*Antimicrobial Practice*

# Sparing Carbapenem Usage

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## Carbapenem-sparing regimens

Synopsis

Background

Carbapenem resistance in Gram-negative bacteria is increasing in many countries and use of carbapenems and antibiotics to which resistance is linked should be reduced to slow its emergence. There are no directly equivalent antibiotics and the alternatives are less well supported by clinical trials. The few new agents are expensive.

Objective

To provide guidance on strategies to reduce carbapenem usage.

Methods

Review of literature was performed as described in the Joint Working Party Report.

Results

Older agents remain active against some of the pathogens, although the expectations of broad spectrum cover for empirical treatment has risen. Education, expert advice on treatment and antimicrobial stewardship can produce significant reductions in use.

Conclusions

More agents may need to be introduced onto the antibiotic formulary of the hospital, despite the poor quality of scientific studies in some cases.

Background

The number of patients with infections caused by Gram-negative bacteria resistant to carbapenems is increasing.[1] However empirical use of these agents, especially meropenem, is rising because of anxiety to ensure empirical regimens for treating sepsis are active against a wide spectrum of pathogens, including those resistant to first line agents.[2] National outbreaks of meropenem resistance have already been seen.[1] Governments are now considering strategies to halt the rise in usage. A systematic literature review was conducted as part of a recent Working Party Report.[1]

Using antimicrobials only when strictly indicated and preferably narrow spectrum (i.e antimicrobial stewardship) is the major defence against antimicrobial resistance other than infection control measures. Molecular tests for identification and resistance profile are becoming useful for targeting antimicrobial prescription. In England, the Chief Medical Officer has produced a strategy to limit the emergence of resistant organisms and is encouraging the pharmaceutical industry to invest in development of new agents.[3] Unless alternative means of funding are devised, the need to restrict prescription of new agents to prevent emergence of resistance remains a disincentive to commercial investment.

Multidrug resistant Gram-negative bacteria may be defined as having three or more antimicrobial resistance mechanisms affecting different antibiotic classes.[2] These include Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., Proteeae), and the non-fermenters: *Pseudomonas aeruginosa*, and *Acinetobacter baumannii.* The main concerns are those resistant to β-lactams, carbapenems, cephalosporins, β-lactamase inhibitor combinations and

fluoroquinolones. *Stenotrophomonas maltophilia* is intrinsically resistant to carbapenem. Strains producing AmpC β-lactamases are resistant to penicillins (except temocillin), cephalosporins, aztreonam and penicillin-β-lactamase-inhibitor combinations. Extended spectrum β-lactamases (ESBL) confer resistance to cefotaxime, ceftriaxone and ceftazidime but are inhibited by clavulanic acid and tazobactam. Carbapenemases, for example KPC, VIM, IMP, NDM and OXA-48, confer resistance to meropenem and ertapenem. Carbapenem resistance due to ESBL or AmpC enzymes combined with porin loss may lead to treatment failure, for example with *Pseudomonas aeruginosa*.

Evidence that carbapenem use and resistance are related depends mostly on observational and retrospective studies. Increased use of carbapenems, for example as the result of cephalosporin restriction, has been associated with increased carbapenem resistance in *Acinetobacter* sp and *Pseudomonas aeruginosa* [4-7]. A matched case control study of multiply-resistant *Acinetobacter* in intensive care units reported similar findings.[8] Conversely, decreased use of carbapenem following antibiotic restriction and education programs has been associated with reduced carbapenem resistance in *Pseudomonas aeruginosa* and *Acinetobacter* sp.[9-12]

A relationship between use of carbapenems and resistance in Enterobacteriaceae was not demonstrated in observational studies conducted in areas where prevalence of resistance was low.[7,12-14] However, meropenem consumption was significantly correlated to resistance rates in *E coli* and *Klebsiella pneumoniae* where prevalence was high.[15] Another study in UK evaluated the impact of antimicrobial stewardship using segmented regression analysis of interrupted time series and pharmacy

consumption data.[16] Reduced meropenem consumption was associated with reduction in the incidence of OXA-48-producing *K. pneumoniae .*

