Review

The new treatment paradigm and the role of carbapenems

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ARTICLE INFO

ABSTRACT

The global increase in antibiotic resistance is promoted by the widespread use of broad-spectrum antibiotics, creating a continuous selective pressure on bacteria. This resistance is depleting the number of effective antimicrobial agents. Since there have been few new agents active against Gram-negative bacteria in particular developed over the last two decades, it is important to make the most of existing antibiotics. Therefore, rational use of antimicrobial agents is vital in establishing a successful strategy to control and prevent both the clinical impact and the development of further resistance. Careful selection of the appropriate antimicrobial agent combined with correct dosing, duration of treatment and route of administration are all important to the success of this strategy and need to be coupled with antimicrobial resistance surveillance. Progress against the treatment strategy approach for optimising clinical outcomes whilst preventing antibacterial resistance based on antibiotic de-escalation will be reviewed with particular emphasis on the role of the carbapenems. This approach attempts to balance the need to provide appropriate initial treatment whilst limiting the emergence of antibacterial resistance.

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1. Introduction

Increasing levels of resistance to antibiotics routinely used against bacteria responsible for nosocomial infections remains a serious and growing global problem [1–6]. This global emergence of antibiotic resistance is fuelled by the widespread use of broad-spectrum antibiotics creating a continuous selective pressure on bacteria, as well as by lapses in infection control, which allow interpatient transmission and the environmental maintenance of resistant pathogens [7,8]. Compared with infections caused by sensitive strains, those due to resistant organisms result in higher morbidity and mortality, prolonged hospitalisation and increased costs [9–12].

Since this resistance is effectively depleting the number of clinically useful antimicrobial agents, and there have been few new agents developed over the last two decades, it is important to make the most of existing antibiotics. The rational use of antimicrobial agents is vital in establishing a successful strategy to control and prevent the development of further resistance whilst maximising patient outcomes. Careful selection of the appropriate antimicrobial agent combined with correct dosing, duration of treatment and route of administration are all important to the success of this strategy and need to be coupled with antimicrobial resistance surveillance [13]. Furthermore, treatment choices that are inappro-

priate, i.e. do not cover the infecting pathogen, have a detrimental effect on patient survival and lead to increased mortality rates, length of hospitalisation and medical costs [14–23].

At the start of this decade, appreciation of these drivers led to the evolution of a new treatment paradigm for the management of severe sepsis, which focused on 'getting it right first time' [24]. This review considers the progress of this new paradigm as a strategy for preventing antibacterial resistance and improving patient care, based on antibacterial treatment de-escalation. The approach attempts to balance the need to provide appropriate initial treatment whilst limiting the emergence of antibacterial resistance. The key principles of this new strategy will be outlined. In light of the impact that increasing antimicrobial resistance is having on reducing the number of antibiotics available to treat serious infections, strategies that can be implemented to preserve the efficacy of the approach will also be described.

2. New treatment paradigm

2.1. Getting it right first time

The new approach to antimicrobial therapy promoted starting with initial empirical broad-spectrum antibiotic treatment, which may be modified following the results of susceptibility testing [25–31] (Table 1). This approach is more tailored and rational than the traditional approach that depended upon the physician's clinical assessment of the patient, with escalating changes to be made as appropriate (Table 2). Overall, the new stratagem aims to optimise antibiotic dosing and administration.

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Table 1
Key principles of the new treatment paradigm

- Getting therapy right first time
- Use broad-spectrum antibiotics early
- Optimise antibiotic dosing and administration
- Base antimicrobial selection on knowledge of local susceptibility patterns
- Tailor or stop antibiotic therapy early and based on microbiological results (de-escalation)
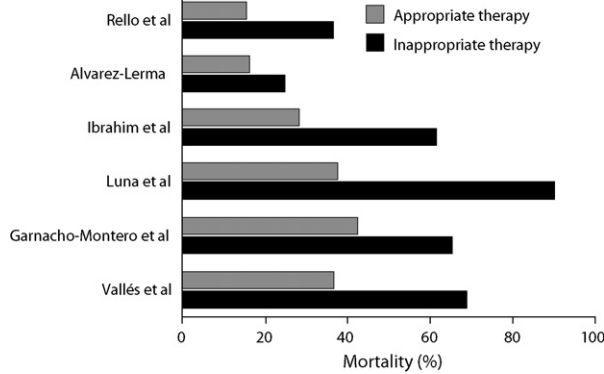- Give antibiotics for the correct duration

