

Comparative Clinical Evaluation of the T2Bacteria Panel versus Blood Culture for the Diagnosis of Bacteremia

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Disclosures

- This clinical trial was funded by T2 Biosystems
- T2 Biosystems provided assistance with the study design and compiled data from each institution in a central database.
 - The authors performed data and statistical analyses and prepared today presentation without assistance.

Background

- Bloodstream infections (BSIs) are associated with significant morbidity and mortality
 - Timely administration of appropriate antibiotics improves outcomes (*Seymour, 2017; Kumar, 2006*)

Background

- Bloodstream infections (BSIs) are associated with significant morbidity and mortality
 - Timely administration of appropriate antibiotics improves outcomes (*Seymour, 2017; Kumar, 2006*)
- Blood culture (BCx) is considered the gold standard for diagnosing BSI, but is limited by
 - Suboptimal sensitivity (*Murray, 2014*)
 - 10% in suspected bacteremia
 - 30% in febrile neutropenia
 - 35% in severe sepsis
 - 50% in septic shock
 - Slow turnaround time
 - Mean: 84 hours (23-199 hours)

Background

- Several nucleic acid amplification tests (NAATS) for detection of bacteria directly from blood have been developed
- Given the poor sensitivity of BCx, it may be more accurate to use composite microbiologic *and* clinical criteria in evaluating the performance of these non-cultural diagnostic tests

Background

- T2Bacteria Panel (T2B) is an automated, rapid, culture-independent diagnostic test that identifies microbes directly from whole blood
- T2B runs on a fully automated T2Dx Instrument
- Results available as early as 3.5 hours



Background

- T2B identifies 6 target organisms responsible for $\geq 50\%$ of BSI
 - can detect bacteria at a density as low as 2 colony forming unit (CFU) per ml of whole blood

Bacteria	LoD (CFU/mL)
<i>Acinetobacter baumannii</i>	3
<i>Enterococcus faecium</i>	5
<i>Escherichia coli</i>	11
<i>Klebsiella pneumoniae</i>	2
<i>Pseudomonas aeruginosa</i>	5
<i>Staphylococcus aureus</i>	2

Goal

- To evaluate the performance of T2B for diagnosing BSI

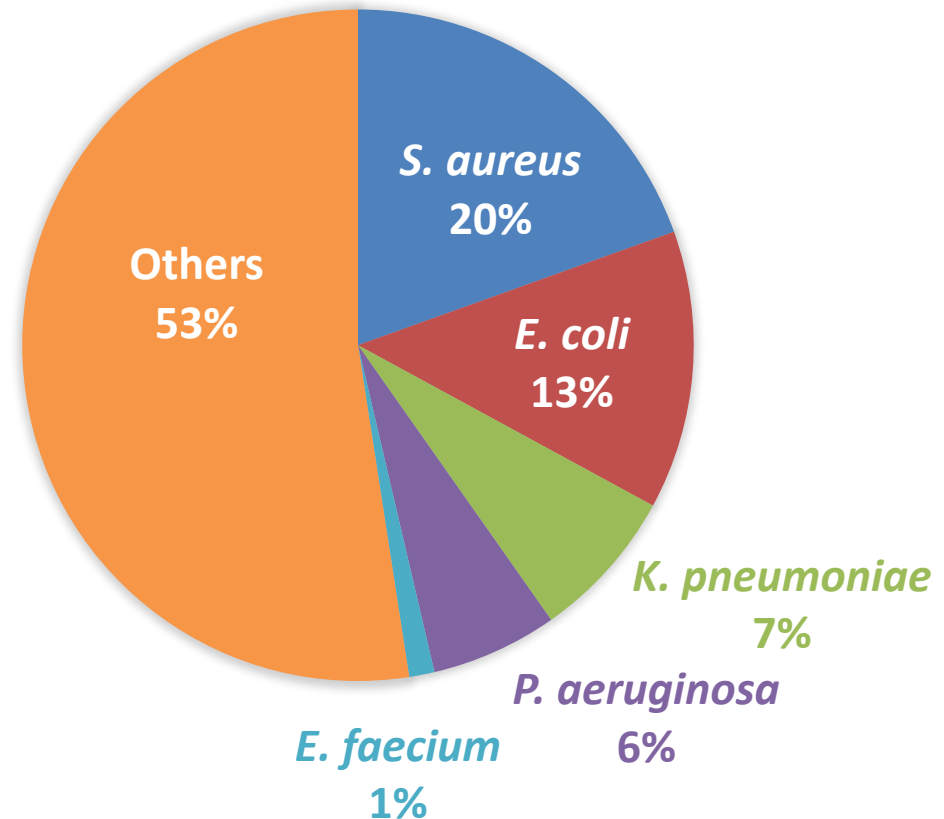
Methods

- Prospective study with sample collections from Dec 2015 – August 2017
 - 11 centers throughout the US
- Inclusion criteria
 - Patients (18-95 years of age) with a diagnostic BCx ordered per standard of care
- Process:
 - Paired BCx and T2B blood drawn, with BCx always drawn first

