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Frontline antibiotic therapy

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Abstract – The need to use front-line antibiotics wisely has never been greater. Antibiotic resistance and multi-drug resistant infection, driven by antibiotic use, remain major public health and professional concerns. To overcome these infection problems, use of older antibiotics active against multidrug-resistant pathogens is increasing – for example, colistin, fosfomycin, pivmecillinam, pristinamycin, temocillin and oral tetracyclines. The number of new antibacterials reaching clinical practice has reduced significantly in the last 20 years, most being focused on therapy of Gram-positive infection – eg linezolid, daptomycin, telavancin and ceftaroline. Recent guidance on antibiotic stewardship in NHS trusts in England is likely to provide a backdrop to antibiotic use in hospitals in the next 5 years.

KEY WORDS: Antibiotic therapy, antibiotic resistance, stewardship

Introduction

Ever since the start of the modern antibiotic era with the discovery of penicillin in 1929,[1] there has been exponential growth worldwide in terms of both availability and use of β-lactam and non-β-lactam agents.[2] Antibiotics currently constitute a significant proportion of the NHS's budget. Antibiotic therapy has improved mortality from acute infections such as meningitis,[3] increased longevity in patients with chronic infections such as HIV[4] and also enabled delivery of more complex care such as transplantation and complex surgeries. However, antimicrobial resistance, which was first noticed early in the modern era, is posing a significant threat.[5] At the same time, availability of newer antimicrobial agents has decreased.[6,7] The implications of antimicrobial resistance for clinical outcome are indisputable.[8] The World Health Organization (WHO) has acknowledged antimicrobial resistance as a top health priority; indeed, it was the theme of World Health Day on 7 April 2011 and European Antibiotic Awareness Day on 18 November 2011.[9,10]

Infections are a common problem faced by frontline clinicians working in both primary and secondary care. In these settings, the causative pathogen and especially antimicrobial susceptibility often are not known. Initiation of an early and appropriate empirical antimicrobial therapy has a positive impact on clinical outcome,[11] particularly in severe infections.[12] Considering the above factors – that is, increasing resistance and decreasing therapeutic options, along with a drive to initiate early appropriate antimicrobial therapy – prescribing antibiotics in frontline clinical services is becoming a challenge. This review article addresses the current trends in antimicrobial resistance from the perspective of the UK and the challenges faced by frontline clinicians in prescribing antimicrobial therapy, giving a brief summary of the use of older and existing agents and forthcoming, newer antimicrobial agents.

Antibiotic resistance: the current situation in the UK

The British Society for Antimicrobial Chemotherapy (BSAC)'s bacteraemia and respiratory resistance surveillance programmes have been monitoring antimicrobial susceptibility patterns for the major organisms in the UK and Ireland since 1999.[13] This is achieved by collecting positive blood culture and respiratory sample isolates from more than 40 laboratories across the UK and Ireland. Data for the past decade from the BSAC show encouraging results for Gram-positive bacteria. *Streptococcus pneumoniae (S. pneumoniae)*, the most common bacterial cause of community-acquired pneumonia (CAP), has excellent susceptibility to penicillin, in both bacteraemic and respiratory isolates, and only 0.3% of the isolates are truly resistant to penicillin.[14,15] This is in contrast to the situation in some southern and eastern European countries, where penicillin resistance among *S. pneumoniae* is estimated to be >30%.[16] A recent study has shown a steep decrease in erythromycin resistance among invasive pneumococci from children aged <2 years in England and Wales since the introduction of the pneumococcal conjugate vaccine in 2006.[17] This is mainly attributable to the reduction in serotype 14, which has been strongly associated with erythromycin resistance.[18]

Resistance patterns of streptococci in general (α, β and non-haemolytic) against β-lactam and non-β-lactam agents (erythromycin, clindamycin, tetracycline and gentamicin) have remained stable over the past decade.[19] On the other hand, resistance to ampicillin, vancomycin and gentamicin has increased among *Enterococcus faecium (E. faecium)*: currently, >95% of *E. faecium* are resistant to amoxicillin, 25% to vancomycin and 50% have high-level resistance to gentamicin.[20] However, most (>95%) vancomycin-resistant enterococci (VRE) are usually susceptible to linezolid, daptomycin and tigecycline.

