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BIOMEDICAL AND HEALTH SCIENCES

The Role of the Clinical Laboratory in Antimicrobial Stewardship

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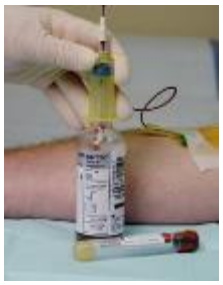
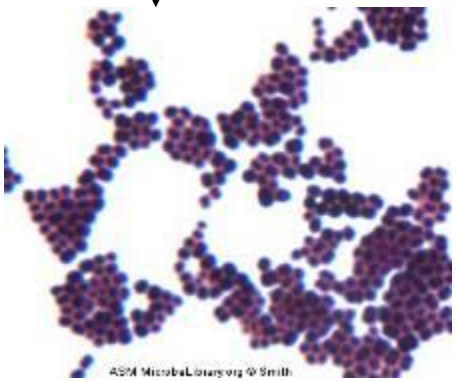
Clinical laboratory support for ASPs

- AST result cascading
- Selective work up/reporting of culture results
- Stat testing for PCT and other biomarkers
- Diagnostic testing stewardship/consultation
- Rapid diagnostic assays that provide early pathogen identification and antimicrobial resistance information
  - Blood cultures
  - Other specimen types

Conventional methods for BSI workup

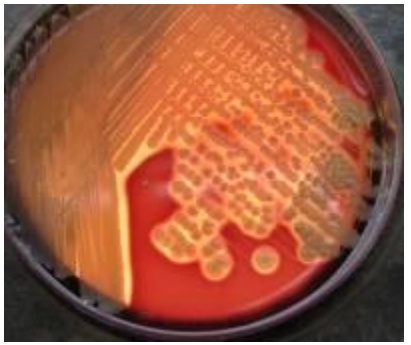


Turn around time (TAT) = ~48-72 hrs from detection of growth



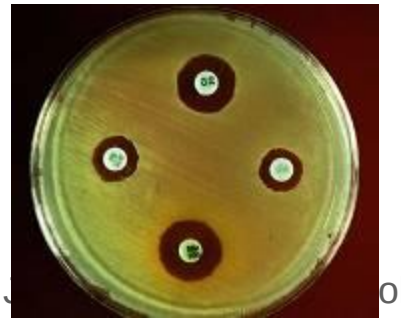
Gram stain

Plating



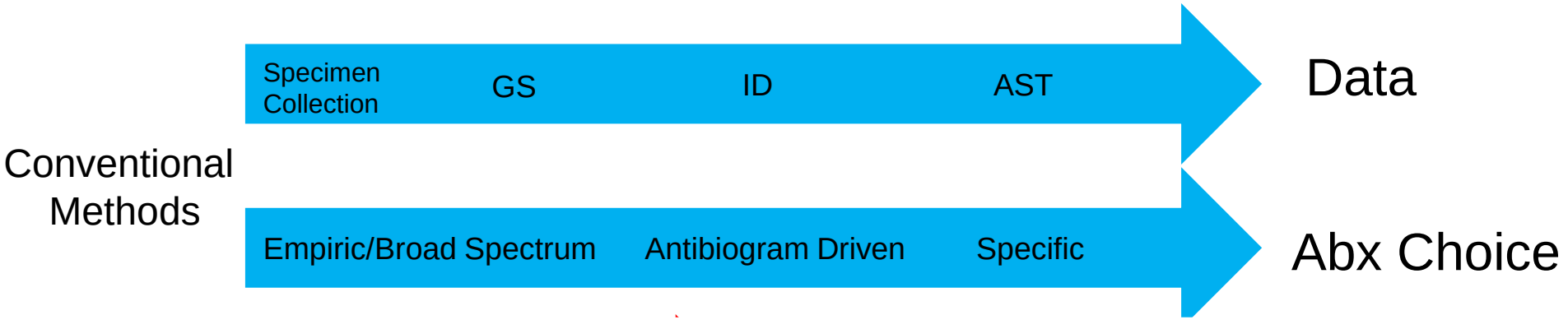
Isolation

Identification



AST

Clinical decisions based on laboratory data using conventional methods



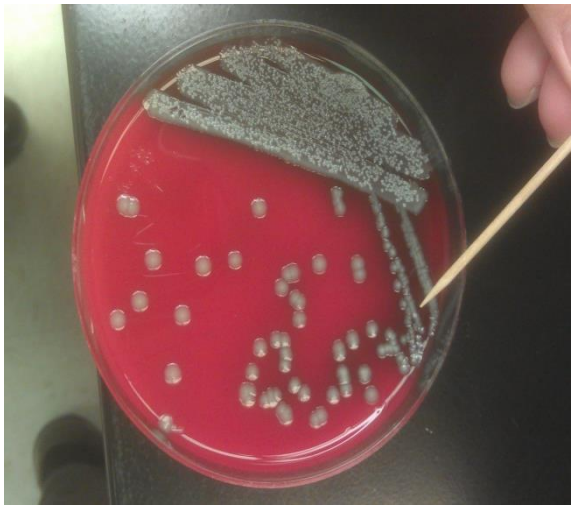
Clinical Goals for Rapid Diagnostic Testing in the Setting of BSI

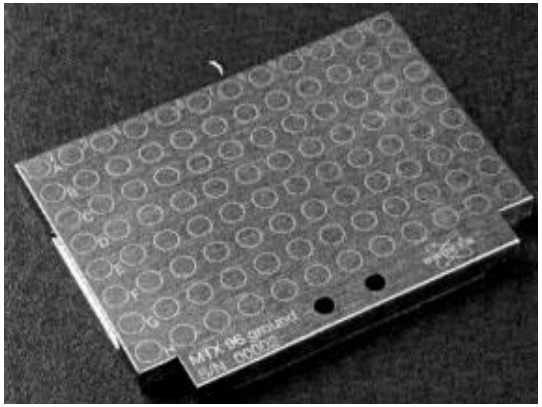
- Ensure early effective therapy
  - Time to effective therapy in sepsis is related to outcome
  - While most patients receive effective, broad spectrum therapy well before diagnostic test results are available this is not always the case
  - In some instances, targeted therapy has been proven superior to empiric effective therapy
    - For e.g., nafcillin vs vancomycin for MSSA bacteremia
  - In other cases, organisms with unusual or unexpected resistance (CRE for example) may not be adequately covered in an atypical host
- Antimicrobial stewardship
  - Narrower therapy earlier to reduce selective pressure for emergence of MDROs
  - Reduce drug cost

BMC Infect Dis. 2011 Oct 19;11:279.
Crit Care Med. 2006 Jun;34(6):1589-96.

