatment. (Sweden, hospital care)	90–100	Decision on antibiotic choice: (preferring first line agents)
5	Female patients older than 18 years with cystitis/other urinary infection receiving quinolones (ATC: J01M) (European indicator)	0–5	Decision on antibiotic choice (avoidance of certain agents)
6	To reduce the prescription rate of fluoroquinolones (and, in particular, ciprofloxacin) for treating uncomplicated urinary tract infections in women aged 20–79 years to less than 8% of all antibiotics prescribed for urinary tract infections in the same patient group. (Norway, ambulatory care)	0–8	Decision on antibiotic choice (avoidance of certain agents)
7	Maximum of 10% of all antibiotics used to treat urinary tract infections in women aged 18–79 years should be fluoroquinolones (Sweden, ambulatory care)	0–10	Decision on antibiotic choice (avoidance of certain agents)
8	Reduction of inappropriate antibiotic prescribing for urinary tract infections minimum 10% reduction in the trimethoprim/nitrofurantoin prescribing ratio prescribed to patients aged ≥70 years due to the higher rates of trimethoprim non-susceptibility in this age group (UK, ambulatory care)	At least a 10% reduction within 2 years	Decision on antibiotic choice (avoidance of certain agents)
9	Reduction of inappropriate antibiotic prescribing for urinary tract infections at least a 10% reduction in trimethoprim items prescribed to patients aged ≥70 years due to the higher rates of trimethoprim non-susceptibility in this age group (UK, ambulatory care)	At least a 10% reduction within 2 years	Decision on antibiotic choice (avoidance of certain agents)

Adriaenssens et al. (2011), Campbell et al. (2003), Donabedian (1998), D'Atri et al. (2019), Hermanides et al. (2008), Le Marechal et al. (2018), Monnier et al. (2018), Norwegian Ministries (2015), Pollack et al. (2016)
J01 Systemic antibacterials, J01EA Trimethoprim and derivatives, J01XX Other antibacterials (e.g. fosfomycin, methenamine), J01XE nitrofuran derivatives (e.g. nitrofurantoin), J01M Quinolones, ATC Anatomical, therapeutic and chemical classification, ICPC-2-R International Classification of Primary Care, Second edition

„collateral damage" (affecting the gastro-intestinal and vaginal flora) has taken center stage in the recent years, when it comes to the therapy of UTIs (Gajdács et al. 2019a; Looft and Allen 2012; Tanne 2008; Weber 2006). These empirical regimens (based on Infectious Diseases Society of America [IDSA] guidelines) should be guided by local susceptibility trends, e.g., TMP/SMX is recommended if resistance rates are lower, than 20%, while this rate is <10% for fluoroquinolones (see previous subsections). Nevertheless, if susceptibility data is available, pharmacotherapy should be tailored to these results (Bischoff et al. 2018). The treatment of UTIs is an increasingly complex challenge for clinicians, due to the plethora of intrinsic and acquired resistance mechanisms they possess; these mechanism should all be taken into consideration when selecting antibiotic therapy

(Doi et al. 2017; Pallett and Hand 2010; Rodríguez-Baño et al. 2018). The mechanism of antibiotic resistance may include porin loss and mutations affecting outer membrane permeability (β-lactam antibiotics), alterations in target sites (aminoglycosides, fluoroquinolones, tetracyclines), energy-dependent efflux pumps (a wide variety of antibiotics), in addition to the production of drug-inactivating enzymes (e.g., AmpC-β-lactamases, carbapenemases, aminoglycoside-inactivating enzymes) (Sanjait and Indrawattana 2016). In some cases, these resistance mechanisms affect the susceptibility of individual antibiotics differently (even in the same group); this is the reason why some isolates may be resistant to meropenem, but not imipenem, or resistant to amikacin, but not tobramycin (this is especially common in non-fermenters) (Ko et al. 2019a, b). CES bacteria are all intrinsically resistant to penicillins, several β-lactam/β-lactamase combinations (e.g., ampicillin/sulbactam, amoxicillin/clavulanic acid), first–second generation cephalosporins, and cephamycins (i.e., cefoxitin), due to their penicillinases and AmpC-β-lactamases (Gajdács et al. 2019a, b, c, d). Additionally, nitrofurantoin, doxycycline, colistin and most of the aminoglycosides (with the exception of streptomycin and amikacin) are also ineffective against *Serratia* spp. (Gupta et al. 2014). Members of the Proteae tribe have similar intrinsic resistance mechanism (nitrofurantoin, tetracyclines, and colistin are ineffective), they produce various β-lactamases (penicillinases, AmpC-β-lactamases) and they also have an intrinsic reduced susceptibility to imipenem (Barnaud et al. 1997; Gajdács et al. 2019a, b, c, d). In fact, due to their clinical significance, and their common AmpC-β-lactamase-production, these pathogens are a part of the "SPICE" group (*Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*) of bacteria (Gajdács et al. 2019a, b, c, d; Moy and Sharma 2017).

Since the beginning of the twenty-first century, several national and global (e.g., the SENTRY Antimicrobial Surveillance Program or the Study for Monitoring Antimicrobial Resistance Trends; SMART) surveillance reports have evaluated and published the resistance trends of various Gram-positive and Gram-negative bacteria; these reports unanimously confirmed the increase in the resistance-levels among common UTI-causing pathogens (both community-associated and hospital-acquired), and the emergence of multidrug resistant strains (MDR), extensively drug resistant (XDR) and even pandrug-resistant (PDR) strains of bacteria (Gajdács et al. 2020a, b; Chen et al. 2015; Morissey et al. 2013; Sader et al. 2014; Ponce-de-Leon et al. 2018). These strains (in addition to their intrinsic resistance mechanisms), express plasmid-encoded (transmissible) resistance determinants, which is both a therapeutic and infection control concern. The increased resistance is these pathogens is one of the main risk factor for a poor prognosis, therapeutic failure and even increased mortality rate in the hospitalized patient population. Conversely, resistance seriously limits the therapeutic options in outpatient settings, which may force clinicians to utilize more expensive antibiotics with a disadvantageous side effect-profile (Gajdács et al. 2019a, b, c, d). Thus, in the current era of high-resistance rates, the knowledge regarding the epidemiological information becomes much more important than ever before.