With respect to *Staphylococcus aureus (S. aureus)*, the incidence of methicillin-resistant *S. aureus* (MRSA) bacteraemia

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continues to fall in England, and only 15.8% of cases of *S. aureus* bacteraemia in 2010 were due to MRSA.[21] The minimum inhibitory concentration (MIC) for vancomycin for *S. aureus* isolates remained stable in the past decade, with no real 'creep in the MIC' as reported elsewhere in the world.[22,23] The occurrence of vancomycin-intermediate *S aureus* (VISA) and hetero-VISA (h-VISA) remains exceptionally rare. In a prospective study involving three hospitals in Liverpool, 3.4% of patients colonised with MRSA and 2.5% of patients with MRSA bacteraemia had reduced susceptibility to glycopeptides.[24]

The antimicrobial resistance trend among Gram-negative bacteria is of real concern. Since 2001 there has been a rapid increase in resistance to cephalosporins and ciprofloxacin among *Escherichia coli (E. Coli)* – the most common cause of bacteraemia in the UK.[25] This is mainly driven by production of extended-spectrum β-lactamase (ESBL) enzymes, which destroy all β-lactam antibiotics. A number of different types of ESBL enzyme, which can be encoded either within a plasmid (transmissible genetic element) or within the bacterial chromosome, have been identified worldwide. CTX-M-15-producing bacteria remain the most prevalent type in the UK. However, trends in bacteraemia caused by ESBL-producing Enterobacteriaceae seem to have reached a plateau, currently remaining at about 6%. Similarly, among *E. coli* isolates from bacteraemia, resistance to ciprofloxacin and gentamicin also seems to have stabilised at 17% and 10%, respectively.[26] However, Gram-negative bacteria that produce carbapenemase (enzymes capable of destroying the carbapenem group of antibiotics) have emerged all over the world.[27] The main carbapenemases that are causing concern include New Delhi metallo-β-lactamase 1 (NDM-1)- and Klebsiella-pneumoniae-carbapenemase (KPC)-producing Enterobacteriaceae, and Verona integron-encoded metallo-β-lactamase (VIM)-, IMP- and oxacillinase (OXA)-producing non-fermenters such as *Pseudomonas* spp and *Acinetobacter* spp. A recent newsletter from the Antibiotic Resistance Monitoring & Reference Laboratory (ARML) of the Health Protection Agency (HPA) reports that at least 20 isolates with suspected carbapenem-resistant Enterobacteriaceae are being referred from all around UK every week.[28] However, bacteraemia surveillance data from the BSAC in 2010 showed that no *E coli* and <2% of other Enterobacteriaceae were resistant to carbapenem.[26] Although most of the carbapenemase-producing Gram-negative bacteria are currently susceptible to colistin and/or tigecycline, pan-resistant (resistant to all known antibiotics) strains have been reported across the world, including the UK.

Current antibiotic prescribing in the UK: older and existing agents

Driven by pressure to decrease the incidence of healthcare-associated infection (HCAI), especially caused by MRSA and *Clostridium difficile (C. difficile),* the use of antibiotics in the UK has changed dramatically in recent times. The common 'culprit' antibiotics such as fluoroquinolones (eg ciprofloxacin) and cephalosporins have been replaced by relatively 'friendly' agents such as co-trimoxazole, gentamicin and piperacillin/tazobactam (pip/taz). As antibiotic resistance increases and few new antimicrobial agents become available, the 'forgotten' older antimicrobial agents have been brought back into use.[29]

Colistin belongs to the polymixin group of antibiotics and is available in intravenous, inhalational and topical preparations. Colistin is currently reserved for use in the treatment of multi-drug resistant (MDR) Gram-negative infections for which conventional agents are ineffective or not tolerated. Dose-dependent renal and neurotoxicity (although relatively rare), the lack of efficacy against Gram-positive bacteria and intrinsic resistance among certain Enterobacteriaceae (such as *Proteus* spp, *Morganella* spp and *Serratia* spp) are the other main limitations of this group of antibiotics. Guidelines were recently published regarding dosage and loading in critically ill patients with varying degrees of renal dysfunction.[30]