The MALDI-TOF Revolution

Matrix Assisted Laser Desorption Ionization-Time Of Flight Spectrometry





Laser Desorption Ionization Matrix-Assisted

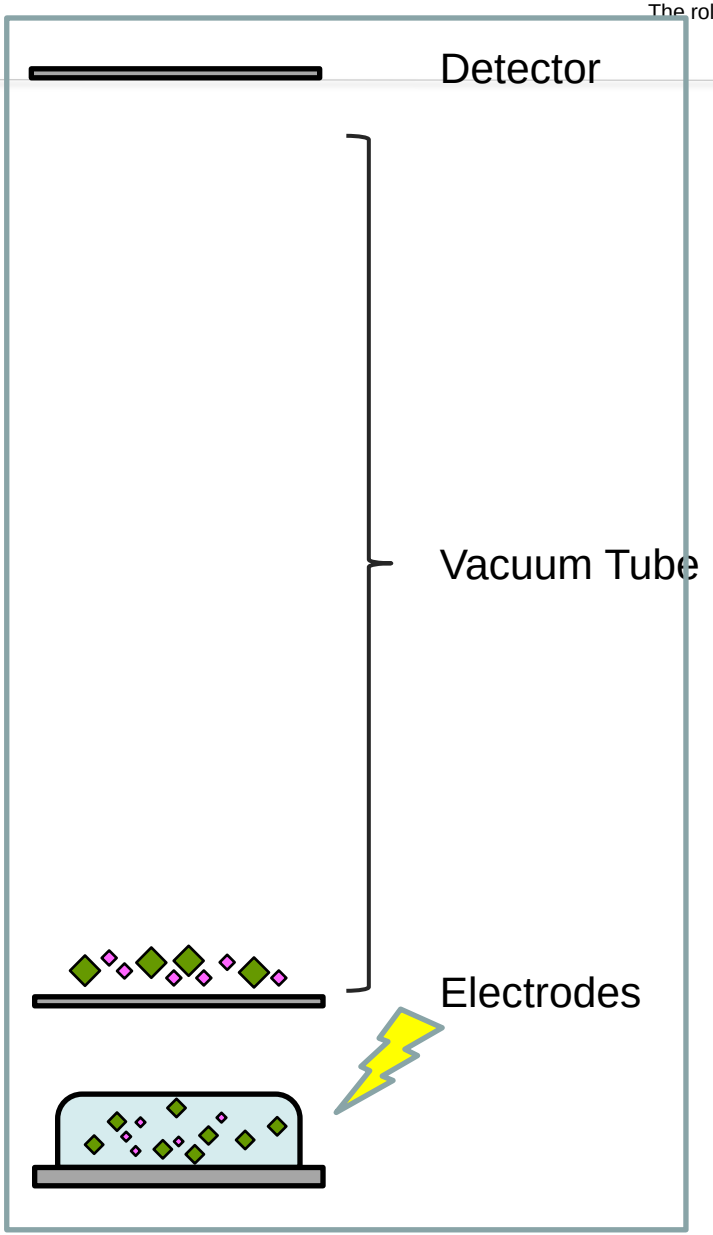


Figure & animation adapted from Bruker Daltonics

Mass Spectrometry

Time-of-Flight

Laser Desorption Ionization

Matrix-Assisted

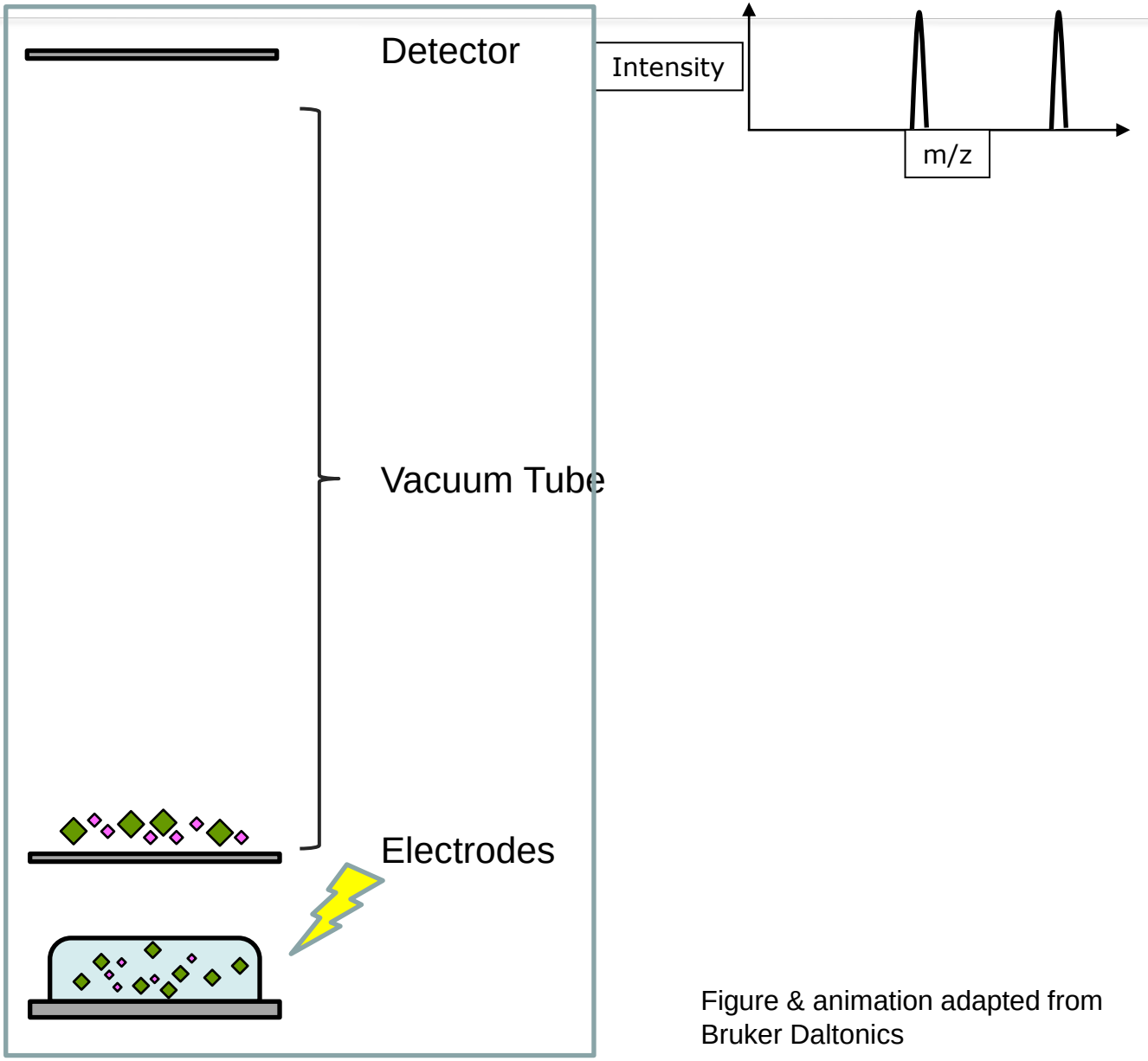
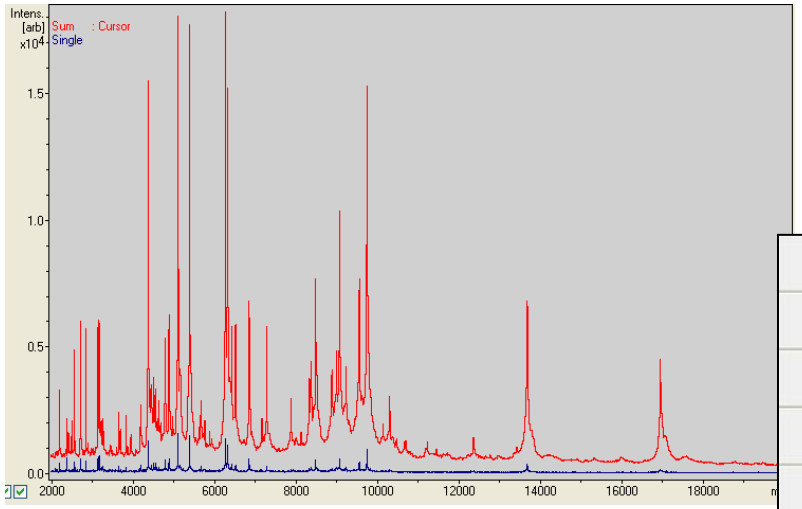


Figure & animation adapted from Bruker Daltonics

MALDI-TOF Spectral Analysis



Spectral Pattern

Rank (Quality)	Matched Pattern	Score Value	NCBI Identifier
1 (+++)	Streptococcus agalactiae 03_198 CTL	2.357	1311
2 (+++)	Streptococcus agalactiae 04_158 CTL	2.352	1311
3 (+++)	Streptococcus agalactiae 03_145 CTL	2.347	1311
4 (+++)	Streptococcus agalactiae V29 CTL	2.346	1311
5 (+++)	Streptococcus agalactiae 03_102 CTL	2.321	1311
6 (++)	Streptococcus agalactiae DSM 6784 DSM	2.244	1311
7 (++)	Streptococcus agalactiae CNR 10 CTL	2.237	1311
8 (++)	Streptococcus agalactiae DSM 2134T DSM	2.075	1311
9 (+)	Streptococcus agalactiae DSM 16828 DSM	1.986	1311
10 (-)	Streptococcus equi ssp zooepidemicus ATCC 43079T THL	1.542	40041

Organism Identification

MALDI-TOF Advantages

- Accuracy
  - Conventional 90-95%
  - MALDI-TOF >95%
- Speed
  - Biochemical 6-18hrs
  - MALDI-TOF 5 mins
- Cost
  - Conventional automated panel $5-10
  - MALDI TOF $0.25-0.50
- Combined with direct AST methods, actionable results may be generated 24-48 hrs earlier than conventional methods

Cherkaoui A, et al. JCM 2010;48:1169; Martiny D, et al. JCM 2012;50:1313;.