Although multidrug resistant organisms are often first recognised in hospitals, they are common in long-term care facilities.[17] Resistance to several types of antibiotic can be carried on a single transferable genetic element. Treatment with carbapenems, aminoglycosides or cephalosporins can be associated with acquisition of resistance to ciprofloxacin as much as following treatment with ciprofloxacin itself.[18] These organisms can remain in the gut for a up to a year. Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter,* whether resistant or not, can be transferred between patients by staff or environment. Although outbreaks of a single species of resistant organism can be recognised and controlled, some outbreaks involve plasmids passed between species.[19] *P. aeruginosa* may be resistant through many mechanisms including reduced permeability. The organism is associated with water sources in the environment and can be transmitted following hand hygiene.[2]

To prevent these organisms spreading requires a high level of compliance to standard infection control precautions (SICP) including hand hygiene, use of personal protective equipment and a clean environment.[2] A national intervention in Israel with mandatory patient screening, cohorting of staff and source isolation was effective in controlling an outbreak of carbapenemase-producing *K. pneumoniae*.[20] Rectal swabs for screening at admission identify and allow isolation of carriers but the cost and need for an invasive investigation has limited adoption of routine screening. Control of carbapenemase–producing *K. pneumoniae* has failed in Greece and Italy.[21]

In patients with haematological malignancies, colonization with ESBL-producing Enterobacteriaceae has been reported in 5.3- 21.8% of patients, encouraging empirical carbapenem usage.[22] Carriage continues in at least 45% of patients for over 6 months.[23] Selective decontamination with non-absorbable as well as intravenous antibiotic only suppresses carriage transiently[24] and can be associated with emergence of resistance to the antibiotics used but may prevent some subsequent infections.[25]

Evidence for specific antimicrobials (Table 1)

*Carbapenems*

Meropenem and imipenem-cilastatin are very broad spectrum agents used in hospital-acquired infections when the primary antibiotic regimen has failed or resistance is suspected, for example, infections due to extended spectrum β-lactamase producers.[26] Ertapenem is not active against *Pseudomonas* or *Acinetobacter* and may be more likely than meropenem to select mutational resistance via porin loss in ESBL-producing *Klebsiella* sp and *Enterobacter* sp.[27]

The common indications for treatment with a carbapenem are urinary infections resistant to other antibiotics, intra-abdominal infection, acute pancreatitis and prevention of necrotizing pancreatitis, nosocomial pneumonia, bacterial meningitis, cystic fibrosis and febrile neutropenia.[26] In some countries, such as UK, the majority of prescriptions follow discussion with a microbiologist, providing the opportunity for an effective intervention. However elsewhere influencing choice may be much more difficult. Although not a major cause of quinolone resistance, the widespread use of

ciprofloxacin for prophylaxis in neutropenic patients may be a driver for linked resistances and increased use of carbapenems.[28] The use of meropenem to treat infections due to carbapenem-resistant Enterobacteriaceae is another potential risk and arises from some retrospective evidence that combinations including meropenem may reduce mortality.[29]

*Alternative antimicrobial drugs*

With very few new agents in prospect, older antibiotics effective against Gram-negative bacteria have been re-examined. Rather than choosing meropenem by default, piptazobactam can be used to treat susceptible ESBL-producing Enterobacteriaceae. In the UK, Working Party guidelines on treatment are soon to be published and provide detailed guidance (P Hawkey, personal communication).

The first group of alternatives are widely available in hospitals already:

Co-trimoxazole (trimethoprim/sulfamethoxazole) is the primary treatment for infections with *Stenotrophomonas maltophilia* .[30] It has a broad spectrum of inherent antibacterial activity, including Enterobacteriaceae, and *Haemophilus* sp although not *P. aeruginosa*. Severe though rare side effects, such as Stevens-Johnson syndrome, and frequent resistance to trimethoprim have limited its use.

