Cluster of carbapenemase-producing Enterobacterales secondary infections during the COVID-19 crisis at a New York City hospital

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ABSTRACT

Background: Patients with COVID-19 may be at increased risk for secondary bacterial infections. At our quaternary care hospital in New York City, the rapid escalation of COVID-19 cases was accompanied by a massive surge in the need for hospital and critical care capacity. During this time, we noted a troubling increase in infections caused by carbapenemase-producing Enterobacterales (CPE).

Methods: We retrospectively assessed microbiology data to identify patients with positive testing for SARS-CoV-2 who had clinical cultures with meropenem-resistant and/or carbapenemase gene-positive Enterobacterales. We obtained microbiological and clinical data by manual chart review. Available clinical isolates underwent long-range whole genome sequencing using the MinION (Oxford) for rapid genotyping, resistance gene detection, and phylogenetic analysis.

Results: From March 1 to May 18, we identified 31 CPE isolates from 13 patients, including 27 Klebsiella pneumonia and four Enterobacter cloacae. Most patients (11/13) had a positive respiratory culture, and 7/13 developed bacteremia. All patients had prolonged, complex hospitalizations with extensive antibiotic exposure. We performed long-range sequencing on 20 isolates from 12 patients. 16/17 *K. pneumoniae* isolates belonged to sequence type (ST) 258 encoding KPC (15 KPC-2; 1 KPC-3); one ST70 isolate encoded KPC-2. All four E. cloacae isolates belonged to ST270 and encoded NDM-1. Phylogenetic analysis of ST258 isolates including historical isolates from our hospital revealed at least four distinct ST258 lineages in COVID-19 patients, which were validated by Illumina sequencing data.

Conclusions: While CPE have declined substantially in New York City in recent years, their increased detection in patients with COVID-19 may signal a reemergence of these highly resistant pathogens in the wake of the global pandemic. System-level factors, such as the rapid scale-up of critical care capacity, while clearly needed to address the unprecedented reach of COVID-19, may have contributed to isolate clustering in these patients. Increased surveillance and antimicrobial stewardship efforts will be needed to mitigate their the impact of CPE in the future.

BACKGROUND

- COVID-19 disease is caused by the novel respiratory tract pathogen SARS-CoV-2
- Secondary infections occur in 4-15% of patients with COVID-19 and were significantly associated with increased mortality in previous studies[1-4]
- Antibacterial use has been widespread in patients with COVID-19, raising concerns for the emergence of multidrug-resistant organisms[5]
- We identified a cohort of patients with COVID-19 who developed secondary infections with carbapenem-resistant Enterobacterales (CPE)

OBJECTIVES

1. **Characterize the population structure and resistance mechanisms of CPE in patients with COVID-19**
2. **Compare phylogenetic analyses generated from rapidly available nanopore versus Illumina whole genome sequencing data**
3. **Assess clinical management, including use of novel agents, and outcomes of CPE infections in this cohort**

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RESULTS

Table 1: Patient and Isolate Characteristics

Patient	Age, sex	Isolate	Organism	Culture site	Genotype	CPE treatment	Outcome at discharge
1	67 M	KP1826	*K. pneumoniae*	Blood	ST258, KPC-2	None	Died
		NK1608	*K. pneumoniae*	Blood (post-mortem)	ST258, KPC-2		
2	50 M	NK1590	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA, PMB^	Died
		KP1827	*K. pneumoniae*	Blood	ST258, KPC-2		
3	70 M	NK1596	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA, PMB	Died
		KP1828	*K. pneumoniae*	Blood	ST258, KPC-2		
		NK1661	*K. pneumoniae*	Respiratory	ST70, KPC-2		
4	72 M	NK1597	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA*, PMB^, MEM^	Died
		NK1677	*K. pneumoniae*	Respiratory	ST258, KPC-2		
5	39 F	NK1593	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA	Alive
		NK1607	*K. pneumoniae*	Urine	ST258, KPC-2		
6	72 M	NK1580	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA, ERV	Alive
7	59 M	KP1829	*K. pneumoniae*	Blood	ST258, KPC-2	CZA	Alive
		NK1586	*K. pneumoniae*	Respiratory	ST258, KPC-2		
8	65 M	NK1594	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA	Alive
9	74 M	NK1595	*K. pneumoniae*	Respiratory	ST258, KPC-2	CZA, MVB^	Alive
10*	71 M	N/A	*K. pneumoniae*	Respiratory	KPC (subtype unavailable)	CZA, LVX	Alive
11	48 M	NK1321	*E. cloacae*	Respiratory	ST270, NDM-1	ERV	Alive
		NK1396	*E. cloacae*	Respiratory	ST270, NDM-1		
12	23 M	NK1513	*K. pneumoniae*	Urine	ST258, KPC-3	CZA	Alive
13	86 F	NK1644	*E. cloacae*	Respiratory	ST270, NDM-1	LVX	Died

*Development of resistance during therapy likely due to a D179Y substitution in the bla_{KPC} gene in NK1677. ^Added or substituted due to treatment failure. Abbreviations: MEM, meropenem; CZA, ceftazidime/avibactam; PMB, polymyxin B; ERV, eravacycline; LVX, levofloxacin