Resistance to β-lactam antibiotics (which may be mediated by a variety of mechanisms, the most common ones in Gram-negative bacteria being the production of β-lactamases [AmpC β-lactamases, ESBLs, carbapenemases] is a severe therapeutic issue in general, especially in case of vulnerable patient groups (e.g., pregnant women, children), where some other therapeutic alternatives are inappropriate due to their toxicity and teratogenicity (Abbo and Hooton 2014; Abraham 2016; Cantón et al. 2019; Gondim et al. 2018; Ulett et al. 2009; Meier et al. 2011). One of the most important developments in resistance was the emergence of strains expressing extended-spectrum β-lactamases (ESBLs), which have become a worldwide public health concern (Dhillon and Clark 2012). ESBLs produced by members of the Enterobacterales order are capable of hydrolyzing amino and ureido penicillins, oxyimino cephalosporins, and monobactams, but not to 7-α-substituted β-lactams (Rupp and Fey 2003). The spread of

ESBLs depends on bacterial conjugation, during which plasmids carrying ESBL genes are transferred. The proximity of bacteria is ensured in case of extensive biofilm-production (where the load of bacteria embedded in biofilm is considerably high), which creates a favourable environment for the exchange of genetic material, especially by conjugative transfer (Dhillon and Clark 2012; Rupp and Fey 2003; Paterson and Bonomo 2005). This is especially true for In nosocomial settings, where the production of biofilm by these species is an important factor for their survival. ESBL-positivity rate is highest in *Klebsiella* spp., due to its pronounced genetic plasticity and heightened ability of taking up plasmids, while it is the lowest in Proteae. (*Klebsiella* > *Escherichia* > *Enterobacter* > *Citrobacter* > *Serratia* > *Proteus* > *Morganella* > *Providencia*) (Bonkat et al. 2011). Since the twenty-first century, the most prevalent (>95%) type of ESBL-enzymes are the $bla_{\text{CTX-M}}$-type β-lactamases (Cantón et al. 2012). Nonetheless, ESBL-producing strains usually also carry resistance-determinants to other antibiotic groups (e.g., aminoglycosides, quinolones, fosfomycin), which significantly reduced treatment options to a limited number of antibiotics (Dhillon and Clark 2012; Rupp and Fey 2003; Paterson and Bonomo 2005). If the local epidemiology suggests that a patient has a high risk for an MDR UTI, ertapenem is one of the suggested drugs as the first line-agent to be used in several therapeutic guidelines (see previous subsections). Carbapenems have been considered safe and effective therapeutic choices in case of ESBL-positive Gram-negative bacteria; however, their extensive use has lead to the development of carbapenem-resistant Gram-negative strains, both among non-fermenters and gut bacteria (Papp-Wallace et al. 2011; El-Gamal et al. 2017). Carbapenem-resistant Gram-negative bacilli (CRGNB) are an important therapeutic problem, as there are limited number of safe and effective therapeutic alternatives available (van Duin et al. 2013). The most prevalent mechanism of carbapenem-resistance is through the production of specific, plasmid-borne β-lactamases called carbapenemases (Meletis 2016). The differentiation of carbapenemase-producing carbapenem resistant strains from non-carbapenemase producers is of utmost importance, as these resistance-determinants are readily transferable on plasmids or integrons, with pivotal roles in nosocomial outbreaks and global dissemination (Karlowsky et al. 2017). Based on their amino-acid sequences, carbapenemase enzymes are classified into Ambler Class A (e.g. KPC, SME, NMC-A, IMI, PER, GES, SFO, SFC and IBC), Class D (e.g. OXA-23 group, OXA-48-group) and Class B (e.g. VIM, GIM, SIM, NDM, IMP, IND, AIM, DIM and SPM) enzymes. Class A and D enzymes are serine-β-lactamases, while the members of Class B are exclusively metallo-β-lactamases. In infections caused by carbapenemase-producing strains, clinicians are left with very few therapeutic alternatives, some of which are toxic (e.g., colistin; nephrotoxicity and neurotoxicity), have disadvantageous pharmacokinetic properties (e.g., tigecycline) or expensive (e.g., ceftazidime/avibactam, meropenem/vaborbactam) (Gajdács et al. 2019a, b, c, d; Gajdács et al. 2020a, b). Carbapenem-resistant Enterobacterales strains have been designated as one of the most important threats by both the Centers for Disease Control (CDC) and the World Health Organization (WHO) (Cantón et al. 2012; David et al. 2019).

5 Conclusions

Urinary tract infections (UTIs) are one of the most common reasons for patients to a visit a physician and to receive antibiotics. The aim of this review paper was to summarize current developments in the global burden of UTI, the diagnostic aspects of these infectious pathologies, the possible etiological agents and their virulence determinants (with a special focus on the members of the Enterobacterales order), current guidelines and quality indicators in the therapy of UTIs. Members of the Enterobacterales order are the most common urinary pathogens; however, many studies have also highlighted that the etiological agents in UTIs are broadening, both in nosocomial and community settings. The emergence of drug resistance in Gram-negative bacteria should be closely monitored, due to their

proclivity to becoming MDR and their plasticity in drug resistance mechanisms. As the therapeutic armametarium of clinicians is largely limited in the current antibiotic resistance climate, energies should also be put into the prudent use of antibiotics. The use of modern diagnostic modalities will definitely improve the quality of patient-care around the globe.

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References

Abbo LM, Hooton TM (2014) Antimicrobial stewardship and urinary tract infections. Antibiotics 3:174–192

Abby SS, Cury J, Guglielmini J et al (2016) Identification of protein secretion systems in bacterial genomes. Sci Rep 6:1–14

Abraham O (2016) Appropriate therapy for carbapenem-resistant Enterobacteriaceae (CRE). Int J Infect Dis 45: e5

Abraham NS, Miao Y (2015) The nature of immune responses to urinary tract infections. Nat Rev Immunol 15:655–663

Adeghate J, Juhász E, Pongrácz J et al (2016) Does Staphylococcus Saprophyticus cause acute cystitis only in Young females, or is there more to the story? A one-year comprehensive study done in Budapest, Hungary. Acta Microbiol Immunol Hung 63:57–67

Adelou M, Alnajar S, Naushad S et al (2016) Genome-based phylogeny and taxonomy of the 'Enterobacteriales': proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov. Int J Syst Evol Microbiol 66:5575–5599

Adriaenssens N, Coenen S, Tonkin-Crine S et al (2011) European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. BMJ Qual Saf 20(7):64–72