Colistin (Polymyxin E) is a current rescue choice for treating infection with carbapenem-resistant Gram-negative organisms. It should not be used as a substitute for carbapenem. It is not active against *Proteus* spp. or *Serratia* spp. Studies of treatment of multidrug resistant bacterial infections have been uncontrolled

and of small size[31] and there are fears of under-dosing at current licensed doses.[32] Higher doses and use in combination may be needed for severe infections or where resistance is endemic. The main adverse effects are nephrotoxicity and neurotoxicity. The UK is one of the largest users of the antibiotic, mostly inhaled for management of cystic fibrosis.

Rifampicin has a broad spectrum of activity but resistance develops readily and use is not recommended. There are no *in vitro* breakpoint recommendations and its activity is probably a synergistic effect.[33]

Aminoglycosides remain active *in vitro* against more than 90% of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp bloodstream and urine isolates reported in UK and can be useful in combination regimens.[34,35] However, over half of Enterobacteriaceae producing CTX-M extended spectrum β-lactamases can be resistant to gentamicin.[36] Although persistent asymptomatic bacteriuria may occur, aminoglycosides can be safely used in the treatment of urinary infection.[37]

The second group of agents are available on the formulary of some hospitals but if an application to the hospital Drug and Therapeutics Committee has to be made, it may be challenging in view of the additional cost and limited supporting controlled clinical trials.

Temocillin is a derivative of ticarcillin, which is stable to some β-lactamases. It is effective against ESBL and AmpC-producing Enterobacteriaceae but not

*Pseudomonas* or *Acinetobacter*. Clinical studies are retrospective but suggest it can be used to treat multi-resistant urinary infection, although relatively expensive.[38]

Aztreonam has activity only against aerobic Gram-negative bacteria (although *P. aeruginosa* is only moderately susceptible). It has been used to treat serious Gram-negative infections and it is safe in penicillin allergy. It may be hydrolysed by extended spectrum β-lactamases but is stable to some metallo- β-lactamases. A Japanese study suggested similar efficacy sulbactam/ampicillin plus aztreonam versus piperacillin/tazobactam plus ceftazidime in febrile episodes paediatric haematology or oncology but carbapenems were not included.[39]

Fosfomycin has been used as an oral agent (single dose) for treating multiresistant lower urinary infections. It is primarily active against *E. coli* (including ESBL*)*, *Citrobacter* and *Proteus mirabilis.* Intravenous fosfomycin is now more widely available but is significantly more expensive than other antibiotics. In combination with colistin or tigecycline, clinical success was reported in 54% of 48 critically ill patients as salvage therapy and a carbapenem-sparing regimen.[40]

Tigecycline is active against Gram-negative bacteria, including Acinetobacter but not *P. aeruginosa* and *Proteeae*. In a double blind randomised comparison of treatment of soft tissue infection, clinical response was similar to vancomycin/aztreonam (86% versus 88%).[41] A double blind randomised comparison with imipenem for complicated intra-abdominal infection (5-14 days) showed similar rate of clinical cure at 14-35 days (81% and 82% n=825).[42] However it was inferior to imipenem in the treatment of ventilator-associated pneumonia.[43] Tigecycline should only be used

when other antibiotics are not suitable because meta-analyses have shown lower cure rates and higher mortality than comparators.[44] Recent research has explored higher doses.[45]

Mecillinam, although a β-lactam antibiotic, resists hydrolysis by common β-lactamases. The oral prodrug, pivmecillinam, is used to treat lower urinary tract infection but usually is not active against carbapenemase-producing organisms. Only case series are published covering treatment of ESBL-producing Enterobacteriaceae.[46]

Chloramphenicol has a broad spectrum of activity. Overall resistance in *E. coli* in UK fell from 20.2% in 1991 to 7.9% in 2004 with a decrease in use but there is more resistance in strains causing bacteremia.[47] Clinical trials are mostly restricted to enteric, ophthalmic and central nervous system infections. However it can cause dose-related or idiosyncratic haemopoietic toxicity and rarely aplastic anaemia.