BioFire FilmArray BCID

Gram-positive bacteria

- *Enterococcus*
- *Listeria monocytogenes*
- ***Staphylococcus***
  - *Staphylococcus aureus*
- ***Streptococcus***
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*

Gram-negative bacteria

- *Acinetobacter baumannii*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- ***Enterobacteriaceae***
  - *Enterobacter cloacae* complex
  - *Escherichia coli*
  - *Klebsiella oxytoca*
  - *Klebsiella pneumoniae*
  - *Proteus*
  - *Serratia marcescens*

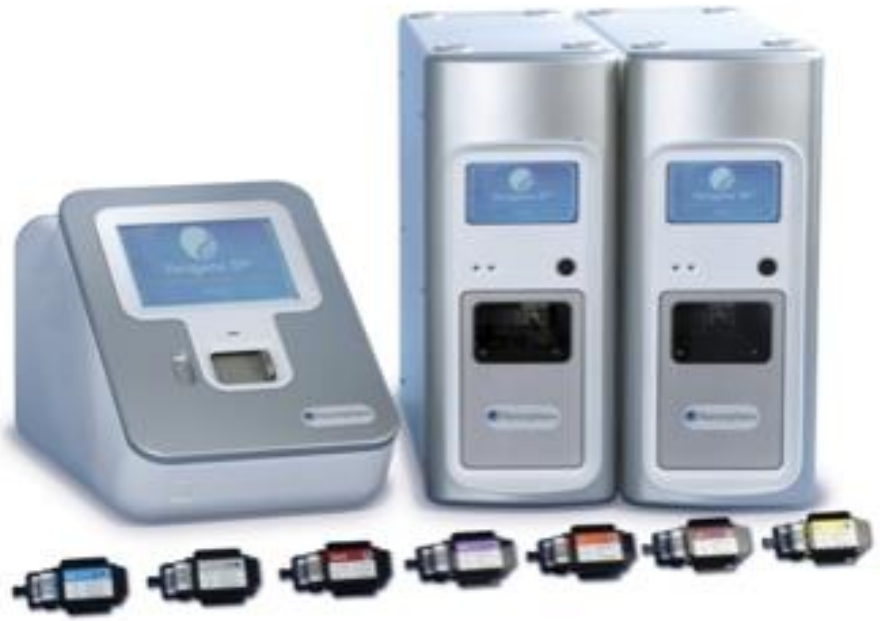
Yeast

- *Candida albicans*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*

Antimicrobial resistance genes

- *mecA* - methicillin resistance
- *vanA/B* - vancomycin resistance
- KPC - carbapenem resistance

Nanosphere Verigene BC-GN Panel



TARGETS
Species
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Pseudomonas aeruginosa
Serratia marcescens
Genus
Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Proteus spp.
Resistance
CTX-M (ESBL)
IMP (carbapenemase)
KPC (carbapenemase)
NDM (carbapenemase)
OXA (carbapenemase)
VIM (carbapenemase)

Nanosphere Verigene BC-GP Panel

TARGETS
Species
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus lugdunensis
Streptococcus anginosus Group
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Enterococcus faecalis
Enterococcus faecium
Genus
Staphylococcus spp.
Streptococcus spp.
Micrococcus spp.
Listeria spp.

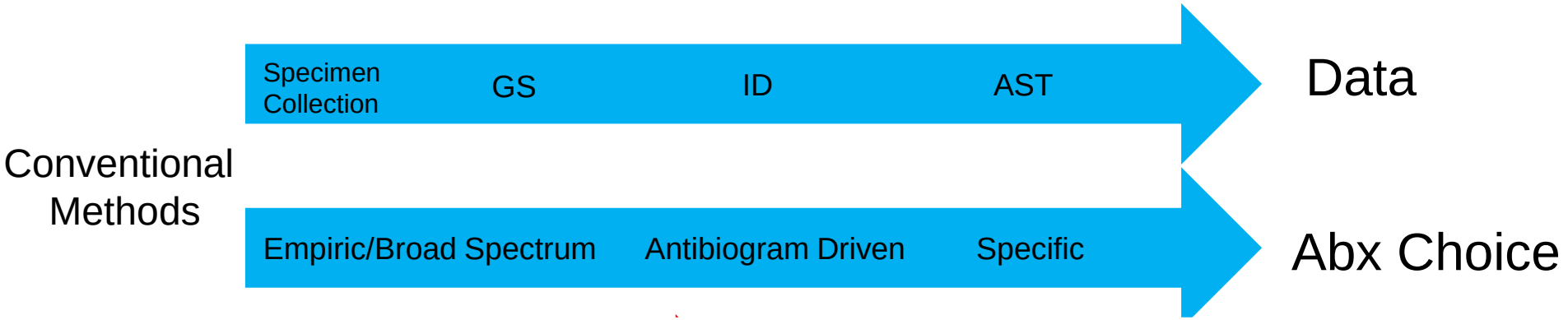
Resistance	
mecA (methicillin)	●
vanA (vancomycin)	●
vanB (vancomycin)	●

BC Panels/Single Target Assays Summary

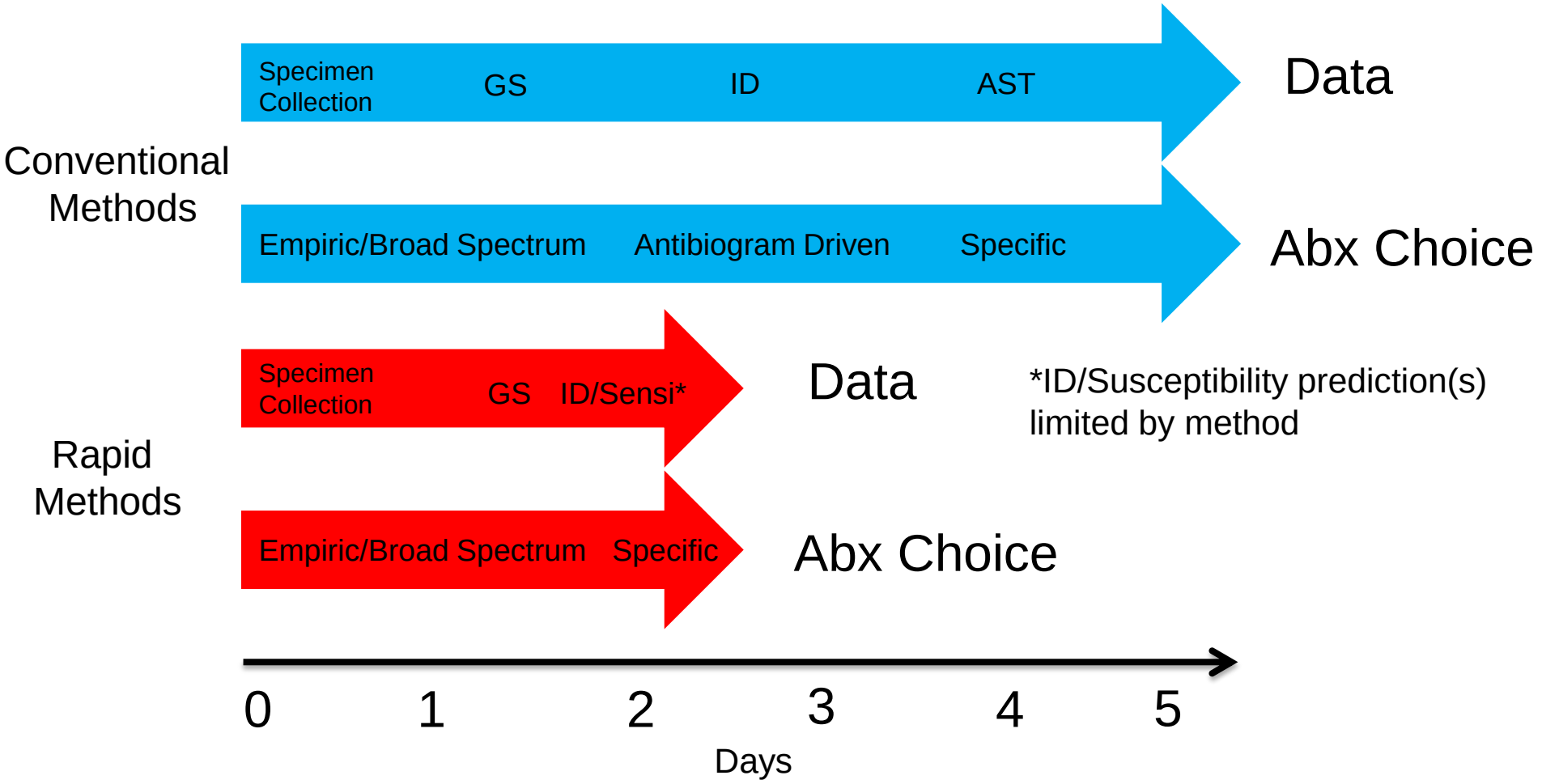
- All performed on broth from signal positive BC bottles
- TAT 1-3 h
- Hands on time minimal
- Bacterial, fungal targets + resistance genes
  - Resistance gene detection is not “assigned” to identified organisms in multiplex assays
- Generally excellent performance characteristics
  - 93-98% accuracy for identification
  - 93-100% agreement for resistance marker detection
  - Better agreement with single pathogen BCs vs polymicrobial cultures
  - Reduced time to ID/resistance marker detection

Rubach and Hanson, Open Forum Infect Dis 2015 2: ofv174
Diagnostic Microbiology and Infectious Disease 81 (2015) 153–157
Wojewoda CM, et al. JCM 2013;51:2072; Altun O et al J Clin Microbiol 2013; 51:4130

Clinical decisions based on laboratory data using conventional methods



Expected impacts of rapid ID and susceptibility prediction on antibiotic selection