Alidjanov JF, Abdufattaev UA, Makhsudov SA et al (2016) The acute cystitis symptom score for patient-reported outcome assessment. Urol Int 97:402–409

Alshareef H, Alfahad W, Albaadani A et al (2020) Impact of antibiotic de-escalation on hospitalized patients with urinary tract infections: a retrospective cohort single center study. J Infect Public Health. https://doi.org/10.1016/j.jiph.2020.03.004

Amaretti A, Righini L, Candeliere F et al (2020) Antibiotic resistance, virulence factors, phenotyping, and genotyping of non-Escherichia coli Enterobacterales from the gut microbiota of healthy subjects. Int J Mol Sci 21:e1847

Anğ-Küçüker M, Küqçükbasmaci O, Tekin M et al (2002) Serotypes, Siderophore synthesis, and serum resistance of Uropathogenic Klebsiella isolates. In: Emoődy L, Pál T, Hacker J, Blum-Oehler G (eds) Genes and proteins underlying microbial urinary tract virulence, Advances in experimental medicine and biology, vol 485. Springer, Boston

Armbruster CE, Mobley HL, Pearson MM (2018) Pathogenesis of Proteus mirabilis infection. EcoSal Plus 8:1

Barabás E, Maier A, Maier I et al (2015) Multidrug-resistant serratia marcescens strain isolated in a urology unit-case report. Acta Microbiol Immunol Hung 62:5–6

Baraboutis IG, Tsagalou EP, Lepinski JL et al (2010) Primary Staphylococcus aureus urinary tract infection: the role of undetected hematogenous seeding of the urinary tract. Eur J Clin Microbiol Infect Dis 29:1095–1101

Barker BAS (2013) Regulation and function of the swarming inhibitor disA in Proteus mirabilis. Emory University, Atlanta, Georga

Barnaud G, Arlet G, Danglot C et al (1997) Cloning and sequencing of the gene encoding the AmpC beta-lactamase of Morganella morganii. FEMS Microbiol Lett 148:15–20

Behzadi P (2018) Uropathogenic Escherichia coli and Fimbrial Adhesins Virulome. In: Jarzembowski T, Daca A, Dębska-Ślizień MA (eds) Urinary tract infection: the result of the strength of the pathogen, or the weakness of the host, 1st edn. InTechOpen, Croatia, pp 65–83

Behzadi P (2020) Classical chaperone-usher (CU) adhesive fimbriome: uropathogenic Escherichia coli (UPEC) and urinary tract infections (UTIs). Folia Microbiol 65:45–65

Behzadi P, Behzadi E (2008) The microbial agents of urinary tract infections at central laboratory of Dr. Shariati Hospital, Tehran, Iran. Turk Klin Tip Bilim 28:445

Behzadi E, Behzadi P (2016) The role of toll-like receptors (TLRs) in urinary tract infections (UTIs). Cent Eur J Urol 69:404

Behzadi P, Behzadi E (eds) (2017) Uropathogenic Escherichia coli: an ideal resource for DNA microarray probe designing. In: 5th international work-conference

on bioinformatics and biomedical engineering (5th IWBBIO). Springer, Granada
Behzadi P, Behzadi E, Yazdanbod H et al (2010) A survey on urinary tract infections associated with the three most common uropathogenic bacteria. Maedica 5:111
Behzadi P, Behzadi E, Ranjbar R (2015) Urinary tract infections and Candida albicans. Cent Eur J Urol 68:96–101
Behzadi P, Najafi A, Behzadi E et al (2016) Microarray long oligo probe designing for Escherichia coli: an in-silico DNA marker extraction. Cent Eur J Urol 69:105
Behzadi P, Behzadi E, Pawlak-Adamska EA (2019) Urinary tract infections (UTIs) or genital tract infections (GTIs)? It's the diagnostics that count. GMS Hyg Infect Control. https://doi.org/10.3205/dgkh000320
Bekal S, Brousseau R, Masson L et al (2003) Rapid identification of Escherichia coli pathotypes by virulence gene detection with DNA microarrays. J Clin Microbiol 41:2113–2125
Bermingham S, Ashe JF (2012) Systematic review of the impact of urinary tract infections on health-related quality of life. BJU Int 110:e830–e836
Bichler KH, Eipper E, Naber K et al (2002) Urinary infection stones. Int J Antimicrob Agents 19:488–498
Bien J, Sokolova O, Bozko P (2012) Role of uropathogenic Escherichia coli virulence factors in development of urinary tract infection and kidney damage. Int J Nephrol 2012:e681473
Bilen M, Dufour JC, Lagier JC et al (2018) The contribution of culturomics to the repertoire of isolated human bacterial and archaeal species. Microbiome 6:e94
Bischoff S, Walter T, Gerigk M et al (2018) Empiric antibiotic therapy in urinary tract infection in patients with risk factors for antibiotic resistance in a German emergency department. BMC Infect Dis 18:e56
Bonkat G, Müller G, Rieken M et al (2011) Epidemiology of urinary tract infections caused by extended-spectrum beta-lactamase (ESBL) producing pathogens at a tertiary care Swiss university hospital. J Urol 185: e545
Bonkat R, Bartoletti R, Bruyere F et al (2019) EUA Guidelines on Urological Infections. EAU Guidelines Office, Arnhem
Brockhurst MA, Harrison E, Hall JP et al (2019) The ecology and evolution of pangenomes. Curr Biol 29: R1094–R1103
Brubauker L, Wolfe A (2016) The urinary microbiota: a paradigm shift for bladder disorders? Curr Opin Obstet Gynecol 28:407–412
Calzi A, Grignolo S, Caviglia I et al (2016) Resistance to oral antibiotics in 4569 gram-negative rods isolated from urinary tract infection in children. Eur J Pediatr 175:1219–1225
Campbell SM, Braspenning J, Hutchinson A et al (2003) Research methods used in developing and applying quality indicators in primary care. BMJ 326:816–819
Cantey JB, Gaviria-Agudelo C, Te Kippe ME et al (2015) Lack of clinical utility of urine gram stain for suspected urinary tract infection in pediatric patients. J Clin Microbiol 53:1282–1285
Cantón R, González-Alba JM, Galán JC (2012) CTX-M enzymes: origin and diffusion. Front Microbiol 3:110
Cantón R, Akóva M, Carmeli Y et al (2019) Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect 18:413–431
Carattoli A, Hasman H (2020) Plasmid Finder and In Silico pMLST: identification and Typing of Plasmid Replicons in Whole-Genome Sequencing (WGS). Horiz Gene Transf (Springer), 2020. p. 285–294
Carattoli A, Zankari E, García-Fernández A et al (2014) In silico detection and typing of plasmids using plasmid finder and plasmid multilocus sequence typing. Antimicrob Agents Chemother 58:3895–3903
Cestari SE, Ludovico MS, Martins FH et al (2013) Molecular detection of HpmA and HlyA hemolysin of uropathogenic Proteus mirabilis. Curr Microbiol 67:703–707
Chapple C, Mangera A (2018) BMJ best practice acute cystitis. BMJ Publishing Group Ltd, London, United Kingdom
Chaux C, Crepy M, Xueref S et al (2002) Comparison of three chromogenic agar plates for isolation and identification of urinary tract pathogens. Clin Microbiol Infect 8:641–645
Chen L, Laham NL, Chavda KD et al (2015) First report of an OXA-48-producing multidrug-resistant Proteus mirabilis strain from Gaza, Palestine. Antimicrob Agents Chemother 59:4305–4307
Christofolini DM, Leuzzi L, Mafra FA et al (2012) Prevalence of cases of Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum and Chlamydia trachomatis in women with no gynecologic complaints. Reprod Med Biol 11:201–205
Chu CM, Lowder JL (2018 Jul) Diagnosis and treatment of urinary tract infections across age groups. Am J Obstet Gynecol 219(1):40–51. https://doi.org/10.1016/j.ajog.2017.12.231
Clarke K, Hall CL, Wiley Z et al (2019) Catheter-associated urinary tract infections in adults: diagnosis, treatment, and prevention. J Hosp Med. https://doi.org/10.12788/jhm.3292
Clermont O, Bonacorsi S, Bingen E (2000) Rapid and simple determination of the Escherichia coli phylogenetic group. Appl Environ Microbiol 66:4555–4558
Clermont O, Christenson JK, Denamur E et al (2013) The Clermont Escherichia coli phylo-typing method revisited: improvement of specificity and detection of new phylo-groups. Environ Microbiol Rep 5:58–65
Combaz-Söhnchen N, Kuhn A (2017) A systematic review of mycoplasma and Ureaplasma in Urogynaecology. Geburtshilfe Frauenheilkd 77:1299–1303
Conway LJ, Carter EJ, Larson EL (2015) Risk factors for nosocomial bacteremia secondary to urinary catheter-associated bacteriuria: a systematic review. Urol Nurs 35:191–203
Cormican M, Murphy AW (2011) Interpreting asymptomatic bacteriuria. BMJ 343:d4780

