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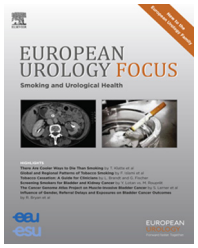

Review – Infections

Trends in Antibiotic Resistance in Urologic Practice

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Abstract

Context: The significant global upsurge in antimicrobial resistance, particularly among Enterobacteriaceae, represents a serious threat to health care systems. The implications for urologic practice are of particular concern.
Objective: To review trends in antibiotic resistance in urologic practice.
Evidence acquisition: We report current European trends of resistance in Gram-negative uropathogens.
Evidence synthesis: In addition to β-lactam resistance, Gram-negative pathogens are often resistant to multiple drug classes, including aminoglycosides, fluoroquinolones, and carbapenems, commonly used to treat urologic infections. Interest is renewed in old antibiotics, and several new antibiotics are in the pipeline to meet the challenge of treating these infections. In this review, we summarise emerging trends in antimicrobial resistance and its impact on urologic practice. We also review current guidelines on the treatment and prevention of urologic infections with these organisms, and some key antibiotics in the era of resistance.
Conclusions: Increasing antimicrobial resistance represents a challenge to urologic practice for both treatment and prophylaxis. Antibiotic choice should be determined according to risk factors for multidrug resistance. Good knowledge of the local microbial prevalence and resistance profile is required to guide antimicrobial therapy.
Patient summary: Antimicrobial resistance represents a challenge in urology. We summarise emerging trends in antimicrobial resistance and review current guidelines on the treatment and prevention of urologic infections, as well as some key antibiotics in the era of resistance.

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1. Introduction

Antimicrobial resistance (AMR) continues to rise, posing a global threat to health care delivery [1]. Worldwide, the prevalence of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae is increasing, and these organisms are frequently resistant to many other key antibiotics such as fluoroquinolones and aminoglycosides. Carbapenem-producing Gram negative bacteria are an emerging threat, leaving few treatment options.

Increasing Gram-negative resistance has major implications for urologic practice, including prophylaxis and treatment of infection-related complications after urologic procedures, particularly transrectal ultrasound biopsy of the prostate (TRUBP), and treatment of other common urologic infections such as urinary tract infections (UTIs), urosepsis, and prostatitis.

The recent Global Prevalence Infection in Urology studies have shown that 10–12% of patients hospitalised in urology wards have a health care–associated infection [2]. The

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strains retrieved from these patients are even more resistant [2]. UTIs are among the most common types of infection in urology practice, with approximately 150–250 million cases globally per year [3–5]. Owing to their high prevalence, UTIs are a major contributor to global antibiotic use and resistance [6,7]. Without effective antibiotics active against common uropathogens, many urologic procedures would carry excessive risk.

Here we summarise current European resistance trends for Gram-negative uropathogens, examine the effect of resistance on common urology procedures, and discuss key antibiotic options in the era of resistance.

2. Evidence acquisition

We report current European trends of resistance in Gram-negative uropathogens.

3. Evidence synthesis

3.1. Mechanism of resistance in Gram-negative bacteria

AMR is not a new phenomenon [8]: since the introduction of penicillin, bacteria have responded to the use of antibiotics via their ability to evolve and transmit resistance to other species. However, the increase in AMR reflects the wide variation and expansion of resistance determinants driven by selection pressure due to increased consumption of antibiotics and their inappropriate use [9]. Furthermore, global travel and migration have played a role in the spread of multidrug-resistant (MDR) pathogens [10].

Gram-negative bacteria possess several mechanisms that confer AMR. β-Lactamase production is the most crucial mediator of resistance to broad-spectrum β-lactam antibiotics and is often encoded on plasmids [11] (Table 1).