Fig. 1. Effect of appropriate and inappropriate therapy on mortality rates [14–19].
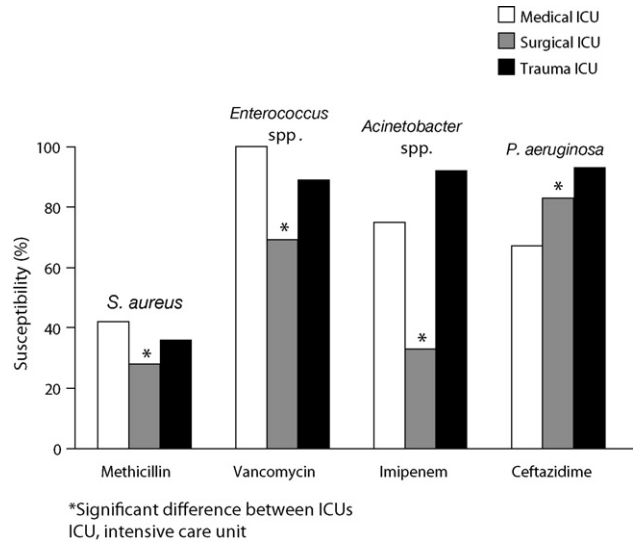

Fig. 2. Susceptibility of *Staphylococcus aureus*, *Enterococcus* spp., *Acinetobacter* spp. and *Pseudomonas aeruginosa* from surgical, trauma and medical ICUs.

Early aggressive therapy against likely pathogens is associated with lower mortality rates (Fig. 1) [14–19,32,33]. In the study by Leibovici et al. [33], the mortality rate was significantly reduced in patients given appropriate empirical therapy. Recent studies focusing on specific pathogens, such as extended-spectrum β-lactamase (ESBL)-producers [34], *Escherichia coli* [35], *Pseudomonas aeruginosa* [36] and meticillin-resistant *Staphylococcus aureus* (MRSA) [37], have confirmed the importance of appropriate initial empirical therapy in reducing mortality and length of Intensive Care Unit (ICU) stay.

The importance of early as well as appropriate empirical treatment has been emphasised in a recent analysis [38]. In this retrospective cohort study that included more than 2000 patients with septic shock, all of whom received appropriate antibiotic therapy, it was found that the time of starting antibiotic therapy had a significant impact on mortality. For these patients with hypotension that was not responsive to volume expansion, every hour of delay up to 6 h after onset in initiating antibiotic therapy was associated with a ca. 8% decreased probability of survival.

In addition to lower mortality rates, appropriate therapy leads to shorter length of stay and fewer mechanical ventilation days. Battleman et al. [32] showed that appropriate antimicrobial agent selection shortened the length of hospitalisation. Furthermore, such shorter lengths of hospitalisation can offset any extra drug acquisition costs associated with treating patients with resistant organisms [12]. In one study, the duration of hospitalisation was 9 days for patients given appropriate treatment compared with 11 days for patients who received inappropriate treatment [33].

An important factor in choosing appropriate empirical therapy is knowledge of the hospital unit's pathogen and resistance profile, since these can vary between and within institutions [39,40]. Namias et al. [39] showed that when susceptibility data from surgical, trauma and medical ICUs within the same hospital were compared, there were significant differences between the ICUs in susceptibility to various antibiotics employed against a range of bacteria (Fig. 2). Another study established that the causes of ventilator-associated pneumonia (VAP) varied considerably across four treatment sites, resulting in the need for variations in antimicrobial prescribing practices [40]. Furthermore, prior antimicrobial administration is a risk factor for the presence of resistant pathogens [41–45].