Ceftolozane/tazobactam is active against Gram-negative bacteria including *Pseudomonas* against which its activity is comparable to colistin.[48] Although ESBL-producing organisms are often susceptible, the antibiotic is not effective against producers of metallo-β-lactamases, or KPC or OXA-48 strains. It has limited Gram-positive activity and is not active against anaerobes. In a randomised controlled trial in abdominal sepsis, the cure rate in combination with metronidazole was not inferior to meropenem (83% versus 87% n=993)[48,49] Against levofloxacin in 1083 patients with urinary infection, it was not inferior. Adverse effects were not found to be significantly different from comparator agents.[50]

Sulbactam is β-lactamase inhibitor often used in combination with ampicillin and is available in many countries (but not UK). It can be used to treat *Acinetobacter* infection, although activity is limited .[51] In complicated soft tissue infections efficacy is similar to tigecycline (77.6% versus 77.5%).[52]

Ceftazidime/avibactam has recently been licensed in Europe. It is active against most Gram negative bacteria except *Acinetobacter*. Producers of ESBL, OXA-48 and KPC (but not metallo β-lactamase) are susceptible.[48] Efficacy (combined with metronidazole) was similar to meropenem in treatment of intra-abdominal infection and as monotherapy to imipenem in treating complicated urinary infection.[48] However the development of resistance during treatment of infection due to *Klebsiella pneumoniae* has resulted in failures, although mutation may restore carbapenem susceptibility.[53] Combination with aminoglycoside may be needed.

None of the alternatives to carbapenems can match their spectrum of activity if used as monotherapy. Therefore to reduce carbapenem usage, prescribers need to identify patients in whom the extent of antimicrobial coverage is not required or can be rapidly de-escalated or where a combination of other agents could be used instead.

*Current antimicrobial usage*

The use of carbapenems is increasing, partly as the result of suspected rising prevalence of multi-resistant Gram-negative pathogens and partly decreased use of cephalosporins and quinolones intended to limit *Clostridium difficile*. There has been

a concurrent rise in the use of piptazobactam. The English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR) report[1] found that although carbapenems formed only 0.3% of overall antibiotic consumption in 2013, use increased by 31.3% in England between 2010 and 2013. Meropenem accounted for 89% of total carbapenem consumption.

The speed of treatment of septic patients with a broad spectrum antibiotic is increasingly used as a performance indicator and may counteract the stewardship principle of using narrower spectrum empiric agents. Quality improvement programmes such as the Sepsis Six Pathway, encompass a bundle of measures developed to reduce mortality of patients with sepsis. Empirical broad spectrum intravenous antibiotic has to be delivered within 1 hour of diagnosis. Starting antibiotic treatment within 3 and 6 hours is associated with lower mortality and the 1 hour threshold has been inferred.[54] This may promote carbapenem use at first presentation with or without subsequent de-escalation.

Current Stewardship Initiatives

A recent Cochrane review has shown interventions to reduce excessive antibiotic prescribing in hospitals reduce antimicrobial resistance without detriment to clinical outcome.[55] On the other hand, interventions that increase effective prescribing can improve clinical outcome, assuming the pathogen is susceptible to the empirical treatment. Restrictive interventions have a greater impact on short term prescribing outcome than persuasive ones. Surveillance and active feedback to prescribers should include the clinical outcome of bacteremia and the antibiotic used.

In UK, NICE[56] recommends antimicrobial stewardship in all settings with regular monitoring and feedback of usage. Repeated review is recommended to ensure antibiotics are given only when necessary and stopped as soon possible. It advocates decision support software which may be useful in implementing carbapenem-sparing regimens. Lew et al [57] found de-escalation of carbapenem treatment in an acute care setting encountering multiresistant Gram-negative infections had no effect on survival and there were fewer acquisitions of carbapenem-resistant *Acinetobacter*. In a carbapenem-sparing programme, temocillin was used for treating urinary tract infections and hospital-acquired pneumonia involving ESBL organisms.[58] Aztreonam and ciprofloxacin were used as alternatives to gentamicin in combination for treatment in febrile neutropenia.[59]

