J Antimicrob Chemother 2018; **73** Suppl 3: iii2–iii78
doi:10.1093/jac/dky027

Journal of Antimicrobial Chemotherapy

Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party†

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The Working Party makes more than 100 tabulated recommendations in antimicrobial prescribing for the treatment of infections caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) and suggest further research, and algorithms for hospital and community antimicrobial usage in urinary infection. The international definition of MDR is complex, unsatisfactory and hinders the setting and monitoring of improvement programmes. We give a new definition of multiresistance. The background information on the mechanisms, global spread and UK prevalence of antibiotic prescribing and resistance has been systematically reviewed. The treatment options available in hospitals using intravenous antibiotics and in primary care using oral agents have been reviewed, ending with a consideration of antibiotic stewardship and recommendations. The guidance has been derived from current peer-reviewed publications and expert opinion with open consultation. Methods for systematic review were NICE compliant and in accordance with the SIGN 50 Handbook; critical appraisal was applied using AGREE II. Published guidelines were used as part of the evidence base and to support expert consensus. The guidance includes recommendations for stakeholders (including prescribers) and antibiotic-specific recommendations. The clinical efficacy of different agents is critically reviewed. We found there are very few good-quality comparative randomized clinical trials to support treatment regimens, particularly for licensed older agents. Susceptibility testing of MDR GNB causing infection to guide treatment needs critical enhancements. Meropenem- or imipenem-resistant Enterobacteriaceae should have their carbapenem MICs tested urgently, and any carbapenemase class should be identified: mandatory reporting of these isolates from all anatomical sites and specimens would improve risk assessments. Broth microdilution methods should be adopted for colistin susceptibility testing. Antimicrobial stewardship programmes should be instituted in all care settings, based on resistance rates and audit of compliance with guidelines, but should be augmented by improved surveillance of outcome in Gram-negative bacteraemia, and feedback to prescribers. Local and national surveillance of antibiotic use, resistance and outcomes should be supported and antibiotic prescribing guidelines should be informed by these data. The diagnosis and treatment of both presumptive and confirmed cases of infection by GNB should be improved. This guidance, with infection control to arrest increases in MDR, should be used to improve the outcome of infections with such strains. Anticipated users include medical, scientific, nursing, antimicrobial pharmacy and paramedical staff where they can be adapted for local use.

†NICE has accredited the process used by the Healthcare Infection Society to produce the 'Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party' guidelines. Accreditation is valid for 5 years from March 2015. More information on accreditation can be viewed at http://www.nice.org.uk/about/what-we-do/accreditation.

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Contents

Lay summary

Multidrug-resistant (MDR) Gram-negative bacteria (GNB) are bacteria (or germs) that remain susceptible to only one or two antibiotics. Gram-negative bacteria usually live in the gut (or in the environment), where they do no harm, but can appear and cause infection at other body sites that normally lack any bacteria, for example in the bladder or blood. This especially occurs in patients who are made vulnerable by underlying disease, injury or hospitalization. MDR GNB may be acquired from other patients who have received antibiotics. Infections caused by MDR GNB are difficult to treat and so may cause more prolonged symptoms in the site of infection and can cause additional complications such as pneumonia or infection in the blood. This can prolong the length of stay in hospital, and in some cases can cause death. Some types of MDR GNB, *Acinetobacter* spp. for example, can be carried on the skin rather than in the gut, again with no obvious signs or symptoms. 'Colonization' describes carriage of bacteria on body surfaces or in the gut without infection. When patients develop infection and require antibiotic treatment, selecting the correct antibiotic can be difficult. This report provides advice on the best choices among the antibiotics currently available.

1. Introduction

This guidance has been prepared by a joint Working Party of the British Society for Antimicrobial Chemotherapy (BSAC), the Healthcare Infection Society (HIS) and the British Infection Association (BIA) to advise on the treatment of infections caused by MDR Gram-negative bacteria. It also describes best practice in antimicrobial prescribing. There is an accompanying guideline describing appropriate infection prevention and control precautions, including hand hygiene, equipment and environmental cleaning and guidance on screening for MDR GNB.[3] The infection control and prevention guideline should be used in conjunction with the present document. There is a glossary of technical terms (Appendix 1, available as Supplementary data at *JAC* Online).

The Working Party comprised a group of medical microbiologists and scientists, infectious disease physicians, infection control practitioners, epidemiologists, and patient representatives nominated by the Societies. The patient representatives were lay members and had direct experience of the treatment of healthcare-associated infections through personal experience, membership of SURF (Healthcare-acquired Infection Service Users Research Forum), patient charities or through involvement in the development of NICE guidelines. The representatives were: Susan Bennett, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK; Jennifer Bostock, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK; and Maria Cann, Trustee, MRSA Action, Kirkham, UK

They were involved in the preparation of the remit of the Working Party (Supplementary data Appendix 3), were invited to all meetings, invited to comment on the final draft prepared by the authors and endorsed the final version.

2. Guideline development team

2.1 Guideline advisory group

Phil Wiffen, Cochrane Pain, Palliative and Supportive Care Group Pain Research, Churchill Hospital Oxford, Nuffield Department of Clinical Neurosciences, Oxford. Karla Soares-Wieser, Enhance Reviews, Ltd, Wantage.

2.2 Responsibility for guidelines

The views expressed in this publication are those of the authors and have been endorsed by the three sponsoring societies following consultation. Patient representatives confirmed the guidelines addressed the questions raised in setting the Working Party's remit.

3. The Working Party Report

Date of publication: March 2018.

3.1 What is the Working Party Report?

This Report is a set of recommendations covering the treatment of infections caused by MDR GNB (i.e. herein defined as susceptible to only one or two different antibiotics). Strains internationally defined as MDR GNB by possession of resistance to three or more classes of antibiotics can nevertheless be treated with a wide range of antibiotics so we argue the case for a re-definition below (see Section 6.2).

The Working Party recommendations have been developed systematically through a multi-professional group and are based on published evidence. They should be used to develop local protocols for acute and long-term healthcare settings.

3.2 Why do we need a Working Party Report for these infections?

MDR GNB have become more prevalent internationally, including in the UK and Europe. The increased use of broad-spectrum agents encourages their proliferation.[4] The spread of these bacteria causes infections that can increase the length of hospital stay and adversely affect the quality of life of patients. Public awareness has been increasing, and the relative lack of new antimicrobial agents to treat infections due to GNB has resulted in the formulation of the 5 year Antimicrobial Resistance Strategy by the UK Department of Health.[5] Outbreaks are associated with considerable physical, psychological and financial costs. Evidence-based treatment regimens are effective in improving the outcome of infections due to these bacteria.

3.3 What is the purpose of the Report's recommendations?

The Report describes appropriate antimicrobial chemotherapy for infections due to MDR GNB.

3.4 What is the scope of these guidelines?

We examine the background information on the mechanisms, global spread, and UK prevalence of resistance, prescribing, and then discuss treatment (i) in hospitals using antibiotics intravenously and (ii) in primary care using agents given orally, ending with a consideration of antibiotic stewardship. Data (and doses, where given) usually refer to adults as there are few data for children and neonates. Extrapolation from adult data for β-lactams seems reasonably secure but this is not necessarily the case for other agents. Another set of guidelines considers appropriate infection control principles, best practice hand hygiene, screening and environmental cleaning.[3] For the detailed scope for this guideline see Appendix 2.5 and for the review questions see Appendix 3.7 (both in the Supplementary data).

3.5 What is the evidence for these guidelines?

In the preparation of these recommendations, systematic reviews were performed of peer-reviewed research using the searches show in Appendix 4. Expert opinion was also derived from published guidelines subjected to validated appraisal.[2] Evidence was assessed for methodological quality and clinical applicability according to protocols of the Scottish Intercollegiate Guidelines Network (SIGN) initially using SIGN 2011[1] guidelines and then updating this as the work continued in order to comply with the SIGN 2014 guidance.[6]

3.6 Who developed these guidelines?

A group of medical microbiologists, scientists, infectious disease physicians, infection control practitioners, epidemiologists and patient representatives.

3.7 Who are these guidelines for?

Any hospital or general practitioner can use these guidelines and adapt them for local use. Expected users include clinical medical, nursing, antimicrobial pharmacy and paramedical staff. Paediatric licences and formulation may limit the suitability of some of the discussed agents for children and neonates. Where there are specific issues relating to dosage, outcome or toxicity that are outside current licence information, these are discussed. The guidelines should be used to improve the treatment of both presumptive and confirmed cases of infection by MDR GNB.

3.8 How are the guidelines structured?

Most areas (defined by questions) comprise an introduction, a summary of the evidence base with levels and a recommendation graded according to the available evidence. The guidelines are not organized by clinical indication.

3.9 How frequently are the guidelines reviewed and updated?

The guidelines will be reviewed and updated every 4 years if warranted by sufficient changes in the evidence or by the availability of new agents or formulations.

3.10 Aim

The primary aim of the review was to assess the current evidence for antimicrobial prescribing in the treatment of MDR Gram-negative infections. The secondary aims were: (i) to evaluate the efficacy of antibiotics to treat community and hospital infections caused by MDR GNB; and (ii) to evaluate the impact of educating and providing support to professionals and patients to reduce unnecessary use of antibiotics, leading to a reduction in the selective pressure for resistance, thereby assisting antibiotic stewardship.

4. Summary of guidelines

The guidance has been derived from current best peer-reviewed publications and expert opinion. Each recommendation is graded according to standard grades[1] and is associated with a class of supporting evidence, or it is presented as a Good Practice Point. General recommendations for stakeholders, including prescribers, are made in Table 1. Specific antibiotic recommendations are made in Table 2.

4.1 How can the guidelines be used to improve clinical effectiveness?

The guidelines can be used to direct and formulate antibiotic policies and to aid the prescribing practice of infection specialists and other clinicians. They provide a framework for clinical audit tools for quality improvement.

4.2 How much will implementation of the guidelines cost?

The majority of the antimicrobial agents that are described in these guidelines are generic and are currently widely used. Newer β-lactam/β-lactamase inhibitors (BL/BLIs) are more expensive than older BL/BLIs and most alternatives to carbapenems against MDR GNB are also more expensive. Extra financial support will be required for the surveillance of outcomes of bacteraemia. Implementation of these guidelines should enable better-focused therapy, with no increase in drug utilization and possibly a modest decrease.

4.3 Summary of suggested audit measures

Patients with infections with MDR GNB should receive empirical (best guess) or definitive (i.e. after results of laboratory tests) appropriate antibiotic treatment (alone or in combination) and the former should be active in at least 80% of cases. It is important to note that the basis on which resistance was defined was changed by EUCAST from predicting failed clinical response to deviation from the normal susceptibility of the species. In an era of multiple resistance, continuing to select for such resistant strains even when the patient has clinically responded to antibiotics to which the organism is resistant is undesirable. Control groups with infections at the same site and caused by the same species, but not MDR, or infections without known aetiology should not receive definitive treatment reserved for patients with MDR GNB. This audit should be conducted first for bacteraemias.

To reduce total antibiotic consumption, measured as defined daily doses.

Quarterly use of carbapenems and piperacillin/tazobactam should be reduced if either is in the top quintile/1000 patient days as assessed in each quarter. Specialist and tertiary care units may have special needs and should be excluded from the quintile assessment. Reductions of use in such units should be undertaken but should be tailored by consideration of their speciality case mix.

Trimethoprim use should be reduced and nitrofurantoin use increased in primary care.

Risk assessment tools for colonization and infection with MDR GNB in patients should be developed for the UK and put in place in all settings. Only infected patients known to be, or at risk of being (by these assessments), colonized with these bacteria should receive empirical treatment with drugs reserved for MDR GNB.

No antibiotic prescriptions for treating the elderly with asymptomatic bacteriuria (ASB), or urinary tract infection (UTI) in the

Table 1. Summary of recommendations for stakeholders including prescribers

Organization	Recommendation	Strength
Central public health authorities	Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of trusts and CCGs or equivalent primary care organizations bacteraemia data in their localities annually. They should ensure computerized record linkage to provide dates of death. They should ensure information is categorized by locality (separately for hospitals and for community with associated separate wider healthcare data), date of onset or acquisition, organism, specific antibiotic resistance and pattern, and mortality rate. These data should be made available, for open interrogation, with rolling cumulative data within the health service.	Strong for
	Make publicly available tabulated incidence and outcome data for bacteraemia giving hospital onset data by region and hospital, and for community and wider healthcare onset data by CCG or equivalent primary care organizations. Correlate these data with similar analysed and tabulated annual data on total antibiotic use and organisms and antibiotic resistance in clinical infections.	Good practice
	Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.	Strong for
Commissioning and quality organizations	Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes for both.	Good practice
	Provide and use active feedback of monitoring to prescribers and nursing staff, ensuring optimization of clinical, microbiological and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.	Conditional for
	Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the community and care home setting.	Strong
	Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare- and hospital-onset infections and audit compliance with these.	Conditional for
Hospital and primary care: general	Provide an ongoing antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance, with guidelines, surveillance of outcome and active feedback.	Strong
	Identify through horizon scanning and make available new antimicrobials that may be required to treat MDR GNB. Monitor use through formulary/drug and therapeutics committees.	Conditional for
	Use restrictive prescribing policies to acutely reduce the incidence of infection or colonization with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor to check whether gains persist.	Strong for
	Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemia's onset was in the community, wider healthcare or hospital, antibiotic resistances of isolate, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and if possible defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals.	Good practice
Hospital and primary care treatment of UTI	Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI. Follow local guidance on what antibiotics to prescribe.	Strong for
	For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients, especially in those with dementia.	Conditional for
	Do not prescribe antibiotics in asymptomatic bacteriuria (ASB) in the elderly with, or without, an indwelling catheter.	Strong for
	Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Base decision on when to prescribe (whatever the age) primarily on symptoms. Use dipstick tests, if no catheter is present, to confirm the diagnosis, before prescribing, especially when symptoms are mild or not localized.	Strong for
	If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility.	Strong for
	Building on previous work, predictive scoring should be developed for the presence of ESBL-producing *E. coli* in primary care and on admission to hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBLs.	Strong for

Continued

Table 1. *Continued*

Organization	Recommendation	Strength
	Need to quantify risks of infection with/carriage of extraintestinal pathogenic *E. coli* and of *Klebsiella* spp. resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy.	Strong for
	If defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.	Strong for
	Personalize empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing, including the presence of MDR GNB in the patient, hospital unit, nursing home or community.	Conditional for
	In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for MDR GNB, including travel. Use an active oral agent only if patient is well enough and if known to have had ciprofloxacin-, trimethoprim- or co-amoxiclav-susceptible MDR GNB in last month.	Conditional for
	If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalization not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL- and AmpC-producing Enterobacteriaceae. If hospitalization required for this or OPAT not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of CPE organism. If the patient is penicillin hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.	Strong for
	Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy for UTI in guidelines are necessary, including recommendations where the risk of antibiotic-resistant bacteraemia is high.	Conditional for
Primary care prescriber for UTI	Always inform the patient or their carer(s) on what to look out for and how to re-consult if symptoms worsen or do not improve as community-onset *E. coli* bacteraemias of urinary origin are increasing.	Strong for
	In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors (see Section 8.4) or recent foreign travel to countries where such strains are highly prevalent.	Strong for
	Use fosfomycin, nitrofurantoin or pivmecillinam, guided where possible (i) by susceptibility testing and (ii) by this guideline's recommendation on choice, dosing and duration, for uncomplicated lower UTI where MDR GNB are suspected.	Strong for
	Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3 g orally as single dose, and repeat on third day only if MDR GNB confirmed to improve bacteriological cure. Pivmecillinam alone at 200 mg three times daily for 7 days may be a third-line choice but consider combination use with amoxicillin/clavulanate depending on clinical trial results at the time.	Conditional for
	Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes.	Conditional for
	To reduce recurrent UTI, consider firstly the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis. Where prophylaxis is used successfully for recurrent infection in adults limit use to 6 months.	Conditional for
	Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.	Conditional for

Table 2. Summary recommendations for specific antibiotics

Antibiotic	Recommendation	Grading
Amikacin	Modernize use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.	Conditional for
Amoxicillin/clavulanate	Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or if using empirically, recent isolates, are fully susceptible.	Conditional for
Ampicillin/sulbactam	Could use against some carbapenem-resistant apparently sulbactam-susceptible *A. baumannii* isolates. Caution needed in the UK because of a higher range of MICs. Absence of a breakpoint prevents categorization as susceptible/resistant.	Conditional for
Aztreonam	Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected.	Strong against
	Do not use aztreonam for CTX-M ESBL- or AmpC-producing bacteria even if these appear susceptible *in vitro*.	Strong against
	Use aztreonam for MBL- or OXA-48-producing strains if it is certain that they do not produce ESBLs or AmpC.	Strong for
	Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.	Conditional for research
Cefepime	Could use cefepime to treat infection caused by ESBL- or AmpC-producing bacteria if susceptible at the EUCAST breakpoint of MIC $\leq$1 mg/L	Conditional for
	Do not use cefepime even at increased dose for isolates with (i) MIC of 2–8 mg/L (CLSI 'susceptible dose dependent') or (ii) MIC 2–4 mg/L (EUCAST intermediate), or (iii) strains with stable derepression of AmpC or (iv) strains that produce both AmpC and ESBLs.	Strong against
	Do not use cefepime to treat infection caused by CPE.	Strong against
Cefixime and other oral cephalosporins	Do not used for treating infection caused by ESBL, AmpC and CPE.	Conditional
Cefoxitin	Confirmation needed of its usefulness as a carbapenem-sparing agent for inpatients to empirically treat urinary infection or use definitively for infections caused by CTX-M-15-producing *E. coli*; its short serum half-life means it is unsuitable for OPAT and probably it has insufficient advantage to displace existing agents.	Research and trials
Ceftazidime	Use ceftazidime for susceptible infections with *P. aeruginosa* including quinolone-resistant or some imipenem-resistant strains.	Strong for
	Do not use ceftazidime to treat infections due to ESBL- or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if *in vitro* tests suggest the isolate is susceptible.	Conditional against
Ceftazidime/avibactam	Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC-producing Enterobacteriaceae but alternatives may be cheaper.	Conditional for
	Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3-producing *Klebsiella* are vulnerable to mutations in the enzyme causing resistance.	Research and trials
	Consider whether ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC-3 producers based on latest evidence at the time of use.	Research and trials
	Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant.	Strong against
Ceftolozane/tazobactam	Use ceftolozane/tazobactam to treat susceptible infections with *P. aeruginosa* resistant to ceftazidime.	Conditional for
	Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis.	Research and trials
	Use ceftolozane-tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infections with ESBL-producing *Klebsiella* spp. owing to a higher resistance rate.	Conditional for
	Do not use for infections due to AmpC- or CPE or MBL/ESBL-producing *P. aeruginosa*.	Strong against
Ertapenem	Use ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or by porin loss.	Strong for
	Prefer carbapenem OPAT of susceptible infections in view of the once-daily dosing regimen.	Conditional for
Fluoroquinolones	Could use orally to treat UTI caused by MDR GNB that are susceptible.	Conditional for

Continued

Table 2. *Continued*

Antibiotic	Recommendation	Grading
Fosfomycin	Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available is useful for ESBL producers after repeated recurrence after nitrofurantoin and potentially for carbapenemase producers.	Conditional for
	Consider dosage and trials of oral formulation for upper UTI.	Research and trials
	Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB; clear indications for use are not yet established. Potential drug of last resort.	Research and trials
	Need comparative clinical trials to establish optimal indications for, and optimal use of, oral and parenteral drug.	Research and trials
	Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.	Strong for
Gentamicin	Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.	Conditional for
	Could use gentamicin as a carbapenem-sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing *E. coli* when susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised.	Conditional for
	Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing *Klebsiella* spp. if strain is resistant to colistin and meropenem (see Section 7.18).	Conditional for
	Use once-daily dosage of gentamicin or tobramycin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to the appropriate 7 or 5 mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs.	Strong for
Imipenem and meropenem	Use meropenem or imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.	Strong for
	Do not use imipenem to treat susceptible *Pseudomonas* infections.	Conditional for
	Introduce in the UK mandatory reporting of meropenem- or imipenem-resistant Enterobacteriaceae from all anatomical sites and specimens.	Strong for
	Test all meropenem- or imipenem- resistant isolates of Enterobacteriaceae immediately for the precise level of resistance and for an indication of the responsible class of carbapenemase. Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents, including, as appropriate, colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.	Strong for
	Consider use of continuous infusion meropenem in combination at dose determined by nomogram if infection with KPC carbapenemase-producing *Klebsiella* with MIC of >8 and <64 mg/L.	Research and trials
Nitrofurantoin	Could use nitrofurantoin for 5 days to treat uncomplicated, lower UTIs with nitrofurantoin-susceptible MDR *E. coli* (not Proteeae or *P. aeruginosa*).	Strong for
	Do not use repeatedly if there is moderate renal impairment (eGFR <45 mL/min/1.73 m^2), or in long-term courses, as these are associated with rare unwanted pulmonary effects.	Conditional against
	Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in *E. coli* infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare.	Conditional for
	Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing *E. coli* and *Klebsiella* spp.	Research and trials
Piperacillin/tazobactam	Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible by EUCAST criteria.	Conditional for
	Consider definitive use of piperacillin/tazobactam to treat infections caused by *P. aeruginosa* if susceptible by EUCAST criteria.	Conditional for

Continued

Table 2. *Continued*

Antibiotic	Recommendation	Grading
Pivmecillinam	Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility.	Conditional for
	Treat lower UTI due to ESBL-negative *E. coli* with pivmecillinam at 200 mg three times daily; do not use for infections caused by Proteeae, *Klebsiella* or *Pseudomonas*.	Conditional for
	Some ESBL-producing *E. coli* respond, but efficacy is poor against CTX-M-15 and OXA-1 enzyme producers: dosing at 400 mg three times daily may be no more effective. Consider combination of the lower dose with 375 mg three times daily amoxicillin/clavulanate for follow-on to parenteral therapy for such infections in hospital or OPAT.	Conditional for
	Requires clinical comparative trials in the public interest (i) alone or together with amoxicillin/clavulanate for UTIs due to ESBL-producing organisms, including particularly those producing CTX-M-15 enzymes, (ii) in uncomplicated lower UTI generally against fosfomycin trometamol and nitrofurantoin as the relative advantages of these drugs have not been directly compared over the last 10 years as MDR GNB have become more problematic.	Trials and research
Polymyxins (including colistin)	Reserve intravenous colistin for infections due to polymyxin-susceptible but multiresistant bacteria and preferably use in combination with other agents.	Conditional for
	Give careful consideration to use of higher dosage regimens in critically ill patients.	Conditional for
	Use colistin with meropenem to treat susceptible KPC-producing *Klebsiella* spp. if the meropenem MIC is $\leq$8 mg/L and consider higher meropenem dose by continuous infusion if the MIC is >8 and $\leq$32 mg/L.	Conditional for
	Consider colistin with aminoglycosides or tigecycline in infections with strains producing KPC or other carbapenemases, which are susceptible to these but resistant to meropenem with MIC >32 mg/L.	Conditional for
	Closely monitor renal function especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents, e.g. aminoglycosides.	Strong for
	Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options against CPE and are more threatened by resistance than previously appreciated.	Good practice
	Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as Proteeae and *Serratia* spp.	Research and trials
	Aerosolized colistin dry powder should be used in cystic fibrosis according to NICE guidelines. Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.	Conditional for
Temocillin	Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL-producing Enterobacteriaceae.	Conditional for
	Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or AmpC-producing bacteria.	Research and trials
	Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL producers, on basis of published *in vitro* data.	Research and trials
Tigecycline	Could use tigecycline in combination in the treatment of multiresistant soft tissue and intra-abdominal infections.	Conditional for
	Use alone in hospital-acquired respiratory infections is unlicensed and not advised as outcomes with current dosing are not clearly satisfactory in *Acinetobacter* and MDR GNB infections.	Conditional against
	Use in combinations in hospital-acquired respiratory infections: precise combinations depend on the antibiotic susceptibility of the MDR GNB causing the infection.	Research and trials
	Use higher-than-licensed dosing such as 100 mg twice daily for infections due to MDR GNB in critical care.	Conditional for
	Investigate if higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible *in vitro*.	Research and trials
Tobramycin	Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC(6′)-I and AAC (6′)-Ib-cr.	Conditional against
	Use tobramycin in preference to other aminoglycosides for susceptible *Pseudomonas* infection.	Conditional for Strong for

Continued

Table 2. *Continued*

Antibiotic	Recommendation	Grading
	Use once-daily dosage of tobramycin if no renal impairment followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to nomogram.	
Trimethoprim	Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless *in vitro* susceptibility has been demonstrated.	Strong against
	Do not use trimethoprim to treat lower UTIs as a first-line agent. Only consider use if there are no risk factors for resistance, or if confirmed *in vitro* susceptibility.	Conditional against
Trimethoprim/ sulfamethoxazole	Use in treatment of infections due to susceptible *S. maltophilia* and consider in infections due to *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp.	Conditional for

presence of a urinary catheter unless bacteraemia or renal infection is suspected.

No antibiotic prophylaxis for urinary catheter insertion or change unless previous history of symptomatic UTI associated with a change of catheter, or if there is trauma during catheter insertion, or if a urinary continence device has been inserted.

Gram-negative bacteraemia incidence should be decreased and outcomes should be improved in cases which developed in primary care, wider healthcare settings, and secondary and tertiary units.

Enhancements to surveillance should be planned and supported by information technology (IT) that allows record linkage and simplification of surveillance from the laboratory to national level.

4.4 *E-learning tools*

Continuing professional development questions and model answers are listed for self-assessment in Appendix 5.

5. Methodology

5.1 *Evidence appraisal*

Methods were in accordance with SIGN 50 and Cochrane Collaboration criteria[1,7] and critical appraisal was applied using AGREE II.[2] Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review (see Appendix 3.7) were derived from the Working Party Group, which included patient representatives in accordance with Patient Intervention Comparison Outcome (PICO).[6]

K. Soares-Wiesner of Enhance Reviews Ltd and Dr P. Wiffen of Pain Research and Nuffield Department of Clinical Neurosciences, Oxford University, used a systematic review process. Guidelines and research studies were identified for each search question. Systematic reviews, randomized controlled trials (RCTs) and observational studies were included. The latter comprised cohort non-RCTs, controlled 'before and after' studies, and interrupted time series. All languages were searched. Search strategies for each area are given in the sections below and in Appendix 4. MeSH headings and free-text terms were used in the Cochrane Library (Issue 11, 2012), Medline (1946–2012), Embase (1980–2012) and Cumulated Index of Nursing and Allied Health Literature (CINAHL) (1984–2012). On 23 May 2014, an update search was conducted on Medline alone using the same strategy for references after 1 January 2013. Reference lists of included studies were searched. Additional references were added in October 2016 and June 2017 to cover specific issues. Two review authors independently screened all citations and abstracts identified, and screened full reports of potentially eligible studies (those that addressed the review questions in primary or systematic secondary research, or a clinical, *in vitro* or in-use study). Disagreements were resolved by discussion, and rationales for exclusion of studies were documented. Pre-tested data extraction forms were used, and study characteristics and results collected. Data were extracted from observational studies for multiple effect estimates: these included the number of cases analysed, adjusted and unadjusted effect estimates, with standard error or 95% CI, confounding variables and methods used to adjust the analysis. If available, data were extracted from contingency tables. Risk of bias was assessed using SIGN critical appraisal checklists. Interrupted time series were assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) Group.[6,8] Quality was judged by report of details of protection against secular changes (intervention independent of other changes) and detection bias (blinded assessment of primary outcomes and completeness of data). For outbreak patterns associated with particular pathogens, the Working Party made additional searches of descriptive studies to extract effective treatments for infections caused by bacteria with specific resistance.

5.2 *Data analysis and interpretation*

Clinical outcomes were mortality, effectiveness of treatment and length of hospital stay. Microbial outcome measures were decreases in the prevalence of MDR GNB or decreases in colonization or infection by specific GNB. Risk ratios (RRs) were used for dichotomous variables, and mean differences with 95% CI were used for continuous variables.[9] Analyses were performed in Revman 5.22.[10] SIGN summary tables were used. Evidence tables and judgement reports were presented and discussed by the Working Party and the guidelines were prepared according to the nature and applicability of the evidence, patient preference and acceptability and likely costs. The level of evidence was as defined by SIGN (Table 3), and the strength of recommendation was based upon Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Table 4).[11] The grading relates to the strength of the supporting evidence and predictive power of the

Table 3. Levels of evidence for intervention studies[1]

Score	Description
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias.
1−	Meta-analyses, systematic reviews or RCTs with a high risk of bias.[a]
2++	High-quality systematic reviews of case–control or cohort studies.
	High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
	Interrupted time series with a control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention.
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal OR controlled before–after studies with two or more intervention and control sites.
2−	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
	Interrupted time series without a parallel control group:
	(i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention. Controlled before–after studies with one intervention and one control site.
3	Non-analytical studies (e.g. uncontrolled before–after studies, case reports, case series).
4	Expert opinion. Legislation.

[a]Studies with an evidence level of 1− and 2− should not be used as a basis for making a recommendation.

Table 4. Grading of recommendations[11]

Grading	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research *and possibly* conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

study designs, rather than the importance of the recommendation. Any disagreements between members were resolved by discussion. For some areas and recommendations, only expert opinion is available; in such cases, a good practice recommendation has been made. A flow chart of the systematic review process is given in Figure 1.

5.3 Consultation process

These guidelines were opened to consultation with circulation to the stakeholders listed (see Appendix 6). The draft report was placed on the BSAC web site for 1 month in June 2016 for open consultation. Views were invited on format, content, local applicability, patient acceptability and recommendations. The Working Party considered and collated comments, and agreed revisions.

6. Rationale for recommendations

6.1 Usage

It is beyond the scope of this guideline to define optimal quantitative usage of antibiotics by hospital beds or community populations and the UK is not an exceptionally high antibiotic user in international terms. Equally, measures to reduce antibiotic usage will depend on what apparent over-usage is occurring in any community or hospital department. For this reason, the assessment of reduction measures whilst based on comparative epidemiology must also consider both clinical outcome measures and usage at the local level. Suggestions for reducing overall usage must therefore be largely implemented at the local level where risk to patients and benefit can be adequately assessed, and they lie beyond the practical scope of this guideline.

6.2 What is the definition of multidrug-resistant Gram-negative bacteria?

Multidrug resistant (MDR) is a vexed term. From 1980 it was used to mean ‘resistant to multiple agents’ without the number or types of agents being specified. More recently the European Centre for Disease Prevention and Control (ECDC) has attempted to formalize the term as ‘resistant to three or more antibiotic classes’, whilst extremely drug resistant (XDR) is ‘susceptible only to one or two drug classes. These definitions, based on those for tuberculosis, are epidemiologically attractive, but can prove to be impractical. An international consensus is difficult to achieve, as not all products are available and tested by laboratories in all countries, and there is no universal testing policy for laboratories (which make

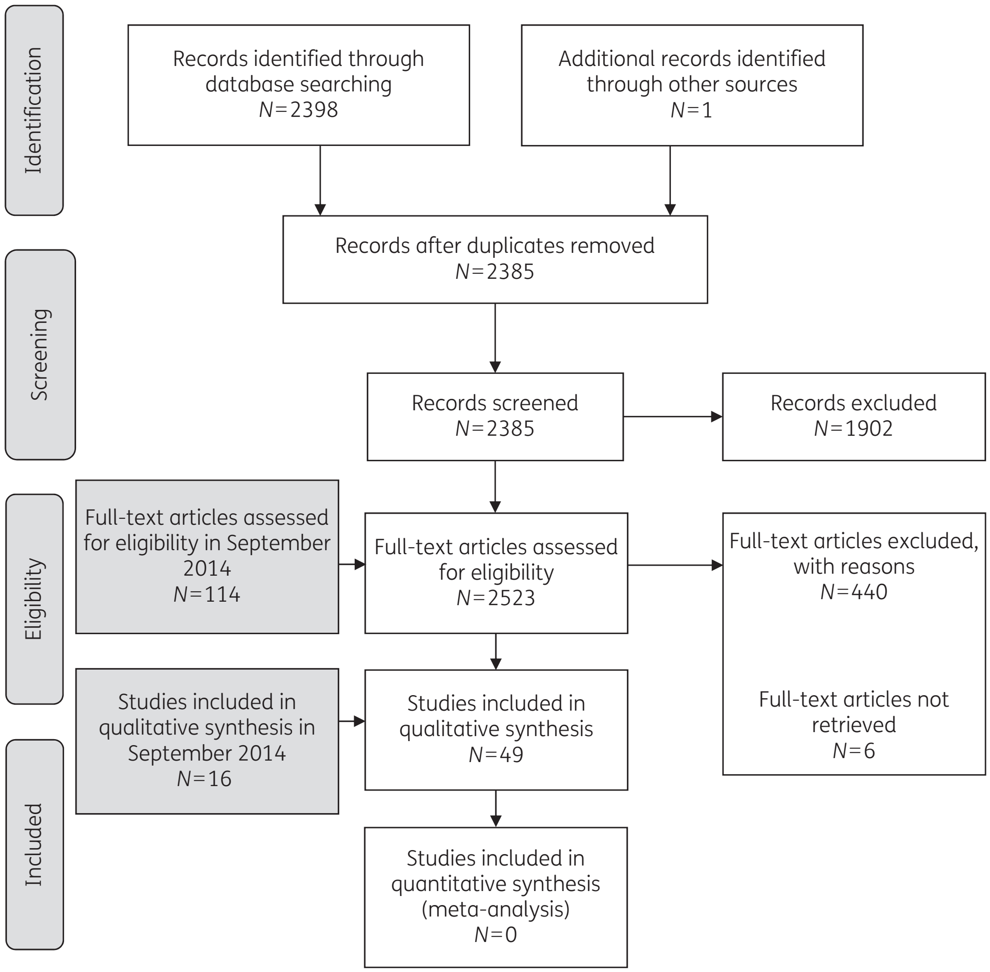

Figure 1. Flow chart of systematic review.

pragmatic decisions on what to test). Some antibiotic resistances are now very common and stable, e.g. to ampicillin and sulphonamides, so they are seldom tested for, but if they are present the organism needs only one further resistance to count as MDR GNB by the 'three classes of resistance' rule. There also is scope for disagreement on which antibiotics should be considered as separate classes; for example, monobactams behave similarly to oxyimino-cephalosporins in respect of most resistance mechanisms but very differently in the case of metallo-lactamases (MBLs).

Difficulties arise also if *in vitro* 'susceptibility' is poorly defined, e.g. with the absence of EUCAST breakpoints, as for e.g. (i) *Acinetobacter* spp. and sulbactam, and (ii) temocillin. Furthermore, differences between European (EUCAST) and US (CLSI or FDA) breakpoints can affect fundamentally whether isolates are regarded as MDR or XDR. These inconsistencies will have an effect on the recruitment and classification of patients in clinical trials. Separate breakpoints for urinary isolates, although needed to take account of high urinary concentrations with some antibiotics, also complicate assessments. Lack of laboratory uniformity in breakpoints can make comparisons and data aggregation meaningless. For example, EUCAST and CLSI breakpoints differ for piperacillin/tazobactam and amoxicillin/clavulanate. EUCAST defines Enterobacteriaceae isolates as piperacillin/tazobactam susceptible if they have an MIC $\leq$8 mg/L [resistance (R) >16 mg/L] compared with $\leq$16+4 mg/L (R $\geq$128+4 mg/L) in CLSI guidance. For amoxicillin/clavulanate susceptibility is defined by EUCAST as $\leq$8+2 mg/L (R >8 mg/L (or 32+2 mg/L for uncomplicated UTI) and by CLSI as $\leq$8+4 mg/L (R $\geq$32+16 mg/L). The FDA regard *Pseudomonas aeruginosa* isolates as susceptible to piperacillin/tazobactam if the MIC is $\leq$64 mg/L (the historical CLSI breakpoint for piperacillin) whereas EUCAST and CLSI now consider the breakpoint should be susceptibility (S) $\leq$16+4 mg/L. The EUCAST and CLSI definitions have changed with time and from previous national guidelines, e.g. the pre-EUCAST BSAC breakpoint for amoxicillin/clavulanate in systemic infections was 8+4 mg/L. Cefepime is a further example of an antibiotic with breakpoint changes: the old CLSI breakpoint for Enterobacteriaceae was $\leq$8 mg/L but is now $\leq$2 mg/L based on 1 g twice daily doses. Organisms with MICs of 4 or 8 mg/L are viewed as being 'susceptible but dose-dependent' by CLSI. EUCAST categorizes an MIC $\leq$1 mg/L as susceptible and >4 mg/L as resistant. A failure rate of 83% in a prospective trial of cephalosporins for 'susceptible' serious infections due to ESBL-producing *Klebsiella* spp. and *Escherichia coli* partly reflected the use of high breakpoints.[12] Breakpoint differences and changes over time in the categorization of isolates with the same MIC as 'susceptible' or 'resistant' profoundly challenge conclusions in the clinical literature, including reports of regulatory trials on the response to be expected of infections due to 'susceptible' or 'resistant' strains or indeed which patients have been included in trials where susceptibility of the organism is a selection criterion.

For all these reasons, the international definitions have not led to better surveillance of MDR strains and their usefulness must still be questioned. In our literature search routines, we have employed the international definitions but have had to augment these with literature on specific resistances. A useful pragmatic approach to the definition of MDR is to consider oral and parenteral drugs separately. The reason being that oral drugs will be largely used in the primary care setting and parenteral drugs in secondary care. Furthermore, one should base definitions on susceptibility rather than resistance as the former is more likely to be sought clinically by further testing with MDR strains. This gives a basis for alternative definitions for MDR. For oral drugs, multiresistance can usefully be defined as a bacterium susceptible to only one or no readily available oral agent active against infections systemically or in the upper urinary tract. This definition is vulnerable to the introduction of new, or newly re-licensed, oral agents, but this is appropriate and may emphasize the importance of new agents to the licensing authorities. By this definition the following would be classed as multiresistant isolates for the community: (i) *E. coli* resistant to co-amoxiclav (amoxicillin with clavulanic acid), oral cephalosporins, quinolones and trimethoprim but susceptible to nitrofurantoin, mecillinam and fosfomycin. Although providing options in cystitis, these oral agents lack evidence of achieving systemically active concentrations and efficacy in upper and complicated UTIs, which is particularly relevant if these are caused by ESBL- and AmpC-producing strains; (ii) *P. aeruginosa* resistant to quinolones. This approach could be modified to exclude agents where the mutation frequency is sufficiently high so that resistance commonly emerges during treatment.

For parenteral antibiotics a similar approach can be considered. Susceptibility to oral agents that have no licensed, or available, parenteral form, e.g. pivmecillinam and nitrofurantoin, should not be taken into account. Specific agents to which impaired susceptibility might be significant include carbapenems, relevant cephalosporins (cefotaxime for Enterobacteriaceae, ceftazidime for *P. aeruginosa*), aztreonam, ceftolozane/tazobactam, ceftazidime/avibactam, temocillin, piperacillin/tazobactam, colistin, quinolones, fosfomycin, tigecycline and aminoglycosides (including amikacin). Given this greater number of agents and the paucity of new pipeline antibiotics active against Gram-negative bacteria, it is pragmatic to consider 'multiresistant' as isolates where only two, or fewer, unrelated antibiotics are active against the bacterium. By such a definition the following would be considered multiresistant isolates in hospitals:

(i) *Acinetobacter baumannii* susceptible to two or fewer of meropenem or imipenem, (third-generation cephalosporins), piperacillin/tazobactam, (tigecycline), aminoglycosides, quinolones, (trimethoprim), colistin, where agents in brackets lack EUCAST breakpoints.
(ii) *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. that are susceptible to two or fewer of carbapenems, third-generation cephalosporins, including with β-lactamase inhibitors, piperacillin/tazobactam, temocillin, tigecycline, aminoglycosides, quinolones, trimethoprim or colistin.
(iii) *Proteus* spp., *Morganella* spp. and *Providencia* spp. that are resistant to third-generation cephalosporin, piperacillin/tazobactam, and aminoglycosides and susceptible only to carbapenems, and the new BL/BLI combinations (ceftolozane/tazobactam or ceftazidime/avibactam). Unlike the species considered in (ii) above, these Proteeae are inherently resistant to tigecycline and colistin.

The following would not be regarded as multiresistant:

(i) *E. coli* that is susceptible to carbapenems, ceftolozane/tazobactam, ceftazidime/avibactam, colistin and fosfomycin but resistant to unprotected third-generation cephalosporins, co-amoxiclav, piperacillin/tazobactam, quinolones and trimethoprim.

The effect of new parenteral antibiotic introductions on the definition of MDR GNB in hospitals is illustrated by the licensing of ceftazidime/avibactam and the availability of parenteral fosfomycin. Both drugs join temocillin, tigecycline or colistin as potentially effective agents against some Enterobacteriaceae with KPC carbapenemases. Such strains would no longer be classified as MDR GNB by our definition. Clearly, acquired resistance of KPC-producing strains to colistin, ceftazidime/avibactam, fosfomycin and tigecycline may all arise so some will be MDR GNB and some will not. From a therapeutic view this is probably appropriate, although all should remain major targets for infection control, given the cost of new agents and the need to conserve their usefulness, along with plasmid-mediated transmission of bla_{KPC} gene and transmission of their host strains. The use of alternative β-lactams or new BL/BLIs rather than carbapenems may be expensive but might reduce the selective pressure for carbapenem-resistant MDR GNB. These antimicrobials, with activities against organisms with different β-lactamases, may have differential effects on the prevalence of particular β-lactamases and other carbapenem-resistant bacteria. They may select more for MBLs that are particularly resistant to β-lactams, which will limit their ultimate usefulness in a locality. The activity of different β-lactamase inhibitors against, and stability of β-lactams to, different β-lactamases is shown in Table 5.

The difficulty in international surveillance of MDR GNB need not preclude the establishment of surveillance for specific organism–antibiotic resistance combinations. This has been adopted by PHE for the English Surveillance Programme for Antibiotic Use and Resistance (ESPAUR) and is weighted towards resistance to third-generation cephalosporins, quinolones and carbapenems of *E. coli*, *Klebsiella* spp. and *P. aeruginosa*.

6.3 What is the global epidemiology of MDR GNB?

6.3.1 Origins and impact of multiresistance

Resistance to multiple agents can develop via successive mutations, through the dissemination of multiresistance plasmids/genes (e.g. transposons), or through a combination of both processes. Resistance narrows antibiotic choices for definitive therapy. More critically, it increases the likelihood that empirical therapy will prove ineffective, increasing mortality in septic patients.

Table 5. Stability of various β-lactam antibiotics and different inhibitor activities against important β-lactamases found in MDR GNB

	Enterobacteriaceae								*Acinetobacter*		*Burkholderia*	*Pseudomonas*
Compound	AmpC	TEM ESBL	SHV-ESBL	CTX-M ESBL	OXA-1	OXA-48	KPC	IMP/VIM/NDM	native	OXA-23/24/58	native	native
Inhibitors												
clavulanate	not inhibited	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited		not inhibited		
sulbactam	not inhibited	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited		not inhibited		
tazobactam	not inhibited[a]	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited		not inhibited		
avibactam	inhibited	inhibited	inhibited	inhibited	?	inhibited	inhibited[b]	not inhibited		not inhibited		
β-Lactams												
temocillin	stable	stable	stable	stable	stable	labile	moderately stable	labile	inherently inactive	inherently inactive	variable	inherently inactive
piperacillin	labile[c]	labile	labile	labile	labile	labile	labile	labile	acquired R near universal	labile	variable	active
ceftazidime	labile[c]	labile	labile	labile	stable	stable	labile	labile	acquired R near universal	labile	variable	active
MEM/IPM	stable	stable	stable	stable	stable	labile	labile	labile	active	labile	variable	active
ertapenem	moderately stable[c]	stable	stable	stable	stable	labile	labile	labile	inherently inactive	inherently inactive	inherently inactive	inherently inactive
aztreonam	labile[c]	labile	labile	labile	stable	labile	labile	stable	inherently inactive	inherently inactive	inherently inactive	active
mecillinam	stable	moderately stable	labile	moderately stable	stable	labile	labile	labile	inherently inactive	inherently inactive	inherently inactive	inherently inactive

MEM/IPM, meropenem/imipenem. R, resistance.
[a]Except *Morganella morganii*.
[b]Inhibition not reliable with KPC-3.
[c]May appear active if AmpC is inducible, as induces weakly.

Plasmids are the main source of MDR in Enterobacteriaceae and *Acinetobacter* spp., except for mutations in DNA gyrase genes *gyrA*/*B* conferring fluoroquinolone resistance, mutational up-regulation of *arcA*/*B*-mediated efflux compromising tigecycline, and for mutational derepression of AmpC β-lactamases giving resistance to third-generation cephalosporins in *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and *Morganella morganii*.[13,14] By contrast, sequential accumulation of mutations is paramount in *Pseudomonas* spp.

A recent review has discussed the emergence of specific resistant lineages and the role of different plasmid groups in emerging resistance problems in *E. coli*.[15] Some clones have spread widely for reasons that are not clear. Resistance may increase their competitiveness, but some strains are adept at acquiring MDR. Several strands of evidence support this view. First, some 'high-risk clones', e.g. *E. coli* ST131, frequently acquire diverse resistance determinants, including different ESBLs, AmpC and even carbapenemases.[16] Second, there is co-selection of hypermutability with resistance in *P. aeruginosa* in patients with cystic fibrosis, facilitating development of further resistance. Third, it is commonplace for plasmids and resistance islands to carry multiple genes encoding resistance to an antibiotic via two or more different mechanisms not all of which can remain under effective selection pressure. Fourth, the presence of toxin–antitoxin systems in plasmids may prevent loss of plasmids even when selective pressure is removed.[17] Fifth, integrons, which provide efficient gene-capture and expression systems, and which are now frequent in plasmids but were not present prior to the widespread use of antibiotics, provide a mechanism whereby resistance acquisition has accelerated. Finally, the presence of MDR GNB in the environment, including foodstuffs and water sources, provides important pathways for amplification and the spread of some resistance genes to man.[18,19,20–23]

Until recently, environmental sources of carbapenemase genes did not appear to exist but the description of high levels of NDM-producing *E. coli* in chicken in China[24] suggests this position will not be maintained with current international practices and biosecurity of food as a source. Surprisingly, the ST131 clone of *E. coli* did not seem to have significant environmental sources in its initial spread, although it has now been described occasionally in chickens.[25,26]

6.3.2 Epidemiological trends among MDR Enterobacteriaceae: cephalosporin and quinolone resistance

Countries historically varied in the prevalence of different CTX-M ESBLs conferring cephalosporin resistance and in the plasmids encoding these enzymes.[27] The prevalence of different CTX-M enzymes has changed with time and latterly in Europe and North America CTX-M-15 has become the dominant enzyme, often associated with *E. coli* ST131.[28] Whole-genome sequencing (WGS) suggests that the acquisition of CTX-M enzymes occurred a number of times in clade C of *E. coli* ST131.[29] Frequent co-carriage of OXA-1 penicillinases impairs susceptibility to combinations of clavulanate and tazobactam with penicillins. Ceftolozane appears stable to this OXA-1 enzyme. Other factors associated with the rise of MDR Enterobacteriaceae include the spread of plasmids encoding AmpC β-lactamase. These seem around 10-fold less frequent than plasmids encoding ESBLs in the UK,[30] although more recently in Canada a plasmid-mediated AmpC enzyme (CMY-2, which shares a promoter gene, ISEcp1, with CTX-M-15) was almost half as common as ESBL production and one-third of such strains belonged to *E. coli* ST131.[31] Distinguishing AmpC and ESBL cephalosporin-resistant strains is important epidemiologically and in routine testing, although both EUCAST and CLSI do not recommend it for guiding treatment.[32] However early information on AmpC/ESBL status in Enterobacteriaceae may predict resistance/susceptibility to ceftolozane/tazobactam. Mutations can augment MDR: for example, porin loss can engender resistance to ertapenem (and, sometimes, other carbapenems) in ESBL- and AmpC-producing Enterobacteriaceae.

6.3.3 Carbapenem resistance

Carbapenem resistance was initially slow to emerge in Enterobacteriaceae but is now steadily increasing, and mediated more and more by acquired carbapenemases (predominantly by KPC, VIM, IMP, NDM and OXA-48-like types).[33–36] Internationally there has been a considerable spread of *K. pneumoniae* clonal complex (CC) 258 isolates with KPC carbapenemases. The rise of NDM and OXA-48 carbapenemases is more often associated with the spread of their encoding plasmids or transposons among bacterial strains. Carbapenem resistance due to ESBL or AmpC enzymes combined with OmpK35 porin loss may lead to treatment failure but is often unstable and may impose a fitness cost on bacteria, meaning that spread of such strains among patients is rare, though not unknown.[33] Loss of the OmpK36 porin conferred resistance to new carbapenem–β-lactamase inhibitor combinations, relebactam with imipenem/cilastatin[37] and meropenem with vaborbactam.[38] Resistance conferred by acquired carbapenemases is of much greater concern, and is generally associated with considerable resistance to other agents.