Table 2
Traditional and new treatment paradigm

Traditional treatment paradigm	New treatment paradigm
Conservative start with 'workhorse' antibiotics	Hit hard and early with appropriate antibiotic(s)
↓	↓
Reserve more potent drugs for non-responders	Short treatment duration; de-escalate where possible

2.2. De-escalation

Effectively managing the risks of resistance and drug acquisition costs associated with adopting the initial broad-spectrum antibiotic regimen approach demands modification of the regimen with a de-escalating strategy based on the patient's clinical response and the results of microbiological testing. This modification should include decreasing the number and/or spectrum of antibiotics. In addition, patients who are shown to have a non-infectious aetiology should have their antibiotics discontinued as soon as possible.

Several studies have shown the efficacy of a de-escalation strategy in the treatment of VAP and bacteraemia [25,46–50]. Berild et al. [46] showed that adjustment of antibiotic therapy for bacteraemia according to the results of blood cultures leads to a reduction in the number and costs of antibiotics used and a narrowing of antibiotic therapy. Adjustment of therapy was performed more often in Gram-negative bacteraemia and polymicrobial cultures than in Gram-positive bacteraemia. Compared with conventional empirical therapy, there was a 22% reduction in the number of antibiotics, and the cost for 7 days of adjusted therapy was 23% less than for 7 days of traditional therapy.

In a study in patients with pneumonia, a clinical pulmonary infection score (CPIS) was used to aid decision-making regarding antibiotic therapy [50]. Patients with a CPIS ≤6, suggesting a low likelihood of pneumonia, were randomised to receive standard therapy or ciprofloxacin monotherapy with re-evaluation after 3 days; ciprofloxacin was discontinued if the CPIS remained ≤6. Antibiotics were continued beyond 3 days in 90% of the patients on standard therapy compared with 28% in the experimental group ($P = 0.0001$). Mortality and length of stay did not differ significantly despite a shorter duration and lower cost of antimicrobial therapy in the experimental group compared with standard therapy. Antimicrobial resistance developed in 15% of the patients in the experimental group versus 35% in the standard therapy group.

A carbapenem-based de-escalating strategy was assessed in patients with nosocomial pneumonia [25]. Initial antibiotics were inadequate in 9% of the patients. Of the remaining patients, antibiotics were streamlined in 23% and remained unchanged in 6% based on microbiology data, in 16% despite microbiology data favouring de-escalation and in 46% where the aetiology was unknown. Overall, de-escalation was implemented in only 23% of patients with potentially multiresistant pathogens compared with 68% of the other patients ($P < 0.001$). Response rates were 53% for patients continuously treated with imipenem-based regimens and 50% for the de-escalated patients. The study highlighted that de-escalation was less likely to occur in the presence of potentially multiresistant pathogens. Soo Hoo et al. [31] studied the impact of locally developed antimicrobial treatment guidelines in the initial empirical treatment of ICU patients with severe hospital-acquired pneumonia. Guideline-treated cases had a higher percentage of adequately treated patients and a lower mortality rate at 14 days. A lower mortality rate, although not at a statistically significant level, was also noted at the end of 30 days and at the end of hospitalisation. Appropriate imipenem use (as defined by the guidelines) occurred in 74% of the cases and there was no increase in the number of imipenem-resistant organisms isolated during the course of the study.

In a more recent study in patients with VAP, de-escalation therapy was defined as either a switch to an agent that was less broad spectrum than initial therapy or the use of fewer drugs [51]. De-escalation occurred in 22.1% of all patients and was achieved more often by reducing the number of drugs than by going from a broader to a narrower spectrum agent. The mortality rate was significantly lower ($P = 0.001$) among patients in whom therapy was de-escalated (17%) compared with those experiencing therapy escalation (42.6%) and those having no change in therapy (23.7%).

The duration of therapy should also be considered when looking to control resistance generation, since some studies have shown that shorter periods of treatment are as effective as longer periods [47,49]. In a randomised, double-blind, multicentre comparison of 8- and 15-day courses of treatment for bronchoscopically diagnosed VAP, patients in the 8-day group had similar mortality rates to those in the 15-day group [47]. In addition, the recurrence of pulmonary infection, the number of mechanical ventilator-free days and the length of stay in the ICU did not differ between the groups. However, in the 8-day group the relapse rates tended to increase when the pathogen was *P. aeruginosa* or *Acinetobacter* spp. Micek et al. [49] evaluated a discontinuation policy in patients with clinically diagnosed VAP. Of the patients in the discontinuation group, 89% had at least one antibiotic discontinued within 48 h. Overall duration of treatment was significantly shorter in the discontinuation group compared with standard therapy. No differences were observed with respect to in-hospital mortality, ICU and hospital length of stay, or the duration of mechanical ventilation. Another study used a clinical guideline employing the goals of de-escalation therapy and promoted a 7-day course of antimicrobial therapy in responding patients with uncomplicated VAP [48]. Upon implementation of the clinical guideline, 98% of patients had one or two antibiotics discontinued by 48 h of treatment. Duration of treatment was significantly shorter during the post-protocol period compared with the pre-protocol period. There were no differences in clinical outcome measures, including ICU or hospital length of stay and in-hospital mortality.