Fosfomycin was first developed in 1969 in Spain and is bactericidal against a wide range of pathogens, such as staphylococci, streptococci and Enterobacteriaceae, including ESBL- and carbapenemase-producing strains.[31] It is available in oral (trometamol, 3 g single dose) and intravenous forms (disodium salt, 4–8 g three times daily) for systemic use. Fosfomycin has a very low molecular weight and almost negligible protein binding, resulting in widespread tissue penetration, including to the central nervous system and eyes. A recent systematic review on fosfomycin showed good antimicrobial activity against ESBL-producing Enterobacteriaceae (96.8% of 1,657 *E. coli* and 81.3% of 748 *Klebsiella pneumoniae* isolates tested susceptible) and good clinical effectiveness in 75/80 (93.8%) patients with mainly urinary tract infections (UTIs).[32] It is generally well tolerated by patients and is safe in pregnancy. Organ toxicity is very rarely reported in the literature. Fosfomycin has been used sparingly in the UK until now because of the lack of licence and marketing authorisation, difficulties in obtaining the drug from foreign manufacturers and the availability of alternative agents. Due to its effectiveness against MDR Gram-negative bacteria and MRSA, testing of fosfomycin sensitivity in all MDR strains should perhaps be considered so that it can be used in the treatment of infections caused by susceptible strains.

Pivmecillinam is an orally active prodrug of mecillinam (extended-spectrum penicillin) and has been used in the treatment of uncomplicated UTIs since the 1970s, especially in the Scandinavian countries. *In vitro* studies have shown efficacy against Enterobacteriaceae producing a wide range of β-lactamase enzymes[33] and its combination with clavulanic acid gives additional activity against ESBL-producing Enterobacteriaceae, especially in high-inoculum circumstances.[34] Despite having a safety record from historic use, including in pregnancy, and 30 years of clinical experience, pivmecillinam is not widely used in the UK at the present time.[35] This may be due to lack of availability and also the lack of robust clinical data in infections caused by MDR strains.

Co-amoxiclav and piperacillin-tazobactam are the main two β-lactam/β-lactamase inhibitor combination therapies used in

the UK. Both are available in intravenous form for systemic use, and co-amoxiclav is also available as an oral therapy. Until recently, the clinical activity of these agents against ESBL-producing Enterobacteriaceae remained controversial. A recent post-hoc analysis of six prospective cohort studies showed that both of these agents are suitable alternatives to carbapenems in the treatment of bacteraemia caused by ESBL-producing *E coli*.[36] Nevertheless, co-amoxiclav has already been used in the treatment of uncomplicated UTIs caused by ESBL-producing Enterobacteriaceae in the community setting. The same uncertainty still exists for the use of third-generation cephalosporins in infections caused by ESBL-producing Enterobacteriaceae that show susceptibility on testing. Recent guidelines from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommend to 'report as tested', ie those that test susceptible can be used for therapy; however, more clinical data are needed in this area.

Pristinamycin belongs to the streptogramin group of antibiotics and acts by inhibiting bacterial protein synthesis by binding to the 50S ribosomal subunit, which is similar to the mode of action of erythromycin. Unlike erythromycin, however, pristinamycin has bactericidal activity against staphylococci, including MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE). It is therefore commonly used as an oral follow on to intravenous treatment in the treatment of skin and soft-tissue infections (SSTIs) and bone and joint infections (BJIs) caused by staphylococci.[37] An intravenous preparation of pristinamycin is not currently available for use in the treatment of severe systemic infections. The only intravenous streptogramin preparation, quinupristin/dalfopristin, has serious toxicity issues in the form of arthralgia/myalgia, gastrointestinal intolerance, thrombophlebitis and hyperbilirubinaemia.[38]

Temocillin, a 6-α-methoxy derivative of ticarcillin, was developed and first marketed in the UK in the 1980s.[39] Temocillin is active only against Enterobacteriaceae and *Burkholderia cepacia*, with no significant activity against *Pseudomonas* spp, *Acinetobacter* spp, anaerobes and Gram-positive organisms. Temocillin is stable against most classic β-lactamases, including TEM-, SHV- and CTX-M-type ESBLs and AmpC (but not OXA-48 or NDM-1). A recent multicentre, retrospective study in the UK showed good clinical and microbiological efficacies of temocillin in UTIs, bloodstream infections and hospital-acquired pneumonia (HAP).[40] The performance of temocillin in this study was unaffected by the presence of ESBLs/AmpC when a dose of 2 g twice daily (or renally adjusted equivalent) was used, confirming its therapeutic potential as a carbapenem-sparing agent.