Costa TR, Felisberto-Rodrigues C, Meir A et al (2015) Secretion systems in gram-negative bacteria: structural and mechanistic insights. Nat Rev Microbiol 13:343–359

D'Atri F, Arthur J, Blix HS et al (2019) Targets for the reduction of antibiotic use in humans in the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) partner countries. Euro Surveill 24. https://doi.org/10.2807/1560-7917.ES.2019.24.28.1800339

Darbro BW, Petroelje BK, Doern GB (2009) Lactobacillus delbrueckii as the cause of urinary tract infection. J Clin Microbiol 47:275–277

Dason S, Dason JT, Kapoor A (2011) Guidelines for the diagnosis and management of recurrent urinary tract infection in women. Can Urol Assoc J 5:316–322

Davenport M, Mach KE, Shortliffe LMD et al (2017) New and developing diagnostic technologies for urinary tract infections. Nat Rev Urol 14:296–310

David S, Reuter S, Harris RS et al (2019) Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. Nat Microbiol 4:1919–1929

Dhillon RHP, Clark J (2012) ESBLs: a clear and present danger? Crit Care Res Prac 2012:e625170

Di Vico T, Morganti R, Cai T et al (2020) Acute cystitis symptom score (ACSS): clinical validation of the Italian version. Antibiotics 9:e104

Dias V (2020) Candida species in the urinary tract: is it a fungal infection or not? Future Microbiol 15. https://doi.org/10.2217/fmb-2019-0262

Doi Y, Bonomo RA, Hooper DC et al (2017) Gram-negative Committee of the Antibacterial Resistance Leadership Group (ARLG) a gram-negative bacterial infections: research priorities, accomplishments, and future directions of the antibacterial resistance leadership group. Clin Infect Dis 64:S30–S35

Donabedian A (1998) The quality of care. How can it be assessed? JAMA 260:1743–1748

Drivsholm T (2014) [Not Available]. Ugeskr Laeger 176:5

El-Gamal MI, Brahim I, Hisham N et al (2017) Recent updates of carbapenem antibiotics. Eur J Med Chem 131:185–195

Emiru T, Beyene G, Tsegaye W et al (2013) Associated risk factors of urinary tract infection among pregnant women at Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. BMC Res Notes 6:e292

Eriksson A, Giske C, Ternhag A (2012) The relative importance of Staphylococcus saprophyticus as a urinary tract pathogen: distribution of bacteria among urinary samples analysed during 1 year at a major Swedish laboratory. APMIS 121:72–78

European Centre for Disease Prevention and Control (2018) Surveillance of antimicrobial resistance in Europe, Annual report of the European antimicrobial resistance surveillance network (EARS-Net) 2017. ECDC, Stockholm

Ferreiro JLL, Otero JÁ, González LG et al (2017) Pseudomonas aeruginosa urinary tract infections in hospitalized patients: mortality and prognostic factors. PLoS One 12:e0178178

Flannery EL, Antczak SM, Mobley HL (2011) Self-transmissibility of the integrative and conjugative element ICEPm1 between clinical isolates requires a functional integrase, relaxase, and type IV secretion system. J Bacteriol 193:4104–4112

Flores-Mireles AL, Walker JN, Caparon M et al (2015) Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 13:269–284

Flower A, Bishop FL, Lewith G (2014) How women manage recurrent urinary tract infections: an analysis of postings on a popular web forum. BMC Fam Pract 15:e162

Foxman B (2003) Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon 49:53–70

Frassetto L (2018) BMJ best practice acute pyelonephritis. BMJ Publishing Group Ltd, London, United Kingdom

Furuse Y (2019) Analysis of research intensity on infectious disease by disease burden reveals which infectious diseases are neglected by researchers. Proc Natl Acad Sci U S A 116:478–483