Despite the growing evidence showing the utility of a de-escalation strategy approach there are still barriers to its adoption, including lack of physician acceptance of the stratagem, the lack of agreed, accepted objective measures to demonstrate clinical improvement against which de-escalation can be decided, and the potentially confounding impact of concomitant infections or other disease states on the patient's status. In addition, as has been shown in some of the previously described studies, de-escalation is less frequent in the presence of infections due to non-fermenting Gram-negative bacilli and is not possible if the pathogen remains unknown.

3. Antibiotic choice for the new treatment paradigm

A key factor in the new treatment paradigm is the early use of empirical antibiotics that have a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including therefore a wide range of potentially resistant pathogens such as *P. aeruginosa*, ESBL-producing Enterobacteriaceae and *Acinetobacter* spp. A variety of antimicrobial regimens are currently employed in this fashion for the initial treatment of serious nosocomial infections, including: combination therapy based on penicillin/anti-β-lactamase combinations; second-, third- or fourth-generation cephalosporins; full-spectrum carbapenems; or quinolones with the addition of an aminoglycoside and/or metronidazole where appropriate. Monotherapy using an antibiotic with a broad spectrum of activity such as a carbapenem is also an option (Table 3).

Empirical coverage against Gram-positive pathogens is also sought in the use of such broad-spectrum antibiotics. However, many units need to cover for meticillin-resistant bacteria and to achieve this a glycopeptide is commonly added to the empirical regimen. This increasing use of glycopeptides has in turn led to resistance problems. Fortunately, new antibiotics active against Gram-positives have recently become available and more are on the way [53,54]. Agents that have become generally available recently include linezolid, daptomycin and tigecycline (an antibiotic that is also active against several Gram-negative bacteria). Antibiotics

Table 3
Appropriate and inappropriate agents for empirical treatment of serious Intensive Care Unit infections (adapted from [52])

Appropriate agents
Combination therapies
A cephalosporin (cefuroxime, ceftazidime or cefepime)
or
piperacillin/tazobactam
and/or
an aminoglycoside (gentamicin/amikacin)
and/or
metronidazole
and/or
a glycopeptide (vancomycin)
Monotherapies
Carbapenems (meropenem, imipenem/cilastatin)
Quinolones (ciprofloxacin or levofloxacin)
Broad-spectrum penicillins (e.g. piperacillin with a β-lactamase inhibitor)
Cephalosporins (cefepime)
Inappropriate agents
Ertapenem: no coverage of *Pseudomonas* spp. or *Acinetobacter* spp.
Quinolones, piperacillin/tazobactam, newer cephalosporins, e.g. when ESBLs, Amp C-encoded β-lactamases or MRSA are suspected
Carbapenems: when MRSA is suspected
Tigecycline: no coverage of *Pseudomonas* spp.

ESBL, extended-spectrum β-lactamase; MRSA, meticillin-resistant *Staphylococcus aureus*.

such as dalbavancin and ceftobiprole are expected to be launched in the near future. These new agents, if used correctly, offer some hope of countering emerging Gram-positive resistance threats.

The quinolones (e.g. ciprofloxacin, levofloxacin), penicillins (e.g. piperacillin, tazobactam) and cephalosporins (e.g. cefepime, ceftazidime) are often used as empirical monotherapy. However, increasing levels of resistance to many of these agents mean that they have become less effective for single use against nosocomial infections [2–4,55,56].

