The Management of Carbapenemase-producing Organism Infections and the Utility of Screening in Predicting Carbapenemase-producing Organism Positive Clinical Cultures in the Fraser Health Authority

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Background

- Infections caused by multidrug resistant carbapenemase-producing organisms (CPO) are difficult to treat with high associated mortality[1-3]
- The antimicrobial regimens used to treat these infections can be complex and highly toxic[4]
- CPO screening may be useful in determining if empiric treatment in presumed infected patients is indicated or if treatment can be de-escalated
- In the Fraser Health Authority (FHA), CPO screening is done in the following patients: new start dialysis, travel and/or hospitalization in CPO endemic regions in the last 12 months and admitted to critical care[5]
- Furthermore, there is a growing need for a local CPO treatment database that can allow for examination of antimicrobial treatment and outcomes

Objectives

PART A

Primary: To determine the accuracy and predictive value of CPO screening for CPO in clinical cultures in patients admitted to the FHA by examining sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)

Secondary:

- To determine the positive and negative likelihood ratios (PLR and NLR) for CPO screening

PART B

Primary: To describe antimicrobial prescribing patterns for patients with CPO positive clinical cultures

Secondary:

- To compare antimicrobial prescribing patterns based on site of CPO positive clinical cultures
- To report % of patients treated with combination therapy
- To determine in-hospital mortality
- To report % of patients that experienced a treatment related adverse drug event
- To report % of patients who are *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi Metallo-beta-lactamase-1 (NDM-1), Oxacillinase-48 (OXA-48) carriers

Methods

Retrospective chart review of patients admitted to FHA from June 2013 to May 2020

Part A

- **Inclusion**: ≥18 years old, CPO screen completed -4 to 30 days from clinical culture collection
- **Exclusion**: CPO screen completed without a clinical culture collected, incomplete health records

Part B

- **Inclusion**: ≥18 years old, CPO positive clinical culture treated with antibiotics as an inpatient
- **Exclusion**: Discharge from hospital prior to identification and treatment of CPO positive culture, incomplete health records

Results Part A

Table 1. CPO Screen and Clinical Culture Results

	CPO Clinical Culture Result		
CPO Screen Result	Culture Positive	Culture Negative	Total Screen
Screen Positive	58	337	395
Screen Negative	29	33,794	33,823
Total Cultures	87*	34,131	34,218

*CPO culture positive prevalence = 0.25%

Table 2. Accuracy and Predictive Validity for CPO Screening

Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)	PLR (95% CI)	NLR (95% CI)
66.7 (55.8-76.4)	99 (98.9-99.1)	99.9 (99.9-99.9)	14.7 (12.4-17.2)	67.5 (56.3-81)	0.34 (0.25-0.45)

Results Part B

Table 3. Patient Characteristics

Patient Characteristics	N=196
Age, years (SD)	71±14.5
Males, n (%)	109 (55.7)
Charlson Comorbidity Index (IQR)	3 (1, 6)
Hospital length of stay, days (IQR)	32 (15, 74)
Duration of antimicrobial therapy, days (IQR)	7 (4, 14)
Time from screen to culture positive, days (IQR)	2 (-4, 47)
In-hospital mortality, n (%)	67 (34.2)
Sterile site cultures*, n (%)	59 (30)

*Sterile site cultures: abscess, deep wound or surgical, fluid/aspirate, bone, tissue, or peripheral blood

Table 4. Antibiotic Usage Stratified by Site of Clinical Culture

Antibiotic	Total Use N=196 (%)	Urinary N=94 (%)	Blood N=46 (%)	Respiratory N=30 (%)	Skin N=15 (%)	GI N=11(%)
Meropenem	67 (34.1)	22 (23.3)	28 (60.9)	6 (20)	7 (46.7)	4 (36.4)
Colistin	35 (17.9)	12 (12.8)	14 (30.4)	7 (23.3)	2 (13.3)	0
Tigecycline	63 (32.1)	21 (22.3)	20 (43.4)	7 (23.3)	9 (60)	6 (54.5)
Fosfomycin	25 (12.8)	25 (26.6)	0	0	0	0
Combination therapy*	102 (52)	33 (35.1)	35 (76.2)	13 (44)	15 (100)	6 (54.5)
Monotherapy	94 (48)	61 (64.9)	11 (23.8)	17 (56)	0	5 (45.5)

*Combination therapy: ≥2 antibiotics

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Results Part B Continued

Figure 1. CPO Genotypes N=196

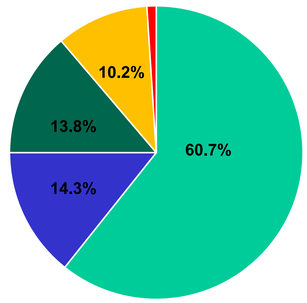

Figure 2. Site of CPO Clinical Culture N=196

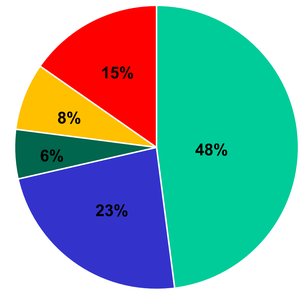

Table 5. Adverse Events

Adverse Event*	N (%)
Acute kidney injury	48 (28.6)
Hepatotoxicity	9 (5.4)
Clostridium difficile infection	4 (2.3)
Neurotoxicity	1 (0.6)

*Serum creatinine rise ≥ 30%, liver function tests ≥ 3 times upper limit normal, new *Clostridium difficile* infection during treatment or documented neurotoxicity

Discussion

- CPO screening had a high NPV making it useful for de-escalation or avoidance of CPO directed therapy
  - These findings are consistent with a study evaluating MRSA screening[6]
- Despite a high specificity, PPV was low, therefore CPO screening cannot be confidently used to rule in CPO positive clinical cultures
  - This is likely impacted by the relatively small number of CPO positive clinical cultures and screens and the low disease prevalence in our cohort
- The predominant genotype present in FHA is the NDM-1, in contrast to other parts of Canada and the United States[1,7]
- Mortality rate in our study was lower than that reported in literature[2,3]
  - This is likely due to studies reporting mortality rates in bacteremic patients only. Our study includes a broad range of CPO positive clinical cultures
- The most common therapies used were tigecycline and colistin aligning with genotype sensitivities[8]
  - Meropenem which is inherently resistant was frequently added to treatment based on benefits seen in bacteremic patients[9,10]
- Study results are limited as clinical cultures and not necessarily true infections were evaluated

Conclusions

- A CPO negative screen can be used to de-escalate/avoid CPO-directed therapy as demonstrated by the study's high NPV
- CPO positive clinical cultures are generally treated with meropenem, tigecycline and colistin, with combination therapy frequently employed.
- The results of our study may assist in development of stewardship guidelines around managing CPO screening results and clinical cultures