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International Journal of Antimicrobial Agents 56 (2020) 106179

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Emerging Co-Pathogens: New Delhi Metallo-beta-lactamase producing *Enterobacterales* Infections in New York City COVID-19 Patients

To the Editor:

COVID-19 patients are at increased risk of secondary bacterial and fungal infections due to factors such as prolonged intubation, ubiquitous use of invasive catheters, and impaired host immunity, adding to the challenge of managing COVID-19 patients [1].

At the height of the COVID-19 pandemic surge at our medical center in the Bronx, NY, 5 cases of New Delhi Metallo-beta-lactamase (NDM) producing *Enterobacterales* infections were diagnosed in patients initially admitted with hypoxemic respiratory failure from severe, SARS-CoV-2 polymerase chain reaction confirmed COVID-19 pneumonia. To our knowledge, these are among the first reported cases of NDM emergence in COVID-19 patients. A potential rise in multidrug resistance secondary to the pandemic is of principal concern.

Enterobacterales isolates were identified by Matrix-assisted Laser Desorption Time-of-Flight Mass Spectrometry and disk diffusion antimicrobial susceptibility testing. Class B carbapenemase gene ($_{bla}$NDM) was detected by Xpert® Carba-R (Cepheid) PCR testing by the New York City Department of Health (NYCDOH) Public Health Laboratory.

All co-infected patients required mechanical ventilation, had central venous catheters, and were managed in newly established surge intensive-care units (ICUs) with unique infection prevention and antimicrobial stewardship challenges. Excess antibiotic exposures and widespread use of immunosuppressive medications contributed to host-susceptibility to multidrug-resistant infections in our population. Additionally, reuse of protective equipment, lapses in standards of care for maintenance of invasive devices, and patient cohorting in surge ICUs likely contributed to spread of multidrug resistant pathogens between patients [2].

Patients were at least 50-years old, were Black or Hispanic, and had comorbidities associated with poor COVID-19 outcomes [3]. All were residents of New York City (NYC) without international healthcare exposure or recent hospitalization. All patients were admitted within a month of each other (March 28 – April 22, 2020) at the height of the NYC pandemic surge All had negative blood cultures on admission; the shortest interval to positive Carbapenem-resistant *Enterobacter cloacae* (CRE) culture was 3 days. All patients received preceding systemic corticosteroids; one patient was enrolled in the sarilumab placebo-controlled trial and another received anakinra. Multiple empiric antibiotics were administered (9.8 average days of therapy prior to positive CRE culture). Targeted antibiotics were selected based on institutional susceptibilities (high-dose tigecycline alone or in combination with gentamicin, ceftazidime/avibactam plus aztreonam) (Table 1).

NDM-producing *E. cloacae* was isolated in both blood and respiratory cultures in 3 patients and respiratory cultures alone in 2 patients, however, these patients were determined to have secondary bacterial pneumonia by treating physicians rather than colonization. All patients additionally had positive cultures with multiple other nosocomial pathogens including *Candida albicans* bloodstream infection in 2 of 5. Two patients had both class B metallo-β-lactamase (MBL)-producing *E. cloacae* and *K. pneumonia* blood stream infections suggesting transfer of resistance elements. Genetic sequencing of NDM isolates and resistance elements is in progress. Four of five patients succumbed to septic shock due to advanced COVID-19, polymicrobial infection, or both. Average length of hospitalization prior to death (n = 4) or discharge (n = 1) was 29.4 days.

Since 2012, NDM has been increasingly reported in US patients without international healthcare exposure [4]. Healthcare-associated NDM-1 *E. cloacae* outbreaks characterized using whole genome sequencing demonstrated persistence of resistant strains for over two years, despite rigorous control measures [5]. Screening for colonization without specific epidemiologic risk factors is not universally performed [4].

Antimicrobial stewardship programs have a crucial role in limiting excess antibiotic use and providing expertise on extensively drug-resistant infections, however, treatment of class B MBLs remains challenging. New β-lactamase inhibitors only have activity against Ambler class A and D serine β-lactamases but not MBLs [6]. The presence of co-existing resistance mechanisms leave few therapeutic options. Polymyxins are limited by unfavorable side effects, emerging resistance and poor outcomes [7]. Tigecycline has limited in-vivo efficacy for severe infections and benefits of higher dosing remains unclear [7]. Certain NDM-producing isolates also possess 16S rRNA methylases, rendering aminoglycosides ineffective [4].