Data from EARS-Net suggest that the prevalence of carbapenem-resistant Enterobacteriaceae causing bacteraemia markedly increased in most parts of Europe between 2013 and 2015.[39] European prevalence of carbapenem-resistant *K. pneumoniae* was higher than 5% in 2015 (and much higher in some of the countries)[40] in Greece, Italy, Cyprus and Romania. In Greece, the proportion of bloodstream *K. pneumoniae* isolates resistant to carbapenems increased from 27.8% in 2005 to 62.3% in 2014. VIM enzymes dominated early in this period but were replaced by KPC types, often carried by CC258. The rise of carbapenem-resistant *K. pneumoniae* in Italy has been dramatic and recent: from 1% of bacteraemias in 2009 to 15% in 2010 and 32.3% in 2014. This increase again is mainly due to CC258 *K. pneumoniae* with KPC enzymes.[41] This clone also spread widely earlier in the USA[42] and then in Israel,[43] where an aggressive, nationwide infection control intervention was successful in bringing it under control.[44,45] In Romania the major problem is *K. pneumoniae* producing OXA-48 carbapenemase.[46]

Outbreaks of carbapenemase-producing Enterobacteriaceae (CPE) have been reported in many other parts of the world, including all US states[47] (where KPC enzymes dominate), South Asia (predominantly NDM enzymes), the Middle East (OXA-48), Brazil and Colombia (KPC).[36,48] The MBL IMP-4 has spread widely in China, often together with KPC-2. IMP-4, without KPC, is the dominant carbapenemase in Australia. Further global spread is to be expected[49] as IMP-4 has now been observed in South London (unpublished observations, D. M. Livermore). In the absence of comprehensive international prevalence data for infection and carriage, risk factors for CPE are difficult to derive, but seem to include travel to high-prevalence areas, notably including the Indian subcontinent for NDM producers, and exposure to healthcare and antimicrobials.[33] Travel locations are becoming convergent with those where ESBLs are prevalent. Case-number trigger points for carbapenem-resistant isolates and regional coordination in control action has recently been modelled in the USA to show the high importance of early intervention with effective control measures[50] for *K. pneumoniae* strains and other Enterobacteriaceae. Carbapenem resistance in Enterobacteriaceae has been associated with increased attributable mortality, probably owing to the greater likelihood that initial empirical therapy proves inadequate.[33,51,52]

6.3.4 Global resistance issues with oral drugs with low resistance rates in the UK

A 2008 study of clinical isolates from women aged 18–65 years with symptoms of uncomplicated lower UTI in 10 countries found susceptibility rates above 90% only for fosfomycin (98%), mecillinam (96%) and nitrofurantoin (95%).[53] Nitrofurantoin resistance in *E. coli* as assessed in European and Canadian isolates collected in 1999–2000 and 2007–08 was associated with a very diverse range of sequence types, although many strains showed multiple resistances: mecillinam resistance was similarly diverse but not associated with multiple resistance.[54] A further study from Munster and Seattle suggests nitrofurantoin resistance is particularly common in ST58.[55] Nitrofurantoin resistance is now described in 11% of the dominant H30 sub-clone of ST131,[56] suggesting the drug may be selective in the upper intestine, although this drug does not usually eliminate Enterobacteriaceae from the faecal flora of patients receiving it. In Canada, nitrofurantoin resistance rates in ESBL-producing *E. coli* were 16% but in ESBL-producing *Klebsiella* spp. were 71% (nosocomial) and 93% (non-nosocomial).[57] Well-described mutations in nitrofuran reductases confer resistance and plasmid-mediated resistance due to an efflux pump (*oqxAB*) has recently been described from Hong Kong.[58] This efflux pump and its encoding plasmid (with the *oqxAB* gene flanked by IS26 insertion sequences) was found in 26/103 nitrofurantoin-resistant or -intermediate human isolates (by CLSI criteria) and was more common in ESBL-producing isolates. The combination of *oqxAB* with the nitroreductase genes caused high-level nitrofurantoin resistance. This two-level resistance process is analogous to the hypothetical role of AAC-6′-Ib-cr in aiding the emergence of quinolone resistance by chromosomal mutation. Notably, *oqxAB* also mediates resistance to mequindox, which is used in China as a growth promoter in animal feed. In China 322/1123 veterinary isolates of *E. coli* carried this gene but these mainly belonged to phylogroups A and B1, which are less associated with extraintestinal pathogenicity in man.[59]

Fosfomycin use has been complicated by the emergence of resistance in some populations.[60] In Spain, when use increased some 50% between 2005 and 2008, resistance rates in CTX-M-15 ESBL-producing *E. coli* rose to 16% and among all ESBL-producing isolates increased from 4.4% in 2005 to 11.4% in 2009. The increase was particularly associated with nursing homes.[61] Fosfomycin resistance developed in *E. coli* ST131 (previously present there but not typed)[62] and was not associated with described mutational mechanisms of fosfomycin resistance.[63] Such mutations involve inactivation of genes encoding the hexose and triose sugar phosphate transport, impairing drug uptake. A different mechanism is present in the acquired *fosA* gene, which encodes a drug-inactivating metalloglutathione transferase.[60] Fosfomycin resistance was present in 2009–10 in 7.8% of human *E. coli* in mainland China and approximately half of this was due to *fos*A$_3$.[64] A recent survey of food animals in Hong Kong found plasmid-mediated *fosA* to be increasing in frequency and associated with CTX-M ESBL-encoding plasmids.[65] A recent Chinese survey of isolates collected from 2010 to 2013 detected fosfomycin resistance in 12% of ESBL-producing *Klebsiella* and 169/278 (61%) of KPC-producing *K. pneumoniae*: 94 KPC-producing strains carried *fosA$_3$* flanked by two IS26 insertions and were clonally related.[66] Similar genetic findings were made in non-clonally related *E. coli* and *Klebsiella* sp. in Korea.[67]

Mecillinam resistance is said to remain uncommon in the clinic, at 5%–7% of ESBL-producing *E. coli* in Sweden.[68] In a wider European study overall susceptibility was similar, with 4.8% resistance in *E. coli* from uncomplicated UTI, although gradually rising,[69] notably in Spain, where the proportion of resistant strains rose from 1% in 2000 to 6.5% in 2014.

6.4 How do MDR Enterobacteriaceae differ from non-fermenters in terms of their prevalence and associated resistance genes?

Carbapenem resistance is more common in non-fermenting GNB than in Enterobacteriaceae. In *A. baumannii*, by the year 2000 it was common to encounter isolates resistant to all treatment options except carbapenems, colistin and tigecycline. Subsequently, carbapenem resistance has proliferated, reaching ∼30% of bloodstream isolates. It is largely associated with acquired OXA-23, -40 or -58-like carbapenemases or with insertion-sequence-mediated up-regulation of the chromosomal OXA-51-like carbapenemase. The strain structure of *A. baumannii* is extremely clonal, making it difficult, without a history of patient transfers, to distinguish place-to-place spread from repeated independent selection of lineage variants that were previously circulating at low frequency. UK *A. baumannii* isolates producing OXA-23 carbapenemases often co-produce *ArmA*-encoded 16S ribosomal methyltransferases conferring pan-aminoglycoside resistance. MDR *Acinetobacter* spp. largely cause outbreaks in ICU settings,[70–72] whereas carbapenem-resistant Enterobacteriaceae, principally *E. coli* and *Klebsiella* spp., cause infection in a wider group of patients, and have far greater potential to spread rapidly when introduced into wider patient populations.[36,44,45,48,73,74]

Most UK *P. aeruginosa* remain susceptible to β-lactams, including ceftazidime, piperacillin/tazobactam and carbapenems, aminoglycosides and fluoroquinolones, with resistance rates of 5%–10% for these agents; and <1% for ceftolozane/tazobactam.[75] Nevertheless, single MDR lineages, some with carbapenemases, have persisted in a few UK hospitals for up to 9 years, causing multiple infections widely scattered over time and possibly reflecting colonization of the hospital water systems. The most frequently encountered carbapenemase is VIM, which may be plasmid mediated, with multiple gene copies conferring high-level meropenem resistance,[76] but is usually integron associated. IMP-9, another

MBL, is as common as VIM in China,[77] and has been shown to be derived (as probably are many carbapenemase genes) from environmental bacteria by horizontal gene transfer.[78] MDR is also a major problem in *P. aeruginosa* from cystic fibrosis patients, with resistance increasing over time in the individual patient's lung microflora. MDR profiles are extremely variable even within widely successful cystic fibrosis lineages, e.g. the Liverpool Epidemic Strain, which has circulated in multiple cystic fibrosis patients and units. Rates of carbapenem resistance in *P. aeruginosa* vary greatly across Europe, with high rates in Eastern Europe; Lithuania, Poland, Slovakia, Hungary, Croatia, Romania, Bulgaria and Greece all have rates of resistance >25% and sometimes >50%.[40] More generally, these rates of resistance show a gradient, rising from north-west to south-east Europe, with extensive spread of carbapenemase-producing clones in Belarus, Kazakhstan and Russia, which are outside the EU surveillance area.[79] In contrast to Enterobacteriaceae, rates of resistance to carbapenems are generally higher than those to ceftazidime, piperacillin/tazobactam or aminoglycosides.

6.5 Prevalence of antibiotic resistance in Gram-negative bacilli in the UK and relevant antibiotic prescribing

There are no epidemiological reports in the UK that specifically study defined MDR GNB. In this section, we discuss information on resistance to individual antibiotics and, where available, their associated resistances. Analysis is complex. Different reports from English, Welsh, Northern Irish and Scottish devolved administrations need to be drawn together to give a UK summary: bacteria and antibiotic resistances do not respect national boundaries.

Reduced prescribing may be followed by reduced resistance (see Section 11.1) but this is not invariable at a national level. Such reduced resistance has not occurred as older antibiotics (e.g. sulphonamides and streptomycin) have been abandoned,[80] perhaps because of resistance linkage and for reasons already discussed (see Section 6.3). Reduced prescribing may reduce the likelihood of new resistance becoming prevalent but this is only a hypothesis set within the modern issues of travel and migration, which may import and spread resistance. Overall antibiotic consumption in England has fallen by 4.5% between 2012 and 2015 to 21.8 DDDs/1000 population/day. It has yet to decline in general practice to the levels seen in 2010. After 5 years of increases in prescribing, hospital antibiotic use declined by 5% in 2014 from 5190 to 4933 DDDs/1000 admissions and is now at approximately 2010 and 2011 levels. This decrease is concentrated in teaching hospitals, which may reflect their case-mix or different pressures in other hospitals.[4]

In Scotland antibiotic use in primary care fell for the third consecutive year in 2015 (by 2.4%) and is now 9.5% lower than the peak rate of use in 2012. The level of prescribing was related to population deprivation scores and to residence in nursing homes where antibiotic use among those aged over 65 years was 83% higher than for similarly aged patients not resident in nursing homes.[81] Since 2012, antibiotic use in Scottish nursing homes has fallen by 7.8% compared with 5.1% in all patients aged >65 years. Nevertheless, hospital use rose by 3.5% and is now 9.9% higher than it was in 2012. The rate of 5880 DDDs/1000 admissions is now 19% higher than in England.[81] Of course, this may reflect use of less-selective combination regimens such as penicillin, metronidazole and gentamicin rather than the number of days a patient receives antibiotics, which is a weakness both of using DDDs and the number of admissions to estimate the number of people exposed to an individual antibiotic. Although England has the lowest antibiotic consumption in the UK, Scottish hospitals show significantly less consumption of carbapenems and piperacillin/tazobactam.

Information on primary and secondary care prescribing for Wales for 2015[82,83] is only available at the level of health board and hospital, respectively, and has not been reported as aggregate totals.

An overview of current antibiotic resistance in Gram-negative serious infections in the UK can be secured in various ways. The BSAC Bacteraemia Surveillance Programme (http://www.bsacsurv.org) provides historical and current information with a marked time lag for centrally tested isolates from a restricted sample of 24–40 hospitals and can be examined on a national or regional basis by species. It has an archive of organisms that can be studied in retrospect, which is an important strength. Other surveillance depends on collection of local data rather than isolates. In England reporting is mandatory for all cases of *E. coli* bacteraemia which has improved case ascertainment. Mandatory data are needed for *Klebsiella*, other Enterobacteriaceae and Proteeae, *Acinetobacter* spp. and *P. aeruginosa* if early national interventions in emerging problems are to be reliably assessed. Mandatory reporting of MRSA bacteraemia in England was established in 2001 and has improved with more comprehensive data capture from 2005 onwards. Health Protection Scotland now has mandatory reporting of *E. coli* bacteraemia but other species of Gram-negative bacilli are only reported across the UK on a voluntary basis. Such voluntary laboratory reporting of all bacteraemias has been in place since the Devonport incident of contaminated intravenous infusions in 1972 and is believed now to capture data for 82% of all bacteraemias. These data include antibiotic susceptibility data that have not been present in mandatory data. The collection of voluntary and mandatory data suggests that voluntary reporting should be replaced by mandatory reporting as soon as possible to reduce the laboratory workload. Most laboratories in England and Wales examining human samples now download bacteria identified and their antibiotic susceptibilities irrespective of anatomical site to regional and national repositories, where trends but not additional information, e.g. demographic details of patients' residence etc., can be analysed.

Bacteraemia due to *E. coli* has increased over the last 10 years in England and Wales, and analysis of the dataset showed that receipt of antibiotics in the 4 weeks preceding bacteraemia was the most important risk factor, followed by age over 65 years, and occurrence during summer months.[84] A study by the *E. coli* subgroup of the UK Department of Health's Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare-Associated Infection on the first 891 cases of *E. coli* bacteraemia with enhanced surveillance data are available in Committee papers for 28 March 2014 online.[85] This showed that urinary catheterization was a factor in only 10% of cases but that 72% of episodes from a urogenital source involved individuals aged ≥65 years. A urogenital infection had been treated in 310/891 (34.8%) cases in the 4 weeks preceding bacteraemia and this sub-population differed very significantly in its antibiotic resistances. Resistance in this subpopulation to ciprofloxacin was 80% versus 17% overall, 76.9% versus 39% to trimethoprim, and 49.3% versus 45% to co-amoxiclav. The third-generation cephalosporin resistance rate in the population overall was 10% but no figure was provided for the resistance rate in this sub-population treated. Although the rates for ciprofloxacin seem surprising, the figures show a marked selection for multiply resistant, if not necessarily MDR, strains because of either failed treatment that did not cover the multiresistant organisms or selection of resistant organisms in the gut flora that subsequently caused a urinary infection that then progressed to bacteraemia. Approximately half of the bacteraemias appeared to be associated only with a lower UTI but this probably represents symptomatically silent upper UTI giving rise to bacteraemia, either initially or through spread to the upper tract despite treatment. The implication of this important study is that failure to give effective antibiotics may be the reason for 70% of *E. coli* bacteraemias, whilst 30% of cases are associated with antibiotic resistance and, possibly, directly with treatment failure. The former requires detailed study, which is beyond the scope of this guideline. The consistent use of an active antibiotic regimen for those either aged >65 years or with signs and symptoms of an upper UTI would make a sizeable contribution to the target of a 50% reduction in the rate of in *E. coli* bacteraemias by 2020 that was announced by the then UK Prime Minister at the Japan 2016 G7 meeting.[86] This enhanced surveillance study has now been analysed and published.[87] Most patients (69.6%) were aged over 65 years. Most patients (68.3%) had a positive blood culture taken within 24 h of admission but 46.7% of these had a healthcare exposure within the previous month and 546 out of these 930 (58.7% of this subgroup, 31.5% overall) had received antibiotics in the preceding month. In 281 there was a clear urinary focus for the bacteraemia, for which 145 had received antibiotics (most commonly trimethoprim or co-amoxiclav). The largest independent risk factor for a bacteraemia's focus being the urogenital tract was previous treatment for UTI within 4 weeks of the bacteraemia's onset [adjusted odds ratio (aOR) 10.7 (95% CI 3.6–8.1)] but details of antibiotic resistance in this subpopulation for the whole study was not given. Twenty one percent of patients had either a urinary catheter *in situ* or had one inserted, removed or manipulated in the previous 7 days. Since the 2014 initial report, PHE has changed its recommendation for first-line treatment of UTI in all but those under 50 years from trimethoprim to nitrofurantoin, which is a urinary antiseptic that is only effective for treating lower UTI, although it can be effective for preventing pyelonephritis associated with bacteriuria of pregnancy. It is too early to tell whether this will be effective in reducing bacteraemia or whether an oral combination regimen that attains systemically active concentrations will be necessary to achieve the desired outcome. The UK Advisory Committee on Antimicrobial Prescribing, Resistance, and Healthcare Associated Infection (APRHAI) on 28 March 2014 opined that in suspected pyelonephritis or upper UTI the patient should be admitted if (i) ciprofloxacin, piperacillin/tazobactam or co-amoxiclav had been used in the previous 2 months and (ii) the patient's symptoms worsened or did not improve in the 12–48 h after prescription. In UK strains of *E. coli* ST131 from various sources collected in 2011–12, when O16 and non-typeable strains are excluded, there is evidence that trimethoprim resistance occurs in at least 69% of CTX-M-positive strains, which constituted 32% of recent UK strains studied but 39%, at most, of CTX-M-negative strains.[88] All CTX-M producers were ciprofloxacin resistant and 71% of non-CTX-M producers were quinolone resistant. Quinolones are not therefore useful if ST131 strains are prevalent even if these strains are not carrying ESBLs.

A study reported that sequence-typed *E. coli* isolates from the BSAC Bacteraemia Surveillance Programme showed that the significant change in *E. coli* bacteraemia was almost exclusively due to an increase in clonal complexes 12, 69, 73, 95 and 131.[84] This reflects the sequence types in these clonal complexes. The clonal complexes, which each may contain more than one sequence type, belong to phylogroups B2 and D, which have the virulence factors associated with extraintestinal spread. Phylogroup A and B1 strains, which may be more antibiotic resistant, are usually confined to the gut and lack these virulence factors. CC131, unlike the other CCs, includes multiresistant isolates (of ST131) hosting CTX-M ESBLs, almost invariably now with resistance to quinolones.[84] In a 2010–12 Yorkshire study of bacteraemias 129/768 were ST131 (39/129 ESBL producers), confirming the importance of ST131 strains even in the absence of production of ESBLs. One hundred and forty-two of 768 were ST73 (3/142 ESBL producers), 81 were ST69 (1 an ESBL producer), 73 were ST95 (1 an ESBL producer), 31 were ST12 (no ESBL producer, quinolone-resistant) and 27 ST127 (no ESBL producers or quinolone-resistant strains).[89] Phylogroup D-ST69 strains (which include the previously designated clonal group A) were not fluoroquinolone resistant in a recent Italian study,[90] although they were commonly detected in Italy in a previous cystitis study.[91] ST69 is usually ampicillin, trimethoprim and sulfamethoxazole resistant. Quinolone-resistant D-ST69 strains were also uncommon in a Spanish survey with isolates from 2009 accounting for 3% of quinolone-resistant strains respectively, compared with 26% for O25:H4-B2 ST131 strains.[92] We did not consider it feasible to introduce control measures for ST131 when preparing our earlier guidance on infection control[3] and indeed cephalosporin resistance has spread into many other STs.[93]

More recent data from 2012 to 2014 on antibiotic resistance in *E. coli* bacteraemia in England were collected on 82% (54301/66512) of cases recorded by mandatory surveillance by record-linking with the national records of all bacterial isolates. Seventy-four percent were classified as community onset whereas 16% of cases occurred 7 or more days after hospital admission. Antibiotic resistances reported were 8439 (18.4%) to ciprofloxacin, 4256 (10.4%) to third-generation cephalosporin, 4694 (10.2%) to piperacillin/tazobactam, 4770 (9.7%) to gentamicin and 91 (0.2%) to carbapenems.[94] Non-susceptibility to quinolones and cephalosporins decreased by 10% and 11% respectively over the 2 years in hospital-onset cases, whereas third-generation cephalosporin resistance increased by 10% in community-onset cases. Trends in hospital or community onset changes in antibiotic susceptibility in other species, such as *Klebsiella*, are precluded by lack of mandatory surveillance of bacteraemia.

A 12 year single-centre study in England suggested that the increase in *E. coli* bacteraemias was essentially confined to ciprofloxacin, co-amoxiclav, cefotaxime and aminoglycoside resistance and accompanied a similar change in urinary isolates.[95] The major rise in cephalosporin and MDR *E. coli* in the UK occurred between 2000 and 2007, largely reflecting the spread of IncF (pEK499 or similar) plasmids, and was associated initially with the internationally successful *E. coli* ST131 lineage with chromosomal fluoroquinolone resistance. These *IncF* plasmids encoding the CTX-M-15 β-lactamase, along with resistances to trimethoprim, sulphonamides, tetracyclines and aminoglycosides [often associated with *aac(6′)-Ib-cr*, also augmenting ciprofloxacin resistance],

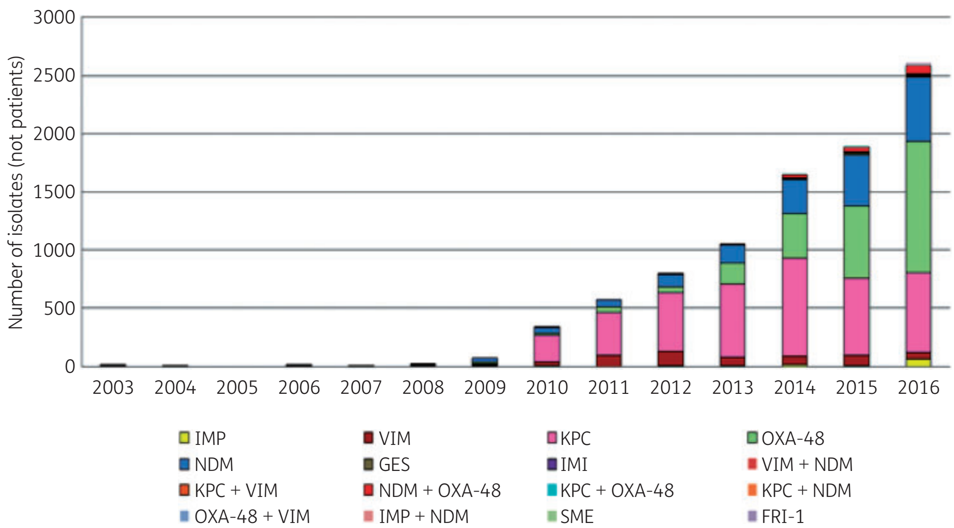

Figure 2. Carbapenemase-producing Enterobacteriaceae submitted to and confirmed by PHE-AMRHAI Colindale from laboratories in England. In a national context, a regional non-PHE centre in an area of KPC endemicity became active in 2014 and did not submit or report isolates. Courtesy of Dr Katie Hopkins, Public Health England.

also spread in other *E. coli* sequence types and other Enterobacteriaceae, notably *K. pneumoniae*. Since approximately 2007 (the date varies with the species and resistance) the rise of cephalosporin- and fluoroquinolone-resistant Enterobacteriaceae has slowed and fluctuated (*E. coli*) or reversed (*Klebsiella* spp. and *Enterobacter* spp.) in the UK, though not in continental Europe.[96] This shift in percentage resistance may reflect the reduction in prescribing of cephalosporins and quinolones in the UK, predicated not only by the Enterobacteriaceae problem but also by concern about *Clostridium difficile*. It is important to know if this reflects an absolute decrease in numbers. Some data suggest that increased quinolone use largely mirrored the selection of such strains.[97] An increase in quinolone resistance in bacteraemias preceded the arrival of ESBL-producing strains. Cephalosporin use in England is now reported to be the lowest in Europe.[4,98] Cephalosporin usage fell by a further 9.2% between 2012 and 2015 following larger previous declines from a peak in 2006–07 because of the national *C. difficile* problems. From 2012 to 2015, oral cefalexin use fell by 25.7% but parenteral cefotaxime use by only 1.6%, whilst parenteral ceftriaxone use increased by 37.4%, probably reflecting use of this once-daily antibiotic in outpatient parenteral antibiotic therapy.[4] The microbiological need for preferring this broad-spectrum agent to teicoplanin or daptomycin, which are only active against Gram-positive bacteria, should be critically reassessed.

General practice quinolone use in terms of DDDs/1000 inhabitants/day has fallen consistently since 2012, reducing by 3.6% between 2014 and 2015. However, the national overall usage of ciprofloxacin has declined only slightly, from approximately 0.48 DDDs/1000 inhabitants/day in 2012 to 0.43 in 2015: quinolone use in hospitals has increased despite an 18.4% incidence of ciprofloxacin resistance in *E. coli* bacteraemia.[94] A 53.6% rise in the respiratory quinolone levofloxacin, which is the L-isomer of ofloxacin, seems unjustifiable but reflects a recommendation for use in penicillin-allergic patients with pneumonia. A similar increase (50.3%) was seen in Scotland, accompanied by a 17% increase in ofloxacin use. An English target of a 10% reduction on 2013–14 levels of cephalosporin, quinolone and co-amoxiclav use in primary care or a reduction in use to be below the 2013–14 median value (11.3%) of Clinical Commissioning Groups (CCGs) for antibiotic prescribing of these agents, was achieved in 189/209 CCGs.[4] Prescribing of these antibiotics is substantially lower in Scotland and is not the subject of targets. Scottish reductions in primary care use in 2015 were 4.9% for co-amoxiclav, 5.8% for fluoroquinolones and 6.0% for cephalosporins, with an 8% overall reduction in use.[81]

Despite these reductions, cephalosporin and quinolone resistances continue to be seen frequently in UK bloodstream and urinary *E. coli* and *K. pneumoniae* isolates, with significant circulation in older patients who move between hospitals, nursing homes and the community, and who have frequent exposure to cross-infection and antibiotics. Resistance to both quinolones and third-generation cephalosporins in *E. coli* bacteraemias is concentrated in those aged $\geq$65 years in England and is at least twice as prevalent in those aged over 74 years compared with those aged 65–74 years.[4] An Italian scoring system for carriage of ESBL-producing organisms has not been tested in the UK or modelled to see if the group of patients at risk of carrying these strains on admission to hospital is increasing.[99]

The total number of *E. coli* bacteraemias in England, and therefore the absolute burden of resistance, continues to rise – by 4.6% from 35659 to 37310 between 2014 and 2015 in England.[4] The same publication notes an increase in *Klebsiella* bacteraemias by 9% over the same period. Over the period from 2000 to 2014 the incidence of *E. coli* bacteraemia in England has risen inexorably from 20 to 50 cases/100000 population.[94]

In England, rates of resistance to piperacillin/tazobactam are said to have increased in *E. coli* bacteraemias from 8.5% to 11.7% and in *Klebsiella* spp. bacteraemias from 12.6% to 18.5% over the period from 2011 to 2015.[4] Equivalent rises in resistance to co-amoxiclav from 31% to 42% in *E. coli* bacteraemias and 18.7% to

28.2% in *Klebsiella* spp. bacteraemias have occurred over the same period.

Record linkage for *E. coli* bacteraemias between 2012 and 2014 showed piperacillin/tazobactam resistance increasing by 15.1% for hospital-onset cases compared with 8.7% for community-onset cases.[94] This study also revealed significant variations in resistance rates by age and sex. Similar trends were seen in Scotland, with an 8.6% increase for piperacillin tazobactam resistance and 6.1% for co-amoxiclav resistance in *E. coli* bloodstream isolates and 14.8% and 28.7%, respectively in *Klebsiella* spp. in 2015. Changes from CLSI to EUCAST criteria may have produced these large rises in resistance in Scotland (see Section 6.2), but there were no changes in EUCAST criteria for these antibiotics between 2013 and 2015[81] and in England few laboratories use CLSI criteria. In Wales 11/18 hospitals in 2015 recorded an increase in piperacillin/tazobactam resistance in *E. coli*.[100] In England piperacillin/tazobactam use rose linearly by 62% between 2010 and 2015 to 135 DDDs/1000 admissions across all hospital types.[4] In Scotland, use fell by 7.9% in 2015.[81]

These changes are important. The main antibiotics used in a recent prospective study in 10 English hospitals of treatment of Gram-negative bacteraemia were co-amoxiclav in 32% of patients and piperacillin/tazobactam in 34%.[101] Despite empirical therapy being inactive against responsible organisms based on *in vitro* tests in 34% of cases, all-cause mortality was said to be low, 8% assessed at 7 days and 15% at 30 days. Given the increasing resistance rates and use, explorations of comparative outcome in relation to resistance and use are needed at each national level and also by source of infection (see Section 11.2). Mortality in *E. coli* bacteraemia throughout England was measured between July 2011 and June 2012 as 18.2% at 30 days or 10.34/100000 population in 1 year. These data were derived by record linkage of *E coli* bacteraemia cases mandatorily reported to PHE, voluntary reporting of antibiotic susceptibilities on all isolates to PHE, and records at the Office for National Statistics Death Registrations and at the NHS Spine.[102] Mortality is high as compared with Finland (8%) and inpatient-only mortality in Canada (11%) and New Zealand (9%). Analysis showed important associated features: 30% of deaths occurred on, or on the day after, the blood sample was taken and 76.3% within 14 days making the separate mortality analysis of community-onset and hospital-onset bacteraemia important. Overall 19174/26216 (73.1%) patients had their bacteraemia recorded within 1 day of admission. Mortality was higher (34.0%) if a respiratory focus of infection was diagnosed or the focus of infection was unknown (25.9%) than if a urogenital focus was diagnosed (13.2%). No information was available on the antibiotics prescribed, precluding any test of whether higher mortality was correlated with failure to provide adequate Gram-negative cover in suspected respiratory or unknown foci of infection; moreover, there were no audit data to show if the reported foci of infection were supported by evidence. A recent audit of coding and diagnosis of pneumonia by the British Thoracic Society did not support the diagnosis in 15.8% of cases and noted a 14.3% rate of mortality in this group.[103] At a population level the high burden of urogenital-related infection for *E. coli* was such as to make this the largest cause of deaths, even though mortality in this group was lower. The lower rate of mortality with urogenital infection correlates with information in an earlier study, which showed that the excess mortality for bacteraemia with ESBL-producing Enterobacteriaceae was confined to non-urinary infections.[104] The study by Abernethy and colleagues[102] identified a urogenital source for 55.3% of community-onset cases of bacteraemia and 45.1% of healthcare-onset cases. In 17.3% of cases the source was unknown. Mortality was lowest in those aged 1–44 years (5.4%) versus those aged 45–84 (17.9%) and >85 years (25.2%). Mortality rates varied by the susceptibility of the isolated causative bacterium; ciprofloxacin susceptible 17.0% (95% CI 16.4%–17.5%), ciprofloxacin intermediate or resistant 21.9% (95% CI 20.5%–23.2%); cephalosporin susceptible 17.5% (95% CI 16.9%–18.1%), cephalosporin intermediate or resistant 21.3% (95% CI 19.4%–23.2%). The inclusion of a factor in the adjusted model to allow for hospital- and case-mix-related mortality eliminated any significance from the difference in mortality by cephalosporin susceptibility. Cephalosporins are unlikely to have been used in infections due to ESBL-producing organisms in England, but piperacillin/tazobactam may have been used and the absence of a difference in mortality may reflect some improved outcome in urinary infection, despite the presence of bacteraemia. Different cephalosporins are not equally associated with *C. difficile*.[105] Oral first-generation cephalosporins would be useful in early treatment. It might be appropriate, whilst keeping *C. difficile* under review, to abandon downward pressure on the whole class of antibiotics and introduce a cephalosporin-specific approach. There were no data on mortality in relation to susceptibility to piperacillin/tazobactam, co-amoxiclav or aminoglycosides: carbapenem resistance rates were too low for robust assessment.

Resistance to any one of quinolones, cephalosporins or carbapenems was associated with a 30% increase in mortality. The association of increased mortality in quinolone-resistant strains needs explanation and it is not clear if this relates to hospital case-mix. Furthermore, if reduced use of oral quinolones is attempted, care is needed in the controversial area of prophylaxis in neutropenia, where quinolones are widely used. Studies of withdrawing quinolones for this indication show an increase in Gram-negative bacteraemia with susceptible strains without any diminution, at least initially, in resistant strains,[106–108] and recent Cochrane reviews support the efficacy of quinolone prophylaxis.[109,110]

Rates of carbapenemase production by Enterobacteriaceae (<2%) remain low in the UK but reference laboratory submissions of these organisms are growing annually (Figure 2), with many of the isolates coming from clinical rather than screening samples. It is noteworthy that surveillance of carbapenem-resistant strains depends on voluntary submission to reference laboratories and that regional molecular testing necessary for rapid turnaround has not been converted into national surveillance.[4] Given the importance of reducing carbapenem resistance, consideration should be given to introducing mandatory reporting of all isolates of carbapenem-resistant Enterobacteriaceae so the evolving picture can be properly assessed. English data suggest the proportion of carbapenem-resistant *Klebsiella* spp. rose from 0.2% to 1.1% between 2011 and 2015.[4] There are pockets of local endemicity, especially of *K. pneumoniae* and other Enterobacteriaceae, with KPC enzymes around Manchester or with VIM and OXA-48 in north Cheshire. These have persisted for 5–6 years (D. M. Livermore, unpublished data). Many other sites, notably London teaching hospitals, are currently being repeatedly challenged with a diversity of carbapenemase producers, many imported from overseas. CC258

K. pneumoniae with KPC carbapenemase remains rare in the UK, despite repeated introduction, and the greater issue, particularly in north-west England, is dissemination of plasmids encoding KPC carbapenemases among different *K. pneumoniae* and Enterobacteriaceae. Carbapenem-resistant isolates submitted to reference laboratories in Scotland increased from 47 in 2014 to 63 in 2015.[81] The dual loss of both quinolone and cephalosporin susceptibility has driven increased usage of carbapenems, particularly meropenem, from some 75 DDDs/1000 admissions in 2010 to 104 DDDs/1000 admissions in 2015 in England, a 38.6% increase, but in 2015 the increase was only 1%.[4,81] In Scotland the picture is different; there was a 6.5% increase in use of carbapenems between 2014 and 2015 but this is now only 9.3% higher than in 2012.

Phenotypic information on aminoglycoside susceptibility is available. Frequent gentamicin resistance was noted in ESBL-producing strains of *E. coli* from all sites in one region, representative of the UK, with resistance rates of 48.7% for *E. coli* ST131 and 55.1% for *E. coli* non-ST131.[93] The record linkage data previously discussed shows that overall gentamicin resistance rates (i.e. irrespective of ESBL production) varied by region between 5.5% and 15.4% in the years 2012–14 and that the overall rate in community-onset cases was 8.6%.[94] The region with lowest rate of resistance had a 34% higher incidence of *E. coli* bacteraemias than that with the highest rates, which suggests the possibility of dilution of the denominator by an increase in more susceptible bacteraemias (e.g. ST73 in northern England). In Wales in 2015 only 5/18 hospitals reported gentamicin resistance rates less than 8.6% in *E. coli* bacteraemia and two had rates over 20%.[100] Rates of 8.6%–15% would seem too high for empirical use of gentamicin alone. However, the 8.6% rate of gentamicin resistance in community-onset bacteraemia is very similar to the 8.7% resistance rate to piperacillin/tazobactam, which is widely used alone.[94] National data on amikacin are hard to interpret because fewer laboratories test it in addition to gentamicin and the amount of testing that is second line because of resistance on first-line testing remains unresolved, potentially skewing the data. Nevertheless, as expected, amikacin resistance is rarer than gentamicin resistance (2% in 2015) in England.[4]

Rates of co-resistance in bacteraemia isolates for 2015 for gentamicin and third-generation cephalosporins were 4.6% for *E. coli* and 5.9% for *Klebsiella* spp. compared with resistance rates to third-generation cephalosporins alone of 7.5% and 5.2%, suggesting some useful activity for gentamicin against ESBL-producing *E. coli* but less against ESBL-producing *Klebsiella* spp. Rates of co-resistance in bacteraemia isolates for 2015 to gentamicin with co-amoxiclav are 7.8% in both *E. coli* and *Klebsiella* spp. compared with resistance rates to co-amoxiclav alone of 35.2% and 19.3%.[4] This confirms the potential utility of an aminoglycoside compared with co-amoxiclav alone for both *E. coli* and *Klebsiella* spp. bacteraemias. The same data source indicates a somewhat different situation with ciprofloxacin/gentamicin combinations. For *E. coli* and *Klebsiella* spp. rates of co-resistance were respectively 6.8% and 5.8% whereas resistance to ciprofloxacin alone occurred in 11.8% and 5.0%, suggesting that addition of an aminoglycoside was seldom advantageous in *Klebsiella* infection. Overall these co-resistance data[4] suggest only a modest improvement on gentamicin monotherapy and the benefit compared with the harm of continuing selection of resistance by the non-aminoglycoside may not be great.

Consumption of aminoglycosides is now low in England in hospital inpatients (approximately 0.08 DDDs/1000 population/day) and fell in 2015. By contrast, use rose in Scotland by 5.9%, becoming 16.9% more frequent than in 2012. Falls in use are likely to reflect concern about resistance in ESBL producers and about potential toxicity; they may also reflect a change in clinical contacts with microbiologists as antibiotic assays are increasingly undertaken by clinical chemistry departments. A comparison with Scotland to understand the differences would be informative.

Bacteraemia represents a group of community infections selected for virulence factors sometimes but not always by antibiotics. Antibiotic resistance in Gram-negative infections in the community was thought, even a decade ago, to be quite uncommon in the UK. A historical European study of acute, community-acquired, uncomplicated, non-recurrent UTI in 2008 caused by *E. coli* involved 12 general practices in the UK and enrolled 200 unselected women aged 18–65 years. Resistance was rare to mecillinam (1%), nitrofurantoin (0%), fosfomycin (0.5%) amoxicillin/clavulanic acid (2.0%) and ciprofloxacin (0.5%), but commoner to amoxicillin (32%), sulfamethoxazole (26%), trimethoprim (15%) and trimethoprim/sulfamethoxazole (14%).[111] In that survey the co-amoxiclav resistance rate seems low in relation to the amoxicillin resistance rate. Reported resistance rates to co-amoxiclav in lower urinary infections have increased since the time of that study partly because of the substitution of EUCAST's (32+2 mg/L) breakpoint for the previous BSAC (16+8 mg/L) value. A contemporaneous UK study with a large community sample reported 12.0% resistance to co-amoxiclav versus 54% for ampicillin.[112] Welsh data in 2014 report the following resistance rates in 'coliforms' from urine in different communities: co-amoxiclav 12.9% (range 5.1%–25.4%), third-generation cephalosporin (ESBL) 6.8% (range 3.3%–17.9%), nitrofurantoin 10.0% (range 8.7%–22.4%), trimethoprim 36.7% (range 30.3–41.8%) and fluoroquinolone 10% (range 7.6%–16.4%).[113] A 2010–13 large UK study[114] of all community urinary isolates from a UK region with a population of 5.6 million found that by 2013 resistance to third-generation cephalosporins in *E. coli* had risen to 5.5% and ciprofloxacin resistance to 15.5%; for *Klebsiella* spp. the cephalosporin resistance rate was higher at 10.1%. Only 0.06% of the *E. coli* isolates were reported as resistant to one or more carbapenems, as were 0.32% of the *Klebsiella* spp. isolates. In this regional survey, VIM enzymes were found in *Pseudomonas* spp., whereas among *E. coli* and *Klebsiella* spp. 16 had NDM genes, 5 KPC and 2 OXA-48. These findings support the view that carbapenemases are rare in the community in the UK. A further study of isolates in the same English region over the period 2007–14 showed, after de-duplication, 69 with bla_{NDM}, 26 with bla_{KPC}, 16 with $bla_{\mathrm{OXA\text{-}48\text{-}like}}$ and 7 with bla_{VIM}.[115]

A historical audit of urine samples taken at presentation from primary and secondary care in South London before the widest dissemination of ESBL-positive *E. coli* ST131 occurred, found that 22.6% of isolates were resistant to trimethoprim, 43.3% to amoxicillin and 10.3% to nitrofurantoin.[116] Since this audit, resistance to trimethoprim has slowly risen across the UK, and in Wales is significantly commoner in isolates from patients over 65 years. Trimethoprim resistance rates vary widely by CCG in England. In 2011 it ranged in these from 16.3% to 66.7% but by 2015 in 86% of CCGs it was >25% with an almost uniform median of 29% in CCGs.[4,82] The reason for these variations in a minority of CCGs remains uncertain. In Wales resistance rates of 38.2% overall are currently reported. A caveat is that high resistance rates may reflect selective testing of previously treated patients in the community and different local policies for submitting samples, and the true rate of resistance to trimethoprim in patients presenting in the community with uncomplicated UTI may be lower than current figures suggest.[117] Trimethoprim use in England fell by 14.5% between 2014 and 2015, reversing the increase seen between 2012 and 2014. This fall should be many times larger in 2016 if there is expeditious compliance with the PHE recommendation in 2014 to substitute nitrofurantoin for trimethoprim as the first-line antimicrobial for cystitis in the older patient. A Swedish trimethoprim-sparing switch in one region resulted in an 86% decline in trimethoprim use between 2004 and 2006.[118] In 2015 in England rates of trimethoprim prescribing were approximately 1.1 DDDs/1000 population/day compared with 0.8 DDDs/1000 population for nitrofurantoin.[4]

UK data on resistance to nitrofurantoin, fosfomycin and mecillinam is scanty. In a single-centre study nitrofurantoin resistance was commoner in *Klebsiella* spp. of community origin (around 15%) than in *E. coli* (3%).[119] English national data for the second quarter of 2016 suggest resistance in *E. coli* in community UTIs varied with CCG between 0.3% and 12.8% with a median of 3.8%,[4] whilst in Scotland 5.9% of isolates tested in 2015 showed nitrofurantoin resistance.[81] Nitrofurantoin resistance is also common in UK CPE isolates.[120] Proteeae are inherently resistant to nitrofurantoin and data on their prevalence in UTI and resistance linkage for nitrofurantoin resistance in England are needed given the recommendation to use this antimicrobial first line (see Section 9.1 for previous experience of changes in prevalent phylogroups and STs of *E. coli*). There are no recent data on fosfomycin resistance in the UK. A survey of fosfomycin resistance in Leeds found *fosA* in two urinary tract isolates collected months after its UK introduction in 1994 despite a lack of use in the study hospital.[121] In the same publication, a study of foods in Leeds in 1995 identified two Enterobacteriaceae isolates carrying *fosA* in vegetables imported from Spain. Fosfomycin resistance (MIC $\geq$64 mg/L was present in 32/81 strains of CPE in 2011; 27 of these were *Klebsiella* spp.[120] In Wales, only 6.2% of cefpodoxime-resistant *E. coli* (i.e. probably ESBL- and AmpC-producing strains) were apparently resistant to mecillinam,[122] but this is discussed further later in the article (see Section 9.4).

The impact of the successful clone ST131 clone of *E. coli* on multiple resistances has been assessed. In one 2011 UK study, resistance rates in ESBL-producing *E. coli* ST131 (mostly with CTX-M-15 enzyme) compared with non-ST131 (producing CTX-M-15 or CTX-M-14) were 99% versus 83%, respectively, for ciprofloxacin and 92% versus 86% for trimethoprim.[93] Fluoroquinolone resistance alleles *gyrA/B* and *parC* are characteristic on WGS of the Clade C of *E. coli* ST131, which is almost exclusively the clade carrying CTX-M ESBLs.[29]

There is no reliable information on acquired colistin resistance. Usage sharply increased by 30% between 2013 and 2015 in England, entirely in specialist and teaching hospitals.[4] Given: (i) the growing use of colistin as a drug of last resort; (ii) the prevalence of colistin resistance in KPC-producing *Klebsiella pneumoniae*, especially in Italy, but also in the USA; (iii) the lack of mandatory surveillance of *Klebsiella* spp.; and (iv) the recognition of plasmid-mediated colistin resistance due to *mcr1* and *mcr2*, there is an urgent need for enhanced surveillance of colistin resistance at a national level.[4] *mcr1* has been found in isolates from British pigs[123] but is widespread in the European food chain, including additionally turkeys and veal calves,[124] and *mcr2* has been found in pork and cattle products.[125]

6.6 What impact have returning travellers made on UK epidemiology?

Whilst mutational resistances often emerge locally, strains with acquired resistance genes are often clearly imported to the UK from other countries. Examples include MDR *K. pneumoniae* with OXA-48 carbapenemases with Libyan conflict casualties and with patient transfers from elsewhere in the Middle East; *K. pneumoniae* with KPC carbapenemases from Greece and Israel and, most significantly, Enterobacteriaceae with the NDM MBL from south Asia and China.[126] Colonization of travellers may be frequent, although precise rates are largely unknown. A systematic review confirms travel to certain areas is a significant risk factor.[127] Most data concern ESBL-producing strains and there is a notable dearth of information on other important resistances, including to aminoglycosides, carbapenems, colistin and fosfomycin. Nevertheless, an Australian study suggests that travel-associated aminoglycoside and quinolone resistance may be even commoner than travel-associated cephalosporin resistance.[128] Interestingly, prolonged carriage was significantly associated with the pathogenic phylogroups B2 and D rather than A and B1 but strains of ST131 were rare even with Asian travel. A Canadian study showed that bacteraemia due to CTX-M-14 ESBL-producing *E. coli* was associated with travel to Europe and Africa whilst CTX-M-15-producing strains were associated with travel to Asia.[129] Analysis of risk factors in Norway for new cases of ESBL-producing infection was undertaken in a case–control study of adults who had been resident for 1 year or more, with no previous hospital or nursing home residence >24 h in the previous 31 days. It identified as risk factors travel to Asia, the Middle East or Africa within the past 6 weeks (OR 21, 95% CI 4.5–97) or 6 weeks to 24 months (OR 2.3, 95% CI1.1–4.4), recent use of fluoroquinolones (OR 16, 95% CI 3.2–80) or recent use of β-lactams other than pivmecillinam (OR 5.0, 95% CI 2.1–12), diabetes (OR 3.2, 95% CI 1.0–11) and freshwater swimming in the last year (OR 2.1, 95% CI 1.0–4.0) were all associated with UTI due to ESBL-producing *E. coli* or *Klebsiella* spp. Factors associated with decreased risk were the number of fish meals/week (OR 0.68/fish meal, 95% CI 0.51–0.90) and increasing age (OR 0.89/5 year increase, 95% CI 0.82–0.97). Almost 1 in 4 (23%) ESBL-positive patients had travelled to the risk countries within the previous 6 weeks and 39% in the 6 week to 24 month period compared with 1% and 19%, respectively. Travel to Europe (11% and 67% in ESBL producers and 7% and 57% in non-ESBL producers), America or Oceania (including Japan) was not a risk factor.[130] This emphasizes that there is a longer-term effect of travel or migration that is often not considered. A placebo-controlled trial of ciprofloxacin to prevent traveller's diarrhoea showed that prophylaxis selected for quinolone- and other drug-resistant GNB, suggesting that such practices need review.[131] Previous travel to destinations where resistance is prevalent is a risk factor for acquired MDR bacteria and should be considered in respect of empirical therapy. However, many patients with MDR organisms lack any relevant travel and it is not known if their organisms represent spread from carriers, especially in the same household, who have a history of high-risk travel,[132–134] or who have asymptomatically acquired the organism in hospital.

The most significant impact that the movement of people can have on the problem of resistance in Gram-negative bacteria is the maintenance of higher levels of resistance in commensal bacteria after return from high-incidence areas. Data on faecal carriage rates may mislead when compared with correlates of clinical infection since it will include phylogroup A and B1 strains of lower pathogenicity than the B2 and D strains seen commonly in urinary and bacteraemia.[135] Tangden in Sweden showed that 7/8 previously uncolonized travellers to South Asia and 10/32 to East Asia returned with carriage of ESBL *E. coli*.[136] One study in Birmingham (UK) showed that 22% of individuals with names of Middle Eastern or south Asian origin had faecal carriage of CTX-M ESBL-producing *E. coli* compared with 8.1% in those with names of European origin.[137] A recent large-scale survey studying 2430 healthy individuals in four areas in England found similar carriage rates of 25% and 5.6%, respectively. In a multivariable logistic regression model the percentage contribution made to risk of colonization was apportioned. Being born in South Asia (India, Pakistan, Bangladesh) or coming from those countries contributed 26.6%, and travel to those countries 12.1%. In contrast, being born in UK of UK origin contributed 9.9% and travel to all other parts of the world 17.8%.[519] Hence, the choice of antibiotics for empirical treatment may need to take into account recent travel history and cultural background.

The second ESPAUR report (2016)[4] includes details from a research study of faecal carriage rates of ESBL-producing Enterobacteriaceae in England. This showed variations in carriage from 4.9% in Shropshire to 16% in Heart of Birmingham Primary Care Trust with intermediate rates in Southampton and Newham (East London). Risk factors in this study included birth in India, Pakistan, Bangladesh, Sri Lanka, Afghanistan (which collectively accounted for 24% of all carriage) or the Middle East (including Egypt, Iraq, Saudi Arabia and other countries in the Persian Gulf) and travel in the last year to Africa, South Asia (Indian subcontinent and Afghanistan), South-East Asia [Thailand, Burma, Cambodia, Laos, Malaysia, Singapore or Pacific Asia (including Vietnam, Koreas, China)] or South or Central America (WHO regions). Until control measures reduce prevalence the following countries are also risk factors for either ESBL carriage or carbapenemase acquisition or both: the Eastern Mediterranean (the Balkans, Greece, Cyprus, Turkey, and Syria) and Eastern Europe and Russia, Belarus and Kazakhstan, and Italy.

There is a need for further studies with controls (non-travellers from different households of the same ethnic background) on the carriage of antibiotic-resistant *E. coli*, with strain typing and phylogroup allocation to better predict the potential for extraintestinal infection. This is further reviewed elsewhere. Studies are needed also of *Klebsiella* spp. and on the time elapsed since travel to specified locations of high prevalence. Information on healthcare and antibiotic exposure is required as well as details of many non-ESBL antibiotic resistance mechanisms.

Evidence

There is a clear indication of association of infection with ESBL-producing *E. coli* and travel. There is no information on other antibiotic resistances in association with travel and minimal information on carriage duration after travel.

Evidence level: 3

Recommendation

Need to quantify risks of infection with/carriage of extraintestinal pathogenic *E. coli* and of *Klebsiella* spp. resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy.

Grading: Strong recommendation for

6.7 What is the clinical importance of carbapenemase- versus CTX-M- and AmpC-producing strains?

ESBL-producing Enterobacteriaceae, MDR *P. aeruginosa*, and *A. baumannii* are associated with increased mortality, length of stay and expense in most but not all studies evaluating the impact of antibiotic resistance in GNB.[138,139] Nevertheless, variability in the setting (mainly ICU), study design, organisms included (most notably, which Enterobacteriaceae species), resistance profile and site of infection make the studies difficult to compare.[138,139] Fluoroquinolone resistance in *P. aeruginosa* was associated with increased hospital costs, and, if associated with imipenem resistance (MDR strains), increased mortality.[140] Four of eight studies in one review of MDR strains of *P. aeruginosa* showed increased mortality.[138] With *A. baumannii*, carbapenem resistance was generally associated with increased length of stay and expense of care; mortality was generally increased, most clearly if bloodstream infection was involved.[138,139] However, two studies of MDR (but carbapenem-susceptible) *A. baumannii* did not identify a significant increase in mortality, whereas studies of carbapenem resistance in *A. baumannii* consistently identify a significant increase in mortality only partly due to use of inactive carbapenems.[139,141–143]

More recently, studies have emerged evaluating the impact of carbapenem resistance in Enterobacteriaceae.[144] Pooled analysis of nine studies comparing mortality in Enterobacteriaceae infections including bacteraemia found that mortality was more than 2-fold higher when infections were caused by CPE. Broad-spectrum antibiotics other than carbapenems can select for colonization (detectable by active surveillance) that precedes later infection with bacteria resistant to a range of other antibiotics because of linkage with multiple resistance factors.[145–149] Carbapenem resistance in *Acinetobacter* spp. is similarly linked with multiple resistances that can be selected for by antibiotics that are not carbapenems, and can be detected as colonization prior to development of infection;[150] this is likely to be the case with Enterobacteriaceae.

Carbapenem resistance is an increasing problem in *Enterobacter* spp. in the absence of carbapenemases. In *E. aerogenes* ertapenem resistance is associated with loss of Omp35, a porin, and meropenem resistance with loss of Omp36 together with derepressed overproduction of AmpC.[151]

Bacteria producing CTX-M are of international importance. In the community they are usually MDR with few and hitherto little-used antibiotics offering the sole effective treatment. The spread of these strains requires widespread changes in primary care prescribing practice, which can be slow to take effect. Further, systemic infection with these strains usually requires parenteral drugs involving additional hospital admissions or outpatient parenteral antibiotics. Particular successful clones such as *E. coli* ST131 and ST69 are frequently involved. The fundamental reason for the success of these clones remains obscure and strategies to counter their spread nationally and internationally have so far been based on antibiotic restriction alone.

AmpC-producing strains of Enterobacteriaceae were a problem when third-generation cephalosporins and monobactams were widely used because stable derepression of this enzyme occurred by mutation at the regulatory gene *ampD*[13] in *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii* and *Morganella morganii*. Selection of such mutants during cephalosporin treatment of bacteraemia with these species can cause treatment failure.[152,153] Amoxicillin/clavulanate, both components of which are strong inducers of AmpC in such species, is not active against such species but piperacillin, although inactive against derepressed mutants, seems less prone than third-generation cephalosporins to select such strains from the induced population. Genes encoding AmpC enzymes have also escaped to plasmids that have spread into *E. coli*; such plasmid-carrying strains are widespread in foodstuffs. The main enzyme is CMY-2. In the UK it remains considerably rarer than ESBLs.[30] Cefepime is more stable to AmpC than other third-generation cephalosporins but in *Enterobacter cloacae* high-level cefepime resistance is associated with mutation in AmpC.[151] Carbapenems and temocillin are active against AmpC-β-lactamase whether of chromosomal or plasmid origin but ertapenem is more labile and, if OmpK35 porin loss occurs, resistance arises from this enzyme's action.

7. Intravenous treatment options for MDR GNB: what is the efficacy of carbapenems, temocillin, fosfomycin, colistin and other antibiotics against specific MDR GNB and what are the recommended antibiotics for secondary/tertiary care?

