First the ESBLs, now the Carbapenemases: Where will it End?

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The see-saw battle between humans and microbes continues. Extended Spectrum Beta-lactamases (ESBLs) in Gram-negative Bacteria (GNB) emerged in the past two decades as a major public health challenge. They spelt disaster for 3rd generation Cephalosporins and Aztreonam. Organisms harbouring them were frequently co-resistant to Fluoroquinolones (FQN) and Aminoglycosides further curtailing treatment choices. Although ESBL producing organisms were susceptible to Carbapenems and Beta-lactam plus Beta-lactamase inhibitor combinations (BL-BLI) it was recommended to use Carbapenems in preference to BL-BLI due to the perceived “inferiority” of the BL-BLI. This was attributed to the inoculum effect, co-existence of other resistance mechanisms that are not inhibited by inhibitors, animal data and some human observational studies showing poor outcomes.¹ The preferential use of Carbapenems would have been “reasonable” when ESBL organisms were a rarity and confined to the hospital. However they rapidly spread through the networks of bacterial populations so that a large proportion of even community-acquired infections were due to ESBL producing organisms.

Keeping this in mind, we had explored the role of BL-BLI in these infections with a view to spare Carbapenem use.² We found that it was possible to treat successfully at least the less serious infections, where source control was carried out and the kinetics of the drugs ensured penetration at the site of infection. We had suggested that Carbapenems should be restricted both for reasons of cost and selection of Carbapenem-resistant organisms.³ This was subsequently borne out by studies across the globe,⁴ although there are conflicting studies⁵ and opinions.⁶ In the absence of randomized controlled trials, an appraisal of treatment schemes has to be, necessarily, based on retrospective, observational case series. The question, as always, is maximizing the outcome for the individual patient and minimizing the selection of further resistance.

There has been a recent lowering of break points to identify the truly susceptible organisms that can be treated with BL-BLI. Besides, there is a trend of optimizing Pharmacokinetic and Pharmacodynamic (PK PD) indices with high-doses and prolonged infusions of Beta-lactams. These factors will undoubtedly help to achieve success with BL-BLI. Thus inhibitors may still protect Beta-lactams, patients and the environment. Should we be using such Carbapenem sparing strategies both for initial treatment and for de-escalation or are we too late and have the Carbapenems already met their doom?⁷

The dangers of overuse of Carbapenems, and indeed of any antimicrobial, are obvious. The study results by Shah et al⁸ is an indication of what is to come in future. They needed only 4 months to collect 42 Carbapenem-resistant Enterobacteriaceae (CRE) isolates from blood culture. Prior antibiotic use was present in the vast majority of these patients. It is not clear however, whether the isolates were also obtained from peripheral venepuncture with a differential time to positivity (DTP) of more than 2 hours. This is an important clinical parameter indicating a blood-stream infection. Gram-negative bacilli otherwise are often colonizers of the central venous catheter. The clinician must make an effort to rule out colonization by the resistant organism. Not treating a colonizer and saving antimicrobial use is an important component of good stewardship.

Whilst patients in this study⁸ were treated with Colistin and Colistin combinations, as is the case elsewhere, these “last resort” strategies may not hold out much longer. Colistin, Tigecycline, Fosfomycin, Aminoglycosides need active companion drugs due to their own individual limitations. The best combinations and dosaging strategies to treat such infections have yet to be unravelled. The scientific world is looking to the areas of high endemicity such as the Indian subcontinent to produce good quality evidence to advise on these issues.

We certainly need new antibiotics.

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with novel mechanisms of action. However we submit that merely having new antibiotics will not solve the problem. We need to introspect why some of the highest rates of resistance are found here. Poor sanitation, overcrowding, sparse diagnostic facilities, growing healthcare expectations with scant attention to infection control practices, easy availability of antibiotics, lack of awareness of antimicrobial resistance issues have all to be addressed at various levels.

References


