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ANTIMICROBIAL SUSCEPTIBILITY PATTERNS AND EMPIRICAL THERAPY IN URINARY TRACT INFECTIONS

JOOST VERHOEVEN^{1*}, PABLO ETXEBERRIA², DAVIDE FERRARESI³

Affiliation

¹Department of Internal Medicine, Twente Institute of Pharmaceutical Technology, Hengelo, Netherlands

²Department of Internal Medicine, Navarre Plain Institute of Pharmacy, Pamplona, Spain

³Department of Clinical Pharmacy, Valtellina Centre for Pharmacology, Sondrio, Italy

*Corresponding author: Joost Verhoeven, j.verhoeven@tipt.nl

ORCID iD: Joost Verhoeven 0000-0001-0123-3701; Pablo Etxeberria 0000-0001-0320-1068; Davide Ferraresi 0000-0001-3544-6852

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1. INTRODUCTION

Few infections are as common as those of the urinary tract. Roughly half of all women will have at least one episode in their lifetime, and a sizeable share will have a recurrence within a year [1, 2]. Costs to health systems are large, mostly because of the sheer number of consultations and prescriptions, with a smaller number of severe cases needing admission [1, 3]. In practice the first dose of an antibiotic is nearly always given before a culture result is back, since waiting two days for a laboratory report is not acceptable for a patient with dysuria or fever. The choice of that first drug is therefore an informed guess,

Abstract

Urinary tract infections are among the commonest bacterial infections treated in primary care and hospitals, and most are first treated before a culture result is available. This review summarises published evidence on the organisms that cause them, how antimicrobial susceptibility is measured and reported, regional resistance patterns, and the guideline logic behind empirical choices such as nitrofurantoin, fosfomycin, trimethoprim and fluoroquinolones. It also covers extended-spectrum beta-lactamase producers and stewardship. The literature shows rising resistance to older oral agents, wide geographic variation, and limited local data in many settings. No new patient data are reported, and conclusions rest on surveillance studies, trials and guidelines produced by others.

and the quality of the guess depends on local susceptibility data.

Resistance has complicated the guess. Two decades ago, trimethoprim-sulfamethoxazole could be given to most women with cystitis

without much worry, and fluoroquinolones were reserved for harder cases [4]. Since then, surveillance studies in North America, Europe and Asia have documented rising resistance in *Escherichia coli* to older oral agents, together with the spread of organisms that produce extended-spectrum beta-lactamases [5, 6, 7]. Clinicians now face a trade-off between narrow-spectrum drugs with high local activity and the collateral damage of broad-spectrum agents, a problem that has pushed guideline writers to rethink first-line recommendations [8, 9].

This review describes what the published literature says about antimicrobial susceptibility patterns of urinary pathogens and how that evidence feeds into empirical therapy. It begins with the microbiology and epidemiology, then the laboratory methods that generate susceptibility data, regional patterns, the major resistance mechanisms and the empirical regimens recommended in current guidelines. The final sections address stewardship and the limits of the data. No new patient data are reported here. The evidence is drawn from surveillance reports, randomised trials, systematic reviews and guideline documents published by others. Gaps and disagreements between sources are pointed out as they arise.

Terminology deserves a quick definition. Uncomplicated cystitis refers to lower urinary tract infection in a non-pregnant woman without structural or functional abnormality. Complicated infection includes any infection in men, in pregnancy, in the presence of catheters, obstruction or immunosuppression, and in patients with systemic signs [8, 10]. The distinction matters because empirical regimens, duration of therapy and the threshold for urine culture differ between the two groups. Asymptomatic bacteriuria is a third category, a laboratory finding without symptoms, and it should not generally be treated except in specific circumstances such as pregnancy or before urological procedures with mucosal bleeding [11, 12].

2. MICROBIOLOGY AND EPIDEMIOLOGY

Escherichia coli, mainly uropathogenic strains carrying adhesins such as type 1

fimbriae and P fimbriae, causes the large majority of community-acquired urinary tract infections. Flores-Mireles and colleagues described how these strains attach to the bladder epithelium, invade cells and form intracellular bacterial communities that can persist and seed recurrences [3]. *Staphylococcus saprophyticus* is the second most common cause in young sexually active women, and *Klebsiella*, *Proteus mirabilis* and *Enterococcus* species account for most of the rest [2, 13]. In hospital and long-term care settings, *Pseudomonas aeruginosa* and other non-fermenting bacteria assume more importance, as do *Candida* species in catheterised patients [3, 14].