Gagyor I, Hummers-Pradier E, Kochen MM et al (2012) Immediate versus conditional treatment of uncomplicated urinary tract infection – a randomized-controlled comparative effectiveness study in general practices. BMC Infect Dis 12:146

Gagyor I, Bleidorn J, Kochen MM et al (2015) Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ 351:h6544

Gajdács M (2019) The continuing threat of methicillin-resistant Staphylococcus aureus. Antibiotics 8:e52

Gajdács M (2020) Carbapenem-resistant but cephalosporin-susceptible Pseudomonas aeruginosa in urinary tract infections: opportunity for Colistin sparing. Antibiotics 9:e153

Gajdács M, Albericio F (2019) Antibiotic resistance: from the bench to patients. Antibiotics 8:e129

Gajdács M, Urbán E (2019a) Resistance trends and epidemiology of Citrobacter-Enterobacter-Serratia in urinary tract infections of inpatients and outpatients (RECESUTI): a 10-year survey. Medicina 55:e285

Gajdács M, Urbán E (2019b) Comparative epidemiology and resistance trends of Proteae in urinary tract infections of inpatients and outpatients: a 10-year retrospective study. Antibiotics 8:e91

Gajdács M, Ábrók M, Lázár A et al (2019a) Microbiology of urine samples obtained through suprapubic bladder aspiration: a 10-year epidemiological snapshot. Dev Health Sci 2:76–78

Gajdács M, Dóczi I, Ábrók M et al (2019b) Epidemiology of candiduria and Candida urinary tract infections in inpatients and outpatients: results from a 10-year retrospective survey. Cent Eur J Urol 72:209–215

Gajdács M, Ábrók M, Lázár A et al (2019c) Comparative epidemiology and resistance trends of common urinary

pathogens in a tertiary-care hospital: a 10-year surveillance study. Medicina 55:e356
Gajdács M, Burián K, Terhes G (2019d) Resistance levels and epidemiology of non-fermenting gram-negative Bacteria in urinary tract infections of inpatients and outpatients (RENFUTI): a 10-year epidemiological snapshot. Antibiotics 8:e143
Gajdács M, Bátori Z, Ábrók M et al (2020a) Characterization of resistance in gram-negative urinary isolates using existing and novel indicators of clinical relevance: a 10-year data analysis. Life 10:e16
Gajdács M, Ábrók M, Lázár A et al (2020b) Anaerobic blood culture positivity at a University Hospital in Hungary: a 5-year comparative retrospective study. Anaerobe 63:e102200
Giessing M (2012) Urinary tract infection in renal transplantation. Arab J Urol 10:162–168
Gilbert D, Chambers H, Eliopoulos G et al (2019) The Sanford guide to antimicrobial therapy. Antimicrobial Therapy, Sperryville
Gondim R, Azevedo R, Braga AANM et al (2018) Risk factors for urinary tract infection in children with urinary urgency. Int Braz J Urol 44:378–383
Govender Y, Gabriel I, Minassian V et al (2019) The current evidence on the association between the urinary microbiome and urinary incontinence in women. Front Cell Infect Microbiol 9:e133
Grahn D, Norman DC, Whitel ML et al (1985) Validity of urinary catheter specimen for diagnosis of urinary tract infection in the elderly. Arch Intern Med 145:1858–1860
Gupta K, Hooton TM, Naber KG et al (2011) International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 52:e103–e120
Gupta N, Hocevar SN, Moulton-Meissner HA et al (2014) Outbreak of Serratia marcescens bloodstream infections in patients receiving parenteral nutrition prepared by a compounding pharmacy. Clin Infect Dis 59:1–8
Guze LB, Beeson PB (1956) Observations on the reliability and safety of bladder catheterization for bacteriologic study of the urine. N Engl J Med 255:474–475
Harper M, Fowlis G (2007) 3. Management of urinary tract infections in men. Trends Urol Gynaecol Sex Health 12:30–35
Hawthorne W, Rouse S, Sewell L et al (2016) Structural insights into functional amyloid inhibition in gram −ve bacteria. Biochem Soc Trans 44:1643–1649
Hayes BW, Abraham SN (2017) Innate immune responses to bladder infection. Microbiology 4. https://doi.org/10.1128/microbiolspec.UTI-0024-2016
Hegstad K, Mikalsen T, Coque TM et al (2010) Mobile genetic elements and their contribution to the emergence of antimicrobial resistant Enterococcus faecalis and Enterococcus faecium. Clin Microbiol Infect 16:541–554
Hellerstein S (1998) Urinary tract infections in children: why they occur and how to prevent them. Am Fam Physician 57:2440–2446
Henderson JT, Webber EM, Bean SI (2019) Screening for asymptomatic bacteriuria in adults: updated evidence report and systematic review for the US preventive services task force. JAMA 322:1195–1205
Hermanides HS, Hulscher MEJL, Schouten JA et al (2008) Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: a first step to measure and improve care. Clin Infect Dis 46:703–711
Higgins A, Garg T (2017) Aerococcus urinae: an emerging cause of urinary tract infection in older adults with multimorbidity and urologic cancer. Urol Case Rep 3:24–25
Holt KE, Wertheim H, Zadoks RN et al (2015) Genomic analysis of diversity, population structure, virulence, and antimicrobial resistance in Klebsiella pneumoniae, an urgent threat to public health. Proc Natl Acad Sci U S A 112:E3574–E3581
Hooper D (2019) Fluoroquinolones [Internet]. UpToDate. Available from: https://www.uptodate.com/contents/fluoroquinolones?search=fluoroquinolones&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=1
Hooton T (2018) Acute simple cystitis in men [Internet]. UpToDate. Available from: https://www.uptodate.com/contents/acute-simple-cystitis-in-men?search=cystitis%20in%20%20men&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
Hooton T, Gupta K (2019a) Acute simple cystitis in women [Internet]. UpToDate. Available from: https://www.uptodate.com/contents/acute-simple-cystitis-in-women?search=acute%20cystitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
Hooton T, Gupta K (2019b) Acute complicated urinary tract infection (including pyelonephritis) in adults [Internet]. UpToDate. Available from: https://www.uptodate.com/contents/acute-simple-cystitis-in-women?search=acute%20cystitis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
Hooton TM, Bradley SF, Cardenas DD et al (2010) Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. Clin Infect Dis 50:625–663
Hou TY, Chiang-Ni C, Teng SH (2019) Current status of MALDI-TOF mass spectrometry in clinical microbiology. J Food Drug Anal 27:401–414
Hozzari A, Behzadi P, Khiabani PK et al (2020) Clinical cases, drug resistance, and virulence genes profiling in Uropathogenic Escherichia coli. J Appl Genet 61 (2):265–273. https://doi.org/10.1007/s13353-020-00542-y