The evidence base (and grading) for all agents is generally weak, as most studies were retrospective case series, only rarely including a comparator agent. Our suggestions for intravenous treatment are summarized in the algorithm in Figure 3. Each intravenous agent is further considered individually.

7.1 Carbapenems

Carbapenems should be regarded as the drugs of choice for serious infections with ESBL-producing Enterobacteriaceae[154] and they are the drugs of choice for the empirical therapy of patients with serious sepsis caused by GNB, depending on local resistance rates and clinical experience.

Meropenem was found to be narrowly superior to imipenem/cilastatin (cilastatin prevents degradation of imipenem by urinary and ileal dehydropeptidase) in both clinical and bacteriological outcomes in one meta-analysis of 27 RCTs.[155] The clinical response rates (complete remission or improvement in signs and symptoms of sepsis) for meropenem and imipenem were 91.4% and 87.2%, whereas bacteriological response rates were 85.1% and 82.8%, respectively. There was no significant difference in mortality in the nine trials reporting data (7.4% for meropenem, 9.7% for imipenem). Meropenem and imipenem (sometimes referred to as 'Group 2' carbapenems, based upon activity against Gram-negative non-fermentative bacteria) are typically preferred to ertapenem for the empirical treatment of bacteraemias (often arising from the urinary tract) because of their broader spectrum (see below). A switch to ertapenem may be rational with susceptible isolates if it leads to earlier discharge with outpatient parenteral antimicrobial therapy (OPAT) but without this it is not a mechanism for reducing selection for carbapenem resistance. In Singapore, de-escalation of meropenem regimens by infectious disease physicians (including, in a small proportion, de-escalation to ertapenem) was associated with no increase in clinical failure rates or hospital mortality, reduced duration of carbapenem treatment from 8 to 6 days, less diarrhoea and *C. difficile* infection and less acquisition of carbapenem-resistant *A. baumannii*.[156]

Meropenem or imipenem select respectively for carbapenem-resistant Gram-negative organisms, including pre-existing carbapenem-resistant *A. baumannii*,[157] and porin *oprD* mutants, the commonest mechanism of imipenem resistance, arising during imipenem treatment of *P. aeruginosa*.[158] Overproduction of AmpC-type enzymes, and efflux pumps (which are common), are implicated in meropenem resistance in *P. aeruginosa*: MBLs, usually of a VIM type, occur but are much less common.[159] A multicentre Spanish study of isolates in 2008 from *P. aeruginosa* bacteraemia showed similar resistance rates to piperacillin/tazobactam, ceftazidime and meropenem. Meropenem resistance was more commonly associated with MexB or MexY and AmpC overexpression whereas resistance to piperacillin/tazobactam and ceftazidime was more commonly associated with AmpC overexpression alone, making non-carbapenems preferable agents for avoidance of MDR strains. Nevertheless, AmpC overexpression was associated with quinolone resistance, which, with aminoglycoside resistance, is already known to be associated with efflux pumps.[160] Whilst both imipenem and meropenem have a similar spectrum of activity, use of imipenem has declined and meropenem is now the most widely prescribed carbapenem in the UK.[154]

Widespread usage, particularly internationally, has driven the emergence of resistance and careful and considered empirical usage is essential. If the bacteria responsible for the infection are subsequently shown to produce neither ESBLs nor AmpC β-lactamase, carbapenem use should reasonably be stepped down to narrower-spectrum agents. An Italian cohort study across five hospitals showed that rectal carriage of KPC-producing *Klebsiella* was predictive of bacteraemia with such strains in the subsequent 2 years; sensitivity and specificity were 93% and 42% respectively; positive and negative predictive values were 29% and 93% respectively. Bacteraemia was associated with ICU admission, invasive abdominal procedures, cancer chemotherapy or radiation therapy and the number of colonization sites.[161] This suggests that screening may play a role in anticipating a requirement for treatment other than carbapenems active against such strains, but this will not necessarily apply to other bacteria with carbapenemases.

The ominous changes and increase in meropenem resistance in Enterobacteriaceae in the UK (shown in Section 8.4), and the

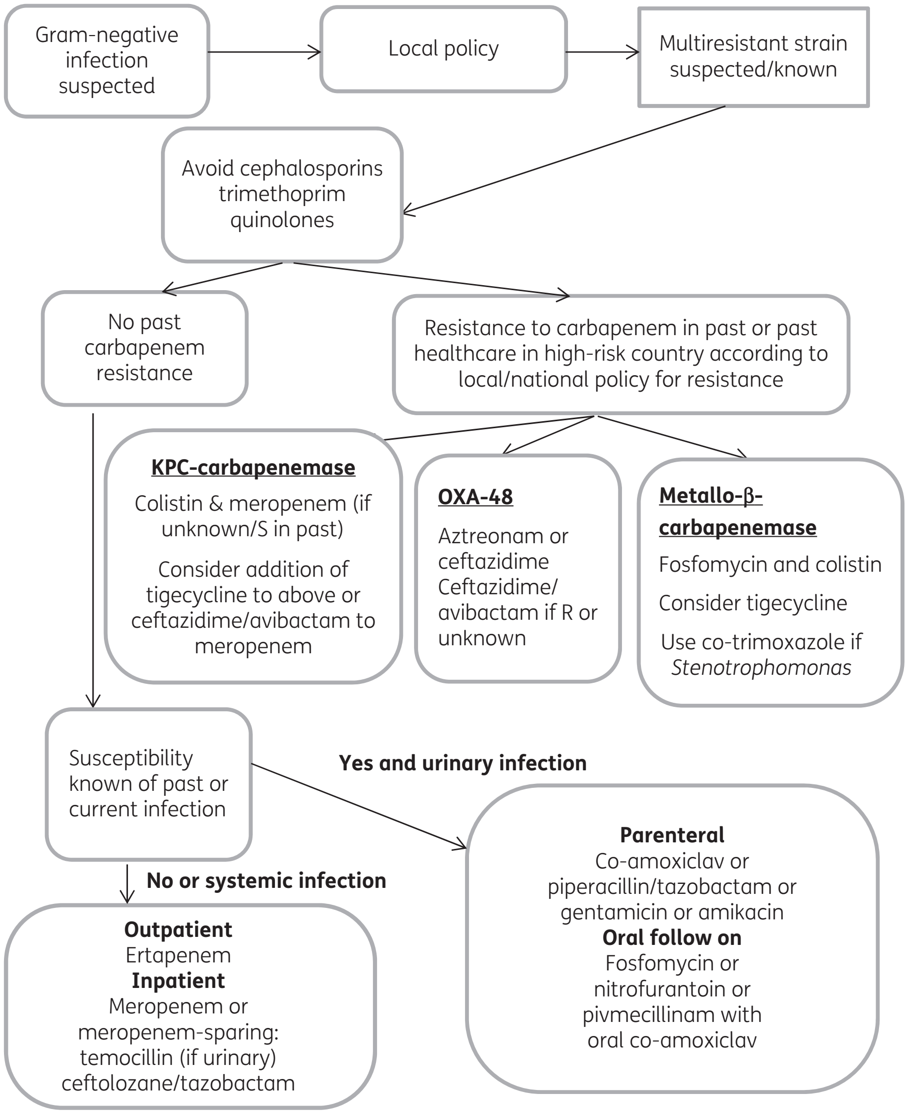

Figure 3. Suggested algorithm for the treatment of MDR Gram-negative bacterial infections admitted to UK hospitals.

clinical importance of such resistance and the need to know the resistance mechanism so that appropriate chemotherapy can be used, mean that an accurate overall view of the emerging picture is essential if appropriate action is to be taken. We include recommendations on this epidemiological matter because of its importance. We recommend the introduction of mandatory reporting of carbapenem-resistant Enterobacteriaceae from all anatomical sites and specimens. Such isolates should be tested contemporaneously to determine the responsible carbapenemase and the meropenem MIC. Isolates should be submitted to reference laboratories to determine susceptibility to a wider range of appropriate agents and for those agents, such as colistin or ceftazidime/avibactam, for which susceptibility testing is technically demanding. The determination of susceptibilities is a part of essential surveillance. Appropriate patient treatment also depends on performing these susceptibility tests in an expeditious manner but the methodology required may be beyond the scope of most routine diagnostic laboratories.

Ertapenem is licensed in Europe for the treatment of intra-abdominal and gynaecological infections and community-acquired pneumonia. In the rest of the world, including in the USA, it is also licensed for skin and skin structure infections and for complicated UTIs (for which it is widely used 'off-label' in the UK). Ertapenem shares the broad spectrum of imipenem and meropenem against Enterobacteriaceae, some Gram-positive species and anaerobes, but is inactive against *Acinetobacter* spp. and *P. aeruginosa*.[162] It is sometimes called a Group 1 carbapenem on this basis. Its main benefit is its once-daily mode of administration.

Use of ertapenem for the treatment of infections caused by Enterobacteriaceae is less well established than for imipenem or meropenem but it has good *in vitro* activity. A retrospective cohort study compared outcomes of bacteraemias due to ESBL-producing *E. coli* and *K. pneumoniae* treated with ertapenem and Group 2 carbapenems. Outcomes were equivalent between patients (mortality rates of 6% and 18%, respectively; $P = 0.18$).

However, more patients treated with Group 2 carbapenems had severe sepsis/septic shock/multi-organ failure: 5/49 (10.2%) for ertapenem versus 36/109 (33.3%) for other carbapenems (OR 0.23, 95% CI 0.08–0.62; $P<0.002$), suggesting clinicians were more likely to treat 'sicker' patients with a Group 2 carbapenem than ertapenem.[163] A retrospective study in Taiwan evaluated 251 patients with bacteraemia caused by ESBL-producing *E. coli* and *K. pneumoniae* isolates treated with a carbapenem.[164] Two hundred and thirty patients received carbapenems appropriately (57 ertapenem, 136 imipenem and 37 meropenem): 21 received carbapenems inappropriately (18 received ertapenem and 3 imipenem when the MICs were respectively >0.5 and >1 mg/L). Among the isolates, rates of susceptibility to ertapenem (MIC ≤0.5 mg/L EUCAST) were 83.8% in *E. coli* and 76.4% in *Klebsiella* spp. and those to meropenem were 100% and 99.3%. Sepsis-related mortality varied if the lower CLSI breakpoint for susceptibility (≤0.25 mg/L) was used. By this criterion, mortality was 5.3% (3/57) in those patients infected with an ertapenem-susceptible strain versus 33% (6/18) for an ertapenem non-susceptible isolate if they were treated with ertapenem. If categorization was based on the EUCAST MIC breakpoints ≤0.5 or >0.5 mg/L, there was no significant difference in mortality. Propensity matching of patients showed that patients with isolates that were ertapenem non-susceptible by CLSI criteria had a similar raised mortality if treated with imipenem or meropenem but numbers were small. A recently published multinational retrospective cohort study of 195 patients given empirical carbapenem and 509 given targeted therapy for bacteraemia with ESBL-producing Enterobacteriaceae found ertapenem to be equivalent to other carbapenems.[165] The authors recognized that as in other similar studies ertapenem was more frequently used in lower-risk patients and that more studies are needed in severely ill patient populations.

Resistance (MIC ≥1 mg/L) and high-level resistance (taken here as MIC 16 mg/L) by EUCAST breakpoints to ertapenem in *Klebsiella* spp. and *Enterobacter* spp. were well recognized before CPE began to spread and were associated with combinations of a β-lactamase (often a CTX-M ESBL in *Klebsiella* spp. or AmpC in *Enterobacter* spp.) plus impermeability due to OmpK35 porin loss. Despite the results of Lee *et al.*,[164] imipenem and meropenem appear to remain active against most isolates with low-level ertapenem resistance caused by these mechanisms but with raised MICs compared with normal levels for the species. An *in vitro* study showed the frequent emergence of this type of resistance in ESBL-producing *E. coli* in a pharmacokinetic model[166] but most resistant isolates are *Klebsiella* spp. or *Enterobacter* spp., not *E. coli*. In a survey of UK isolates in 2007 only one of 95 ertapenem-resistant isolates of *K. pneumoniae* produced a defined carbapenemase, namely IMP-1, with the remainder inferred to have impermeability-mediated resistance (porin loss).[167] However, this situation has changed radically as KPC, OXA-48 and NDM are enzymes now regularly encountered in the UK.[168,169] A retrospective case–control study from the eastern USA found that risk factors for infection caused by ertapenem-resistant Enterobacteriaceae with such impermeability-mediated resistance included exposure to any antibiotic (not just β-lactams and carbapenems) during the 30 days before a positive culture result.[170] A study from Singapore found that hospitalization and fluoroquinolone treatment were predictors for the appearance of ertapenem-resistant imipenem-susceptible variants.[171]

The use of ertapenem has no detrimental effect in terms of selecting for *P. aeruginosa*.[172] Results from 10 clinical studies showed that use of ertapenem did not result in decreased susceptibility to carbapenems in *Pseudomonas* spp. This was confirmed in a study of hospitals in Queensland.[173] A further study found that one hospital's use of ertapenem was balanced by less use of imipenem and ciprofloxacin, and this may have contributed to a reduced prevalence of resistance of *P. aeruginosa* to imipenem.[174] In contrast to these findings a study in Singapore associated increasing consumption of ertapenem with a rising incidence density of carbapenem-resistant *P. aeruginosa*.[175] Ertapenem use had no impact on the susceptibility of *A. baumannii* to imipenem.[176]

Prolonged infusion therapy with meropenem for MDR GNB including carbapenem-resistant organisms has been advocated on pharmacokinetic grounds in children for *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae with meropenem MICs up to 8 mg/L.[177] There is a general trend towards considering continuous infusion of β-lactams in critically ill patients with severe Gram-negative sepsis (see Section 7.18).[178] Continuous infusion meropenem has been assessed in 375 obese patients for its ability to produce steady-state levels above the MIC at levels from 2 to >16 mg/L.[179] Dosing nomograms to sustain this had previously been constructed in critical care patients.[180]

Meropenem combined with vaborbactam (RPX7009), a boronic-acid-derived β-lactamase inhibitor, is progressing through Phase 3 trials and may cover Enterobacteriaceae strains producing KPC carbapenemases but not those with MBLs or OXA-48-like enzymes. Some isolates with OmpK36 porin loss (see Sections 6.3.3 and 6.7) are resistant.[38] Relebactam in combination with imipenem/cilastatin is entering Phase 3 trials with trials against imipenem-resistant bacteria compared with a combination of colistin and imipenem/cilastatin and a comparative study against piperacillin/tazobactam in ventilator-associated pneumonia. Phase 2 studies are as yet unpublished. *In vitro* studies show no enhanced activity against *Acinetobacter* spp. but activity against KPC-producing *K. pneumoniae* (unless it has an OmpK36 porin loss, which is responsible for meropenem resistance; see Sections 6.3.3 and 6.7), and many but not all *P. aeruginosa* with enhanced AmpC production and depressed *oprD*.[37]

Evidence

Carbapenems are drug of choice for treatment of serious infection with Enterobacteriaceae including those producing ESBLs or AmpC.

Evidence level: 1+

Imipenem use is associated with emergence of resistance in *P. aeruginosa*.

Evidence level: 3

Ertapenem treatment is associated with emergence of resistance via porin loss in ESBL- and AmpC-producing *Klebsiella* spp. and *Enterobacter* spp.

Evidence level: 3

Recommendations

- Use meropenem, imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae. Grading: Strong recommendation for

- Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.
  Grading: Strong recommendation for
- Do not use imipenem to treat susceptible *Pseudomonas* infections.
  Grading: Conditional recommendation against use
- Introduce in the UK mandatory reporting of meropenem- or imipenem-resistant Enterobacteriaceae from all anatomical sites and specimens.
  Grading: Strong recommendation for
- Test immediately for the precise level of meropenem resistance and for an indication of the responsible class of carbapenemase (e.g. MBL/KPC/OXA48-like) all meropenem- or imipenem-resistant isolates of Enterobacteriaceae. Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents, including, as appropriate, colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.
  Grading: Strong recommendation for
- Prefer ertapenem for OPAT of susceptible infections in view of the once-daily dosing regimen.
  Grading: Conditional recommendation for

7.2 Ceftazidime

Observational studies of ceftazidime-susceptible ESBL-producing *E. coli* and *Klebsiella* spp. infections treated with ceftazidime frequently show treatment failure, mainly during bacteraemias.[12,181–184] One study of seven patients treated with ceftazidime in China suggested useful activity but this may reflect the type of ESBL; CTX-M-14, -27 and -9 enzymes predominate in parts of China (and Spain) and have weak activity against ceftazidime as compared with CTX-M-15 enzymes with lower ceftazidime MICs. The higher CLSI susceptible breakpoint ($\leq$4 mg/L) was found to classify 34% of CTX-M-positive *E. coli* as susceptible to ceftazidime with normal inocula. Most CTX-M-14 isolates became resistant at higher inocula.[185] The EUCAST breakpoint for susceptibility is <1 mg/L, reducing this problem. Early problems arose with apparent ceftazidime susceptibility by disc testing of CTX-M-15-producing *E. coli* ST131 isolates in the UK down-regulated by an IS26 insertion between promoter and structural gene.[186] Ceftazidime is active against some OXA-48-producing CPE, principally those that do not co-produce ESBLs or AmpC enzymes. Ceftazidime retains activity against many isolates of *P. aeruginosa*, including in the presence of mutation to imipenem or ciprofloxacin resistance.[187] However, strains with derepressed class C (AmpC) β-lactamases or strongly up-regulated efflux mechanisms are resistant, as are strains producing MBLs, other carbapenemases or ESBLs.

Evidence

Ceftazidime is usually ineffective in treating multiresistant infections with Enterobacteriaceae except against some OXA-48 carbapenemase-producing strains.

Evidence level: 3

Ceftazidime remains useful for infections due to quinolone or imipenem-resistant *P. aeruginosa*.

Evidence level: 3

Recommendations

- Use ceftazidime for susceptible infections with *P. aeruginosa* including quinolone- or some imipenem-resistant strains.
  Grading: Strong recommendation for
- Do not use ceftazidime to treat infections due to ESBL- or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if *in vitro* tests suggest the isolate is susceptible.
  Grading: Conditional recommendation against use

7.3 Ceftazidime/avibactam

Ceftazidime has recently been combined with the β-lactamase inhibitor avibactam. This combination has broad Gram-negative activity including Enterobacteriaceae and *P. aeruginosa*. Ceftazidime-susceptible bacteria remain susceptible to the combination, but avibactam protects additionally against class A (TEM, SHV, CTX-M, KPC) class C (AmpC) and some class D (OXA) β-lactamases.[188–192] Ceftazidime/avibactam has no inhibitory activity against the MBLs (NDM-1, IMP and VIM) but it is the first BL/BLI combination to retain activity against KPC-2 carbapenemase-producing and most OXA-48 carbapenemase-producing strains. Ceftazidime/avibactam has minimal activity against *Acinetobacter* spp., anaerobic or Gram-positive organisms.[190,193,194] A recent susceptibility study that included 120 KPC-producing Enterobacteriaceae collected from US hospitals found that ceftazidime/avibactam had $MIC_{50/90}$ values of 0.5/2 mg/L.[195] The first case series of use of ceftazidime/avibactam against carbapenem-resistant Enterobacteriaceae has recently been published.[196] Among 37 patients with severe infections due to these organisms, 31 had strains with KPC carbapenemases. Resistance to ceftazidime/avibactam emerged independently in three cases infected by *K. pneumoniae* ST258 with KPC-3 enzymes. In two of these isolates meropenem MICs were reduced $\geq$4-fold to the susceptible range in parallel with the rise in ceftazidime/avibactam MICs. The overall clinical success rate was 59% of patients whilst microbiological failure occurred in 10 patients, including the 3 patients where resistant mutants were selected. An earlier epidemiological study had shown that ceftazidime/avibactam median MICs of ceftazidime/avibactam are higher for KPC-3-producing isolates than those with KPC-2 enzymes, although it was unclear if this represents enzyme specificity or quantity.[197] Isolates that produce KPC-3 enzyme are internationally widespread, including in South America and Southern Europe. Ceftazidime/avibactam-resistant isolates with similar or identical mutations can be selected *in vitro*.[198] The mechanism involves the enzyme becoming a stronger ceftazidime-destroying enzyme, not in it becoming avibactam resistant. The licensing of avibactam (a non-β-lactam β-lactamase inhibitor) with ceftazidime offers a new choice where organisms that produce both AmpC and an ESBL, or KPC2 carbapenemase cause systemic infection.

In Phase 2 double-blind randomized trials, the efficacy of ceftazidime/avibactam was similar to that of imipenem/cilastatin in the treatment of complicated UTI (19/27 and 21/35 respectively).[199] A Phase 3 RCT of doripenem versus ceftazidime/avibactam in complicated UTI or pyelonephritis, with patients not selected for antibiotic resistance, showed equivalence with microbiological eradication in 304/393 (77.4%) in the ceftazidime/avibactam arm and 296/417 (71%) in the doripenem arm.[200] Efficacy combined with metronidazole was similar to meropenem in an RCT of 203 patients with intra-abdominal infection.[201] A Phase 3 RCT comparison of meropenem against ceftazidime/avibactam with metronidazole in 1066 complicated intra-abdominal infections, with the exclusion of a standardized set of highest-mortality surgical indications, again showed equivalence.[202] On ITT analysis response rates were 82.5% to the ceftazidime/avibactam or metronidazole combination and 84.9% to meropenem. There was no difference in patient outcome in the combination arm if a ceftazidime-resistant strain of Enterobacteriaceae was present or absent. Only one case of *C. difficile* was recognized in either arm of the study. An RCT of ceftazidime/avibactam and metronidazole against meropenem of 333 patients, largely with patients with complicated UTI but with some patients treated for intra-abdominal infections, all with infections with ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa*, showed 91% response rates at a test-of-cure visit.[203] None of these patients was infected with carbapenemase-producing strains.

Evidence

Ceftazidime/avibactam has similar efficacy to carbapenems in abdominal and complicated UTI, the former requiring combination of ceftazidime/avibactam with metronidazole.

Evidence level: 1+

Although clinical experience is limited in MDR GNB largely to ceftazidime-resistant organisms in complicated UTI, it would be expected to be effective when OXA-48-producing MDR GNB cause infection.

Evidence level: 4

Clinical experience against *Klebsiella* spp. producing KPC carbapenemase is limited but, ominously, efficacy is only some 60% with resistance emerging in 10% of treated patients.

Evidence level: 2+

Recommendations

- Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC-producing Enterobacteriaceae but alternatives may be cheaper.
  Grading: Conditional recommendation for
- Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3-producing *Klebsiella* spp. are vulnerable to mutations in the bla_{KPC-3} gene causing resistance.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant.
  Grading: Strong recommendation against

7.4 Ceftolozane/tazobactam

Ceftolozane is an oxyimino-cephalosporin that has been combined with tazobactam. Ceftolozane/tazobactam is active against many Gram-negative organisms, including Enterobacteriaceae and *P. aeruginosa*.[193,204,205] It is active against *P. aeruginosa* isolates that are resistant to standard agents such as ceftazidime because of derepressed AmpC β-lactamases or up-regulated efflux. In terms of MIC, ceftolozane is the most active β-lactam against *P. aeruginosa*, with resistance (MIC 4 mg/L EUCAST) largely confined to those with MBLs or unusual ESBLs such as VEB and GES types. $MIC_{50}/_{90}$ values against 310 MDR isolates of *P. aeruginosa* were 2/8 mg/L.[205] Activity against *Acinetobacter* spp. is variable.[193] Ceftolozane/tazobactam has *in vitro* activity against Enterobacteriaceae producing ESBLs including most TEM, SHV, and CTX-M types.[205–207] Since oxyimino-cephalosporins are stable to the inhibitor-resistant OXA-1 enzyme, ceftolozane is not compromised by co-production of this enzyme in CTX-M-15-producing Enterobacteriaceae as happens with piperacillin/tazobactam. Activity is less against ESBL-producing *Klebsiella* spp., possibly owing to high ESBL levels arising from production of additional SHV enzymes.[208] Activity against Enterobacteriaceae with copious AmpC enzyme is variable, but many *Enterobacter* spp. with derepressed AmpC are resistant. The combination has no activity against strains with MBLs (NDM-1, IMP and VIM) or against those with KPC carbapenemases. Ceftazidime-resistant strains with OXA-48-like enzymes are mostly resistant: ceftazidime-susceptible OXA-48 producers are susceptible to ceftolozane/tazobactam (D. M. Livermore, unpublished data).

Ceftolozane/tazobactam therefore has potentially different uses from ceftazidime/avibactam and should not be used in infections due to AmpC- or KPC-producing Enterobacteriaceae. The absence of clinical comparisons of piperacillin/tazobactam and ceftolozane/tazobactam means that choices must be made on *in vitro* grounds. The apparent enhanced activity of ceftolozane/tazobactam against strains that co-produce the enzyme OXA-1, including the internationally prevalent *E. coli* ST131 lineage, needs full laboratory and clinical verification but may make this drug more likely to produce clinical cure. Caution on clinical outcome is necessary because of the potential, as with ceftazidime/avibactam, for superinfection with *C. difficile*. Ceftolozane activity against *P. aeruginosa* including ceftazidime-resistant strains *in vitro* may offer clinical advantages where MDR *Pseudomonas* infections are a problem, such as in cystic fibrosis,[209] but this needs confirmation in a clinical trial. Optimal dosing in cystic fibrosis needs to be established but the drug's pharmacokinetics appears to be the same as in unaffected patients.[210]

Ceftolozane/tazobactam is licensed, at present, for complicated intra-abdominal infection and complicated urinary tract infection.[211] In a prospective, randomized, double-blind trial, 993 hospitalized patients with complicated intra-abdominal infection received either ceftolozane/tazobactam (1.5 g q8h iv) plus metronidazole, or meropenem (1 g q8h iv) for 4–14 days.[212] Non-inferiority was demonstrated overall and MIC was not related to outcome. In 50 patients an ESBL-producing organism was isolated. In these patients, the clinical cure rate was 95.8% (23/24) in the ceftolozane/tazobactam plus metronidazole group and 88.5% (23/26) in the meropenem group. In patients with CTX-M-14/15 ESBL-producing Enterobacteriaceae, clinical cure was observed in 13 of 13 (100%) and 8 of 11 (72.7%) patients, respectively. A double-dummy, double-blinded RCT compared ceftolozane/tazobactam against levofloxacin in 1083 patients with complicated UTI.[213] Patients received ceftolozane/tazobactam (1.5 g q8h iv) or intravenous levofloxacin (750 mg q24h). The majority of participants (82%) had pyelonephritis. Overall, ceftolozane/tazobactam was found to be non-inferior in clinical and superior in microbiological outcome to levofloxacin therapy. In the ITT population, 20/731 (2.7%) of Gram-negative pathogens were resistant to ceftolozane/tazobactam at baseline, whereas 195/731 (26.7%) were resistant to levofloxacin. Two (0.3%) of 594 *E. coli* isolates were resistant to ceftolozane/tazobactam and 144/594 (24.2%) were resistant to levofloxacin. For patients with levofloxacin-resistant uropathogens (based on CLSI criteria) clinical cure was seen in 90 (90.0%) of 100 patients in the ceftolozane/tazobactam group compared (surprisingly) with 86/112 (76.8%) in the levofloxacin group. In patients with ESBL-producing uropathogens, cure with ceftolozane/tazobactam was 55/61 (90.2%) compared with 42/57 (73.7%) for levofloxacin (95% CI 2.6–30.2). Treatment choice in complicated UTI and pyelonephritis involving MDR GNB between piperacillin/tazobactam, carbapenems, ceftolozane/tazobactam, temocillin or ceftazidime/avibactam depends on the bacteria present and their patterns of susceptibility.

Evidence

Ceftolozane/tazobactam is not active against CPE strains, excepting ceftazidime-susceptible OXA-48 producers, but otherwise, when combined with metronidazole, is non-inferior to meropenem in intra-abdominal infection.

Evidence level: 1+

Ceftolozane/tazobactam is non-inferior to intravenous levofloxacin in complicated UTIs, including those caused by ESBL-producing *E. coli* (most of which are resistant to levofloxacin).

Evidence level: 2−

Ceftolozane/tazobactam is the most active β-lactam *in vitro* against *P. aeruginosa*.

Evidence level: 4

Recommendations

- Use ceftolozane/tazobactam to treat susceptible *P. aeruginosa* infections resistant to ceftazidime.
  Grading: Conditional recommendation for
- Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Use ceftolozane/tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infection due to ESBL-producing *Klebsiella* spp. owing to a higher resistance rate.
  Grading: Conditional recommendation for
- Do not use for infections due to AmpC- or carbapenemase-producing Enterobacteriaceae or MBL/ESBL-producing *P. aeruginosa*.
  Grading: Strong recommendation against use

7.5 Aztreonam

Aztreonam is labile to AmpC and ESBL enzymes. It is stable to MBLs and OXA-48-like carbapenemases but most Enterobacteriaceae with these enzymes also express ESBLs or AmpC, which confer resistance.[214,215] Isolates with MBLs or OXA-48 and no ESBL or AmpC production may be susceptible (those with OXA-48 alone are likely also to be susceptible to ceftazidime and ceftolozane/tazobactam). At EUCAST breakpoints (S $\leq$1 mg/L, R $>$16 mg/L) most *P. aeruginosa* are intermediate in susceptibility and the drug is usually less active than ceftazidime or ceftolozane/tazobactam except against MBL producers resistant to all other β-lactams, which may be intermediate (rarely susceptible) to aztreonam.

An aztreonam/avibactam combination is in Phase 2 development. This creates a combination with very promising activity against Enterobacteriaceae with MBLs, OXA-48, AmpC, ESBLs and other β-lactamases (including AmpC, OXA-1 and CTX-M class).[214,215,216]

Evidence

Aztreonam is not active against Gram-negative bacteria producing ESBLs, AmpC or KPC carbapenemase; it is only moderately active against *P. aeruginosa*.

Evidence level: 4

It is stable to MBLs but strains possessing these often have ESBL or AmpC as well, resulting in resistance. Similar limitations apply to strains with OXA-48-like enzymes.

Evidence level: 3

Combination with a β-lactamase inhibitor such as avibactam would potentially make aztreonam useful against MBL (NDM, IMP and VIM)-producing bacteria that also have ESBLs or AmpC enzymes.

Evidence level: 4

Recommendations

- Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected.
  Grading: Strong recommendation against use
- Do not use aztreonam for CTX-M ESBL- or AmpC-producing bacteria even if these appear susceptible *in vitro*.
  Grading: Strong recommendation against use
- Use aztreonam for MBL- or OXA-48-producing strains if it is certain that they do not produce ESBLs or AmpC.
  Grading: Conditional recommendation for
- Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.
  Grading: Recommendation for research

7.6 Cefepime

Cefepime is not available in the UK. It appeared to be active *in vitro* against ESBL-producing Enterobacteriaceae, especially when the old NCCLS/CLSI breakpoint of $\leq$8 mg/L was used. A retrospective, case-controlled study compared the clinical and microbiological responses for 10 infections due to ESBL-producing *Klebsiella* spp. and *E. coli* from a non-urinary source with 20 matched controls receiving cefepime for non-ESBL strains. Four patients with ESBL producers had strains that were resistant to cefepime by broth microdilution MIC, one of whom responded: three of the remaining six with strains then regarded as susceptible (NCCLS/CLSI breakpoint MIC $\leq$8 mg/L) failed on treatment. Patients receiving cefepime for infection with ESBL-producing bacteria were 9.7 times more likely to have an unsuccessful clinical and microbiological response than those with non-ESBL-producing bacteria.[217] A randomized evaluator-controlled trial of ICU patients compared cefepime with imipenem for the treatment of hospital-acquired pneumonia. The failure rate was 31% in the cefepime group compared with 0% in the imipenem group. Cefepime MICs of 2–4 mg/L, then interpreted as susceptible by the NCCLS/CLSI breakpoint of $\leq$8 mg/L but now regarded as susceptible dose-dependent by current CLSI and intermediate by EUCAST criteria, were noted in strains from treatment failures.[218] A retrospective case–control study of cefepime-susceptible bacteraemia caused by ESBL producers in the period 2012–17 compared 30 day mortality amongst 17 patients treated with cefepime versus 161 cases treated with a carbapenem.[219] Mortality in the cefepime group was 58.8% versus 16.8% for carbapenem treatment and, in multivariate analysis, cefepime treatment was strongly associated with mortality (OR 9.9, 95% CI 2.8–319; $P = 0.001$). Mortality with cefepime in definitive treatment was also related to MIC, being 16.7% (1/6) in those with an MIC ≤1 mg/L, 45% (5/11) in those with an MIC of 2–8 mg/L and 100% (4/4) in those with an MIC of ≥16 mg/L.[220] In a retrospective study of 305 adults with monomicrobial *E. cloacae* infections, those with MICs of 4–8 mg/L (i.e. with CLSI dose-dependent susceptibility and straddling the EUCAST intermediate/resistant breakpoint) had significantly higher mortality than those treated with a carbapenem (71.4% versus 18.2%; $P = 0.045$).[14] Fifty-eight percent of strains in the cefepime-treated group produced an ESBL in addition to AmpC. In those definitively treated with cefepime, ESBL production (16/40 versus 3/32; $P = 0.006$) and susceptible dose-dependent strains (10/16 versus 9/56; $P \leq 0.001$) were independently associated on multivariate analysis with increased mortality.[14] ESBL production was more frequent in those strains with cefepime MICs of 4–8 mg/L (32/36 compared with 61/138 with MIC ≤2 mg/L; $P \leq 0.001$). Mortality was not reduced even when high-dose regimens (2 g q8h iv) were used. Mortality in infections due to ESBL non-producers (with median MICs of 0.5 mg/L) treated with definitive cefepime was similar to that in those that received definitive carbapenem therapy (9/56 versus 16/72; $P = 0.5$). This study demonstrates the efficacy of cefepime against the presumptive AmpC producer *E. cloacae* but only in the absence of additional ESBL production or absence of MIC 2 mg/L. Nevertheless, in another retrospective study between 2005 and 2007, for bacteraemia due to ESBL-producing pathogens, receipt of empirical cefepime alone ($n = 43$) was associated with increased mortality compared with cefepime combination ($n = 69$) or carbapenem combination ($n = 44$) regimens: mortality was unlinked to MIC, being 5/13 for those with organisms having MIC ≤2 mg/L, 2/6 for those having MICs of 4 or 8 mg/L and 10/24 for those having MICs ≥16 mg/L.[221]

The concept of 'susceptible dose dependent' isolates of Enterobacteriaceae was suggested by CLSI in order to maximize cefepime use and spare carbapenems, but these findings suggest this is unwise. A recent systematic review did not support the use of cefepime in empirical therapy of critically ill patients when ESBL-producing *E coli* or *Klebsiella* spp. infection is suspected. Even in patients with ESBL strains susceptible to cefepime (≤2 mg/L CLSI; <1 mg/L EUCAST), treatment failure can be seen.[220]

Evidence

Cefepime has a higher failure rate in treatment of infections due to ESBL-producing GNB than carbapenems unless cefepime MICs are ≤1 mg/L.

Evidence level: 2+

Bacteraemia due to *E. cloacae* strains without ESBLs and with MIC ≥2 mg/L <8 mg/L can be successfully treated with cefepime.

Evidence level 2+

Recommendations

- Could use cefepime to treat infection caused by ESBL- or AmpC-producing bacteria if susceptible to the EUCAST breakpoint of MIC ≤1 mg/L.
  Grading: Conditional recommendation for
- Do not use cefepime even at increased dose for isolates with (i) MIC of 2–8 mg/L (CLSI 'susceptible dose dependent') or (ii) MIC 2–4 mg/L (EUCAST intermediate) or (iii) strains that produce both AmpC and ESBLs.
  Grading: Strong recommendation against use
- Do not use cefepime to treat infection caused by CPE.
  Grading: Strong recommendation against use

7.7 Cefoxitin

Cefoxitin, the original parenteral cephamycin, was developed by Merck and is now a generic. It is no longer available in Europe but has several suppliers in the USA. Cefoxitin was licensed at the same time as second-generation cephalosporins such as cefuroxime but differs in having activity against gut *Bacteroides* spp. but minimal activity against *Haemophilus influenzae*. Cefoxitin is on the list of forgotten antibiotics that may be useful against MDR GNB.[222] It is active against ESBL-producing *E. coli* but is not active against AmpC-inducible species of Enterobacteriaceae, e.g. *Enterobacter* spp., *C. freundii*, *Serratia* spp., *M. morganii* and *Providencia stuartii*, nor against *P. aeruginosa*. Cefoxitin differs from temocillin (which has a 6-α-methoxy group corresponding to the 7-α-methoxy group of cefoxitin) in having activity against Gram-positive bacteria including penicillin-susceptible *Streptococcus pneumoniae* and methicillin-susceptible *Staphylococcus aureus*, which may be advantageous if a urinary infection is diagnosed but the patient actually has infection due to these organisms elsewhere.

EUCAST no longer cites MIC breakpoints but BSAC had a breakpoint of S <8 mg/L and R >8 mg/L. Typical MICs for *E. coli* and *Klebsiella* spp. are slightly below this level, meaning that small reductions in susceptibility can confer resistance. These can arise by reductions in permeability or (in *E. coli* only) by mutation in promoter or attenuator sequences for *ampC*. Cefoxitin resistance is very common in the Middle East, India and China. In a multicentre study of 1762 isolates from urinary infection in the Asia–Pacific region 50.3% of strains were resistant to cefoxitin.[223] Resistance also occurs in *E. coli* and *Klebsiella* spp., from plasmid-mediated AmpC production. Porin loss combined with other mechanisms of β-lactam resistance, such as ESBL production, is described as emerging during treatment of some *Klebsiella* infections (see Sections 6.3.3 and 6.7).

Cefoxitin is used in selective media for *C. difficile* and would be expected to trigger infection with this pathogen. In one recent study antibiotic prophylaxis with cefoxitin was an independent risk factor for *C. difficile* infection.[224] The absolute frequency at which this will occur relative to other antibiotics is not known.

In murine models of pyelonephritis cefoxitin was effective against an OXA-1- and CTX-M-15-producing transconjugant *E. coli*[225] and in combination with fosfomycin prevented selection for fosfomycin-resistant mutants.[226] Only one human trial of cefoxitin against current ESBL producers has been reported. In that 2015 French study, largely of urinary and catheter-related bacteraemia, 30/33 patients responded in the first 48 h and 20/24 patients responded who were evaluable at follow-up. Six microbiological failures were documented with emergence of resistance in two patients with *Klebsiella* infection.[227] A pharmacological model suggests 1 h infusion of 2 g four times daily would be effective.[228]

Although cefoxitin appears active against CTX-M-15-producing *E. coli* and *Klebsiella* spp., it lacks temocillin's activity against strains with copious inducible, derepressed[229] or plasmid-mediated AmpC. Cefoxitin may be more prone than temocillin to select *C. difficile*.[230] Temocillin, unlike cefoxitin, has no Gram-positive spectrum so in empirical use in the elderly where it is not clear if the urinary tract or the chest/skin is the source of infection, it may need supplementation with another antibiotic. It is not clear if cefoxitin's reintroduction would offer any sustainable or competitive advantage apart from its carbapenem-sparing capacity as its four-times daily intravenous dosing makes it only usable in inpatient treatment, not OPAT.

Evidence

Cefoxitin is an intravenous cephamycin antibiotic, formerly licensed in the UK. Inducible, derepressed or plasmid-mediated AmpC production confers resistance, as does porin loss, especially in association with ESBL production. Nevertheless, *in vitro*, animal and human studies indicate activity against ESBL-producing strains of *E. coli* and *Klebsiella* spp. Treatment can be complicated by emergence of resistance due to porin loss.

Evidence level: 3.

Recommendations

- Could use as a carbapenem-sparing agent for infections caused by CTX-M-15-producing *E. coli* but is only suitable for inpatient use, not OPAT, because of the short serum half-life. Narrower Gram-negative spectrum than temocillin so less suitable for empirical use in UTI.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.8 Temocillin

Temocillin is a semi-synthetic 6-α-methoxy derivative of ticarcillin that is highly stable to most β-lactamases except MBLs (e.g. IMP, NDM and VIM) and OXA-48-like enzymes. It lacks activity against anaerobes, Gram-positive bacteria and most Gram-negative non-fermenters such as *P. aeruginosa* and *Acinetobacter* spp. It retains *in vitro* activity against ESBL- and AmpC-producing Enterobacteriaceae[231,232] and some KPC-producing *E. coli* and *Klebsiella pneumoniae*,[233] and *Burkholderia cepacia* complex.[234] It is active against Enterobacteriaceae strains whose AmpC production is stably derepressed.[235] No EUCAST breakpoint for susceptibility to the drug has yet been published but the CA-SFM has a rate of S$\leq$8 mg/L, R>8 mg/L and the BSAC had a systemic value of S $\leq$8 mg/L, R >8 mg/L and an uncomplicated UTI value of S$\leq$32 mg/L, R> 32 mg/L. MICs of temocillin for KPC-producing bacteria are in the range of 4–32 mg/L (mode 16 mg/L). In a lethal mouse model of intra-abdominal infection using strains of KPC-producing *E. coli*, temocillin was effective against KPC-2.[236] Temocillin has poor activity against carbapenem-resistant isolates of Enterobacteriaceae lacking carbapenemases—presumptively due to porin loss.[237] This antibiotic has no activity against OXA-48- or MBL-producing strains.[238] Caution is also needed in predicting results of treatment of systemic infections from *in vitro* susceptibility and further trials of temocillin alone at defined and possibly greater doses than the licensed 2 g twice daily are necessary. Outcomes should be correlated with MIC.

At present, clinical studies are limited to non-comparative series. The largest multicentre study (non-randomized retrospective case series) involved 92 patients who were treated with at least 3 days of therapy.[239] Urinary tract and bacteraemia (42 episodes each) were the most frequent indications followed by hospital-acquired pneumonia. Dosages of $\geq$4 g/day, rather than 1 g twice daily, were associated with improved outcome. Patients with strains producing AmpC or ESBL enzymes responded microbiologically in 23/27 or 18/22 cases in respectively UTI or bacteraemia. Higher dosage regimens, including 2 g three times daily and 6 g by continuous infusion, and use in veno-venous haemofiltration are reported in the literature with suggestions that these improve efficacy in critically ill patients. These data have led to a modification of the licensed posology with the usual dose increased to 4 g/day and the higher dose, particularly in critically ill patients, to 6 g/day.[240] In a retrospective case review of bacteraemia caused by KPC-producing Enterobacteriaceae, 14/14 patients treated with temocillin either alone or in combination survived, whereas 6/30 treated similarly with tigecycline died.[241] Two studies have been published on the use of temocillin in cystic fibrosis patients with *B. cepacia* complex and sometimes *P. aeruginosa*. Both were retrospective non-randomized audits, the first showing equivalence of combinations of temocillin with tobramycin versus other agents with tobramycin against *Burkholderia cenocepacia* and the second showing that 18/32 courses of temocillin resulted in improvement in the patient's infection.[242,243]

Evidence

Temocillin at a dose of 2 g twice daily is an effective and well tolerated drug for UTI and bacteraemia with AmpC- or ESBL-producing bacterial infection.

Evidence level: 3

Although *in vitro* work suggests activity against many KPC-producing bacteria, there is little published clinical evidence to support this. Respiratory infections, including CF infections with *B. cepacia*, and other sites of systemic infection requires further clinical trials.

Evidence level: 4

Recommendations

- Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL- producing Enterobacteriaceae.
  Grading: Conditional recommendation for
- Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or AmpC-producing bacteria.
  Grading: Recommendation for research and possible conditional recommendation for use restricted to trials
- Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL producers, on basis of published *in vitro* data.
  Grading: Recommendation for research and possible conditional recommendation for use restricted to trials

7.9 Ampicillin/sulbactam

Sulbactam has *in vitro* microbiological activity against some strains of *A. baumannii*, including some carbapenem-resistant lineages.

Microbiological studies showed that sulbactam alone (without ampicillin) was active against these bacteria.[244] In an uncontrolled study, 42 patients with infections caused by MDR *A. baumannii* were treated with sulbactam or ampicillin/sulbactam. Eighteen received sulbactam alone and 24 received ampicillin/sulbactam; no difference in cure rate was observed between the two groups. Another study compared ampicillin/sulbactam with colistin therapy in a retrospective review of patients who had nosocomial infections caused by carbapenem-resistant *Acinetobacter* spp. from 1996 to 2004.[245] Eighty-two patients received polymyxins and 85 were treated with ampicillin/sulbactam. The authors concluded that ampicillin/sulbactam appeared to be more efficacious than polymyxins. More generally, and predictably, multivariate analysis found that prognostic factors for in-hospital mortality were older age, septic shock and higher APACHE II score. A small retrospective non-blinded trial compared treatment with ampicillin/sulbactam versus imipenem and tried also to address the benefit of combining ampicillin/sulbactam with colistin. There was no difference in outcome.[246,247] Two small RCTs have tried to assess differences in dosing regimens and efficacy compared with colistin.[248,249] Overall the evidence base is poor and interpretation is difficult without consideration of the MIC for the organism. In context, sulbactam MICs for most UK isolates of carbapenem-resistant *A. baumannii* are 16–32 mg/L, implying poor rates of susceptibility (D. M. Livermore, unpublished data).

Evidence

Ampicillin/sulbactam appears effective in treating infections due to some carbapenem-resistant *Acinetobacter* spp. but many isolates in the UK have relatively high sulbactam MICs.

Evidence level: 3

Recommendations

- Could use against some carbapenem-resistant, apparently sulbactam-susceptible *A. baumannii* isolates. Caution needed in the UK because of a higher range of MICs. Absence of a breakpoint prevents categorization as susceptible/resistant.
  Grading: Conditional recommendation for

7.10 Co-amoxiclav

Co-amoxiclav is a combination of the broad-spectrum amoxicillin with the β-lactamase inhibitor clavulanic acid. Co-amoxiclav is known to select for Enterobacteriaceae resistant to the clavulanate component as well as amoxicillin in the gastrointestinal flora.[250] Co-amoxiclav has been successfully used to treat UTIs due to ESBL producers, as described in case reports and an observational study.[251,252] The cure rate among 37 patients with cystitis treated with co-amoxiclav was 93% for those with susceptible isolates (MIC $\leq$8 mg/L) and 56% for those with intermediate or resistant isolates (MIC $\geq$16 mg/L) ($P = 0.02$).[251] The study was performed in Spain, where many ESBL producers have CTX-M-14 enzyme; in the UK more have CTX-M-15 and many of these co-produce OXA-1, an inhibitor-resistant penicillinase, raising co-amoxiclav MICs to the intermediate or resistant range. Furthermore, MIC determinations were done with a β-lactam:β-lactamase inhibitor ratio of 2:1 and higher MICs would likely be obtained using the fixed clavulanate concentration of 2 mg/L now advocated by EUCAST. The outcomes for bacteraemias treated with co-amoxiclav or piperacillin/tazobactam have been reviewed and the findings are discussed in the section on piperacillin/tazobactam (Section 7.11).[253]

Evidence

These studies suggest that co-amoxiclav is effective in lower UTIs caused by ESBL-producing bacteria but efficacy was only reliably predicted in strains where these organisms were fully susceptible *in vitro* and lacked co-production of OXA-1 β-lactamase.

Evidence level: 3

Recommendations

- Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or, if using empirically, recent isolates, are fully susceptible.
  Grading: Conditional recommendation for

7.11 Piperacillin/tazobactam

Different susceptibility standards are used worldwide and so correlations of mortality with *in vitro* susceptibility cannot be reliably transferred between countries. EUCAST regards more isolates as resistant than CLSI. Some countries, such as the UK, have a higher prevalence of Enterobacteriaceae with CTX-M-15 and, in *E. coli*, OXA-1 β-lactamase, and these are more resistant than the CTX-M-14 ESBL producers circulating, for example, in Spain. This may critically affect the validity of evidence collected from different laboratories and hospitals about the adequacy of these combinations against ESBL-producing bacteria.

The use of piperacillin/tazobactam for treating bacteraemias caused by ESBL-producing bacteria consequently remains contentious. One recent retrospective analysis of 331 patients in a US hospital with bacteraemia due to ESBL-producing bacteria suggested carbapenems were superior to piperacillin/tazobactam.[254] One hundred and three (48%) patients received piperacillin/tazobactam empirically and 110 (52%) received carbapenems empirically. The adjusted risk of death was 1.92 times higher for patients receiving empirical piperacillin/tazobactam compared with empirical carbapenem therapy. Another retrospective study of bacteraemic patients with ESBL-producing *P. mirabilis* compared the outcomes of patients treated with piperacillin/tazobactam or a carbapenem for at least 48 h.[255] Forty-seven patients with available clinical data were studied, of whom 34 were included. Only 11% of strains were imipenem susceptible but MICs of the drug for Proteeae typically clustered around the breakpoint. The overall 30 day mortality rate was 29.8%. Three of 21 patients treated with carbapenems (all imipenem) died within 30 days (all in hospital) versus 4/13 treated with piperacillin/tazobactam, a non-significant difference. Furthermore, among those treated with piperacillin/tazobactam, the mortality rate was lower in those infected by the isolates with lower piperacillin/tazobactam MICs ($\leq$0.5/4 mg/L) when compared with isolates with MICs of $\geq$1/4 mg/L (0/7 versus 3/5; $P = 0.045$). A study of 39 episodes of bacteraemia due to ESBL-producing *E. coli* from Spain found a statistically significant reduction in 30 day mortality in infections from non-urinary sources if the MIC was $\leq$2 mg/L (0/11) compared with those strains with higher MIC (7/17).[256] This suggests that even the current EUCAST breakpoints (S <8 mg/L, R >16 mg/L) are too high to give guidance on clinical response. An analysis of patients with bacteraemias due to ESBL-producing *E. coli* was performed to assess the efficacy of combinations of piperacillin/tazobactam or co-amoxiclav compared with carbapenems.[253] Mortality in patients treated with such BL/BLI combinations or carbapenem was compared in two cohorts: empirical therapy and definitive therapy. Mortality rates at day 30 for those treated with BL/BLI versus carbapenems were 9.7% versus 19.4% for empirical therapy and 9.3% versus 16.7% for definitive therapy respectively. After adjustment for confounders, no association was found between either empirical therapy or definitive therapy and increased mortality. The study suggested that co-amoxiclav and piperacillin/tazobactam may be suitable alternatives to carbapenems for treating patients with bacteraemias due to ESBL-producing *E. coli* but only in the minority that were susceptible *in vitro*. The study was not randomized, and confounding due to unmeasured variables may have occurred. This retrospective observational study has been repeated on a multinational basis and extended to 627 patients and showed that BL/BLI combinations were statistically as effective as carbapenems in empirical and directed therapy against ESBL-producing Gram-negative bacteraemia.[257] A subset of 207 patients had the ESBL genes of their pathogens examined by PCR: 42 were identified as CTX-M-15, 27 as CTX-M-1, 31 as CTX-M-14 and 18 as CTX-M-9. No details were given of response rates in relation to the presence of specific resistance genes and co-production of OXA enzymes was not sought. In another study co-amoxiclav and piperacillin/tazobactam susceptibility of the bacteria causing bacteraemia, particularly for *E. coli* ST131, were not correlated: 51% of the isolates also had OXA-1 and 90% of isolates were reported susceptible to piperacillin/tazobactam versus 26% susceptible to co-amoxiclav by CLSI criteria.[258] Such discrepancies with different BL/BLIs may relate to whether the EUCAST or CLSI breakpoints are used, as the MICs for many isolates with a combination of CTX-M-15 and OXA-1 enzymes cluster around 16 mg/L. The relationship of the BL/BLI used and its MIC for the infecting strain with efficacy in lower UTIs (where urinary concentrations are higher than in serum) or bacteraemia needs to be established. More generally, individual drug/inhibitor combinations must be separately studied for efficacy, and related to both the β-lactamase genes present and *in vitro* susceptibility. As American commentators have pointed out,[259] it is important to note the dosing regimen when considering the response to piperacillin/tazobactam of many ESBLs. Many Spanish studies used piperacillin/tazobactam at 4.5 g q6h, not the usual licensed UK dose of 4.5 g q8h. For β-lactams, increasing the time above the MIC substantially decreases mortality.[260] It is possible that more frequent dosing would achieve this. More materially, this can be achieved with continuous infusion, albeit with higher daily drug dosage (which might breach targets to reduce use) and could be considered to increase efficacy of piperacillin/tazobactam. It cannot be anticipated with biliary excretion whether this will change selection pressure for superinfecting organisms or *C. difficile* in the gastrointestinal flora.