The combination of aztreonam and ceftazidime-avibactam has theoretic activity against NDM-producing *Enterobacterales*. Aztreonam is not hydrolyzed by MBLs but its use is limited by co-existing serine β-lactamases [7] Avibactam has no activity against MBLs but may protect aztreonam against serine β-lactamases. Marshall et. al. demonstrated in vitro synergy and bactericidal activity in a murine model [8]. Shaw et. al. reported clinical success in 6 of 10 patients with NDM-producing *K. pneumoniae* infections treated with aztreonam and ceftazidime-avibactam including 5 with bacteremia [9].

Cefiderocol is a novel siderophore cephalosporin with uniquely broad-spectrum activity and stability against all classes of carbapenemases, (KPC, OXA, NDM, VIM and IMP) [10]. Fosfomycin may have synergy with carbapenems and/or colistin against NDM-producing *K. pneumoniae* but resistance via metalloenzymes has been described and the intravenous formulation is not available in the U.S. [4].

https://doi.org/10.1016/j.ijantimicag.2020.106179

Table 1
Patient Characteristics and Results.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Male	Male	Female	Male
Age (years)	68	57	63	63	54
Race/Ethnicity	Black/African American	Hispanic/Latino	Black/African American	Hispanic/Latino	Hispanic/Latino
NYC Borough of primary residence	Bronx	Bronx	Brooklyn	Bronx	Bronx
Travel	No	No	No	No	No
Recent hospital or long term care admission	No	No	No	No	No
Comorbidities	Seizures, Hypertension	Hypertension	DMII, Hypertension, past PE	DMII	DMII, Hypertension
Admission date	3/28/2020	4/1/2020	4/7/2020	4/8/2020	4/22/2020
Hospital day expired or discharged	34 (exp)	24 (exp)	6 (exp)	39 (exp)	44 (discharged)
SARS-CoV-2 result (hospital day)	0	0	0	0	0
Blood culture results on admission	Negative	Negative	Negative	Negative	Negative
First positive culture date, result and source	4/13 *C. albicans* (peritoneal fluid and urine -catheter)	4/16 CR *E. cloacae* (urine - catheter)	4/9 S. capitis (blood)	4/19 MSSA (resp)	5/2 MRSA (resp)
Other (+) culture and source	4/15 *C. albicans, E. faecalis, S. epi* (blood) 4/18 *C. albicans* (blood) 4/20 CR *E. cloacae* (respiratory) 4/26, 4/29, 4/30 CR *E. cloacae* (blood) 4/29 *CR K. pneumoniae*** (blood)	4/20 *E. aerogenes* x 2* (blood) 4/20 CR *E. cloacae* (Resp)	4/10, 4/11, 4/12 CR *E. cloacae* (blood) 4/12, 4/13 *C. albicans* (blood) 4/13 CR *E. cloacae* (resp)	4/28 *C. koseri* (resp) 5/8 CR *E. cloacae, P. aeruginosa* (susceptible isolate) (resp) 5/12 CR *E. cloacae* (urine – catheter) 5/16 CR *E. cloacae* & Vancomycin-resistant *E. faecalis* (urine – catheter)	*5/6 CR E. cloacae &* MRSA (resp) *5/9 CR E. cloacae &* MRSA, *S. marcescens* (resp) *5/10 CR E. cloacae & CR K. pneumoniae* (blood) *5/11-5/14 E. cloacae* (blood)
$_{bla}$NDM, class B carbapenemase gene confirmation by PHL	Yes	Yes	Yes	Yes	Yes
Charlson Comorbidity Index	2	1	4	3	3
SOFA score	6	7	7	4	5
Max PCT, ng/mL	7	29.8	45.4	5.2	0.6
Max WBC, k/uL	16.3	31.2	29.8	34	22.3
Max CRP, mg/dL	34.7	39	16.7	29.4	26.2
Intubation status	Intubated	Intubated	Intubated	Intubated	Intubated
ICU location	Surge ICU A	Surge ICU A	Surge ICU B	Surge ICU A	Surge ICU C
Central venous catheter	Yes	Yes	Yes	Yes	Yes
Acute dialysis	PD, HD	PD, CVVH	HD	No	No
Preceding corticosteroids or biologics	Corticosteroids; Sarulimab placebo-controlled trial	Corticosteroids	Corticosteroids	Corticosteroids; Anakinra	Corticosteroids
Preceding antimicrobial exposure	Ceftriaxone Doxycycline Ampicillin Micafungin Fluconazole Piperacillin-tazobactam	Azithromycin Ceftriaxone Vancomycin Piperacillin-tazobactam Gentamicin Fluconazole	Ceftriaxone Azithromycin Vancomycin Cefepime Piperacillin-tazobactam	Vancomycin Piperacillin-tazobactam Cefepime Micafungin	Ceftriaxone Doxycycline Piperacillin-tazobactam Vancomycin Cefoxitin Linezolid
Antimicrobial days of therapy preceding CR *E. cloacae*	9	8	2	16	14
Targeted antimicrobial treatment	Tigecycline*** Ceftazidime-Avibactam Aztreonam	Tigecycline***	Tigecycline*** + Gentamicin	Ceftazidime-Avibactam Aztreonam	Tigecycline*** Gentamicin Aztreonam Ceftazidime-Avibactam
E.cloacae Susceptibilities					
Aztreonam	Resistant (MIC >16 ug/ml)	Resistant (DOH report)	Resistant (MIC >16 ug/ml)	Resistant (MIC >16 ug/ml)	Resistant (MIC >16 ug/ml)
Ceftazidime-avibactam	Resistant (MIC >8/4 ug/ml)	Resistant (MIC >8/4 ug/ml)	Resistant (MIC >8/4 ug/ml)	Resistant (MIC >8/4 ug/ml)	Resistant (MIC >8/4 ug/ml)
Colistin	Sensitive (MIC ≤0.25 ug/ml)	Sensitive (MIC 0.5 ug/ml)	Sensitive (MIC 0.5 ug/ml)	Intermediate (< = 0.25 ug/ml)	Intermediate (< = 0.25 ug/ml)

