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Retrospective analysis of colistin-resistant bacteria in a tertiary care centre in India

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The incidence of carbapenem-resistant *Enterobacteriaceae* has been steadily rising. The morbidity, mortality and financial implications of such patients are significant. We did a retrospective analysis of the case records of 11 patients who had culture report positive for pan drug-resistant (PDR) organisms. There were total 15 isolates of PDR organisms in 11 patients. These were associated with catheter-associated urinary tract infections (7), tracheitis (4), bacteraemia (2), meningitis (1) and soft-tissue infection (1). Average APACHE II score was 23.72 (range 7-36) indicating patients with multiple co-morbidities and organ dysfunction. The average length of hospital stay was 60.72 (25-123) days. The overall mortality rate was 81.81 per cent, while PDR infection-related mortality was 18.18 per cent. Strict implementation of antibiotic stewardship programme is essential to limit use and prevent abuse of colistin.

Key words Antibiotic abuse - carbapenem resistance - colistin - mortality - pan drug-resistance

The first report of a multiclonal cluster of *Klebsiella pneumoniae* was published by Antoniadou *et al*[1] in 2007 from a Greek intensive care unit (ICU). They reported 18 isolates of *K. pneumoniae* in 13 patients. There were six distinct clones identified by repetitive extragenic palindromic polymerase chain reaction (REP-PCR). A cluster of five cases of carbapenem-resistant colistin-resistant *K. pneumoniae* was identified at Detroit Medical Center[2]. Genotyping in this cluster revealed two closely related clones which indicated a strong link for patient-to-patient transmission[2]. Ghafur *et al*[3] reported such pan drug-resistant (PDR) organisms in 13 patients from India. Colistin is an old antibiotic which has resurfaced in past few years due to rising incidence of multidrug resistance organisms[3].There have been reports of colistin-resistant and tigecycline-resistant *Acinetobacter baumanii* (resistant to both tigecycline and colistin) from north India[4] which was 3.5 per cent of total and 16 per cent of all MDR organisms isolated from urine samples. Prior colistin exposure has been considered as an important association though not established in literature[3-10].

We did a retrospective analysis of the case records of the patients who had any culture report positive for PDR organisms between May 1, 2016 and January 31, 2017 admitted in the three ICUs of Apollo Hospitals, Bhubaneswar, India. An organism was considered PDR if it was resistant to all antipseudomonal agents such as penicillins, cephalosporins, carbapenems, aminoglycosides, quinolones, monobactams and polymyxins. Cultures were done using VITEK-2

compact (Biomerieux India Pvt. Ltd, software version 8.01) for all specimens. The report of VITEK-2 and European Committee for Antimicrobial Susceptibility Testing (EUCAST) breakpoints (S≤2, R≥2) [3] were followed for *Enterobacteriaceae, Pseudomonas* and *Acinetobacter* isolates which were considered resistant to colistin if the minimum inhibitory concentration (MIC) was ≥8 and 4 µg/ml, respectively, as per the Clinical and Laboratory Standards Institute (CLSI) guidelines[3].

The reports of colistin resistance were confirmed by e-strip method [Colistin Ezy MIC™ Strip (0.016-256 mcg/ml) from HiMedia Laboratories Pvt. Ltd., Mumbai] in these isolates. Determination of an isolate as an infective pathogen or colonizer was done by two independent investigators who were blinded to the study design. The Acute Physiology Assessment and Chronic Health Evaluation (APACHE) II score on admission for all patients, their culture reports, antibiotics received and length of stay (LOS) in hospital along with outcome were analyzed.

There were a total of 1448 ICU admissions in three ICUs of the hospital during the study period. There were a total of 15 isolates of PDR organisms from 11 patients. There were six male and five female patients. Detailed information of these patients is summarized in the Table. Average length of hospital stay was 60.72 (range 25-123) days. The mean age of the patients was 61.8 (28-84) yr. *K. pneumoniae* was isolated from 10 cases, *Pseudomonas* from four (*P. aeruginosa* in 3 and *P. luteola* in 1 case) and *A. baumanii* from one case. These isolates were considered to be colonizer in five and infective pathogens in six patients. These PDR isolates were associated with catheter-associated urinary tract infection (7), tracheitis (4), bacteraemia (2), meningitis (1) and soft-tissue infection (1). Average APACHE II score was 24 (7-36) indicating sick patients with multiple co-morbidities and organ dysfunction. Nine patients had received prior (*i.e.,* before the development of PDR infections) colistin therapy due to the growth of multidrug-resistant bacteria isolates while two had no history of prior colistin treatment. Of the nine patients, eight had combined colistin therapy while one had colistin monotherapy.

