NDM–producing Klebsiella pneumoniae causing complex upper urinary tract infection treated with Ceftazidime-Avibactam and Aztreonam combination therapy

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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, [1,2] and require enhanced infection prevention and control measures[3]. Increasing numbers of carbapenemase-producing Enterobacteriales (CPE) are being identified in the UK[4]. Of the five most common enzyme types (KPC, IMP, VIM, NDM & OXA) NDM (New Delhi metallo-beta-lactamase) often provide 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 with activity against ESBL, ampC, KPC CPE and some OXA-like CPE[5]. 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 NDM carrying organisms. Avibactam in combination with aztreonam has been demonstrated to have *in vitro* activity against strains producing both NDM and ESBL[6]. Avibactam is not currently available as a single agent or in combination with aztreonam but a regimen of ceftazideime-avibactam in combination with aztreonam has been used to treat infections caused by NDM producing CPE[7]. 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-lactamse (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.

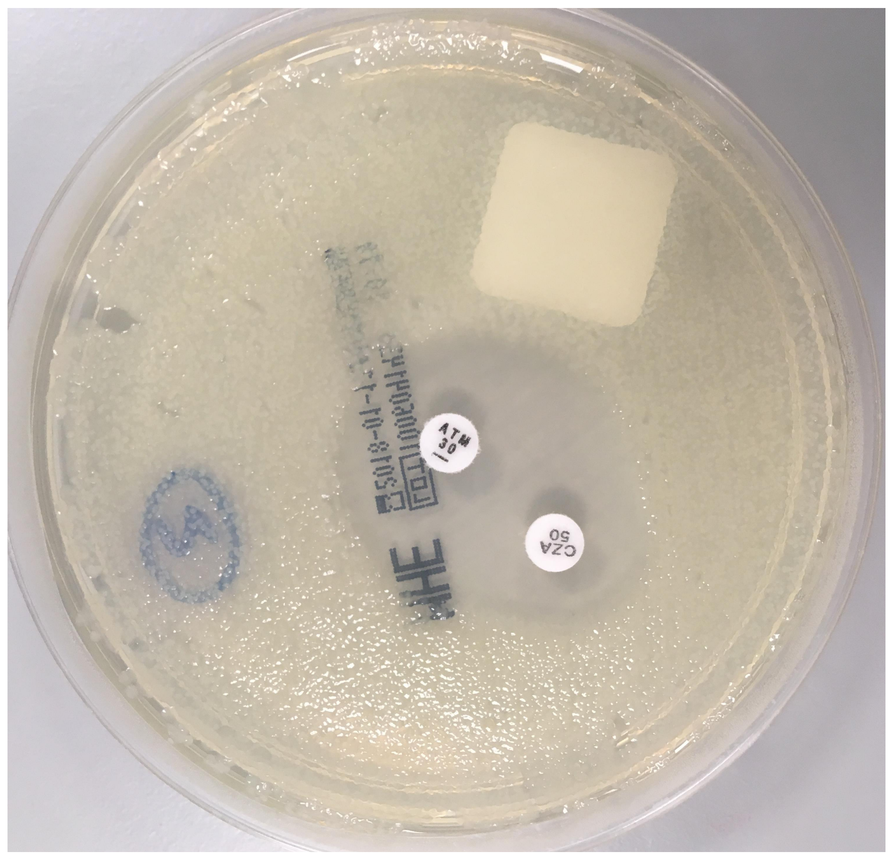

Figure 1. Synergy testing on Mueller Hinton agar

SCIENTIFIC FINDINGS

We present a case of a 57 year old man with a past medical history of ischaemic heart disease, type-2 diabetes, previous myocardial infarction and angina. The patient had chronic high pressure retention as a result of benign prostatic hyperplasia, bilateral nephrostomies, a urinary catheter and recurrent urinary tract infections, for which he had received multiple courses of antibiotics. The patient was born in Pakistan and returned there frequently to visit friends and relations. He was first known to be colonised (detected by rectal screening) with an NDM-producing *Klebsiella pneumoniae* approximately two months prior to admission for a flexible diagnostic cystoscopy. The patient became unwell six days after this procedure. He underwent a urinary catheter change and the right-sided nephrostomy was removed. He was commenced on ceftazidime-avibactam (0.75g/0.1875g 12-hourly), aztreonam (2g loading dose, followed by 500mg 8-hourly). He received a stat dose of amikacin (7.5mg/kg) despite variation in the minimum inhibitory concentration (MIC) to this agent. A summary of MICs and interpretation of 13 NDM-producing *Klebsiella pneumoniae* isolates (four rectal screens and nine from urine) is listed in Table 1. All doses were adjusted for his reduced renal function (eGFR 16). The patient did not respond initially and appeared to clinically worsen so IV tigecycline was added. The higher dose (100mg 12-hourly) was used due to the small percentage (14%) excreted in urine, although penetration into the renal parenchyma is much higher[8]. Over the next few days the patient started to show signs of clinical improvement. Tigecycline was discontinued after seven days due to intolerable nausea despite anti-emetics. In total the patient received a five week course of ceftazidime-avibactam and aztreonam for a complicated upper UTI. Treatment length was guided by clinical response, which was initially slow. Source control measures were also required, in this case bilateral nephrostomy change. To date there has been no recurrence of infection with this organism. It has not been re-cultured from any subsequent clinical samples obtained from this patient. He received prophylactic doses of ceftazidime-avibactam pus aztreonam for two subsequent nephrostomy changes approximately two months after this episode.

Table 1. Summary of patient's NDM isolate, minimum inhibitory concentrations (MIC) and interpretation .

Antimicrobial	MIC (mg/L)	Interpretation
Meropenem	≥16	R
Gentamicin	≥16	R
Amikacin	8 – 32	S - R
Temocillin	≥32	R
Fosfomycin	≥256	R
Ciprofloxacin	≥4	R
Tigecycline	1	S
Colistin	2	S
Ceftazidime-avibactam	≥32	R
Aztreonam	≥16	R

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 X-pert Carba-R cartridge (Cepheid) to asses 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 (30ug) and ceftazidime-avibactam (14-4ug) (Oxoid) on Mueller Hinton agar, the discs were placed with a 1 – 1.5cm gap between the edges and incubated overnight (18+/- 2hrs) 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 ceftazadime-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 nephrotic, tigecycline achieves poor concentrations in urine, and the use of duel beta-lactams risks seizures and sensitisation. No adverse effects attributable to aztreonam and ceftazadime-avibactam were noted. Nausea was seen with the addition of tigecycline. *In vitro* synergy was determined 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[9]. The management of CPE infections are challenging with often limited options for treatment. Its is important to share such experiences and to work towards evidence based guidance to improve patient outcomes.

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