Hu KK, Boyko EJ, Scholes D et al (2004) Risk factors for urinary tract infections in postmenopausal women. Arch Intern Med 164:989–993

Imade PE, Izekor PE, Eghafona ON (2010) Asymptomatic bacteriuria among pregnant women. N Am J Med Sci 2:263–266

Issakhanian L, Behzadi P (2019) Antimicrobial agents and urinary tract infections. Curr Pharm Des 25:1409–1423

Jacobsen SM, Stickler DJ, Mobley HLT et al (2008) Complicated catheter-associated urinary tract infections due to Escherichia coli and Proteus mirabilis. Clin Microbiol Rev 21:26–59

Jahandeh N, Ranjbar R, Behzadi P et al (2015) Uropathogenic Escherichia coli virulence genes: invaluable approaches for designing DNA microarray probes. Cent Eur J Urol 68:452

Jamison DT, Alwan A, Mock CN et al (2018) Universal health coverage and intersectoral action for health: key messages from disease control priorities, 3rd edition. Lancet 391:7–23

Jhang JF, Kuo HC (2017) Recent advances in recurrent urinary tract infection from pathogenesis and biomarkers to prevention. Ci Ji Yi Xue Za Zhi 29:131–137

Karlowsky JA, Lob SH, Kazmierczak KM et al (2017) In vitro activity of imipenem against Carbapenemase-positive Enterobacteriaceae isolates collected by the SMART global surveillance program from 2008 to 2014. J Clin Microbiol 55:1638–1649

Ko JH, Kang CI, Cornejo-Juárez P et al (2019a) Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of Stenotrophomonas maltophilia infections: a systematic review and meta-analysis. Clin Microbiol Infect 25:546–554

Ko YH, Choi JY, Song PH (2019b) Host-pathogen interactions in urinary tract infections. Urogenit Tract Infect 14:71–79

Konovalova A, Silhavy TJ (2015) Outer membrane lipoprotein biogenesis: lol is not the end. Philos Trans R Soc B 370:e20150030

Köves B, Magyar A (2017 Nov 22) Peter Tenke Spectrum and antibiotic resistance of catheter-associated urinary tract infections. GMS Infect Dis 5:Doc06. https://doi.org/10.3205/id000032

Kranz J, Schmidt S, Lebert C et al (2018a) The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and Management of Uncomplicated Urinary Tract Infections in adult patients: part 1. Urol Int 100:263–270

Kranz J, Schmidt S, Lebert C et al (2018b) The 2017 update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and Management of Uncomplicated Urinary Tract Infections in adult patients. Part II: therapy and prevention. Urol Int 100:271–278

Kroneberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, Meli DN, Frey P, Limacher A, Reichenbach S (2017 Nov 7) Peter Jüni symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised. Double Blind Trial BMJ 359:j4784. https://doi.org/10.1136/bmj.j4784

Kulchavenya E, Cherednichenko A (2018) Urogenital tuberculosis, the cause of ineffective antibacterial therapy for urinary tract infections. Ther Adv Urol 10:95–101

Kumar A, Turney JH, Brownjohn AM et al (2001) Unusual bacterial infections of the urinary tract in diabetic patients—rare but frequently lethal. Neprhol Dial Transplant 16:1062–1065

Laupland KB, Parkins MD, Gregson DB et al (2007) Population-based laboratory surveillance for Serratia species isolates in a large Canadian health region. Eur J Clin Microbiol Infect Dis 27:89–95

Le Marechal M, Tebano G, Monnier AA et al (2018) Quality indicators assessing antibiotic use in the outpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. J Antimicrob Chemother 73:vi40–vi49

Li B, Zhao Y, Liu C, Chen Z et al (2014) Molecular pathogenesis of Klebsiella pneumoniae. Future Microbiol 9:1071–1081

Looft T, Allen HK (2012) Collateral effects of antibiotics on mammalian gut microbiomes. Gut Microbiomes 3:463–467

Lotte R, Lotte L, Riumy R (2016) Actinotignum schaalii (formerly Actinobaculum schaalii): a newly recognized pathogen-review of the literature. Clin Microbiol Infect 22:28–36

Magyar A, Alidjanov J, Pilatz A et al (2018) The role of the acute cystitis symptom score questionnaire for research and antimicrobial stewardship. Validation of the Hungarian version. Cent Eur J Urol 71:134–141

Maharjan G, Khadka P, Shilpakar GS et al (2018) Catheter-associated urinary tract infection and obstinate biofilm producers. Can J Infect Dis Med Microbiol 2018:7624857

Martin RM, Bachman MA (2018) Colonization, infection, and the accessory genome of Klebsiella pneumoniae. Front Cell Infect Microbiol 8:e4

Masha SC, Cools P, Descheemaeker P et al (2018) Urogenital pathogens, associated with trichomonas vaginalis, among pregnant women in Kilifi, Kenya: a nested case-control study. BMC Infect Dis 18:e549

Mazzariol A, Bazaj A, Cornaglia G (2017) Multi-drug-resistant gram-negative bacteria causing urinary tract infections: a review. J Chemother 29:2–9

McLellan LK, Hunstad DA (2016) Urinary tract infection: pathogenesis and outlook. Trends Mol Med 22:946–957

Meier S, Weber R, Zbinden R et al (2011) Extended-spectrum β-lactamase-producing gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection 39:333–340

Meletis G (2016) Carbapenem resistance: overview of the problem and future perspectives. Ther Adv Infect Dis 3:15–21

Melia M (2017) Bacterial cystitis, acute, uncomplicated [Internet]. John Hopkins Antibiotic Guide. Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540046/all/Bacterial_Cystitis_Acute_Uncomplicated?q=cystitis

Melia M, DeMaio J (2017) Urinary Tract Infection, Complicated (UTI) [Internet]. John Hopkins Antibiotic Guide. Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540573/all/Urinary_Tract_Infection_Complicated__UTI_?q=complicated

