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1756. Prediction of Bloodstream Infection Prior to Onset of Symptoms by Plasma Metagenomic Sequencing in Pediatric Patients With Relapsed or Refractory Malignancy (PREDSEQ)

Kathryn Goggin, MD[1]; Yuki Inaba, BS[1]; Veronica Gonzalez-Pena, PhD[1]; Kim J. Allison, BSN[1]; Ka Lok Chan, MS[2]; Desiree Hollemon, MSN, MPH[2]; Asim Ahmed, MD[2]; David Hong, MD[2]; Gabriela Maron, MD[1]; Randall Hayden, MD[1]; John Choi, MD, PhD[1]; Jeffrey Rubnitz, MD PhD[1]; Charles Gawad, MD, PhD[1] and Joshua Wolf, MBBS FRACP[1], [1]St. Jude Children's Research Hospital, Memphis, Tennessee and [2]Karius Inc., Redwood City, California

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Saturday, October 6, 2018: 10:30 AM

Background. Patients undergoing treatment for relapsed or refractory malignancies are at high risk of life-threatening bloodstream infection (BSI). A predictive screening test for BSI might allow pre-emptive therapy, but no validated test is currently available. We tested the hypothesis that plasma metagenomic next generation pathogen sequencing (NGS) would predict BSI before the onset of attributable symptoms.

Methods. We enrolled 31 pediatric patients receiving for treatment relapsed or refractory malignancy in an IRB-approved prospective cohort study (PREDSEQ) of predictive sequencing. Episodes of febrile neutropenia or documented infection were collected prospectively from the medical record. BSI was defined according to NHSN criteria. Control Samples were defined as samples collected ≥7 clear days before or after any fever or documented infection. Residual clinical samples were stored for NGS; after filtering human sequences, reads were aligned to a curated pathogen database, and organisms above a predefined threshold were reported (Karius Inc., Redwood City, CA). Only bacteria and fungi were included in this analysis.

Results. A total of 11 BSI episodes occurred in 9 participants (Table 1) during the study period. Predictive sensitivity of NGS in the 2 days before onset of infection ($n = 9$) was 78% (95% CI 45–94%), and diagnostic sensitivity on the day of infection ($n = 11$) was 82% (95% CI 52–95%). Specificity of NGS for development of fever or infection within 7 days ($n = 16$) was 81% (95% CI 57–93%). NGS was positive up to 6 days prior to onset of BSI. In samples collected before or during documented infections, NGS also identified additional bacteria and fungi that were not detected by standard clinical testing.

Conclusion. Plasma NGS shows promise for the detection of BSI prior to onset of symptoms in high-risk patients.

	Expected	NGS Prediction	NGS Diagnosis	Additional Organisms
BSI		√	√	No
1	*S. epidermidis*	√	√	No
2	*E. coli*	√	√	Yes
3	*E. faecium*	√	√	Yes
4	*E. faecium*	√	√	Yes
5	*R. mucilaginosa*	√	√	Yes
6	*S. epidermidis*	√	√	Yes
7	*E. coli/R. mucilaginosa*	√	√	Yes
8	*E. coli*	X	X	Yes
9	*C. kruzei*	X	X	Yes
10	*S. epidermidis*	N/A	√	No
11	*C. jeikeium*	N/A	√	Yes
Control				
1	N/A	N/A	N/A	*V. parvula*
2	N/A	N/A	N/A	*F. magna*
3	N/A	N/A	N/A	*H. pylori* and *L. fermentum*
4–10	N/A	N/A	N/A	No

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1757. Using the Desirability of Outcome Ranking for Management of Antimicrobial Therapy (DOOR-MAT) to Assess Antibiotic Therapy Guided by Rapid Molecular Diagnostics (RMD) in Bloodstream Infection (BSI) Caused by *Escherichia coli* and *Klebsiella pneumoniae*

Brigid Wilson, PhD[1]; Roberto Viau, MD[1]; Federico Perez, MD, MS[2]; Hongyu Jiang, MS[3]; Vance G. Fowler, Jr MD[4]; Henry F. Chambers, MD[5]; Barry N. Kreiswirth, PhD[6]; Robert A. Bonomo, MD[1]; Scott R. Evans, PhD[7] and ARLG, [1]Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, [2]Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio, [3]Biostatistics, Harvard School of Public Health, Boston, Massachusetts, [4]Duke University Medical Center, Durham, North Carolina, [5]Clinical Research Services, University of California San Francisco, Clinical and Translational Sciences Institute, San Francisco, California, [6]Public Health Research Institute, Rutgers New Jersey Medical School, Newark, New Jersey and [7]Harvard School of Public Health, Boston, Massachusetts

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Background. In the setting of *Escherichia coli* and *Klebsiella pneumoniae* BSI, empiric antibiotic therapy is determined by clinical judgement and Gram stain (GS) of the positive blood culture bottle up to 2 days before antibiotic susceptibility test (AST) results become available. Within hours of GS, RMD can detect *E. coli* and *K. pneumoniae* and predict the pattern of susceptibility to β-lactams (BL) of differing spectrum. In this study, our objective was to compare "real-life" empiric therapy for *E. coli* and *K. pneumoniae* BSI administered between GS and AST results with simulated RMD-guided therapy.