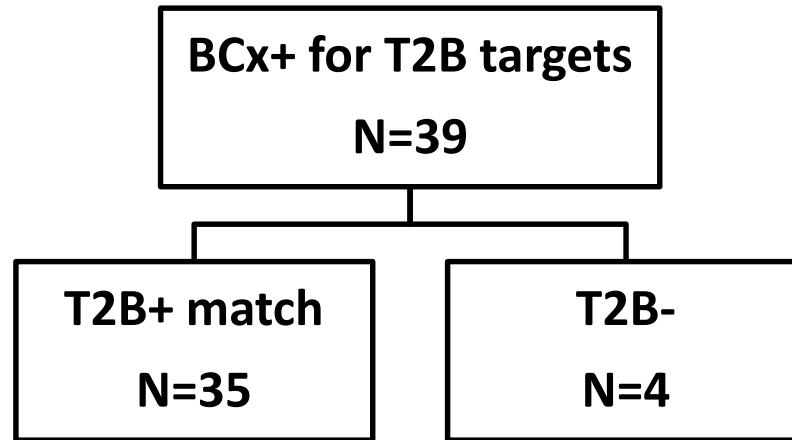
Results

- Paired samples from 1,427 unique patients were obtained
- 6% (82) of BCx were positive
 - 47% (39) were due to 5 target T2B
 - No BSI due to *A. baumannii* recovered from BCx
- Mean time to BCx+: 72 hours (24 - 177 hours)

Organisms Recovered from Companion BCx



Sensitivity of T2B compared with BCx



T2B Target	Sensitivity	95% CI
Overall	90% (35/39)	75-97%
<i>E. coli</i>	91% (10/11)	62-98%
<i>E. faecium</i>	100% (1/1)	21-100%
<i>K. pneumoniae</i>	100% (6/6)	61-100%
<i>P. aeruginosa</i>	100% (5/5)	57-100%
<i>S. aureus</i>	81% (13/16)	57-100%

Sensitivity of T2B compared with BCx

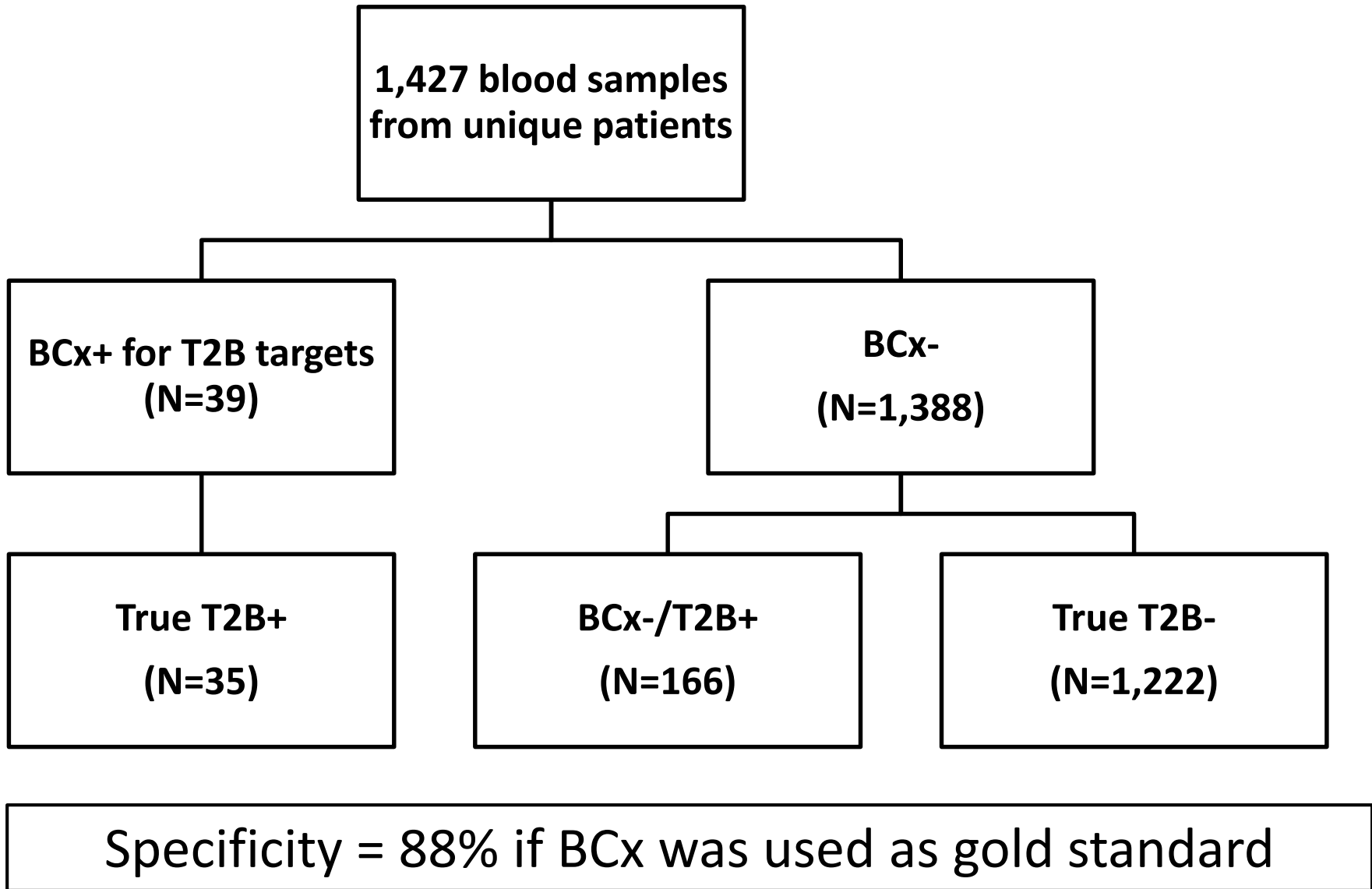
T2B Target	Sensitivity	False Negative Paired T2B Result
<i>E. coli</i>	91% (10/11)	1
<i>S. aureus</i>	81% (13/16)	3