The first plasmid-mediated β-lactamase in Gram-negative bacteria was discovered in Greece in the 1960s. It was named TEM after the patient from whom it was isolated [12]. Subsequently, a closely related enzyme was discovered and named TEM-2. These two enzymes are the most common plasmid-mediated β-lactamases in Gram-negative bacteria, including Enterobacteriaceae. They hydrolyse penicillins and narrow-spectrum cephalosporins. The resistance of Gram-negative bacteria was stable until the 1980s, and not long after cefotaxime came into clinical use in Europe, ESBLs emerged. In Germany, strains of *Klebsiella pneumoniae* were discovered with transferable resistance to the oxyimino-cephalosporins (SHV enzyme) [13], and TEM-related ESBLs were discovered in France in 1984.

ESBLs confer resistance to several antibiotics, including third- and fourth-generation cephalosporins and monobactams. There are several ESBL variants, including TEM, SHV, CTX-M, and OXA. Globally, the most common disseminated ESBL associated with uropathogenic Enterobacteriaceae is the CTX-M type. More than 160 CTX-M enzymes have been described [14]; the most prevalent type in *Escherichia coli* is CTXM-15 (ST 131) [15].

Carbapenem resistance in Enterobacteriaceae is an emerging problem caused primarily by plasmid-encoded carbapenemases [16–22] such as KPC-type (*K. pneumoniae*) [23], NDM-type (new Delhi metallo-β-lactamase) [24] and OXA 48-type [25] enzymes. Carbapenem resistance can also arise via other mechanisms such as efflux mechanisms and Amp-C/ESBL combined with porin loss [26]. The increase in carbapenem consumption to treat ESBL Gram-negative infections coupled with international travel has contributed to the concerning spread of carbapenem resistance, particularly in *E. coli* and *Klebsiella*, the most common uropathogens causing the majority of urologic infections.

MDR strains of Enterobacteriaceae are increasingly reported worldwide owing to the spread of resistance genes on mobile elements (plasmids, transposons, integrons). The combination of these with chromosomally encoded resistance genes often results in strains with multiple resistance traits: MDR, nonsusceptibility to one antibiotic in three or more classes; XDR, nonsusceptibility to one in all but two classes; and PDR, nonsusceptibility to all agents in all classes [27–29].

In addition to β-lactamases, Gram-negative bacteria can develop resistance to other commonly used antibiotics in urologic infections. Fluoroquinolone resistance can be conferred by either plasmid- or chromosome-encoded genes [30–33] and is frequently associated with β-lactam resistance genes (CTX-M14 and CTX-M15) [17,34–36]. Several mechanisms can result in bacterial resistance to aminoglycosides, another critically important antibiotic class against Gram-negative organisms [37–40]. Of particular concern, the gene encoding the antibiotic-modifying enzyme armA that can confer pandrug resistance is often co-located with the carbapenemase gene on the same mobile genetic element [16,41,42].

3.2. Epidemiology and resistance trend for Gram-negative bacteria

In Europe, AMR in Gram-negative bacteria is on the rise, and is the most frequent cause of invasive infections in European countries [16,34,35,47–54]. The rate of resistance varies substantially between countries and there is a north-to-south gradient, with southern regions showing the highest resistance prevalence.

A report by national experts from 39 countries in Europe revealed that carbapenem-producing Enterobacteriaceae (CPE) are continuing to spread in Europe. Among the 31 countries that participated in the 2010 and 2013 assessments, 17 countries were upgraded to higher epidemiologic stage 3. In the last annual surveillance report of the European Centre for Disease Prevention and Control [55], more than half of the *E. coli* isolates and more than one-third of *K. pneumoniae* reported to the European Antimicrobial Resistance Surveillance Network in 2014 were resistant to at least one antimicrobial group under surveillance. Resistance to aminopenicillins and fluoroquinolones was most commonly reported, both as single resistance and as combinations with other antimicrobial groups. The mean percentage for third-generation cephalosporin resistance and combined resistance to fluoroquinolones, third-generation cephalosporins, and aminoglycosides

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