Pathogenesis shapes both recurrence and treatment response. Bacteria reach the bladder by the ascending route from the periurethral flora, and the gut is the usual reservoir for *E. coli*. Once inside bladder cells, they can form quiescent reservoirs that escape both host defences and many antibiotics, which is one proposed explanation for early recurrence after an apparently successful course [2, 3]. In catheterised patients, biofilm on the catheter surface protects organisms from antimicrobials and from the immune system, and eradication usually requires catheter removal or replacement as well as drug therapy [3, 14]. These features explain why in vitro susceptibility is only an imperfect guide to outcome.

The ECO·SENS project, an international survey of uncomplicated infections in women across Europe and Canada, remains a landmark. Kahlmeter reported that *E. coli* accounted for the great majority of isolates, followed by *Proteus*, *Klebsiella* and *Staphylococcus saprophyticus*, and showed substantial variation in resistance between countries [6]. Subsequent national surveillance has confirmed that the proportion of resistant isolates is not simply a function of income or antibiotic consumption but also of local prescribing culture, travel and the spread of particular clones [5, 15]. Anyone applying a published resistance figure to their own practice should keep that geographic variation in mind.

Risk factors for infection and for resistant infection overlap but are not identical. Sexual

activity, previous infection, spermicide use and genetic factors predispose women to cystitis [2, 13]. Resistant organisms are associated with recent antibiotic exposure, hospital admission, residence in long-term care, travel to regions with high resistance and, in some studies, older age and diabetes [7, 14]. A recent course of a fluoroquinolone or a cephalosporin predicts resistance to that class, which is why a medication history is part of the empirical decision. Patients with a previous resistant isolate in the preceding months should have that result honoured when choosing a drug [8, 10].

Diagnosis traditionally hinged on a quantitative count. Kass proposed in the 1950s, on the basis of studies in women with pyelonephritis and in asymptomatic women, that 10^5 colony-forming units per millilitre separate true bacteriuria from contamination [11]. Later work showed that symptomatic women can have lower counts. Stamm and colleagues found that counts of 10^2 per millilitre or more of a coliform in a dysuric woman were clinically meaningful [16], and Hooton and colleagues, comparing midstream cultures with catheter specimens, found that the traditional threshold missed many culture-confirmed infections [17]. Current guidelines accept lower counts in symptomatic patients, and laboratories vary in the thresholds they report [8, 10].

3. SUSCEPTIBILITY TESTING AND REPORTING

Susceptibility data come from a few standard methods. In disk diffusion, a standardised inoculum is spread on Mueller-Hinton agar, antibiotic disks are applied and the inhibition zone is measured after overnight incubation, an approach whose EUCAST version is described by Matuschek and colleagues [18]. Broth microdilution and agar dilution determine the minimum inhibitory concentration (MIC) directly, and their use in guiding antimicrobial therapy has been reviewed [19]. Automated systems used in most hospital laboratories rely on miniaturised broth dilution. Each method has strengths and limitations, and results from different methods are not always interchangeable, particularly near the breakpoint [19, 20].

The quality of the specimen limits the quality of the result. Contamination with periurethral or vaginal flora is common in voided samples, particularly from women, and gives mixed growth that cannot be interpreted. Clean-catch collection, prompt transport and refrigeration or boric acid preservative reduce overgrowth in transit. A urine left at room temperature for many hours can turn a modest count into a large one [11, 16]. Laboratories that culture every dipstick-positive sample also generate many results from patients without infection. These practical points seldom feature in resistance surveys, yet they affect which isolates enter the data and therefore how representative the percentages are [17, 21].

Interpretation requires breakpoints, and two bodies set them. The Clinical and Laboratory Standards Institute publishes its M100 supplement annually, and the consequences of its breakpoint revisions for laboratories have been reviewed, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) publishes its own breakpoint tables [20, 22]. The two systems differ in some categories, for example in the treatment of the intermediate category, which EUCAST renamed susceptible, increased exposure. Differences in breakpoints mean that the same isolate and the same MIC may be classed differently, and resistance percentages in published surveys are not strictly comparable unless the standard and its version are stated. Urinary breakpoints for some agents, such as nitrofurantoin and fosfomycin, apply to uncomplicated cystitis only [20, 22].

