Personalised randomised controlled trial designs – a new paradigm to define optimal treatments for carbapenem-resistant infections

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Abstract (143 words):

Substantial obstacles exist to the design and conduct of treatment trials for carbapenem-resistant bacterial infections. These include the lack of a widely acceptable optimised standard of care, control regimen, with varying antimicrobial susceptibilities and clinical contraindications making specific intervention regimens infeasible, combined with diagnostic and recruitment challenges. To address these obstacles we propose extending the network meta-analysis approach to individual randomisation of patients. Specifically, of a "network" of X regimens of interest for life-threatening carbapenem-resistant infections, each patient would be randomised only to regimens considered clinically reasonable for that patient at that time, incorporating susceptibility, toxicity profile, pharmacokinetic/pharmacodynamics data, availability and physician judgement. We propose a novel trial design, building on network meta-analysis methods, to maximise the relevance to each individual patient, and to enable the top-ranked regimens from any personalised randomisation list to be identified, in terms of both efficacy and safety.

Text (2945 words):

Broad-spectrum antimicrobial resistance (AMR) and/or multi-drug resistance is impacting treatment decisions and patient outcomes from bacterial infections worldwide, particularly in Asia and southern Europe. Infections with carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumanii* or *Pseudomonas aeruginosa* are the clearest threat, with multiple documented mechanisms of carbapenem resistance.[1] Many of these mechanisms co-occur with resistance to multiple antibiotic classes and are carried on mobile genetic elements, including plasmids, which facilitate their spread. This leads to "mosaic" patterns of resistance, requiring personalisation of antibiotic therapy using antimicrobial susceptibility testing.

Numerous areas of clinical uncertainty surround the treatment of these highly resistant infections, particularly because *in vitro* data (e.g. from hollow fibre models) suggests antibiotic combinations may be synergistic[2] or antagonistic.[3] The situation is made more complex by a lack of standardisation of *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) models and dose optimisation methods for single antibiotic drug development programs,[4] recently highlighted by National Institute of Allergy and Infectious Diseases workshops.[5,6] There is further lack of clarity on the relationship between *in vitro* data and clinical outcomes for combination therapy, but outstanding questions, highlighted in recent reviews,[7-11] include whether high-dose carbapenems might overcome lower-level resistance; whether old, potentially toxic drugs, such as colistin, are more effective in combination with other drugs; and whether alternative agents synergistically increase antimicrobial potency e.g. polymixin-zidovudine[12]?

Randomised controlled trials (RCT) provide the most robust evidence regarding the relative efficacy of different therapeutic options.[13] However, despite the plethora of questions, there are few randomised trials in carbapenem-resistant infections. Clinical practice is currently guided by retrospective observational cohort studies, such as the INCREMENT study, where combination therapy was associated with improved clinical outcomes in higher risk patients.[14] The challenges of undertaking RCTs are illustrated by the recent FDA-approved trial of plazomicin, which screened 2000 adults to randomise only 39 over 2 years.[15] Of note, the parallel trial of plazomicin versus meropenem for complicated urinary tract infection recruited 609 adults but had 0.2% mortality overall,[16] making extrapolation to more serious infections challenging. One of the largest trials in carbapenem-resistant infections to date randomised 406 adults to colistin monotherapy vs colistin+meropenem.[17] Whilst overall the trial found no evidence of benefit from colistin+meropenem, failure rates were numerically lower in the combination arm. A further challenge for comparative clinical efficacy studies is the future pipeline of antibiotics active against carbapenem-resistant infections.[18] The great majority now in Phase 1 trials are active only against specific pathogens or resistance mutations, making broader comparisons of efficacy even more problematic.

In a traditional 2-arm or multi-arm trial, eligible patients are randomised between control and all intervention regimens. First, there is no accepted optimal standard of care regimen that can be used as a control regimen for carbapenem-resistant infections. Second, any specific regimen may be contraindicated or unavailable for many patients with carbapenem-resistant infections for different reasons, greatly restricting eligibility and recruitment. For example, the antimicrobial susceptibility

of the infecting organism or the patient's condition (e.g. renal impairment) may contraindicate either the control or intervention regimen.