A retrospective case review of empirical treatment of bacteraemia caused by ESBL-producing *E. coli* or ESBL-producing *Klebsiella* spp. showed a mortality rate of 18/70 (25.7%) when patients received carbapenems. If they received piperacillin/tazobactam 8/44 (18.2%) died if the strain was retrospectively susceptible by CLSI criteria, but 3/6 died if the strain was resistant or intermediate. Similarly, if they received co-amoxiclav 3/40 (7.5%) died if the strain was retrospectively susceptible by CLSI criteria, but 10/27 (37%) died if the strain was resistant or intermediate to piperacillin/tazobactam.[261] Data on the genotypes of the ESBL producers present were not provided.

The findings of all these studies cannot be simply applied to the UK, where many ESBL-producing strains are more resistant than CTX-M-14, as they co-produce CTX-M-15 and OXA-1 β-lactamases, with the latter enzyme compromising susceptibility to piperacillin/tazobactam. Variable dosing further complicates the picture.

Piperacillin/tazobactam is commonly used to treat infections caused by *P. aeruginosa*. A retrospective cohort study of bacteraemic patients showed that in 34 episodes of bacteraemia caused by strains with a piperacillin/tazobactam MIC of 32 or 64 mg/L, the 30 day mortality was significantly greater than that for controls given other appropriate therapy.[262] At the time, CLSI defined strains as susceptible if they had an MIC of ≤64 mg/L whereas EUCAST, then as now, has a breakpoint for susceptibility of ≤16+4 mg/L and for resistance >16+4 mg/L.

Evidence

Could use piperacillin/tazobactam in some bloodstream infections where ESBL producers appear susceptible *in vitro* but mortality may be higher than with carbapenems.

Evidence level: 2−

Mortality when piperacillin/tazobactam is used in bloodstream infection due to ESBL-producing Enterobacteriaceae without regard to *in vitro* susceptibility appears higher than with carbapenems.

Evidence level: 2+

In vitro susceptibilities by EUCAST and CLSI recommendations on what is a susceptible organism differ for Enterobacteriaceae but only 2-fold. There is no good analysis of the impact of this difference in relation to: (i) strain MIC; (ii) clinical outcome of infections at different sites; and (iii) different ESBL genotypes.

Evidence level: 4

Breakpoints for piperacillin/tazobactam against Enterobacteriaceae have changed with time. Better outcomes may be seen with isolates that are much more susceptible (MIC ≤2 mg/L) than the currently agreed piperacillin/tazobactam Enterobacteriaceae breakpoints (EUCAST S if MIC ≤8+4 mg/L, R if MIC 16+4 mg/L; CLSI S if MIC ≤16+4 mg/L, R if MIC ≥128+4 mg/L).

Evidence level: 3

Recommendations

- Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible.
  Grading: Conditional recommendation for
- Consider definitive use of piperacillin/tazobactam to treat infections caused by *P. aeruginosa* if susceptible by EUCAST standards.
  Grading: Conditional recommendation for

7.12 Aminoglycosides

Parenteral broad-spectrum aminoglycosides are potentially important carbapenem-sparing drugs for infections due to MDR-GNB. Three such antibiotics, gentamicin, tobramycin and amikacin, remain available in the UK following the withdrawal of netilmicin and sisomicin. These antibiotics have intrinsic activity against all *P. aeruginosa*, *Acinetobacter* spp. and Enterobacteriaceae, but plasmid-borne resistance (and chromosomal resistance in *Providencia* spp. and *Serratia* spp.) now limits their spectrum. Resistance is mostly due to: (i) bacterial aminoglycoside-modifying enzymes, which acetylate, phosphorylate or adenylate vulnerable hydroxyl or amino groups; or (ii) 16S ribosomal methyltransferases, which alter the binding site for aminoglycosides. The latter mechanism produces pan-resistance to aminoglycosides except the veterinary product apramycin.[263] By contrast, the vulnerability of aminoglycosides to modifying enzymes varies, with amikacin inactivated by fewer enzymes than gentamicin or tobramycin.[264] Initially aminoglycoside-modifying enzymes were restricted to certain species but integron and transposon carriage have mediated their wide dissemination.

Amikacin evades AAC(3) and AAC(2′) enzymes but remains vulnerable to AAC(6′)-I as does tobramycin. AAC(6′)-Ib-cr arose from AAC(6′)-Ib by the substitutions Trp102Arg and Asp179Tyr and can acetylate ciprofloxacin (but not levofloxacin) as well as aminoglycosides causing their deactivation. This enzyme, formerly rare in the UK,[265] is commonly found in *E. coli* ST131. Amikacin MICs typically are raised to just below the susceptible breakpoint. Such reductions nevertheless may be important since efficacy of aminoglycosides is proportional to the ratio of peak concentration to MIC.[266] EUCAST currently suggests that reports on isolates with this enzyme are edited to amikacin resistant but this is under review. In contrast to other common aminoglycoside-modifying enzymes, AAC(6′)-I spares gentamicin. Aminoglycoside-nucleotidyl transferases (ANT-6, ANT-9, ANT-4′, ANT-2″ and ANT-3″) do not confer amikacin resistance nor [except APH (3)-V1, which is mostly confined to *A. baumannii*] do aminoglycoside phosphotransferases in Gram-negative species.

Overall the resistance rate to gentamicin in community-onset *E. coli* bacteraemia in 2012–14 was 8.6%. This is a similar figure to the 8.7% resistance rate to piperacillin/tazobactam in community-onset cases. Such data must be considered when empirically treating probable Gram-negative bacteraemia of likely urinary or unknown origin.[94] In the 1980s, parenteral aminoglycoside therapy rarely selected for resistant Enterobacteriaceae in the gut flora,[267] but oral aminoglycosides given for selective digestive decontamination in haematological malignancy frequently did so[268] and continued to do so over a 20 year period once resistance emerged, even when combined with oral colistin.[269]

There is limited surveillance of the genotypic distribution of aminoglycoside-modifying enzymes except in specific strains and in those with other resistances (e.g. ESBL producers). Little is known of travel associations beyond those with gentamicin and tobramycin (but to a lesser extent amikacin) associated with acquisition of ESBL or carbapenemase producers, for which there are clear links with travel.[270]

Aminoglycoside activity against *P. aeruginosa* varies between patients with cystic fibrosis, where aminoglycosides continue to be heavily used, and patients with other comorbidities. Resistance due to efflux pumps and permeability defects is common, as well as aminoglycoside-modifying enzymes. Tobramycin, which has greater intrinsic activity than gentamicin against this species (offsetting its lower activity against Enterobacteriaceae) and which causes less toxicity than gentamicin, continues to be the aminoglycoside most likely to remain active. A recent meta-analysis continues to suggest that use of β-lactam/aminoglycoside combinations in the absence of cystic fibrosis offers no statistically significant advantage in terms of outcome compared with use of an active β-lactam alone.[271]

A new aminoglycoside, plazomicin (ACHN 490, Achaeogen),[272,273,274] has completed clinical trials. This evades modification by almost all aminoglycoside-modifying enzymes except the AAC(2′) chromosomal enzymes of *Providencia* spp. It is, however, compromised by the plasmid-mediated ArmA and Rmt 16S ribosomal methyltransferases, which are currently rare in UK MDR GNB except in Enterobacteriaceae strains producing NDM-1 carbapenemase[263] or OXA-23 carbapenemase-producing *A. baumannii*, which have spread globally over the last 10 years.

Aminoglycosides have a narrow margin between being effective and toxic to the auditory and vestibular apparatus or to the kidneys. They fell from favour as broader-spectrum β-lactams were developed. For acceptably safe use, intervals between doses are increased, usually to a minimum of once daily, but with doses related to renal clearance and MIC and the presumption of a post-antibiotic effect. If the dosage is based on the patient's weight it is possible, using a nomogram, to model the likely blood concentration at varying intervals after the dose. Measuring plasma levels between 6 and 14 h after the dose, usually now by immunoassay, and relating these levels to the nomogram permits more precise dosing intervals than those determined by measuring renal function. Nomograms for gentamicin and tobramycin at doses of 7 mg/kg[275] and 5 mg/kg[276] in adults have been constructed and their use is associated with a low incidence of detected ototoxicity (3/2184 cases in the former). The dosage recommendation for amikacin is 15 mg/kg/day, reflecting that amikacin MICs are 2- to 4-fold higher than gentamicin MICs for susceptible strains. Much higher incidences of toxicity with all aminoglycosides are well recorded and it is still common to encounter in the UK deficiencies in: (i) weight-related dosage; (ii) dosage interval, especially if there is renal impairment; (iii) measuring levels in every case; and (iv) taking blood for assay at the correct interval after dosing and recording both the time of administration and time of sample collection to enable later interpretation of assay results by other staff. Validation of expected and achieved serum levels has been undertaken for the 7 mg/kg dose but not for the 5 mg/kg dose, which is based on exclusion of some patients considered in the former study. There is no validated nomogram for amikacin[277] and immunoassays for this antibiotic are not widely available on automated immunoassay platforms. There are no trial data on amikacin use in *E. coli* ST131. Vestibular toxicity with all aminoglycosides commonly presents after the drug has been stopped and the patient has left hospital.[278,279] Toxicity can occur after normal courses of five daily doses or even a single dose.[278] Auditory toxicity is initially often subclinical, requiring audiograms to detect it. The true incidence of toxicity is difficult to determine. Renal toxicity can be measured by quantitative renal function tests or qualitative urinary renal tubular enzymes. These critical steps to safe use, as determined by case follow-up after the patient has left hospital, have not yet been assessed for plazomicin, although there are no described cases of toxicity yet in clinical trials. In older studies before the adoption of once-daily regimens and weight-related dosage, auditory toxicity appears to have been commoner with amikacin than gentamicin, whilst vestibular toxicity rates were not significantly different;[280] toxicity was commoner with increasing age, paralleling a decline in renal function.[281] This creates an issue, insofar as infections with MDR GNB and ESBL producers occur more frequently among those aged over 65 years and especially over 75 years. It is noteworthy that one recent Scottish national intervention in surgery as part of targeted antimicrobial stewardship measures to reduce the incidence of *C. difficile* by 30% in 2 years was to substitute use of gentamicin for cephalosporins in prophylaxis in surgery. In Tayside, an interrupted time series with segmented regression in 7666 patients undergoing orthopaedic surgery (excluding fractured neck of femur), where two doses of flucloxacillin 1 g and one dose of 4 mg/kg gentamicin were substituted for cefuroxime was performed. An unacceptable 94% increase in acute kidney injury in gentamicin-treated patients occurred and the gentamicin use was stopped.[282] Patients undergoing implant surgery had a mean age of 71 years and 36% had received non-steroidal anti-inflammatory drugs in the last year and 38% received a diuretic, which are known cofactors for gentamicin nephrotoxicity, but this was adjusted for in the study. One-year mortality was higher in the acute kidney injury group (20.8% versus 8.2%). There was no association of acute kidney injury in a further 4816 patients in other surgical specialties where gentamicin was substituted. It is not certain whether the effect was due to gentamicin, flucloxacillin, or the combination, or whether all patients additionally received gentamicin bone cement.

Evidence

Aminoglycosides retain activity against a similar proportion of Enterobacteriaceae to piperacillin/tazobactam (8.6%–8.7%). However, approximately 50% of ESBL-producing *E. coli* in the UK are resistant to gentamicin and more to tobramycin.

Evidence level: 3

Overall resistance rates to amikacin are lower than to gentamicin and tobramycin in the UK. However, bacteria producing AAC(6′) are usually amikacin resistant and bacteria producing the AAC(6′)-Ib-cr enzymes, including many *E. coli* ST131, often have reduced amikacin susceptibility. Strains producing NDM carbapenemase often carry 16S ribosomal methyltransferases that confer high-level pan-resistance to aminoglycosides, including amikacin and plazomicin. 16S ribosomal methyltransferases are also frequent in UK *A. baumannii*.

Evidence level: 3

Plazomicin, a new aminoglycoside, evades almost all aminoglycoside-modifying enzymes but is inactive if 16S ribosomal methyltransferases are present. It has recently completed a Phase 3 RCT with superiority to meropenem in complicated UTI, so far reported only in a press release.

Evidence level: 3

Historically, parenteral aminoglycosides rarely proved selective for resistance among Enterobacteriaceae in the faecal flora. However, because of resistance linkage and carriage on transposons and integrons, aminoglycoside resistance may be selected by use of other antibiotics.

Evidence level: 3

Evidence from travel-associated ESBL producers suggests that aminoglycoside resistance may also be travel associated. The co-carriage of 16S ribosomal methyltransferases by strains with NDM carbapenemase linked to the Indian subcontinent is noteworthy.

Evidence level: 3

The narrow therapeutic index of aminoglycosides demands attention to the detail of weight-related dosing and frequency of doses, collection of blood at an appropriate time for assays, and the careful interpretation of antibiotic assays by nomograms. These actions are essential for adequately safe management of patients treated with gentamicin and tobramycin. Similar modern safety measures are likely to be necessary for amikacin and plazomicin but nomograms are not, and assays may not be widely available.

Evidence level: 4

When strains are susceptible and safety measures are well organized and reviewed in hospitals, gentamicin and tobramycin are useful carbapenem-sparing agents for definitive treatment.

Evidence level: 4

Recommendations

- Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.
  Grading: Conditional recommendation for
- Could use gentamicin as a carbapenem-sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing *E. coli* when susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised.
  Grading: Conditional recommendation for
- Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing *Klebsiella* spp. if strain is resistant to colistin and meropenem (see Section 7.18).
  Grading: Conditional recommendation for
- Use once-daily dosing of gentamicin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to the appropriate 7 or 5 mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs.
  Grading: Strong recommendation for
- Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC(6′)-I and AAC(6′)-Ib-cr.
  Grading: Conditional recommendation against use
- Use tobramycin in preference to other aminoglycosides for susceptible *Pseudomonas* infection.
  Grading: Conditional recommendation for
- Use once-daily dosing of tobramycin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to nomogram.
  Grading: Strong recommendation for
- Modernize use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.
  Grading: Conditional recommendation for

7.13 Polymyxins

The polymyxins are a group of five chemically different bactericidal antibiotics (polymyxins A to E). Only polymyxin B and polymyxin E (colistin) have been used in clinical practice. Intravenously administered colistin methane sulfonate is most widely used, and requires conversion in the body to the active colistin molecule.

Polymyxins have a wide spectrum of activity against Gram-negative organisms, including most Enterobacteriaceae, *A. baumannii*, *P. aeruginosa* and *Stenotrophomonas maltophilia*, but are inactive against *B. cepacia*, *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia marcescens*. Resistance to colistin occurs in some *P. aeruginosa* isolates[283] but remains rare and almost exclusive to cystic fibrosis isolates. Acquired colistin resistance is generally rare but has become common in *K. pneumoniae* in Italy. Colistin heteroresistance is defined as the emergence of resistance to colistin in a subpopulation of an otherwise susceptible (MIC of $\leq$2 mg/L) population.[284] This may be related to exposure to suboptimal polymyxin concentrations. Detection of resistance or heteroresistance is difficult,[506] and is reviewed elsewhere.[507]

Etest®, disc diffusion, Microscan®[285] and VITEK2® detection methods are currently unreliable,[286] and data for Phoenix® are only published for *A. baumannii*. A comparison of broth microdilution (BMD) was made with VITEK2®, Sensititre™ and Etest® using a collection of 76 Enterobacteriaceae, including 21 MCR-1-positive strains.[508] Both Etest® and VITEK2® performed poorly against BMD with very major error (VME) rates of 12% (Etest®) and 36% (VITEK2®) for colistin.[508] Poor performance of both Phoenix® and VITEK2® with substantial under-reporting of resistance has been reported when using these systems for testing *Acinetobacter baumanii*.[509]

The difficulty of detecting colistin resistance in routine laboratories was evident in a recent US study.[287] Resistance to gentamicin was rarer and tigecycline resistance commoner in colistin-resistant isolates. Colistin resistance was associated with increased hospital mortality. Most colistin resistance is chromosomally mediated, involving various mutations that modulate two-component regulatory systems (e.g. *pmrAB*, *phoPQ* and its negative regulator *mgrB* in the case of *K. pneumoniae*), leading to modification of lipid A with moieties such as phosphoethanolamine or 4-amino-4-arabinose, or in rare instances to total loss of the lipopolysaccharide.[288] Of concern is the recent reporting of plasmid-mediated polymyxin resistance lipid A-modifying enzymes (MCR-1 and -2) that confer resistance in Enterobacteriaceae.[24] MCR-1 was first found in China but is now being detected worldwide, mainly in Enterobacteriaceae of animal origin but also in occasional human isolates. It remains much rarer than mutational resistance. China plans to stop use of 8000 tons of colistin in animal feed from April 2017. A recent study shows *mcr*-1 genes are very widespread (50%–100%) in chicken in hatcheries, commercial farms and supermarkets and a slaughterhouse in Shandong. Although testing of hatcheries was negative, NDM carbapenemase-producing *E. coli* were recovered from 21.8% of samples; 23% of carbapenem-resistant *E. coli* tested MCR-1 positive and multiple sequence types and NDM subtypes were found.[289] There are widespread reports of MCR-1 in the European (including UK) food chain.[510]

Synergy studies suggested many years ago[290–294] that polymyxins, trimethoprim and sulphonamides might be useful together in therapy, and these studies need repeating with other agents and newer strains.

Pharmacokinetic and pharmacodynamic data have been limited, particularly in critically ill patients. Polymyxins were developed before the advent of contemporary drug evaluation. Colistin methane sulfonate is an inactive prodrug converted *in vivo* to the active drug and different brands may produce different concentrations of active drug. Data suggested drug concentrations are very variable and dosing in excess of data-sheet recommendations may be required commonly on the basis of pharmacokinetic parameters.[295] Recently the FDA and EMA have made new, but different, recommendations for intravenous colistin in patients with various degrees of renal function. These have been assessed using data from 162 adult critically ill patients with varying renal function. A comparison showed that adequate serum levels with impaired renal function were more likely to be attained with European guidelines and a later paper suggests that in the critically ill target concentrations are difficult to achieve if creatinine clearance is $\geq$80 mL/min/1.73 m^2.[296,297] Data are also now available on the implications of haemodialysis.[298] Therapeutic drug monitoring is advisable, if available, and depends critically on maintaining stability of the drug in separated plasma.

Colistin can be given intravenously, or in respiratory infection via the aerosol route (typically in patients with cystic fibrosis, either alone or combined with intravenous administration), or intrathecally.

Polymyxin B or colistin sulphate can be given orally as a non-absorbed major component of selective digestive decontamination regimens. Selective digestive decontamination has been widely used for general infection prevention in neutropenia and intensive care. Polymyxins given orally were widely added in haematology to aminoglycosides, trimethoprim/sulfamethoxazole[299] or ciprofloxacin[269] to prevent emergence of resistance and in ICUs to parenteral cephalosporins and oral tobramycin.[300] Recent findings that colistin resistance is difficult to detect accurately and that its frequency is usually underestimated, the clear emergence in China and elsewhere of plasmid-mediated resistance and the emergence of colistin resistance in KPC-producing *Klebsiella* spp. in Italy, China and the USA imply that it can no longer be relied on to prevent emergence of resistant strains in patients who have strains that are already frequently resistant to the drugs to which it was added for protection. Use of colistin in all patients in such a unit might well now become a mechanism for selection for XDR GNB or indeed pan-drug resistant MDR GNB in the critical care and haematology units where it is used. This is an enduringly controversial area[301] which we do not have space to fully review, but such selection of colistin resistance in ESBL-producing *Klebsiella* spp. in an ICU has already been reported.[302] We consider that continued use of colistin-containing decontamination regimens should be reviewed urgently within specialties[303] and at the local level, and in our judgement its use is now unwise.

Clinical reports and reviews of experience with colistin are relatively encouraging, with side effects (principally nephrotoxicity and neurotoxicity) observed less often than expected from historical data.[304–309] These studies are summarized in Table 6. In Italy strict rules for the use of colistin are advocated to stop the spread of colistin-resistant KPC-producing *Klebsiella* spp., which have increased 3-fold in 4 years among bacteraemic patients. A case–control study of this guidance showed associations of resistance with previous colistin therapy, previous colonization or infection with KPC-producing *Klebsiella* spp., and a Charlson comorbidity score >3 (all of which were associated with mortality) and also with neutropenia and more than three hospitalizations.[310]

The addition of aerosolized to intravenous colistin has been compared with intravenous colistin alone for the treatment of

Table 6. Studies of the efficacy of colistin

Study	No. of patients	Conditions treated	Pathogens	Duration (mean)	Outcome
Levin *et al.* 1999[305]	59	VAP 33%; UTI 20%; BSI 15%; CNS 8%	*A. baumannii* 65%; *P. aeruginosa* 35%	12 days	58% success overall. Worst in pneumonia group (25%)
Garnacho-Montero *et al.* 2003[304]	21	VAP 100%	*A. baumannii* 100%	14 days	57% success
Linden *et al.* 2003[306]	23	VAP 78%; BSI 35%; intra-abdominal 26%	*P. aeruginosa* 100%	17 days	61% favourable
Markou *et al.* 2003[307]	24	VAP 63%; catheter related 12%; meningitis 4%	*A. baumannii* 24%; *P. aeruginosa* 76%	13.5 days	73% success
Michalopoulos *et al.* 2005[308]	43	VAP 73%; BSI 33%	*A. baumannii* 19%; *P. aeruginosa* 81%	18.6 days	69% clinical cure
Reina *et al.* 2005[309]	55	VAP 53%; UTI 18%; BSI 16%	*A. baumannii* 65%; *P. aeruginosa* 35%	13 days	15% cure on day 6 of treatment
Koomanachai *et al.* 2007[505]	78	VAP 58%; BSI 10%	*A. baumannii* 91%; *P. aeruginosa* 9%	12 days	81% clinical response

BSI, bloodstream infection; VAP, ventilator-associated pneumonia.

ventilator-associated pneumonia in several studies. Korbila and colleagues[311] demonstrated an improvement in outcome with the addition of aerosolized colistin but no benefit was demonstrated in another study.[312] Both had methodological flaws. NICE has recently reviewed the usefulness of aerosolized colistin or tobramycin dry powders in patients with cystic fibrosis and concluded there were some patients who would benefit from colistin dry powder and there would be cost reduction.[313]

Polymyxin B is more toxic than colistin (polymyxin E) but has the advantage of not requiring subject-variable conversion to an active form. A recent retrospective cohort study compared 45 patients with *P. aeruginosa* bacteraemia treated with polymyxin B at a median dose of 141±54 mg/day usually in two divided doses: 11 received >200 mg/day. Eighty-eight patients were treated with a comparator (typically a β-lactam). The in-hospital mortality was 66% in the arm treated with polymyxin B versus 28% for those treated with a comparator, even when matched for mechanical ventilation and sepsis score, suggesting polymyxin B was inferior.[314] This was regardless of dosing regimens. A higher dose (≥200 mg/day) of polymyxin B was found to be associated with reduced mortality but increased renal impairment in another retrospective cohort study.[315] We do not recommend use of polymyxin B in the light of these results.

Combinations including colistin are more effective than monotherapy in treating infections with *K. pneumoniae* carbapenemase (KPC)-producing organisms (see Section 7.18).[316,317]

Nephrotoxicity and neurotoxicity are the principal side effects associated with parenteral administration of polymyxins. The toxicity demonstrated in earlier studies was almost certainly related to lack of understanding of the drug's pharmacokinetics/pharmacodynamics (PK/PD) and the use of inappropriate doses.[318] Studies now suggest that age, high doses, prolonged courses, concomitant vancomycin, hypoalbuminaemia and non-steroidal anti-inflammatory drugs, are independent risk factors for nephrotoxicity[319,320] and it is likely that other nephrotoxic drugs are also associated. Monitoring renal function closely is essential for patients receiving colistin. Recent expert opinion suggests the risk–benefit ratio should be carefully considered, with strategies applied to reduce toxicity.[321] There is no information on the relationship of dose with reversible neurotoxicity or encephalopathy; in a recent large paediatric series they occurred in 2% of patients.[322]

There are gaps in our knowledge about these agents. Although they were developed some 70 years ago they have only recently been used extensively. Much of the current knowledge is summarized in the Prato consensus report.[323]

Dosing of intravenous colistin remains contentious. In adult cystic fibrosis patients, colistin is typically given at a standard dose of 2 MU q8h. However, evidence is emerging that higher-dose regimens may be more appropriate in the ICU setting (with therapeutic drug monitoring: to target a peak of 5–15 mg/L and a trough of 2–6 mg/L). A recent study of significant infections caused by a range of MDR GNB suggested that a loading dose of 9 MU followed by 4.5 MU q12h (reduced in renal impairment) was effective (23/28 responses) and resulted in a reversible mild renal injury in only five patients.[324] Further clinical and PK/PD studies are required to confirm appropriate regimens, including in relation to a loading dose, combination therapy and the need for monitoring. In the meantime EMA guidance should be followed.

Evidence

Colistin is effective in treatment of infections caused by MDR GNB with low mortality at higher-than-previous, but well-controlled dosage.

Evidence level: 3

The role of loading doses of colistin, monitoring of serum levels and optimal combination therapy are inadequately researched.

Evidence level: 4

Use of aerosolized colistin dry powder has recently been accepted by NICE in cystic fibrosis.

Evidence level: 3

Use of aerosolized colistin dry powder in ventilator-associated pneumonia as an addition to intravenous chemotherapy appears useful.

Evidence level: 3

The dose relationship of colistin nephrotoxicity and the rarer neurotoxicity and encephalopathy require investigation.

Evidence level: 4

Recommendations

- Reserve intravenous polymyxins for infections due to susceptible multiresistant strains and preferably use them in combination with other agents.
  Grading: Conditional recommendation for
- Give careful consideration to use of higher dosage regimens in critically ill patients.
  Grading: Conditional recommendation for
- Closely monitor renal function, especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents, e.g. aminoglycosides.
  Grading: Strong recommendation for
- Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options against CPE and are more threatened by resistance than previously appreciated.
  Grading: Good practice point
- Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as Proteeae and *Serratia* spp.
  Grading: Recommendations for research
- Aerosolized colistin dry powder should be used in cystic fibrosis according to NICE guidelines. Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.
  Grading: Conditional recommendation for

7.14 Fluoroquinolones

Fluoroquinolones suppress susceptible Enterobacteriaceae in the intestinal flora and also select for quinolone-resistant MDR GNB.[250,131] Such suppression has been used in neutropenic patients alone or with colistin.[269] The continued efficacy of this combination in suppression and non-selection of resistance to either agent needs re-establishing, with the increasing recognition of colistin resistance that may well emerge alongside existing quinolone resistance. Prophylaxis with quinolones alone in neutropenia against susceptible bacteraemia seems effective even when quinolone resistance levels in the treated population reach a high level. Trials of withdrawing prophylaxis have been reported and show problematic increases in Gram-negative bacteraemia (see Section 6.5).

Fluoroquinolones (intravenous and oral) may be suitable for complicated UTIs due to ESBL-producing Enterobacteriaceae if there is no resistance *in vitro*; however, most ESBL-producing strains in the UK are resistant to fluoroquinolones, including ciprofloxacin and levofloxacin. Furthermore, quinolone resistance without ESBL production is now frequent, particularly in the multiply resistant if not MDR *E. coli* ST131.[89] Newer quinolones in development are unlikely to provide substantial additional benefits over ciprofloxacin for infections due to Gram-negative pathogens. Three observational clinical studies have assessed the relative merits of quinolones and carbapenems for serious infections due to ESBL-producing organisms.[181,325,326] Two of these found that carbapenems were superior to quinolones, although most strains were quinolone susceptible, whereas one study found equivalent effectiveness.

Fluoroquinolones have been used to treat infections caused by *S. maltophilia*; however, resistance is not uncommon, so combination with one or more of trimethoprim/sulfamethoxazole, ceftazidime or tigecycline has been proposed.[327] These combinations have not been shown to offer any advantages over trimethoprim/sulfamethoxazole alone.

A wide range of resistance mechanisms exist; high-level resistance almost always involves mutations in the genes encoding subunits of the target enzymes, DNA gyrase and topoisomerase IV (*gyrA* and *parC* respectively), but reduced susceptibility can arise from plasmid-acquired genes e.g. *aac(6′)-Ib-cr*, *oqxAB*, *qnrA*, etc. or via up-regulation of outer-membrane efflux pumps and porin loss.[328]

Evidence

Quinolones are effective in treatment of complicated UTI caused by susceptible ESBL-producing Gram-negative bacteria, but resistance is common and limits their usefulness.

Evidence level: 2+

Recommendations

- Could use orally to treat UTI caused by MDR GNB that are susceptible.
  Grading: Conditional recommendation for

7.15 Tigecycline and eravacycline

Tigecycline is a semisynthetic glycylglycine derivative of minocycline and like other tetracyclines is bacteriostatic.[329] The main determinant of acquired plasmid-mediated resistance to older tetracyclines in Gram-negative bacteria, namely active efflux by Tet pumps, is overcome by steric hindrance by a large substituent group. Tigecycline has *in vitro* activity against most Enterobacteriaceae except Proteeae, i.e. *Proteus* spp., *Providencia* spp. and *M. morganii*. MICs for *A. baumannii* (including many carbapenem-resistant strains) and *S. maltophilia* are low (mostly 0.25–2 mg/L) but there are no breakpoints or convincing efficacy studies. In common with other tetracyclines, tigecycline lacks useful activity against *P. aeruginosa*. Tigecycline is vulnerable to the chromosomal resistance–nodulation–cell division (RND) multidrug efflux pumps, including MexXY–OprM of *P. aeruginosa*, and the AcrAB pump found in *Proteus mirabilis*, which explains the intrinsic resistance of these species.[330,331]

Whilst tigecycline-resistant isolates of Enterobacteriaceae have been described from treatment-naive patients, another potential problem is the development of resistance during treatment of infections with Enterobacteriaceae and *Acinetobacter* spp. by the mutational up-regulation of RND pumps, but the frequency is unclear, particularly when used in combination.[332–336] Use of tigecycline is an independent predictor of emergence of tigecycline resistance when treating multiresistant *K. pneumoniae* infection.[337] Further studies are required, possibly including different dosing regimens and in combination with other agents. Tigecycline has a potential to favour superinfections by *P. aeruginosa*, Proteeae[338] and sometimes *Klebsiella* spp.;[337,339] again, these aspects require further investigation.

Subject to the earlier caveat about the lack of breakpoints, tigecycline has *in vitro* activity against *S. maltophilia*, and susceptibility rates of >87% have been reported.[340] However, there is little clinical experience with the drug in treating infections caused by this organism.

Intravenous tigecycline is licensed for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections.[341,342] However, the US FDA issued a warning describing an increased mortality risk with its use when compared with other drugs.[343,344] The highest risk was in patients treated for ventilator-associated pneumonia, which was not a licensed indication. However even in FDA-approved uses there was a higher risk of death among patients given tigecycline compared with those given other antibacterial drugs.[345,346] There are no RCTs comparing tigecycline with polymyxins, fosfomycin, sulbactam and other antibiotics against infections due to MDR GNB, alone or in combinations.[347] Several meta-analyses examine the efficacy and safety of tigecycline in general (not just against MDR GNB) and these reported conflicting findings. One very recent analysis reviews the earlier studies and includes a number of new trials. Clinical success rates were lower than comparator for hospital-acquired pneumonia and diabetic foot infection, with increased gastrointestinal adverse events and higher all-cause mortality, probably due to reduced efficacy.[348]

Further work on tigecycline is needed, as its efficacy in ventilator-associated pneumonia might be improved using higher doses (i.e. 200 mg initially and then 100 mg twice daily); an increase in adverse events was not seen with this regimen.[349] Tigecycline in combination with other antibiotics (e.g. carbapenems and polymyxins) is a potentially valuable approach for infections caused by carbapenemase-producing *Klebsiella* spp., as shown by Tumbarello *et al.*[350] In this retrospective cohort study, largely of infections due to strains with KPC-3 carbapenemase, 9/19 patients survived on tigecycline monotherapy, 0/11 on colistin monotherapy and 16/23 with tigecycline and colistin combinations. Two comparisons of monotherapy and combination therapy for infections with carbapenemase-producing *Klebsiella* spp. give further survival data on monotherapy: survival in one study was 71/116 for tigecycline and 70/132 for colistin[316] and in the other study 16/27 for tigecycline and 12/22 for colistin.[351]

Whilst the *in vitro* data support use of tigecycline in respiratory infection, there is poor correlation between the laboratory results and clinical outcome.[334,352,353]

Eravacycline is a novel intravenous fluorocycline with a similar spectrum to tigecycline. It showed non-inferiority to ertapenem in a Phase 3 trial of complicated intra-abdominal infection but failed to show non-inferiority to levofloxacin in an intravenous/oral switch Phase 3 trial of complicated UTI.[354–356]

Evidence

The role of tigecycline remains uncertain in the treatment of infections due to MDR GNB.

Evidence level: 1−

Recommendations

- Could use tigecycline in combination in the treatment of multi-resistant soft tissue and intra-abdominal infections.
  Grading: Conditional recommendation for
- Use alone in hospital-acquired respiratory infections is unlicensed and not advised with licensed dosing, as outcomes are not clearly satisfactory in *Acinetobacter* and MDR GNB infections.
  Grading: Conditional recommendation against
- Use in combinations in hospital-acquired respiratory infections; precise combinations depend on the antibiotic susceptibility of the MDR GNB causing the infection.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Use higher than licensed dosing, such as 100 mg twice daily, for infections due to MDR GNB in critical care.
  Grading: Conditional recommendation for
- Investigate whether higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible *in vitro*.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.16 Fosfomycin

Fosfomycin, a strongly hydrophilic phosphonic acid (unrelated to aminoglycoside or macrolide antibiotics), inhibits the addition of phosphoenol-pyruvate to *N*-acetyl-glucosamine in synthesis of the bacterial cell wall. Fosfomycin MICs for *E. coli* vary from 1 to 4 mg/L: those for *Klebsiella* spp. are higher at 2–64 mg/L. EUCAST breakpoints for both intravenous and oral formulations are S ≤32 mg/L, R >32 mg/L, available for *E. coli* only. *M. morganii* and *Bacteroides* spp. are inherently resistant and activity against *P. aeruginosa* is controversial, particularly in combination. The drug is otherwise very broad in its spectrum. Fosfomycin was active against 72% of Enterobacteriaceae resistant to carbapenems in a German study.[357] *In vitro* testing with discs required the addition of glucose-6-phosphate to the disc. In this study there were 22% major discrepancies between agar dilution in medium containing glucose-6-phosphate and disc or Etest testing and it is not clear if glucose-6-phosphate was present in discs and MIC gradient strips, an area for quality control development. There are similarly no published details on the reliability of automated susceptibility testing methods.

Fosfomycin trometamol is used as an oral treatment for patients with uncomplicated lower UTI due to fosfomycin-susceptible organisms resistant to first-line agents. At the conventional dosage of 3 g on a single occasion, this oral formulation gives an adequate urinary concentration for 2 days (see Section 9.3). An earlier oral product was a calcium salt, only 30%–40% of which was absorbed: this gave peak plasma levels of 7–9 mg/L 4 h after a 3 g dose. The trometamol salt that replaced this is better absorbed (60% bioavailable), reaching peak plasma levels of 32 mg/L 2 h after a 3 g dose).

Experience with intravenous fosfomycin disodium (not a trometamol formulation) is limited in the UK, where it has only recently been introduced, specifically for treatment of infection with multi-resistant bacteria. It has been more widely used elsewhere in Europe. The intravenous sodium salt reaches levels of 25 mg/L after a 1 g dose. A very early single open comparison of 38 patients with acute pyelonephritis showed that 7 days of intravenous fosfomycin 2 g q6h achieved only a 44% response rate;[358] the authors therefore concluded the drug had no role in pyelonephritis; the oral trometamol salt has never been examined for pyelonephritis. Intravenous dosage with MDR GNB is now usually at 24 g/day in three divided doses but dosage reduction is needed in renal impairment as the drug is exclusively renally excreted, unchanged. The formulation has a high sodium load and the most frequently encountered side effect is hypokalaemia (26% patients).[359] Fosfomycin exhibits excellent penetration into tissue after an intravenous dose as it is a small (138 Da) molecule with negligible protein binding; it also has a long serum half-life of 4–8 h.[360]

A prospective salvage study of 11 ICU patients with serious infections caused by carbapenem-resistant *K. pneumoniae* reported an all-cause mortality of 2/11, although analysis of the claimed successes is complicated because six patients were also treated with colistin and three with gentamicin.[361] A larger outcome study of 48 patients (mainly with ventilator-associated pneumonia) infected with KPC-producing *K. pneumoniae* and to a lesser extent VIM-producing *P. aeruginosa* reported clinical success when fosfomycin was used mainly in combination with colistin or tigecycline in 54.2% patients and 28 day all-cause mortality of 37.5%.[362] Of 15 patients with colistin-, tigecycline-, aminoglycoside- and carbapenem-resistant KPC-producing *Klebsiella* infection (one with an additional carbapenem-resistant *P. aeruginosa*), 9 responded to fosfomycin combinations and in 8 microbiological eradiation was achieved.

The use of intravenous fosfomycin has been reviewed extensively. Clinical cure was described in 1242/1529 patients (81.2%) overall (for both Gram-positive and Gram-negative pathogens).[363] Most of the Gram-negative infections in this series were due to *P. aeruginosa* (which most would regard as resistant), but also included infections due to *Enterobacter* spp., *Klebsiella* spp., *E. coli*, *Proteus* spp. and *Salmonella typhi*. Most patients also received concomitant antibiotics, so again interpretation is difficult. A wide variety of infections was treated and fosfomycin was well tolerated. Despite *in vitro* resistance to fosfomycin, most patients with infections caused by *P. aeruginosa* improved, although this may reflect concomitant antibiotics.

Further detailed studies of the parenteral form used alone in single indications (such as UTI and ventilator-associated pneumonia) are required to establish its relative efficacy and usefulness for specific MDR GNB. Similarly, in combination therapy comparisons of specific combinations are required.

Evidence

Further details and regimens for the oral formulation are given in Section 9.3.

The parenteral formulation may be a valuable treatment alternative for infections due to MDR GNB including carbapenemase- and MBL-producing strains. However, further detailed comparative trial experience is necessary to determine its optimal use.

Evidence level: 3

Recommendations

- Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB: clear indications for use are not yet established.
  Grading: Conditional recommendation for
- Need comparative clinical trials to establish optimal indications for, and optimal use of, parenteral fosfomycin, a potential drug of last resort against MDR GNB.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.17 Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole (available as intravenous and oral formulations) has *in vitro* activity against *S. maltophilia*[340] and some less-frequently encountered non-fermenting Gram-negative bacilli (e.g. *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp.).[364] These species have inherent resistance to most other antibiotics and often produce MBLs. *Stenotrophomonas* spp. typically have similar percentage susceptibility at the CLSI breakpoint to sulphonamides alone and trimethoprim/sulfamethoxazole but are resistant to trimethoprim alone. The combination has greater *in vitro* potency than either trimethoprim or sulfamethoxazole. A similar comment applies to *Achromobacter* spp. and with few exceptions to *Alcaligenes* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp.[364] These genera are susceptible to trimethoprim and more strains of these genera and *Burkholderia* spp. are susceptible to trimethoprim/sulfamethoxazole than either component alone.[364] The clinical use of sulphonamides alone against non-fermenters has not been explored and the combination of trimethoprim/sulfamethoxazole is usually used in *S. maltophilia* infections and, for simplicity, against those due to these other unusual species. Problems occur with disc susceptibility testing of *S. maltophilia* and there are few data on the performance of automated susceptibility systems. Trailing endpoints are frequent and results vary with the temperature of incubation and the susceptibility testing medium used. Occasional resistance to trimethoprim/sulfamethoxazole is not well understood in these non-fermenters but resistance to trimethoprim/sulfamethoxazole caused via the *sulI* gene has been described repeatedly in *S. maltophilia*.[365] A recent systematic review suggested that some strains of *Acinetobacter* spp. are susceptible to trimethoprim/sulfamethoxazole and that use against this genus can be guided by *in vitro* testing.[366] However, over half the UK strains of *A. baumannii* show high-level resistance.[364]

Evidence

Trimethoprim/sulfamethoxazole has wide *in vitro* activity against *S. maltophilia*, *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. *and Elizabethkingia* spp. Susceptibility testing methods for these organisms are not well established but some *S. maltophilia* have resistance to trimethoprim and sulfamethoxazole. Carbapenem resistance is inherent to most of these species.

Evidence level: 3

Recommendations

- Use in treatment of infections due to susceptible *S. maltophilia* and consider in infections due to *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and

Elizabethkingia spp.
Grading: Conditional recommendation for

7.18 Intravenous combination therapy for infections due to carbapenemase producers

Although results of RCTs will become available, most of the current evidence for the advantage of combination therapy for carbapenem-resistant infections derives from observational studies and reports mainly focus on severely ill patients or those where the pathogen has reduced susceptibility to colistin.[367] An international working group report recommended combinations including a carbapenem as optimal treatment but only in settings where NDM carbapenemases are infrequent.[368] However, retrospective studies are liable to bias in that investigators have no control over antibiotic use.

Different studies and reviews of combination therapy have reached contradictory conclusions. One systematic review identified that evidence for combination treatment was poor quality and inherently biased, being based on small observational studies with heterogeneity of: (i) antibiotic choice and activity against responsible pathogens; (ii) antibiotic dosage; and (iii) severity of illness.[369] These authors concluded that any benefit in outcome between monotherapy with colistin and combination of colistin with other agents (aminoglycoside, tigecycline, carbapenem or rifampicin) was uncertain. There were methodological problems in the studies reviewed. Another systematic review[370] which lacked quality assessments likewise found only observational studies with marked heterogeneity, and suggested no proven benefit in terms of mortality between combination treatment and monotherapy except for three more homogeneous studies exclusively of bacteraemias due to KPC-producing *Klebsiella* spp. in critically ill patients, which are worth detailed consideration.[350,371,372]

Firstly, Tumbarello *et al.*[350] in a three-centre retrospective cohort study found 16/23 patients survived with tigecycline and colistin combinations and 12/14 with colistin/tigecycline/carbapenem combinations compared with 11/22 with colistin monotherapy and 10/19 with tigecycline monotherapy. Secondly, Qureshi *et al.*[371] in a two-centre retrospective cohort study showed that 3/7 receiving polymyxin monotherapy, 1/5 receiving tigecycline monotherapy, 2/4 receiving carbapenem monotherapy and 2/3 other antibiotics as monotherapy survived 28 days compared with 5/6 receiving colistin combinations and 6/6 receiving tigecycline combinations. Thirdly, Zarkotou *et al.*[372] noted 3/7 survivals with colistin, 3/5 with tigecycline and 0/1 on carbapenem, all as monotherapy, compared with 9/9 receiving combined tigecycline and colistin, 3/3 receiving tigecycline and carbapenems and 8/8 among those treated with other combinations. Two studies of bacteraemias involving VIM-1 producers considered in this review produced even less interpretable results. A third systematic review of polymyxin treatment found mortality at 30 days was lower in patients given combination treatment.[373] A 2017 systematic review and meta-analysis favours combination use of polymyxins.[374]

Given this background, conclusions from further individual non-RCT studies must be interpreted with caution, but some support combination treatment. A larger retrospective cohort study of 661 infections caused by KPC carbapenemase-producing strains of *K. pneumoniae* reported improved survival in patients treated with two or more active drugs versus those given monotherapy.[316] Mortality at 14 days in bacteraemias with an unknown or non-urinary source was 52.8% with monotherapy and 34.1% with combination treatment. A similar result with 49.1% and 24.8% mortality respectively was seen with lower respiratory tract infection. There was no significant difference in bacteraemias from a known urinary source. Overall death rates on monotherapy were 62/132 (47%) with colistin, 45/116 (39%) with tigecycline and 28/70 (40%) with gentamicin. With two-drug therapy mortality was 38/134 (28%) and with three-drug therapy it was 67/217 (31%). Only the use of meropenem in a combination produced a statistically significant improvement to 54/205 (26%). Use of meropenem was associated with lower mortality only if the MIC was $\leq$8 mg/L, as was the case for 37% of the isolates. Colistin resistance was significantly associated with increased mortality. Overall, combinations including tigecycline, colistin and meropenem were associated with the lowest mortality (12.5%, OR 0.11, 95% CI 0.02–0.69). Epidemiologically, overall colistin, tigecycline and gentamicin resistance rates were 11%, 9% and 6% in 2010 but by 2014 were 21%, 27% and 25%.

A further review including some previously reviewed studies suggested superiority of combination therapy over monotherapy, with mortality rates of 27.4% versus 38.7% respectively. Again, carbapenem-containing regimens had the lowest mortality (18.8%) and this was associated with isolates that were not resistant by the EUCAST breakpoint.[375] Similar findings were reported in a retrospective observational study of 205 bacteraemias caused by carbapenemase-producing *K. pneumoniae*.[351] Combination therapy was associated with a lower mortality rate of 27% compared with 44% for monotherapy, 11/27 with tigecycline, 10/22 with colistin and 7/12 with carbapenems. The difference in mortality was most marked in the more severe cases. Furthermore, mortality with a carbapenem-containing combination was 19.3% (6/31) compared with 30.6% (22/72) without a carbapenem (5/16 in those treated with tigecycline and colistin alone). Mortality on carbapenem-containing regimens in this study was lower only if the carbapenem MIC was $\leq$8 mg/L. The authors comment that 40% of isolates with MICs by Etest $\leq$8 mg/L were found resistant by automated testing. These studies suggest: (i) that KPC-carbapenemase-producing *Klebsiella* spp. commonly appear meropenem susceptible *in vitro*; and (ii) that treatment combinations containing conventionally dosed carbapenems are advisable in such cases with lower MICs.

Much higher doses of meropenem by continuous infusion can also be used (see Section 7.1). This extends the MIC range of strains that can be treated. Continuous infusion therapy of meropenem with doses up to 13.2 g daily with levels optimized by therapeutic drug monitoring when used in combinations (mainly with colistin and tigecycline) were associated with 73% clinical cures in patients with KPC-producing *K. pneumoniae* with MIC 16 to <64 mg/L.[376] These are better outcomes in treatment of more-resistant KPC-producing *Klebsiella* than apparent in earlier studies of these more-resistant KPC-producing *Klebsiella*. Direct comparisons have not been made including comparison with high-dose continuous infusion meropenem alone. The application of this approach to other carbapenem-resistant isolates with MICs within the attainable range has not been assessed.

Anecdotal reports suggest double carbapenem combinations of ertapenem plus either meropenem or doripenem can be effective as last-resort treatment for infections due to *K. pneumoniae* producing KPC carbapenemase but not those with NDM enzymes.

This is perhaps because ertapenem binds tightly to the KPC enzyme, acting as an inhibitory substrate and thereby protecting the meropenem or doripenem.[377,378]

In cases where the *Klebsiella* spp. strain was resistant to colistin and carbapenems, the use of gentamicin in combination with various agents was independently associated with reduced mortality in a retrospective cohort study.[379] However, this was in the epidemiological context of a clonal *K. pneumoniae* ST512 (CC258) lineage with a KPC enzyme. This lineage commonly has the AAC(6′)-Ib enzyme, which confers resistance to amikacin but largely spares gentamicin; it is unlikely to be true for isolates with NDM carbapenemases, which mostly have ArmA or Rmt ribosomal methyltransferases, conferring high-level resistance to all standard aminoglycosides, including gentamicin and plazomicin. Plazomicin might have a future role with non-NDM-producing, gentamicin-resistant strains.

Evidence for efficacy of tigecycline in combination largely derives from observational studies but microbiological cure rates with monotherapy are lower than clinical cure rates and mortality rates are high. Pooled results from five observational studies suggested a clinical response rate of 77% (567/733) for all patients and 81% (329/408) for tigecycline monotherapy in the treatment of complicated intra-abdominal infection.[380] Another review of five observational studies of uncomplicated soft tissue and intra-abdominal infection with tigecycline similarly found monotherapy was effective.[381] These studies contain no data on response by resistances present and studies were with the licensed dose of 50 mg twice daily.

In an open-label RCT of treatment of ventilator-associated or hospital-acquired pneumonia caused by MDR *Acinetobacter* spp., addition of rifampicin to colistin did not affect 30 day mortality or length of hospital stay, but was associated with a higher rate of microbiological eradication.[382] A retrospective observational study of 251 bloodstream infections treated with colistin, colistin/sulbactam, colistin/carbapenem or another colistin combination reached the similar conclusion that mortality was not affected but microbiological eradication was higher with combination treatment.[383] Another observational study of 101 patients with MDR *Acinetobacter* infections did not show any improvement in mortality rates for combination therapy (e.g. colistin plus tigecycline or carbapenem plus tigecycline) over a single agent (usually colistin) but the group size in this study was small.[384]

In the case of MDR *Pseudomonas* infections a prospective cohort study showed no outcome advantage in combination versus monotherapy.[385] Combination therapy with aminoglycosides did not reduce the development of resistance.[386] Fosfomycin in combination with tigecycline or colistin was effective in 54% of 48 patients with infections with MDR GNB, some of whom had *Pseudomonas* infection.[362]

The recent introduction of ceftazidime/avibactam and the possibilities of using this in treatment may change the need to use combination treatment for some KPC- or ceftazidime-resistant OXA-48 carbapenemase-producing strains.

Evidence

Two of four systematic reviews do not show a benefit of combination therapy over monotherapy.

Evidence level: 2++

In infections with KPC-carbapenemase producing *Klebsiella* spp., combination therapy including meropenem is associated with lower mortality than colistin monotherapy if the meropenem MIC is <8 mg/L but this was not the case with strains with higher MICs unless continuous infusion therapy with higher than licensed doses was used (see Section 7.1). Combinations with other agents such as tigecycline or an aminoglycoside to which carbapenemase-producing strains are susceptible also seem advantageous, but only the expected results of a new RCT will resolve this.

Evidence level: 3

Paul *et al.*[369] detail the hazards of bias in favour of combination therapy that arise without an RCT. Data from a subset with bacteraemia with *Klebsiella* spp. producing KPC carbapenemases in the second systematic review performed by Falagas *et al.*[370] suggest that in treatment of carbapenem-resistant Enterobacteriaceae infection, colistin used in combination with other agents is associated with a lower mortality than colistin alone, and this is also a finding in the review of Ni *et al.*[373]

Evidence level: 1+

The evidence that tigecycline combinations, including other antibiotics active against Enterobacteriaceae, are more effective than tigecycline alone in intra-abdominal infections is poor.

Evidence level: 1−

Ertapenem in combination with meropenem may be effective as salvage therapy for infections with KPC carbapenemase producers but the evidence is very weak.