Turnaround time is the other practical constraint. A conventional culture and susceptibility report takes one to two days after the sample arrives, and in the meantime the patient has been treated empirically for better or worse. Rapid methods, including automated systems that read growth kinetics and molecular panels for resistance genes, can shorten this interval, although they add cost and are used mostly for blood cultures and severe infection rather than for routine cystitis [14, 23]. For outpatients with simple symptoms, the pragmatic approach remains empirical therapy followed by review if

culture, when sent, shows resistance to the drug chosen [8, 21].

Cumulative susceptibility reports, often called antibiograms, summarise the proportion of isolates susceptible to each agent. They are produced annually by many hospital laboratories, usually stratified by location, and they guide empirical choice. A good antibiogram counts only the first isolate per patient, includes a minimum number of isolates, and separates urinary from other sites, because urinary isolates have a different profile from blood or wound isolates. Pooling urinary and non-urinary isolates can misrepresent agents that are concentrated in urine, such as nitrofurantoin, so the source should be stated [24]. Without these precautions, the figures can mislead as easily as they inform.

Detection of ESBL production uses phenotypic confirmation. Screening is based on reduced susceptibility to oral or third-generation cephalosporins, and confirmation relies on enhanced inhibition zones with clavulanic acid in combination disks or double-disk synergy tests [20, 22, 23]. Automated systems apply expert rules to flag the phenotype. Misclassification occurs when AmpC enzymes or porin changes mask the clavulanate effect, and molecular tests for CTX-M genes are used in reference laboratories. Because beta-lactam susceptibility results for ESBL producers can look favourable in vitro and still predict failure in vivo, expert rules that report such isolates as resistant to penicillins and cephalosporins are widely applied [20, 25].

4. RESISTANCE PATTERNS IN UROPATHOGENS

Ampicillin and amoxicillin have long since lost their value for empirical treatment of *E. coli* cystitis, since resistance in many surveys exceeds 30 to 50 per cent. Trimethoprim and trimethoprim-sulfamethoxazole follow a similar trajectory, with resistance commonly reported above the 20 per cent mark at which the IDSA and ESCMID guideline advises against empirical use for cystitis [4, 5, 8]. Karlowsky and colleagues documented a rise in resistance to trimethoprim-sulfamethoxazole among US

outpatient isolates from the late 1990s [15], and the later US analysis by Sanchez and colleagues showed continued increases, including in fluoroquinolone resistance [5]. These trends underlie most of the recent change in guideline recommendations.

Fluoroquinolone resistance has risen steadily in many regions, often linked to mutations in the gyrase and topoisomerase genes and to plasmid-mediated mechanisms [5, 7]. The consequences go beyond treatment failure. Fluoroquinolones carry a recognised set of adverse effects, including tendon injury, neuropathy and central nervous system effects, and their use is best restricted in uncomplicated infection where alternatives exist [26]. Even in countries where local resistance is modest, there is little justification for using them as a first choice in simple cystitis. They remain important for pyelonephritis, prostatitis and some complicated infections, where local resistance is low [8, 10].

Older drugs have retained surprising activity. Nitrofurantoin resistance among *E. coli* remains low in most surveys, despite decades of use, probably because the drug acts at multiple targets and reaches only low systemic concentrations [27, 28]. Fosfomycin trometamol likewise retains activity against most *E. coli*, including many ESBL producers, though resistance in *Klebsiella* and *Proteus* species is higher [28, 29]. Pivmecillinam, widely used in Scandinavia and now in the United Kingdom, is also still active against most *E. coli*, and its use is a notable example of an old drug being reintroduced because of resistance elsewhere [6, 9]. Mecillinam activity against *Proteus* is less reliable.

Definitions affect how resistance is counted. Definitions of multidrug resistance have differed widely between publications, with some requiring resistance to three or more antibiotic classes and others using different thresholds, which makes direct comparison of reported rates unreliable [30]. Adopting the same terms across studies allows comparison, though the categories were designed for a defined list of organisms and agents. For urinary *E. coli*, many reports of multidrug resistance rely on co-resistance among agents

that are not first-line for cystitis, and the clinical meaning of the label is therefore variable [14, 30].

The table in this review brings together representative findings on organisms, resistance mechanisms, laboratory methods and therapy options, as presented in table 1. Several themes recur. Resistance to the older oral drugs is frequent, nitrofurantoin and fosfomycin remain active against most urinary *E. coli*, and breakpoint standard and method choice both affect the reported figures. The balance of entries by theme (fig. 1) shows that the evidence is richest for organisms and therapy, with fewer entries on the laboratory methods that generate the data, even though that is the part on which comparability depends.