Studies of combination regimens for treatment of carbapenem-resistant infections are poor quality and heterogeneous.[59] Patients treated with a combination regimen including polymyxin have a lower mortality at 30 days than patients treated with polymyxins alone.[60] Similarly, for infections caused by carbapenemase-producing *K. pneumoniae*, mortality was lower when two or more active antimicrobials were used compared with monotherapy.[61] Survival was improved with combinations including tigecycline, colistin and high-dose meropenem. Combinations including gentamicin resulted in reduced mortality when colisitin resistance was present.[62] Tigecycline in combination regimens was only assessed in observational studies.[63]

In clinical practice, the choice of alternative agents needs to be adjusted according to local existing susceptibility patterns. If a hospital is overwhelmingly reliant on one or two antibiotics proliferation of resistant organisms can be rapid. A diversity of

antibiotic use as well as synergistic combination regimens is advisable but requires resource to allow monitoring.[64] The infection specialist has an important role in this respect for individual patient management.

## Strategies for reducing carbapenem use

A package of measures for reduction of carbapenem will usually be needed, the components of which depend on local circumstances and prevalence of resistance. A multidisciplinary team approach involving microbiologists, infectious diseases physicians and antimicrobial pharmacists is required. Advice should aim to ensure prescriptions are appropriate and stopped when signs of infection have resolved. Dose reduction carries a risk of under-treatment and is not effective in overcoming resistance where MIC>128 mg/L, although longer infusion may be beneficial for meropenem.[65,66]

## Local measures

A number of strategies are being used to reduce carbapenem usage:

*Education*

Education of all grades of doctors is important in addressing the indications for using carbapenems and when and how treatment can be de-escalated. Mandatory e-learning programs are used widely but behavioural change is difficult to achieve particularly in the more senior staff. Unfortunately education programmes are usually reported only as a component of an intervention package including screening, cleaning, antimicrobial stewardship and source isolation.[67,68] Trainee-led computerised ‘time-out’ audits conducted twice a week resulted in adjustment of antibiotic prescriptions in 15% of patients treated for infection. Although changes in

carbapenem comprised only 6% of changes made during audit, the majority of cost savings ($54000 in 2 years) was due to reduction in meropenem use.[69] If prescribers take responsibility for education programmes and audit themselves, these can be inexpensive and effective measures.

*Changing the Formulary*

Adjusting the hospital formulary to encourage the use of alternatives to carbapenem is effective. However simply switching to other agents is expensive. Instead heterogenous use of antibiotics can reduce emergence of multiresistant Gram negative infections. In one study [70] when antibiotic choice was changed every three months according to resistance and usage density, carbapenem usage fell from 58% to 31% and isolation of multiresistant Gram negative bacteria fell from 1.7% to 0.5% over 18 months. The number of patients from whom metallo-β-lactamase-producing organisms were isolated out of those from whom Gram negative pathogens were isolated fell significantly from 1.2% to 0.3%.

Smartphone applications are an easily accessed and updated format for antimicrobial formularies. In one study, an antimicrobial application encouraged challenging of inappropriate prescriptions and knowledge of stewardship, but it was overruled by some senior physicians.[71] Compliance with formulary is nevertheless promoted.

*Susceptibility Reporting*

Meropenem susceptibility may not be routinely released in pathology reports. Changing the order of presentation of susceptibilities can be effective, if the software allows, or encourage discussion with the microbiologist or infectious diseases physician. An antibiotic is more likely to be prescribed if the susceptibility has been released in the microbiology report.[72] However, susceptibility release did not influence the appropriateness of antibiotic therapy. The microbiologist was contacted

in response to 19% of 169 reports but in the 22% of remaining reports where antibiotic treatment was changed only one fifth were appropriate.