Evidence level: 3

In treatment of MDR *Acinetobacter* respiratory infections, addition of rifampicin to colistin does not affect 30 day mortality.

Evidence level: 1+

Recommendations

- Use colistin with meropenem to treat susceptible KPC-producing *Klebsiella* infection if the meropenem MIC is ≤8 mg/L and consider a higher meropenem dose by continuous infusion if the MIC is >8 and ≤32 mg/L.
  Grading: Conditional recommendation for
- Consider colistin with aminoglycosides or tigecycline in infections with strains producing other carbapenemases or KPC strains that are susceptible to these agents but resistant to meropenem.
  Grading: Conditional recommendation for
- Consider whether ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC-3 producers based on latest evidence at the time of use.
  Grading: recommendation for research and possibly conditional recommendation for use restricted to trials

8. Oral agents for secondary/tertiary care treatment

8.1 Mecillinam and pivmecillinam

Pivmecillinam (the oral form of mecillinam) can be considered alone as oral therapy for lower UTI caused by AmpC-producing Enterobacteriaceae. The antibiotic is not active against carbapenemase producers. It has been suggested to be active against ESBL-producing *E. coli*. Patients with infections with such strains referred from the community for intravenous treatment with carbapenems might be considered for oral follow-on therapy with pivmecillinam alone for UTI because of mecillinam's apparent activity *in vitro*. However, additional measures are desirable and this oral treatment is dealt with under community use (see Section 9.4 for more detail). Patients should be carefully monitored both clinically and microbiologically if pivmecillinam is prescribed alone in hospital for infections involving ESBL producers as treatment failure is a risk.

8.2 Cefixime and oral cephalosporins

Cefixime is an oral third-generation cephalosporin that has been used as an oral switch for patients with pyelonephritis. Among uropathogenic Enterobacteriaceae, it is not active alone against ESBL-producing *E. coli* because of their multiple resistances, including quinolones,[387] but is useful if ESBL-producing organisms or CPE are not present. Cefixime could be used in combination with co-amoxiclav against ESBL-producing Enterobacteriaceae, as supported by *in vitro* data.[388] Data from transconjugant *E. coli* further suggest that cefixime plus clavulanate is effective against strains producing CTX-M-15 enzyme, which have higher cefixime MICs than strains producing CTX-M-9 enzyme.[389] Other oral cephalosporins, including cefdinir, ceftibuten and cefpodoxime, also showed synergy with clavulanate, whereas sulbactam was less effective as a potentiator. Cefixime, with or without clavulanate, was not active against AmpC-producing organisms nor would it be expected to be active against CPE. Consequently cefixime/co-amoxiclav combinations should not be used against cephalosporin-resistant organisms without tests to distinguish AmpC and ESBL production. No clinical trials of cefixime together with clavulanate or amoxicillin/clavulanate against ESBL-producing *E. coli* have been published. Cefixime is detectable in faeces after administration. Other cephalosporins, e.g. cefalexin, which are fully absorbed, are not detectable in faeces and less frequently provoke *C. difficile*, may be better partners for clavulanate, although *in vitro* data to support this combination are lacking.[105] Synergy *in vitro* between cephalosporins and mecillinam because of their different target penicillin-binding proteins is likely, and synergy of cefalexin with fosfomycin (earlier known as alafosfalin or fosfonomycin), another cell-wall active antibiotic, is also recorded.[390]

Evidence

Cefixime with clavulanate, which is not available commercially, has reliable *in vitro* activity against ESBL-producing *E. coli* and *Klebsiella* spp. (not *Enterobacter* spp., where AmpC will cause resistance). Cefixime is not useful alone against MDR GNB and no clinical studies with oral cephalosporins and clavulanate or amoxicillin/clavulanate have been published.

Evidence level: 3

Recommendations

- Do not use cefixime or other oral cephalosporins alone for treating infections caused by ESBL-, AmpC- or carbapenemase-producing Enterobacteriaceae.
  Grading: Conditional recommendation against use
- Oral cephalosporins need clinical trials with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

8.3 What are the recommended antibiotics for community care, including care homes?

Most MDR GNB infections encountered in the community involve the urinary tract. As described earlier, ESBL-producing isolates of Enterobacteriaceae are a significant and growing problem, whereas there are few community infections in the UK involving CPE. There are no published RCTs of antibiotic treatment of UTIs due to ESBL-producing organisms in the community or care homes. Recommendations must rely on observational studies of ESBL-producing GNB, or RCTs of effectiveness of antibiotics against UTIs caused by GNB lacking ESBLs.

8.4 What are the risk factors for patients with urinary tract infections caused by MDR GNB in the UK?

In order to help the assessment of patients we reviewed risk factors for MDR GNB and suitable oral agents for acute uncomplicated and complicated UTIs. Prospective and retrospective epidemiological studies identified several risk factors for carriage of ESBL-producing *E. coli*.[99,136,184,391–393,394,395] Patients are at increased risk if they have:

- Recurrent UTI
- Persistent urinary symptoms after an initial antibiotic
- Over 7 days hospital admission in the last 6 months
- Residence in a care home
- Recent travel and especially healthcare in a country with increased antimicrobial resistance.
- Previously known UTI (within 1 year) caused by bacteria resistant to amoxicillin/clavulanate, cephalosporins or quinolone or recent treatment with these agents.[396]

There are no UK data validating an Italian scoring system devised and tested in 2009 for carriage of ESBL-producing bacteria on admission to hospital or incorporating information on travel, overseas healthcare in the previous 2 years or migration. The Italian scoring system identifies risk based on hospitalization within the previous 12 months (OR 5.69, 95% CI 2.94–10.99), transfer from another healthcare facility (OR 5.61, 95% CI 1.65–19.08), Charlson comorbidity score >4 (OR 3.80, 95% CI 1.90–7.59), β-lactam or fluoroquinolone prescription within the previous 3 months (OR 3.68, 95% CI 1.96–6.91), recent urinary catheterization (OR 3.52, 95% CI 1.96–6.91) and age >70 years (OR 3.20, 95% CI 1.79–5.70).[99] This model of risk factors has been re-assessed in the USA to see if it can be used to realistically restrict the need for carbapenem treatment to an identifiable high-risk subgroup.[397] In the US evaluation, risk factors for community-onset clinical infection involving MDR GNB diagnosed within 48 h of admission were: hospitalization (OR 2.63, 95% CI 1.323–5.41), inter-hospital transfer (OR 5.30, 95% CI 2.67–10.71), urinary catheterization (OR 6.89, 95% CI 3.62–13.38), β-lactam or quinolone prescription (OR 3.47, 95% CI 1.91–6.41) and additionally immunosuppression in the preceding 3 months (OR 2.34, 95% CI 1.14–4.8). Age over 70 was not a risk factor but age was not examined as a continuous variable. In this model, the sensitivity and specificity were ≥94% and ≤65% for scores of ≤3 and ≤58% and ≥95% for scores of 8 or above. Urinary catheterization was also a risk factor in a Spanish study.[398] A further paired US retrospective case–control study compared infections with CTX-M ESBL-producing *E. coli* infections with *E. coli* lacking CTX-M enzymes with uninfected controls; carbapenemase producers were excluded. Patients with infections with CTX-M producers were more likely to be male, have dementia or dependency, have higher median Charlson scores, receive H2 antagonists and have exposure to healthcare settings.[393] Recent antibiotics did not differ between the two groups, except that trimethoprim/sulfamethoxazole use was commoner in the non CTX-M-producing group. Exposure to immunosuppressives was also commoner in the CTX-M group. A similar 75%–77% of strains were present within 48 h of admission. When patients with strains producing CTX-M-ESBLs were compared with controls, the former had a higher incidence of comorbidity (Charlson score ≥5), and were more often resident in nursing homes with greater exposure to healthcare and more indwelling urinary catheters. They were more likely to be receiving H2 antagonists or proton pump inhibitors and to have exposure to oxyimino cephalosporins within the last 3 months.

Evidence

Quoted rates of resistance in the community are biased to an unknown extent by infection occurring shortly after hospital discharge, care home cross-infection, an excess of treatment failures represented in the samples tested and an unknown proportion of patients with risk factors and recent antibiotic use.

Evidence level: 2−

UK surveillance suggests MDR GNB remain uncommon in community UTIs, with few carbapenemase producers.

Evidence level: 3

Empirical antibiotic choice for lower UTI can be guided by the presence of established risk factors for a multiresistant organism.

Evidence level: 2+

Predictive models have been established in Italy and the USA for ESBL-producing *E. coli* infections and colonization on admission to hospital, but these have not been validated in the UK nor do they consider travel-, migration- or household-associated risks.

Evidence level: 2+

Recommendations

- In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors or recent foreign travel to countries where such strains are highly prevalent.
  Grading: Strong recommendation for
- If the defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.
  Grading: Strong recommendation against use
- Building on previous work, predictive scoring should be developed in the UK for the presence of ESBL-producing *E. coli* in primary care and on admission to hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBL-producing organisms.
  Grading: Strong recommendation for

9. Which oral antibiotics are preferred for use in treating uncomplicated UTIs due to MDR GNB in the community?

9.1 Trimethoprim

Owing to increasing resistance, trimethoprim is no longer the suggested first-line empirical therapy for post-menopausal women and older men in PHE guidance and nitrofurantoin is advised instead. In Wales trimethoprim remained until 2016 the suggested first-line empirical therapy for uncomplicated UTI in the community except for the elderly and for patients who have received antibiotics in the preceding 3 months.

Following advice to decrease trimethoprim use, an 86% reduction in trimethoprim use was seen in a Swedish region (hospitals and community) from 2004 to 2006 with a compensatory increase in nitrofurantoin, pivmecillinam and ciprofloxacin use. This programme resulted in no overall change in trimethoprim resistance. Before the intervention, trimethoprim resistance was more prevalent in *E. coli* phylogroups A, B1 and D than in phylogroup B2 strains, although rates were high in ST131, which belongs to phylogroup B2.There was a marked change after the intervention in the distribution of resistance between phylogroups and associated sequence types, with an increase in the trimethoprim resistance in phylogroup B2 (including ST131) and a decrease in trimethoprim resistance in phylogroup A and B1 strains (which seldom cause extraintestinal infection) and to a lesser extent in phylogroup D. Trimethoprim resistance was associated with a change in prevalence of *dfrA1*. Resistance to other antibiotics, including those substituted for trimethoprim increased in phylogroup A and B1 strains.[118] Amongst 273 urine isolates of *E. coli* collected in 2006 versus the same number collected in 2004, strains of ST69 (which includes the former clonal group A), ST12 and unusual strains became more prevalent, increasing respectively from 4.8% to 8.1%, from 2.6% to 4.8% and from 42% to 51%. By contrast strains of ST131, ST127, and ST80 declined in prevalence from 4.8% to 2.2%, 8.1% to 3.7% and 5.1% to 1.1%. There were statistically significant increases in trimethoprim resistance rates in the strains of ST131 and ST127. This would suggest that in types ST131 and ST127 susceptible strains were eliminated by the antibiotics substituted for trimethoprim (quinolones, pivmecillinam and nitrofurantoin) but because of resistance linkage trimethoprim resistance increased in these sequence types. Information is lacking on ST80. The increase in strains ST69 and ST12 suggests they may have been selected by the antibiotics substituted for trimethoprim, but it is not clear which antibiotics would have this effect as these STs are usually only resistant to ampicillin and, in the case of ST69, trimethoprim. In a structured survey of extraintestinal strains from US veterans in 2011, quinolone-resistant ST131 accounted for 78% of quinolone-resistant strains, which constituted 29% of reported strains overall. It accounted for 56% of trimethoprim-resistant strains and 52% of quinolone- and trimethoprim-resistant strains.[399] This suggests that quinolones have the potential to select against trimethoprim-susceptible ST131 strains, decreasing in the Swedish intervention study the overall prevalence at that time but potentially selecting for later increased prevalence of the ST131. Thus, because of resistance linkage, community-wide change in use of a single antibiotic may unpredictably change the epidemiology and the prevalence of antibiotic resistance in more pathogenic phylogroups. It cannot be assumed that risk factors for multiresistance or the likelihood of success with an antibiotic in reinfection or recurrent infection will stay the same after abandonment of trimethoprim as a first-line agent. This aspect of change needs urgent study.

Trimethoprim-resistant strains are much more frequently resistant to amoxicillin than trimethoprim-susceptible strains and this is a feature of ST69. Trimethoprim resistance rates in ESBL-producing *E. coli* in 2010 in the West Midlands were between 86% and 92% depending on whether the strain was not, or was, ST131. Ciprofloxacin resistance is also usual in these strains.[93] Trimethoprim consequently is a poor choice for patients with treatment failures on amoxicillin with, or without, clavulanate, cephalosporins or quinolones who require an urgent prescription before samples can be tested for antibiotic susceptibilities.

More generally, trimethoprim should not be used as empirical treatment for UTI if there are risk factors for an antibiotic-resistant bacterium unless: (i) susceptibility has been confirmed in the previous month; (ii) there are no new risk factors for resistance; and (iii) there have been no treatment failures with trimethoprim. In the absence of resistance, trimethoprim attains excellent bacteriological cure: 2 weeks after completion of treatment 94% of women using a 3 day course achieved bacteriological cure compared with 97% of those using a 10 day course ($n = 135$).[400]

Evidence

Trimethoprim use has not been explored as a risk factor for MDR GNB infection but resistance is common generally and very common in ESBL-producing bacteria. Trimethoprim is no longer recommended as a first-line antibiotic choice for post-menopausal women and older men with UTI and has little place in treatment of infection due to MDR GNB.

Evidence level: 3

3 day courses are almost as effective as longer courses in bacteriological cure of susceptible infections.

Evidence level: 1+

Recommendations

- Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless *in vitro* susceptibility has been demonstrated.
  Grading: Strong recommendation against use
- Do not use trimethoprim to treat lower UTIs as a first-line agent if $\geq$50 years old. Only consider use if there are no risk factors for resistance, or if *in vitro* susceptibility is confirmed.
  Grading: Conditional recommendation against use

9.2 Nitrofurantoin

Nitrofurantoin is widely used for acute uncomplicated UTI in the community, and is now the recommended first-line treatment in England. It attains only low concentrations in renal tissue and the bloodstream and should not be used if pyelonephritis or bacteraemia is suspected; treatment may fail if used for ascending infection.[401] Nitrofurantoin resistance is inherent in *Proteus* spp., *M. morganii*, *Providencia* spp. and *Serratia* spp. and the drug may not be effective in the alkaline urine produced by urease-producing bacteria such as these and possibly *Staphylococcus saprophyticus*, which is apparently susceptible *in vitro* but also produces large amounts of urease. Nitrofurantoin resistance is very common in CPE.[120]

In early studies nitrofurantoin had a minimal effect on rectal flora and a recent metagenomics study supports this.[402,403] Resistant strains of *E. coli* and increased numbers of Proteeae may be detected in the faecal flora[404,405] but UTIs breaking through prophylaxis in recurrent infection are usually due to strains that remain susceptible, unlike the situation with trimethoprim.[404,405] Recurrent UTIs after nitrofurantoin treatment of ESBL-producing *E. coli* may reflect relapse or recurrent infection arising from persistent carriage in the gastrointestinal flora; these possibilities cannot easily be distinguished. Frequent recurrence of UTI due to ESBL strains may justify using an alternative antibiotic regimen such as fosfomycin, or amoxicillin/clavulanate with pivmecillinam, with a greater theoretical chance of changing the gastrointestinal flora, which may act as the source for reinfection.

If a patient has a reduced glomerular filtration rate (GFR), urinary concentrations of nitrofurantoin may be too low to be effective. Estimated GFR (eGFR) frequently declines with age, on average by between 6 and 9 mL/min/1.73 m^2 per decade. Around half of women over 75 years and men over 85 years have an eGFR under 60 mL/min/1.73 m^2, which used to be the lower limit for use of nitrofurantoin.[401] In a cohort study of lower UTI in 21317 women treated with nitrofurantoin and 7926 treated with trimethoprim, there was no greater risk of nitrofurantoin treatment failure in patients with creatinine clearance of 30–50 mL/min; however, the risk of pulmonary adverse events was significantly increased with creatinine clearance <50 mL/min (HR 4.1, 95% CI 0.31–13.09).[406] In 2014, and in the context of increasing antibiotic resistance to trimethoprim in the UK, the Medicine and Healthcare Regulatory Agency (MHRA) reviewed the evidence for use of nitrofurantoin in reduced renal function.[407] They concluded on evidence[401,406] that the eGFR below which nitrofurantoin should not be used could be lowered to 45 mL/min/1.73 m^2. The MHRA further stated that a short course (3–7 days) may be used with caution in patients with an eGFR of 30–44 mL/min/1.73 m^2, but only advocates prescribing in such patients for lower UTIs with suspected or proven MDR pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects. Long-term or repeated courses of nitrofurantoin are associated with severe pulmonary fibrosis.[408] Nevertheless, 219 courses of prophylaxis for 1 year for recurrent UTI in normal patients were not associated with a single case, so this unwanted effect may be rare under controlled conditions where the drug is very effective.[405] Nitrofurantoin is poorly tolerated by some patients, but the modified-release form has fewer side effects.[409] When used in this formulation, an open RCT over 20 years ago ($n = 538$) found that nitrofurantoin had equivalent clinical cure rates to trimethoprim/sulfamethoxazole and trimethoprim (both given for 7 days) in a group of patients with acute uncomplicated lower UTI.[409] The rate of gastrointestinal adverse effects was similar between groups (7%–8%). At this time the rate of nitrofurantoin resistance across all pathogens isolated was 3.9% whereas the rate of trimethoprim resistance was 12.5%. Trimethoprim but not nitrofurantoin resistance is now far commoner.

A recent review and meta-analysis suggested nitrofurantoin had a similar clinical cure rate to comparators but with a 5 rather than 3 day course for nitrofurantoin apparently producing better cure rates.[410] However 5 and 3 day courses have not been directly compared in adequate numbers and the PHE has not recommended 5 day courses. We consider in MDR GNB UTI that course lengths should be those that produce the best rates of bacteriological cure. There is no convincing evidence that shorter courses are equivalent to longer courses specifically in MDR GNB infections nor that the risk of serious unwanted effects is increased with longer courses. Whether such longer courses should be used more generally for nitrofurantoin is therefore unresolved. Unwanted effects in the systematic review were mainly gastrointestinal and no pulmonary events were reported, although this may reflect short follow-up periods.[410] There are no specific studies of nitrofurantoin in UTI caused by ESBL-producing organisms, but UTIs that are susceptible to nitrofurantoin have a similar response rate irrespective of ESBL production. However, ESBL-producing members of the *E. coli* ST131 clone, which are common in the UK and elsewhere, often have urinary virulence factors that are associated with recurrence, infection of the upper urinary tract and bacteraemia,[411] and when infection reaches the upper tract nitrofurantoin is ineffective. Nitrofurantoin resistance has appeared in this sequence type (see Section 6.3.4). Further comparative studies in UTIs due to ESBL-producing *E. coli* are needed.

Evidence

Nitrofurantoin is effective in lower, uncomplicated UTI and resistance rates remain low in *E. coli*, although new plasmid-mediated mechanisms of resistance are now described. Mechanisms of acquired resistance in the UK, including in travellers, have not been studied recently. Resistance is intrinsic in *Proteus* spp. and *Serratia* spp.

Evidence level: 1+

There is usually no change in faecal Enterobacteriaceae during or immediately after use. Breakthrough infection, when the drug is used prophylactically, remains susceptible, unlike with trimethoprim.

Evidence level: 3

Nitrofurantoin's activity is reduced in alkaline urine.

Evidence level: 4

Use of nitrofurantoin in moderate renal impairment, as seen with increasing age, has been controversial, but unrestricted use down to an eGFR of >45 mL/min may be acceptable.

Evidence level: 1+

Use in moderate renal impairment or in long-term/repeated courses may be associated, albeit rarely, with serious pulmonary unwanted effects.

Evidence level: 3

5 day, not 3 day, courses are recommended for susceptible ESBL-producing *E. coli*.

Evidence level: 1+

Recommendations

- Could use nitrofurantoin for 5 days to treat uncomplicated lower UTIs with nitrofurantoin-susceptible MDR *E. coli* (not Proteeae or *P. aeruginosa*).
  Grading: Strong recommendation for
- Do not use repeatedly if there is moderate renal impairment, or in long-term courses, as these are associated with rare unwanted pulmonary effects.
  Grading: Conditional recommendation against
- Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in *E. coli* infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare.
  Grading: Conditional recommendation for
- Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing *E. coli* and *Klebsiella* spp.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

9.3 Fosfomycin trometamol

Fosfomycin has not been widely used in the UK, where the oral form was available between February 1994 and 1996; it was thereafter withdrawn and not marketed for nearly two decades until 2013. Its use elsewhere in Europe has been associated with clinical success in lower UTIs. Fosfomycin suppresses Enterobacteriaceae in the faecal flora of 60% of patients by day 3 after a single dose but this rapidly drops to 30% at days 10–14: in contrast, nitrofurantoin does not suppress these organisms.[403]

Oral fosfomycin should be administered while fasting or 2 or 3 h before meals, as food can slow its absorption, leading to lower concentrations in the urine.[412] Oral fosfomycin is licensed solely for the treatment of uncomplicated cystitis. A single oral dose of 3 g results in a plasma C_{max} of 22–32 mg/L and a urine maximum concentration (U_{max}) of 1053–445 mg/L.[413] The urinary concentration remains inhibitory for *E. coli* for at least 48 h. In elderly patients with a mean GFR of 40 mL/min, concentrations after 24 h exceeded those reported for healthy young subjects but there was considerable variation in excretion rates.[414]

Treatment with a 3 g single dose of fosfomycin trometamol was associated with clinical success rates (defined as the resolution of symptoms after treatment) between 77.8% and 94.2% in four observational studies (some complicated and some receiving more than one dose) of treatment of lower UTI due to multiresistant bacteria.[415] Oral fosfomycin trometamol has been used successfully for prophylaxis of pyelonephritis in patients with ASB in pregnancy, and there are reports of its use, sometimes in combination, in chronic prostatitis. The use and kinetics of fosfomycin have recently been extensively reviewed following its re-introduction to Canada.[413]

Evidence

Fosfomycin is effective and well tolerated in treatment of UTI but the oral drug has only been studied in lower UTI.

Evidence level: 2++

Plasmid and chromosomally mediated resistance has emerged in populations where fosfomycin is widely used.

Evidence level: 2−

Recommendations

- Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available. Useful for infections with ESBL producers or carbapenemase producers. No trials of oral formulation for upper UTI.
  Grading: Strong recommendation for

- Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.
  Grading: Strong recommendation for

9.4 Mecillinam and pivmecillinam

Pivmecillinam is an oral inactive ester and prodrug that is converted to microbiologically active mecillinam after intestinal absorption. Mecillinam has *in vitro* activity against most Enterobacteriaceae (including those with copious AmpC and some with ESBLs), but innate resistance occurs in *Proteus* spp., *M. morganii*, *Providencia* spp., some *Serratia* spp. and most non-fermenters, including *Acinetobacter* spp. and *P. aeruginosa*. Mecillinam has no activity against enterococci or *S. saprophyticus*.

Some TEM and SHV ESBLs confer clear resistance[389,416] and an inoculum effect on testing is common for other ESBL producers.[417] In one study of ESBL-producing *E. coli* the MIC_{50} by agar dilution was 1 mg/L with an inoculum of 10^4 cfu/spot but the MIC_{90} was 4 mg/L.[418] Experiments with *E. coli* transconjugants showed that mecillinam MICs rose to 8 mg/L when CTX-M-15 or -3 was present but only to 0.25–0.5 mg/L with CTX-M-9 or -14. Combination with clavulanate reduced all mecillinam MICs for ESBL producers (except SHV-4) to $\leq$4 mg/L at high inocula and $\leq$2 mg/L with the usual light inocula.[389] In another study of combination with clavulanate,[418] 47/48 ESBL producers were susceptible to mecillinam. Most of these produced CTX-M-3 (found in Northern Ireland) not the commoner CTX-M-15 enzymes usual in England, Wales and Scotland. There was no difference between the MICs for transconjugants producing CTX-M-3 and -15 in the earlier study. Synergy with clavulanate was detected in 40%–60.4% of ESBL-producing isolates depending on the method of assessment. When a high inoculum was used, there was a marked inoculum effect, raising the MIC of mecillinam alone but not that of mecillinam plus clavulanate. This study needs to be repeated with *E. coli* ST131 strains producing CTX-M-15 enzyme and also often OXA-1, which is not inhibited by clavulanate but said to have little activity against mecillinam

Mutants resistant to mecillinam by non-ESBL mechanisms can readily be obtained by laboratory selection. These show mutations in many different cellular functions.[68] However, a recent study of mecillinam-resistant clinical isolates found them all to have mutations leading to inactivation of the *cysB* gene. Reduced cysteine biosynthesis results in accumulation of the transcriptional regulator guanosine 3′-diphosphate 5′-diphosphate (ppGpp) so that the mecillinam-targeted PBP2 becomes non-essential.[419] Addition of cysteine to the growth medium *in vitro* reversed the resistance to mecillinam for such mutants, raising possible issues with regard to current *in vitro* testing media.

Mecillinam is inactive against Enterobacteriaceae with KPC enzymes but some published data suggest *in vitro* activity against isolates with OXA-48-like enzymes[68,389] and even some with NDM-1 enzymes, as reflected in an MIC_{50} of 4 mg/L for NDM carbapenemase-producing *E. coli*,[420] although this low value is disputed by others (D. M. Livermore, unpublished data).

Pivmecillinam at 200 mg three times daily only produces sustained inhibition in Monte Carlo simulations if the mecillinam MIC is $\leq$0.25 mg/L, suggesting a higher dose or lower EUCAST breakpoint may be required to produce and predict clinical response, respectively.[421]

Pivmecillinam is used mainly for lower UTI, where it has similar short-term symptomatic efficacy to amoxicillin and trimethoprim/sulfamethoxazole if organisms are susceptible[422,423] and also to norfloxacin in 3 or 7 day regimens.[424] Seven day pivmecillinam regimens are associated with more frequent clinical success than 3 day regimens.[425] Pivmecillinam prophylaxis in children with vesicoureteric reflux markedly reduced faecal *E. coli* and urinary breakthrough with *E. coli*; unlike nitrofurantoin, breakthrough infection with enterococci was common, reflecting different *in vitro* resistance.[426] Urinary concentrations are very high.[427]

Clinical trials of pivmecillinam against ESBL-producing Enterobacteriaceae are limited to case series. In one small trial pivmecillinam was used alone with 30/39 patients receiving 400 mg three times daily and 9/39 receiving 200 mg three times daily. Dosage did not clearly affect the cure rates regardless of whether the UTI was complicated. Twenty-eight patients were noted to have calculi, prostatic hypertrophy or urinary catheters (i.e. complicated UTI) and six of these were bacteriological failures. Two other bacteriological failures were seen among the remaining 11 patients. Bacteriological cure was attained in 31/39 (79% overall), but five relapsed; clinical cure was attained in 16/19 patients but the rest were lost to follow-up.[428] There is no theoretical, trial or practice evidence to support a regimen with a loading dose of 400 mg followed by 200 mg three times daily, which has been recommended in the UK as a compromise.[429] A population-based Norwegian study of pivmecillinam treatment of community-acquired UTIs examined the impact of MICs and ESBL production in *E. coli*; it is not clear whether this was restricted to uncomplicated lower UTIs, for which, alone, pivmecillinam is licensed.[430] A total of 343 patients were included, of whom 158 (46%) were treated with pivmecillinam. Eighty-one patients had infections caused by ESBL-producing *E. coli*, and 41 (51%) received pivmecillinam as the primary treatment, usually at a dose of 200 mg three times daily for at least 7 days. Mecillinam MICs were higher for ESBL producers than non-producers: 68% of strains had CTX-M Group 1 enzymes (including CTX-M-15) and 28% had Group 9 enzymes (including CTX-M-9 and -14). Treatment failure was (atypically) defined as a new antibiotic prescription appropriate for UTI within 2 weeks of the initial therapy or failure to clinically improve. Clinical treatment failure with pivmecillinam was observed in 18 (44%) patients infected by ESBL-producing strains and in 16 (14%) patients with ESBL non-producing strains. Mecillinam MICs for isolates from treatment failures ($n = 34$, 18 ESBLs) averaged 2 mg/L (range 1–4 mg/L) compared with MICs of $<$1 mg/L for all isolates from treatment successes ($n = 124$, 23 ESBLs). Treatment failures occurred in 50% of cases with mecillinam MICs of 2 mg/L, rising to 63% at MICs of 4 mg/L This compares with a EUCAST breakpoint of S $\leq$8 mg/L, R $>$8 mg/L for mecillinam, again suggesting inadequate levels or too high a breakpoint. Multivariate analysis showed that ESBL status (OR 3.2, 95% CI 1.3–7.8; $P = 0.009$) and increased MIC of mecillinam (OR 2.0 for each doubling value of MIC, 95% CI 1.4–3.0; $P < 0.001$) were associated with pivmecillinam treatment failure. Treatment failure rates above 25% were associated with mecillinam MICs $\geq$2 mg/L for ESBL producers and $>$4 mg/L for isolates lacking ESBL. From the transconjugant study cited earlier it is likely that UK CTX-M-15-producing isolates will be in this more-resistant category and will respond poorly if pivmecillinam is used alone. This study must be seen also in the context of the earlier studies on the doses necessary to achieve adequate urinary concentrations.

There has been controversy over whether studies should be repeated with higher doses, such as 400 mg three times daily, but a more effective action to improve cure rates may be combined use of a regimen of 200 mg three times daily together with amoxicillin/clavulanate at 375 mg three times daily. We recommend this combination if oral pivmecillinam follow-on therapy is prescribed following hospital or OPAT intravenous treatment for UTI involving an ESBL producer. Co-administration of amoxicillin/clavulanate may not only provide efficacy via inhibition of ESBL but also 10- to 100-fold bactericidal synergy by combining amoxicillin's action on PBP1 and 3 and mecillinam's action on PBP2.[431]

Future use of co-amoxiclav, rather than clavulanate without amoxicillin, in combination with mecillinam is partly supported by a high-quality double-blind multicentre RCT of mecillinam and ampicillin-congeners without clavulanate in pyelonephritis in 1995, in the era before CTX-M enzymes. Equivalent results to cefotaxime/cefadroxil were achieved with an oral switch from parenteral mecillinam (no longer available) and ampicillin to pivmecillinam (at 400 mg three times daily) plus an oral ampicillin prodrug, suggesting that synergy of amoxicillin and pivmecillinam potentially would be clinically useful in follow-on therapy for pyelonephritis. In modern circumstances, including against ESBL producers, this efficacy might be restored by protecting both mecillinam and amoxicillin by using them with clavulanate. A clinical success rate of 93% for pivmecillinam as against 53% with pivampicillin in a study in 1986 of pyelonephritis suggests the drug has activity in the upper urinary tract.[432] However, it is important to note that clinical trials of the combination of amoxicillin/clavulanate with pivmecillinam have never been undertaken in pyelonephritis, and pivmecillinam has no licence for pyelonephritis.

Further clinical comparative studies with outcome data are urgently required for pivmecillinam, with and without clavulanate (probably administered as amoxicillin/clavulanate), for both complicated (including upper urinary tract) and lower UTI against ESBL producers. Amoxicillin/clavulanate, unlike clavulanate alone, is available and licensed for upper UTI. These trials would determine pivmecillinam's role and its potential to reduce the need for hospitalization or OPAT admissions to administer intravenous agents active against ESBL producers.

Pivmecillinam is claimed to have a minimal effect on the intestinal and vaginal flora of the host with little selection for resistant bacteria, vaginal *Candida* or *C. difficile*.[433] However, the earlier study[426] suggests it markedly reduces faecal *E. coli*, at least in children. In an *in vitro* human gut model, it did not elicit *C. difficile* germination, proliferation or toxin production, suggesting that superinfection with this pathogen should be rare if the drug is used alone.[434] Clinical studies with pivmecillinam/amoxicillin/clavulanate regimens should include studies on persistence of ESBL-producing *E. coli* gut colonization and new infections with *C. difficile*.

Overall there are uncertainties about how pivmecillinam should best be used in the modern era. The drug has very valuable potential and these uncertainties need resolution by large clinical trials, which are now urgent. Selection for resistant strains (such as SHV producers) in the interim would be unfortunate and for this reason we await further substantive trials and action and do not include its use alone in our general recommendations.

Evidence

Pivmecillinam is a prodrug for mecillinam and is the sole oral β-lactam (excluding tebipenem and faropenem, which are available only in Asia) with some activity against ESBL- and AmpC-producing organisms. It has a European licence, and is widely and effectively used for lower UTI in some countries. Parenteral mecillinam has been manufactured in the past but is now unavailable.

Evidence level: 2++

Pivmecillinam has no published clinical trials against CPE and *in vitro* activity appears poor or non-existent.

Evidence level: 4

Urinary levels following doses of 200 mg three times daily are inadequate to inhibit some ESBL-producing MDR GNB, including some with CTX-M-15 considered susceptible by the current EUCAST breakpoint (S $\leq$8 mg/L).

Evidence level: 3

Failure rates with 200 mg of pivmecillinam three times daily used alone against lower UTIs due to ESBL-producing *E. coli* are too high to recommend regular use in such infections. A higher dose, 400 mg three times daily, has been proposed but there is no convincing evidence to show it is more effective. Comparative studies with fosfomycin have not been reported but there are no suggestions of such ESBL-related failures in existing fosfomycin studies in the absence of resistance.

Evidence level: 3

There are inadequate trial data to support the use of pivmecillinam in *Klebsiella* infection, especially where the strain responsible produces ESBLs.

Evidence level: 4

In vitro evidence and early trials of combination with ampicillin or pivampicillin suggest that a useful measure to increase efficacy would be combination with amoxicillin as well as clavulanate (see below).

Evidence level: 2+

In vitro studies suggest that clavulanate (available clinically only as amoxicillin/clavulanate) would protect mecillinam from destruction by ESBLs and lower its MICs for Enterobacteriaceae. If pivmecillinam is prescribed as follow-on to OPAT or inpatient treatment, use of the combination is recommended.

Evidence level: 3

Clinical trials of pivmecillinam alone versus pivmecillinam with amoxicillin/clavulanate in lower UTI would be in the public interest. These should be sized to give information on efficacy against ESBL-producing bacteria and should include studies on the bowel flora and associated recurrence rates and *C. difficile*. If results of combination treatment are satisfactory, consideration should be given to trials in upper UTI, including economic assessment against OPAT treatment. Comparative trials with nitrofurantoin or fosfomycin trometamol for MDR GNB lower UTI are also required.

Evidence level: 4

Recommendations

- Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility.
  Grading: Conditional recommendation for
- Treat lower UTI due to ESBL-negative *E. coli* with pivmecillinam at 200 mg three times daily: do not use for infections caused by Proteeae, *Klebsiella* or *Pseudomonas*. Some ESBL-producing

E. coli respond, but efficacy is poor against CTX-M-15 enzyme producers: dosing at 400 mg three times daily may be no more effective. Consider combination of the 200 mg dose with 375 mg amoxicillin/clavulanate for follow-on to parenteral therapy for such infections in hospital or OPAT.
Grading: Conditional recommendation for

- Requires clinical comparative trials in UTI in the public interest: (i) alone or together with amoxicillin/clavulanate for UTI involving ESBL-producing organisms, including particularly those producing CTX-M-15 enzymes; (ii) in uncomplicated lower UTI generally compared with fosfomycin trometamol and nitrofurantoin, as the relative advantages of these drugs have not been directly compared by industry over the least 10 years as MDR GNB have become more problematic.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

10. Managing urinary tract infection

10.1 Diagnosis and the need for treatment or prophylaxis

Because UTIs are the major group of infections due to antibiotic-resistant Gram-negative infections in primary care, we have chosen to make specific recommendations about their diagnosis and about specific antibiotic stewardship.

Good practice in differentiating urinary infections from other infections and asymptomatic bacteriuria is vital to reduce the unnecessary use of antibiotics. When clinical variables were examined in a validation study[435] of a previously derived predictive dipstick rule, based on having nitrite or both leucocytes and blood,[436] the positive predictive value for urinary infection was 82% for women with all three of cloudy urine, dysuria and nocturia. The negative predictive value for urinary infection was 67% when none of these three features was present.[436] When individual clinical features were considered alone, cloudy urine or dysuria was predictive of UTI, but nocturia or smelly urine was not,[435] which brings into question its value in the assessment above of the combination of cloudy urine, dysuria and nocturia. In women aged 17–70 years with uncomplicated UTI, the negative predictive value when nitrite, leucocytes and blood are ALL negative was 76%.[435] The positive predictive value for having nitrite alone or nitrite together with either blood or leucocytes was 92%.[435] A systematic review of diagnostic studies found that the presence of vaginal discharge or vaginal irritation reduced the probability of urinary infection to 20%–30%.[437]

Several different studies have shown the prevalence of asymptomatic bacteriuria is about 6% in men and 16% in women aged over 65 years[438] and is higher in older age groups and in the institutionalized elderly. In a cohort study, 1173 elderly female residents without catheters in care homes were followed for 9 years with urine cultures every 6 months.[439] No relationship was found between ever having had asymptomatic bacteriuria and death after adjusting for covariates (HR 1.10, 95% CI, 0.78–1.55). The death rate in the group who never had asymptomatic bacteriuria was similar to that in those who had bacteriuria but either received no treatment or were treated ($P > 0.2$).[439] The lack of benefit in treating asymptomatic bacteriuria was confirmed in another smaller study: neither mortality nor the frequency of symptomatic episodes was reduced, but for every three women with asymptomatic bacteriuria in a care home given antibiotics (the type was not specified in this study), one experienced adverse effects (such as rash or gastrointestinal symptoms).[440] Cumulatively, 3%–6% of people acquire bacteriuria per day of urinary catheterization even with best practice for insertion and care of the catheter, and therefore many older people with long-term catheters have bacteriuria.[441,442] Intermittent catheterization is associated with a lower incidence of asymptomatic bacteriuria than long-term catheterization.[443] Catheterized patients should only receive antibiotic treatment when they are systemically symptomatic, to reduce the risk of colonization by antibiotic-resistant bacteria.[441,442] Differentiating UTI from asymptomatic bacteriuria can be particularly challenging in elderly patients with dementia as they cannot always describe their symptoms. A positive urine culture or dipstick test will not differentiate between UTI and ASB.[439] Patients with asymptomatic bacteriuria may have white blood cells in the urine just as in true infection. In older patients, including those with dementia, diagnosis should be based on a full clinical assessment, including vital signs.

A Canadian RCT of a diagnostic and treatment algorithm for UTI implemented in care homes, using a multifaceted approach, reduced antibiotics for urinary indications by 31% compared with control care homes, with no increase in hospital admissions or mortality.[444] Patients were considered for antibiotic treatment based primarily on presence of fever greater than 37.9°C or 1.5°C increase above baseline on at least two occasions over last 12 h and one or more signs of UTI.[444] The full algorithm used is shown in Figure 5. Fewer courses of antibiotics for suspected UTIs per 1000 resident days were prescribed in the intervention nursing homes than in control care homes (1.17 versus 1.59 courses per 1000 resident days). Antimicrobials for suspected UTI represented 28.4% of all courses of drugs prescribed in the intervention nursing homes compared with 38.6% prescribed in the control care homes (weighted mean difference –9.6%, 95% CI −16.9% to –2.4%). No significant difference was found in admissions to hospital or mortality between the study arms.

In recurrent UTI, deciding whether to give prophylaxis is a balance between the benefits of reducing symptomatic relapse and pyelonephritis versus side effects and the risks of selecting antibiotic resistance. Guidance is based on a systematic review of 19 trials. Nightly prophylaxis in non-pregnant women with recurrent urinary infection showed that prophylaxis reduced the relative risk (RR) of having one microbiological recurrence by 5-fold (RR 0.21, 95% CI 0.13–0.34), giving a number-needed to treat (NNT) of 1.85 over 6–12 months.[445] However, adverse effects occurred, particularly following nitrofurantoin, and 30% of women did not adhere to treatment. Any benefit was lost as soon as the prophylaxis stopped. Post-coital antibiotics were equally effective as nightly prophylaxis.[445,446] Previous studies before the rise in resistance showed the same effect with post-coital single-dose cefalexin when used for recurrent urinary infection in pregnancy.[447] If recurrence is not too frequent it may be better to provide the patient with standby nitrofurantoin, to take as soon as symptoms occur; this approach was shown to result in less use of antibiotics and intuitively should result in less antibiotic resistance. Studies with cefalexin before the rise of ESBLs showed a slight increase in use, with post-coital cefalexin offset considerably by antibiotics used in treatment of UTI recurrences.[448] The offset needs to be taken into account in individual patients if standby nitrofurantoin is used. Prophylaxis, if used, can usually be stopped after a year without a resumption of the recurrences[405] and there are now European guidelines that this review should be made at 6 months.[449] The increase in trimethoprim resistance makes prophylaxis with this drug less suitable than it was and prolonged nitrofurantoin is associated with an increased risk of unwanted pulmonary damage, although this is rare. Patients on prophylaxis for >6 months should be reviewed. If the patient wishes to continue with a prophylactic regimen, consideration should be given in advance as to which antibiotic would be appropriately substituted for trimethoprim, nitrofurantoin or indeed ciprofloxacin (which can also be used in prophylaxis), if resistance develops or a breakthrough infection occurs. Persisting with an agent where breakthrough with a resistant strain has occurred will be ineffective. Cranberry juice prophylaxis is less effective in preventing breakthrough infection but co-trimoxazole generates more multiple resistance in breakthrough strains.[450] Prophylaxis with β-lactam antibiotics commonly selects for resistant Enterobacteriaceae in the faecal flora and is not recommended.[451] There are relevant studies of prophylaxis after symptomatic UTI in infants who show similar problems with emergence of resistance on continuous prophylactic antibiotics, including resistance to cephalosporins due to ESBL production.[452,511]

NICE notes that prophylactic antibiotics given at catheter change or insertion do not reduce infections in those with urological conditions and recommends that they should not be used;[453] such use for any indication contributes to pressure on emergence of resistance and should be avoided. NICE recommends that clinicians should consider antibiotic prophylaxis at change of catheter for patients who: (i) have a history of symptomatic UTI after catheter change; or (ii) experience trauma during catheterization (frank haematuria after catheterization or two or more attempts of catheterization). Placement of an incontinence implant is also an indication for short-term prophylaxis but the recent insertion of an orthopaedic implant is not.

Evidence

Specific symptoms and signs hitherto accepted as characteristic of urinary infection have different predictive values.

Evidence level: 1+

In women with uncomplicated urinary infection the highest positive predictive value for strip testing was for having nitrite alone or nitrite with either positive leucocyte esterase or blood.

Evidence level 1+

There is no patient benefit in treating asymptomatic bacteriuria except in pregnancy.

Evidence level: 1+

Using an algorithm based on fever and at least one sign of urinary infection reduces the number of antibiotic prescriptions in nursing homes.

Evidence level: 3

Treatment or prophylaxis with antibiotics in catheterized patients increases colonization by antibiotic-resistant strains.

Evidence level: 1+

Prophylactic antibiotics given short-term at catheter change or insertion do not reduce infections but are indicated with specific criteria of: (i) traumatic catheterization; (ii) previous severe symptomatic infection on catheter change; or (iii) to cover placement of a urinary continence implant.

Evidence level: 4

In recurrent UTI, antibiotic prophylaxis is very effective whether given daily (Evidence level: 1++) or post-coitally (Evidence level: 1+) but an alternative is to consider pre-prescribed standby antibiotics to take at the onset of symptoms.

Evidence level 4.

If prophylaxis is used and effective it should be usually restricted to 6 months prescription.

Evidence level 3

Previous resistances or breakthrough of resistant isolates on prophylaxis should preclude use of an agent and consideration should be given to unwanted effects with long courses and what antibiotic would be chosen for breakthroughs.

Evidence level 4

Recommendations

- Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Use dipstick tests, if no catheter is present, to confirm the diagnosis before prescribing, especially when symptoms are mild or not localized.
  Grading: Strong recommendation for
- For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients, especially in those with dementia.
  Grading: Conditional recommendation for
- Do not prescribe antibiotics in ASB in the elderly with or without an indwelling catheter.
  Grading: Strong recommendation for
- Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.
  Grading: Conditional recommendation for
- To reduce recurrent UTI, consider first the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis.
  Grading: Conditional recommendation for
- Where prophylaxis is used successfully for recurrent infection in adults limit use to 6 months.
  Grading: Conditional recommendation for

10.2 Choosing a suitable antibiotic

Choosing an antibiotic to which a uropathogen is susceptible is important, as UTI symptoms resolve more slowly when an inappropriate antibiotic is given.[454] All patients should be given advice on when to seek further medical advice, i.e. if their symptoms worsen (even if, after taking antibiotics, on the same day) or do not improve after several days. Treating patients with infections due to MDR GNB in the community is a challenge as oral antimicrobial treatment is preferred. ESBL-producing bacteria are generally resistant to trimethoprim, ciprofloxacin, amoxicillin and cephalosporins; susceptibility to amoxicillin/clavulanate is variable and interpretation by the laboratory is affected by different breakpoints used formerly by BSAC, and currently by EUCAST, or CLSI.

Local community antibiotic guidance should be informed by national and local surveillance data. An algorithm on choices based on the individual agents discussed is given in Figure 4. Choosing between fosfomycin, pivmecillinam and nitrofurantoin is difficult as there are no direct comparisons of these three antibiotics in infections due to ESBL-producing organisms. High failure rates with pivmecillinam may be due to the precise ESBL present and not using the drug in combination with amoxicillin/clavulanate, or possibly inadequate dosage: optimal ways to use the drug now in the UK have not been proven. In urinary infections due to non-ESBL-producing organisms, nitrofurantoin for 3 days (or 7 days, which is not significantly different from the results of a 5 day course)[410] and a single dose of fosfomycin have similar efficacy.[455,456]

In a systematic review of the length of antibiotic treatment for acute uncomplicated urinary infection before the rise in prevalence of ESBL-producing Enterobacteriaceae, therapy for 3 days, delivered in the case of fosfomycin trometamol by a single 3 g dose, was similarly effective to prolonged therapy in achieving symptomatic cure for cystitis.[512] However, in this systematic review bacteriological failure rates in the subgroup of trials where the same antibiotic was used in both short and long treatment arms of the trial were higher in the short-duration arms (RR 1.37, 95% CI 1.07–1.74; $P = 0.01$). After a single dose of fosfomycin, high concentrations are usually maintained in the urine for 2 days. This is usually curative in uncomplicated UTI in women, but for infection due to confirmed ESBL producers, or in males, a second dose on the third day has been suggested to promote bacteriological cure.[457] On the same basis 7 not 3 days of nitrofurantoin would be recommended for confirmed ESBL-producing bacteria and 7 days for pivmecillinam regimens. Although frequently used as an endpoint in regulatory trials, it is uncertain if bacteriological cure immediately after treatment is of any long-term clinical or bacteriological significance in patients with UTIs involving MDR GNB, but the precautionary principle of adequate elimination of infections with MDR GNB would suggest regimens for best bacteriological cure should be followed in such cases. Eight studies in the systematic review included pivmecillinam at various doses and durations. An analysis of *E. coli* strains from persistent or relapsed infection after pivmecillinam showed an increased frequency of phylogenetic group B2 (which includes ST131) and showed that, when matched by virulence factors, 7 days of treatment was preferable to 3 days of therapy because it was less likely to be followed by persistence or relapse.[458] Studies of urinary infection with strains producing the CTX-M-15-ESBL suggest that pivmecillinam alone at 200 mg three times daily is inadequate treatment. *In vitro* studies suggesting use with amoxicillin/clavulanate have not been followed by clinical trials.

Based on evidence collected before the spread of ESBL-producing strains, nitrofurantoin (100 mg twice daily) should be given for 3 days, not 7 days, for fully susceptible strains. No trials of nitrofurantoin 100 mg twice daily with ESBL-producing strains have been published, although the antibiotic is widely used. Efficacy, relapse/recurrence rates or incidence of spread to the upper urinary tract or bloodstream are all uncertain and no studies have been published on the emergence of resistance during or after treatment or in relapses. MDR *Klebsiella* spp., but not *E. coli*, are commonly resistant to nitrofurantoin but the mechanisms for resistance in the UK have not been investigated recently.

Evidence

Local community antibiotic guidance on empirical treatment of urinary infection should be informed by national and local surveillance data.

Evidence level: 4

In lower uncomplicated UTI where risk factors for MDR GNB are present these four treatment options can be used rather than trimethoprim:

(i) Fosfomycin trometamol.

Evidence level: 2+

(ii) Nitrofurantoin (unless patient's eGFR is less than 45 mL/min/1.73 m^2).

Evidence level: 2+

(iii) Pivmecillinam, but *in vitro* and clinical data suggest this is less successful than fosfomycin trometamol or nitrofurantoin for ESBL-producing bacteria likely to be present in the UK.

Evidence level: 3

(iv) Another other relevant antibiotic if the causative organism is confirmed as susceptible.

Evidence level: 4

Recommendations

- Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI.
  Grading: Strong recommendation for
- If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility testing
  Grading: Strong recommendation for
- Always inform the patient or their carer(s) on what to look out for and how to re-consult if symptoms worsen or do not improve as community-onset *E. coli* bacteraemias of urinary origin are increasing.
  Grading: Strong recommendation for
- Use fosfomycin, or nitrofurantoin or as third-line choice pivmecillinam, guided where possible by: (i) susceptibility testing; and (ii) this guideline's recommendation on choice, combinations, dosing and duration, for uncomplicated lower UTI where MDR GNB are suspected.
  Grading: Strong recommendation for
- Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3 g orally as a single dose, and repeat on the third day only if MDR GNB are confirmed to improve bacteriological cure. Pivmecillinam at 200 mg three times daily for 7 days may be a third-line choice but consider combination use with amoxicillin/clavulanate. Clinical trial results on pivmecillinam for MDR GNB in the UK are urgently required.
  Grading: Conditional recommendation for

10.3 Treatment of pyelonephritis and complicated UTI caused by MDR GNB

Whenever resistant pathogens are anticipated, it is essential to send a urine specimen for culture and susceptibility testing before empirical treatment and such specimens will be useful in this condition even if resistant pathogens are not anticipated.