5. EXTENDED-SPECTRUM BETA-LACTAMASES AND OTHER MECHANISMS

Extended-spectrum beta-lactamases (ESBLs) hydrolyse penicillins and most cephalosporins, including third-generation agents, and are inhibited by clavulanic acid. Pitout and Laupland described their emergence as a public health concern, with the CTX-M family becoming dominant worldwide in *E. coli* from the early 2000s [7, 23]. ESBL genes sit on plasmids that often carry resistance to aminoglycosides and fluoroquinolones, which explains the cross-resistance seen in clinic. Community acquisition of ESBL-producing *E. coli*, once rare, is now documented in many parts of the world, and travel to endemic regions is a recognised risk factor [7, 14].

Treatment of ESBL infection has been debated for years. Carbapenems have been regarded as the drugs of choice for serious infection, but concern about carbapenem resistance has encouraged attempts to use other agents. Tamma and Rodriguez-Baño reviewed non-carbapenem beta-lactams and concluded that piperacillin-tazobactam carried a risk when used for ESBL bloodstream infection, a view that was strengthened by the MERINO trial, in which 30-day mortality was higher with piperacillin-tazobactam than with meropenem in patients with ceftriaxone-resistant *E. coli* or

Klebsiella bacteraemia [25, 31]. For lower tract disease the position differs, because oral options are available and urinary concentrations are high [28, 29].

Table 1: Representative published findings on urinary pathogens, susceptibility testing and empirical therapy

Topic	Reported finding	Ref.
<i>Escherichia coli</i> uropathogenic strains	Cause the large majority of community cystitis; adhesins and intracellular communities favour persistence	[3, 6]
<i>Staphylococcus saprophyticus</i>	Second most frequent cause of cystitis in young sexually active women	[2, 13]
Recent antibiotic exposure	Predicts resistance to the class used; prior cultures should guide the next choice	[7, 14]
Disk diffusion and MIC methods	Standardised methods with zone or MIC results interpreted against breakpoints	[18, 19]
CLSI and EUCAST breakpoints	Systems differ, so resistance percentages are comparable only if standard and version are stated	[20, 22]
Trimethoprim-sulfa methoxazole	Resistance above 20 per cent argues against empirical use for cystitis	[4, 8, 15]
Fluoroquinolones	Rising resistance and safety concerns limit use in uncomplicated cystitis	[5, 26]
Nitrofurantoin	Low resistance in <i>E. coli</i> and efficacy similar to comparators in short courses	[27, 32]
Fosfomycin trometamol	Active against most <i>E. coli</i> including many ESBL producers; single-dose option	[28, 29]
ESBL producers CTX-M type	Cross-resistance common; piperacillin-tazobactam inferior to meropenem in bloodstream infection	[23, 31]
Asymptomatic bacteriuria	Treatment not advised except in pregnancy or before certain urological procedures	[12]

For ESBL-producing organisms in cystitis, nitrofurantoin and fosfomycin are the oral drugs most often recommended, with mecillinam as a further option where

available [10, 28, 29]. Falagas and colleagues, in a systematic review of fosfomycin for multidrug-resistant Enterobacteriaceae infections, reported favourable clinical and microbiological outcomes, mostly in urinary infection, though most of the underlying studies were observational [29]. Aminoglycosides given as a single dose or a short course have also been used, and temocillin is used in some countries. For pyelonephritis due to ESBL organisms, carbapenems or, if susceptible, other agents such as aminoglycosides may be needed [14, 25, 31].

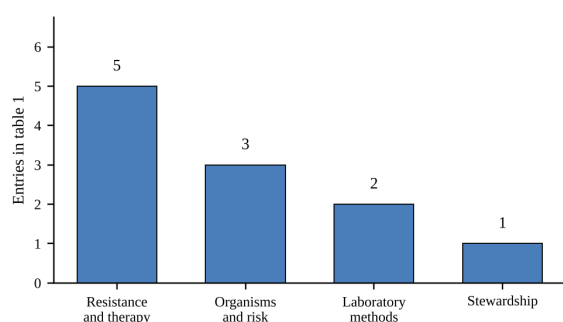


Fig. 1: Number of entries in table 1 by theme

New agents add options but also questions. Ceftazidime-avibactam was compared with doripenem in complicated urinary tract infection and acute pyelonephritis in the RECAPTURE trials and found to be non-inferior, which supported its approval for resistant Gram-negative infection [33]. Such agents are intended for infections with limited alternatives and are reserved to preserve activity.