(*continued on next page*)

Table 1 (*continued*)

Gentamicin	Sensitive (MIC ≤2 ug/ml)	Sensitive (MIC ≤2 ug/ml)	Sensitive (MIC 4 ug/ml)	Sensitive (MIC ≤2 ug/ml)	Sensitive (MIC ≤2 ug/ml)
Meropenem	Resistant (MIC >8 ug/ml)	Resistant (MIC >8 ug/ml)	Resistant (MIC >8 ug/ml)	Resistant (MIC >8 ug/ml)	Resistant (MIC >8 ug/ml)
Meropenem-vaborbactam	Resistant (MIC 16/8 ug/ml)	Resistant (MIC 16/8 ug/ml)	Resistant (MIC 16/8 ug/ml)	Resistant (MIC 16/8 ug/ml)	Resistant (MIC 16/8 ug/ml)
Tigecycline	Sensitive (MIC ≤1 ug/ml)	Sensitive (MIC ≤1 ug/ml)	Sensitive (MIC ≤1 ug/ml)	Sensitive (MIC ≤1 ug/ml)	Sensitive (MIC ≤1 ug/ml)

Abbreviations: NYC, New York City; CR, Carbapenem-resistant; $_{bla}$NDM, gene producing New Delhi Metallo-beta-lactamase; NDM, New Delhi Metallo-beta-lactamase, PHL, public health laboratory; MSSA, Methicillin-sensitive *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment; DM, diabetes mellitus; PE, pulmonary embolism; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein; HD, hemodialysis; PD, peritoneal dialysis; CVVH, continuous veno-venous hemofiltration; ICU, intensive care unit.

* E. *aerogenes* (2 isolates), susceptible to 3rd generation cephalosporins, quinolones, piperacillin/tazobactam, aztreonam, trimethoprim-sulfamethoxazole.

** CR *K. pneumoniae* confirmed as class B by automated card.

*** High-dose tigecycline 100mg every 12 hours.

Hospital acquisition of infection is plausible for the following reasons: 1) All patients were from the local community without traditional risk factors such as hospitalization outside of the United States or residence in a long-term care facility [4]. 2) All patients acquired infection within 30 days of each other during the NYC pandemic surge. 3) Antibiotic use at our hospital was extensive; 4130/5853 (71%) of COVID-19 patients admitted between March 1 and May 31,2020 received antibiotics, yet <5% acquired bacterial co-infections. Furthermore, <20% of co-infected patients had multidrug resistant Gram negative isolates [11]. Possible etiologies under investigation include patient cohorting on COVID-19 units, extreme healthcare worker strain, personal protective equipment limitations, challenges with adherence to infection prevention standards of care, and deployment of non-traditional staff to COVID-19 units. Genomic analysis by the NYC public health laboratory on clinical NDM strains isolated during this timeframe is planned.

In conclusion, hospitals should conduct close monitoring for excess antibiotic use and digression from infection prevention bundles during the COVID-19 pandemic to prevent emergence of extensively drug resistant infections with limited antibiotic options. Intensified commitment to new drug development is urgently needed as part of pandemic planning. Coordinated hospital and public health antimicrobial resistance surveillance will be required for many years post COVID-19.

Funding

No funding source.

Competing interests

No conflicts of interest.

Ethical approval

Not required.

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