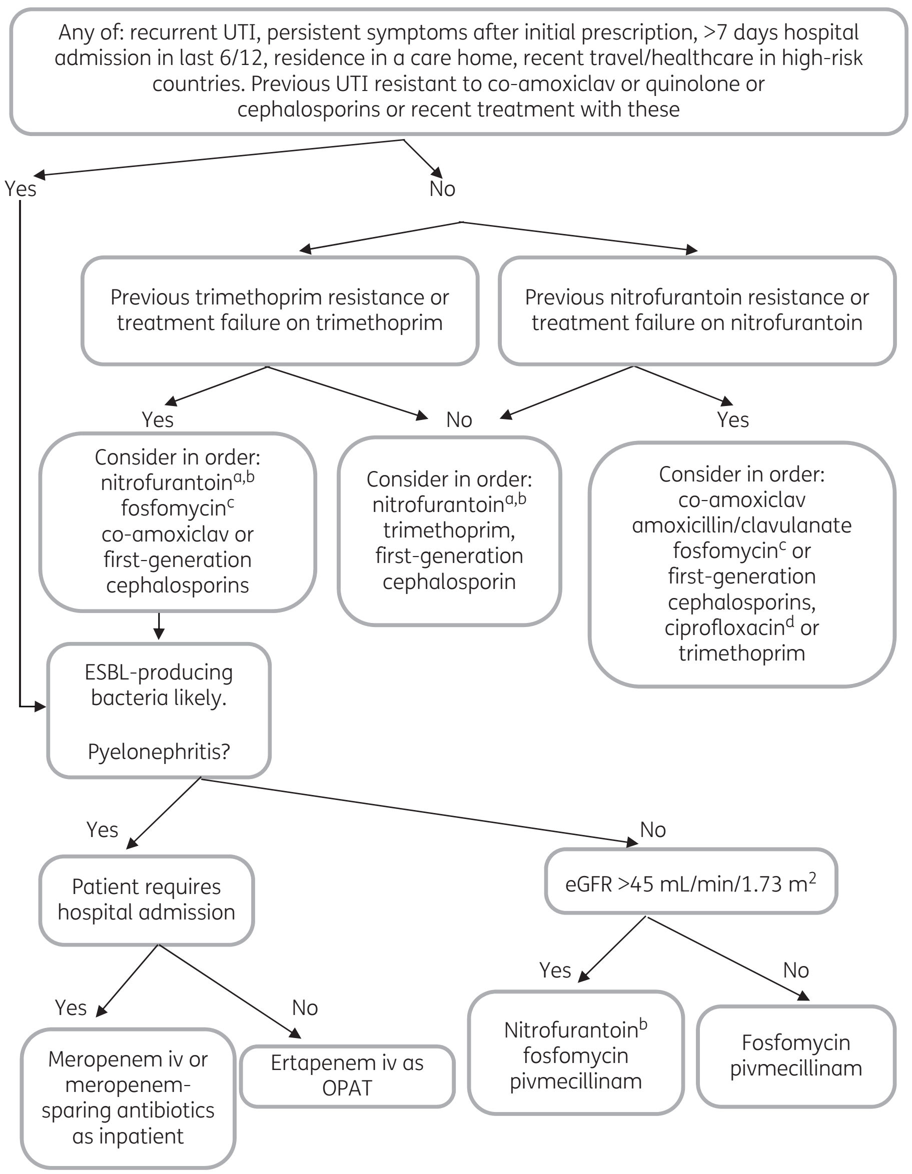

Figure 4. Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB. [a]Not nitrofurantoin if pyelonephritis or eGFR <45 mL/min or age <50 years. [b]Caution regarding prolonged/frequently repeated courses. [c]Not fosfomycin if pyelonephritis. [d]Unlike co-amoxiclav, first-generation cephalosporins, fosfomycin and pivmecillinam, ciprofloxacin is generally active against *Proteus vulgaris*, *Morganella* and *Providencia*.

As nitrofurantoin, pivmecillinam and oral fosfomycin are currently considered inappropriate in suspected or confirmed pyelonephritis, intravenous ertapenem (unlicensed in Europe for this indication) should be given in an OPAT setting to treat patients with pyelonephritis confirmed or suspected to be caused by ESBL-producing pathogens that are resistant to trimethoprim and quinolones.[163,164] If the patient requires admission to hospital, meropenem or, depending on costs and local policy, ceftolozane/tazobactam or temocillin should be given for infection due to ESBL-producing strains. Piperacillin/tazobactam may be considered if the isolate has been shown to be susceptible. Amikacin might be considered but activity may be impaired if AAC(6′)-Ib-cr is produced. In practice strains with this enzyme may be reported as either susceptible or resistant and the enzyme cannot easily be detected: no trials of amikacin use against such strains have been reported. Measuring amikacin levels promptly and adjusting doses is less likely to be easily supportable than use of gentamicin, but the latter is unsuitable for infection with ESBL producers unless susceptibility is known.

Ceftazidime/avibactam or non-β-lactam agents in combination perhaps with meropenem should be considered for infections with CPE (Figure 4). Temocillin may have a place for more susceptible strains with KPC carbapenemases but this has not been established by trials; it does not have a role against strains with MBLs or OXA-48-like carbapenemases. Such factors and choices are important when empirically treating pyelonephritis caused by probable or confirmed MDR GNB as this may be complicated by bacteraemia.[94]

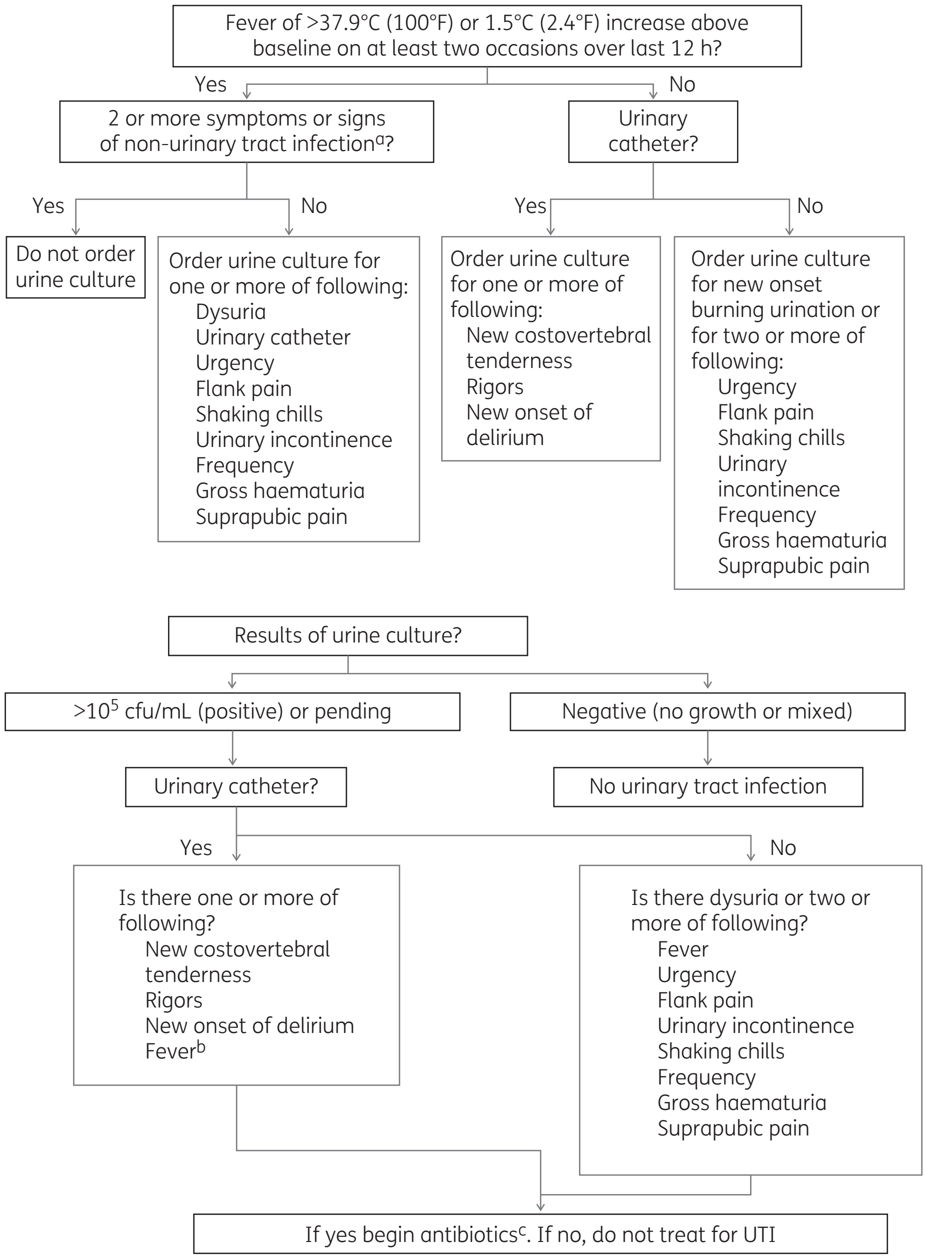

Figure 5. Diagnostic algorithm for ordering urine cultures and starting antibiotics if positive for nursing home residents in the intervention arm in the Loeb trial.[444] Reproduced from 'Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomized controlled trial' *BMJ* 2005; **331**: 669, with permission from BMJ Publishing Group Ltd.[444] [a]Respiratory symptoms include increased shortness of breath, increased cough, increased sputum production and new pleuritic chest pain. Gastrointestinal symptoms include nausea or vomiting, new abdominal pain and new onset of diarrhoea. Skin and soft tissue symptoms include new redness, warmth, swelling and purulent drainage. [b]>37.9°C (100°F) or 1.5°C (2.4°F) above baseline on two occasions over last 12 h. [c]Stop antibiotics if urine culture is negative or no pyuria is present.

If a patient with pyelonephritis due to ESBL-producing bacteria has penicillin or cephalosporin hypersensitivity, there are two alternative strategies. Firstly meropenem can be given despite a risk of cross-allergenicity, which is now thought to be largely hypothetical. In this case caution must be exercised, with appropriate drugs ready to treat any severe acute reaction. This seems to be safe.[154] Alternatively, urgent susceptibility tests by automated methods should be performed. Depending on any previous results for the patient's isolates, intravenous gentamicin or amikacin (which has more auditory than vestibular toxicity but a lower resistance rate than gentamicin) may initially be used until a less-toxic antibiotic can be identified from the concurrent susceptibility testing. Trimethoprim, ciprofloxacin or co-amoxiclav can be used in pyelonephritis if the pathogen is known to be susceptible (or a susceptible organism has been isolated in the preceding month with a satisfactory therapeutic response). A retrospective cohort study of community-onset acute pyelonephritis due to ESBL-producing *E. coli* compared 85 patients receiving carbapenems with 67 receiving other agents to which the infecting bacterium was susceptible *in vitro*. There was no difference in rates of clinical or microbiological failure.[459] A randomized double-blind controlled trial showed that 7 days of ciprofloxacin 500 mg twice daily was as effective as 14 days of trimethoprim/sulfamethoxazole against susceptible organisms. However, trimethoprim and quinolone resistance are now common and therefore none of these agents remains suitable for empirical use in any case of pyelonephritis.[460] The substitution of OPAT therapy for oral antibiotic use in early pyelonephritis has not been costed for its effects on services.

Evidence

Pending antibiotic susceptibility testing, patients at increased risk of MDR GNB and suspected of pyelonephritis or complicated UTIs (i.e. indwelling catheter, recent urinary instrumentation, renal stones, prostatic obstruction, diabetes, immunosuppression, pregnancy, functional or anatomical urological abnormality)[437] can be treated empirically with:

(i) OPAT with intravenous ertapenem.
Evidence level: 2+

(ii) Admission for (a) intravenous meropenem, temocillin or ceftolozane/tazobactam if infected by ESBL-producing *E. coli* or *Klebsiella* spp.; (b) intravenous fosfomycin and colistin with or without meropenem or ceftazidime/avibactam therapy if infected by a susceptible carbapenemase producer.
Evidence level: 1+
If hypersensitive to penicillin treat with meropenem with caution or gentamicin (if no past evidence of resistance) or amikacin.
Evidence level: 4

(iii) Trimethoprim, ciprofloxacin or co-amoxiclav if urine testing shows an organism that was susceptible in the preceding month and there has been no history of clinical failure.
Evidence level: 1+

Recommendations

- In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for an MDR isolate, including travel. Use an active oral agent only if the patient is well enough and if known to have had ciprofloxacin-, trimethoprim- or co-amoxiclav-susceptible MDR GNB in last month.
  Grading: Conditional recommendation for
- If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalization not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL- and AmpC-producing Enterobacteriaceae. If the patient needs hospitalization, or OPAT is not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of a CPE organism. If the patient is penicillin hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.
  Grading: Strong recommendation for

10.4 What is the threshold level of resistance for changing the choice of empirical treatment for UTIs?

Most patients with UTI are treated empirically, particularly in a first episode of lower UTI. Failure of empirical therapy, particularly in complicated UTI (e.g. pyelonephritis), is a common source of Gram-negative bacteraemia where increased 30 day mortality is associated with ineffective empirical therapy,[256,461] though perhaps only in patients with sepsis syndrome. The probability of ineffective empirical therapy would be predicted to increase as the proportion of ESBL-producing, or carbapenem-resistant, bacteria rises. Older narrower-spectrum antibiotics may be recommended for empirical use in order to slow the emergence of resistance. One group of authors asserts that the right of future patients to come to less harm outweighs the right of the present patient to share in decisions on antibiotic treatment,[462] but this is a view many do not share. There is no agreement within the Working Party on the threshold resistance rate to an antibiotic that would justify substitution of other agents, nor on the degree to which routine laboratory testing of submitted samples overestimates the 'true' resistance rate.[463] Rates of 20% have been suggested as justifying a change of empirical treatment in UTI. Confounders are: (i) that resistance rates are affected by duplicates within the series, including when infection control sampling is intensive;[464] (ii) a bias towards performing culture and susceptibility only for difficult/unresponsive cases; (iii) sequential testing of second-line agents only for resistant strains according to local laboratory policy;[117] and (iv) differences in breakpoints between laboratories. These sources of variation may justify central susceptibility testing of all UTI from sentinel groups of general practitioners (GPs) in regions for national surveillance purposes or requirements for national notification and annual updating of method changes and assessment of their effects.[465] Local and regional variations exist in resistance rates for ESBLs as demonstrated by regional and national surveys. Quinolone resistance rates in *E. coli* are below 20% in most reported susceptibility surveys but resistance in bacteraemia is associated with increased mortality and with the ST131 group of strains, which have an unrivalled ability to acquire other resistances. The risk of selection for resistance with a switch from trimethoprim leads us not to recommend their widespread use.

When the probability of bacteraemia arising from UTI rises, a lower threshold for altering normal treatment to cover a resistant strain is needed owing to the greater risk to the individual patient. A threshold of $<$5% resistance may be appropriate for higher-risk situations.

Evidence

There are no accurate current figures on the prevalence of antibiotic resistance in UTI. Routine clinical data are subject to sample bias. These probably lead to overestimated resistance.

Evidence level: 2−

A threshold of 20% true resistance has been suggested as an indication to change 'first-line' empirical treatment of lower UTI. A lower threshold of, perhaps, 5% is appropriate when the risk of the patient becoming bacteraemic is increased. The Working Party consider that, in the absence of accurate national resistance surveillance, these or similar thresholds presently can only be applied at a local laboratory level with (i) careful de-duplication,

(ii) precisely understood testing policies, and (iii) consistent local methodology.

Evidence level: 4

Recommendations

- Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy in UTI are necessary, including recommendations where the risk of antibiotic-resistant bacteraemia is high.
  Grading: Conditional recommendation for
- Personalize empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing, including the presence of MDR GNB in the patient or unit.
  Grading: Conditional recommendation for

11. What effect does good antibiotic stewardship have on rates of MDR GNB?

11.1 The impact of good antibiotic stewardship in secondary/tertiary care facilities

The evidence base and practice of antibiotic stewardship in the UK has been recently promulgated in the PHE 'Guidelines for Antimicrobial Prescribing and Stewardship Competencies'[466] and the guidance from NICE Guideline 15 'Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use'.[467] This report will focus on aspects of stewardship that pertain to MDR GNB: more general aspects can be found also in the above sources. A Cochrane systematic review showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients might reduce antimicrobial resistance and that interventions to increase effective prescribing can improve clinical outcome.[468] Of the 89 studies cited to 2009 (reporting 95 interventions), 56 were interrupted time series (ITS), 25 were RCTs, 5 were controlled before–after studies (CBAs) and three were controlled clinical trials (CCTs). The reporting of outcomes was very variable (only 13/25 RCTs reported on mortality and only 5 on readmissions), complicating the comparative assessment of studies. Interventions that enhanced the quality of prescribing in patients (defined softly as prescribing in accordance with guidelines) with any infection had no effect on mortality whereas interventions to increase compliance with evidence-based guidelines in community-acquired pneumonia, usually due to Gram-positive *S. pneumoniae*, were associated with reduced mortality. Reducing prescribing for all indications, determined as excessive by reference to evidence-based guidelines, was associated with increased re-admission but not with increased mortality or length of stay. Restrictive and persuasive interventions were associated with improved prescribing outcomes based on median outcome effect (proportion of subjects with an improvement or change in antibiotic selection, dose, route or duration versus control). Multifaceted interventions were common but not necessarily more effective than simple interactions. Most (80/95, 84%) of the interventions targeted the antibiotic prescribed (choice of antibiotic, timing of first dose and route of administration). The remaining 15/95 interventions aimed to change exposure of patients to antibiotics by targeting the decision to treat or the duration of treatment. Only nine studies reported the effect of interventions on colonization or infection with antibiotic-resistant Gram-negative bacteria. Seven of these were ITSs, with a median effect size of 47%.[469–474]

Although most studies reported >25% reduction in colonization/infection with resistant Gram-negative bacteria, the confidence intervals were wide and in two studies the effects were not statistically significant[471,475] and one crossover study of cycling empirical gentamicin, ceftazidime and piperacillin/tazobactam showed an unintended increase of 39% in colonization with GNB resistant to any of the target drugs.[476] One cluster CCT in neonatal units showed, as intended, a reduction from baseline in colonization/infection of 68% by cefotaxime-resistant organisms, predominantly *E. cloacae*, when the initial empirical treatment was penicillin and tobramycin rather than ampicillin/cefotaxime.[477] That study, the only one of the nine to report on mortality, showed a small increase in mortality when penicillin and tobramycin was substituted for cefotaxime/ampicillin in matched neonatal units. A 2017 update of this Cochrane review[478] concluded that there was still no statistically significant evidence that antibiotic stewardship reduced multiple antibiotic resistance, although the impact on *C. difficile* is undoubted. Additionally this updated unwanted effects from stewardship interventions, including an aminoglycoside substitution producing acute kidney injury[282] (see Section 7.12) and studies where there was consequent delay in instituting antibiotics. Furthermore, some studies reported a disruption of interaction between physicians and infection specialists as guidelines were used more frequently. Nevertheless, an editorial on this review called for stewardship to be adopted in every healthcare institution.[479] One must now consider the homogeneity and quality of local hospital guidelines, given guideline compliance is being used as a criterion of good stewardship.

In the 2013 Cochrane review,[468] 11 studies of attempts to reduce excessive prescribing reported data on mortality with no significant overall effect seen (and this continued to be the case in the 2017 revision).[513] Interestingly, one of the ITS studies examined the impact of a switch from penicillin and gentamicin to penicillin and amikacin in a neonatal unit with gentamicin-resistant *E. cloacae* infections and showed a reduction in gentamicin-resistant *E. cloacae* but an increase is *E. aerogenes* and enterococci.[474]

Kaki *et al.*[480] produced another systematic review of antibiotic stewardship programmes, limited to the critical care unit. These included three RCTs, three ITSs and 18 uncontrolled before-and-after studies. Introduction of various antibiotic stewardship interventions led to 11%–38% reductions in antimicrobial DDDs/1000 patient-days (except in a single study that found an increase of 6%), and lower total antimicrobial costs. Stewardship programmes led to shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic-related adverse events. They also found some reductions in antimicrobial resistance rates extending beyond 6 months.

A meta-analysis of 52 ITSs was used to compare restrictive versus persuasive interventions.[468] Restrictive interventions had significantly greater impact on prescribing outcomes at 1 month (32%, 95% CI 2%–61%; $P=0.03$) and on microbial outcomes at 6 months (53%, 95% CI 31%–75%; $P=0.001$) but there were no significant differences at 12 or 24 months. Clinical outcome data were limited, with 11 studies reporting on all-cause mortality but with no defined time-boundary, 4 studies showing increased mortality and 7 finding decreased mortality, giving a non-significant overall effect (0.92, 95% CI 0.81–1.06; $P = 0.25$).

In the USA, the Department of Veterans Affairs (VA) recently commissioned a systematic review of antimicrobial stewardship programmes (ASPs).[481,482] The key findings have been published and the reader is referred to these publications for details.[483,484] To avoid duplication, the VA systematic review only included papers meeting their eligibility criteria but not included in the 2013 Cochrane review. The review reported mixed results for clinical/microbial outcomes and overall improvement in prescribing. Because (i) few studies of different interventions reported each outcome, (ii) there was inconsistency across studies and (iii) there was medium/high risk of bias, the strength of evidence for all clinical outcomes was low: no single ASP was found to be superior but amongst studies since 2000 the greatest body of evidence of effectiveness was for decreasing inappropriate or increasing appropriate antibiotic use. Effects were seen across all species of Gram-negative bacteria and broad-spectrum antimicrobials.

There are individual studies of high quality. Introduction of a stewardship programme in one US hospital reduced the use of broad-spectrum agents, and was associated with a reduction in hospital-acquired infections caused by MDR GNB from 37% to 8% over 6 years.[485] Similarly, resistance in *P. aeruginosa* declined when state guidelines on stewardship were implemented using a computerized programme in an Australian ICU.[486] In another study in Israel, a carbapenem-restriction policy was used as part of a successful infection control strategy also including emergency department flagging of colonized or infected patients, building an isolation facility, eradication of clusters, and environmental and personnel hand cultures, with rectal screening of 8376 patients. This was effective in controlling an outbreak of carbapenem-resistant *K. pneumoniae*. Although there was a significant reduction in meropenem use, prescription of colistin rose.[487] Restriction of use of some antibiotics may need, or lead to, use of a diversity of other agents and even introduction of newly available antibiotics or appropriate use of older agents. These aspects also need to be subject to stewardship with appropriate actions in responsible bodies within hospitals and reporting to users. This can be complex and time consuming. Some effective interventions are simple; for example, a high-quality study compared 8 and 15 day antibiotic treatment of ventilator-associated pneumonia ($n = 401$) and did not find any difference in mortality or unfavourable outcome. Patients who received 8 days of treatment had significantly less emergence of MDR pathogens (42% versus 62%; $P = 0.04$) but had a higher recurrence rate if they initially had non-fermenting organisms as pathogen [40.6% versus 25.4% (risk difference 15.2%), 95% CI 3.9%–26.6%].[488]

Effective antibiotic stewardship requires the use of timely bacterial antimicrobial susceptibility testing. Relatively simple phenotypic tests, such as a comprehensive antibiogram by automated methods, screening for resistance in bacteraemia isolates by direct disc testing,[514] double disc diffusion tests for ESBL, and biochemical carbapenemase detection, can provide useful information for treatment and infection control purposes.[515] Automated diagnostic tests for bacterial identification (e.g. MALDI-TOF) and PCR-based resistance gene detection (e.g. Cepheid® for carbapenemase and ESBL detection) can provide even more detailed information within the same day for MDR GNB. More rapid susceptibility testing methods for resistance detection are being developed. Further information may be found in recent reviews.[515–518]

This information together with promptly administered appropriate antibiotics is likely to improve prognosis. All UK laboratories should have access to the phenotypic and basic genotypic methods described above within their resources. As a performance measure, overall time elapsed from sample collection to administration of treatment appropriate to the bacterial susceptibility can and should be assessed and repeatedly audited against what could best be achieved with modern methods. Particular attention should be paid to MDR GNB as defined either for community- or hospital-originating strains. Audit of outcomes associated with bacteraemia provides an objective measure of the appropriateness of antimicrobial treatment, particularly for MDR GNB.

The deployment of antibiotic stewardship programmes is variable, as shown by a survey of 660 hospitals in 67 countries.[489] That study included the first data from sites in Asia, Africa and South America, many with considerable problems with MDR GNB. There is an urgent need for the adoption of an international antibiotic stewardship timetable.

Evidence

Up-to-date local resistance and outcome surveillance data are needed to inform guidelines on empirical antibiotic advice and must be persuasive to medical and nursing staff, to all prescribers and to pharmacists advising on guidelines.

Evidence level: 4

Interventions intended to decrease prescribing that is excessive (by reference to guidelines) for specific antibiotics have been associated with reductions in both colonization and infections caused by carbapenem, aminoglycoside or cephalosporin-resistant bacteria, but this is not a consistent finding across all stewardship initiatives.

Evidence level: 2++

Restrictive rather than persuasive prescribing interventions cause a significant short-term change in prescribing and there is scanty evidence that they may contribute to reductions in the prevalence of resistant GNB. Persuasive prescribing interventions should also be used and are as effective over a 1–2 year period.

Evidence level: 2++

Clinical outcome data on infections that is linked to antibiotic prescribing should be collected as well as data on resistance and prescriptions of antimicrobials to ensure stewardship approaches do not degrade outcomes, and ensure high and consistent standards between hospitals.

Evidence level: 2++

Audit and feedback should be used to reduce antimicrobial use in hospitals. Local and national advice on which antibiotics to prescribe are a useful standard against which to conduct audits and to explore clinical and microbiological outcomes.

Evidence level: 4

Recommendations

- Provide an on-going antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance with guidelines, surveillance of outcomes, and

active feedback.
Grading: Strong recommendation for

- Use restrictive prescribing policies to acutely reduce the incidence of infection, or colonization, with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor to check whether gains persist.
  Grading: Strong recommendation for
- Identify through horizon scanning, and make available, new antimicrobials that may be required to treat MDR GNB. Monitor their use through formulary/drug and therapeutics committees.
  Grading: Conditional recommendation for

11.2 The national monitoring of good antibiotic stewardship in secondary/tertiary care facilities

Antibiotic therapy differs from other treatment in man in being directed against diverse and frequently unknown organisms and in exercising selection for resistant organisms; these change the potential target for drug action and may then cause infection either in the same or other patients. Treatment options for infections due to MDR GNB are restricted and failure to deploy appropriate treatment in these infections may be associated with a poor outcome whereas excessive use of a single agent in a hospital or unit is more likely to select for superinfection caused by resistant organisms. The clinical governance of antibiotic policies is therefore a balance between treatment of the individual and management of the community's antibiotic armamentarium.

Antibiotic use and the prevalence of MDR GNB are now widely monitored in communities and hospitals but (i) monitoring use does not indicate whether use was appropriate, and (ii) monitoring the accumulative prevalence of resistant strains is no guide to the incidence rate of new cases caused by MDR GNB. Root cause analysis of individual cases is burdensome and very complex if it is intended to relate to outcome. It also runs the risk of bias with regard to outcome unless the proportions of resistant or susceptible organisms that are examined match the overall population. It does not produce reliable statistically comparable data between institutions to support good practice. Nevertheless, such comparisons were used with MRSA bacteraemia and *C. difficile* in the past in the UK, but these are acute events unlike the chronic prevalence of antibiotic-resistant strains.

Clinical trials early in a product's availability offer guidance on efficacy against susceptible organisms and, with some agents, an indication of potential for selection for resistance. However, antibiotic efficacy is not usually sustained as resistance emerges, and unlike other classes of drug, early clinical trials become less relevant with the passage of time. Anticipating when empirical therapy should include coverage against MDR GNB is difficult but is a key part of local guidelines. Recommendations that (i) limit use of broad-spectrum drugs such as carbapenems or (ii) reserve particular agents for patients with MDR GNB present in infections that have a potential high mortality need also to consider the potential hazard of poor clinical outcomes.

Despite assistance from other professions, deployment of infection and microbiology specialists into surveillance and away from patient care is frequent, and mundane tasks in surveillance employing specialists should be reduced to a minimum, without excessively compromising data quality. Routine national reporting systems on bacteraemia in the UK should be routinely linked to public health date-of-death data held nationally for each person by the Office for National Statistics, as has been described in one study restricted to *E. coli* bacteraemia.[102] Such linked information should be fed back annually to, and within, individual hospitals and summarized findings should be provided to hospitals to enable comparisons of performance. Incidence and mortality rates in bacteraemia at the local level would provide key assurance on the prevention of systemic infections and the quality of outcomes. If these data on outcome were provided by patients, it would provide a focus to examine and attempt to reduce the increasing incidence of bacteraemias and their associated mortality. Furthermore, these data would ensure locally that overall and specific audit could be made of the antibiotic resistance in organisms and the antibiotics actually deployed to treat the serious infections that they caused. Added to existing data, such audit and source information could nationally and locally identify locations where there is high mortality either in primary or secondary/tertiary care, enabling appropriate investigation and action to be taken locally. A crucial foundation has already been organized in England and Scotland via mandatory reporting of bacteraemia data for *E. coli* which specifically include, *inter alia*, data on community or hospital onset and nursing home residency entered locally by laboratories. In England, laboratories voluntarily and automatically (via computer links) submit antibiotic susceptibility data for 82% (54301/66512 over 2 years) of cases of *E. coli* bacteraemia reported by the mandatory programme, which does not itself capture susceptibility data. This could be built upon to deliver local and nationally useful data on outcome by antibiotic resistance.[94] Furthermore, this process should be expanded to capture mortality information on other important bacteraemias, e.g. *Klebsiella* spp., where prevalence is increasing and resistance is a major global threat, or indeed to all bacteraemias. Reduction in the absolute number of associated deaths from bacteraemia may well involve changes other than in chemotherapy, provided audit suggests chemotherapy is actively employed and appropriate. This requires multidisciplinary joint engagement and clinical management expertise in the community quite as much as in hospital to avoid sepsis and improve its management. A decrease in prevalence of bacteraemia and MDR within such infections is one aspect of this. Quantitative reduction in the number of deaths, and not changes in the comparative position of hospitals and communities in their respective peer groups, should be the focus.

Bacteraemias should be assigned reliably as being of community-, wider healthcare- or hospital-onset so that responsibility can be assigned and accepted for performance by relevant commissioning groups, public health services and hospitals. Whilst the date of sampling of bacteraemia can be recorded, patients may become colonized by the causative bacterium much earlier and the exact timing of acquisition usually cannot be proven from existing laboratory records. IT coordination and shared responsibility across the health economy is needed to access the last date of discharge from hospital, which may be a practical proxy for date of colonization in cases of apparent community acquisition that are actually hospital-acquired. Where care does not involve transfer to a tertiary centre and the patient is not being admitted to multiple hospitals in a conurbation, such information should already be available in many localities, but non-automated extraction is time consuming. It is important for securing improvement that the bacteria isolated from bacteraemias can be related to likely acquisition in hospital, wider healthcare or community and not simply to onset in hospital or community and that responsibility for resistant strains falls accurately on hospitals or community commissioners of healthcare. Targeting reductions in MDR GNB in potentially life-threatening infection is problematic because of variations between community populations in ethnic origin associated apparently with antibiotic resistance such as ESBL production.[4,137] For this reason a simple process of commissioned reduction in resistance may be unachievable in some communities and their associated hospitals.

Residence in a nursing home is a marker of healthcare acquisition, not general community acquisition, and nursing-home patients should be separately and reliably categorized. Dates of hospital discharge of patients admitted from nursing homes may be relevant to intervention if the patient has moved between the nursing home and hospital recently—say within the last 2 years.

Tertiary and international referral in some hospitals (including referrals from armed forces deployed overseas[490]), even if the hospitals are not formally categorized as specialist hospitals, may also skew their resistance profile towards multiple resistance,[491,492] so it is important to keep a balance between recognizing that this may be a reason for high resistance rates and ensuring that such resistant strains should be, as they always have been, a target for effective infection control. Again for this reason, targeting antibiotic resistance reduction appropriately within a national context may be more straightforward if it is directed at a local level.

Dates of collection of blood cultures, as recorded in laboratory computer systems, may be distorted by entry of default dates of registration on Monday mornings after submission of samples from Friday night on wards. There is no information on the frequency of this problem but it is time consuming to retrospectively correct or prospectively avoid. An interval of <3 days since admission is recommended for defining ‘community onset’ as more practical than the 48 h limit suggested internationally and probably without important consequence, if permitted. This should be investigated if the mandatory programme is expanded as recommended. Laboratory data should not be reported multiple times and should utilize as little manual entry as possible and hospital trusts should ensure the automated transfer of data from laboratory systems to monitoring bodies. Information transfer should be frequent. However in the presence of good infection control and absence of an ongoing MDR GNB outbreak, annual batch processing of mortality linkage and annual central audit should be adequate in most hospitals for governance monitoring of hospitals, and this would be adequate to support changes to infection management, including antibiotic policy (which are seldom made more frequently). Not only good performance in reducing antibiotic use but also better-than-average performance in bacteraemia reduction and better outcomes in bacteraemia (including that which is antibiotic resistant) should be rewarded.

Such laboratory-based extended surveillance of all bacteraemias would address: (i) the diversity of organisms and, at a local level, the match to antibiotics prescribed (which itself could be centrally reported, if pharmacy systems and laboratory systems are linked by patient/NHS number and then ordered by concatenated patient/NHS number and reversed Julian date); (ii) the usual, but not invariable, progression in antibiotic resistance rates; and (iii) the need for organizations to make changes to prescribing policy with document control, feedback to clinicians and corporate responsibility of CCGs and hospitals for infection management. To address bacterial species- and resistance-specific aspects in any locality, analysis (including trend analysis) of data cumulated over 5 years may be needed to avoid problems with small numbers of some pathogens. Individual hospitals need more local as well as the existing national data to systematically analyse, explain and address unsatisfactory outcomes. The already striking increase in incidence of *E. coli* bacteraemia, often in patients being admitted from the community, will probably increase further with better ascertainment of sepsis. Commissioning attention needs to be paid to the appropriateness of prior chemotherapy (i.e. for UTIs in the community) to attempt to reduce such rising incidence and associated mortality. Owing to the rise of MDR GNB, central monitoring of, and action on, informatics is required in all hospitals. Collation of information is required to explain clinical and resistance outcomes by patient and to plan action in hospital- and community-onset cases. Early Warning Scores, which are required for such analysis, are frequently now available on computerized systems to monitor vital signs. Separate patient-based prescribing systems record the date of prescription and antibiotics given. Laboratory data systems record: (i) the date of collection of the first positive blood culture for an organism-episode from a patient; and (ii) the organism and its antimicrobial susceptibilities. These datasets should be linked electronically along with, from hospital patient administration systems, the admission date, the date of last hospital discharge and place of residence (i.e. home or residential care). Early Warning Scores of 6 or more within 3 days of the bacteraemia indicate a poorer prognosis in bacteraemia, but these data are collected continuously and may be difficult to link as single values. The most difficult area to address is usually the unequivocal assessment of outcome. Mortality is associated with poor functional state and comorbidities, which may link to age and have been assessed automatically from computerized discharge records of diagnoses (ICDs or diagnosis-related group codes) in the USA[493] and France.[494] Defining mortality at a point less than 30 days after bacteraemia could tighten linkages to resistance and inappropriate prescribing, and should be studied. Acute renal injury is also a useful outcome measure, as is subsequent development of *C. difficile* infection within 28 days. Sometimes these linkages can be made expediently without linking systems by exporting data and linking it in databases or spreadsheets, but the mechanics of this should not be dependent directly and solely on infection specialists, although they must advise on what should be done.

Quality and commissioning organizations should ensure hospitals are collecting and analysing all such data to explain and improve their results in the treatment of serious infections such as bacteraemia, not just those with MDR GNB. Particular scrutiny of year-on-year improvement in outcome of bacteraemia and reduction in prevalence according to onset in hospital or the community is needed both in CCGs and hospitals. Application of enhanced definitions of place of likely acquisition, together with the Working Party’s definitions of multiresistance as applied to hospitals and the community and within the context of the local communities population make-up, may explain the reasons for, and sometimes enable multifaceted action on, problematic multiple resistance as a whole health economy approach. Hospital-, community–healthcare- and community-onset bacteraemia therefore require separate analysis.

Evidence

Key components of an effective antimicrobial stewardship programme are consistent effort and audit of outcome by specialists with full communication and support from electronic prescribing/laboratory and clinical records. Computerized systems can and should be integrated. Also required are full accountability of responsible organizations for occurrence of serious infections and the outcomes of treating them. Accurate information is required on serious infections with MDR GNB but must not be assessed in isolation.

Evidence level: 2+

Hospital or community antibiotic use (by DDDs, or perhaps better in the context of resistance selection, number of patients exposed to each agent) should be reviewed locally together with antibiotic resistance data. These datasets are available from pharmacy and microbiology systems respectively. Audit on compliance with local guidelines can be undertaken, but this provides no assurance on clinical outcome in severe infections; these require comparison with performance of other similar institutions and analysis to ensure the quality of care.

Evidence level: 2++

Extended surveillance of bacteraemia with appropriate record linkage both centrally and in the hospital would provide clinical outcome assurance in the most severe infections and also a means of comparing improvement in hospitals and communities. Furthermore, this would lead to a sharp focus on improvements to antibiotic guidance, usage and infection control

Evidence level: 2+

Recommendations

- Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare- and hospital-onset infections, and audit compliance with these.
  Grading: Conditional recommendation for
- Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemia's onset was in the community, wider healthcare or hospital, antibiotic resistances of isolates, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and, if possible, defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals.
  Grading: Good practice recommendation
- Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of Trusts and CCGs or equivalent primary care organizations annually. They should ensure computerized record linkage gives dates of death that can be added to, organism, specific antibiotic resistance and pattern, date of collection, nursing home residency, and optionally local records on last hospital discharge before bacteraemia. These data should be made available, for open interrogation and downloading, with rolling cumulative data within the health service. They should ensure mortality rate is categorized by locality (separately for hospitals and for community with associated separate wider healthcare data).
  Grading: Strong recommendation for
- Make publicly available tabulated incidence and outcome data for bacteraemia, giving hospital onset data by region and hospital, and, for community and wider healthcare outcome data, by CCG or equivalent primary care organization. Correlate these data with similar analysed and tabulated annual data on total antibiotic use and organism and antibiotic resistance in clinical infections.
  Grading: Good practice recommendation
- Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes for both, locally and appropriately within health economies.
  Grading: Good practice recommendation
- Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.
  Grading: Strong recommendation for

11.3 Antibiotic stewardship in the community and care homes to reduce MDR Gram-negative infections

Several RCTs in UK communities have shown that prescribing has been improved by multifaceted interventions that included (i) general practice staff education and (ii) education of the patient through improving communication during the doctor–patient consultation.[495,496] There have also been several Cochrane reviews that included studies in hospitals, but which should be transferable to the community and care homes, aiming to improve antibiotic prescribing. In one Cochrane review, restrictive interventions (selective reporting of laboratory susceptibilities, formulary restriction, and antibiotic policy change strategies) had a greater effect in the short term in reducing use of broad-spectrum antibiotics than persuasive interventions (distribution of educational materials; educational meetings; local consensus processes; educational outreach visits; local opinion leaders; reminders provided verbally, on paper or on computer; audit and feedback). However, both were equally effective in controlling antibiotic use and antimicrobial resistance after 6 months.[468] In a separate Cochrane review, printed educational materials alone had an effect on the practice of healthcare professionals and patient health outcomes.[497] Based on seven RCTs and 54 outcomes, the median absolute risk difference in categorical practice outcomes was 0.02 when printed educational materials were compared with no intervention (range from 0 to +0.11).[497] Other Cochrane reviews show multifaceted interventions are more effective. Moreover, interventions that are based on cognitive theories and consider personal attitudes, subjective norms and perceived behavioural controls (confidence and other barriers) are more likely to be successful, e.g. posters raise awareness and change subjective norms but are ineffective when used alone.

In an audit and feedback process, an individual's professional practice or performance is measured and then compared with professional standards or targets. The results of this comparison are then fed back to the individual. In general practices this will probably be via the medicine manager, local GP prescribing champions or in collaboration with local microbiologists. The aim is to encourage the individual to follow professional standards.[498] A Cochrane review considered 82 comparisons from 49 studies of any healthcare interventions in which audit and feedback were core and evaluated effects on professional practice.[498] There was a median

4.3% increase in healthcare professionals' compliance with desired practice (IQR 0.5%–16%) when: (i) baseline performance was low; (ii) the source was a supervisor or colleague; (iii) it was provided more than once; (iv) it was delivered in both verbal and written formats; and (v) when it included both explicit targets and an action plan. In addition, the effect size varied based on the clinical behaviour targeted by the intervention.[498] An RCT evaluating a multifaceted intervention in English general practice that was aimed at improving antibiotic prescribing included feedback of practice level data on antibiotic prescribing and resistance: this led to a 4.2% fall in total antibiotic use.[495] In some parts of the UK, audit with action plans, and intense infection control measures, have been associated with falls in quinolone and cephalosporin use and resistance.[4,499] Incentives attached to action plans can be very effective but, without personal attitude changes, the change may reverse when the incentive is reduced.[500] Any audit indicators need to be well monitored, as implementation of an effective multiple-intervention strategy achieved no reduction of antibiotic prescription rates when deployed at a larger scale in general practice: the authors attributed the failure to a less tight monitoring of the intervention and audit.[501] It is necessary to demonstrate by further study that such interventions can be effective at practice or hospital unit/hospital level.

Relevant outcomes, which should be monitored, include mortality from systemic infections such as bacteraemia, hospital admission, emergency room attendance, requirement for outpatient parenteral antibiotic therapy, re-consultation in person or by telephone, time-limited re-prescription of antibiotics and microbiological and clinical persistence of infection.

Evidence

Restrictive and persuasive interventions are equally effective in controlling antibiotic use and antimicrobial resistance and a multifaceted approach is most effective.

Evidence level: 1+

Audit and feedback interventions result in an increase in healthcare professionals' compliance with desired practice.

Evidence level: 1++

Local and national surveillance data are needed to determine appropriate empirical antibiotic guidelines.

Evidence level: 3

Collection and analysis of outcome data are important in assessment of measures needed to improve the management of infection and to reduce the increase in antibiotic use and resistance.

Evidence level 2+

Recommendations

- Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the community and care homes.
  Grading: Strong recommendation for
- Provide and use active feedback of monitoring to prescribers and nursing staff, ensuring optimization of clinical, microbiological and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.
  Grading: Strong recommendation for
- Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes.
  Grading: Conditional recommendation for

12. Conclusions

The selection of antibiotics for the treatment of infections caused by GNB has always been difficult. Following the introduction of the first antibiotics with activity against GNB, such as tetracycline, chloramphenicol and streptomycin, introduced in the late 1940s, resistance in *E. coli* causing UTI was observed at rates of 5%–10% as early as 1953.[502] Subsequently it emerged that Enterobacteriaceae can exchange and re-assort antibiotic resistance genes with great ease via plasmids, transposons, integrons and other mobile, or potentially mobile, genetic elements. This meant that resistances to antimicrobials no longer being used were easily and stably maintained as the relevant resistance genes commonly become genetically linked. These linked resistances became transferable to a wider and more versatile range of strains.

As each class of new agent was introduced, so resistance negated its reliable empirical use for the treatment of serious sepsis and also undermined any future reliance on the older agents. This is exemplified in the UK by the rise of plasmid-mediated TEM β-lactamase conferring resistance to ampicillin in the 1960s, aminoglycoside-modifying enzymes conferring gentamicin resistance in the 1970s, extended-spectrum TEM and SHV β-lactamases conferring cephalosporin resistance in the 1980s and, beginning in the 1990s, CTX-M ESBLs, DNA gyrase mutations and dihydrofolate reductases conferring resistance to third-generation cephalosporins, fluoroquinolones and trimethoprim, respectively. We are now facing a similar process with carbapenems and polymyxins.

The bacterial ability to maintain older resistances may undermine any benefit from the introduction of more resolute antibiotic stewardship. Over-reliance on stewardship as the sole strategy for reducing MDR GNB may not be productive, although reductions in antibiotic use, if they are substantial enough to reduce selection in the human microflora for resistant strains, are welcome. Use of a diversity of agents focused on proven bacterial infection may be more important than restricting[478] entirely the use of certain antibiotics and classes. Empirical prescribing based on generic clinical diagnoses will also need to be safely reduced.

Because of widely differing usage of antibiotics active against GNB in both medicine and agriculture in different parts of the globe since the 1980s, we have created widely differing rates of occurrence of MDR GNB in these different locations and in some cases between food animals and man. Furthermore, the increasing recognition of reservoirs of pathogenic *E. coli* and *Klebsiella* spp. in different animal species suggests that animal husbandry quality and control of these strains may be variable. Higher rates of MDR GNB pose therapeutic problems for these countries. In addition, over the last decade the movement of people, goods and food has resulted in countries such as the UK meeting unpredictable and alarming appearances of MDR GNB by importation.[49] Imported food-producing animals from overseas founder stock, and foodstuffs, need to be free of important antibiotic resistance in GNB to just as great an extent as returned travellers for biosecurity and as a foundation for enhanced antimicrobial stewardship.

In order to produce relevant guidelines for the empirical treatment of infections caused by MDR GNB, an understanding of the local epidemiology and susceptibility patterns is essential. The unpredictability of horizontal gene transfer and nosocomial spread may necessitate specific guidelines being produced for individual hospitals/communities. The present guideline has attempted to assess the relative clinical efficacy of different agents. We have found very few good-quality clinical trials to support treatment regimens, particularly for licensed older agents, formerly little used, that have been re-introduced into regular use. Finding a mechanism to address this deficit in trials much more rapidly is an important overarching research objective as the existing pattern of industry-sponsored initial regulatory trials fails to address the need.

It is self-evident that selection of antibiotic treatment based on susceptibility testing is the optimum strategy for treating infections caused by MDR GNB. The initiative to develop and deploy molecular and rapid phenotypic susceptibility testing methods will help refine antibiotic usage. Any additional expense must be funded within the healthcare system for these to be introduced. Risk factor, rule-based prescribing for MDR GNB is unlikely to be sufficiently predictive alone for the reasons outlined above but risk assessment of travel, household spread, and screening on admission to hospitals needs urgent improvement. However, we have attempted to present an evidence base and suggestions to support the development of local prescribing policies and possibly for the future application of such technologies and overall improvement in outcomes.

Over-reliance on empirical piperacillin/tazobactam and, for treatment failure, meropenem has driven and will drive selection for resistance to these agents, and UK health policy is attempting to contain this upsurge in usage. For patients presenting with serious sepsis convincingly caused by GNB and in the absence of prior exposure to healthcare in countries/hospitals with endemic CPE, carbapenems remain the best empirical therapy, with early and embedded shift to alternative definitive treatment. The overall prevalence of resistance in *E. coli* alone to piperacillin/tazobactam or gentamicin (approximately 10%) is the basis for this superiority of carbapenems, although factors such as aminoglycoside toxicity and *C. difficile* risk must be considered. Combinations of these agents or cephalosporins without β-lactamase inhibitors increase antibiotic use and are unlikely to produce adequate activity against ESBLs because of resistance linkage. Algorithms for predicting accurately the presence of ESBLs need urgent validation in the UK health service so piperacillin/tazobactam or gentamicin can be safely used to provide Gram-negative cover in their absence, and cephalosporin/BLI combinations in their presence thus diversify antibiotic use in serious infections within a stewardship framework. Use of piperacillin/tazobactam or existing licensed aminoglycosides as empirical therapy where ESBL-producing strains are prevalent, such as after overseas travel or hospitalization, in communities where such travel has been frequent, and with hospital or nursing home exposure, is unwise. Historical evidence suggests these agents continue to be appropriate for sepsis if these risk factors are not implicated.

In England, use of the Commissioning for Quality and Innovation (CQUIN) payments framework (or public health control of institutions and community healthcare) needs to be sensitive to the requirement to have safe effective antibiotics to use in sepsis caused by non-MDR GNB, which remain the majority of GNB causing serious infections in UK hospitals. The role and utility of the latest generation of BL/BLI combinations is yet to fully emerge. The early reports of emergence of resistance to ceftazidime/avibactam in KPC-3-producing carbapenem-resistant Enterobacteriaceae is ominous.[503] Nevertheless, at the moment new BL/BLIs and fosfomycin offer the only immediate new help to treat the latest MDR GNB, particularly for carbapenemase producers and ESBL-producing GNB. Further development of BLI combinations for oral use is an urgent need in primary care.

Initiatives are being put in place to address the paucity of new agents but it will take time for these agents to be produced and their success is by no means inevitable. A greater emphasis in communities should be given to the better use of existing treatments for effective treatment of complicated and upper UTI with prevention of bacteraemia, and in hospitals to an auditable improved outcome in well-defined groups of patients with life-threatening Gram-negative infections such as bacteraemia. This effort should match the attention given to reducing inappropriate use of wide-spectrum agents for less important infections and should ensure that reductions in antibiotic use are appropriate and do not adversely affect patients. Computerized support to spare infection professional time is necessary locally for surveillance of bacteraemia to focus attention on improvements in performance in life-threatening infection.

Greater research and deployment efforts in the area of very rapid diagnostics to guide immediate prescribing are needed. In the healthcare environment, stopping spread of infection with MDR GNBs is of paramount importance and such infection control measures have been dealt with comprehensively in another Working Party publication.[3]

The greatest long-term threat arises from the fundamental epidemiology of GNB, with their large faecal reservoirs in both humans and food animals leading to dissemination into the environment.[21] This leads to unpredictable acquisition by individuals, with high rates of commensal carriage and subsequent infection. Not only antibiotic control in man but parallel control of use of the same agents in food animals is important. This is exemplified by use of colistin, mequindox and fosfomycin[504] in food animals in China and other parts of the world, and consequent emergence of plasmid-mediated colistin, nitrofurantoin and fosfomycin resistance mediated by *mcr*-1, *oqxAB* and modified nitroreductases, and *fosA* as discussed previously (see Section 6.3.4). The close association of NDM MBL with connections with the Indian subcontinent is likely to change with the demonstration of this carbapenemase in poultry, farm workers, flies and wild birds in Shandong, China.[289] Practical measures to contain human importations of carbapenemases but also assessment and potentially prevention of any spread in foodstuffs are urgent at this early stage. Variations in the prevalence of MDR GNB in different localities and cultural backgrounds even within the UK need to be further explored and considered in empirical therapy. Separate effects of migration, travel, household cross-colonization/infection and food consumption need to be rapidly studied to make risk assessments practical and effective.

Internationally, public health hygiene measures to reduce faecal–oral transmission, such as clean water initiatives and sewerage and irrigation systems to prevent transmission, are of major importance. Foodstuffs, including imports, should be regulated for the presence of GNB resistant to third-generation cephalosporins, quinolones and possibly in the future carbapenems. Failure to address these under-recognized threats will undo our ability to treat infections caused by MDR GNB. If we do not control human and agricultural use of antibiotics and the spread of MDR GNB from faeces back into humans and food animals as a consistent multifaceted, global-scale public-health programme we will suffer greatly.

13. Further research and development

Apart from research needed for new compounds and formulations in the antibiotic pipeline, there are numerous areas which require research with a 5 year horizon for completion.

- Diagnostic tests and/or serum markers should be formally and comprehensively assessed for safety and efficacy as aids in deciding when to start and stop antimicrobial treatment, particularly in critically ill patients and those with haematological malignancies.
- Develop and introduce new cheap, rapid, and preferably bedside, diagnostic tests for important multiple antibiotic-resistant organisms in urine and blood.
- Undertake RCT studies of antimicrobial agents (both new and old) in the treatment of Gram-negative infection in areas where multiresistance is likely, e.g. admissions units, critical care and urology in hospitals and in treatment of infections due to ESBL-producing bacteria in the community. Identified research areas in this guideline include:

(i) Use of continuous-infusion meropenem at dose determined by nomogram if infection with KPC carbapenemase-producing *Klebsiella* with MIC of >8 and <64 mg/L.
(ii) Use of temocillin for non-urinary infections with trials to establish the optimal dosage.
(iii) Use of temocillin alone, or in combination, in UTIs caused by Enterobacteriaceae with KPC enzyme.
(iv) Use of ceftazidime/avibactam alone when non-MBL carbapenemase-producing organisms cause infection in comparison with alternatives, including combination therapy.
(v) Use of ceftolozane/tazobactam in *P. aeruginosa* infections in cystic fibrosis.
(vi) *In vitro* and *in vivo* research to identify the usefulness of aztreonam in combination with avibactam for infections due to Enterobacteriaceae with MBLs and other carbapenemases.
(vii) Research into the role of loading doses of colistin, monitoring of serum levels and optimal combination therapy.
(viii) Research into use of polymyxin-containing and non-containing selective digestive decontamination regimens and the prevalence of newly identified polymyxin resistance mechanisms.
(ix) Optimal rapid and practical methods of colistin susceptibility testing outside intrinsically resistant species such as Proteeae and *Serratia* spp.
(x) Higher dosing studies with tigecycline to investigate if the unexpectedly high mortality in infections with strains that are apparently susceptible *in vitro* can be reduced.
(xi) Optimal use of high-dose tigecycline in combinations in hospital-acquired respiratory infections.
(xii) Specific system-based and resistance-mechanism-based indications for use of parenteral fosfomycin, in infections due to MDR GNB.
(xiii) Cefixime (or other oral cephalosporin) with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.
(xiv) Nitrofurantoin versus fosfomycin trometamol versus pivmecillinam (with or without amoxicillin/clavulanate) in patients with ESBL-producing *E. coli* and *Klebsiella* spp.
(xv) Use of meropenem, temocillin or ceftolozane/tazobactam in community-onset pyelonephritis where hospitalization is required and where MDR GNB excluding CPE are, or are likely to be, present. These studies should include assessment of meropenem or aminoglycosides if the patient describes penicillin hypersensitivity.

