# Clinical challenges in antimicrobial resistance

Antimicrobial resistance is one of the great challenges for twenty-first century healthcare. While new therapeutics are undoubtedly required, there are major challenges in rapidly identifying resistant infections and tailoring therapy accordingly; and in how we deploy antimicrobials with suppression of resistance in mind.

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There has been considerable focus on the need for new therapeutics for highly resistant infections, particularly due to extensively drug-resistant (XDR) Gram-negative pathogens, but major technological developments in infection prognostics and diagnostics are required. Optimal integration of old or new antimicrobials into practice will require high-quality clinical data. There is also a need to identify and investigate novel antimicrobial stewardship strategies that could potentially minimize resistance (Fig. 1).

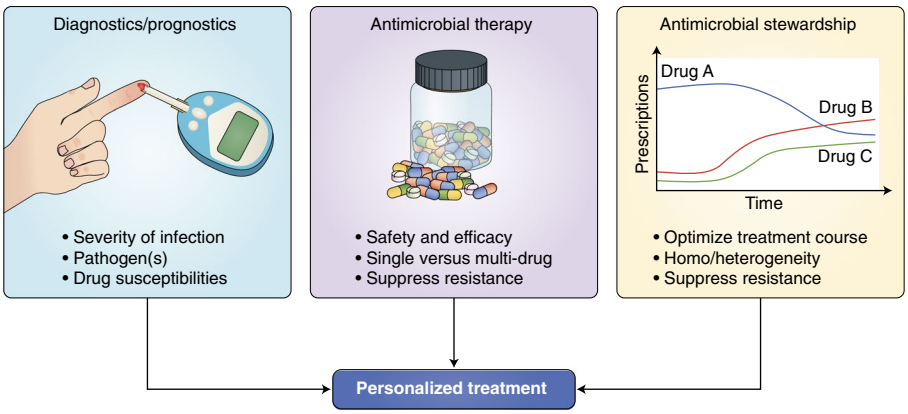


**Fig. 1 | Clinical challenges in personalizing treatment and suppressing resistance.** New diagnostics and prognostics are needed to identify patients that require antimicrobials to improve their clinical outcomes and inform prescribers about the optimal drugs to use. Successful integration of new drugs, as well as new combinations of current antimicrobials, into clinical practice will require robust clinical testing to evaluate safety and efficacy, ideally in patient cohorts that truly represent those seen in clinical practice. Antimicrobial use at patient, organization and population levels needs to be deployed in a way that minimizes emergence of drug resistance.

## Challenges in diagnosis

Making a diagnosis of infection has historically been based on the fundamentals of clinical practice (that is, the patient's story and examination) but it is often challenging, even when supported by rapid but non-specific tests such as white blood cell counts, C-reactive protein and procalcitonin measurements, and radiography (generally available within 2–3 hours in well-resourced hospitals). Ideally, infections requiring antimicrobials should only be treated with the narrowest-spectrum agent that the pathogen is susceptible to, at the right dose and frequency, at the right time and using the shortest efficacious duration. However, making a microbiological diagnosis remains predominantly culture-based, typically taking 12–24 hours to reach preliminary identification from time of venesection (and starting therapy) and even longer to confirm antimicrobial susceptibilities. Additionally, many patients with bacterial infections produce negative cultures.

In those with positive cultures, new technologies such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry[1] and whole-genome sequencing[2] are increasingly used to reduce the time to pathogen identification. But more often than not, clinicians must use guidelines (or guess) when prescribing empiric antibiotics that are subsequently shown to be unnecessarily broad-spectrum or, for some patients, too narrow. Prescribers at the coalface need two key pieces of information to optimize prescribing: (1) if an antibiotic is not prescribed, the probability that harm will occur (that is, severity); and (2) the nature of the infection, including pathogen drug susceptibilities.

Severity assessment links the probability that a patient will to come to harm (and the nature of that harm) with the level of intervention required to prevent it. Most antimicrobials are prescribed in the community, often for self-limiting infections (for example, upper respiratory tract) that are generally low-risk and do not require antibiotics. Infections managed in hospitals are usually more severe with patients having higher risk of death. Treatment within one hour of recognition is mandatory in sepsis because death occurs quickly; a pathogen-specific diagnosis is less important than administering life-saving therapy. Although sepsis 'red flags' and early warning scores (for example, CURB-65 in community-acquired pneumonia) are commonly used and quick and easy to apply, they only have moderate predictive value and often perform poorly in sub-groups (for example, in elderly or immunocompromised patients)[3]. Thus, there is a need to identify highly accurate biological predictors of infection outcomes and translate these into cost-effective rapid prognostics.

