# 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<br>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<br>Critically ill : Cefepime 2 g IV Q8H | Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H OR<br>Aztreonam 2 g Q8H |
| ***K. oxytoca*** | Clinically stable: Ceftriaxone 2 g IV Q24H OR Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H<br>Clinically ill: Cefepime 2 g IV Q8H | Ciprofloxacin 750 mg PO Q12H or 400 mg IV Q8H OR<br>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