Carbapenemase-producing Enterobacterales remain a minority of urinary isolates in most regions but are a growing worry. The practical lesson for empirical decisions in the community is simple: new drugs belong in specialist hands, and the main work lies in using older agents well [14, 33].

Carriage matters as much as infection. Patients colonised in the gut with ESBL-producing organisms after hospital stay or travel may carry them for months, and a later urinary infection is likely to involve the same strain [7, 14]. Rectal screening is used in some intensive care units, though not for community patients. A history of ESBL isolation in the previous year is therefore a sensible reason to avoid cephalosporins and amoxicillin-clavulanate empirically, and to prefer an agent known to be active against the

previous isolate, provided the site and severity allow it [10, 23].

6. EMPIRICAL THERAPY IN GUIDELINES AND TRIALS

For acute uncomplicated cystitis, the IDSA and ESCMID guideline recommended nitrofurantoin for five days, trimethoprim-sulfamethoxazole for three days where local resistance is below 20 per cent, or a single dose of fosfomycin as first-line options, reserving fluoroquinolones and beta-lactams for situations in which these cannot be used [8]. NICE guidance in the United Kingdom is broadly similar, with nitrofurantoin or trimethoprim (where resistance is low) as first choices and pivmecillinam or fosfomycin as alternatives [9]. The European Association of Urology guidance also favours fosfomycin trometamol, nitrofurantoin and pivmecillinam, adding that choice should reflect local epidemiology and patient factors [10].

Trial evidence supports these choices. Gupta and colleagues compared a five-day course of nitrofurantoin with a three-day course of trimethoprim-sulfamethoxazole in women with cystitis and found similar clinical and microbiological cure rates, [32]. Hooton and colleagues compared amoxicillin-clavulanate with ciprofloxacin in uncomplicated cystitis and found that the beta-lactam combination was less effective, with lower cure rates and more persistent vaginal colonisation by *E. coli* [34]. Huttner and colleagues pooled controlled trials of nitrofurantoin and judged efficacy comparable to that of other first-line agents with an acceptable safety record in short courses [27].

Beta-lactams other than pivmecillinam occupy a second-line place. Oral cephalosporins and amoxicillin-clavulanate are less effective than first-line agents in cystitis, with higher failure rates in trials and more effect on bowel flora, and the guidelines accordingly describe them as alternatives to be used when first-line drugs cannot be given [8, 10, 34]. Amoxicillin alone is not recommended empirically because of resistance. In practice, a patient with a nitrofurantoin contraindication and a

trimethoprim-resistant history may be offered fosfomycin or pivmecillinam, and if those are not available, a short course of an oral cephalosporin guided by the latest susceptibility result [9, 32].

Safety also shapes the empirical choice. Nitrofurantoin is contraindicated or avoided when renal function is substantially reduced, because efficacy falls and adverse effects rise, and rare pulmonary and hepatic reactions have been reported mainly with long-term use [27, 28]. Trimethoprim raises serum creatinine and potassium and interacts with some drugs, including methotrexate and certain angiotensin-converting enzyme inhibitors. Fosfomycin is usually well tolerated, with gastrointestinal complaints the main problem. Fluoroquinolones carry the broadest set of safety concerns, which argues for restraint in uncomplicated infection [26]. A good empirical decision therefore weighs renal function, pregnancy, allergy, interactions and prior culture results as well as local susceptibility [8, 9].

Pyelonephritis and complicated infection call for different thinking. Oral fluoroquinolones remain a standard option where local resistance is low, and Sandberg and colleagues showed that seven days of ciprofloxacin was non-inferior to 14 days in women with acute pyelonephritis [35]. Where fluoroquinolone resistance exceeds about 10 per cent, the IDSA and ESCMID guideline suggests an initial intravenous dose of a long-acting agent such as ceftriaxone or an aminoglycoside before oral therapy [8]. Cultures should be taken before treatment, and therapy adjusted when results return. Durations have shortened over time, and many guidelines now accept seven days for the majority of patients who respond promptly [10, 35].

Point-of-care testing can sharpen the decision. A urine dipstick showing nitrite or leukocyte esterase supports the diagnosis in women with symptoms, and a negative result in a woman with few symptoms lowers the probability of infection enough to prompt a search for other diagnoses, such as vaginitis or sexually transmitted infection [8, 21]. Guideline panels warn against relying on dipstick results in older adults, patients with

catheters or those with atypical symptoms. For recurrent cystitis, culture-confirmed episodes, a review of behavioural risk factors and consideration of prophylaxis are the usual steps [2, 13, 21].