Better diagnostics are also needed to quickly identify pathogens (that is, bacterial from viral from fungal from polymicrobial) at the species level, and their associated antimicrobial resistances, in a range of clinical presentations and specimens. Although rapid tests are available for use in certain clinical presentations (for example, group A streptococcal throat and respiratory virus infections), these are currently of limited breadth and do not inform on antimicrobial susceptibilities. Longer-term, we need to move away from slower laboratory-based tests to those that are truly bedside, performed immediately at strategically sited machines in emergency departments, admissions and high-dependency wards, and also in community-based clinics. Even an inexpensive point-of-care test that quickly reports the presence of resistant Gram-negative bacteria in a patient's blood (or other bodily fluids/

tissues) would be a leap forward and result in better prescribing.

## Challenges in prescribing

In recent years, several new antibiotics likely to be useful for resistant infections have come to market (for example, ceftolozane–tazobactam, tedizolid and dalbavancin). Integrating these into clinical practice in a way that provides an acceptable return on investment and encourages further drug development, while maintaining the principles of antimicrobial stewardship and minimizing further resistance, is tricky. The commonly held paradigm that expensive new agents should remain on the shelf for a rainy day, in keeping with the World Health Organization's watch and reserve approach for essential medicines[4], is unlikely to encourage antimicrobial development within the current reimbursement framework, and may even promote homogeneity of prescribing. Although prescribers and patients will often accept a higher risk when treating highly resistant infections, they are likely to have concerns about limited efficacy and safety data, particularly as new agents are generally investigated in cohorts of patients dissimilar to those they are then prescribed in. Hospital administrators are also concerned about costs.

The Combating Antibiotic-Resistant Enterobacteriaceae (CARE) trial recently suggested that a novel aminoglycoside, plazomicin, is superior to and safer than colistin (in combination with either tigecycline or meropenem) against severe carbapenem-resistant Enterobacteriaceae infections[5]. This important trial highlights the major challenges in recruiting patients for high-severity, high-resistance infections; and despite its small size ($n = 39$), by testing drugs in clinically challenging to treat infections, such as hospital-acquired or ventilator-associated pneumonia and bacteraemia, it may be an exemplar for future drug development. It also suggests that emerging therapies, at least for high-severity, high-resistance infections, may have to be investigated in combination with existing agents, although it is possible that similar results would have been achieved with monotherapy. The response of regulatory bodies to the trial will be of interest, and will likely prompt further questions regarding which drug combinations, in what clinical circumstances, will add value to monotherapy and how they will influence resistance.

From clinical necessity, XDR Gram-negative infections have forced clinicians to prescribe clinically untested novel combinations of existing drugs (for example, colistin and tigecycline with or without meropenem). However, the evidence base for combinations improving clinical outcomes is unfavourable. For example, a meta-analysis of clinical trials found that aminoglycoside-based combinations, including for Gram-negative infections, cause more harm (nephrotoxicity) than good[6]; and recent studies show that rifampicin-based combinations in *Staphylococcus aureus* bacteraemia[7] and clindamycin combinations in cellulitis[8] also have more negative effects than benefits. The clinical evidence base for using combinations (versus monotherapy) in XDR Gram-negative infections is currently only observational[9]; keenly awaited are the results of randomized trials of colistin-based combination versus monotherapy (the trials have been registered with ClinicalTrials.gov under the identifiers NCT01732250 and NCT01597973).

Nevertheless, some combinations show promise. An emerging approach is double β-lactam therapy, which had become an anathema of clinical practice due to stewardship concerns. A β-lactam combined with a different β-lactam or a β-lactam/β-lactamase inhibitor may provide clinical benefit in highly resistant infections. Ceftazidime–avibactam with aztreonam was efficacious in New Delhi metallo-β-lactamase-producing *Klebsiella pneumoniae* infections[10], and a colleague and I have recently successfully treated an XDR *Burkholderia multivorans* infection. Such combinations may work by targeting different or the same (if overexpressed) penicillin-binding proteins and/or one of the partner β-lactams (or the β-lactamase inhibitor) protecting the other agent. However, these promising combinations of new and existing drugs need more robust clinical evaluation.

Another potential advantage of combination therapy is that it might suppress resistance. At Hull and East Yorkshire Hospitals NHS Trust, one-third of patients prescribed an antibiotic receive combination therapy for several reasons: to cover what monotherapy cannot (for example, metronidazole with non-anti-anaerobic antibiotics such as gentamicin in intra-abdominal infection); when monotherapy is undesirable (for example, fluoroquinolones and *Clostridium difficile* risk); and to mitigate against resistance to empiric therapy subsequently being identified (for example, use of gentamicin with co-amoxiclav or piperacillin–tazobactam for Gram-negative bacteraemia[11]). Combinations are infrequently prescribed, however, to primarily suppress resistance. Apart from tuberculosis, the current clinical evidence base for such an approach to infections due to faster-growing bacteria is unconvincing. Even for *Pseudomonas* infections, for which combinations are often prescribed with suppression of resistance in mind, there is a surprising lack of clinical data[12]. Thus, given concerns about the collateral damage of new combinations and novel approaches on the diversity of (and amplification of resistance within) the human microbiota and other negative effects, further clinical evaluation of prescribing approaches that target suppression of resistance in common infections, while maintaining efficacy, is critical.