*Stewardship rounds*

Although both microbiologists/infectious disease physicians and pharmacists advise on treatment of individual patients, joint antimicrobial stewardship reviews of ward patients are becoming common. In both cases, advice on alternatives to carbapenems can usually be given. De-escalation and stopping of antibiotics are effective stewardship measures. The main limitation is the low number of patients that can be covered in the time available. The treating team may not be contactable at the time and the reason for antibiotic prescription may not be well documented or clinical notes available. In one study sufficient resources were made available for infection control team visits to all patients on intravenous antibiotics, with twice weekly review of carbapenem prescriptions, followed by telephone contact with the clinician.[68] Coupled with an education programme, these measures were effective in reducing carbapenem usage significantly. In particular inappropriate course length was reduced. A full time pharmacist was required for the work. However, the rate of carbapenem-resistant infections was unchanged. Restriction of antibiotic prescription, for example by an authorisation code from microbiology, is effective in the short term but time consuming. In a cross-over study comparing pre-prescription authorization versus post-prescription review and feedback (n=2686, 2693, 29% versus 27% given antibiotic), the latter had a greater impact in reducing days of antibiotic treatment and should be given priority.[73]

*Electronic Prescribing*

Electronic prescribing can be helpful in providing continuous audit and feedback of prescription levels to clinical teams. However a survey of 13 UK hospitals found no

relationship between use of such a system and compliance with antimicrobial stewardship guidelines.[74] Computer decision support systems can be standalone, incorporated in electronic record, based on surveillance or used for antibiotic pre-prescription authorisation.[75] System interventions increased appropriate use of antimicrobials in a meta-analysis (pooled RR: 1.49, 95%CI: 1.07-2.08). However when only high quality studies were included the benefit was not apparent.

Whichever measures are adopted based on local availability of resources, a carbapenem-sparing strategy should be agreed between the stakeholders and the local Drug & Therapeutics Committee.

National measures

Governments can apply incentives for hospitals to formulate a strategy. Routine collection of carbapenem prescription data and feedback reveals the outliers in numbers of prescriptions. Measures to slow the rise in carbapenem prescriptions are already being used in some countries and in UK antibiotic prescription rates are now available for public scutiny.[76]

Putting plans into action

New prescriptions using carbapenem-sparing regimens can be advised whenever microbiologists or infectious diseases physicians are consulted. Diversity of prescribing can be promoted by advice to use cephalosporins and quinolones, although these agents are discouraged when rates of MRSA and *C difficile* are high. A decision support system linked to an antimicrobial App is a potential aid. Documented antimicrobial advice should be supported by regular antimicrobial audit

to assess compliance. Introduction of a greater diversity onto the hospital formulary should be considered but stakeholders should be consulted. When considering additions to the formulary, the paucity of clinical trial evidence has to be balanced against the impending problem of multiresistance.[56]

For severe infections known or suspected to be resistant to first line agents, temocillin, colistin or ceftazolone/tazobactam can be used instead of a carbapenem. For uncomplicated lower urinary infections, fosfomycin, pivmecillinam or nitrofurantoin is appropriate if the pathogen is susceptible. If resistance to meropenem and the above agents is known or suspected, tigecycline, intravenous fosfomycin, ceftazidime/avibactam (not for metallo-β-lactamase producers) or combinations including colistin or high dose meropenem can be considered. The genetic basis of carbapenem resistance is important in predicting the likely efficacy of a treatment choice and needs to be based in hospital laboratory rather than the reference laboratory.[1]

## Conclusions

Carbapenem reduction can be achieved by education, local stewardship rounds and national prescription data collection and feedback. The microbiologists themselves can have a major effect through restrictive advice if the hospital practice is to seek their advice. Alternative antimicrobial strategies may involve combinations of antibiotics but evidence base of clinical trials is poor for some older agents and needs to be improved urgently.

## Recommendations

*High efficacy, low cost*

1. Clinician-led education and audit
2. Formulary presenting a diversity of antibiotic choices with support of a Smartphone application and liaison advice from microbiology and infectious disease physicians

*Low Efficacy, low cost*

1. Antimicrobial susceptibility release in microbiology reports to influence prescribing

*Moderate efficacy, high cost*

1. Post prescription review and feedback as part of antimicrobial stewardship round with aim of de-escalation, appropriate course length and reduced unnecessary use of carbapenem.

