Microbial Cell-Free DNA Sequencing for *Prediction* of Culture-Negative Infection Events in Children with Cancer

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ABSTRACT

BACKGROUND

Culture-independent diagnostics may help diagnose or predict infection; microbial cell free DNA sequencing (mcfDNA-seq), can detect a wide range of pathogens directly from plasma. Immunocompromised children who develop febrile neutropenia (FN) without documented bloodstream infection (BSI) may have undiagnosed bacterial infection, but identification of this is difficult, and the proportion of such episodes is unknown, as is the relative contribution of non-bacterial etiologies. We analyzed mcfDNA-seq results in a convenience sample of FN cases without known etiology.

METHODS

Participants were <25 years of age and undergoing treatment for cancer. Remnant plasma was prospectively obtained and stored. Samples from Days 0 and -1 underwent mcfDNA-seq by Karius Inc., reported in molecules per microliter (MPM) of plasma. Samples from participants without impending or recent fever or infection were also tested.

RESULTS

There were 8 episodes in 7 patients; 4 (50%) had a common bacterial pathogen identified by mcfDNA-seq on Day 0 (Table 1). In 2 (50%) of these cases, the same organism was also identified on Day -1, at a lower concentration. One fungal pathogen was identified prior to and at onset of FN. A common bacterial pathogen was identified in 3/64 (5%) control samples from the population.

Culture-negative sepsis was the final diagnosis in two episodes; *Streptococcus mitis* an important cause of neutropenic sepsis, was found in Day 0 and Day -1 samples. In an episode where *E. coli* was identified by mcfDNA-seq, FN recurred after antibiotic discontinuation.

CONCLUSIONS

In this sample of culture-negative FN episodes in pediatric patients with leukemia, mcfDNA-seq identified a bacterial pathogen in 50% of cases and the same organism was found on the day before FN in 25% of cases, suggesting that predictive testing might be feasible.

BACKGROUND

Microbial cell-free DNA sequencing *detects* bloodstream infection (BSI) organisms several days *before* onset of infection and might predict BSI.[a]

Figure 1. Sensitivity of mcfDNA-seq for the Prediction or Diagnosis of BSI by Day Before the Onset of Infection