These factors make it hard to find any two specific regimens which most patients meeting other inclusion criteria could be randomised to, even though physicians may have many questions regarding an individual patient's treatment. This makes conventional trial designs difficult, including "platform" designs, which maintain a control group over a longer period of time, against which different intervention regimens are compared, with the control potentially changing if a more effective regimen is identified.[19,20]

What is the clinical question?

Faced with a severely unwell patient with a life-threatening carbapenem-resistant infection (with a probable underlying mortality ≥10-20%), a clinician wishes to know, out of the X possible regimens (including combinations) that they could treat this patient with, which will provide the greatest probability of success (cure)? Given the high mortality associated with such infections, we argue that absolute confidence in identifying "the best" regimen is less important than avoiding the worst regimens. That is, choosing a regimen that is likely to be one of the best of the available options at that time for the individual patient is more important than choosing the perfectly optimal regimen. These are the clinical compromises that physicians make continuously: personalising decisions for each individual patient, balancing efficacy, toxicity, resistance, availability and cost.

This scenario has an analogy in network meta-analysis,[21] which compares multiple treatments in an evidence synthesis, to identify, overall, what is the best treatment out of a set of available treatments to recommend, and/or how do these different treatments rank against each other? The difference is that in network meta-analysis the unit is an RCT, directly comparing two or more regimens (potentially with different "control" comparators). The statistical challenge is ensuring that the individual pairwise within-trial comparisons are pooled together into a consistent coherent whole, taking into account uncertainty within each individual trial and between-trial variation. However, much theoretical work has gone into determining the best statistically principled methods to make indirect inferences about the relative performance of different regimens across the network,[22,23] even when these may not have been directly compared within any one RCT.

A new trial design

We propose to exploit and extend the network meta-analysis approach to individual randomisation of patients in what we term a "Personalised RAndomised Controlled Trial" (PRACTical) design. Here we summarise its design principles; detailed statistical methodology will be reported elsewhere.

There are multiple drugs or regimens that might be effective for carbapenem-resistant infections. Specifically, of a "network" of X regimens of interest, each patient would be randomised only to those regimens that were considered clinically reasonable for that patient at that time (i.e. reflecting individualised equipoise), incorporating antimicrobial susceptibility, toxicity profile, and physician judgement. We denote the subset of clinically acceptable regimens each patient's "personalised randomisation list". The set of patients with the same personalised randomisation list would then form the unit analogous to the trial in network meta-analysis. The full regimen list would be created by reviewing current literature, in discussion with industry if new drugs were included, and in

consultation with participating physicians across trial sites, as the proposed regimens must be widely acceptable and available. An example of how individual patients might be randomised in such a trial is shown in **Table 1** with a flow diagram in **Figure 1**.

We envisage the eligible population would be patients with bloodstream infections and hospital/ventilator associated pneumonia (HAP/VAP, as defined by FDA[24]/EMA[25]), highly likely or proven to be caused by a carbapenem-resistant organism (CRO) (CRE, *Acinetobacter baumanii* or *Pseudomonas aeruginosa*). These infections are still relatively uncommon in high-income settings but are now common in Asia,[26] where such trials should be conducted. Patients would be randomised when the clinician decides to initiate therapy to treat a life-threatening proven or highly-likely carbapenem-resistant infection. Generally, this decision requires the results of culture and antimicrobial susceptibility testing, but may be influenced by known prior CRO colonisation or other epidemiological risk factors.

The physician would consider the treatment options for each individual patient from the full regimen list based upon their assessment of the nature and antimicrobial susceptibility of the infecting organisms, clinical presentation, pharmacokinetic/pharmacodynamic properties of the drugs available, and the patient's characteristics (**Table 1**). This could be conceptualised as a list of pre-defined inclusion/exclusion criteria that the physician would use to determine the initial randomisation possibilities for each patient, which could then be further individualised into a "personal randomisation list" based on physician preference/local availability. Whilst there would likely be some clinician or site-specific preferences for certain regimens, given combination therapy choices in studies to date,[26] this would likely vary markedly between sites, and even clinicians within sites. In practice, sufficient numbers of participating sites and prior assessment of site/physician preferences would ensure variation in the "personal randomisation lists" and overcome potential risks of restricted prescribing. A single protocol would harmonise delivery of each regimen and management. The number of different regimens and complexity of dosing would preclude blinding, but standard 2-arm trials in this area have been open-label for similar reasons.