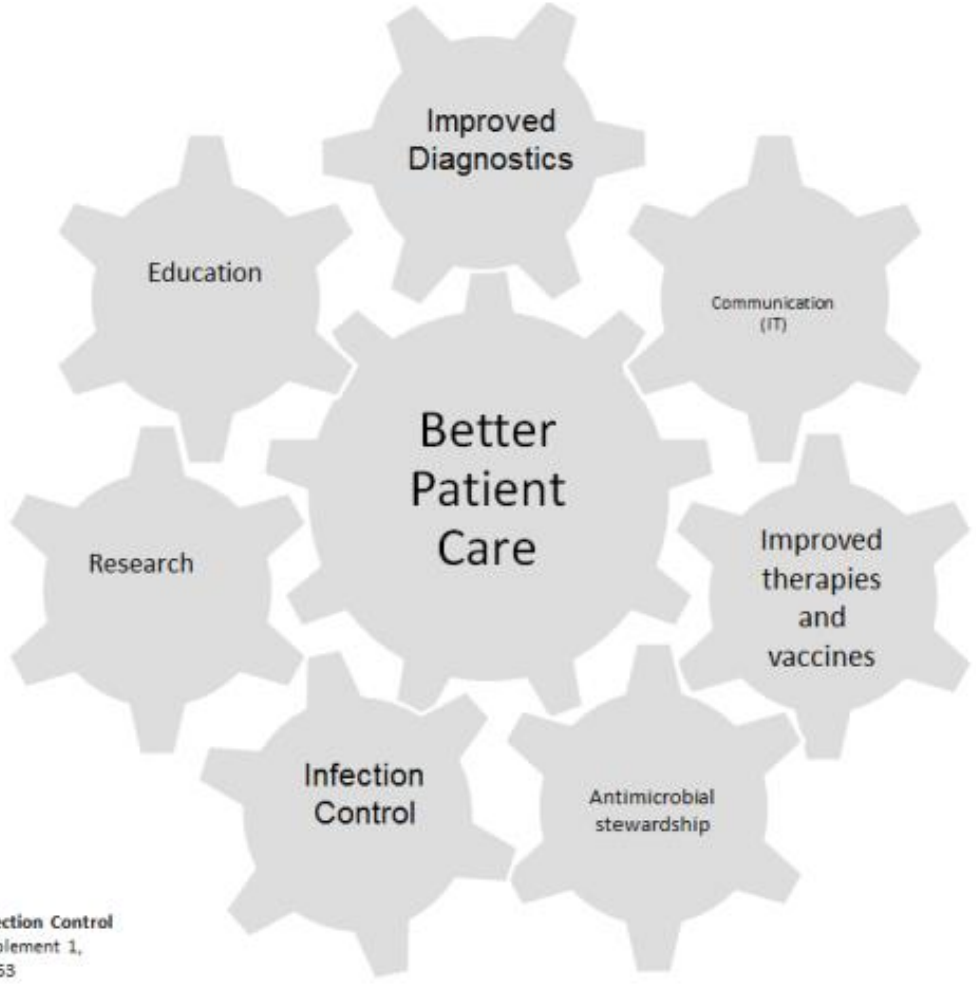


Multiplex BC Panels – Clinical Impact

- The intervention by an infectious disease and/or critical care pharmacist on 74 patients with enterococcal bacteremia led to a significant decrease in the mean time to appropriate antimicrobial therapy in the postintervention group (23.4 h; P = 0.005) compared with the preintervention group.
- Clinical and economic outcome evaluation on 156 patients showed that the mean time to switch from empiric vancomycin to cefazolin or nafcillin in patients with methicillin-susceptible *S. aureus* bacteremia was 1.7 days shorter (P = 0.002), the mean length of stay was 6.2 days shorter (P = 0.07), and the mean hospital costs were $21,387 less (P = 0.02) after PCR.
- Reductions in time to acceptable antibiotic overall (1.9 versus 13.2 h, respectively; P = 0.04) and time to appropriate antibiotic for patients with vancomycin-resistant Enterococcus (4.2 versus 43.7 h; P = 0.006) and viridans group Streptococcus (0.2 versus 7.1 h; P = 0.02).

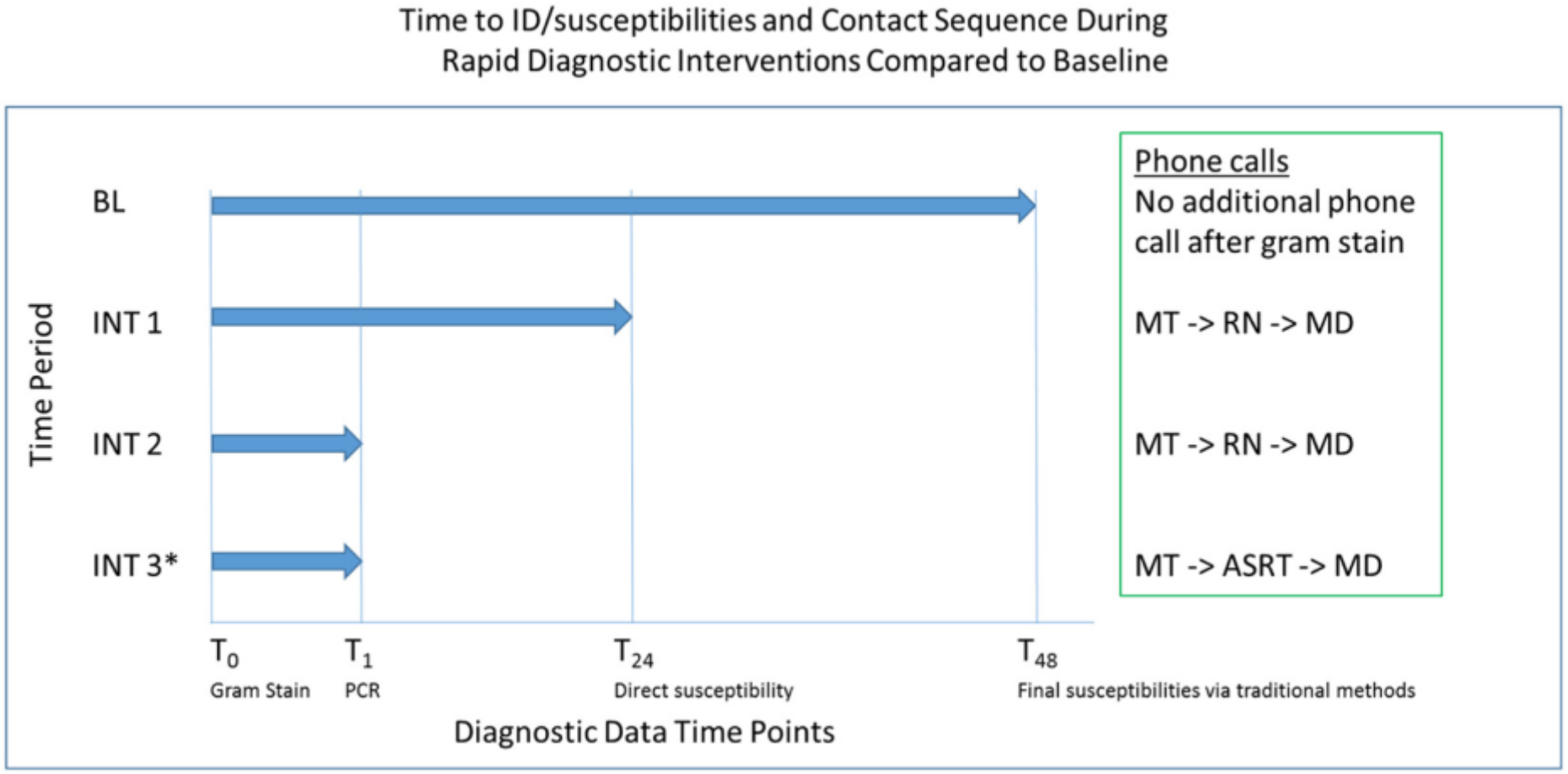
J Clin Microbiol 2013;51(12):4008–4011
J Clin Microbiol. 2015 Apr;53(4):1411-4
Clin Infect Dis 2010;51(9):1074–1080.

