Implementation of Empiric Organism Specific Guidelines for Gram-negative Bacteremia in Conjunction with Rapid Diagnostic Testing

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Background

- Gram-negative bacteremia (GNB) is associated with significant morbidity and mortality[1]
- The use of rapid diagnostic tests can improve the time to effective antimicrobial therapy in patients with bacteremia[2]
- The GenMark Dx® ePlex® Blood Culture Identification Panels (BCIDP) were implemented at The Johns Hopkins Hospital (JHH) for GNB
- The JHH Antimicrobial Stewardship (AS) team created and implemented institution specific guidelines for empiric antibiotic therapy for targeted Gram-negative organisms based on antibiograms, patient clinical status, presence of resistance markers, and existing evidence for optimal organism specific therapy

Objectives

Primary objective:

- To confirm the validity of the institution specific empiric treatment recommendations targeting organisms identified by GenMark Dx® ePlex® BCIDP

Secondary objectives:

- To assess compliance with the institution specific guidelines
- To determine the impact of GenMark Dx® ePlex BCIDP results on antibiotic therapy (escalation, de-escalation) prior to susceptibility results
- To define frequency of GenMark Dx® ePlex® failure to identify targeted organisms

Methods

Prospective, single-center study

- **Inclusion**: Adults with blood cultures positive for Gram-negative rods in which Genmark Dx® ePlex® BCIDP was performed

Rapid Test Implementation & AS Interventions

- Genmark Dx® ePlex® BCIDP was implemented by the Medical Microbiology Laboratory at JHH on December 16, 2019
  - •Detects and identifies nucleic acids of 21 Gram-negative bacterial genera/species and 6 resistance markers: CTX-M, KPC, OXA, IMP, NDM, VIM
  - •Results of the test are reported in the electronic medical record 3-4 hours after blood cultures turn positive
- Guidelines were made available to medical and pharmacy staff at JHH to assist with most appropriate empiric therapy for identified organisms
- From December 16, 2019 to June 30, 2020 infectious diseases (ID) pharmacists prospectively reviewed all positive blood cultures twice daily, Monday – Friday, assessed compliance with guidelines, and intervened as needed

Sample of Institution Specific Guideline Recommendations

Organism	Preferred Therapy	Alternative therapy
E. coli	Clinical stable/biliary source: Ceftriaxone 2 g Q24H Critically ill/unstable: Cefepime 2 g IV Q8H	Severe PCN allergy: Aztreonam 2 g IV Q8H
Enterobacter cloacae complex	Cefepime 2g IV Q8H	Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H

Methods, *cont.*

Organism	Preferred Therapy	Alternative therapy
K. pneumoniae	Clinical stable : Ceftriaxone 2 g Q24H Critically ill : Cefepime 2 g IV Q8H	Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H OR Aztreonam 2 g Q8H
K. oxytoca	Clinically stable: Ceftriaxone 2 g IV Q24H OR Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H Clinically ill: Cefepime 2 g IV Q8H	Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H OR Aztreonam 2 g Q8H
P. aeruginosa	Cefepime 2 g IV Q8H OR Piperacillin/tazobactam 4.5 g IV Q6H ± Gentamicin or Tobramycin if critically ill	Severe PCN allergy: Aztreonam 2 g IV Q8H ± Gentamicin or Tobramycin if critically ill
***Citrobacter* spp.**	Cefepime 2 g IV Q8H	Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H
S. maltophilia	TMP/SMX 15 mg/kg/day IV/PO (in divided doses Q6-8H)	Levofloxacin 750 mg IV/PO Q24H
Any organism above with resistance marker(s) listed below		
CTX-M	Meropenem 1 g IV Q8H	Consult ID/AS
KPC, OXA	Ceftazidime/avibactam 2.5 q IV Q8H and Consult ID/AS	Consult ID/AS
IMP, NDM, VIM	Consult ID/AS	Consult ID/AS

Results

Table 1: Blood Cultures

Blood Cultures	N (%)
Genmark Dx ® ePlex® BCIDP was performed	272 (100)
Targeted organisms identified	237/272 (87)
• **Number of organisms**	251
•**Aerobes**	244
•**Anaerobes**	7
Polymicrobial cultures	49/237 (21)
Genmark Dx ® ePlex® negative for all targets	35/272 (13)
• **Failure to identify organisms***	6/272 (2)

**E. coli (3), K. oxytoca (1), Citrobacter spp. (1), Bacteroides fragilis (1)*

Table 2: Organisms Identified

Organism	Total N (%) - 251	Organism	Total N (%) - 251	Organism	Total N (%) - 251
E. coli	92 (37)	***S. marcescens***	11 (4)	***Salmonella spp.***	2 (0.8)
K. pneumoniae	55 (22)	***P. mirabilis***	5 (2)	***M. morganii***	2 (0.8)
P. aeruginosa	24 (10)	***Citrobacter spp.***	3 (1)	***H. infleunzae***	1 (0.4)
Enterobacter spp.	26 (10)	***A. baumannii***	3 (1)	***B. fragilis***	4 (2)
K. oxytoca	17 (7)	***S. maltophilia***	3 (1)	***F. nucleatum***	3 (1)

Results, *cont.*

Table 3: Multidrug Resistant Organisms

Resistance Marker	Organisms, N (%)
Extended spectrum beta-lactamase	41 (100)
• **CTX-M**	36 (88)
• **Non-CTX-M ESBL**	5 (12)
Carbapenem resistant organism	3 (100)
• **KPC**	2 (66)
• **Non-KPC CRE**	1 (33)

Table 4: Validation of Guideline Recommendations

Susceptibilities	Organisms, N (%)
Susceptible to all preferred guideline recommended therapy	240/251 (95.5)
Susceptible to all alternative guideline recommended therapy	191/204 (93.6)

Table 5: Guideline Compliance

Compliance	N (%)
Compliant	142/237 (60)
Noncompliant	95/237 (40)
• **Acceptable deviation from guideline***	39/95 (41)

**Acceptable deviations included neutropenia and resistant organisms present at other sites*

Table 6: Impact of Rapid Diagnostic on Antibiotic Therapy

Impact	N (%)
No change	120/237 (51)
Escalation in therapy	48/237 (20)
De-escalation in therapy	32/237 (13)
Initiation of therapy	28/237 (12)
Similar spectrum of therapy with improved susceptibility profile	9/237 (4)

Conclusion

- The preferred therapy recommendations within our institution-specific empiric guidelines for Gram-negative bacteremia provided effective coverage in 95% of cases
- Genmark Dx® ePlex® BCID identified at least one organism from positive blood cultures in 98% of bacteremia cases

References

1. Suljagić V, et al. Nosocomial bloodstream infections in ICU and non-ICU patients. Am J Infect Control. 2005;33(6):333-340. doi:10.1016/j.ajic.2005.03.010
2. Timbrook T, et al. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infec Dis. 2017;64(1):15-23. https://doi.org/10.1093/cid/ciw649