The carbapenems (meropenem and imipenem/cilastatin) represent a realistic option for initial empirical therapy in many serious infections owing to their broad spectrum of activity and the continued susceptibility of difficult-to-treat and antibiotic-resistant pathogens to these agents. The carbapenems are a group of potent β-lactam antibiotics, of which there are three generally available worldwide, meropenem, imipenem/cilastatin and ertapenem. In addition, doripenem is now becoming generally available. Although ertapenem has a useful once-daily dosing schedule, the gaps in its spectrum of bacterial activity, e.g. *P. aeruginosa* and *Acinetobacter* spp., means that it normally has no role in the empirical management of serious ICU infections [57–59]. In contrast, meropenem and imipenem/cilastatin represent a realistic option for initial empirical therapy in many serious nosocomial infections. They and the forthcoming doripenem have a broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens, including anaerobes and difficult-to-treat organisms such as Gram-negative pathogens resistant to many other antibiotics [1,5,6,57,60,61]. However, they lack activity against *Enterococcus faecium*, MRSA and *Stenotrophomonas maltophilia*. Importantly, despite their availability for more than 20 years, the development of resistance to carbapenems has been remarkably low. Full-spectrum carbapenems are particularly useful because of their proven in vitro activity against pathogens producing extended spectrum and AmpC β-lactamases [1].

There are some differences between the two established full-spectrum carbapenems meropenem and imipenem/cilastatin [52,62]. Meropenem is more active then imipenem/cilastatin against Gram-negative pathogens including *P. aeruginosa*. A recent study showed that meropenem was active against

20.4% of imipenem-resistant strains whereas imipenem/cilastatin was active against only 4.2% of meropenem-resistant strains [63]. However, imipenem/cilastatin is slightly more active than meropenem against staphylococci and enterococci. Unlike with imipenem/cilastatin, the meropenem dose can be increased (up to 6 g/day) owing to its good tolerability profile. Furthermore, there is reduced nausea and vomiting and seizure potential with meropenem compared with imipenem/cilastatin [64].

Two recent extensive reviews of carbapenem experience in clinical practice have been published. Edwards et al. [65] presented a systematic review of randomised controlled trials exploring the performance of carbapenems versus other β-lactams in treating severe infections in intensive care. Only 12 of the 265 papers identified were appropriate for inclusion in the meta-analysis, although there were insufficient data to assess the fourth-generation cephalosporins. However, the results showed that in the management of serious infection and compared with antipseudomonal penicillins the carbapenems were associated with a significant reduction in all-cause mortality (relative risk (RR) 0.62, 95% confidence interval (CI) 0.41–0.95; $P = 0.03$), and withdrawals due to adverse events (RR 0.65, 95% CI 0.45–0.96; $P = 0.03$) were also reduced. Similarly, in the treatment of febrile neutropenia, carbapenems demonstrated a significant increase both in the clinical response during the initial 72 h of treatment (RR 1.37, 95% CI 1.09–1.74; $P = 0.008$) and in the bacteriological response (RR 1.73, 95% CI 1.03–2.89; $P = 0.04$). In another more general review dealing with meropenem specifically, non-inferiority was shown for that antibiotic when assessed across severe sepsis indications and against a number of comparator antibiotics including imipenem/cilastatin [66]. Included in the work was a pharmacoeconomic analysis of meropenem in these circumstances and relating to its use in the UK, USA and Russia, where it was predicted that meropenem was a cost-effective therapy relative to other antibacterials, including imipenem/cilastatin or conventional combination antibacterial treatments in ICUs.

Despite the above evidence that has been available for some time now, traditionally meropenem and imipenem/cilastatin have not been used earlier in the treatment pathway mainly because of the perceived cost impact and the fear of resistance developing to these agents related to such increased usage. In addition, there is concern over the lack of further treatment options should carbapenem therapy fail. In view of the clinical and other successes of the new treatment paradigm, this approach seems over cautious and there is arguably a clear role for using full-spectrum carbapenems as initial empirical therapy in defined types of serious nosocomial infections, e.g. nosocomial pneumonia (including VAP), serious nosocomial intra-abdominal infections and septic shock. It is appropriate to use meropenem and imipenem/cilastatin as early empirical therapy in patients who are at high risk of death, bacterial superinfection or exposure to hospital flora (including colonisation by ESBL-producers and other multiresistant Gram-negative organisms, having received previous multiple antibiotic therapy or where there is a known ESBL outbreak) (Table 4) [52,62,67]. In cases where prior therapy has failed, meropenem and imipenem/cilastatin are also valid as second-line therapy owing to their broad spectrum of in vitro activity and because they retain activity against Gram-negative organisms resistant to other antimicrobial classes such as the cephalosporins and fluoroquinolones. However, when MRSA or vancomycin-resistant enterococci are potential pathogens, the full-spectrum carbapenems should be used in combination with an agent active against these strains, such as vancomycin. If microbiology results show that a resistant Gram-positive organism is the sole cause of the infection, then in line with the de-escalation approach described above carbapenem use should be discontinued.