Communication of results is critical



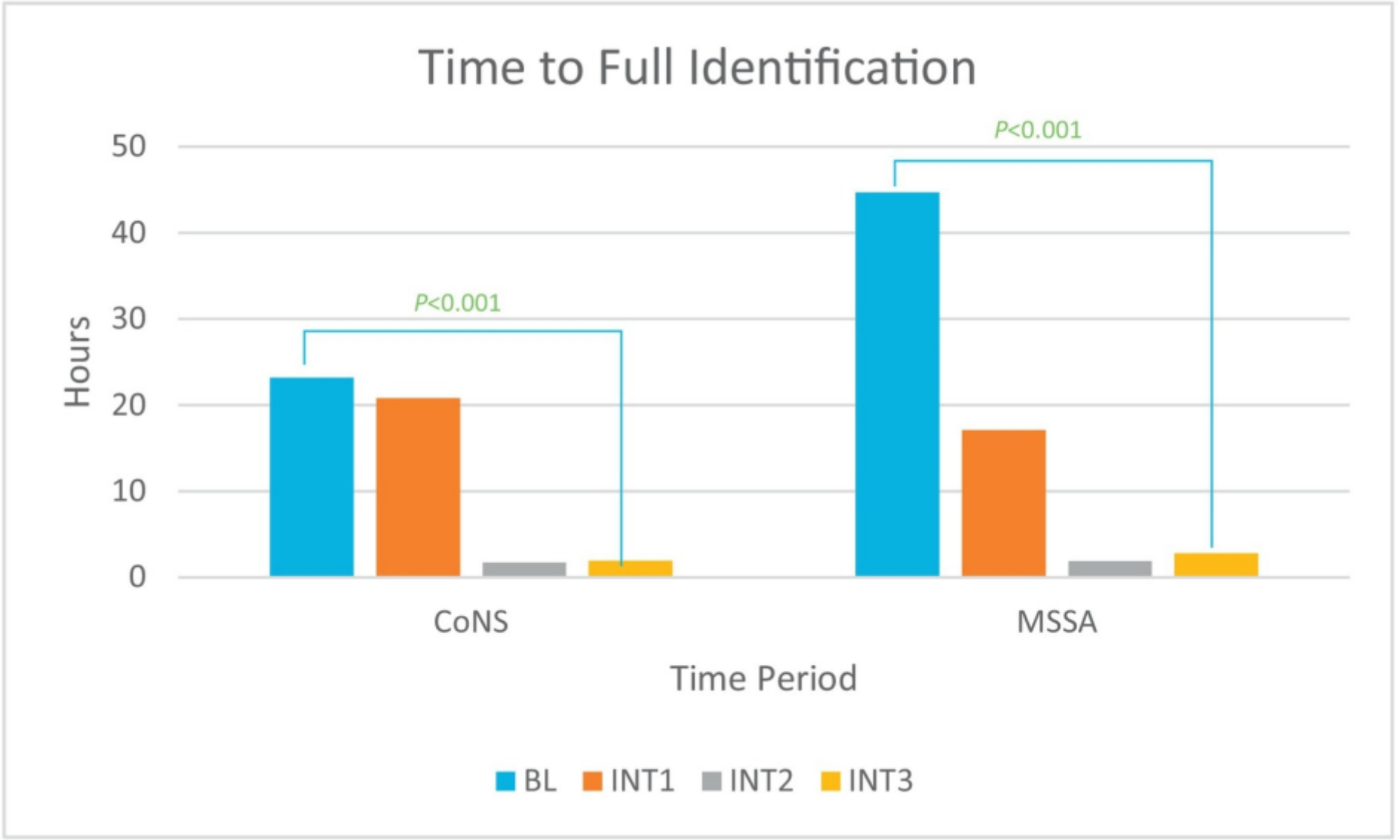
Adapted from:
American Journal of Infection Control
Volume 34, Issue 5, Supplement 1,
June 2006, Pages S55-S63

RWJUH Data – Rapid ID/AST of GPC in Clusters from Blood Cultures



Diagnostic Microbiology and Infectious Disease xxx (2018) xxx–xxx

RWJUH Data – Rapid ID/AST of GPC in Clusters from Blood Cultures



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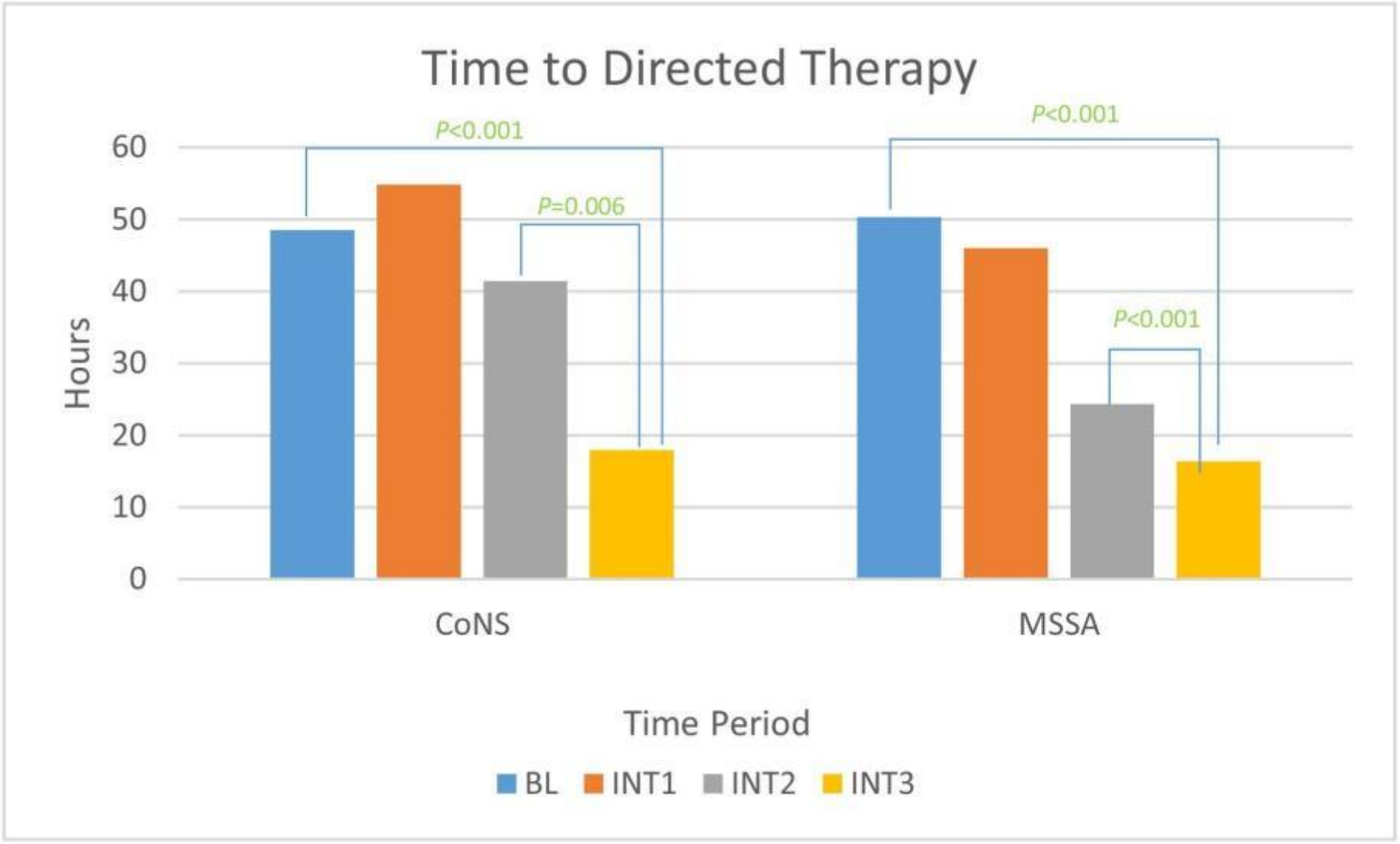
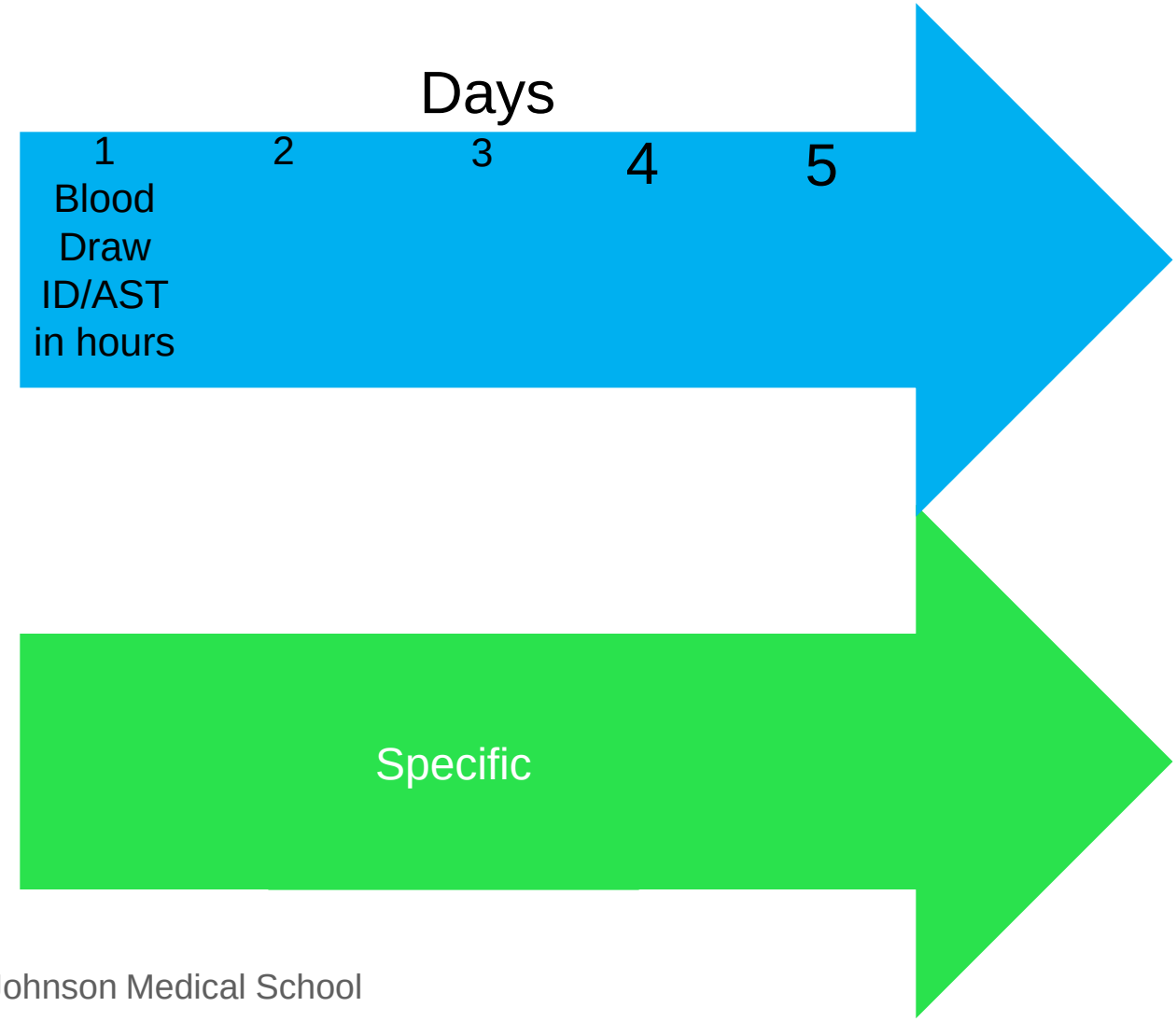