Metri BC, Jyothi P, Peerapur BV (2013) Antibiotic resistance in Citrobacter spp. isolated from urinary tract infection. Urol Ann 5:312

Miri ST, Dashti A, Mostaan S et al (2017) Identification of different Escherichia coli pathotypes in north and north-west provinces of Iran. Iran J Microbiol 9:33–37

Mittal R, Aggarwal S, Sharma S et al (2009) Urinary tract infections caused by Pseudomonas aeruginosa: a minireview. J Infect Pubic Health 2:101–111

Monnier AA, Schouten J, Le Maréchal M et al (2018) Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. J Antimicrob Chemother 73:vi30–vi39

Morissey I, Hackel M, Badar R et al (2013) A review of ten years of the study for monitoring antimicrobial resistance trends (SMART) from 2002 to 2011. Pharmaceuticals 6:1335–1346

Morris L (2018) PURLs: an easy approach to obtaining clean-catch urine from infants. J Fam Pract 67:166–169

Moy S, Sharma R (2017) Treatment outcomes in infections caused by "SPICE" (Serratia, Pseudomonas, indole-positive Proteus, Citrobacter, and Enterobacter) organisms: Carbapenem versus Noncarbapenem regimens. Clin Ther 39:170–176

Najafi A, Hasanpour M, Askary A et al (2018) Distribution of pathogenicity island markers and virulence factors in new phylogenetic groups of uropathogenic Escherichia coli isolates. Folia Microbiol 63:335–343

Navarro-García F, Ruiz-Perez F, Larzabal M et al (2016) Secretion systems of pathogenic escherichia coli. Escherichia coli in the Americas. Springer, Cham, pp 221–249

Negus M, Phillips C, Hindley R (2020) Recurrent urinary tract infections: a critical review of the currently available treatment options. Obstet Gynecol 22:115–121

Network SIG (2012) Management of suspected bacterial urinary tract infection in adults. A national clinical guideline. Available from: http://www.sign.ac.uk

Nicolle EL (2014) Catheter associated urinary tract infections. Antimicrob Resist Infect Control 3:e23

Nicolle EL, Bradley S, Colgan R et al (2005) Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 40:643–654

Nitzan O, Elias M, Chazan B et al (2015) Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. Diabetes Metab Syndr Obes 26:129–136

Norwegian Ministries (2015) National strategy against antibiotic resistance 2015–2020 [Internet]. Norwegian Ministries. Available from: https://www.regjeringen.no/contentassets/5eaf66ac392143b3b2054aed90b85210/antibiotic-resistance-engelsk-lavopploslig-versjon-for-nett-10-09-15.pdf

Paczosa MK, Mecsas J (2016) Klebsiella pneumoniae: going on the offense with a strong defense. Microbiol Mol Biol Rev 80:629–661

Pallett A, Hand K (2010) Complicated urinary tract infections: practical solutions for the treatment of multiresistant gram-negative bacteria. J Antimicrob Chemother 65:iii25–iii33

Papp-Wallace KM, Endimiani A, Taracila MA et al (2011) Carbapenems: past, present, and future. Antimicrob Agents Chemother 55:4943–4960

Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 18:657–686

Pearson MM, Rasko DA, Smith SN et al (2010) Transcriptome of swarming Proteus mirabilis. Infect Immun 78:2834–2845

Pollack LA, Plachouras D, Sinkowitz-Cochran R et al (2016) A concise set of structure and process indicators to assess and compare antimicrobial stewardship programs among EU and US hospitals: results from a multinational expert panel. Infect Control Hosp Epidemiol 37:1201–1211

Ponce-de-Leon A, Rodríguez-Noriega E, Morfín-Otero R et al (2018) Antimicrobial susceptibility of gram-negative bacilli isolated from intra-abdominal and urinary-tract infections in Mexico from 2009 to 2015: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). PLoS One 13:e0198621

Ponka D, Baddar F (2013) Suprapubic bladder aspiration. Can Fam Physician 59:50

Prywer J, Torzewska A, Płociński T (2012) Unique surface and internal structure of struvite crystals formed by Proteus mirabilis. Urol Res 40:699–707

Ranjbar R, Tabatabaee A, Behzadi P et al (2017) Enterobacterial repetitive intergenic consensus polymerase chain reaction (ERIC-PCR) genotyping of escherichia coli strains isolated from different animal stool specimens. Iran J Pathol 12:25

Rastegar S, Moradi M, Kalantar-Neyestanaki D et al (2019) Virulence factors, capsular serotypes and antimicrobial resistance of Hypervirulent Klebsiella pneumoniae and classical Klebsiella pneumoniae in Southeast Iran. Infect Chemother 51:e39

Renald J, Ballarini S, Mascarenhas T et al (2015) Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: a prospective, observational study. Infect Dis Ther 4:125–135

Rizwan M, Akhtar M, Najmi AK, Singh K (2018 Jul) Escherichia Coli and Klebsiella Pneumoniae sensitivity/resistance pattern towards antimicrobial agents in primary and simple urinary tract infection patients visiting university hospital of Jamia Hamdard new Delhi. Drug Res (Stuttg) 68(7):415–420. https://doi.org/10.1055/a-0576-0079

Roberts KB, Wald ER (2018) The diagnosis of UTI: Colony count criteria revisited. Pediatrics 141: e20173239

Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I (2018) Treatment of infections caused by extended-spectrum-beta-lactamase-, ampC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 31. https://doi.org/10.1128/CMR.00079-17

Rozenfeld KL, Nitzan O, Peretz A (2018) Presence of anaerobic bacteria in the urinary tract of catheterized ICU patients. Eur J Clin Microbiol Infect Dis 37:2131–2136

Rupp ME, Fey PD (2003) Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment. Drugs 63:353–365

Sabir N, Ikram A, Zaman G et al (2017) Bacterial biofilm-based catheter-associated urinary tract infections: causative pathogens and antibiotic resistance. Am J Infect Control 45:1101–1105

Sader HS, Farrell DJ, Flamm RK et al (2014) Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. Int J Antimicrob Agents 43:328–334

Samonis G, Karageorgopoulos DE, Kofteridis DP et al (2009) Citrobacter infections in a general hospital: characteristics and outcomes. Eur J Clin Microbiol Infect Dis 28:61–68

Sana TG, Voulhoux R, Monack DM et al (2020) Protein export and secretion among bacterial pathogens. Front Cell Infect Microbiol 9:e473