Nine of these patients died while the two were discharged. The overall mortality (9/11, 81.81%) was due to the primary disease process and other co-morbid conditions. The high APACHE II scores of all the patients who died indicated the severity of the illness and co-morbid conditions. Two of the nine deaths were attributed to PDR infections (infection-related mortality 18.18%). One patient with traumatic brain injury (TBI) died due to pulmonary embolism after discharge from the hospital. Eight of the 11 patients had neurological issues (stroke and TBI) and had prolonged hospitalization. In two reports from a Greek ICU by Falagas *et al*[5,6], the overall death rate was 29 and 41.7 per cent, respectively. The infection-related mortality in the second series was 33.3 per cent[6]. In the study reported by Tsioutis *et al*[7], mortality was 23.8 per cent (5 of 21). In these studies, PDR infections were treated with colistin along with carbapenems and quinolones[5-7]. Duration of treatment was between 8 and 34 days in these studies[5,6]. Except one, all our PDR-infected patients were treated with polymyxin along with third-generation cephalosporins or carbapenems for 14-20 days. Polymyxin was preferred over colistin due to its presumed lower nephrotoxicity[11] as most patients had deranged renal parameters. In the previous studies, the patients were treated with colistin even though the isolates had *in vitro* resistance to the same drug[5-7]. Tsioutis *et al*[7] implicated a better cure rate with tigecycline in PDR cases than colistin. None of our patients were given tigecycline.

Multidrug-resistant organisms were present in nine of 11 patients before the development of PDR organisms. Three out of four colonizers were treated with colistin. The duration of colistin therapy was between 10 and 14 days. The growth of PDR organisms in two patients, who did not have any prior exposure to colistin, was thought to be transferred from other infected patients. The genetic analysis could not be done which was a limitation of our study. Increased exposure to colistin has been viewed as the single most important risk factor for the development of colistin resistance among Gram-negative bacteria in the previous studies[1,8-10,12].

The average length of stay (LOS) was around 60 days which matched with other studies[8,10-12]. In such critical cases, the average LOS before PDR culture report was 34.18 days (11-70 days). The time gap between the identification of PDR infection and death in the nine patients varied between 8 and 53 days. All patients with PDR infections had long LOS with high APACHE II scores.

It is important that culture reports should be judiciously interpreted to differentiate between colonizer and infective pathogen before the treatment.

Table. Details of patients included in the study (n=11)

Age (yr)	Gender	APACHE II score	Diagnosis	Sample	Pan drug resistant (PDR) organism	Prior colistin intake	Culture clearance	Infective pathogen/ colonizer	LOS before PDR culture (days)	Treatment for PDR infection	Survival after PDR report	LOS (days)	General status around PDR report	Outcome
84	Male	36	Brain stem bleed with CKD	Urine	*Pseudomonas aeruginosa*	Yes	Not cleared	Pathogen	54	Polymyxin with meropenem for 14 days	30	84	GCS-5 Dialysis and ventilator dependent	Death
62	Male	34	Urosepsis with acute kidney injury	Urine	*P. aeruginosa*	Yes	Cleared	Pathogen	15	Polymyxin with imipenem for 10 days	19	34	Improvement	Discharged
72	Female	33	Meningitis, pneumonia and septic shock	Tracheal secretions	*Acinetobacter baumannii*	Yes	Not repeated	Colonizer	17	Polymyxin with meropenem for eight days	8	25	In septic shock and previous bed-bound status	Death
28	Female	21	ARDS with critical illness polyneuropathy	Urine	*Klebsiella pneumoniae*	Yes		Colonizer	30	Not treated	Survived	31	Improvement	Discharge
63	Male	18	TBI, multiple contusion	Urine	*P. aeruginosa*	Yes	No growth	Pathogen	25	Polymyxin with meropenem for 14 days	30	55	Moribund on dialysis	Death
77	Male	26	Severe TBI	Blood trachea	*K. pneumoniae*	No	MDR *Klebsiella*	Pathogen	11	Colistin with meropenem for 14 days	38	49	Poor GCS (3), in shock	Death
46	Female	7	Post-operative cranial tumour	CSF	*K. pneumoniae*	Yes	Not cleared	Pathogen	53	Polymyxin with meropenem for 21 days	42	95	Poor GCS (5), in shock and MODS	Death
51	Male	13	TBI	Urine	*P. luteola*	No	Not done	Colonizer	23	Not treated	9	32	Improvement	Death due to pulmonary embolism
56	Female	24	TBI	Urine trachea	*K. pneumoniae*	Yes	Not cleared	Colonizer	38	Polymyxin plus meropenem for 14 days	50	88	Poor GCS	Death
72	Female	23	Toxic epidermal necrosis and sepsis	Blood urine CVC tip	*K. pneumoniae*	Yes	Not cleared	Pathogen	40	Polymyxin B with meropenem for 14 days	10	50	Poor status, Renal failure on dialysis	Death