Diagnostic Microbiology and Infectious Disease xxx (2018) xxx–xxx

Direct Detection of Pathogens in Blood Specimens

Direct ID/(AST) from Blood Specimens



September 2014: FDA clearance of T2Dx Instrument and T2Candida Panel for direct detection of *Candida* species in human whole blood specimens

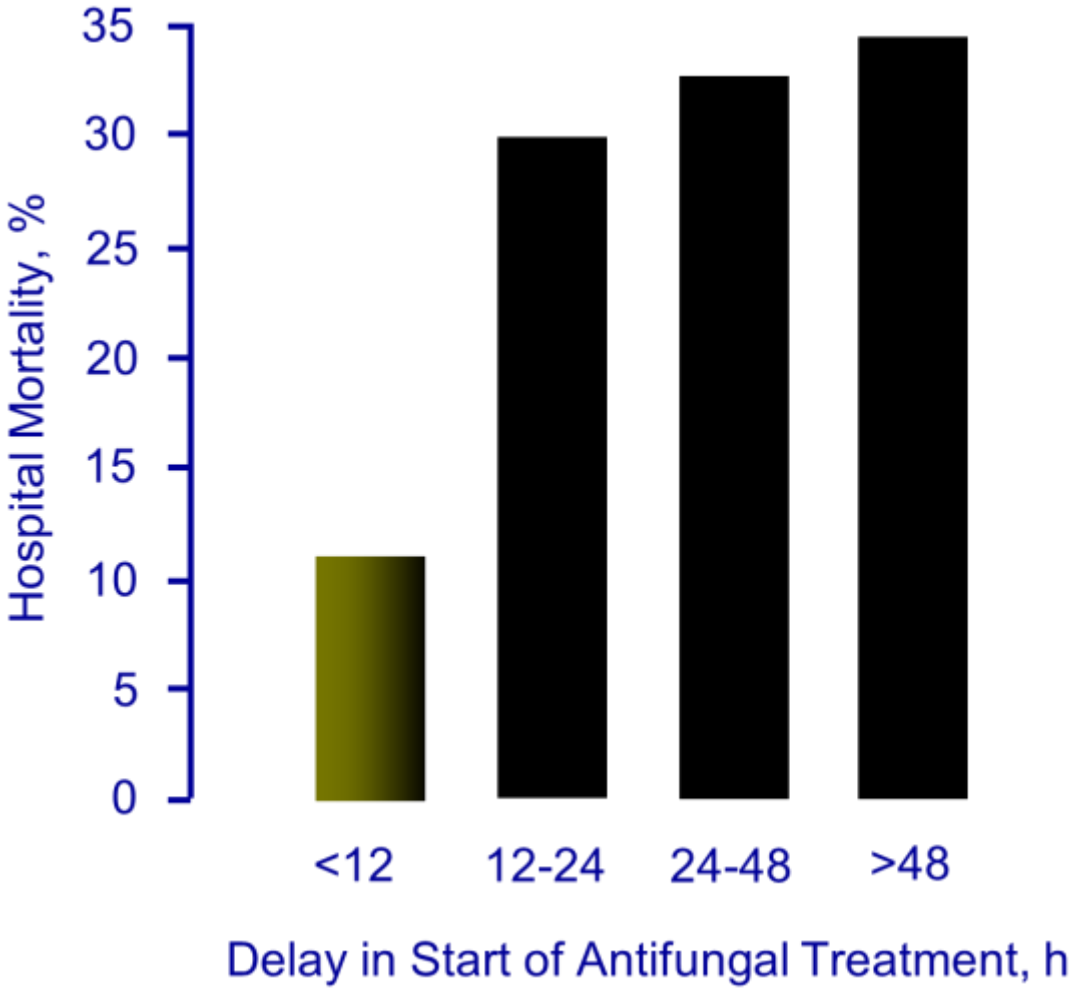
May 2018: FDA clearance of T2Bacteria Panel for detection of bacteria in whole blood samples of patients with suspected BSI

Candidemia Risk and Outcomes

- High Risk Patients
  - Abdominal surgery
  - Neutropenia
  - Transplant
  - Prematurity
  - Elderly
- Exposures that increase risk
  - ICU > 7 days
  - CVC
  - Dialysis
  - Abx
  - TPN
  - Colonization
- Outcomes
  - ~40% Mortality
  - Average excess LOS ~30d

Arch Intern Med. 1989;149:2349-53.
Clin Infect Dis. 2003;37:1172-7.

Appropriate and Timely Rx for Candida Infection is Critical



Morrell et al. ***Antimicrob Agents Chemother.*** 2005;49:3640-3645.

Avoiding Unnecessary Candida Coverage

- Reduced cost
- Reduced toxicity
- Reduced selective pressure for resistance

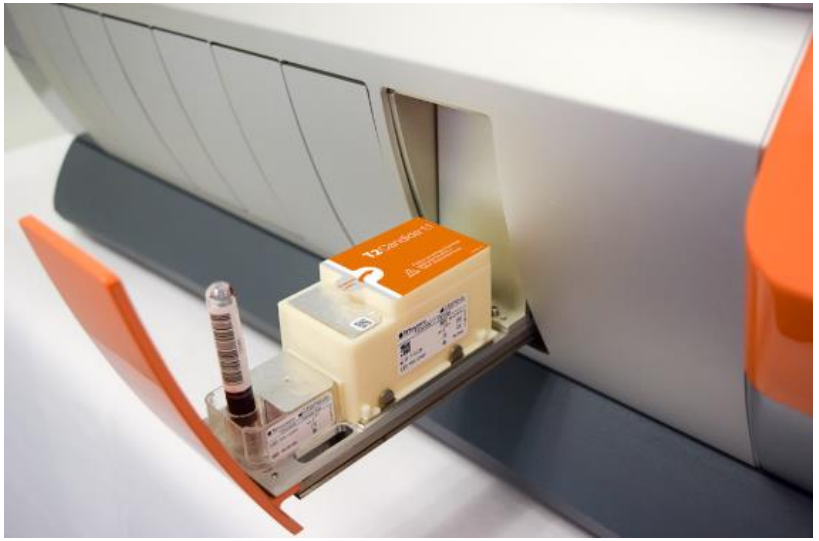
Advantage: Relatively Predictable Antibiogram for *Candida spp*.