T2B retest using archived tubes



Paired BCx Result	Paired T2B Result	Archived Sample T2B Result
<i>E. coli</i>	<i>E. coli</i> NEGATIVE	<i>E. coli</i> POSITIVE
<i>S. aureus</i>	<i>S. aureus</i> NEGATIVE	<i>S. aureus</i> POSITIVE
<i>S. aureus</i>	<i>S. aureus</i> NEGATIVE	<i>S. aureus</i> NEGATIVE
<i>S. aureus</i>	<i>S. aureus</i> NEGATIVE	<i>S. aureus</i> NEGATIVE

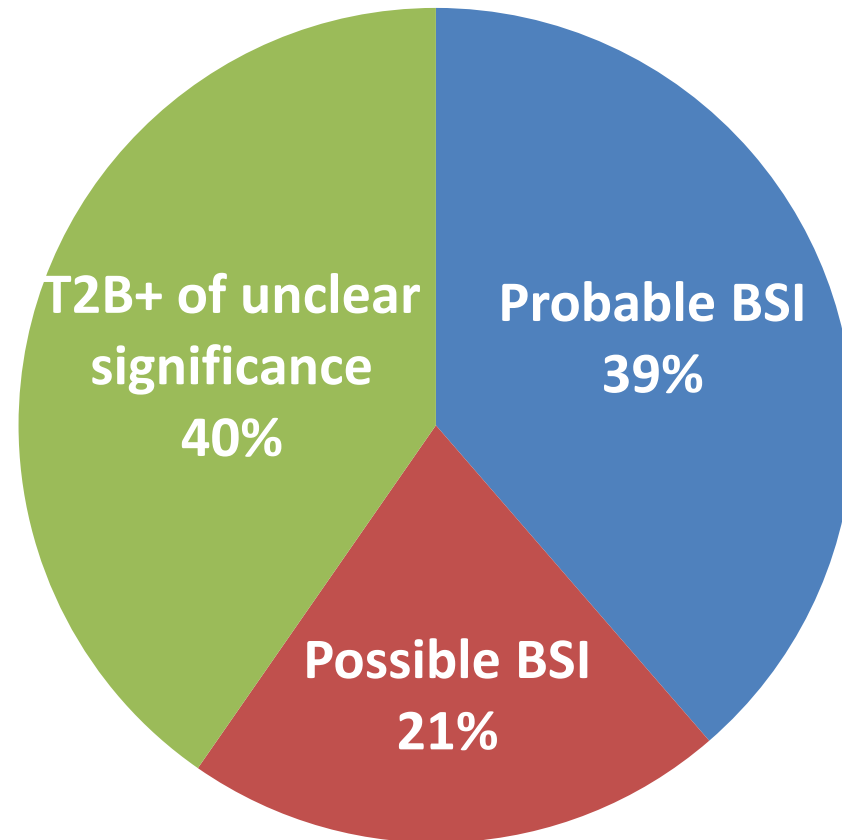
Specificity of T2B compared with BCx