Figure 1: Phylogenetic trees generated using nanopore and Illumina-sequenced genomes of *K. pneumoniae* ST258 isolates derived from patients with COVID-19 and historical isolates

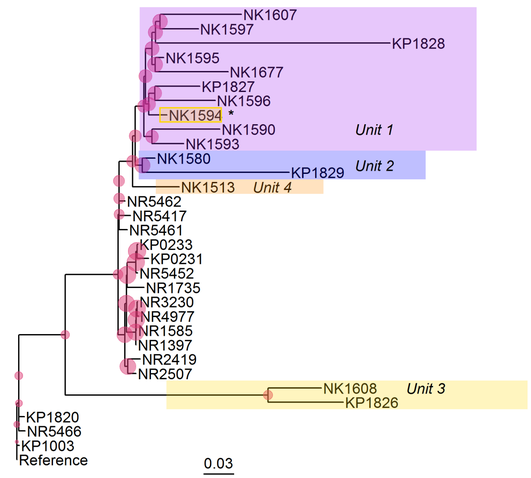

Figure 1A: Phylogenetic analysis of *K. pneumoniae* ST258 genomes generated using nanopore sequencing data

- We identified at least four distinct ST258 lineages derived from patients with COVID-19
- COVID-19 isolates fell within two distinct clades; one also included historical isolates with available nanopore sequencing data Further clustering of COVID-19 isolates largely corresponded to four hospital units; one isolate (KP1594*) which clustered with Unit 1 genomes was derived from a separate hospital unit

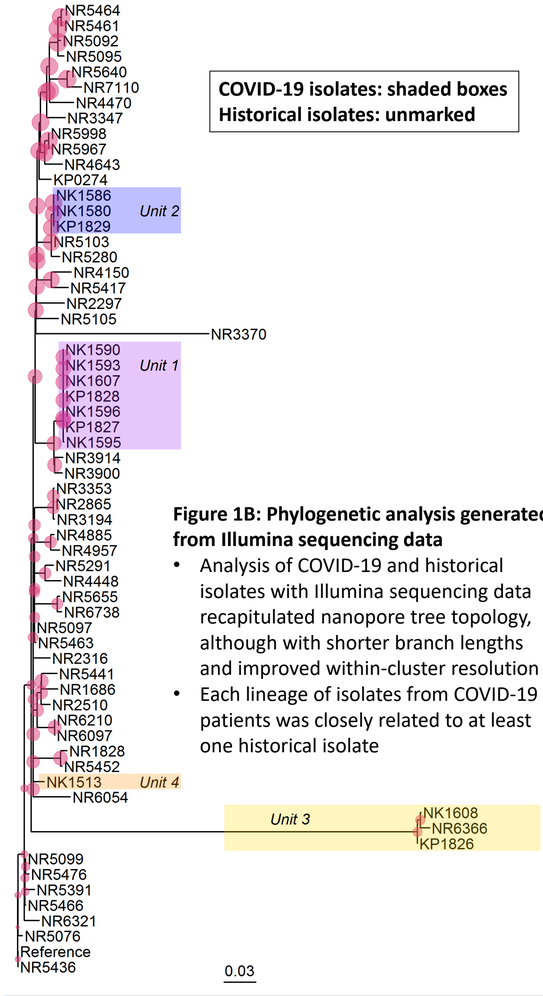

Figure 1B: Phylogenetic analysis generated from Illumina sequencing data

- Analysis of COVID-19 and historical isolates with Illumina sequencing data recapitulated nanopore tree topology, although with shorter branch lengths and improved within-cluster resolution
- Each lineage of isolates from COVID-19 patients was closely related to at least one historical isolate

METHODS

- Retrospective review of 31 CPE isolates from 13 patients with COVID-19 hospitalized at CUIMC between 3/1/20-5/18/20
- Clinical information including microbiology data, antibiotic use, and outcomes were collected from electronic medical records
- CPE isolates underwent whole genome sequencing using MinION (Oxford) and/or Illumina MiSeq platforms
  - Rapid Barcoding Sequencing Kit (Oxford) used to multiplex and prepare libraries for nanopore sequencing
  - Resulting long reads were assembled using Canu[6]
  - Detection of the isolate MLST and resistance genes derived from long reads using Krokus[7]
  - Variant detection was performed using Snippy (https://github.com/tseemann/snippy) and phylogenetic trees generated using RaxML[8]

CONCLUSIONS

- Multiple factors likely contributed to the development of CPE in this patient cohort
  - Rapid escalation of inpatient and critical care capacity, including ICU patient cohorting and extended use of PPE
  - Disease severity, prolonged hospitalization, and prior exposure to antibiotics and immunomodulators
- Treatment failure was common, particularly among patients treated with CZA, indicating optimal therapies remain unclear
- Rather than representing a clonal outbreak, CPE were diverse, suggesting host environments supportive of CPE emergence
- Nanopore sequencing enabled rapid genotyping and was successfully used in phylogenetic analysis
- Increased antibiotic stewardship, infection control measures and surveillance are needed to mitigate CPE in this setting

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