7. STEWARDSHIP AND LIMITATIONS

Urinary tract infection is a central target for antimicrobial stewardship because it generates so many prescriptions. MacDougall and Polk reviewed the framework for institutional stewardship programmes, and the elements most relevant here are formulary restriction, prospective audit with feedback, guidelines tied to local data, and education [24]. Community programmes follow similar principles, with prescribing feedback and delayed prescribing strategies. The World Health Organization global action plan places optimising antimicrobial use at the heart of its strategy, and the threat described by Spellberg and colleagues and the burden documented by Murray and colleagues gives the policy its urgency [36, 37, 38].

Treating asymptomatic bacteriuria is one of the commonest forms of unnecessary prescribing. The IDSA guideline recommends against screening or treating asymptomatic bacteriuria in most populations, including older residents of long-term care, patients with diabetes and those with indwelling catheters, with specific exceptions for pregnancy and urological procedures [12]. Positive dipstick or culture results in an older patient with confusion but no urinary symptoms are a frequent trigger for needless treatment. Education of prescribers and nurses, along with diagnostic algorithms, reduces this practice, and the evidence from stewardship interventions in this area is among the more convincing in the field [12, 24].

Access and cost shape what is actually prescribed. Fosfomycin sachets, pivmecillinam and newer agents are not universally available or reimbursed, and in many countries the realistic choice is still between trimethoprim-sulfamethoxazole, a fluoroquinolone and an oral cephalosporin, whatever the guidelines of other regions recommend [36, 38]. Guideline authors increasingly note that recommendations must

be adapted to what is on the local formulary. This is an argument for locally produced susceptibility data and for central procurement of narrow-spectrum agents with good urinary activity, since a recommendation that cannot be implemented has no effect on resistance [9, 37].

Limitations of the underlying literature should be stated plainly. Surveillance data differ in sampling, method and breakpoints, which complicates comparison. Many studies are laboratory-based and lack clinical information, so they cannot say whether a resistant isolate led to treatment failure. Randomised trials of short-course regimens are mostly from the United States and Europe in otherwise healthy women, and their findings may not apply to older patients, men or settings with high ESBL prevalence [8, 27, 32]. Cost and drug availability, which strongly affect real prescribing, are rarely examined. In many low-income countries, local data are absent altogether, and guideline authors have to extrapolate [36, 38].

Surveillance design deserves comment. National programmes such as those summarised in the ECO·SENS reports and in US outpatient studies offer the most reliable trend data, but they tend to capture only a fraction of community prescribing [5, 6]. Linking laboratory results to prescribing records and outcomes would allow resistance to be tied to clinical failure, which is the question that prescribers actually need answered. Some health systems now do this, but the published reports remain few, and those that exist cover populations with good record systems. Wider adoption would also help clarify whether breakpoint changes alter clinical outcomes, a question that cannot be answered from laboratory data alone [20, 22].

8. CONCLUSION

The published evidence shows that urinary tract infections are caused mainly by *E. coli*, that resistance to older oral drugs such as ampicillin, trimethoprim and the fluoroquinolones has risen, and that nitrofurantoin, fosfomycin and pivmecillinam retain high activity against most community isolates [5, 8, 28]. ESBL-producing organisms are now an established part of the

picture, and the choice of drug for them depends on the site of infection and local availability [23, 31]. Susceptibility data are produced by standard methods, but breakpoint standard, sampling and reporting practices differ [20, 22].

Empirical therapy is best seen as a local decision informed by guidelines and by recent antibiograms, tempered by patient factors such as renal function, pregnancy and previous cultures [8, 9, 10]. Stewardship measures, including avoiding the treatment of asymptomatic bacteriuria and limiting fluoroquinolone use, are supported by reasonably consistent evidence [12, 24, 26]. The main gaps are a shortage of community-based surveillance, the lack of trial data in older patients and men, and poor comparability of published resistance figures, all of which deserve attention before the next round of guideline revisions.

9. ABBREVIATIONS

ESBL-Extended-spectrum beta-lactamase, MIC-Minimum inhibitory concentration, CLSI-Clinical and Laboratory Standards Institute, EUCAST-European Committee on Antimicrobial Susceptibility Testing, IDSA-Infectious Diseases Society of America, ESCMID-European Society of Clinical Microbiology and Infectious Diseases, MERINO-Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infection due to ceftriaxone-resistant *E. coli* and *Klebsiella*, NICE-National Institute for Health and Care Excellence

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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