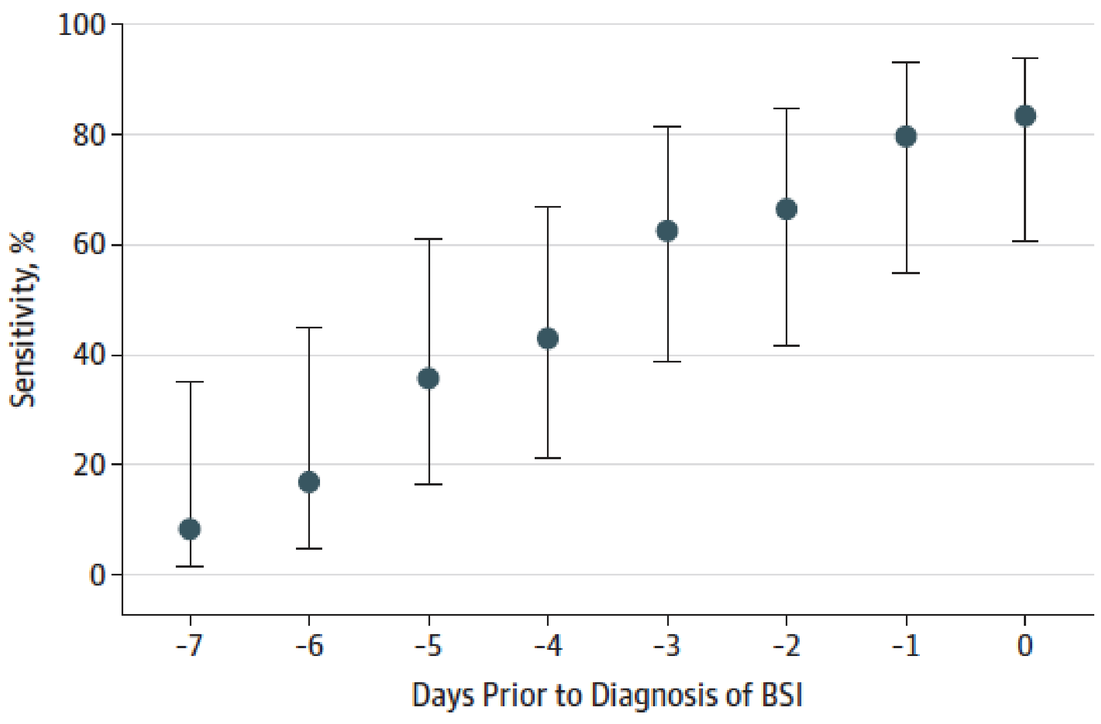
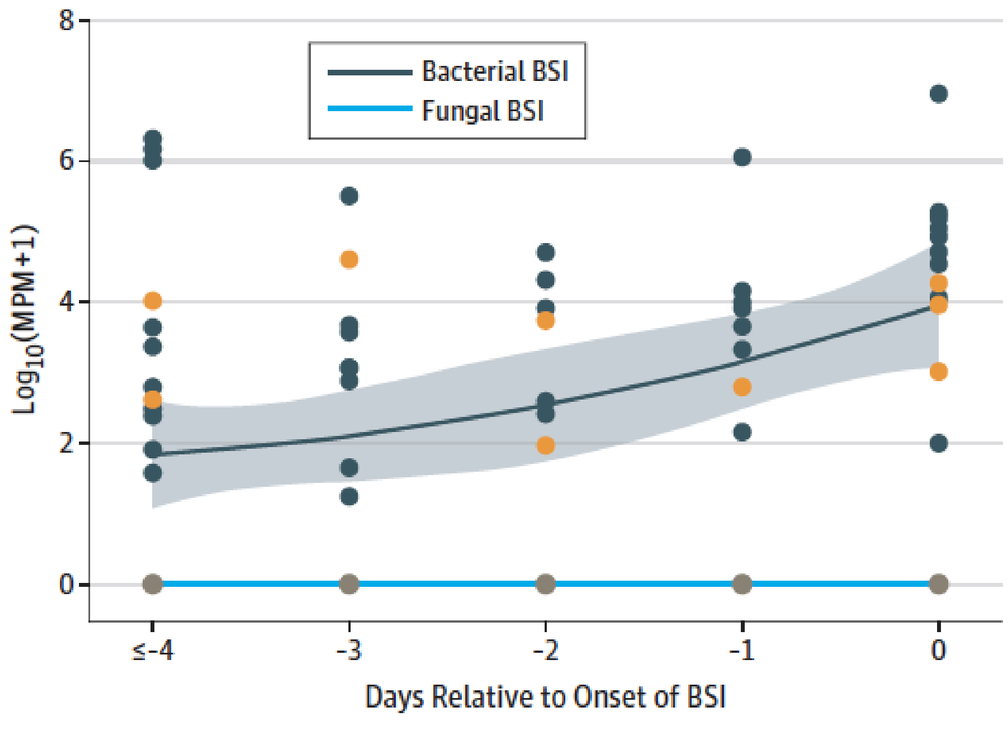


Figure 2. Population Kinetics of Pathogen DNA by Day Before the Onset of BSI



[a]Goggin KP *et al*, "Evaluation of plasma microbial cell-free DNA sequencing to predict bloodstream infection in pediatric patients with relapsed or refractory cancer", *JAMA Oncol*, 2019

RESULTS

In eight cases of *unexplained febrile neutropenia* in children with leukemia, microbial cell-free DNA sequencing (mcfDNA-Seq) by the Karius Test *identified* common bacterial pathogens in four and *predicted* the same pathogens before onset of fever in two.

		Common Bacterial Pathogens Found by mcfDNA-Seq	
Episode	**HCT**	**Predictive (Day -1)**	**Diagnostic (Day 0)**
1*	Yes	*Streptococcus mitis*	*Streptococcus mitis*
2	No	*Escherichia coli*	*Escherichia coli*
3	Yes	None	*Streptococcus mitis*
4	No	*Staphylococcus epidermidis*	*Streptococcus oralis* *Streptococcus sanguinis* *Fusobacterium nucleatum*
5	Yes	None	None
6	Yes	None	None
7	Yes	None	None
8	No	None	None

*Sepsis requiring ICU admission; *Common bacterial pathogens* are organisms identified in >1% of episodes of CLABSI in children with cancer (Children's Hospital Association Childhood Cancer & Blood Disorders Network, August 2013 – December 2015); all other organisms excluded

Bacterial Pathogen DNA in Unexplained Febrile Neutropenia

Day -1, Day prior to inset of febrile neutropenia; Day 0, Day of onset of febrile neutropenia;

CONCLUSIONS

mcfDNA-seq *identified* a common bacterial pathogen as a plausible etiology in half of episodes of unexplained febrile neutropenia. Predictive testing might allow *pre-emptive* recognition in some cases.

STUDY COHORT

Characteristic		n	(%)
Age	Median (range)	10.9	(2.0-17.8)
Sex	Female	2	(25%)
	Male	6	(75%)
Race	White	5	(63%)
	All others	3	(38%)
Leukemia	ALL	4	(50%)
	AML	4	(50%)

METHODS

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