Scottish Medicines Consortium

Scottish Antimicrobial Prescribing Group

NHS SCOTLAND

POSITION PAPER ON OPTIMISING ANTIMICROBIAL PRESCRIBING IN POSSIBLE OR SUSPECTED INFECTIONS DUE TO MULTI-DRUG RESISTANT GRAM NEGATIVE BACTERIA

This advice has been developed by the Scottish Antimicrobial Prescribing Group (SAPG) through consultation with clinical specialists to provide practical advice for Antimicrobial Management Teams and Infection Specialists. The aims are to:

1. **Support** clinical management of Gram negative infections
2. **Reduce** emergence of MDRGNB
3. **Promote** more judicious use of broad spectrum antimicrobials
4. **Protect and preserve** the carbapenem and other key classes of antibiotics.

This is not definitive guidance on management of multi-drug resistant Gram negative bacteria (MDRGNB) infections but has been produced by SAPG to support development of local guidance to preserve the activity of ultra-broad spectrum antibiotics against Gram negative bacterial infections. A BSAC Joint Working Party has been convened and their 'Report on Multi resistant Gram-negative Infection: Treatment', expected to be published in 2016, will provide a comprehensive update on the recent evidence and approaches to managing these infections. The value of stewardship in controlling the spread of and managing multi -drug resistant Gram negative bacterial infection in hospital has been documented by ESCMID (European Society for Clinical Microbiology and Infectious Diseases) [1] and together with a review paper on older antibiotics [2] provide some pragmatic recommendations relevant to the Scottish context.

Why is reduction of MDRGNB infections important?

MDRGNB are increasing worldwide, have become endemic in some areas of Asia and have spread rapidly in some European countries. A global meeting highlighted the need for action [3] and the Department of Health has identified a preliminary list of 'critically important' antimicrobials which should be protected and preserved to treat infections due to MDRGNB [4]. These are: for Secondary Care, carbapenems and anti-pseudomonals and for Primary Care, quinolones, co-amoxiclav, and cephalosporins.

In Scotland levels of MDRGNB are currently stable [5] but extended spectrum beta-lactamase (ESBL) producing bacteria are widespread and carbapenemase producing organisms have been reported in most NHS board areas, some of which have not been reported to relate to foreign travel. The use of carbapenems in Scotland has increased by 14% since 2011 [5], driven partly by reductions in 3rd generation cephalosporin and quinolone use as an intervention to reduce *Clostridium difficile* infection (CDI) rates. Surveillance suggests the majority of the increase in carbapenem use appears focused within the critical care setting, haematology/oncology and in some surgical units and is often initiated following advice from infection specialists or as second or third line empirical therapy for severe infection. In many instances the empirical use of these agents is inappropriate and current strategies to review and de-escalate therapy are inadequate and hampered by poor initial microbiological investigation. The consequence of overuse is increased emergence of MDRGNB and in particular, resistance to piperacillin-tazobactam and carbapenems. Although carbapenem resistance in enterobacteriaceae is so far rarely observed in Scotland, resistance to piperacillin tazobactam is increasingly observed particularly amongst *Klebsiella pneumonia* [5]. Ultimately our ability to effectively treat serious infections may become compromised, as seen in other countries such as Greece [6] and India [7].

What national and international guidance is already available?

The importance of stewardship in this specific area has been recognised by most guidelines for controlling the emergence of carbapenamase resistance [8,9] including Health Protection Scotland infection prevention control guidance on Carbapenemase-Producing Enterobacteriaceae in acute settings [8] and Public Health England guidance for non-acute settings (10). A systematic evaluation of the literature on antibiotic treatment of Carbapenem-resistant Enterbacteriaceae (CPE) has provided some evidence to support treatment strategies (11) and the recent ESCMID paper [2] provides additional evidence across all MDRGNB.

Current practice in Scotland

In Scotland there is ongoing concern that success in control of *Clostridium difficile* infection, through a combination of stewardship measures and infection control, is not destabilised by a return to widespread use of cephalosporins and indiscriminate use of beta-lactam/beta-lactamase inhibitor combinations and carbapenems.

However, controlled re-introduction of cephalosporins for some specific indications on specialist advice may have benefits in reducing carbapenem use without increasing CDI rates.