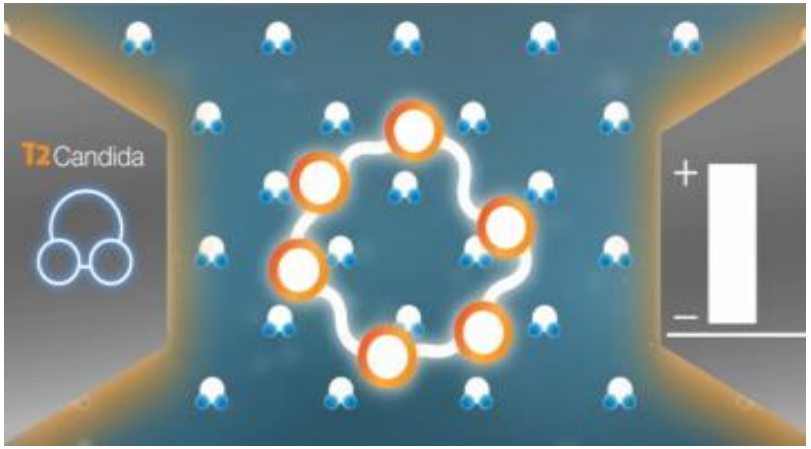
Candida spp.	AMB*	FLUC	ITRA	VOR	Echino-candins
C. albicans	S	S	S	S	S
C. tropicals	S	S	S	S	S
C. parapsilosis	S	S	S	S	S/?
C. glabrata	S / NS	S^{DD} / R	S^{DD} / R	S / NS	S / R
C. krusei	S / NS	R	S^{DD} / R	S	S

* No established breakpoints

S = susceptible; S^{DD} = susceptible-dose dependent; R = resistant; I = intermediate; NS, non-susceptible

T2 Candida Test



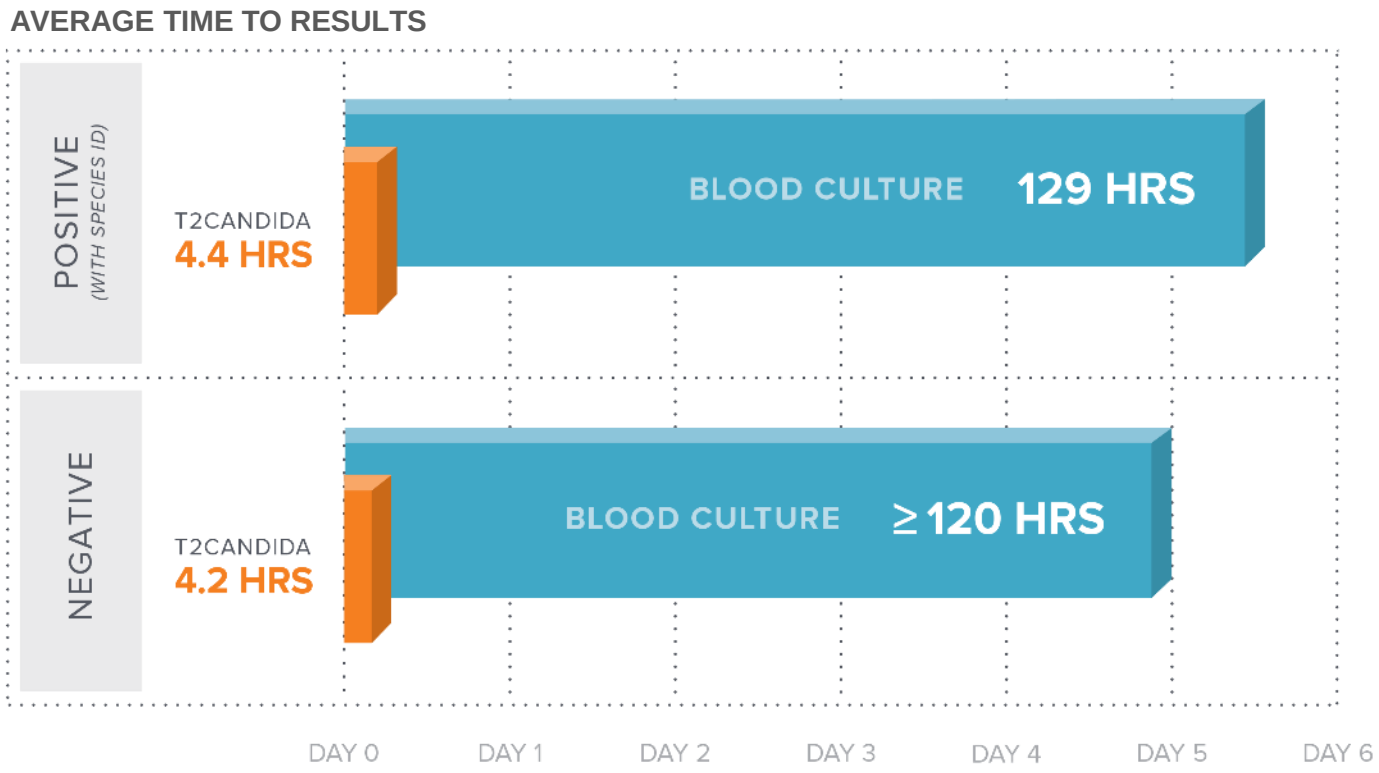


T2 Candida Result Reports

- Reports indicate
  - Negative for the 5 *Candida* species targets
  - *Candida albicans/tropicalis* detected
    - Recommend fluconazole
  - *Candida parapsilosis* detected
    - Use azole; higher MICs for echinocandins
  - *Candida krusei/glabrata* detected
    - Azole resistance/elevated MICs
    - Use echinocandin (e.g., micafungin)

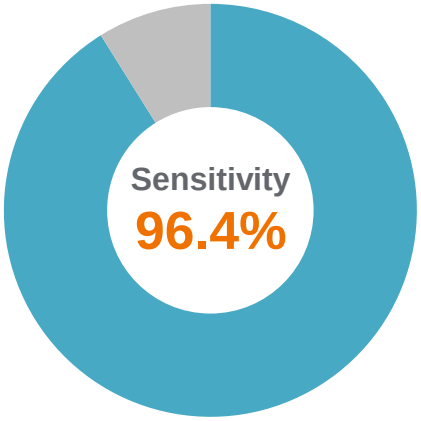
T2Candida – Time to Result

SPECIES-SPECIFIC RESULTS IN HOURS VERSUS DAYS



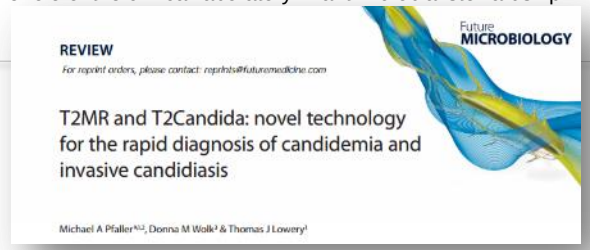
Mylonakis, E., Clancy, C.J., Ostrosky-Zeichner, L., et al. (2015). T2 Magnetic Resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. *Clinical infectious diseases,* 2015: ciu959.

T2Candida - Range of Negative Predictive Values



Prevalence of disease	Negative Predictive Value (NPV)
2%	99.93%
3%	99.89%
5%	99.81%
10%	99.60%
30%	98.47%

Source: Mylonakis et al. Clinical Infectious Diseases 2015 DOI: 10.1093/cid/ciu959.



Additional T2Candida Data Analysis

- In patients with proven and probable candidiasis:
  - T2Candida detected 53 of 55 cases. (96.4%)
  - Blood culture only detected 33 of 55 patients. (60%)

