Comparative effectiveness of pediatric and neonatal antimicrobial stewardship treatment algorithms in rapid diagnostic-detected bacteremia

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ABSTRACT

Introduction: Verigene blood culture (BC) rapid diagnostic testing (RDT) has been shown to have a specificity greater than 95% in children. Limited clinical experience exists incorporating RDT results into a treatment algorithm to systematically tailor therapy in pediatric patients. This study aims to assess the proportion of appropriate therapy recommendations for a validated pediatric antimicrobial stewardship algorithm (PAMSA) as compared to the standard of care (SC) in pediatric bacteremia.

Study Design: Retrospective cohort of all neonatal and pediatric patients admitted to the Intensive Care and Progressive Care Units with RDT performed on positive blood cultures from Sept 2015 through Oct 2018.

Methods: Chart review provided information on the standard of care, including antibiotics administered, time to administration, and clinical data such as renal function and allergies. Appropriateness of antimicrobials received was compared to PAMSA recommended antimicrobials to determine accuracy and potential clinical benefit by two independent reviewers. A Gwet's AC1 was used for inter-rater reliability and adjudication completed as needed. Descriptive statistics were reported as mean, median, and confidence interval, as appropriate.

Results: 86 study participants with a median age of 10.2 months were included. A total of 15 organism strains were identified. Microbial appropriateness of therapy for the SC and PAMSA treatments was 94.2% (81/86) and 97.7% (84/86), respectively. SC was clinically appropriate in only 43% (37/86) of patients.

Conclusion: Use of a validated treatment algorithm which incorporates Verigene® BC results and local antibiogram data would be more effective than the standard of care administered in the study participants.

BACKGROUND

- Verigene® Blood-Culture Gram Positive (VBC-GP) RDT identifies nine organisms, and resistance determinants mecA, vanA, vanB
- Verigene® Blood-Culture Gram Negative (VBC-GN) RDT identifies eight gram-negative organisms and resistance determinants KPC, NDM, CTX-M, VIM, IMP, and OXA
- University of Maryland Children's Hospital Verigene® RDT has a specificity of 98.2%
- Prior studies demonstrated use of RDT in combination with antimicrobial stewardship as an effective means of improving antibiotic prescribing, mainly through appropriate escalation/de-escalation of therapy
- Limited clinical experience exists incorporating RDT results with a treatment algorithm to systematically tailor therapy in pediatric patients

OBJECTIVES

Primary

- Assess the proportion of appropriate therapy recommendations for the PAMSA and SC patients with confirmed pediatric bacteremia

Secondary

- Determine potential time savings for PAMSA-guided de-escalation of antibiotics

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METHODS

Study Design

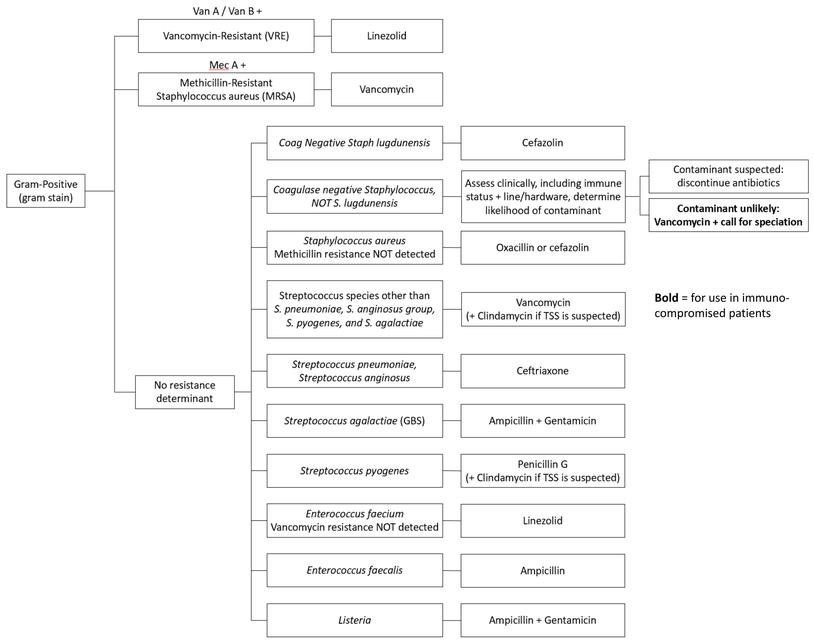
- Retrospective observational study of pediatric patients age ≤ 18 years admitted to the University of Maryland Children's Hospital Neonatal Intensive Care Unit (NICU), Pediatric Intensive Care Unit (PICU), or Pediatric Progressive Care Unit (PPCU) with blood cultures positive for Verigene® RDT target organisms from September 2015 through October 2018
- Microbial appropriateness defined as *in vitro* sensitivity against the organism identified through traditional clinical microbiology, any overly broad-spectrum therapy was considered clinically inappropriate
- SC antimicrobials were those administered within 12 hours of the Verigene RDT result
- Time to de-escalation of antimicrobials was calculated as the time of Verigene RDT result to the time of appropriate antimicrobial order change