Table 4
Appropriate empirical treatment with the full-spectrum carbapenems (adapted from [57])

Empirical therapy
Late-onset nosocomial pneumonia
When multidrug-resistant pathogens, including ESBL-producers (e.g. *Klebsiella* spp.) and AmpC β-lactamase-producers (e.g. *Citrobacter* spp. and *Enterobacter* spp.) are suspected
Patients who have been recently hospitalised, have been resident in a nursing home or who have recently received antibiotic therapy
The patient is immunosuppressed or has undergone an organ transplant
Severe nosocomial infections in critically ill patients in the ICU
Directed treatment according to the results of culture and susceptibility testing
Chronic multiresistant pseudomonal infections
Neutropenic sepsis
Severe nosocomial intra-abdominal sepsis
Second-line therapy
Failure of previous therapy with cephalosporins, aminoglycosides and fluoroquinolones

ESBL, extended-spectrum β-lactamase; ICU, Intensive Care Unit.

4. Maximising the utility of the carbapenems

As previously mentioned, the increasing incidence of antimicrobial resistance is reducing the number of antibiotics available to treat serious infections. If the carbapenems are going to be used as an early general empirical therapy, it is important to deploy them in an efficient way that maximises their clinical potential but that minimises the rate of resistance development. Important strategies that can be implemented to preserve the efficacy of the carbapenems in this way include applying pharmacokinetic/pharmacodynamic principles, adapting the dosing regimen or adopting antibiotic rotation.

4.1. Pharmacokinetic/pharmacodynamic considerations

Proper application of pharmacokinetic principles to antimicrobial dosing strategies can help to optimise antimicrobial exposure, improve clinical and microbiological outcomes and may slow the emergence of antimicrobial resistance [68–70]. An ideal dosing strategy for an antibiotic would be one in which the drug dose is sufficient to produce a high probability of attaining the necessary exposure to kill the organism, with a low likelihood of toxicity to the patient. Optimal dosing would also decrease the probability that a resistant clone would dominate the population owing to selective pressure from the therapeutic agent [69].

A new modelling technique called OPTAMA (Optimising Pharmacokinetic Target Attainment using the MYSTIC [Meropenem Yearly Susceptibility Test Information Collection] Antibiogram) has been developed, which can aid clinicians in selecting appropriate antibiotic therapy. Complementing traditional minimum inhibitory concentration (MIC)/susceptibility data as an aid to making clinical decisions, OPTAMA incorporates pharmacokinetic parameter estimates, dosing regimens and relevant MIC pathogen distribution data through the use of Monte Carlo simulation. This enables the clinician to calculate the probability of reaching the critical pharmacodynamic target set to ensure maximal bacterial killing and therefore the best chance of a clinically successful outcome [71–73]. Monte Carlo simulation allows for predictions of the effectiveness of an antibiotic in a large number and wide variety of patients, based on known pathogen susceptibility. The probability of target attainment (PTA) is calculated for each antibiotic dosing regimen and organism over a range of bacterial target values. The antibiotic with the highest target attainment (or cumulative fraction of response) would be optimal for empirical antimicrobial therapy, as
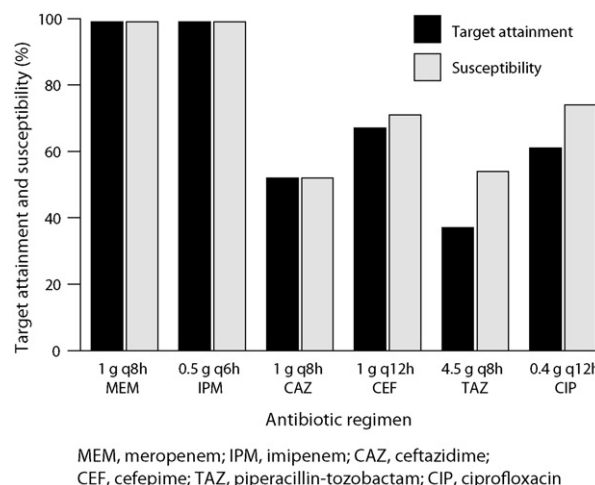