- Undertake surveillance in both the hospital and community populations, and households of newly detected colonized individuals, for incidence of known mechanisms of resistance and the emergence of novel resistance mechanisms to currently used antimicrobials. Link this surveillance to travel, prior hospitalization as inpatient, or residential healthcare.
- Develop new models of licensing and funding of antimicrobials for treating MDR GNB infections. Develop non-microbial therapies for MRGNB (e.g. phage, antibacterial peptides, etc.)

Acknowledgements

We thank the patient representatives Susan Bennett, Jennifer Bostock and Maria Cann, as contributors who set the remit of the Working Party, were invited to its limited number of meetings, and commented on and endorsed the final draft inasmuch as this was within their technical competency.

We would like to acknowledge the support of the associations, societies, Royal Colleges and patient groups who helped with the external review. A. P. R. W. was part supported by National Institute for Health Research University College London Hospitals Biomedical Research Centre and P. M. H. was part supported by the National Institute for Health Research Centre for Surgical Reconstruction and Microbiology, University of Birmingham. We thank Samantha Cole and Eileen Hamilton for administrative and secretarial support and Carolyne Horner for editorial support.

Funding

This report was supported by a grant funded equally by British Infection Association, Healthcare Infection Society, and British Society for Antimicrobial Chemotherapy. This grant funded Karla Soares-Wieser and others at Enhance Reviews Ltd., Lyford, Wantage, expertly advised by Phil Wiffen, to perform the systematic review.

Transparency declarations

The BSAC, BIA and HIS commissioned the authors to undertake the Working Party Report. All authors but not the members of the patient advisory panel are, or have been, members of one or more of these societies.

P. M. H. declares: Consultancy: BioMérieux, Becton-Dickinson, Eumedica, Merck, Novartis, Magus Communications, Pfizer, Wyeth; director of ModusMedica (medical education company); Funded research: Astra-Zeneca, Merck, Novartis, and Pfizer. R. E. W. declares: family shareholdings in Astra Zeneca, Bayer, GSK, Johnson & Johnson, Merck, Pfizer and Roche amounting to approx. 15% of portfolio value. C. A. M. declares Travel expenses paid by Merieux Diagnostics. D. M. L. declares: Advisory Boards or *ad-hoc* consultancy: Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Basilea, BioVersys, Centauri, Discuva, Meiji, Merck, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx, Wockhardt, Zealand. Paid lectures: AstraZeneca, Beckman-Coulter, Cardiome, Merck and Nordic. Relevant shareholdings: Dechra, GSK, Merck, Perkin Elmer, Pfizer amounting to <10% of portfolio. Contract research: Achaogen, Allecra, AstraZeneca, Melinta, Meiji, Merck, Roche, Wockhardt. D. A. E. declares funding to attend conferences from MSD, Eumedica, Gilead and Astellas. J. A. O: was employed part-time by Bioquell Ltd. during the preparation of this manuscript. He is now a consultant to Gama Healthcare and Pfizer Ltd. These consultancies began after this Working Party report was written. A. P. R. W. is a consultant on Drug Safety Monitoring Boards for Roche and Genentech and is on an Advisory Panel for 3 M.

Supplementary data

Appendices 1–7 (glossary, remit and related NICE guidelines, guideline development process, systematic review, CPD material, consultation stakeholders and response from stakeholders) are available as Supplementary data at *JAC* Online.

References

1 SIGN. *Publication No. 50 A Guideline Developer's Handbook*. Scottish Intercollegiate Guidelines Network, 2011. http://www.sign.ac.uk/assets/sign50_2011.pdf.

2 Brouwers MC, Kho ME, Browman GP *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**: E839–42.

3 Wilson AP, Livermore DM, Otter JA *et al*. Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party. *J Hosp Infect* 2016; **92**: S1–44.

4 Public Health England. *2nd English Surveillance Program for Antimicrobial Utilisation and Resistance (ESPAUR) Report*. PHE, 2016. https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report.

5 Department of Health. *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018*. https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018. 2013.

6 Scottish Intercollegiate Guidelines Network. *SIGN 50: A Guideline Developer's Handbook*, Revised edn. 2014. http://www.sign.ac.uk/guidelines/fulltext/50/index.html.

7 Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. 2011. http://handbook-5-1 cochrane org; Version 5.1.0.

8 Cochrane Organisation. *Cochrane Effective Practice and Organisation of Care (EPOC)*. Interrupted Time Series (ITS) Analyses. EPOC Resources for review authors, 2017. http://epoc.cochrane.org/epoc-specific-resources-review-authors.

9 Borestein M, Hedges L, Higgins JPT *et al*. *Introduction to Meta-Analysis*. Chichester: John Wiley & Sons, 2009.

10 Review Manager. *Review Manager*. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

11 Guyatt G, Gutterman D, Baumann MH *et al*. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; **129**: 174–81.

12 Paterson DL, Ko WC, Von Gottberg A *et al*. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory. *J Clin Microbiol* 2001; **39**: 2206–12.

13 Sanders WE Jr, Sanders CC. Inducible beta-lactamases: clinical and epidemiologic implications for use of newer cephalosporins. *Rev Infect Dis* 1988; **10**: 830–8.

14 Lee NY, Lee CC, Li CW *et al*. Cefepime therapy for monomicrobial *Enterobacter cloacae* bacteremia: unfavorable outcomes in patients infected by cefepime-susceptible dose-dependent isolates. *Antimicrob Agents Chemother* 2015; **59**: 7558–63.

15 Vila J, Saez-Lopez E, Johnson JR *et al*. *Escherichia coli*: an old friend with new tidings. *FEMS Microbiol Rev* 2016; **40**: 437–63.

16 Peirano G, Bradford PA, Kazmierczak KM *et al*. Global incidence of carbapenemase-producing *Escherichia coli* ST131. *Emerg Infect Dis* 2014; **20**: 1928–31.

17 Doumith M, Dhanji H, Ellington MJ *et al*. Characterization of plasmids encoding extended-spectrum beta-lactamases and their addiction systems circulating among *Escherichia coli* clinical isolates in the UK. *J Antimicrob Chemother* 2012; **67**: 878–85.

18 Leverstein-van Hall MA, Dierikx CM, Cohen SJ *et al*. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect* 2011; **17**: 873–80.

19 Overdevest I, Willemsen I, Rijnsburger M *et al*. Extended-spectrum β-lactamase genes of *Escherichia coli* in chicken meat and humans, the Netherlands. *Emerg Infect Dis* 2011; **17**: 1216–22.

20 Kluytmans JA, Overdevest IT, Willemsen I *et al*. Extended-spectrum β-lactamase-producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. *Clin Infect Dis* 2013; **56**: 478–87.

21 Wellington EM, Boxall AB, Cross P *et al*. The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. *Lancet Infect Dis* 2013; **13**: 155–65.

22 Amos GC, Hawkey PM, Gaze WH *et al*. Waste water effluent contributes to the dissemination of CTX-M-15 in the natural environment. *J Antimicrob Chemother* 2014; **69**: 1785–91.

23 Davis GS, Waits K, Nordstrom L *et al*. Intermingled *Klebsiella pneumoniae* populations between retail meats and human urinary tract infections. *Clin Infect Dis* 2015; **61**: 892–9.

24 Liu YY, Wang Y, Walsh TR *et al*. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016; **16**: 161–8.

25 Ghodousi A, Bonura C, Di CP *et al*. Extraintestinal pathogenic *Escherichia coli* sequence type 131 H30-R and H30-Rx subclones in retail chicken meat, Italy. *Int J Food Microbiol* 2016; **228**: 10–3.

26 Mora A, Herrera A, Mamani R *et al*. Recent emergence of clonal group O25b: K1: H4-B2-ST131 ibeA strains among *Escherichia coli* poultry isolates, including CTX-M-9-producing strains, and comparison with clinical human isolates. *Appl Environ Microbiol* 2010; **76**: 6991–7.

27 Bonnet R. Growing group of extended-spectrum beta-lactamases: the CTX-M enzymes. *Antimicrob Agents Chemother* 2004; **48**: 1–14.

28 Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M beta-lactamases—temporal and geographical shifts in genotype. *J Antimicrob Chemother* 2017; **72**: 2145–55.

29 Petty NK, Ben Zakour NL, Stanton-Cook M *et al*. Global dissemination of a multidrug resistant *Escherichia coli* clone. *Proc Natl Acad Sci USA* 2014; **111**: 5694–9.

30 Potz NA, Hope R, Warner M *et al*. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. *J Antimicrob Chemother* 2006; **58**: 320–6.

31 Denisuik AJ, Lagace-Wiens PR, Pitout JD *et al*. Molecular epidemiology of extended-spectrum beta-lactamase-, AmpC beta-lactamase- and carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from Canadian hospitals over a 5 year period: CANWARD 2007-11. *J Antimicrob Chemother* 2013; **68**: i57–65.

32 Livermore DM, Andrews JM, Hawkey PM *et al*. Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly? *J Antimicrob Chemother* 2012; **67**: 1569–77.

33 Gupta N, Limbago BM, Patel JB *et al*. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clin Infect Dis* 2011; **53**: 60–7.

34 Ho J, Tambyah PA, Paterson DL. Multiresistant Gram-negative infections: a global perspective. *Curr Opin Infect Dis* 2010; **23**: 546–53.

35 Nordmann P, Poirel L. Strategies for identification of carbapenemase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2013; **68**: 487–9.

36 Canton R, Akova M, Carmeli Y *et al*. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; **18**: 413–31.

37 Lapuebla A, Abdallah M, Olafisoye O *et al*. Activity of imipenem with relebactam against Gram-negative pathogens from New York City. *Antimicrob Agents Chemother* 2015; **59**: 5029–31.

38 Lapuebla A, Abdallah M, Olafisoye O *et al*. Activity of meropenem combined with RPX7009, a novel beta-lactamase inhibitor, against Gram-negative clinical isolates in New York City. *Antimicrob Agents Chemother* 2015; **59**: 4856–60.

39 Glasner C, Albiger B, Buist G *et al*. Carbapenemase-producing Enterobacteriaceae in Europe: a survey among national experts from 39 countries, February 2013. *Euro Surveill* 2013; **18**: pii=20525.

40 European Centre for Disease Prevention and Control. *Antimicrobial Resistance in Europe*. ECDC, 2015. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf.

41 Giani T, Pini B, Arena F *et al*. Epidemic diffusion of KPC carbapenemase-producing *Klebsiella pneumoniae* in Italy: results of the first countrywide survey, 15 May to 30 June 2011. *Euro Surveill* 2013; **18**: pii=20489.

42 Bradford PA, Bratu S, Urban C *et al*. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. *Clin Infect Dis* 2004; **39**: 55–60.

43 Leavitt A, Navon-Venezia S, Chmelnitsky I *et al*. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. *Antimicrob Agents Chemother* 2007; **51**: 3026–9.

44 Schwaber MJ, Lev B, Israeli A *et al*. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011; **52**: 848–55.

45 Schwaber MJ, Carmeli Y. An ongoing national intervention to contain the spread of carbapenem-resistant Enterobacteriaceae. *Clin Infect Dis* 2014; **58**: 697–703.

46 Lixandru BE, Cotar AI, Straut M *et al*. Carbapenemase-producing *Klebsiella pneumoniae* in Romania: a six-month survey. *PLoS One* 2015; **10**: e0143214.

47 CDC. *Carbapenem Resistant Enterobacteriaceae*. 2016. www.cdc gov/hai/organisms/cre/trackingcre.html.

48 Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17**: 1791–8.

49 Hawkey PM. Multidrug-resistant Gram-negative bacteria: a product of globalization. *J Hosp Infect* 2015; **89**: 241–7.

50 Lee BY, Bartsch SM, Wong KF *et al*. The potential trajectory of carbapenem-resistant Enterobacteriaceae, an emerging threat to health-care facilities, and the impact of the centers for disease control and prevention toolkit. *Am J Epidemiol* 2016; **183**: 471–9.

51 Daikos GL, Petrikkos P, Psichogiou M *et al*. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. *Antimicrob Agents Chemother* 2009; **53**: 1868–73.

52 Patel G, Huprikar S, Factor SH *et al*. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; **29**: 1099–106.

53 Schito GC, Naber KG, Botto H *et al*. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. *Int J Antimicrob Agents* 2009; **34**: 407–13.

54 Poulsen HO, Johansson A, Granholm S *et al*. High genetic diversity of nitrofurantoin- or mecillinam-resistant *Escherichia coli* indicates low propensity for clonal spread. *J Antimicrob Chemother* 2013; **68**: 1974–7.

55 Tchesnokova V, Billig M, Chattopadhyay S *et al*. Predictive diagnostics for *Escherichia coli* infections based on the clonal association of antimicrobial resistance and clinical outcome. *J Clin Microbiol* 2013; **51**: 2991–9.

56 Johnson JR, Tchesnokova V, Johnston B *et al*. Abrupt emergence of a single dominant multidrug-resistant strain of *Escherichia coli*. *J Infect Dis* 2013; **207**: 919–28.

57 Lowe CF, McGeer A, Muller MP *et al*. Decreased susceptibility to noncarbapenem antimicrobials in extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates in Toronto, Canada. *Antimicrob Agents Chemother* 2012; **56**: 3977–80.

58 Ho PL, Ng KY, Lo WU *et al*. Plasmid-mediated OqxAB is an important mechanism for nitrofurantoin resistance in *Escherichia coli*. *Antimicrob Agents Chemother* 2015; **60**: 537–43.

59 He T, Wang Y, Qian M *et al*. Mequindox resistance and in vitro efficacy in animal-derived *Escherichia coli* strains. *Vet Microbiol* 2015; **177**: 341–6.

60 Karageorgopoulos DE, Wang R, Yu XH *et al*. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. *J Antimicrob Chemother* 2012; **67**: 255–68.

61 Oteo J, Bautista V, Lara N *et al*. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. *J Antimicrob Chemother* 2010; **65**: 2459–63.

62 Oteo J, Navarro C, Cercenado E *et al*. Spread of *Escherichia coli* strains with high-level cefotaxime and ceftazidime resistance between the community, long-term care facilities, and hospital institutions. *J Clin Microbiol* 2006; **44**: 2359–66.

63 Oteo J, Orden B, Bautista V *et al*. CTX-M-15-producing urinary *Escherichia coli* O25b-ST131-phylogroup B2 has acquired resistance to fosfomycin. *J Antimicrob Chemother* 2009; **64**: 712–7.

64 Li Y, Zheng B, Li Y *et al*. Antimicrobial susceptibility and molecular mechanisms of fosfomycin resistance in clinical *Escherichia coli* isolates in Mainland China. *PLoS One* 2015; **10**: e0135269.

65 Ho PL, Chan J, Lo WU *et al*. Prevalence and molecular epidemiology of PLASMID-mediated fosfomycin resistance genes among blood and urinary *Escherichia coli* isolates. *J Med Microbiol* 2013; **62**: 1707–13.

66 Jiang Y, Shen P, Wei Z *et al*. Dissemination of a clone carrying a fosA3-harbouring plasmid mediates high fosfomycin resistance rate of KPC-producing *Klebsiella pneumoniae* in China. *Int J Antimicrob Agents* 2015; **45**: 66–70.

67 Lee SY, Park YJ, Yu JK *et al*. Prevalence of acquired fosfomycin resistance among extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* clinical isolates in Korea and IS26-composite transposon surrounding fosA3. *J Antimicrob Chemother* 2012; **67**: 2843–7.

68 Giske CG. Contemporary resistance trends and mechanisms for the old antibiotics colistin, temocillin, fosfomycin, mecillinam and nitrofurantoin. *Clin Microbiol Infect* 2015; **21**: 899–905.

69 Kahlmeter G, Ahman J, Matuschek E. Antimicrobial resistance of *Escherichia coli* causing uncomplicated urinary tract infections: a European update for 2014 and comparison with 2000 and 2008. *Infect Dis Ther* 2015; **4**: 417–23.

70 Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant *Acinetobacter baumannii* infections. *Lancet Infect Dis* 2008; **8**: 751–62.

71 Towner KJ. *Acinetobacter*: an old friend, but a new enemy. *J Hosp Infect* 2009; **73**: 355–63.

72 Coelho JM, Turton JF, Kaufmann ME *et al*. Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. *J Clin Microbiol* 2006; **44**: 3623–7.

73 Reynolds R, Potz N, Colman M *et al*. Antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001-2002: the BSAC Bacteraemia Resistance Surveillance Programme. *J Antimicrob Chemother* 2004; **53**: 1018–32.

74 Khan AS, Dancer SJ, Humphreys H. Priorities in the prevention and control of multidrug-resistant Enterobacteriaceae in hospitals. *J Hosp Infect* 2012; **82**: 85–93.

75 British Society for Antimicrobial Chemotherapy. *Resistance Surveillance Project: Bacteraemia*. BSAC, 2017. http://www.bsacsurv.org/reports/respiratory/.

76 San Millan A, Toll-Riera M, Escudero JA *et al*. Sequencing of plasmids pAMBL1 and pAMBL2 from *Pseudomonas aeruginosa* reveals a blaVIM-1 amplification causing high-level carbapenem resistance. *J Antimicrob Chemother* 2015; **70**: 3000–3.

77 Qu TT, Zhang JL, Wang J *et al*. Evaluation of phenotypic tests for detection of metallo-beta-lactamase-producing *Pseudomonas aeruginosa* strains in China. *J Clin Microbiol* 2009; **47**: 1136–42.

78 Xiong J, Alexander DC, Ma JH *et al*. Complete sequence of pOZ176, a 500-kilobase IncP-2 plasmid encoding IMP-9-mediated carbapenem resistance, from outbreak isolate *Pseudomonas aeruginosa* 96. *Antimicrob Agents Chemother* 2013; **57**: 3775–82.

79 Edelstein MV, Skleenova EN, Shevchenko OV *et al*. Spread of extensively resistant VIM-2-positive ST235 *Pseudomonas aeruginosa* in Belarus, Kazakhstan, and Russia: a longitudinal epidemiological and clinical study. *Lancet Infect Dis* 2013; **13**: 867–76.

80 Bean DC, Livermore DM, Papa I *et al*. Resistance among *Escherichia coli* to sulphonamides and other antimicrobials now little used in man. *J Antimicrob Chemother* 2005; **56**: 962–4.

81 NHS National Services Scotland. *Scottish Antimicrobial Use and Resistance in Humans*. National Services Scotland, 2015. http://www.hps.scot.nhs.uk/resourcedocument.aspx?id=5655.

82 Public Health Wales. *Antimicrobial Usage in Primary Care in Wales 2006-2015*. Public Health Wales, Microbiology Division, 2016. https://www.wales.nhs.uk/sitesplus/documents/888/Antibacterial%20Usage%20in%20Primary%20Care%20in%20Wales%202006%2D2015.pdf.

83 Public Health Wales. *Antimicrobial Usage in Secondary Care in Wales 2006-2015*. Public Health Wales, Microbiology Division. 2016. http://www.wales.nhs.uk/sitesplus/documents/888/Antibacterial%20Usage%20in%20Secondary%20Care%20in%20Wales%202006-2015.pdf.

84 Day MJ, Doumith M, Abernethy J *et al*. Population structure of *Escherichia coli* causing bacteraemia in the UK and Ireland between 2001 and 2010. *J Antimicrob Chemother* 2016; **71**: 2139–42.

85 Department of Health. *Advisory Committee on Antibiotic Resistance and Hospital-Acquired Infection (ARHAI)*. Meeting Minutes (28/03/14). Department of Health, ARHAI, 2014. https://app.box.com/v/ARHAI-Minutes-Papers/file/18606239996.

86 Anon. *UK Doctors Told to Halve Inappropriate Antibiotic Prescriptions by 2020*. The Guardian, 2016. https://www.theguardian.com/society/2016/may/26/uk-doctors-told-to-halve-inappropriate-antibiotic-prescriptions-by-2020.

87 Abernethy J, Guy R, Sheridan EA *et al*. Epidemiology of *Escherichia coli* bacteraemia in England: results of an enhanced sentinel surveillance programme. *J Hosp Infect* 2017; **95**: 365–75.

88 Ciesielczuk H, Doumith M, Hope R *et al*. Characterization of the extra-intestinal pathogenic *Escherichia coli* ST131 clone among isolates recovered from urinary and bloodstream infections in the United Kingdom. *J Med Microbiol* 2015; **64**: 1496–503.

89 Horner C, Fawley W, Morris K *et al*. *Escherichia coli* bacteraemia: 2 years of prospective regional surveillance (2010-12). *J Antimicrob Chemother* 2014; **69**: 91–100.

90 Giufre M, Graziani C, Accogli M *et al*. *Escherichia coli* of human and avian origin: detection of clonal groups associated with fluoroquinolone and multidrug resistance in Italy. *J Antimicrob Chemother* 2012; **67**: 860–7.

91 Cagnacci S, Gualco L, Debbia E *et al*. European emergence of ciprofloxacin-resistant *Escherichia coli* clonal groups O25:H4-ST131 and O15:K52:H1 causing community-acquired uncomplicated cystitis. *J Clin Microbiol* 2008; **46**: 2605–12.

92 Blanco J, Mora A, Mamani R *et al*. National survey of *Escherichia coli* causing extraintestinal infections reveals the spread of drug-resistant clonal groups O25b:H4-B2-ST131, O15:H1-D-ST393 and CGA-D-ST69 with high virulence gene content in Spain. *J Antimicrob Chemother* 2011; **66**: 2011–21.

93 Xu L, Shabir S, Bodah T *et al*. Regional survey of CTX-M-type extended-spectrum beta-lactamases among Enterobacteriaceae reveals marked heterogeneity in the distribution of the ST131 clone. *J Antimicrob Chemother* 2011; **66**: 505–11.

94 Bou-Antoun S, Davies J, Guy R *et al*. Descriptive epidemiology of *Escherichia coli* bacteraemia in England, April 2012 to March 2014. *Euro Surveill* 2016; **21**: pii=30329.

95 Schlackow I, Stoesser N, Walker AS *et al*. Increasing incidence of *Escherichia coli* bacteraemia is driven by an increase in antibiotic-resistant isolates: electronic database study in Oxfordshire 1999-2011. *J Antimicrob Chemother* 2012; **67**: 1514–24.

96 Livermore DM, Hope R, Reynolds R *et al*. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *J Antimicrob Chemother* 2013; **68**: 2667–74.

97 Aldeyab MA, Harbarth S, Vernaz N *et al*. The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. *Br J Clin Pharmacol* 2012; **74**: 171–9.

98 European Centre for Disease Prevention and Control. *Antimicrobial Consumption Database (ESAC-Net)*. ECDC, 2017. https://ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview.

99 Tumbarello M, Trecarichi EM, Bassetti M *et al*. Identifying patients harboring extended-spectrum-beta-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. *Antimicrob Agents Chemother* 2011; **55**: 3485–90.

100 Public Health Wales. *Antibacterial Resistance in Wales 2006-2015*. Public Health Wales, Microbiology Division, 2016. http://www.wales.nhs.uk/sitesplus/documents/888/Antimicrobial%20Resistance%20in%20Wales%202006-2015.pdf.

101 Fitzpatrick JM, Biswas JS, Edgeworth JD *et al*. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. *Clin Microbiol Infect* 2016; **22**: 244–51.

102 Abernethy JK, Johnson AP, Guy R *et al*. Thirty day all-cause mortality in patients with *Escherichia coli* bacteraemia in England. *Clin Microbiol Infect* 2015; **21**: 251–8.

103 Daniel P, Bewick T, Welham S *et al*. Adults miscoded and misdiagnosed as having pneumonia: results from the British Thoracic Society pneumonia audit. *Thorax* 2017; **72**: 376–9.

104 Hyle EP, Lipworth AD, Zaoutis TE *et al*. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae: variability by site of infection. *Arch Intern Med* 2005; **165**: 1375–80.

105 Wilcox MH, Chalmers JD, Nord CE *et al*. Role of cephalosporins in the era of *Clostridium difficile* infection. *J Antimicrob Chemother* 2017; **72**: 1–18.

106 Verlinden A, Jansens H, Goossens H *et al*. Clinical and microbiological impact of discontinuation of fluoroquinolone prophylaxis in patients with prolonged profound neutropenia. *Eur J Haematol* 2014; **93**: 302–8.

107 Kern WV, Klose K, Jellen-Ritter AS *et al*. Fluoroquinolone resistance of *Escherichia coli* at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. *Eur J Clin Microbiol Infect Dis* 2005; **24**: 111–8.

108 Martino R, Subira M, Altes A *et al*. Effect of discontinuing prophylaxis with norfloxacin in patients with hematologic malignancies and severe neutropenia. A matched case-control study of the effect on infectious morbidity. *Acta Haematol* 1998; **99**: 206–11.

109 Gafter-Gvili A, Fraser A, Paul M *et al*. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev* 2012; issue **1**: CD004386.

110 Gafter-Gvili A, Paul M, Fraser A *et al*. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. *J Antimicrob Chemother* 2007; **59**: 5–22.

111 Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO.SENS study revisited. *Int J Antimicrob Agents* 2012; **39**: 45–51.

112 Bean DC, Krahe D, Wareham DW. Antimicrobial resistance in community and nosocomial *Escherichia coli* urinary tract isolates, London 2005-2006. *Ann Clin Microbiol Antimicrob* 2008; **7**: 13.

113 Heginbothom M, Howe R. *A Report from Public Health Wales Antimicrobial Resistance Programme Surveillance Unit: Antibacterial Resistance in Wales 2005-2013*. http://www.wales.nhs.uk/sites3/Documents/457/Report%20on%20Antimicrobial%20Resistance%20in%20Wales%202005-2013.pdf.

114 Ironmonger D, Edeghere O, Bains A *et al*. Surveillance of antibiotic susceptibility of urinary tract pathogens for a population of 5.6 million over 4 years. *J Antimicrob Chemother* 2015; **70**: 1744–50.

115 Findlay J, Hopkins KL, Alvarez-Buylla A *et al*. Characterization of carbapenemase-producing Enterobacteriaceae in the West Midlands region of England: 2007-14. *J Antimicrob Chemother* 2017; **72**: 1054–62.

116 Newell A, Bunting P, Anson K *et al*. Multicentre audit of the treatment of uncomplicated urinary tract infection in South Thames. *Int J STD AIDS* 2005; **16**: 74–7.

117 Heginbothom ML, Magee JT, Bell JL *et al*. Laboratory testing policies and their effects on routine surveillance of community antimicrobial resistance. *J Antimicrob Chemother* 2004; **53**: 1010–7.

118 Sundqvist M, Granholm S, Naseer U *et al*. Within-population distribution of trimethoprim resistance in *Escherichia coli* before and after a community-wide intervention on trimethoprim use. *Antimicrob Agents Chemother* 2014; **58**: 7492–500.

119 Horner CS, Abberley N, Denton M *et al*. Surveillance of antibiotic susceptibility of Enterobacteriaceae isolated from urine samples collected from community patients in a large metropolitan area, 2010-2012. *Epidemiol Infect* 2014; **142**: 399–403.

120 Livermore DM, Warner M, Mushtaq S *et al*. What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *Int J Antimicrob Agents* 2011; **37**: 415–9.

121 Gray KJ, Gascoyne BDM, Nicholson P *et al*. Transmissible fosfomycin resistance markers in urinary isolates and imported foodstuffs in the UK during 1994 and 1995. *J Antimicrob Chemother* 2001; **48**: 744–5.

122 Wootton M, Walsh TR, Macfarlane L *et al*. Activity of mecillinam against *Escherichia coli* resistant to third-generation cephalosporins. *J Antimicrob Chemother* 2010; **65**: 79–81.

123 Duggett NA, Sayers E, AbuOun M *et al*. Occurrence and characterization of mcr-1-harbouring *Escherichia coli* isolated from pigs in Great Britain from 2013 to 2015. *J Antimicrob Chemother* 2017; **72**: 691–5.

124 Skov RL, Monnet DL. Plasmid-mediated colistin resistance (mcr-1 gene): three months later, the story unfolds. *Euro Surveill* 2016; **21**: pii=30155.

125 Xavier BB, Lammens C, Ruhal R *et al*. Identification of a novel plasmid-mediated colistin-resistance gene, mcr-2, in *Escherichia coli*, Belgium, June 2016. *Euro Surveill* 2016; **21**: pii=30280.

126 Kumarasamy KK, Toleman MA, Walsh TR *et al*. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; **10**: 597–602.

127 Hassing RJ, Alsma J, Arcilla MS *et al*. International travel and acquisition of multidrug-resistant Enterobacteriaceae: a systematic review. *Euro Surveill* 2015; **20**: pii=30074.

128 Rogers BA, Kennedy KJ, Sidjabat HE *et al*. Prolonged carriage of resistant *E. coli* by returned travellers: clonality, risk factors and bacterial characteristics. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2413–20.

129 Pitout JD, Gregson DB, Campbell L *et al*. Molecular characteristics of extended-spectrum-beta-lactamase-producing *Escherichia coli* isolates causing bacteremia in the Calgary Health Region from 2000 to 2007: emergence of clone ST131 as a cause of community-acquired infections. *Antimicrob Agents Chemother* 2009; **53**: 2846–51.

130 Soraas A, Sundsfjord A, Sandven I *et al*. Risk factors for community-acquired urinary tract infections caused by ESBL-producing Enterobacteriaceae—a case-control study in a low prevalence country. *PLoS One* 2013; **8**: e69581.

131 Wistrom J, Gentry LO, Pa mgren AC *et al*. Ecological effects of short-term ciprofloxacin treatment of travellers' diarrhoea. *J Antimicrob Chemother* 1992; **30**: 693–706.

132 Hilty M, Betsch BY, Bogli-Stuber K *et al*. Transmission dynamics of extended-spectrum beta-lactamase-producing Enterobacteriaceae in the tertiary care hospital and the household setting. *Clin Infect Dis* 2012; **55**: 967–75.

133 Rodriguez-Bano J, Lopez-Cerero L, Navarro MD *et al*. Faecal carriage of extended-spectrum beta-lactamase-producing *Escherichia coli*: prevalence, risk factors and molecular epidemiology. *J Antimicrob Chemother* 2008; **62**: 1142–9.

134 Valverde A, Grill F, Coque TM *et al*. High rate of intestinal colonization with extended-spectrum-beta-lactamase-producing organisms in household contacts of infected community patients. *J Clin Microbiol* 2008; **46**: 2796–9.

135 Valverde A, Turrientes MC, Norman F *et al*. CTX-M-15-non-ST131 *Escherichia coli* isolates are mainly responsible of faecal carriage with ESBL-producing Enterobacteriaceae in travellers, immigrants and those visiting friends and relatives. *Clin Microbiol Infect* 2015; **21**: 252–4.

136 Tangden T, Cars O, Melhus A *et al*. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* 2010; **54**: 3564–8.

137 Wickramasinghe NH, Xu L, Eustace A *et al*. High community faecal carriage rates of CTX-M ESBL-producing *Escherichia coli* in a specific population group in Birmingham, UK. *J Antimicrob Chemother* 2012; **67**: 1108–13.

138 Giske CG, Monnet DL, Cars O *et al*. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother* 2008; **52**: 813–21.

139 Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med* 2009; **37**: 1463–9.

140 Gasink LB, Fishman NO, Weiner MG *et al*. Fluoroquinolone-resistant *Pseudomonas aeruginosa*: assessment of risk factors and clinical impact. *Am J Med* 2006; **119**: 526–5.

141 Lee NY, Lee HC, Ko NY *et al*. Clinical and economic impact of multidrug resistance in nosocomial *Acinetobacter baumannii* bacteremia. *Infect Control Hosp Epidemiol* 2007; **28**: 713–9.

142 Kwon KT, Oh WS, Song JH *et al*. Impact of imipenem resistance on mortality in patients with *Acinetobacter* bacteraemia. *J Antimicrob Chemother* 2007; **59**: 525–30.

143 Sunenshine RH, Wright MO, Maragakis LL *et al*. Multidrug-resistant *Acinetobacter* infection mortality rate and length of hospitalization. *Emerg Infect Dis* 2007; **13**: 97–103.

144 Falagas ME, Tansarli GS, Karageorgopoulos DE *et al*. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerg Infect Dis* 2014; **20**: 1170–5.

145 Selden R, Lee S, Wang WL *et al*. Nosocomial *Klebsiella* infections: intestinal colonization as a reservoir. *Ann Intern Med* 1971; **74**: 657–64.

146 Wingard JR, Dick J, Charache P *et al*. Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. *Antimicrob Agents Chemother* 1986; **30**: 435–9.

147 Thom KA, Johnson JA, Strauss SM *et al*. Increasing prevalence of gastrointestinal colonization with ceftazidime-resistant Gram-negative bacteria among intensive care unit patients. *Infect Control Hosp Epidemiol* 2007; **28**: 1240–6.

148 Schimpff SC, Young VM, Greene WH *et al*. Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. *Ann Intern Med* 1972; **77**: 707–14.

149 Corbella X, Pujol M, Ayats J *et al*. Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant *Acinetobacter baumannii*. *Clin Infect Dis* 1996; **23**: 329–34.

150 Latibeaudiere R, Rosa R, Laowansiri P *et al*. Surveillance cultures growing carbapenem-Resistant *Acinetobacter baumannii* predict the development of clinical infections: a retrospective cohort study. *Clin Infect Dis* 2015; **60**: 415–22.

151 Babouee FB, Ellington MJ, Hopkins KL *et al*. The differential importance of mutations within AmpD in cephalosporin resistance of *Enterobacter aerogenes* and *Enterobacter cloacae*. *Int J Antimicrob Agents* 2016; **48**: 555–8.

152 Chow JW, Fine MJ, Shlaes DM *et al*. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115**: 585–90.

153 Choi SH, Lee JE, Park SJ *et al*. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. *Antimicrob Agents Chemother* 2008; **52**: 995–1000.

154 Hawkey PM, Livermore DM. Carbapenem antibiotics for serious infections. *BMJ* 2012; **344**: e3236.

155 Edwards SJ, Emmas CE, Campbell HE. Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005; **21**: 785–94.

156 Lew KY, Ng TM, Tan M *et al*. Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an ESBL-endemic setting. *J Antimicrob Chemother* 2015; **70**: 1219–25.

157 Kuo HY, Chang KC, Kuo JW *et al*. Imipenem: a potent inducer of multidrug resistance in *Acinetobacter baumannii*. *Int J Antimicrob Agents* 2012; **39**: 33–8.

158 Fournier D, Richardot C, Muller E *et al*. Complexity of resistance mechanisms to imipenem in intensive care unit strains of *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 2013; **68**: 1772–80.

159 Rodriguez-Martinez JM, Poirel L, Nordmann P. Molecular epidemiology and mechanisms of carbapenem resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009; **53**: 4783–8.

160 Cabot G, Ocampo-Sosa AA, Tubau F *et al*. Overexpression of AmpC and efflux pumps in *Pseudomonas aeruginosa* isolates from bloodstream infections: prevalence and impact on resistance in a Spanish multicenter study. *Antimicrob Agents Chemother* 2011; **55**: 1906–11.

161 Giannella M, Trecarichi EM, De Rosa FG *et al*. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. *Clin Microbiol Infect* 2014; **20**: 1357–62.

162 Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. *J Antimicrob Chemother* 2003; **52**: 331–44.

163 Collins VL, Marchaim D, Pogue JM *et al*. Efficacy of ertapenem for treatment of bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2012; **56**: 2173–7.

164 Lee NY, Lee CC, Huang WH *et al*. Carbapenem therapy for bacteremia due to extended-spectrum-beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*: implications of ertapenem susceptibility. *Antimicrob Agents Chemother* 2012; **56**: 2888–93.

165 Gutierrez-Gutierrez B, Bonomo RA, Carmeli Y *et al*. Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study. *J Antimicrob Chemother* 2016; **71**: 1672–80.

166 Tangden T, Adler M, Cars O *et al*. Frequent emergence of porin-deficient subpopulations with reduced carbapenem susceptibility in ESBL-producing *Escherichia coli* during exposure to ertapenem in an in vitro pharmacokinetic model. *J Antimicrob Chemother* 2013; **68**: 1319–26.

167 Woodford N, Dallow JW, Hill RL *et al*. Ertapenem resistance among *Klebsiella* and *Enterobacter* submitted in the UK to a reference laboratory. *Int J Antimicrob Agents* 2007; **29**: 456–9.

168 Jain A, Hopkins KL, Turton J *et al*. NDM carbapenemases in the United Kingdom: an analysis of the first 250 cases. *J Antimicrob Chemother* 2014; **69**: 1777–84.

169 Thomas CP, Moore LS, Elamin N *et al*. Early (2008-2010) hospital outbreak of *Klebsiella pneumoniae* producing OXA-48 carbapenemase in the UK. *Int J Antimicrob Agents* 2013; **42**: 531.

170 Hyle EP, Ferraro MJ, Silver M *et al*. Ertapenem-resistant Enterobacteriaceae: risk factors for acquisition and outcomes. *Infect Control Hosp Epidemiol* 2010; **31**: 1242–9.

171 Teo J, Cai Y, Tang S *et al*. Risk factors, molecular epidemiology and outcomes of ertapenem-resistant, carbapenem-susceptible Enterobacteriaceae: a case-case-control study. *PLoS One* 2012; **7**: e34254.

172 Nicolau DP, Carmeli Y, Crank CW *et al*. Carbapenem stewardship: does ertapenem affect *Pseudomonas* susceptibility to other carbapenems? A review of the evidence. *Int J Antimicrob Agents* 2012; **39**: 11–5.

173 McDougall DA, Morton AP, Playford EG. Association of ertapenem and antipseudomonal carbapenem usage and carbapenem resistance in *Pseudomonas aeruginosa* among 12 hospitals in Queensland, Australia. *J Antimicrob Chemother* 2013; **68**: 457–60.

174 Goldstein EJ, Citron DM, Peraino V *et al*. Introduction of ertapenem into a hospital formulary: effect on antimicrobial usage and improved in vitro susceptibility of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009; **53**: 5122–6.

175 Lim CL, Lee W, Lee AL *et al*. Evaluation of ertapenem use with impact assessment on extended-spectrum beta-lactamases (ESBL) production and Gram-negative resistance in Singapore General Hospital (SGH). *BMC Infect Dis* 2013; **13**: 523.

176 Sousa D, Castelo-Corral L, Gutierrez UJM *et al*. Impact of ertapenem use on *Pseudomonas aeruginosa* and *Acinetobacter baumannii* imipenem susceptibility rates: collateral damage or positive effect on hospital ecology? *J Antimicrob Chemother* 2013; **68**: 1917–25.

177 Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. *Clin Infect Dis* 2014; **58**: 1439–48.

178 Roberts JA, Abdul-Aziz MH, Davis JS *et al*. Continuous versus intermittent beta-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. *Am J Respir Crit Care Med* 2016; **194**: 681–91.

179 Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: a step toward dose optimization for the treatment of severe gram-negative bacterial infections. *Clin Pharmacokinet* 2015; **54**: 933–41.

180 Pea F, Viale P, Cojutti P *et al*. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. *Antimicrob Agents Chemother* 2012; **56**: 6343–8.

181 Kang CI, Kim SH, Park WB *et al*. Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. *Antimicrob Agents Chemother* 2004; **48**: 4574–81.

182 Ho PL, Chan WM, Tsang KW *et al*. Bacteremia caused by *Escherichia coli* producing extended-spectrum beta-lactamase: a case-control study of risk factors and outcomes. *Scand J Infect Dis* 2002; **34**: 567–73.

183 Lautenbach E, Patel JB, Bilker WB *et al*. Extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis* 2001; **32**: 1162–71.

184 Rodriguez-Bano J, Navarro MD, Romero L *et al*. Bacteremia due to extended-spectrum beta -lactamase-producing *Escherichia coli* in the CTX-M era: a new clinical challenge. *Clin Infect Dis* 2006; **43**: 1407–14.

185 Kang CI, Cha MK, Kim SH *et al*. Extended-spectrum cephalosporins and the inoculum effect in tests with CTX-M-type extended-spectrum beta-lactamase-producing *Escherichia coli*: potential clinical implications of the revised CLSI interpretive criteria. *Int J Antimicrob Agents* 2014; **43**: 456–9.

186 Woodford N, Ward ME, Kaufmann ME *et al*. Community and hospital spread of *Escherichia coli* producing CTX-M extended-spectrum beta-lactamases in the UK. *J Antimicrob Chemother* 2004; **54**: 735–43.

187 Wiskirchen DE, Nordmann P, Crandon JL *et al*. Efficacy of humanized carbapenem and ceftazidime regimens against Enterobacteriaceae producing OXA-48 carbapenemase in a murine infection model. *Antimicrob Agents Chemother* 2014; **58**: 1678–83.

188 Chalhoub H, Tunney M, Elborn JS *et al*. Avibactam confers susceptibility to a large proportion of ceftazidime-resistant *Pseudomonas aeruginosa* isolates recovered from cystic fibrosis patients. *J Antimicrob Chemother* 2015; **70**: 1596–8.

189 Crandon JL, Schuck VJ, Banevicius MA *et al*. Comparative in vitro and in vivo efficacies of human simulated doses of ceftazidime and ceftazidime-avibactam against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2012; **56**: 6137–46.

190 Sader HS, Castanheira M, Mendes RE *et al*. Ceftazidime-avibactam activity against multidrug-resistant *Pseudomonas aeruginosa* isolated in U.S. medical centers in 2012 and 2013. *Antimicrob Agents Chemother* 2015; **59**: 3656–9.

191 Flamm RK, Farrell DJ, Sader HS *et al*. Ceftazidime/avibactam activity tested against Gram-negative bacteria isolated from bloodstream, pneumonia, intra-abdominal and urinary tract infections in US medical centres (2012). *J Antimicrob Chemother* 2014; **69**: 1589–98.

192 Coleman K, Levasseur P, Girard AM *et al*. Activities of ceftazidime and avibactam against beta-lactamase-producing Enterobacteriaceae in a hollow-fiber pharmacodynamic model. *Antimicrob Agents Chemother* 2014; **58**: 3366–72.

193 Sader HS, Castanheira M, Flamm RK *et al*. Antimicrobial activity of ceftazidime-avibactam against Gram-negative organisms collected from U.S. medical centers in 2012. *Antimicrob Agents Chemother* 2014; **58**: 1684–92.

194 Citron DM, Tyrrell KL, Merriam V *et al*. In vitro activity of ceftazidime-NXL104 against 396 strains of beta-lactamase-producing anaerobes. *Antimicrob Agents Chemother* 2011; **55**: 3616–20.

195 Castanheira M, Mills JC, Costello SE *et al*. Ceftazidime-avibactam activity tested against Enterobacteriaceae isolates from U.S. hospitals (2011 to 2013) and characterization of beta-lactamase-producing strains. *Antimicrob Agents Chemother* 2015; **59**: 3509–17.

196 Shields RK, Chen L, Cheng S *et al*. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* Infections. *Antimicrob Agents Chemother* 2017; **61**: e02097–16.

197 Shields RK, Clancy CJ, Hao B *et al*. Effects of *Klebsiella pneumoniae* carbapenemase subtypes, extended-spectrum beta-lactamases, and porin mutations on the in vitro activity of ceftazidime-avibactam against carbapenem-resistant *K. pneumoniae*. *Antimicrob Agents Chemother* 2015; **59**: 5793–7.

198 Livermore DM, Warner M, Jamrozy D *et al*. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. *Antimicrob Agents Chemother* 2015; **59**: 5324–30.

199 Vazquez JA, Gonzalez Patzan LD, Stricklin D *et al*. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012; **28**: 1921–31.

200 Wagenlehner FM, Sobel JD, Newell P *et al*. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016; **63**: 754–62.

201 Lucasti C, Popescu I, Ramesh MK *et al*. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. *J Antimicrob Chemother* 2013; **68**: 1183–92.

202 Mazuski JE, Gasink LB, Armstrong J *et al*. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. *Clin Infect Dis* 2016; **62**: 1380–9.

203 Carmeli Y, Armstrong J, Laud PJ *et al*. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis* 2016; **16**: 661–73.

204 Sader HS, Farrell DJ, Flamm RK *et al*. Ceftolozane/tazobactam activity tested against aerobic Gram-negative organisms isolated from intra-abdominal and urinary tract infections in European and United States hospitals (2012). *J Infect* 2014; **69**: 266–77.

205 Farrell DJ, Flamm RK, Sader HS *et al*. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. Hospitals (2011-2012). *Antimicrob Agents Chemother* 2013; **57**: 6305–10.

206 Sader HS, Rhomberg PR, Jones RN. Post-beta-lactamase-inhibitor effect of tazobactam in combination with ceftolozane on extended-spectrum-beta-lactamase-producing strains. *Antimicrob Agents Chemother* 2014; **58**: 2434–7.

207 Vanscoy B, Mendes RE, Castanheira M *et al*. Relationship between ceftolozane-tazobactam exposure and drug resistance amplification in a hollow-fiber infection model. *Antimicrob Agents Chemother* 2013; **57**: 4134–8.

208 Melchers MJ, van Mil AC, Mouton JW. In vitro activity of ceftolozane alone and in combination with tazobactam against extended-spectrum-beta-lactamase-harboring Enterobacteriaceae. *Antimicrob Agents Chemother* 2015; **59**: 4521–5.

209 Kuti JL, Pettit RS, Neu N *et al*. Microbiological activity of ceftolozane/tazobactam, ceftazidime, meropenem, and piperacillin/tazobactam against *Pseudomonas aeruginosa* isolated from children with cystic fibrosis. *Diagn Microbiol Infect Dis* 2015; **83**: 53–5.

210 Monogue ML, Pettit RS, Muhlebach M *et al*. Population pharmacokinetics and safety of ceftolozane-tazobactam in adult cystic fibrosis patients admitted with acute pulmonary exacerbation. *Antimicrob Agents Chemother* 2016; **60**: 6578–84.

211 Scott LJ. Ceftolozane/tazobactam: a review in complicated intra-abdominal and urinary tract infections. *Drugs* 2016; **76**: 231–42.

212 Solomkin J, Hershberger E, Miller B *et al*. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). *Clin Infect Dis* 2015; **60**: 1462–71.

213 Wagenlehner FM, Umeh O, Steenbergen J *et al*. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015; **385**: 1949–56.

214 Livermore DM, Mushtaq S, Warner M *et al*. Activities of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2011; **55**: 390–4.

215 Papp-Wallace KM, Bajaksouzian S, Abdelhamed AM *et al*. Activities of ceftazidime, ceftaroline, and aztreonam alone and combined with avibactam against isogenic *Escherichia coli* strains expressing selected single beta-lactamases. *Diagn Microbiol Infect Dis* 2015; **82**: 65–9.

216 Wang X, Zhang F, Zhao C *et al*. In vitro activities of ceftazidime-avibactam and aztreonam-avibactam against 372 Gram-negative bacilli collected in 2011 and 2012 from 11 teaching hospitals in China. *Antimicrob Agents Chemother* 2014; **58**: 1774–8.

217 Kotapati S, Kuti JL, Nightingale CH *et al*. Clinical implications of extended spectrum beta-lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness. *J Infect* 2005; **51**: 211–7.

218 Zanetti G, Bally F, Greub G *et al*. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003; **47**: 3442–7.

219 Lee NY, Lee CC, Huang WH *et al*. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. *Clin Infect Dis* 2013; **56**: 488–95.

220 Nguyen HM, Shier KL, Graber CJ. Determining a clinical framework for use of cefepime and beta-lactam/beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2014; **69**: 871–80.

221 Chopra T, Marchaim D, Veltman J *et al*. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. *Antimicrob Agents Chemother* 2012; **56**: 3936–42.

222 Pulcini C, Bush K, Craig WA *et al*. Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. *Clin Infect Dis* 2012; **54**: 268–74.

223 Lu PL, Liu YC, Toh HS *et al*. Epidemiology and antimicrobial susceptibility profiles of Gram-negative bacteria causing urinary tract infections in the Asia-Pacific region: 2009-2010 results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2012; **40**: S37–43.

224 Carignan A, Allard C, Pepin J *et al*. Risk of *Clostridium difficile* infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis* 2008; **46**: 1838–43.

225 Lepeule R, Ruppe E, Le P *et al*. Cefoxitin as an alternative to carbapenems in a murine model of urinary tract infection due to *Escherichia coli* harboring CTX-M-15-type extended-spectrum beta-lactamase. *Antimicrob Agents Chemother* 2012; **56**: 1376–81.

226 Lefort A, Chau F, Lepeule R *et al*. Activity of fosfomycin alone or combined with cefoxitin in vitro and in vivo in a murine model of urinary tract infection due to *Escherichia coli* harbouring CTX-M-15-type extended-spectrum beta-lactamase. *Int J Antimicrob Agents* 2014; **43**: 366–9.

227 Kerneis S, Valade S, Geri G *et al*. Cefoxitin as a carbapenem-sparing antibiotic for infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *Infect Dis (Lond)* 2015; **47**: 789–95.

228 Guet-Revillet H, Emirian A, Groh M *et al*. Pharmacological study of cefoxitin as an alternative antibiotic therapy to carbapenems in treatment of urinary tract infections due to extended-spectrum-beta-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2014; **58**: 4899–901.

229 Stapleton P, Shannon K, Phillips I. The ability of beta-lactam antibiotics to select mutants with derepressed beta-lactamase synthesis from *Citrobacter freundii*. *J Antimicrob Chemother* 1995; **36**: 483–96.

230 Boon RJ, Beale AS. Studies with temocillin in a hamster model of antibiotic-associated colitis. *Antimicrob Agents Chemother* 1985; **27**: 980–1.

231 Livermore DM, Hope R, Fagan EJ *et al*. Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England. *J Antimicrob Chemother* 2006; **57**: 1012–4.

232 Rodriguez-Villalobos H, Bogaerts P, Berhin C *et al*. Trends in production of extended-spectrum beta-lactamases among Enterobacteriaceae of clinical interest: results of a nationwide survey in Belgian hospitals. *J Antimicrob Chemother* 2011; **66**: 37–47.

233 Adams-Haduch JM, Potoski BA, Sidjabat HE *et al*. Activity of temocillin against KPC-producing *Klebsiella pneumoniae* and *Escherichia coli*. *Antimicrob Agents Chemother* 2009; **53**: 2700–1.

234 Bonacorsi S, Fitoussi F, Lhopital S *et al*. Comparative in vitro activities of meropenem, imipenem, temocillin, piperacillin, and ceftazidime in combination with tobramycin, rifampin, or ciprofloxacin against *Burkholderia cepacia* isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 1999; **43**: 213–7.

235 Yang Y, Livermore DM. Activity of temocillin and other penicillins against beta-lactamase-inducible and -stably derepressed enterobacteria. *J Antimicrob Chemother* 1988; **22**: 299–306.

