INTRODUCTION

Infections caused by organisms producing carbapenemases are challenging due to the limited arsenal of available antimicrobial agents, are associated with high morbidity and mortality, and require enhanced infection prevention and control measures. Increasing numbers of carbapenemase-producing Enterobacteriaceae (CPE) are being identified in the UK. Of the five most common enzyme types (KPC, IMP, VIM, NDM & OXA) NDM (New Delhi metallo-beta-lactamase) often provides the largest challenge in terms of effective treatment options due to resistance to multiple antimicrobial classes. Ceftazidime-avibactam is a combination of ceftazidime and a novel non-beta-lactam beta-lactamase inhibitor of activity against ESBL, AmpC, KPC CPE and some OXA-like CPE. It has no activity against metallo-beta-lactamases such as NDM. Aztreonam, a monobactam, is stable against NDM but hydrolysed by extended spectrum beta lactamases (ESBL), commonly also expressed carrying CPE organisms. Avibactam in combination with aztreonam has been demonstrated to have in vitro activity against strains producing both NDM and ESBL. Avibactam is not currently available as a single agent or in combination with aztreonam but a regimen of ceftazidime-avibactam in combination with aztreonam has been used to treat infections caused by NDM producing CPE. We describe the use of ceftazidime-avibactam and aztreonam in combination for the treatment of a complicated urinary tract infection caused by New Delhi metallo-beta-lactamase (NDM) producing Klebsiella pneumoniae in a 57 year old man with longstanding obstructive renal failure. We also describe the laboratory methods used to determine susceptibility.

LABORATORY METHODS

Susceptibility to standard agents was established using a Vitek2XL system (Biomerieux). Colistin susceptibility was determined by microbroth dilution (Merlin, Germany) (Table 1). Isolates showing resistance to carbapenems were analysed using Xpert Carba-R cartridge (Cepheid) to assess the underlying mechanism. Ceftazidime-avibactam MIC was established using an Etest (Biomerieux) on Mueller-Hinton agar (EUCAST). A synergy disc test was performed using aztreonam (30μg) and ceftazidime-avibactam (14-4ug) (Oxoid) on Mueller-Hinton agar, the discs were placed with a 1.5cm gap between the edges and incubated overnight (18-24hrs) at 35°C (±1°C). Synergy was defined as an expanse in the zone size of ceftazidime-avibactam at the point at which the two agents had diffused (Figure 1).

DISCUSSION

This complex infection caused by NDM-producing Klebsiella pneumoniae was treated successfully with aztreonam in combination with ceftazidime-avibactam achieving clinical and microbiological cure. The challenges of treatment were a paucity of effective agents to which the pathogen was susceptible and the risk of side effects and toxicity to the patient of those agents; colistin is nephrotoxic, ticagrel tolerance achieves poor concentrations in urine, and the use of dual-beta-lactams risks seizures and sensitisation. No adverse effects attributable to aztreonam and ceftazidime-avibactam were noted. Nausea was seen with the addition of ticagrel. In vitro synergy was defined by a non-validated methodology and suggested activity against this organism. However, there are no standardised methods to suggest what increase in zone size relates to activity in vivo. There is a requirement to establish evidence based testing so that zone sizes can be defined and applied in diagnostic laboratories. Furthermore, there are reported challenges in the accurate measurement of colistin susceptibility that further complicate the use of this toxic agent. The management of CPE infections are challenging with often limited options for treatment. It is important to share such experiences and to work towards evidence based guidance to improve patient outcomes.

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