Tetracyclines (doxycycline and minocycline) are increasingly being used in the treatment of common infections, such as exacerbations of chronic obstructive pulmonary disease (COPD)[41] and non-severe MRSA infections,[42] in addition to their traditional uses in malaria, rickettsia, *Chlamydia* infections and genital infections. Similarly, cotrimoxazole has made a slow comeback into therapeutic usage in the treatment of common day-to-day infections such as UTIs, HAPs, MRSA-associated SSTIs[42] and prosthetic joint infections (PJIs).[43]

Newer agents – promises and pitfalls

Linezolid is a synthetic antibiotic belonging to the oxazolidinone group. It is mainly active against Gram-positive bacteria, including MRSA and VRE. It acts by inhibiting bacterial protein synthesis by binding to the 30S ribosome and is bacteriostatic against staphylococci and enterococci but bactericidal against *S. pneumoniae*. It is available in intravenous as well as oral forms, with 100% bioavailability. It is currently licensed for use in community-acquired SSTIs (c-SSTIs), when microbiological testing has established that the infection is caused by susceptible Gram-positive bacteria, and in HAP and community-acquired pneumonia (CAP) known or suspected to be caused by susceptible Gram-positive bacteria. Because of linezolid's effectiveness against MDR Gram-positive organisms, good tissue penetration and the availability of an oral formulation, it has been used in the treatment of a wide variety of clinical infections, including penicillin-resistant *S. pneumoniae* (PRSP), BJIs and endocarditis. Despite the manufacturer's claim of superiority over vancomycin in c-SSTIs and ventilator-associated pneumonia (VAP)/HAP caused by MRSA, further clarification is needed.[44] Few meta-analyses and randomised controlled trials have found conclusive evidence supporting superiority of linezolid over vancomycin.[45–48]

Daptomycin is a bactericidal antibiotic that belongs to the cyclic lipopeptide group. It acts by binding to the cell membrane via a calcium-dependent mechanism that causes deep polarisation of bacterial membrane and thus results in rapid cell death. It is active against Gram-positive organisms such as staphylococci, streptococci and entercocci, including strains resistant to vancomycin and linezolid; h-VISA phenotypes have higher MICs, but the significance of this is unclear. Daptomycin is available only in an intravenous preparation and is licensed for use in c-SSTIs, right-sided endocarditis (RSE) caused by *S. aureus*,[49,50] and *S. aureus* bacteraemia secondary to c-SSTIs or RSE.[51] In addition, it has been used to treat a variety of infections, including BJIs. However, daptomycin is not effective in the treatment of pneumonia because surfactant binding inactivates the drug. It is licensed for use at doses of 4–6 mg/kg; higher doses up to 10 mg/kg have been used with no additional toxicity. As it can be given once daily, it has become increasingly popular as an outpatient antibiotic therapy (OPAT), especially for prolonged courses, as in the case of BJIs. Some strains of MRSA with higher MICs for vancomycin have shown reduced susceptibility against daptomycin; MICs therefore should be determined in all cases before daptomycin is started. Nephrotoxicity and rhabdomyolysis are the two most significant, albeit uncommon, side effects, so creatinine kinase and renal function should be monitored regularly during therapy.

Telavancin is a lipoglycopeptide antibiotic that has been approved by the European Medicines Agency (EMEA) for the treatment of nosocomial pneumonia known or suspected to be due to MRSA. It has also been approved for use in c-SSTIs in the USA. A recent study has shown that telavancin is non-inferior to vancomycin in the treatment of HAP caused by Gram-positive

bacteria, mainly MRSA.[52] It is available only in intravenous form and has a long half-life, which makes it suitable for OPAT. Renal toxicity and its interference with coagulation tests, such as prothrombin time, are the main side effects of this drug.