236 Alexandre K, Chau F, Guerin F *et al*. Activity of temocillin in a lethal murine model of infection of intra-abdominal origin due to KPC-producing *Escherichia coli*. *J Antimicrob Chemother* 2016; **71**: 1899–904.

237 Mutters NT, Zimmermann S, Kaase M *et al*. Activity of temocillin, mecillinam, ceftazidime, and ceftazidime/avibactam against carbapenem-non-susceptible Enterobacteriaceae without carbapenemase production. *Eur J Clin Microbiol Infect Dis* 2015; **34**: 2429–37.

238 Woodford N, Pike R, Meunier D *et al*. In vitro activity of temocillin against multidrug-resistant clinical isolates of *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., and evaluation of high-level temocillin resistance as a diagnostic marker for OXA-48 carbapenemase. *J Antimicrob Chemother* 2014; **69**: 564–7.

239 Balakrishnan I, Awad-El-Kariem FM, Aali A *et al*. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC beta-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2011; **66**: 2628–31.

240 Laterre PF, Wittebole X, Van de Velde S *et al*. Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. *J Antimicrob Chemother* 2015; **70**: 891–8.

241 Sweeney L, Wilson R, Cleary P *et al*. *Clinical Outcomes and Predictors of Mortality Following Bacteraemia with KPC-Producing Enterobacteriaceae in a Large Teaching Hospital in the UK: a retrospective case review*. Poster EP0085. The European Society of Clinical Microbiology and Infectious Diseases, 2016.

242 Lekkas A, Gyi KM, Hodson ME. Temocillin in the treatment of *Burkholderia cepacia* infection in cystic fibrosis. *J Cyst Fibros* 2006; **5**: 121–4.

243 Kent L, Bradley JM, France M *et al*. Temocillin in cystic fibrosis: a retrospective pilot study. *J Cyst Fibros* 2008; **7**: 551–4.

244 Corbella X, Ariza J, Ardanuy C *et al*. Efficacy of sulbactam alone and in combination with ampicillin in nosocomial infections caused by multiresistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 1998; **42**: 793–802.

245 Oliveira MS, Prado GV, Costa SF *et al*. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant *Acinetobacter* spp. *J Antimicrob Chemother* 2008; **61**: 1369–75.

246 Kalin G, Alp E, Akin A *et al*. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Infection* 2014; **42**: 37–42.

247 Wood GC, Hanes SD, Croce MA *et al*. Comparison of ampicillin-sulbactam and imipenem-cilastatin for the treatment of *Acinetobacter* ventilator-associated pneumonia. *Clin Infect Dis* 2002; **34**: 1425–30.

248 Betrosian AP, Frantzeskaki F, Xanthaki A *et al*. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect* 2008; **56**: 432–6.

249 Betrosian AP, Frantzeskaki F, Xanthaki A *et al*. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. *Scand J Infect Dis* 2007; **39**: 38–43.

250 Edlund C, Nord CE. Effect on the human normal microflora of oral antibiotics for treatment of urinary tract infections. *J Antimicrob Chemother* 2000; **46**: 41–8.

251 Rodriguez-Bano J, Alcala JC, Cisneros JM *et al*. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008; **168**: 1897–902.

252 Lagace-Wiens PR, Nichol KA, Nicolle LE *et al*. Treatment of lower urinary tract infection caused by multidrug-resistant extended-spectrum-beta-lactamase-producing *Escherichia coli* with amoxicillin/clavulanate: case report and characterization of the isolate. *J Antimicrob Chemother* 2006; **57**: 1262–3.

253 Rodriguez-Bano J, Navarro MD, Retamar P *et al*. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2012; **54**: 167–74.

254 Tamma PD, Han JH, Rock C *et al*. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum beta-lactamase bacteremia. *Clin Infect Dis* 2015; **60**: 1319–25.

255 Tsai HY, Chen YH, Tang HJ *et al*. Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum beta-lactamase-producing *Proteus mirabilis*. *Diagn Microbiol Infect Dis* 2014; **80**: 222–6.

256 Retamar P, Lopez-Cerero L, Muniain MA *et al*. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-beta-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2013; **57**: 3402–4.

257 Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E *et al*. A multinational, preregistered cohort study of beta-lactam/beta-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother* 2016; **60**: 4159–69.

258 Merino I, Shaw E, Horcajada JP *et al*. CTX-M-15-H30Rx-ST131 subclone is one of the main causes of healthcare-associated ESBL-producing *Escherichia coli* bacteraemia of urinary origin in Spain. *J Antimicrob Chemother* 2016; **71**: 2125–30.

259 Perez F, Bonomo RA. Can we really use β-lactam/β-lactam inhibitor combinations for the treatment of infections caused by extended-spectrum β-lactamase-producing bacteria? *Clin Infect Dis* 2012; **54**: 175–7.

260 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26**: 1–10.

261 Peralta G, Lamelo M, Alvarez GP *et al*. Impact of empirical treatment in extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. bacteremia. A multicentric cohort study. *BMC Infect Dis* 2012; **12**: 245.

262 Tam VH, Gamez EA, Weston JS *et al*. Outcomes of bacteremia due to *Pseudomonas aeruginosa* with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. *Clin Infect Dis* 2008; **46**: 862–7.

263 Livermore DM, Mushtaq S, Warner M *et al*. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. *J Antimicrob Chemother* 2011; **66**: 48–53.

264 Ramirez MS, Tolmasky ME. Aminoglycoside modifying enzymes. *Drug Resist Updat* 2010; **13**: 151–71.

265 Jones GL, Warren RE, Skidmore SJ *et al*. Prevalence and distribution of plasmid-mediated quinolone resistance genes in clinical isolates of *Escherichia coli* lacking extended-spectrum beta-lactamases. *J Antimicrob Chemother* 2008; **62**: 1245–51.

266 Mattie H, Craig WA, Pechere JC. Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24**: 281–93.

267 Heritage J, Dyke GW, Johnston D *et al*. Selection of resistance to gentamicin and netilmicin in the faecal flora following prophylaxis for colo-rectal surgery. *J Antimicrob Chemother* 1988; **22**: 249–56.

268 King K. Prophylactic non-absorbable antibiotics in leukaemic patients. *J Hyg (Lond)* 1980; **85**: 141–51.

269 Prentice HG, Hann IM, Nazareth B *et al*. Oral ciprofloxacin plus colistin: prophylaxis against bacterial infection in neutropenic patients. A strategy for the prevention of emergence of antimicrobial resistance. *Br J Haematol* 2001; **115**: 46–52.

270 Ostholm-Balkhed A, Tarnberg M, Nilsson M *et al*. Travel-associated faecal colonization with ESBL-producing Enterobacteriaceae: incidence and risk factors. *J Antimicrob Chemother* 2013; **68**: 2144–53.

271 Vardakas KZ, Tansarli GS, Bliziotis IA *et al*. β-Lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *Pseudomonas aeruginosa* infections: a meta-analysis. *Int J Antimicrob Agents* 2013; **41**: 301–10.

272 Endimiani A, Hujer KM, Hujer AM *et al*. ACHN-490, a neoglycoside with potent in vitro activity against multidrug-resistant *Klebsiella pneumoniae* isolates. *Antimicrob Agents Chemother* 2009; **53**: 4504–7.

273 Almaghrabi R, Clancy CJ, Doi Y *et al*. Carbapenem-resistant *Klebsiella pneumoniae* strains exhibit diversity in aminoglycoside-modifying enzymes, which exert differing effects on plazomicin and other agents. *Antimicrob Agents Chemother* 2014; **58**: 4443–51.

274 Walkty A, Adam H, Baxter M *et al*. In vitro activity of plazomicin against 5,015 Gram-negative and Gram-positive clinical isolates obtained from patients in Canadian hospitals as part of the CANWARD study, 2011-2012. *Antimicrob Agents Chemother* 2014; **58**: 2554–63.

275 Nicolau DP, Freeman CD, Belliveau PP *et al*. Experience with a once-daily aminoglycoside program administered to 2, 184 adult patients. *Antimicrob Agents Chemother* 1995; **39**: 650–5.

276 Urban AW, Craig WA. Daily dosage of aminoglycosides. *Curr Clin Top Infect Dis* 1997; **17**: 236–55.

277 Jenkins A, Thomson AH, Brown NM *et al*. Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affect either outcome or adverse events? A systematic review. *J Antimicrob Chemother* 2016; **71**: 2754–9.

278 Ahmed RM, Hannigan IP, MacDougall HG *et al*. Gentamicin ototoxicity: a 23-year selected case series of 103 patients. *Med J Aust* 2012; **196**: 701–4.

279 Black FO, Pesznecker S, Stallings V. Permanent gentamicin vestibulotoxicity. *Otol Neurotol* 2004; **25**: 559–69.

280 Kahlmeter G, Dahlager JI. Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13**: 9–22.

281 Gatell JM, Ferran F, Araujo V *et al*. Univariate and multivariate analyses of risk factors predisposing to auditory toxicity in patients receiving aminoglycosides. *Antimicrob Agents Chemother* 1987; **31**: 1383–7.

282 Bell S, Davey P, Nathwani D *et al*. Risk of AKI with gentamicin as surgical prophylaxis. *J Am Soc Nephrol* 2014; **25**: 2625–32.

283 Landman D, Bratu S, Alam M *et al*. Citywide emergence of *Pseudomonas aeruginosa* strains with reduced susceptibility to polymyxin B. *J Antimicrob Chemother* 2005; **55**: 954–7.

284 Li J, Nation RL, Turnidge JD *et al*. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6**: 589–601.

285 Perez LR. Evaluation of polymyxin susceptibility profile among KPC-producing *Klebsiella pneumoniae* using Etest and MicroScan WalkAway automated system. *APMIS* 2015; **123**: 951–4.

286 Maalej SM, Meziou MR, Rhimi FM *et al*. Comparison of disc diffusion, Etest and agar dilution for susceptibility testing of colistin against Enterobacteriaceae. *Lett Appl Microbiol* 2011; **53**: 546–51.

287 Rojas LJ, Salim M, Cober E *et al*. Colistin resistance in carbapenem-resistant *Klebsiella pneumoniae*: laboratory detection and impact on mortality. *Clin Infect Dis* 2017; **64**: 711–8.

288 Cannatelli A, D'Andrea MM, Giani T *et al*. In vivo emergence of colistin resistance in *Klebsiella pneumoniae* producing KPC-type carbapenemases mediated by insertional inactivation of the PhoQ/PhoP mgrB regulator. *Antimicrob Agents Chemother* 2013; **57**: 5521–6.

289 Wang Y, Zhang R, Li J *et al*. Comprehensive resistome analysis reveals the prevalence of NDM and MCR-1 in Chinese poultry production. *Nat Microbiol* 2017; **2**: 16260.

290 Simmons NA. Colistin, sulphamethoxazole, and trimethoprim in synergy against Gram-negative bacteria. *J Clin Pathol* 1970; **23**: 757–64.

291 Nord CE, Wadstrom T, Wretlind B. Synergistic effect of combinations of sulfamethoxazole, trimethoprim, and colistin against *Pseudomonas maltophilia* and *Pseudomonas cepacia*. *Antimicrob Agents Chemother* 1974; **6**: 521–3.

292 Montgomerie JZ, Kalmanson GM, Guze LB. Synergism of polymyxin and sulfonamides in L-forms of *Staphylococcus aureus* and *Proteus mirabilis*. *Antimicrob Agents Chemother* 1973; **3**: 523–5.

293 Rosenblatt JE, Stewart PR. Combined activity of sulfamethoxazole, trimethoprim, and polymyxin B against gram-negative bacilli. *Antimicrob Agents Chemother* 1974; **6**: 84–92.

294 Thomas FE Jr, Leonard JM, Alford RH. Sulfamethoxazole-trimethoprim-polymyxin therapy of serious multiply drug-resistant *Serratia* infections. *Antimicrob Agents Chemother* 1976; **9**: 201–7.

295 Garonzik SM, Li J, Thamlikitkul V *et al*. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother* 2011; **55**: 3284–94.

296 Nation RL, Garonzik SM, Thamlikitkul V *et al*. Dosing guidance for intravenous colistin in critically-ill patients. *Clin Infect Dis* 2017; **64**: 565–71.

297 Nation RL, Garonzik SM, Li J *et al*. Updated US and European dose recommendations for intravenous colistin: how do they perform? *Clin Infect Dis* 2016; **62**: 552–8.

298 Jitmuang A, Nation RL, Koomanachai P *et al*. Extracorporeal clearance of colistin methanesulphonate and formed colistin in end-stage renal disease patients receiving intermittent haemodialysis: implications for dosing. *J Antimicrob Chemother* 2015; **70**: 1804–11.

299 Donnelly JP, Maschmeyer G, Daenen S. Selective oral antimicrobial prophylaxis for the prevention of infection in acute leukaemia-ciprofloxacin versus co-trimoxazole plus colistin. The EORTC-Gnotobiotic Project Group. *Eur J Cancer* 1992; **28A**: 873–8.

300 Noteboom Y, Ong DS, Oostdijk EA *et al*. Antibiotic-induced within-host resistance development of Gram-negative bacteria in patients receiving selective decontamination or standard care. *Crit Care Med* 2015; **43**: 2582–8.

301 Krueger WA, Heininger A, Grabein B *et al*. Selective digestive tract decontamination and spread of colistin resistance: antibiotic prophylaxis is not a substitute for hygiene. *Antimicrob Agents Chemother* 2014; **58**: 3574–5.

302 Halaby T, Al NN, Kluytmans J *et al*. Emergence of colistin resistance in Enterobacteriaceae after the introduction of selective digestive tract decontamination in an intensive care unit. *Antimicrob Agents Chemother* 2013; **57**: 3224–9.

303 Rawson TM, Moore LS, Hatcher JC *et al*. Plasmid-mediated colistin resistance mechanisms: is it time to revise our approach to selective digestive decontamination? *Lancet Infect Dis* 2016; **16**: 149–50.

304 Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ *et al*. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin Infect Dis* 2003; **36**: 1111–8.

305 Levin AS, Barone AA, Penco J *et al*. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999; **28**: 1008–11.

306 Linden PK, Kusne S, Coley K *et al*. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis* 2003; **37**: e154–60.

307 Markou N, Apostolakos H, Koumoudiou C *et al*. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. *Crit Care* 2003; **7**: R78–83.

308 Michalopoulos AS, Tsiodras S, Rellos K *et al*. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. *Clin Microbiol Infect* 2005; **11**: 115–21.

309 Reina R, Estenssoro E, Saenz G *et al*. Safety and efficacy of colistin in *Acinetobacter* and *Pseudomonas* infections: a prospective cohort study. *Intensive Care Med* 2005; **31**: 1058–65.

310 Giacobbe DR, Del BV, Trecarichi EM *et al*. Risk factors for bloodstream infections due to colistin-resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case-control-control study. *Clin Microbiol Infect* 2015; **21**: 1106–8.

311 Korbila IP, Michalopoulos A, Rafailidis PI *et al*. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect* 2010; **16**: 1230–6.

312 Kofteridis DP, Alexopoulou C, Valachis A *et al*. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. *Clin Infect Dis* 2010; **51**: 1238–44.

313 Nolan K, Knight H, Clark P. NICE guidance on colistimethate sodium and tobramycin for *Pseudomonas* lung infection in cystic fibrosis. *Lancet Respir Med* 2013; **1**: 102–3.

314 Kvitko CH, Rigatto MH, Moro AL *et al*. Polymyxin B versus other antimicrobials for the treatment of *Pseudomonas aeruginosa* bacteraemia. *J Antimicrob Chemother* 2011; **66**: 175–9.

315 Elias LS, Konzen D, Krebs JM *et al*. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. *J Antimicrob Chemother* 2010; **65**: 2231–7.

316 Tumbarello M, Viale P, Bassetti M *et al*. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study—authors' response. *J Antimicrob Chemother* 2015; **70**: 2922.

317 Lee GC, Burgess DS. Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a review of published case series and case reports. *Ann Clin Microbiol Antimicrob* 2012; **11**: 32.

318 Li J, Nation RL, Milne RW *et al*. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. *Int J Antimicrob Agents* 2005; **25**: 11–25.

319 Deryke CA, Crawford AJ, Uddin N *et al*. Colistin dosing and nephrotoxicity in a large community teaching hospital. *Antimicrob Agents Chemother* 2010; **54**: 4503–5.

320 Kim J, Lee KH, Yoo S *et al*. Clinical characteristics and risk factors of colistin-induced nephrotoxicity. *Int J Antimicrob Agents* 2009; **34**: 434–8.

321 Kelesidis T, Falagas ME. The safety of polymyxin antibiotics. *Expert Opin Drug Saf* 2015; **14**: 1687–701.

322 Tamma PD, Newland JG, Pannaraj PS *et al*. The use of intravenous colistin among children in the United States: results from a multicenter, case series. *Pediatr Infect Dis J* 2013; **32**: 17–22.

323 Nation RL, Li J, Cars O *et al*. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. *Lancet Infect Dis* 2015; **15**: 225–34.

324 Dalfino L, Puntillo F, Mosca A *et al*. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis* 2012; **54**: 1720–6.

325 Endimiani A, Luzzaro F, Perilli M *et al*. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment outcome of patients receiving imipenem or ciprofloxacin. *Clin Infect Dis* 2004; **38**: 243–51.

326 Paterson DL, Ko WC, Von GA *et al*. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. *Ann Intern Med* 2004; **140**: 26–32.

327 Chang YT, Lin CY, Chen YH *et al*. Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options. *Front Microbiol* 2015; **6**: 893.

328 Fabrega A, Madurga S, Giralt E *et al*. Mechanism of action of and resistance to quinolones. *Microb Biotechnol* 2009; **2**: 40–61.

329 Livermore DM. Tigecycline: what is it, and where should it be used? *J Antimicrob Chemother* 2005; **56**: 611–4.

330 Visalli MA, Murphy E, Projan SJ *et al*. AcrAB multidrug efflux pump is associated with reduced levels of susceptibility to tigecycline (GAR-936) in *Proteus mirabilis*. *Antimicrob Agents Chemother* 2003; **47**: 665–9.

331 Dean CR, Visalli MA, Projan SJ *et al*. Efflux-mediated resistance to tigecycline (GAR-936) in *Pseudomonas aeruginosa* PAO1. *Antimicrob Agents Chemother* 2003; **47**: 972–8.

332 Wang YF, Dowzicky MJ. In vitro activity of tigecycline and comparators on *Acinetobacter* spp. isolates collected from patients with bacteremia and MIC change during the Tigecycline Evaluation and Surveillance Trial, 2004 to 2008. *Diagn Microbiol Infect Dis* 2010; **68**: 73–9.

333 Peleg AY, Potoski BA, Rea R *et al*. *Acinetobacter baumannii* bloodstream infection while receiving tigecycline: a cautionary report. *J Antimicrob Chemother* 2007; **59**: 128–31.

334 Gordon NC, Wareham DW. A review of clinical and microbiological outcomes following treatment of infections involving multidrug-resistant *Acinetobacter baumannii* with tigecycline. *J Antimicrob Chemother* 2009; **63**: 775–80.

335 Hornsey M, Loman N, Wareham DW *et al*. Whole-genome comparison of two *Acinetobacter baumannii* isolates from a single patient, where resistance developed during tigecycline therapy. *J Antimicrob Chemother* 2011; **66**: 1499–503.

336 Navon-Venezia S, Leavitt A, Carmeli Y. High tigecycline resistance in multidrug-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 2007; **59**: 772–4.

337 Nigo M, Cevallos CS, Woods K *et al*. Nested case-control study of the emergence of tigecycline resistance in multidrug-resistant *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2013; **57**: 5743–6.

338 Park GE, Kang CI, Wi YM *et al*. Case-control study of the risk factors for acquisition of *Pseudomonas* and *Proteus* species during tigecycline therapy. *Antimicrob Agents Chemother* 2015; **59**: 5830–3.

339 Papakonstantinou I, Angelopoulos E, Baraboutis I *et al*. Risk factors for tracheobronchial acquisition of resistant Gram-negative bacterial pathogens in mechanically ventilated ICU patients. *J Chemother* 2015; **27**: 283–9.

340 Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis* 2007; **45**: 1602–9.

341 Babinchak T, Ellis-Grosse E, Dartois N *et al*. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin Infect Dis* 2005; **41**: S354–67.

342 Ellis-Grosse EJ, Babinchak T, Dartois N *et al*. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005; **41**: S341–53.

343 FDA. *Tygacil (tigecycline): Label Change—Increased Mortality Risk*. U.S. Food and Drug Administration, 2010. https://www.fda.gov/Drugs/DrugSafety/ucm224370.htm.

344 FDA. *Tigecycline*. 2013. https://www.fda.gov/Drugs/DrugSafety/ucm369580.htm.

345 Tanaseanu C, Bergallo C, Teglia O *et al*. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. *Diagn Microbiol Infect Dis* 2008; **61**: 329–38.

346 Freire AT, Melnyk V, Kim MJ *et al*. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* 2010; **68**: 140–51.

347 Curcio D. Tigecycline for severe infections: the gap between the warning and the necessity. *J Antimicrob Chemother* 2011; **66**: 454–6.

348 Shen F, Han Q, Xie D *et al*. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. *Int J Infect Dis* 2015; **39**: 25–33.

349 De PG, Montini L, Pennisi M *et al*. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Crit Care* 2014; **18**: R90.

350 Tumbarello M, Viale P, Viscoli C *et al*. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin Infect Dis* 2012; **55**: 943–50.

351 Daikos GL, Tsaousi S, Tzouvelekis LS *et al*. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Agents Chemother* 2014; **58**: 2322–8.

352 Karageorgopoulos DE, Kelesidis T, Kelesidis I *et al*. Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) *Acinetobacter* infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008; **62**: 45–55.

353 Kelesidis T, Karageorgopoulos DE, Kelesidis I *et al*. Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies. *J Antimicrob Chemother* 2008; **62**: 895–904.

354 Sutcliffe JA, O'Brien W, Fyfe C *et al*. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. *Antimicrob Agents Chemother* 2013; **57**: 5548–58.

355 Abdallah M, Olafisoye O, Cortes C *et al*. Activity of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including multidrug-resistant isolates, from New York City. *Antimicrob Agents Chemother* 2015; **59**: 1802–5.

356 Solomkin JS, Ramesh MK, Cesnauskas G *et al*. Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. *Antimicrob Agents Chemother* 2014; **58**: 1847–54.

357 Kaase M, Szabados F, Anders A *et al*. Fosfomycin susceptibility in carbapenem-resistant Enterobacteriaceae from Germany. *J Clin Microbiol* 2014; **52**: 1893–7.

358 Ode B, Haidl S, Hoffstedt B *et al*. Fosfomycin versus ampicillin in the treatment of acute pyelonephritis. *Chemioterapia* 1988; **7**: 96–100.

359 Florent A, Chichmanian RM, Cua E *et al*. Adverse events associated with intravenous fosfomycin. *Int J Antimicrob Agents* 2011; **37**: 82–3.

360 Parker S, Lipman J, Koulenti D *et al*. What is the relevance of fosfomycin pharmacokinetics in the treatment of serious infections in critically ill patients? A systematic review. *Int J Antimicrob Agents* 2013; **42**: 289–93.

361 Michalopoulos A, Virtzili S, Rafailidis P *et al*. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. *Clin Microbiol Infect* 2010; **16**: 184–6.

362 Pontikis K, Karaiskos I, Bastani S *et al*. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. *Int J Antimicrob Agents* 2014; **43**: 52–9.

363 Falagas ME, Giannopoulou KP, Kokolakis GN *et al*. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008; **46**: 1069–77.

364 Livermore DM, Mushtaq S, Warner M *et al*. Comparative in vitro activity of sulfametrole/trimethoprim and sulfamethoxazole/trimethoprim and other agents against multiresistant Gram-negative bacteria. *J Antimicrob Chemother* 2014; **69**: 1050–6.

365 Barbolla R, Catalano M, Orman BE *et al*. Class 1 integrons increase trimethoprim-sulfamethoxazole MICs against epidemiologically unrelated *Stenotrophomonas maltophilia* isolates. *Antimicrob Agents Chemother* 2004; **48**: 666–9.

366 Falagas ME, Vardakas KZ, Kapaskelis A *et al*. Tetracyclines for multidrug-resistant *Acinetobacter baumannii* infections. *Int J Antimicrob Agents* 2015; **45**: 455–60.

367 Doi Y, Paterson DL. Carbapenemase-producing Enterobacteriaceae. *Semin Respir Crit Care Med* 2015; **36**: 74–84.

368 Levy HG, Gould I, Endimiani A *et al*. Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: recommendations from an International Working Group. *J Chemother* 2013; **25**: 129–40.

369 Paul M, Carmeli Y, Durante-Mangoni E *et al*. Combination therapy for carbapenem-resistant Gram-negative bacteria. *J Antimicrob Chemother* 2014; **69**: 2305–9.

370 Falagas ME, Lourida P, Poulikakos P *et al*. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. *Antimicrob Agents Chemother* 2014; **58**: 654–63.

371 Qureshi ZA, Paterson DL, Potoski BA *et al*. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother* 2012; **56**: 2108–13.

372 Zarkotou O, Pournaras S, Tselioti P *et al*. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin Microbiol Infect* 2011; **17**: 1798–803.

373 Ni W, Cai X, Wei C *et al*. Efficacy of polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. *Braz J Infect Dis* 2015; **19**: 170–80.

374 Zusman O, Altunin S, Koppel F *et al*. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. *J Antimicrob Chemother* 2017; **72**: 29–39.

375 Tzouvelekis LS, Markogiannakis A, Piperaki E *et al*. Treating infections caused by carbapenemase-producing Enterobacteriaceae. *Clin Microbiol Infect* 2014; **20**: 862–72.

376 Pea F, Della SP, Cojutti P *et al*. Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing *Klebsiella pneumoniae*? *Int J Antimicrob Agents* 2017; **49**: 255–8.

377 Ceccarelli G, Falcone M, Giordano A *et al*. Successful ertapenem-doripenem combination treatment of bacteremic ventilator-associated pneumonia due to colistin-resistant KPC-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2013; **57**: 2900–1.

378 Oliva A, D'Abramo A, D'Agostino C *et al*. Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections. *J Antimicrob Chemother* 2014; **69**: 1718–20.

379 Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F *et al*. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother* 2015; **70**: 905–13.

380 Eckmann C, Montravers P, Bassetti M *et al*. Efficacy of tigecycline for the treatment of complicated intra-abdominal infections in real-life clinical practice from five European observational studies. *J Antimicrob Chemother* 2013; **68**: ii25–35.

381 Heizmann WR, Dupont H, Montravers P *et al*. Resistance mechanisms and epidemiology of multiresistant pathogens in Europe and efficacy of tigecycline in observational studies. *J Antimicrob Chemother* 2013; **68**: ii45–55.

382 Durante-Mangoni E, Signoriello G, Andini R *et al*. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis* 2013; **57**: 349–58.

383 Batirel A, Balkan II, Karabay O *et al*. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1311–22.

384 Lopez-Cortes LE, Cisneros JM, Fernandez-Cuenca F *et al*. Monotherapy versus combination therapy for sepsis due to multidrug-resistant *Acinetobacter baumannii*: analysis of a multicentre prospective cohort. *J Antimicrob Chemother* 2014; **69**: 3119–26.

385 Pena C, Suarez C, Ocampo-Sosa A *et al*. Effect of adequate single-drug vs combination antimicrobial therapy on mortality in *Pseudomonas aeruginosa* bloodstream infections: a post hoc analysis of a prospective cohort. *Clin Infect Dis* 2013; **57**: 208–16.

386 Paul M, Silbiger I, Grozinsky S *et al*. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2006; issue **1**: CD003344.

387 Pistiki A, Tsaganos T, Galani I *et al*. In vitro activity of oral cephalosporins (cefprozil and cefixime) against ciprofloxacin-resistant Enterobacteriaceae from community-acquired urinary-tract infections. *Infect Dis Ther* 2015; **4**: 425–32.

388 Bingen E, Bidet P, D'humieres C *et al*. In vitro interaction between cefepime and amoxicillin-clavulanate against extended-spectrum beta-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2013; **57**: 2437–9.

389 Livermore DM, Mushtaq S, Nguyen T *et al*. Strategies to overcome extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases in shigellae. *Int J Antimicrob Agents* 2011; **37**: 405–9.

390 Atherton FR, Hall MJ, Hassall CH *et al*. Antibacterial properties of alafosfalin combined with cephalexin. *Antimicrob Agents Chemother* 1981; **20**: 470–6.

391 Ben-Ami R, Rodriguez-Bano J, Arslan H *et al*. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis* 2009; **49**: 682–90.

392 Rooney PJ, O'Leary MC, Loughrey AC *et al*. Nursing homes as a reservoir of extended-spectrum beta-lactamase (ESBL)-producing ciprofloxacin-resistant *Escherichia coli*. *J Antimicrob Chemother* 2009; **64**: 635–41.

393 Hayakawa K, Gattu S, Marchaim D *et al*. Epidemiology and risk factors for isolation of *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamase in a large U.S. Medical Center. *Antimicrob Agents Chemother* 2013; **57**: 4010–8.

394 Karanika S, Karantanos T, Arvanitis M *et al*. Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis* 2016; **63**: 310–8.

395 Rogers BA, Ingram PR, Runnegar N *et al*. Community-onset *Escherichia coli* infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. *Antimicrob Agents Chemother* 2014; **58**: 2126–34.

396 Titelman E, Hasan CM, Iversen A *et al*. Faecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae is common 12 months after infection and is related to strain factors. *Clin Microbiol Infect* 2014; **20**: O508–15.

397 Johnson SW, Anderson DJ, May DB *et al*. Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae on hospital admission. *Infect Control Hosp Epidemiol* 2013; **34**: 385–92.

398 Rodriguez BJ, Picon E, Gijon P *et al*. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli*: risk factors and prognosis. *Clin Infect Dis* 2010; **50**: 40–8.

399 Colpan A, Johnston B, Porter S *et al*. *Escherichia coli* sequence type 131 (ST131) subclone H30 as an emergent multidrug-resistant pathogen among US veterans. *Clin Infect Dis* 2013; **57**: 1256–65.

400 Gossius G, Vorland L. The treatment of acute dysuria-frequency syndrome in adult women: double-blind, randomized comparison of three-day vs ten-day trimethoprim therapy. *Curr Ther Res Clin Exp* 1985; **37**: 34–42.

401 Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 mL/min: looking for the evidence. *Ann Pharmacother* 2013; **47**: 106–11.

402 Vervoort J, Xavier BB, Stewardson A *et al*. Metagenomic analysis of the impact of nitrofurantoin treatment on the human faecal microbiota. *J Antimicrob Chemother* 2015; **70**: 1989–92.

403 Gupta K, Hooton TM, Stamm WE. Isolation of fluoroquinolone-resistant rectal *Escherichia coli* after treatment of acute uncomplicated cystitis. *J Antimicrob Chemother* 2005; **56**: 243–6.

404 Stamey TA, Condy M, Mihara G. Prophylactic efficacy of nitrofurantoin macrocrystals and trimethoprim-sulfamethoxazole in urinary infections. Biologic effects on the vaginal and rectal flora. *N Engl J Med* 1977; **296**: 780–3.

405 Brumfitt W, Hamilton-Miller JM. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother* 1998; **42**: 363–71.

406 Geerts AF, Eppenga WL, Heerdink R *et al*. Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. *Eur J Clin Pharmacol* 2013; **69**: 1701–7.

407 Medicines and Healthcare Regulatory Agency. *Nitrofurantoin now Contraindicated in Most Patients with an Estimated Glomerular Filtration Rate (eGFR) of Less Than 45 ml/min/1.73m^2*. 2014. https://www.gov.uk/drug-safety-update/nitrofurantoin-now-contraindicated-in-most-patients-with-an-estimated-glomerular-filtration-rate-egfr-of-less-than-45-ml-min-1-73m2.

408 Goemaere NN, Grijm K, van Hal PT *et al*. Nitrofurantoin-induced pulmonary fibrosis: a case report. *J Med Case Rep* 2008; **2**: 169.

409 Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother* 1994; **33**: 121–9.

410 Huttner A, Verhaegh EM, Harbarth S *et al*. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. *J Antimicrob Chemother* 2015; **70**: 2456–64.

411 Cha MK, Kang CI, Kim SH *et al*. Comparison of the microbiological characteristics and virulence factors of ST131 and non-ST131 clones among extended-spectrum beta-lactamase-producing *Escherichia coli* causing bacteremia. *Diagn Microbiol Infect Dis* 2016; **84**: 102–4.

412 Borgia M, Longo A, Lodola E. Relative bioavailability of fosfomycin and of trometamol after administration of single dose by oral route of fosfomycin trometamol in fasting conditions and after a meal. *Int J Clin Pharmacol Ther Toxicol* 1989; **27**: 411–7.

413 Zhanel GG, Walkty AJ, Karlowsky JA. Fosfomycin: a first-line oral therapy for acute uncomplicated cystitis. *Can J Infect Dis Med Microbiol* 2016; **2016**: 2082693.

414 Janknegt R, Hooymans PM, Fabius GT *et al*. Urinary concentrations of fosfomycin after a single 3 g dose of fosfomycin to elderly nursing-home patients. *Pharm World Sci* 1994; **16**: 149–53.

415 NICE. *Multidrug Resistant Urinary Tract Infections: Fosfomycin Trometamol—Evidence Summary (ESUOM17)*. National Institute for Health and Care Excellence, 2013. https://www.nice.org.uk/advice/esuom17/chapter/Key-points-from-the-evidence.

416 Sougakoff W, Jarlier V. Comparative potency of mecillinam and other beta-lactam antibiotics against *Escherichia coli* strains producing different beta-lactamases. *J Antimicrob Chemother* 2000; **46**: 9–14.

417 Thomas K, Weinbren MJ, Warner M *et al*. Activity of mecillinam against ESBL producers in vitro. *J Antimicrob Chemother* 2006; **57**: 367–8.

418 Lampri N, Galani I, Poulakou G *et al*. Mecillinam/clavulanate combination: a possible option for the treatment of community-acquired uncomplicated urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2012; **67**: 2424–8.

419 Thulin E, Sundqvist M, Andersson DI. Amdinocillin (mecillinam) resistance mutations in clinical isolates and laboratory-selected mutants of *Escherichia coli*. *Antimicrob Agents Chemother* 2015; **59**: 1718–27.

420 Marrs EC, Day KM, Perry JD. In vitro activity of mecillinam against Enterobacteriaceae with NDM-1 carbapenemase. *J Antimicrob Chemother* 2014; **69**: 2873–5.

421 Jenson K, Henriksen A, Frimodt-Moeller N. *Pivmecillinam: Estimation of Adequate Dosage for Susceptible and ESBL-Producing E. coli by Monte Carlo - PK/PD Simulation*. Poster P1255. The European Society of Clinical Microbiology and Infectious Diseases, 2008.

422 Cox CE. Parenteral amdinocillin for treatment of complicated urinary tract infections. *Am J Med* 1983; **75**: 82–4.

423 Damsgaard T, Jacobsen J, Korner B *et al*. Pivmecillinam and trimethoprim/sulfamethoxazole in the treatment of bacteriuria. A bacteriological and pharmacokinetic study. *J Antimicrob Chemother* 1979; **5**: 267–74.

424 Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; **46**: 35–9.

425 Ferry SA, Holm SE, Stenlund H *et al*. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. *Scand J Prim Health Care* 2007; **25**: 49–57.

426 Carlsen NL, Hesselbjerg U, Glenting P. Comparison of long-term, low-dose pivmecillinam and nitrofurantoin in the control of recurrent urinary tract infection in children. An open, randomized, cross-over study. *J Antimicrob Chemother* 1985; **16**: 509–17.

427 Neu HC. Amdinocillin: a novel penicillin. Antibacterial activity, pharmacology and clinical use. *Pharmacotherapy* 1985; **5**: 1–10.

428 Jansaker F, Frimodt-Moller N, Sjogren I *et al*. Clinical and bacteriological effects of pivmecillinam for ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* in urinary tract infections. *J Antimicrob Chemother* 2014; **69**: 769–72.

429 Public Health England. *Management of Infection Guidance for Primary Care for Consultation and Local Adaption*. 2017. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/612744/Managing_common_infections_summary_tables.pdf.

430 Soraas A, Sundsfjord A, Jorgensen SB *et al*. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PLoS One* 2014; **9**: e85889.

431 Neu HC. Mecillinam–an amidino penicillin which acts synergistically with other beta-lactam compounds. *J Antimicrob Chemother* 1977; **3**: 43–52.

432 Eriksson S, Zbornik J, Dahnsjo H *et al*. The combination of pivampicillin and pivmecillinam versus pivampicillin alone in the treatment of acute pyelonephritis. *Scand J Infect Dis* 1986; **18**: 431–8.

433 Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. *J Antimicrob Chemother* 2014; **69**: 303–8.

434 Baines SD, O'Connor R, Huscroft G *et al*. Mecillinam: a low-risk antimicrobial agent for induction of *Clostridium difficile* infection in an in vitro human gut model. *J Antimicrob Chemother* 2009; **63**: 838–9.

435 Little P, Turner S, Rumsby K *et al*. Validating the prediction of lower urinary tract infection in primary care: sensitivity and specificity of urinary dipsticks and clinical scores in women. *Br J Gen Pract* 2010; **60**: 495–500.

436 Little P, Turner S, Rumsby K *et al*. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative. *Heath Technol Assess* 2009; **13**: 1–73.

437 Bent S, Nallamothu BK, Simel DL *et al*. Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 2002; **287**: 2701–10.

438 Ipe DS, Sundac L, Benjamin WH Jr *et al*. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. *FEMS Microbiol Lett* 2013; **346**: 1–10.

439 Abrutyn E, Mossey J, Berlin JA *et al*. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Ann Intern Med* 1994; **120**: 827–33.

440 Nicolle LE, Bradley S, Colgan R *et al*. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; **40**: 643–54.

441 Shapiro M, Simchen E, Izraeli S *et al*. A multivariate analysis of risk factors for acquiring bacteriuria in patients with indwelling urinary catheters for longer than 24 hours. *Infect Control* 1984; **5**: 525–32.

442 Warren JW, Platt R, Thomas RJ *et al*. Antibiotic irrigation and catheter-associated urinary-tract infections. *N Engl J Med* 1978; **299**: 570–3.

443 Shekelle PG, Morton SC, Clark KA *et al*. Systematic review of risk factors for urinary tract infection in adults with spinal cord dysfunction. *J Spinal Cord Med* 1999; **22**: 258–72.

444 Loeb M, Brazil K, Lohfeld L *et al*. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *BMJ* 2005; **331**: 669.

445 Albert X, Huertas I, Pereiro II *et al*. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004; issue **3**: CD001209.

446 Stapleton A, Latham RH, Johnson C *et al*. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo-controlled trial. *JAMA* 1990; **264**: 703.

447 Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary infections during pregnancy. *Clin Infect Dis* 1992; **14**: 810–4.

448 Pfau A, Sacks TG. Effective prophylaxis for recurrent urinary tract infections during pregnancy. *Clin Infect Dis* 1992; **14**: 810–4.

449 Grabe M, Bartoletti R, Bjerklund Johansen T *et al*. *Guidelines on Urological Infections*. European Association of Urology, 2015. http://uroweb.org/wp-content/uploads/EAU-Guidelines-Urological-Infections-v2.pdf.

450 Beerepoot MA, ter Riet G, Nys S *et al*. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. *Arch Intern Med* 2011; **171**: 1270–8.

451 Ludwig M, Hoyme U, Weidner W. Recurrent urinary tract infection in women: long-term antibiotic prophylaxis. *Urologe (Ausg A)* 2006; **45**: 436–42.

452 Bitsori M, Maraki S, Galanakis E. Long-term resistance trends of uropathogens and association with antimicrobial prophylaxis. *Pediatr Nephrol* 2014; **29**: 1053–8.

453 NICE. *Urinary Incontinence in Neurological Disease; Assessment and Management*. National Institute of Care and Health Excellence, Clinical Guidance CG148, 2012. https://www.nice.org.uk/guidance/cg148.

454 McNulty CA, Richards J, Livermore DM *et al*. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *J Antimicrob Chemother* 2006; **58**: 1000–8.

455 Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clin Ther* 1999; **21**: 1864–72.

456 Van Pienbroek E, Hermans J, Kaptein AA *et al*. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharm World Sci* 1993; **15**: 257–62.

457 Sabada-Diaz de Rada B, Azanza-Perea JR, Garcia-Quetglas E *et al*. Fosfomycin trometamol: multiple dose regimen for the treatment of lower urinary tract infections. *Enfermedades Infecciosas y Microbologia Clinica* 2006; **24**: 546–50.

458 Ejrnaes K, Stegger M, Reisner A *et al*. Characteristics of *Escherichia coli* causing persistence or relapse of urinary tract infections: phylogenetic groups, virulence factors and biofilm formation. *Virulence* 2011; **2**: 528–37.

459 Park SH, Choi SM, Chang YK *et al*. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum beta-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2014; **69**: 2848–56.

460 Talan DA, Stamm WE, Hooton TM *et al*. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. *JAMA* 2000; **283**: 1583–90.

461 Morata L, Cobos-Trigueros N, Martinez JA *et al*. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 2012; **56**: 4833–7.

462 Leibovici L, Paul M, Ezra O. Ethical dilemmas in antibiotic treatment. *J Antimicrob Chemother* 2012; **67**: 12–6.

463 Hillier S, Bell J, Heginbothom M *et al*. When do general practitioners request urine specimens for microbiology analysis? The applicability of antibiotic resistance surveillance based on routinely collected data. *J Antimicrob Chemother* 2006; **58**: 1303–6.

464 Magee JT. Effects of duplicate and screening isolates on surveillance of community and hospital antibiotic resistance. *J Antimicrob Chemother* 2004; **54**: 155–62.

465 Livermore DM, Threlfall EJ, Reacher MH *et al*. Are routine sensitivity test data suitable for the surveillance of resistance? Resistance rates amongst *Escherichia coli* from blood and CSF from 1991-1997, as assessed by routine and centralized testing. *J Antimicrob Chemother* 2000; **45**: 205–11.

466 Public Health England. *Antimicrobial Prescribing and Stewardship Competencies*. PHE, 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/253094/ARHAIprescrcompetencies__2_.pdf.

467 NICE. *Antimicrobial Stewardship: Systems and Processes for Effective Antimicrobial Medicine Use, NICE Guideline NG15*. National Institute for Health and Care Excellence, 2015. https://www.nice.org.uk/guidance/ng15.

468 Davey P, Brown E, Charani E *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; issue **2**; CD003543.

469 Calil R, Marba ST, von NA *et al*. Reduction in colonization and nosocomial infection by multiresistant bacteria in a neonatal unit after institution of educational measures and restriction in the use of cephalosporins. *Am J Infect Control* 2001; **29**: 133–8.

470 Carling P, Fung T, Killion A *et al*. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003; **24**: 699–706.

471 Gerding DN, Larson TA. Aminoglycoside resistance in gram-negative bacilli during increased amikacin use. Comparison of experience in 14 United States hospitals with experience in the Minneapolis Veterans Administration Medical Center. *Am J Med* 1985; **79**: 1–7.

472 Leverstein-van Hall MA, Fluit AC, Blok HE *et al*. Control of nosocomial multiresistant Enterobacteriaceae using a temporary restrictive antibiotic agent policy. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 785–91.

473 Meyer KS, Urban C, Eagan JA *et al*. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. *Ann Intern Med* 1993; **119**: 353–8.

474 de Champs C, Franchineau P, Gourgand JM *et al*. Clinical and bacteriological survey after change in aminoglycoside treatment to control an epidemic of *Enterobacter cloacae*. *J Hosp Infect* 1994; **28**: 219–29.

475 Landman D, Chockalingam M, Quale JM. Reduction in the incidence of methicillin-resistant *Staphylococcus aureus* and ceftazidime-resistant *Klebsiella pneumoniae* following changes in a hospital antibiotic formulary. *Clin Infect Dis* 1999; **28**: 1062–6.

476 Toltzis P, Dul MJ, Hoyen C *et al*. The effect of antibiotic rotation on colonization with antibiotic-resistant bacilli in a neonatal intensive care unit. *Pediatrics* 2002; **110**: 707–11.

477 de Man P, Verhoeven BA, Verbrugh HA *et al*. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet* 2000; **355**: 973–8.

478 Davey P, Marwick CA, Scott CL *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; issue **2**: CD003543.

479 Plachouras D, Hopkins S. Antimicrobial stewardship: we know it works; time to make sure it is in place everywhere. *Cochrane Database Syst Rev* 2017; issue **2**: CD000119.

480 Kaki R, Elligsen M, Walker S *et al*. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011; **66**: 1223–30.

481 Drekonja D, Filice G, Greer N *et al*. *Antimicrobial Stewardship Programs in Outpatient Settings: A Systematic Review*. Washington DC, USA: Department of Veterans Affairs (US), Evidence based Synthesis Program (ESP) Center, Minneapolis, 2014. https://www.hsrd.research.va.gov/publications/esp/default.cfm.

482 Filice G, Drekonja D, Greer N *et al*. *Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review [Internet]*. Washington DC, USA: Department of Veteran Affairs (US), VA Evidence-based synthesis program reports, 2013. https://www.hsrd.research.va.gov/publications/esp/antimicrobial.cfm.

483 Wagner B, Filice GA, Drekonja D *et al*. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. *Infect Control Hosp Epidemiol* 2014; **35**: 1209–28.

484 Drekonja D, Filice G, Greer N *et al*. *Antimicrobial Stewardship Programs in Outpatient Settings: A Systematic Review*. Washington DC, USA: Department of Veterans Affairs (US), 2015; 142–152.

485 Dortch MJ, Fleming SB, Kauffmann RM *et al*. Infection reduction strategies including antibiotic stewardship protocols in surgical and trauma intensive care units are associated with reduced resistant gram-negative healthcare-associated infections. *Surg Infect (Larchmt)* 2011; **12**: 15–25.

486 Yong MK, Buising KL, Cheng AC *et al*. Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. *J Antimicrob Chemother* 2010; **65**: 1062–9.

487 Borer A, Eskira S, Nativ R *et al*. A multifaceted intervention strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant *Klebsiella pneumoniae* in Southern Israel. *Infect Control Hosp Epidemiol* 2011; **32**: 1158–65.

488 Chastre J, Wolff M, Fagon JY *et al*. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003; **290**: 2588–98.

489 Howard P, Pulcini C, Levy HG *et al*. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother* 2015; **70**: 1245–55.

490 Murray CK, Yun HC, Griffith ME *et al*. Recovery of multidrug-resistant bacteria from combat personnel evacuated from Iraq and Afghanistan at a single military treatment facility. *Mil Med* 2009; **174**: 598–604.

491 Shannon KP, King A, Phillips I *et al*. Importance of organisms producing broad-spectrum SHV-group beta-lactamases into the United Kingdom. *J Antimicrob Chemother* 1990; **25**: 343–51.

492 Woodford N, Turton JF, Livermore D. Multiresistant Gram-negative bacteria: the role of high risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011; **35**: 736–55.

493 Kallogjeri D, Gaynor SM, Piccirillo ML *et al*. Comparison of comorbidity collection methods. *J Am Coll Surg* 2014; **219**: 245–55.

494 Bannay A, Chaignot C, Blotiere PO *et al*. The best use of the Charlson comorbidity index with electronic health care database to predict mortality. *Med Care* 2016; **54**: 188–94.

495 Butler CC, Simpson SA, Dunstan F *et al*. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012; **344**: d8173.

496 Francis NA, Butler CC, Hood K *et al*. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009; **339**: b2885.

497 Giguere A, Legare F, Grimshaw J *et al*. Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; issue **10**: CD004398.

498 Ivers N, Jamtvedt G, Flottorp S *et al*. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; issue **6**: CD000259.

499 Dancer SJ. The effect of antibiotics on methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 2008; **61**: 246–53.

500 Ashiru-Oredope D, Sharland M, Charani E *et al*. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: start smart—then focus. *J Antimicrob Chemother* 2012; **67**: i51–63.

501 Smeets HM, Kuyvenhoven MM, Akkerman AE *et al*. Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: a controlled before and after study. *Fam Pract* 2009; **26**: 183–7.

502 Garrod LP, Shooter RA, Curwen MP. The results of chemotherapy in urinary infections. *Br Med J* 1954; **2**: 1003–8.

503 Shields RK, Potoski BA, Haidar G *et al*. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis* 2016; **63**: 1615–8.

504 Chen X, Zhang W, Yin J *et al*. *Escherichia coli* isolates from sick chickens in China: changes in antimicrobial resistance between 1993 and 2013. *Vet J* 2014; **202**: 112–5.

505 Koomanachai P, Tiengrim S, Kiratisin P *et al*. Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand. *Int J Infect Dis* 2007; **11**: 402–6.

506 EUCAST. *Recommendations for MIC determination of colistin (polymyxin E) as recommended by the joint CLSI-EUCAST Polymyxin Breakpoint Working Group*. 2016. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/General_documents/Recommendations_for_MIC_determination_of_colistin_March_2016.pdf.

507 Vasoo S. Susceptibility testing for the polymyxins: two steps back, three steps forward? *J Clin Microbiol* 2017; **55**: 2573–82.

508 Chew KL, La MV, Lin RTP *et al*. Colistin and polymyxin B susceptibility testing for carbapenem-resistant and mcr-positive Enterobacteriaceae: comparison of Sensititre, MicroScan, Vitek 2, and Etest with BROTH MICRODILUTION. *J Clin Microbiol* 2017; **55**: 2609–16.

509 Vourli S, Dafopoulou K, Vrioni G *et al*. Evaluation of two automated systems for colistin susceptibility testing of carbapenem-resistant *Acinetobacter baumannii* clinical isolates. *J Antimicrob Chemother* 2017; **72**: 2528–30.

510 El Garch F, Sauget M, Hocquet D *et al*. mcr-1 is borne by highly diverse *Escherichia coli* isolates since 2004 in food-producing animals in Europe. *Clin Microbiol Infect* 2017; **23**: 51 e1–e4.

511 Dayan N, Dabbah H, Weissman I *et al*. Urinary tract infections caused by community-acquired extended-spectrum beta-lactamase-producing and non-producing bacteria: a comparative study. *J Pediatrics* 2013; 1417–21.

512 Milo G, Katchman EA, Paul M *et al*. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev* 2005; issue **2:** CD004682.

513 Davey P, Marwick CA, Scott CL *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; issue **2**: CD003543.

514 Weinbren MJ, Borthwick MA. Rapid detection of extended-spectrum beta-lactamase (ESBL)-producing organisms in blood culture. *J Antimicrob Chemother* 2005; **55**: 131–2.

515 Decousser JW, Poirel L, Nordmann P. Recent advances in biochemical and molecular diagnostics for the rapid detection of antibiotic-resistant Enterobacteriaceae: a focus on β-lactam resistance. *Expert Rev Mol Diagn* 2017; **17**: 327–50.

516 Lupo A, Papp-Wallace KM, Sendi P *et al*. Non-phenotypic tests to detect and characterize antibiotic resistance mechanisms in Enterobacteriaceae. *Diagn Microbiol Infect Dis* 2013; **77**: 179–94.

517 Deurenberg RH, Bathoorn E, Chlebowicz MA *et al*. Application of next generation sequencing in clinical microbiology and infection prevention. *J Biotechnol* 2017; **243**: 16–24.

518 Jagtap P, Sritharan V, Gupta S. Nanotheranostic approaches for management of bloodstream bacterial infections. *Nanomedicine* 2017; **13**: 329–41.

519 McNulty CAM, Lecky DM, XU-McCrae L *et al*. CTX-M ESBL-producing Enterobacteriaceae: estimated prevalence in adults in England in 2014. *J Antimicrob Chemother* 2018; **73**: doi:10.1093/jac/dky007.