The trial endpoints should be objective (reducing the impact of lack of blinding) with direct relevance to patients and physicians. Both bloodstream infections and HAP/VAP are life-threatening infections. Therefore, we consider that Phase III trials, which aim to provide definitive, practice-changing, evidence, should have mortality as their primary endpoint.[27] Syndrome-specific outcomes have been defined by regulators assessing licensing trials and these could also be included as endpoints.

The primary analysis would be intention-to-treat, making a generalisability assumption that changes to antimicrobial therapy happening during the trial would represent those that happen outside the trial, and therefore the "as-randomised" comparison most closely reflects real-world effectiveness. However, one possibility would be to re-randomise such patients needing to change treatment for lack of response/deterioration or treatment-emergent toxicity to a new personalised list of acceptable regimens, exploiting the inverse probability weighting methods that underpin the Sequential Multiple Assignment, Randomized Trial (SMART) design[28] to account for the subsequent randomisation. If cure was the primary efficacy endpoint, and change of regimen counted as a failure, then inverse probability weighting methods would not be required and patients could simply

be re-randomised, and this adjusted for in analysis.[29] Changes from randomised treatment could also be adjusted for using inverse probability weighting methods.[30]

Statistical considerations

Extrapolating from network meta-analysis, initial simulations show that, of the various potential analysis methods, both a "network" analysis method and a "pairwise" analysis method give appropriate inference about differences between regimens. The network method corresponds to a common-effect network meta-analysis, combining direct and indirect evidence by assuming consistency (that relative treatment effects are the same for each patient type)[23]. Failure of consistency would be manifested by interactions as discussed in next paragraph. In the pairwise method, all data for each pairwise comparison of any two regimens (a "pair-wise" trial) are stacked and analysed using robust variance adjustments. Both methods ensure that direct comparisons between any pair of regimens are informed only by patients who are eligible for both regimens and are therefore comparable. Uncertainty will be expressed via confidence intervals around relative treatment effects, but our aim is not to demonstrate statistical significance and so there is no need to allow for multiple testing. In contrast, across a network the goal is essentially to "rank" the options and provide some degree of assurance that the top-ranked regimen that is relevant for any individual patient is one of the best regimens for that patient. That is, suppose a new patient can take regimens A, B, D, F, H and I from **Table 1**: the goal of a personalised randomised trial is to ensure that there is a high probability that the top-ranked regimen from this list based on the trial's results provides an expected improvement in the primary outcome compared to any randomly chosen regimen from this list.

One important challenge for all trials is variation in differences between regimens by, for example, heterogeneous types and severity of co-morbidity/underlying disease, i.e. subgroup effects or interactions, which even traditional trial designs are rarely powered to detect. However, the fact that our new design uses both indirect and direct evidence in any regimen comparison requires specific consideration and checking of consistency in the analysis. In all trials, not just this new proposed design, the main approach to dealing with heterogeneity in regimen comparisons is to restrict eligibility criteria to a more homogenous group and try to answer the questions within this group. The challenge is then generalising such results more broadly. The alternative is to enrol a broad and generalizable group of patients, and accept that power to detect all but the strongest interactions will be low. We favour the latter approach, since, given the underlying mechanism of action (bacterial killing), it is plausible that only qualitative (effect vs no effect) interactions are likely to be clinically important. The ranking analysis method above, however, could be applied within specific subgroups to investigate, for example, whether the top three regimen choices from any personalised randomisation list varied substantially across different patient subgroups.

This raises the question as to whether such a trial should recruit adults/adolescents only, infants/children only or both, given the threat that CRO infections pose across the ages. Assuming appropriate dose adjustment for maturation, weight and kidney function (thus overcoming major age-driven differences in pharmacokinetics), the antimicrobial action of different drugs and combinations are unlikely to vary substantially by age. There is a recognised ethical obligation to ensure that children benefit from research to identify the best treatments for them the same as for adults.[31] We can identify no current trials on CRO in children. A recent review of the global literature

noted a mortality of 36% from a total of 23 children and 38 neonates (Dona 2017). Therefore, we strongly advocate including all ages in the trial. A single independent Data Monitoring Committee would monitor safety and efficacy, e.g. using single-group Bayesian stopping rules to halt randomisation to regimens with unacceptable toxicity,[32]overall and by age group.