Sanjait S, Indrawattana N (2016) Mechanisms of antimicrobial resistance in ESKAPE pathogens. Biomed Res Int 2016:2475067

Saust LT, Monrad RN, Hansen MP et al (2016) Quality assessment of diagnosis and antibiotic treatment of infectious diseases in primary care: a systematic review of quality indicators. Scand J Prim Health Care 34:258–266

Schaeffer AJ, Nicolle LE (2016) Urinary tract infections in older men. N Engl J Med 374:562–571

Schaffer JN, Pearson MM (2017) Proteus mirabilis and urinary tract infections. In: Urinary tract infections: molecular pathogenesis and clinical management. ASM Press, Washington, DC, pp 383–433

Schmiemann G, Kniehl E, Gebhadt MM et al (2010) The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int 107:36–367

Scholes D, Hooton TM, Roberts PL et al (2000) Risk factors for recurrent urinary tract infection in Young women. J Infect Dis 182:1177–1182

Schubert S, Kostrzewa M (2017) MALDI-TOF MS in the microbiology laboratory: current trends. Curr Issues Mol Biol 23:17–20

Shrestha LB, Baral R, Khanal B (2019) Comparative study of antimicrobial resistance and biofilm formation among Gram-positive uropathogens isolated from community acquired urinary tract infections and catheter-associated urinary tract infections. Infect Drug Resist 12:957–963

Simmering JE, Tang F, Cavanaugh JE et al (2017) The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998–2011. Open Forum Infect Dis 4:ofw281

Sobel JD, Kaye D (2015) 74-urinary tract infections. In: Bennett JE, Dolin R, Blaser MJ (eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 8th edn. Content Repository Only, Philadelphia, pp 886–913.e3. ISBN 978-1-4557-4801-3

Stefaniuk E, Suchocka U, Bosacka K et al (2016) Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tract infections in Poland. Eur J Clin Microbiol Infect Dis 35:1363–1369

Storme O, Saucedo JT, Garcia-Mora A et al (2019) Risk factors and predisposing conditions for urinary tract infection. Ther Adv Urol 11:1756287218814382

Subashchandrabose S, Mobley HL (2017) Virulence and fitness determinants of uropathogenic Escherichia coli. In: Urinary tract infections: molecular pathogenesis and clinical management. ASM Press, Washington, DC, pp 235–261

Swaminathan S, Alangaden GJ (2010) Treatment of resistant enterococcal urinary tract infections. Curr Infect Dis Rep 12:455–464

Tan CW, Chlebicki MP (2016) Urinary tract infections in adults. Singap Med J 57:485–490

Tangdogdu Z, Wagenlehner FM (2016) Global epidemiology of urinary tract infections. Curr Opin Infect Dis 29:73–79

Tanne JH (2008) FDA adds "black box" warning label to fluoroquinolone antibiotics. BMJ 337:135

Terlizzi ME, Gribaudo G, Maffei ME (2017) Uro pathogenic Escherichia coli (UPEC) infections: virulence factors, bladder responses, antibiotic, and non-antibiotic antimicrobial strategies. Front Microbiol 8:1566

The National Institute for Health and Care Excellence (NICE) (2018) Urinary tract infection (lower): antimicrobial prescribing [Internet]. The National Institute for Health and Care Excellence (NICE). Available from: https://www.nice.org.uk/guidance/ng109

Trautner BW, Darouiche RO (2004) Role of biofilm in catheter-associated urinary tract infection. Am J Infect Control 32:177–183

Ulett KB, Benjamin WH Jr, Zhuo F, Xiao M, Kong F, Gilbert GL, Schembri MA (2009 May 13) Ulett GC diversity of group B streptococcus serotypes causing urinary tract infection in adults. J Clin Microbiol 47 (7):2055–2060. https://doi.org/10.1128/jcm.00154-09

van Duin D, Kaye KS, Neuner EA et al (2013) Carbapenem-resistant enterobacteriaceae: a review of treatment and outcomes. Diagn Microbiol Infect Dis 75:115–120

Walters MS, Mobley HL (2009) Identification of uropathogenic Escherichia coli surface proteins by shotgun proteomics. J Microbiol Methods 78:131–135

Weber DJ (2006) Collateral damage and what the future might hold. The need to balance prudent antibiotic

utilization and stewardship with effective patient management. Int J Infect Dis 10:S17–S24

White B (2011) Diagnosis and treatment of urinary tract infections in children. Am Fam Physician 15:409–415

World Health Organisation (WHO). ATC/DDD Index (version 2019) [Internet]. WHO Collaborating Centre for Drug Statistics Methodology. Elérhető: http://www.whocc.no/

Wiedemann B, Heisig A, Heisig P (2014) Uncomplicated urinary tract infections and antibiotic resistance-epidemiological and mechanistic aspects. Antibiotics 3:341–352

Wingert A, Pillay J, Sebastianski M et al (2019) Asymptomatic bacteriuria in pregnancy: systematic reviews of screening and treatment effectiveness and patient preferences. BMJ Open 9:e021347

Wuorela M (2018) EBM Guidelines, Urinary tract infections [Internet]. Duodecim Medical Publications Ltd. Available from: https://login.duodecim.fi/iam/login?p_service=EBMG&p_url=https%3A%2F%2Flogin.duodecim.fi%2Foauth2%2Fauth%3Fresponse_type%3Dcode%26client_id%3Debmg%40app.duodecim.fi%26redirect_uri%3Dhttps%253A%252F%252Fwww.ebm-guidelines.com%252Fiam%252Fcallback%26scope%3Dauth%26state%3D5W3AYP96ICQ29NZRUWQ67IZGXQAA0KSH%26service%3DEBMG

Wyres KL, Lam MM, Holt KE (2020) Population genomics of Klebsiella pneumoniae. Nat Rev Microbiol 2020:1–16

Yang B, Yang F, Wang S et al (2018) Analysis of the spectrum and antibiotic resistance of uropathogens in outpatients a. tertiary hospital. J Chemother 30:145–149

Young JL, Soper DE (2001) Urinalysis and urinary tract infection: update for clinicians. Infect Dis Obstet Gynecol 9:249–255

Zee A, Roorda L, Bosman G et al (2016) Molecular diagnosis of urinary tract infections by semi-quantitative detection of Uropathogens in a routine clinical hospital setting. PLoS One 11:e0150755