SAPG guidance issued in 2013 recommended that alternative agents (aztreonam [13], temocillin [14], pivmecillinam [15] and fosfomycin [16,17]) should be considered as part of a strategy to reduce use of carbapenems. Secondary care prescribing data show wide variability in prescribing volume between boards for both piperacillin tazobactam and meropenem although most boards are demonstrating increased use in both agents [5].

To further investigate these differences a survey of local antimicrobial guidelines and practice has been undertaken. Carbapenems were observed to be restricted across all health boards but controls on use of piperacillin/tazobactam were more variable. Data yet to be published by SAPG from a bespoke point prevalence survey confirmed good compliance with local policy for carbapenems but lower compliance for piperacillin/tazobactam. Other key findings were:

- Documentation of review of prescriptions and treatment duration was poor for both carbapenems and piperacillin/tazobactam
- Low uptake of alternative anti-Gram negative agents in many boards
- Variation in laboratory practice in terms of testing for and reporting of carbapenems and piperacillin/tazobactam and alternative antibiotics.

Carbapenem-sparing approaches for suspected or proven Gram negative infections

Here we offer clinicians pragmatic advice on alternative options to carbapenems (and to an extent piperacillin-tazobactam) until more definitive evidence-based guidance becomes available. It is recognised that in Critical Care settings daily multi-professional ward rounds and in other clinical areas antimicrobial ward rounds are a key method of optimising antimicrobial therapy. Ultimately, the decision to use carbapenems and/or alternative antibiotics for MDRGNB should be based on an individual patient risk benefit assessment.

Cost and supply of alternative agents

SAPG recognises that the cost of using some of these alternative agents e.g. temocillin and aztreonam may add to the drug acquisition cost pressures. However, it is recognised that costs associated with the occurrence of drug resistant infections far outweighs this [supply references here] therefore the cost-benefit approach should be rehearsed with local AMTs and Area Drug and Therapeutics committees where applicable.

SAPG also recognises some intermittent challenges in relation to reliable supply of agents such as aztreonam and co-trimoxazole. SAPG is exploring options at national level to alleviate these issues but AMTs need to plan flexible measures proactively to manage these pressures.

Key considerations in the management and prevention of MDRGN infections

1. Initiation (and early escalation) of antimicrobial therapy

Many problems with inappropriate broad spectrum antibiotic prescribing can be traced back to incomplete clinical assessment, failure to perform critical baseline microbiological investigations and failure to identify and control the source of infection. In addition, premature empirical escalation of therapy during the first 48 hours of therapy is an important source of inappropriate antimicrobial prescribing. These are fundamentals issues in infection management and it is recommended these are reinforced in hospital infection management guidelines.

2. Review of antimicrobial treatment

It is recognised good practice that as part of the daily clinical review of patients with infection, all antimicrobial therapy prescriptions and microbiology results are reviewed. This is to ensure prompt de-escalation (or escalation) when required and early intravenous to oral switch or stopping of antimicrobials when infection has been excluded. The "Sepsis 6 campaign", introduced in NHS Scotland between 2011 and 2012 has delivered benefits in terms of recognition and prompt management of sepsis and is likely also to have has increased the number of patients commenced on (or escalated to) broad spectrum agents such as piperacillin/tazobactam and carbapenems. Review of antimicrobial therapy in these circumstances is of particular importance and is aligned with the key stewardship metric of documented 72 hour review.

3. Treatment duration

There are emerging data to support shorter course therapy in many infections including those caused by MDRGNB [18,19]. It is recommended that in the majority of patients with MDRGN infections without a deep source of infection (e.g. urosepsis without an associated abscess or collection and including those with bacteraemia) a 7 day course of antibiotics is sufficient. In more complex cases the duration should be discussed and agreed in conjunction with the local infection expert.

Choice of route of administration of antibiotic and timing of IV to oral switch is dependent on site of involvement, presence of sepsis and the PK/PD characteristics of the antimicrobial. Oral antibiotic options are limited for MDRGN infections but in principle the narrowest spectrum agent available with the most favourable PK/PD characteristics for the site of the infection should be selected for the minimal duration. In patients with deep seated infection it is essential to control the source of infection surgically or radiologically.