Inclusion Criteria	Exclusion Criteria
• Admitted to pediatric service • Verigene RDT target organism • Final speciation reported	• Polymicrobial bacteremia • Missing final sensitivities • Suspected meningitis or complex multisource infection • Incomplete SC antibiotic administration data

Statistical Analysis

- Comparisons between SC therapy received and PAMSA proposed therapy using Chi squared
- Inter-rater agreement assessed using Gwet's AC1 to account for paradoxes found in Cohen's Kappa when a high portion of all responses fall into a single nominal category
- Analyses were performed with SAS v 9.4 (SAS Institute, Cary, NC) and R 3.6.1 (R Core Team, 2019)

Figure 1. PAMSA for PICU/PPCU Patients with VBC-GP confirmed bacteremia



Algorithm is based on institution-specific antibiogram data and evidence based practice. Recommendations are not to supersede clinical judgement. Not intended for use with polymicrobial infections or for patients with concern for meningitis

RESULTS

- A total of 176 participants screened for inclusion; 30 excluded for suspected meningitis or complex multisource infection, 43 excluded for missing final sensitivities, and 17 excluded for incomplete antibiotic administration data
- A total of 86 participants included in the final study analysis

Table 1. Baseline Demographics

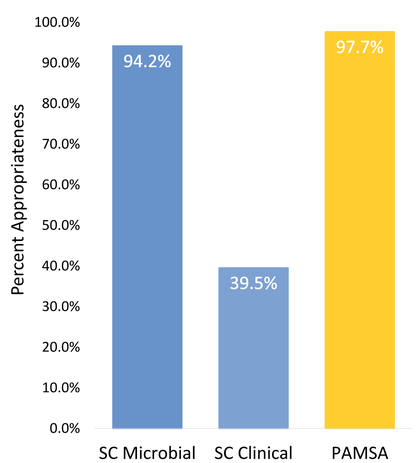
Participant Characteristics	Total (n=86)
Median Age (years, IQR)	0.85 (0.14,5.9)
Female (n, %)	34 (39.5)
Race/ethnicity (n, %)	
Black	41 (47.7)
White	27 (31.4)
Latino	9 (10.5)
Other/Non-specific	6 (7)
Asian	3 (3.4)
Admitting Pediatric Unit (n, %)	
PPCU	34 (39.5)
NICU	27 (31.4)
PICU	25 (29.1)
Median Length of Stay (days, IQR)	29.5 (9,80.8)
Central line >48 hours (n, %)	38 (44.2)
Oncologic diagnosis (n, %)	12 (14)
Reported antibiotic allergy (n, %)	6 (7)

Table 2. Verigene® Detected Organisms

Identified Organism Strain	n (%)
Escherichia coli	13 (15)
Methicillin-sensitive *Staphylococcus aureus (MSSA)*	13 (15)
Coagulase negative Staphylococcus	12 (14)
Streptococcus spp. Other	9 (10.5)
Streptococcus pneumoniae	8 (9.3)
Enterobacter species	7 (8.1)
Enterococcus faecalis	6 (7)
Methicillin-resistant *Staphylococcus aureus (MRSA)*	6 (7)
*Klebsiella pneumoniae**	5 (5.8)
Klebsiella oxytoca	2 (2.3)
Citrobacter species	1 (1.2)
Enterococcus faecium	1 (1.2)
Pseudomonas aeruginosa	1 (1.2)
Staphylococcus lugdunensis	1 (1.2)
Streptococcus anginosus group	1 (1.2)

* CTX-M resistance determinant detected on Verigene® RDT for 1 sample

Figure 2. Comparison of Therapy Appropriateness for SC versus PAMSA Recommendation



- Blinded review of appropriateness of both SC and PAMSA had almost perfect agreement with a Gwet's AC1 of 0.99 (CI 0.96, 1.0) and 0.92 (CI 0.85, 0.99) respectively
- No statistically significant difference between the SC and PAMSA treatment observed in the comparison of microbial appropriateness 81/86 vs 84/86, p = 0.44
- Once clinical appropriateness was incorporated, only 37/86 SC were on appropriate therapy, a statistically significant difference compared to PAMSA, p < 0.001
- Antibiotic allergy and concomitant necrotizing enterocolitis accounted for the 2 participants assessed as inappropriate for receipt of PAMSA therapy
- For the 15 patients appropriately de-escalated after receipt of Verigene® RDT results, median time to change in therapy was 5.4 hours (IQR 2.3,9.8) – a median time savings of 42.7 hours (IQR 40.6,49.4) as compared to waiting for final sensitivities
- All 49 patients deemed microbially and/or clinically inappropriate were not de-escalated to organism-tailored therapy until final sensitivity results or later

CONCLUSIONS

- Use of a validated treatment algorithm that incorporates Verigene® BC results and local antibiogram data was more effective to the standard of care therapy administered in the study participants
- Modification of therapy to PAMSA guided treatment in light of Verigene® BC results could result in a majority of participants being de-escalated to narrower, organism-tailored therapy which may help lower risk of developing antimicrobial resistance within the local institution and decrease adverse events from prolonged broad-spectrum antibiotics