Fig. 3. Target attainment and susceptibility results for *Klebsiella pneumoniae* in Eastern Europe. q8h, every 8 h; q6h, every 6 h; q12h, every 12 h.

MEM, meropenem; IPM, imipenem; CAZ, ceftazidime; CEF, cefepime; TAZ, piperacillin-tozobactam; CIP, ciprofloxacin

it would provide the highest likelihood of obtaining bactericidal exposure against the bacteria at a simulated dose, which is based on the actual therapeutic regimens in use.

European MIC data were obtained from the MYSTIC programme, and pharmacodynamic target attainment was calculated for meropenem, imipenem/cilastatin, ceftazidime, cefepime, piperacillin/tazobactam and ciprofloxacin against *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *P. aeruginosa* [71]. Significant differences in PTA were found, with Northern Europe demonstrating the highest PTAs and Eastern Europe the lowest. The carbapenems had the highest target attainments and susceptibility levels across all regions and pathogens, with piperacillin/tazobactam and ciprofloxacin displaying the lowest levels for both parameters in all regions (Fig. 3). Except for carbapenems in Northern Europe, desirable target attainment was not achieved for *A. baumannii* and *P. aeruginosa*, suggesting that combination therapy may be the appropriate empirical therapy for these pathogens in Southern and Eastern Europe. The study also highlighted that the probability of attaining bactericidal exposure did not always concur with the reported percentage susceptibility. Susceptibility rates underestimated the predicted bactericidal effect of some antibiotics (including higher doses of ceftazidime and cefepime), whilst overestimating the potential impact of other antibiotics (including piperacillin/tazobactam and ciprofloxacin).

4.2. Dosing strategies

Antibacterial agents vary markedly in the time course of antimicrobial activity and these differences in pharmacodynamic activity have implications for optimal dosing regimens aimed at maximising clinical efficacy and minimising the development of resistance.

The carbapenems have been characterised as concentration-dependent or time-dependent antibiotics, although it is generally accepted that their efficacy is primarily based on maintaining concentrations of the antibiotic above the MIC of the organism for prolonged periods [68]. Owing to the wide dosing range of meropenem used in clinical practice and its good safety profile, flexibility is available to clinicians wishing to optimise drug exposures. Drug exposures can be maximised by increasing the dose, increasing the frequency of administration or prolonging the duration of infusion. Pharmacokinetic and pharmacodynamic research has investigated new dosing regimens such as altered frequency of administration and extended infusion [74]. Although new dosing regimens are not currently licensed for carbapenems, these new

strategies are promising [75–77]; however, their potential needs to be confirmed by randomised controlled clinical trials. These studies are now starting to be published, with a recent evaluation of a 4-h infusion of 500 mg doripenem (1.5 g daily in three doses) being compared with imipenem/cilastatin (2 g daily in four doses or 3 g daily in three doses) in the management of VAP. Although there were no statistically significant differences in the primary endpoints, potential benefits of this approach were demonstrated with only 18% (5/28) of *P. aeruginosa* isolates having MICs $\geq$8 µg/mL at baseline or following therapy in the doripenem arm compared with 64% (16/25) in the imipenem/cilastatin treatment group (P = 0.001) and the clinical cure rate was higher with doripenem than imipenem/cilastatin at higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores and older ages [78].