The following oral antibiotics are suggested as step-down oral therapy for gram negative infections if organisms are sensitive:

- Ciprofloxacin 500mg twice daily or 750mg twice daily (consider CDI risk)
- Co-amoxiclav 625mg three times daily (consider CDI risk)
- Pivmecillinam 400mg three times daily or fosfomycin 3g stat. in women and dose repeated in men
- Nitrofurantoin MR 100mg twice daily (in lower UTI)

4. Carbapenem-sparing approaches for suspected or proven Gram negative infections

Here we provide national consensus based recommendations that aim to offer clinicians pragmatic advice on alternative options to carbapenems (and to an extent piperacillin-tazobactam) until more definitive evidence-based guidance becomes available. It is recognised that in Critical Care settings daily multi-professional ward rounds and in other clinical areas antimicrobial ward rounds are a key method of optimising antimicrobial therapy. Ultimately, the decision to use carbapenems and/or alternative antibiotics for MDRGNB should be based on an individual patient risk benefit assessment.

5. Microbiology laboratory practical advice

AZTREONAM is available on the VITEK 2 AST-N297 (systemic Enterobacteriaceae) and AST-N253 (systemic non-fermenter) cards.

FOSFOMYCIN is available on the VITEK 2 AST –N254 (urine Enterobacteriaceae) card. This can also be used, if required, for systemic isolates.

PIVMECILLINAM cannot be included on a VITEK 2 AST card for technical reasons. Disc testing remains the only way to assess sensitivity.

TEMOCILLIN is available on the AST-N297 (systemic Enterobacteriaceae) card, having replaced chloramphenicol at the request of SMVN. It is also available on the VITEK 2 AST-N254 (urine Enterobacteriaceae) card.

6. Surveillance of antimicrobial use and resistance

Antimicrobial use and resistance will continue to be monitored by SAPG (via ISD and HPS) at national level with annual reports published each year.

NHS boards should continue to monitor use of antimicrobials for Gram negative infections and Gram negative isolates at ward level through local pharmacy and microbiology systems. Some drug-bug combinations, if not available nationally, may need to be tested locally after discussion and agreement with the laboratory. In particular boards should monitor use of piperacillin/tazobactam, carbapenems and any alternative antibiotics introduced into practice (e.g. aztreonam and temocillin) in critical care/high dependency units and wards with haematology/oncology patients to evaluate the impact of interventions.

The following tables provide advice on suggested options for management of Gram negative infections:

Sepsis – empirical IV treatment
Aminoglycoside-based combination therapy should be considered for sepsis and severe sepsis of unknown source without septic shock e.g. in combination with amoxicillin and flucloxacillin and/or metronidazole. Standard dosage of aminoglycosides as per local policy should be used
Piperacillin/ tazobactam monotherapy is recommended in standard risk patients with suspected neutropenic sepsis (i.e. those without severe sepsis or septic shock). Dosage is 4.5g 6-8 hourly.
Combination therapy with a beta-lactam plus aminoglycoside e.g. Piperacillin/ tazobactam plus gentamicin**,** improves outcome in severe sepsis and septic shock including neutropenic sepsis with severe sepsis or septic shock [20-24].
Aztreonam can be used in patients with renal impairment (as an aminoglycoside alternative) and for empirical treatment of sepsis, including in beta-lactam allergy (except anaphylaxis). Consider additional gram positive and anaerobic cover when used empirically. Does not have extended cover for ESBL producing organisms. Dosage is 1 g every 8 hours *or* 2 g every 12 hours; 2 g every 6–8 hours for severe infections.
Ciprofloxacin may be a suitable option for empirical treatment of sepsis in true beta-lactam allergy when aminoglycosides are contraindicated. Dosage is 400mg 12 hourly; 400mg 8 hourly in severe or deep-seated infections.
Temocillin can be used in patients with renal impairment (as an aminoglycoside alternative). Consider additional gram positive and anaerobic cover when used empirically. Does not have extended cover for Pseudomonal species and Acinetobacter. Dosage is 1–2 g every 12 hours; ESBL infections 2g every 12 hours.