Composite Clinical/Microbiologic Criteria

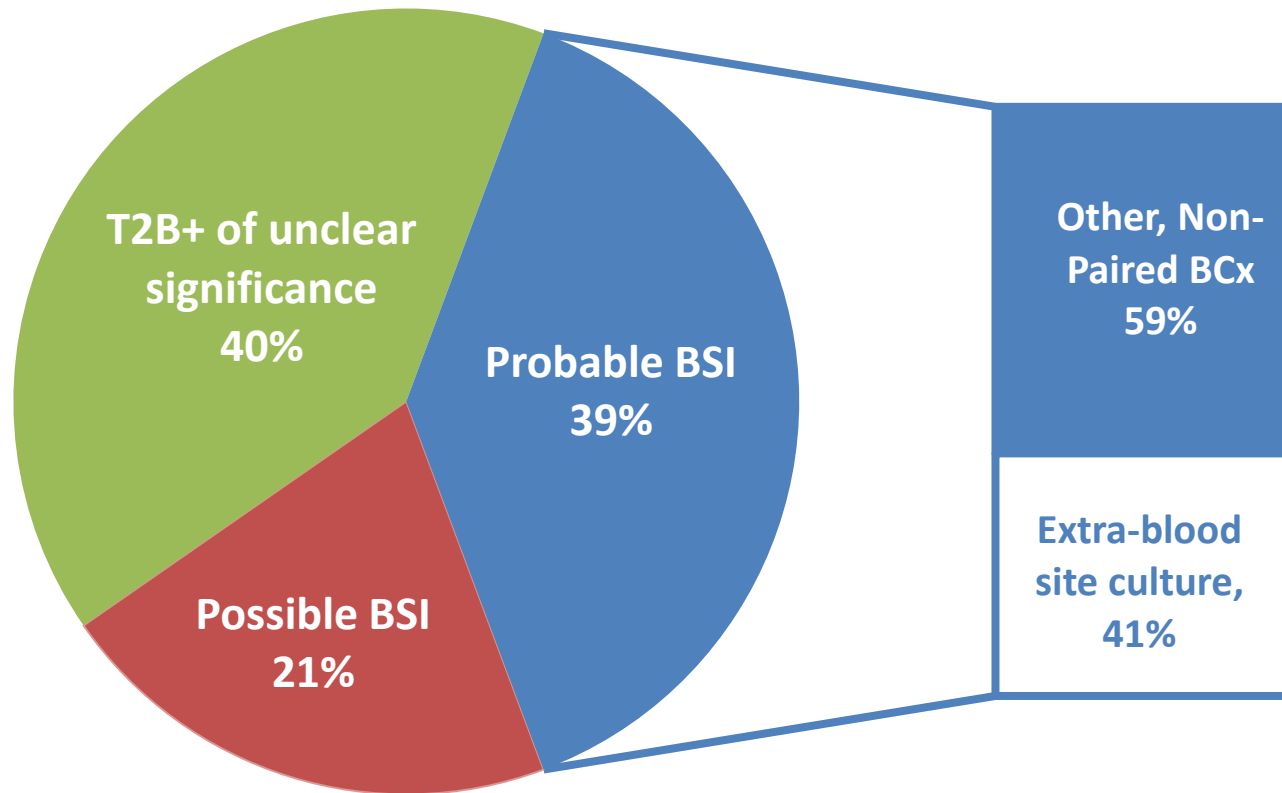
Definitions	Clinical/Microbiologic Criteria
Proven	Paired BCx+ and T2B+ for same organism
Probable	BCx-/T2B+ but with positive culture for T2B organism in 1) blood or 2) extra-blood site within 14 days of paired sample
Possible	BCx-/T2B+ associated with infectious syndromes that fit clinical scenario of T2B+ result, but cultures were either not performed or negative