4.2.1. High dose

Owing to its propitious safety profile, which includes good central nervous system tolerability and a low incidence of nausea and vomiting, the dosage of meropenem can also be increased when necessary [79]. Higher doses of meropenem may be needed for specific populations of patients with compromised immune systems, altered pharmacokinetics or infections with bacteria exhibiting higher than conventional meropenem MICs [80]. An interesting group of patients who may be underdosed due to altered pharmacokinetics are those with severe sepsis prior to the development of organ dysfunction. These patients have increased antibiotic clearance due to the supportive use of inotropes and volume expanders [81].

4.2.2. Increased frequency of administration

The pharmacokinetic properties and pharmacodynamic characteristics of meropenem may allow it to be administered as a smaller dose more frequently [76,77]. Kuti et al. [76] used Monte Carlo simulation to compare different doses of meropenem over different infusion periods. Their computer modelling suggested that if lower doses were administered more frequently, a similar percentage of the dosing interval with drug concentrations remaining above the MIC (%T > MIC) was observed compared with standard doses. A retrospective review of clinical outcomes in a group of 85 patients showed that meropenem 500 mg administered every 6 h resulted in similar clinical outcomes to a regimen of 1000 mg every 8 h [77]. However, this 6-hourly dosing of meropenem is not a licensed regimen and further clinical trial data are needed before recommending these approaches.

4.2.3. Extended infusion

Another approach to maximising β-lactam %T > MIC is via continuous or extended infusion, a topic that has been reviewed by Roberts et al. [82]. Whereas β-lactams can be continuously infused, the stability issues related to doripenem and meropenem mean that only extended infusions, e.g. over 3 h, are possible. For example, compared with a 30-min infusion, prolonging infusion of meropenem to 3 h will increase the %T > MIC. The infusion duration of meropenem has successfully been extended to 3 h both in healthy volunteers and in patients with VAP [74,75,83,84], and a recent doripenem study evaluated a 4-h infusion [78].

4.3. Antibiotic rotation

Antibiotic rotation has been suggested as one possible approach towards reducing resistance [85,86]. This approach is based on the hypothesis that withdrawal of an antibiotic or antibiotic class from use for a defined period of time will limit antibiotic pressure as a stimulus for antibiotic resistance. Antibiotic rotation has been shown to reduce ICU nosocomial infections, particularly VAP,

and ICU mortality rates [85–88]. In critically ill medical patients a strategy of monthly rotation of antipseudomonal β-lactams and ciprofloxacin performed better than a strategy of normal selection mixing in the acquisition of *P. aeruginosa* resistance to selected β-lactamases [87]. However, not all studies have demonstrated a benefit with antibiotic rotation, with some showing an increased frequency of highly resistant organisms such as *Acinetobacter* spp., *Pseudomonas* spp. and ESBLs, and an increased total antibiotic use following cycling, e.g. with quinolones and piperacillin/tazobactam [89]. Furthermore, a systematic review evaluating the efficacy of antibiotic cycling concluded that owing to multiple methodological flaws and a lack of standardisation, the results were inconclusive with regard to the efficacy of cycling [90]. It is possible that the beneficial effects observed merely flow from the improved antibiotic husbandry associated with the discipline of the cycling approach.

5. Summary

The new treatment paradigm ensures the provision of appropriate initial treatment to patients with serious bacterial infections whilst avoiding unnecessary use of antibacterials in order to prevent the emergence of resistance. De-escalation is now proven to work and so changes can be made as appropriate following result availability and the physician's clinical assessment of the patient. The full-spectrum carbapenems are the most appropriate antibiotic class for deployment in this stratagem as they have a proven performance with a broad spectrum of in vitro activity. They therefore represent an appropriate first-line empirical treatment for serious nosocomial infections where it is vital that the initial therapy provides effective cover against all suspected pathogens. Their choice depends on the local susceptibility data and may require extension of the spectrum to cover their gaps, e.g. the addition of a glycopeptide.

Given the increasing tide of antimicrobial resistance, the best approach to combating resistance and to providing effective therapy is by optimising the use of currently available antimicrobial agents. Antibiotic rotation is unlikely to offer such a tool, although dosing approaches appear much more promising. Whilst there are initial promising data about how antibiotic care can be optimised by adopting pharmacokinetic/pharmacodynamic principles, and by adapting the dosing regimen with high doses or continuous infusion, further studies are needed to demonstrate the clinical utility of such strategies before they can confidently be introduced into widespread practice.

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