Urinary tract infections – Directed oral and IV therapy
Use oral therapy whenever possible for uncomplicated non-bacteraemic lower urinary tract infection due to confirmed ESBLs.
Oral trimethoprim or **nitrofurantoin** should be used unless contra-indicated due to renal impairment or if the organism is resistant.
Oral co-amoxiclav [25] or **co-trimoxazole** may be suitable if organism is sensitive.
Oral pivmecillinam or **fosfomycin** may be considered as initial directed oral therapy or as step-down agents for those receiving anti-Gram negative IV therapy for a urinary source.
IV aztreonam (0.5–1 g every 8–12 hours) or **temocillin** (1–2 g every 12 hours; ESBL infections 2g every 12 hours) may be suitable for directed therapy of urosepsis. Temocillin is the preferred agent for ESBL infections. Aztreonam is not suitable for ESBL infections but is often suitable for piperacillin-tazobactam resistant, non-ESBL isolates.

Directed treatment of Gram negative sepsis: IV therapy where organism and sensitivities known
Use narrow spectrum agents where possible and consider alternatives to carbapenems. Aminoglycosides remain an option following local epidemiology and sensitivity patterns.
Aztreonam suitable for treatment of bacteraemia, urosepsis, pneumonia, intra-abdominal sepsis and spontaneous bacterial peritonitis. Dosage is 1 g every 8 hours *or* 2 g every 12 hours; 2 g every 6–8 hours for severe infections.
Temocillin suitable for treatment of severe infections due to gram negative bacteria including ESBLs – licensed for septicaemia, urosepsis, pneumonia. Dosage is 1–2 g every 12 hours; ESBL infections 2g every 12 hours.
Co-trimoxazole may be used IV for urosepsis, pneumonia and bacteraemia if the organism is sensitive to trimethoprim. Dosage is 960-mg every 12 hours.
Fosfomycin should be used in combination with other agents when used for treatment of systemic infections, due to its propensity for development resistance. IV dose is 8 – 16g daily in divided doses. Multi-resistant infections use 4g 6 hourly.
Chloramphenicol may be considered for IV treatment of infections due to resistant organisms where other antibiotics are not suitable but consider risks of adverse effects and clinical benefits on an individual patient basis. Data from widespread use in Southampton suggests that toxicity is rare [26]. Dosage is 1g every 6-8 hours.
Tigecycline may be considered where the organism is sensitive. Standard dosing (100mg loading dose followed by 50mg BD) and high dose regimen of 100mg BD in CPE.
Cephalosporins may be considered where the organism is sensitive but consider risk of CDI on an individual patient basis. Ceftriaxone should be considered for Out Patient Antimicrobial Therapy as CDI risk is observed to be low in this patient population and care setting. Ceftazidime may be considered for treatment of Pseudomonal infections.

Specific approach for infections due to carbapenemase-producing *Enterobacteriaceae* (CPE)
• Combination therapy is advisable as associated with less treatment failures [10, 27, 28, 29]. • For bacteraemias and severe infection including respiratory tract infections use a minimum of two antibiotics. There is insufficient evidence to conclude which combinations are most effective but colistin plus a carbapenem may be a suitable first choice. • Even where there is resistance when carbapenems are used in combination with other agents outcomes are likely to be improved if in vitro testing appears sensitive (meropenem, imipenem MIC ≤ 1µg/mL, ertapenem ≤ 0.5µg/mL) or close to the breakpoint. There is limited data to support the addition of meropenem to other agents if the MIC is ≤ 4µg/mL. • For treatment of pneumonia colistin nebules may be used in combination with systemic treatment to increase delivery of the drug to the site of infection. • Due to safety concerns tigecycline should only be used when other antibiotics are not suitable. If used for treatment of respiratory tract infections use in combination with a second agent. • Temocillin and aztreonam may be used in combination with non-beta-lactams if they appear to be sensitive. Temocillin is not active against most CPE but remains effective against KPC-producing Enterobacteriaceae in in vitro studies. • Rifampicin has been shown to have synergistic activity with meropenem and colistin, and may also be considered for combination therapy.

Further details on use of high dose colistin are available within a separate guidance document
http://www.scottishmedicines.org.uk/files/sapg1/SAPG_High_Dose_Colistin_Treatment__in_Adults_-_Consensus_Guidance.pdf

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