Methods. We identified a subset of patients hospitalized within VHA between 2006 and 2015 who had a blood culture positive for *E. coli* or *K. pneumoniae,* and received empiric BLs between GS and AST Results. We further restricted the cohort to those with observed or implied AST results for 4 representative BLs: cefazolin, ceftriaxone, piperacillin–tazobactam, and imipenem. We extracted BL resistance patterns and, based on previously analyzed RMD performance on 195 *E. coli* and *K. pneumoniae*, we simulated RMD results for our cohort by resampling RMD results stratified by resistance pattern at the observed frequencies of resistance patterns in our clinical isolates. We simulated therapy guided by RMDs and compared with the observed empiric BLs using a DOOR-MAT score (Figure 1).

Results. A total of 36,531 BSI cases were identified. Of these, 9,981 *E. coli* and 4,545 *K. pneumoniae* met our inclusion criteria (Figure 2). Among these, susceptibility to all BLs occurred in 88% of cases; resistance to all BLs occurred in <0.5%. The isolates previously analyzed using RMD included more resistant phenotypes (Figure 3). Empiric BLs were active in 98% of BSIs, with a mean DOOR-MAT score of 66.1 and 59% of cases classified as "moderate overtreatment." Simulated RMD-guided BL therapy would be active in 95% of cases with a mean DOOR-MAT score of 91.4 (95% CI, 91.2–91.7), and 7% of cases would be classified as overtreatment.

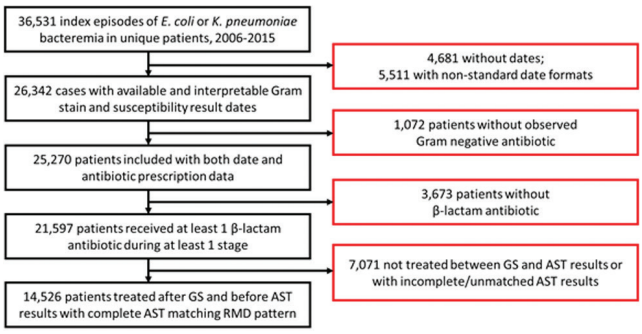
Conclusion. In a large cohort of BSI patients where rates of BL resistance were low, we observed that empiric BL therapy, although highly effective, is of broader spectrum than necessary. RMD-guided therapy has the potential to reduce overtreatment without compromising effective therapy. DOOR-MAT provides a flexible framework for measuring appropriateness of therapy for BSI.

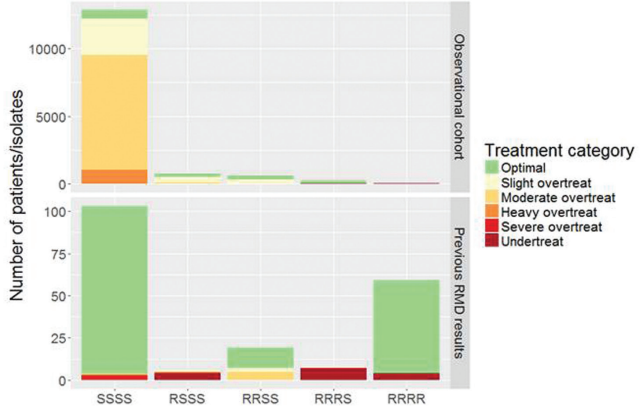
DOOR-MAT: Scoring for combinations of susceptibility-resistance phenotype and treatment selection

Classification of Antibiotic Spectrum in Simulated/Observed Treatment	Susceptibility (*S*) - Resistance (*R*) Phenotype for Cefazolin-Ceftriaxone-Piperacillin/Tazobactam-Imipenem				
	S-S-S-S	*R-S-S-S*	*R-R-S-S*	*R-R-R-S*	*R-R-R-R*
Narrow	100	0	0	0	0
Intermediate I	80	100	0	0	0
Intermediate II	60	80	100	0	0
Broad	40	60	80	100	0
Last Resort	20	40	60	80	100

0 = inactive therapy to 100 = optimal therapy, higher scores indicate more active and appropriate therapy

Undertreat	Optimal treatment	Slight overtreat	Moderate overtreat	Heavy overtreat	Severe overtreat





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