Sample size

Standard methods for determining sample size (e.g. in order to detect a clinically relevant improvement in outcome from "intervention" vs "comparator" regimen) do not apply to a network of regimens. Assuming 10 regimens in a network have overall 30-day mortality uniformly distributed between 10-30%, if hypothetically we could choose the true top-ranked regimen for each patient then we would reduce mortality by 5.5% on average across simulations compared to choosing a random regimen for each patient from the personalised randomisation list. This is therefore the maximum possible average reduction in mortality were perfect information on the true mortality under each regimen available. Randomising 1000 patients provides an expected mortality gain of 4.6% from choosing the "top-ranked" regimen based on the trial's results vs choosing a random regimen from the personalised randomisation list before the trial, i.e. gains 82% (4.6%/5.5%) of the maximum possible gain. It also provides a 90% probability that selecting the "top-ranked" regimen reduces an individual patient's mortality risk vs choosing randomly. Mortality gains would be greater if some regimens have mortality much worse or better than 10-30%. One advantage of the regimen network is that, intrinsically to the design, most information is obtained about regimens which are acceptable to more patients, which will have proportionately greater numbers enrolled to them at the trial's end. This maximises information available on these regimens and increases precision in their ranking, but without requiring patients to all have the potential to be randomised to a common control regimen.

Implementation and impact

The trial results would rank the regimens according to their efficacy, safety and cost (**Figure 2**). When faced with a new patient, their key characteristics and their infection (e.g. organism and its susceptibility profile, infection type, renal or liver function impairment) would determine which regimens are acceptable, and the ranking of these acceptable regimens on the primary outcome (30-day mortality) would then suggest the obvious treatment choice in many situations (e.g. regimen A in **Figure 2**). Any major qualitative interactions could change the ranking for some key characteristics. However, the trial can also rank secondary outcomes, which may have different degrees of importance in different settings and for licensing trials. Similarly, if the two top-ranked regimens on mortality have very different toxicity profiles or ease of dosing, physicians may make different trade-offs depending on patient characteristics. These kinds of decisions could be facilitated by electronic clinical decision support systems for physicians, or formalised into institutional, national or eventually, WHO guidelines.

Challenges

Table 2 presents some advantages and disadvantages of the new design. There is no doubt that implementation would raise challenges, not least explaining the design to ethics committees in multiple sites across multiple countries. Interestingly, despite concerns about explaining more complex designs to patients and clinicians, multi-arm trials have generally recruited faster than standard 2-arm trials, possibly because they more closely reflect real-world uncertainties and hence

have greater salience.[33] Regulatory approval for use of some drugs in a trial might be difficult, and could vary by country, but this might simply further restrict the personalised randomisation list for some patients. There will be competition for similar patients from innovator company CRO studies, which will provide high per-patient fees, but many patients are not eligible for such standard two-arm licencing trials as noted above, but could enter the proposed personalised randomisation trial. Whether and how data from this novel design could support licensing applications would need discussion with FDA/EMA. Clinicians might potentially only wish to randomise between their top two choices for an individual patient, reducing power across the network of regimens: clear criteria for inclusion/exclusion of specific regimens and minimising the number of regimens that can be rejected for physician preference could mitigate this and increase generalisability. Recommending doses in patients likely to have at least moderate renal insufficiency (which may then improve on treatment) is challenging, particularly where access to therapeutic drug monitoring is limited and as most of the drugs under consideration do not have adequate pharmacokinetic data in individuals with severe infections.

Conclusions

The major challenge to obtaining robust evidence on the most effective regimens for life-threatening carbapenem-resistant infections is that a large number of treatment options that are of interest in routine clinical care may not be relevant for any individual patient, preventing successful conduct of a traditional 2-arm or even multi-arm RCTs. The current, largely innovator company-led, single comparator trials are not designed to answer the urgent public health question, identified as a high priority by the WHO, of the best regimens out of the available options for an individual that will significantly reduce morbidity, costs, and mortality. We thus propose a novel trial design, building on network meta-analysis methods, to maximise the relevance to each individual patient, and enable the top-ranked regimens from any personalised randomisation list to be identified, in terms of both efficacy and safety.