*Low efficacy, high cost*

1. Microbiology authorisation code pre-prescription to restrict antibiotic use
2. Electronic prescribing systems for decision support

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Transparency Declaration

APRW has no conflict of interests but has delivered lectures sponsored by Merck Sharp & Dohme. He participates in Drug Safety Monitoring Boards for trials of therapeutic monoclonal antibodies and an advisory board for 3M. He is a member of the Antimicrobial Resistance and Hospital-acquired infection Advisory Committee of the Department of Health, London UK.

Table 1. Meropenem and alternative antimicrobials

| Animicrobial | Indication | Gram-negative Activity | Adverse effect |
|---|---|---|---|
| | | | |
| Aztreonam | Gram-negative bacteremia, osteomyelitis, respiratory, febrile neutropenia | Gram negative aerobic bacilli *except* ESBL or AmpC producers | Bronchospasm, rash |
| Ceftazidime - avibactam | ESBL, OXA-48 & KPC, abdominal, urinary. Combination with aminoglycoside. | Broad *except* Acinetobacter, metallo- β-lactamase. | Nausea, diarrhoea, Coombs positive, rash |
| Ceftolozane-tazobactam | ESBL producers, abdominal, urinary | Broad *except* metallo- β-lactamase, KPC and OXA-48. | Headache, nausea, diarrhoea |
| Chloramphenicol | Abdominal, meningitis, respiratory | Broad *except Pseudomonas* sp | Idiosyncratic and dose related haemopoietic toxicity |
| Colistin | Carbapenem resistance Gram negatives in combination | Broad *except Proteus* sp, *Serratia* sp | Nephrotoxicity, neurotoxicity |
| Co-trimoxazole | Stenotrophomonas maltophilia | Enterobacteriaceae, *Haemophilus influenzae* not *P aeruginosa* | Headache, diarrhoea, hyperkalemia, rash; rarely Stevens-Johnson |
| Ertapenem | Urinary, abdominal, respiratory, outpatient ESBL-producers | Broad *except P aeruginosa, Acinetobacter* | Diarrhoea, headache, pruritus, rash, vomiting |
| Fosfomycin IV | Combination regimen in ICU | *Escherichia coli, Citrobacter, Proteus mirabilis* | Dyspnoea, fatigue, heaache |
| Fosfomycin oral | Urinary ESBL producers | *Escherichia coli, Citrobacter, Proteus mirabilis* | Diarrhoea, dizziness, headache |
| Gentamicin | Combination regimens only | *E coli, Klebsiella* sp, *Enterobacter* sp (not CTX-M) | Nephrotoxicity, ototoxicity |
| Imipenem | Urinary, abdominal, respiratory, ESBL-producers | Very broad | Diarrhoea, vomiting, rash |
| Pivmecillinam | Urinary, ESBL | Broad | Abdominal pain, |

| | | | |
|---|---|---|---|
| | producers | | dizziness, headache, vomiting |
| Meropenem | Urinary, abdominal, respiratory, meningitis, febrile neutropenia, ESBL-producers | Very broad | Abdominal pain, diarrhoea, headache, rash, vomiting |
| Piptazobactam | Urinary, abdominal, respiratory, febrile neutropenia, Susceptible ESBL-producers | Broad | Rash, hypersensitivity, nausea, vomiting |
| Rifampicin | Synergistic in combination regimens | Broad | Liver function abnormality, renal failure, headache, |
| Sulbactam | Combination with ampicillin, soft tissue | *Acinetobacter* | Diarrhoea, vomiting, hypersensitivity |
| Temocillin | Urinary, ESBL-producers | Broad except *Pseudomonas* or *Acinetobacter* | Diarrhoea, hypersensitivity rash |
| Tigecycline | Soft tissue, abdominal | Broad except *Pseudomonas* Proteeae | Higher mortality, abdominal pain, dizziness, headache |
| | | | |

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*Further reading*

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https://www.scottishmedicines.org.uk/files/sapg1/Position_paper_to_Optimise_Antimicrobial_Prescribing_in_MDRGNB.pdf