Tigecycline is the first of the new glycylcycline class of antibiotics. It acts by inhibiting protein synthesis by binding to the 30S ribosomal subunit of the bacteria – in a similar way to tetracycline but with greater affinity. It has a broad spectrum of activity against bacteria, including MDR organisms such as MRSA, VRE, PRSP and ESBL- and carbapenemase-producing Enterobacteriaceae but not *Pseudomonas aeruginosa (P. aeruginosa)*. It has been licensed for use in the treatment of c-SSTIs (excluding diabetic foot infections) and complicated intra-abdominal infections (IAIs) in which other alternative agents are not suitable. Although phase III trials have shown non-inferiority in the treatment of CAP compared with levofloxacin,[53] studies comparing tigecycline with imipenem/cilastin in HAP/VAP have failed to show similar results.[54] Because of tigecycline's activity against MDR organisms, it has also been increasingly used in the treatment of HAP/CAP and also healthcare-associated bloodstream infections. However, recent systematic reviews have shown higher mortality and clinical plus microbiological failure rates among patients treated with tigecycline monotherapy.[55,56] In addition, the incidence of adverse events, including discontinuations secondary to adverse events, were higher in patients treated with tigecycline. The Food and Drug Administration (FDA) of the USA has therefore issued a warning against the use of tigecycline as monotherapy in the treatment of Gram-negative bloodstream infections.

Doripenem is the newest carbapenem in the formulary and has a broad spectrum of antimicrobial activity, including *P. aeruginosa* and *Acinetobacter* spp.[57] *In vitro* studies have shown better anti-pseudomonal activity for doripenem compared with other carbapenem agents.[58] It is currently licensed for the treatment of complicated IAIs and complicated UTIs in the USA, and for HAP/VAP in Europe. However, a recent post-marketing trial comparing doripenem with imipenem for patients with VAP was halted because interim results showed higher mortality among patients receiving doripenem.[59] In addition, data regarding its efficacy in the treatment of infections in patients with cystic fibrosis and neonates is still outstanding.

Newer agents on the horizon

Ceftaroline and ceftobiprole are broad-spectrum cephalosporins with anti-pseudomonal activity similar to cefepime and are active against MRSA. Ceftaroline already has approval from the FDA and is awaiting European licensing.

Conclusion

With the rapid increase in resistant organisms and the lack of availability of new therapeutic options, the time has come for clinicians in the frontline to use antibiotics more judiciously than ever before. Infection societies around the world, including the BSAC, have put in place several initiatives, via antibiotic stewardship programmes, to curtail antibiotic use in the community and hospital settings. Infection societies across the Atlantic have called for '10 × 20 initiatives' (that is, 10 new antibiotics by 2020) in order to put pressure on governmental licensing authorities to ease the regulatory process to facilitate the rapid approval of antibiotics in the near future. It currently takes, on average, 20 years from when an antibiotic molecule is developed from scratch for it be licensed for clinical use. In addition, conducting clinical trials to prove superiority over existing antimicrobial agents is a daunting task for the pharmaceutical industry.

Recent guidance from the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) of the Department of Health on antimicrobial stewardship, *Start smart – then focus*, emphasises the importance of judicious use of antimicrobial agents in hospitals in England.[60] Frontline clinicians involved in unselected takes who are managing patients with suspected infections should use antibiotics more prudently and ask themselves whether an antibiotic is really indicated in each case. Once an antibiotic is initiated, daily review of ongoing therapy, including conversion to oral agents, and steps to minimise the duration of therapy are also equally important. In this era of antibiotic resistance, it is mandatory to collect appropriate microbiological samples before initiating therapy. The microbiological results will guide the appropriateness and duration of the antibiotic therapy and possible oral options. The current generation of medical students, trainee doctors and senior clinicians should receive education and ongoing training about antibiotic resistance and prudent use of antimicrobial agents throughout their career. Drug and therapeutic committees should also play an important role by designing stringent antimicrobial guidelines. Regular auditing of the use of antibiotics and antibiotic stewardship programmes should be part of the clinical governance of each healthcare organisation. Public involvement and engagement of patients and their carers is also important in terms of the use of antibiotics in all healthcare settings, especially in the community. Generous and inappropriate use of antibiotics should be discouraged – for example, in the treatment of common upper respiratory tract infections, which are often caused by viruses. Not so long ago, the battle against infectious diseases was thought to be won. Bacteria, the longest free-living agents on the planet, have fought back and the battle against them looks even more daunting than ever.

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