## Challenges in antimicrobial stewardship

Even if armed with rapid diagnostics and new antimicrobials, we still need to learn to prescribe optimally. Frustratingly, even when susceptibilities are available or there is no evidence of infection, patients often remain on broad-spectrum antimicrobials longer than required. Important factors likely to influence both outcomes and resistance, such as pharmacokinetics and pharmacodynamics, are inadequately considered. More sophistication in post-prescription assessment is therefore required: for example, therapeutic drug monitoring (possibly for agents traditionally unmonitored, such as β-lactams[13]) and defining optimal time-points for stopping therapy across different types and severities of infections. We should ultimately be aiming for individualization rather than the current broad-brush, fixed-dose, fixed-duration 'complete the course' approach. National guidelines, such as *Start Smart Then Focus*[14], which concentrates on key moments in prescribing, and research such as the Antibiotic Review Kit (ARK)[15] (which categorizes prescriptions as provisional or definitive to aid review and early cessation) are likely to be important medium-term strategies to curb overuse, but are not long-term solutions.

How we deploy antimicrobials at organizational and population levels to minimize resistance is also important, but this has been under-investigated and is poorly understood. In the UK, predominantly fuelled by concern about *C. difficile* infection, guidelines have tended to be homogeneous, leading to prescription of large amounts of relatively few antibiotics (predominantly β-lactams), an approach that some have suggested has contributed to resistance. Two proposed approaches to increase heterogeneity of antimicrobial use and potentially suppress resistance are cycling and sequencing of antibiotics. Cycling can be applied at guideline/

institutional levels (for example, for a specific indication, antibiotic A for month 1, antibiotic B for month 2, and so on)[16] or at prescription levels (for example, antibiotic X day 1, antibiotic Y day 2, and so on)[17]. Sequencing (for example, antibiotic Z days 1, 2 and 5 with antibiotic W days 3 and 4)[18] is also being studied but, as with daily cycling within a prescription, is yet to be clinically investigated. Weekly or monthly cycling has also been used to suppress resistance in patients taking long-term antibiotics (for example, recurrent urinary tract infection), although the clinical evidence base for this is low quality (observational only).

More clinical data are available for cycling as a stewardship strategy. Wiesch et al.[16] performed a meta-analysis of clinical studies and found that cycling reduced resistant infections compared to random mixing of antibiotics. Their study also demonstrated considerable problems with existing data—most studies have been of small specialist wards (few hospital-wide studies) over relatively short periods. Although some organizations have adopted cycling as a stewardship strategy, for example within intensive care, the clinical evidence is sub-optimal, and the Infectious Diseases Society of America does not currently recommend this approach[19]. Even if cycling was shown to be effective more widely, logistical challenges in implementation and surveillance across numerous indications in hospitals or across the community are likely to be considerable, especially within the context of limited resources for stewardship programmes.

Of course, if heterogeneity of antimicrobial use proves to be important in suppressing resistance, it does not require cycling to achieve it. Carefully designed and implemented guidelines providing a range of stewardship-equivalent therapy options and, in the future, synthesis of e-prescribing and/or clinical decision support with other technologies such as wearables and artificial intelligence, may achieve greater heterogeneity. Key research questions remain: (1) does heterogeneity of antimicrobial use suppress resistance; and if so, (2) what is the optimal way to achieve it?

## Conclusions

Extremely drug-resistant infections have become a fact of life in global clinical practice. To avoid historical mistakes and jeopardizing new agents, highly accurate, cost-effective point-of-care prognostics and diagnostics are key to high-fidelity prescribing. We also need to learn how to prescribe and deploy antimicrobials optimally, with resistance in mind. Old prescribing paradigms, such as the importance of cidality[20], will be challenged while new ones emerge. Research funding should be on par with, if not more than, that for new therapeutics. How to achieve this in low-income settings, where the clinical need and resistance is greatest, is a continuing conundrum. Ultimately, while developing new therapeutics is certainly important, there are complex clinical challenges (not all discussed here), which prevent optimal prescribing. In an age of increasing antimicrobial resistance, we need to be mindful that what we currently want may not be what we really need. ❐

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## Competing interests

The author declares no competing interests.