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Contributions

The concept was developed by ASW, IRW, BT, MS and GT, with input from all other authors. The manuscript was drafted by ASW, IRW, MS and GT with review and comment from all authors.

Conflict of Interest

MS is Chair of the Antibiotic Working Group of the WHO Expert Committee on the Selection and Use of Essential Medicines.

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Table 1 Example of a personalised randomised trial design

Possible regimens	Patient 1 moderate renal impairment (CrCl <40ml/min)	Patient 2 history of myocardial infarction	Patient 3 meropenem MIC ≥64	Patient 4 VAP/HAP	Patient 5 *Pseudomonas aeruginosa* infection	Patient 6 Known Class B (NDM, IMP, VIM) infection	Patient 7 Presence of 16S-RMT genes**	Patient 8 History of moderate-severe cephalosporin allergy
A: plazomicin	No/maybe†					No	No	
B: ceftazidime/avibactam	No/maybe†					No		No
C: cefiderocol	maybe†							No
D: high-dose meropenem*	maybe†		No					
E: polymixin B±zidovudine	No/maybe†			No				
F: high-dose meropenem*+ertapenem	maybe†		No		No			
G: high-dose meropenem*+imipenem	No/maybe†		No					
H: high-dose meropenem*+polymixin B±zidovudine	No/maybe†		No	No				
I: high-dose meropenem*+high-dose tigecyline	maybe†	No	No		No			
J: high-dose meropenem*+fosfomycin	maybe†		No					
K: high-dose tigecyline+polymixin B±zidovudine	No/maybe†	No		No	No			
L: high-dose tigecyline+fosfomycin	maybe†	No			No			
M: fosfomycin+polymixin B±zidovudine	No/maybe†			No				
Physician decides patient can be randomised to:	C D F I J L	A B C D E F G H J M	A B C K M	A B C D F G I J L	A B C D E G H J M	All except A and B	All except A	All except B and C

* using continuous or prolonged infusion (over at least 3h).

† dose adjustments required in patients with renal impairment which may or may not be judged feasible in an individual patient.

** based on plausibility as assessed by high MIC

Note: MIC=median inhibitory concentration, VAP/HAP=ventilator acquired pneumonia/hospital-acquired pneumonia. High-dose meropenem 2g every 8h. High-dose tigecycline 200mg loading dose and a maintenance dose of 100mg every 12h.

Table 2. Advantages and disadvantages of personalised randomised controlled trial designs

Advantages	Disadvantages
No requirement for pre-defined standard of care control group, facilitating wide recruitment across ages, centres and countries.	Complex statistical methods supporting the design (no hypothesis testing), potentially reducing wider understanding and future buy-in
No requirement that both control and all intervention(s) groups can be taken by all randomised patients, enhancing recruitment	Standard sample size calculations cannot be used
Pre-trial engagement with physicians in construction of full randomisation list increasing trial buy-in and subsequent recruitment	Novel concept of ranking regimens according to efficacy and safety: direct clinical utility may take time
Pragmatic eligibility criteria enhancing recruitment	Likely to require multiple participating sites and physicians to overcome risk of limited prescribing and restricted use of the full randomisation list
Provides outcomes that can inform individual countries public health decisions	Design may be perceived as “too complicated”
Faster recruitment and multiple randomised groups gives quicker results on more relevant regimens	Ethical committees may not understand or easily approve the design
Personalised randomisation list enhances potential benefit to patient from joining the trial, by enabling the regimens they can be randomised to be more individually relevant	Will require substantial discussions with regulators to become applicable to licensing trials
Trial mirrors normal clinical practice, easing on-the-ground delivery	
Trial produces an easy to understand ranking of multiple patient and physician focused outcomes	
Results may lead to electronic clinical decision support systems that provide better targeted therapy for individual patients	

Figure legends

Figure 1 Flow diagram of participants through the trial

Figure 2 Hypothetical ranking of regimens from a personalised randomisation list (A B D F H I, from table 1) for a future individual patient after the trial