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Age (yr)	Gender	APACHE II score	Diagnosis	Sample	Pan drug resistant (PDR) organism	Prior colistin intake	Culture clearance	Infective pathogen/ colonizer	LOS before PDR culture (days)	Treatment for PDR infection	Survival after PDR report	LOS (days)	General status around PDR report	Outcome
69	Male	26	Ischaemic stroke	Trachea	*K. pneumoniae*	Yes	Cleared	Colonizer	70	Not treated	53	123	Poor	Death due to cardiac issues

TBI, traumatic brain injury; GCS, Glasgow coma scale; MODS, multiorgan dysfunction; CKD, chronic kidney disease; ARDS, acute respiratory distress syndrome; CVC, central venous catheter; CSF, cerebrospinal fluid; LOS, length of stay; PAN, pan drug resistant; MDR, multidrug resistant; APACHE, acute physiology and chronic health evaluation

Widespread indiscriminate use of colistin to treat carbapenem resistant Enterobacteriacae (CRE) and other Gram-negative organisms can lead to the emergence of PDR organisms. Strict implementation of antibiotic stewardship programme is essential to limit use and prevent abuse of colistin. A large prospective study is required to delineate the risk factors for such PDR infections in Indian hospitals.

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References

1. Antoniadou A, Kontopidou F, Poulakou G, Koratzanis E, Galani I, Papadomichelakis E, *et al.* Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in Intensive Care Unit patients: First report of a multiclonal cluster. *J Antimicrob Chemother* 2007; *59* : 786-90.
2. Marchaim D, Chopra T, Pogue JM, Perez F, Hujer AM, Rudin S, *et al.* Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan detroit, michigan. *Antimicrob Agents Chemother* 2011; *55* : 593-9.
3. Ghafur A, Vidyalakshmi PR, Murali A, Priyadarshini K, Thirunarayan MA. Emergence of pan-drug resistance amongst gram negative bacteria! The first case series from India. *J Microbiol Infect Dis* 2014; *4* : 86-91.
4. Taneja N, Singh G, Singh M, Sharma M. Emergence of tigecycline & colistin resistant *Acinetobacter baumanii* in patients with complicated urinary tract infections in North India. *Indian J Med Res* 2011; *133* : 681-4.
5. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A, *et al.* Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. *BMC Infect Dis* 2005; *5* : 24.
6. Falagas ME, Rafailidis PI, Matthaiou DK, Virtzili S, Nikita D, Michalopoulos A, *et al.* Pandrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections: Characteristics and outcome in a series of 28 patients. *Int J Antimicrob Agents* 2008; *32* : 450-4.
7. Tsioutis C, Kritsotakis EI, Maraki S, Gikas A. Infections by pandrug-resistant Gram-negative bacteria: Clinical profile, therapeutic management, and outcome in a series of 21 patients. *Eur J Clin Microbiol Infect Dis* 2010; *29* : 301-5.
8. Matthaiou DK, Michalopoulos A, Rafailidis PI, Karageorgopoulos DE, Papaioannou V, Ntani G, *et al.* Risk factors associated with the isolation of colistin-resistant Gram-negative bacteria: A matched case-control study. *Crit Care Med* 2008; *36* : 807-11.
9. Zarkotou O, Pournaras S, Voulgari E, Chrysos G, Prekates A, Voutsinas D, *et al.* Risk factors and outcomes associated with acquisition of colistin-resistant KPC-producing *Klebsiella pneumoniae*: A matched case-control study. *J Clin Microbiol* 2010; *48* : 2271-4.
10. Kontopoulou K, Protonotariou E, Vasilakos K, Kriti M, Koteli A, Antoniadou E, *et al.* Hospital outbreak caused by

Klebsiella pneumoniae producing KPC-2 beta-lactamase resistant to colistin. *J Hosp Infect* 2010; *76* : 70-3.

11. Zavascki AP, Nation RL. Nephrotoxicity of polymyxins: Is there any difference between colistimethate and polymyxin B? *Antimicrob Agents Chemother* 2017; *61*. pii: e02319-16.
12. Kontopidou F, Plachouras D, Papadomichelakis E, Koukos G, Galani I, Poulakou G, *et al.* Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients. *Clin Microbiol Infect* 2011;*17* : E9-11.

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