Analysis of Discordant BCx-/T2B+

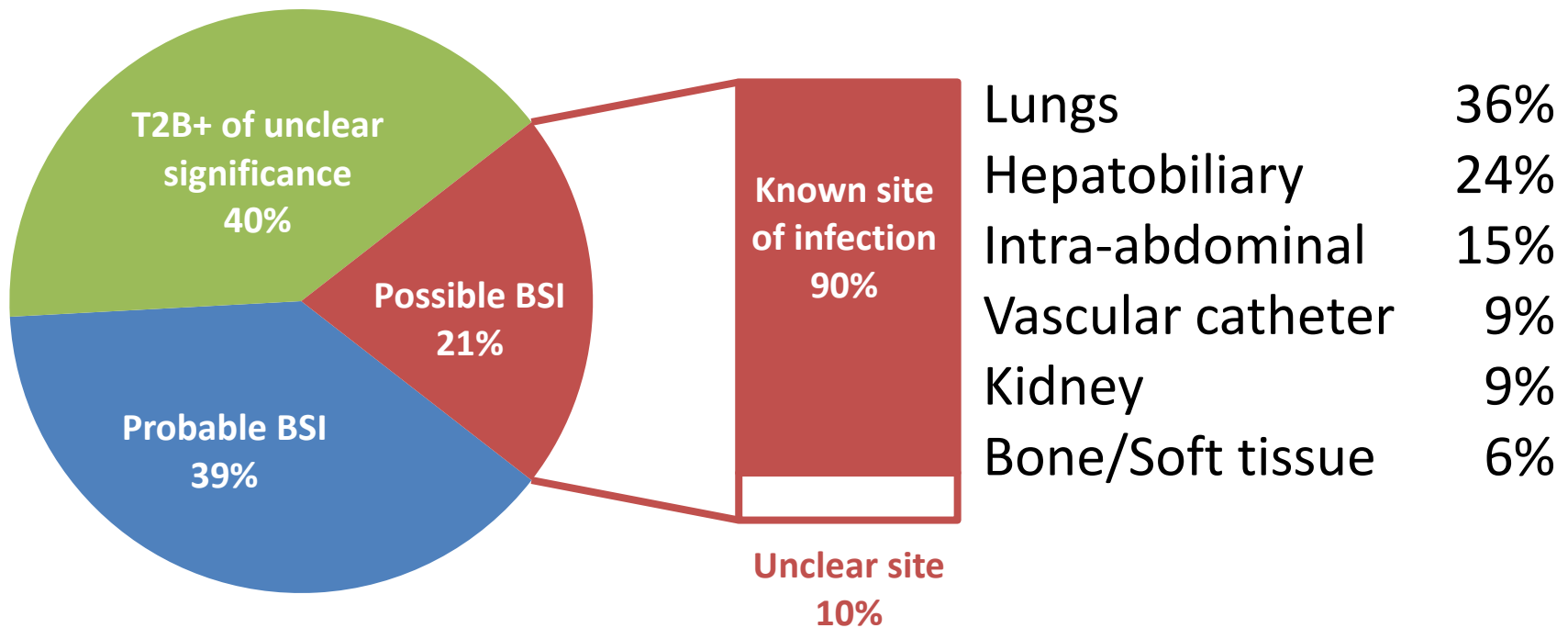


52% (86/166) of samples were associated with antecedent antibiotics that potentially had activity against T2B identified organisms

Analysis Discordant BCx-/T2B+



Analysis of Discordant BCx-/T2B+



Specificity analysis

T2B Target Organism	Proven BSI	Proven and probable BSI	Proven, probable and possible BSI
Overall	88.0%	92.6%	95.2%

- Data suggest that T2B detected at least some BSIs that were missed due to the poor sensitivity of BCx

Conclusions

- T2B demonstrates excellent performance in detecting BSI
 - Overall sensitivity: 90%
 - Detects 5 bacteria accounting for $\geq 50\%$ of BSI
 - Use T2B in conjunction with BCx
- The specificity of T2B was:
 - 88% when BCx was used as gold standard comparator
 - $>95\%$ when composite clinical/microbiologic criteria was used

Conclusions

- Our data clearly demonstrate the limitations of BCx as gold standard for both diagnostic and study design purposes
- Among the patients with discordant BCx-/T2B+ samples, evidence of infection were identified in 60%
 - Had the same bacteria recovered from blood or non-blood site cultures
 - Had clinical pictures that fit infection syndromes caused by bacteria identified by T2B
 - 52% of patients received antecedent antibiotics

Conclusions

- Potential sources of T2B+ results of unclear significance:
 - Non-viable bacteria in patient's blood
 - Transient bacteremia
 - Antibiotics
 - Contamination (environment, reagent, during blood drawn):
 - 88% of BCx-/T2B+ were negative upon retesting and sequencing (data not shown)

Conclusions

- Potential advantages of T2B over BCx
 - detect bacteremia several days before BCx (3-5 hours versus 2-3 days)
 - diagnose infections missed by BCx
 - Patients with antecedent antibiotics
 - Patients with extra-blood site infections
 - informed target of therapy within hours of blood drawn
- In the future, it is important to evaluate how to strategically incorporate this assay in clinical practice