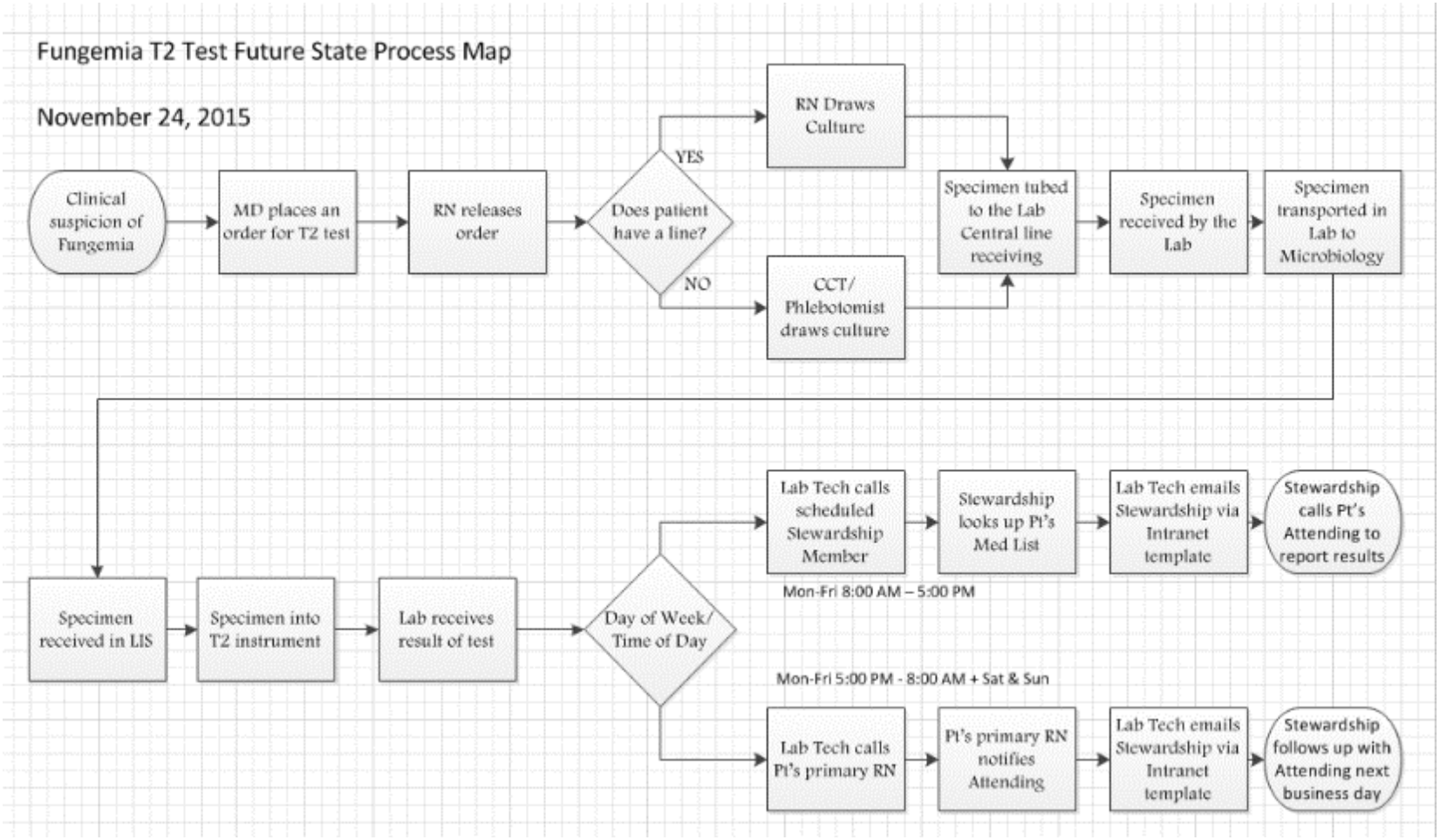
Summary of T2Candida detection of invasive candidiasis and candidemia			
Disease detected	**T2Candida**	**Blood culture**	**Total *Candida* infections**
Candidemia	31	33	33
Invasive candidiasis	12	0	12
Probable or suspected invasive candidiasis	10	0	10
Total cases	53	33	55
Sensitivity	**96.4% (53/55)**	**60.0% (33/55)**	

Pfaller, M. A., Wolk, D. M., & Lowery, T. J. (2016). T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. Future microbiology, 11(1), 103-117.

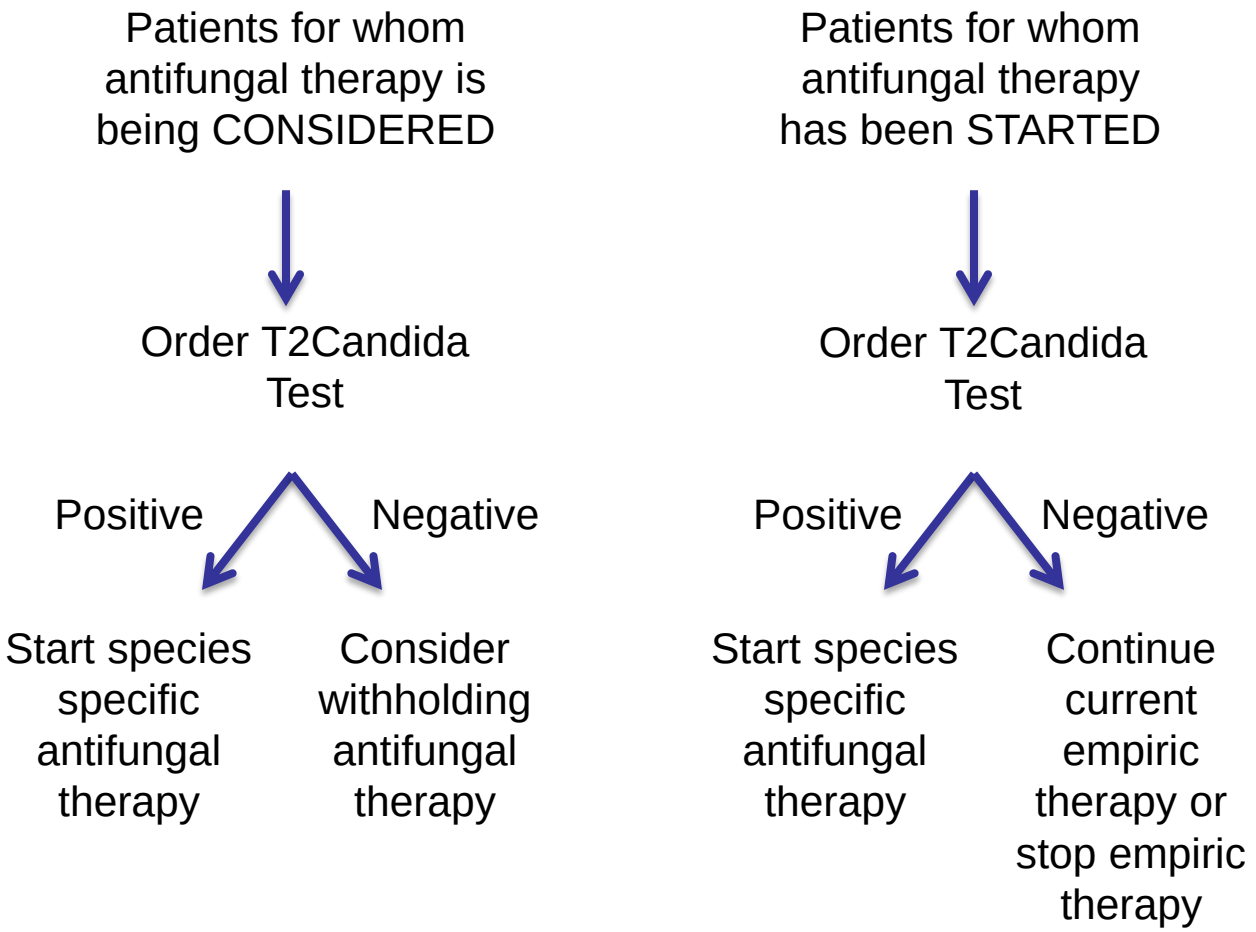
Potential Benefits of T2Candida Assay

- Screen all high-risk patients with T2Candida to ensure you are diagnosing *Candida* species within 3-5 hours
- Rule out negative patients rapidly and de-escalate to reduce exposure, cost and resistance

Future State Map



RWJUH T2Candidemia Algorithm



Implementation of T2Candida Test

- Live March 2016
- Target = Critically ill or immunocompromised patients
  - Medical/Cardiac/Surgical/Pediatric ICU
  - Oncology/Transplant
- Can be ordered by ID physicians on other units
- Education
  - Nursing (online training module)
  - Physicians (newsletter, presentations)
- Positive BC gram stain results called to pt's nurse (std)
- T2 results
  - Follow already established rapid diagnostic reporting scheme

Total Positive T2Candida Results

- From March 1, 2016 to April 1, 2018: **27 positive T2Candida patients**
  - **15** *C. albicans/C. tropicalis*
  - **10** *C. parapsilosis*
  - **4** *C. glabrata/ C. krusei*
    - 2 patients also positive for *C. albicans/C. tropicalis* and *C. parapsilosis*

- By location: ICU versus medical floors
  - **19** ICU patients
  - **8** medical floor patients
    - 4 oncology units

Positive T2Candida, Negative Blood Cultures

- Total of **15 unique patients** (up to March 1, 2018) with positive T2Candida and negative blood cultures – 11 ICU and 4 oncology units
  - **8** *C. albicans/C. tropicalis*, **6** *C. parapsilosis*, **1** *C. glabrata/C. krusei*

Characteristic	n (%)
Immunocompromised	8 (53)
Solid tumor	4 (27)
Hematologic malignancy	3 (20)
Kidney transplant	1 (7)
Median Charlson comorbidity index	6
Median Candida scores	9
Median SOFA score	6
14-day mortality	6 (40)
In-hospital mortality	8 (53)

Positive T2Candida, Negative Blood Cultures

- What were the clinical reactions to these results?

- Two patients on azole prophylaxis (hematologic malignancy) → both patients **escalated to echinocandin therapy**

- Remaining 13 patients not on any antifungal therapy at time of positive T2Candida results → **all started on antifungal therapy**

Negative T2Candida Results

- From March 1, 2016 to April 1, 2018: 233 negative T2Candida results
  - 143 ICU patients
  - 40 oncology units

- Rough data from ID fellow project (research credit: Rashi Sharma)
  - March 1, 2016 to March 1, 2017
  - **90** negative T2Candida results (only first result per patient)
    - **50** not on antifungal therapy
    - **40** on empiric/prophylactic antifungal therapy → **n=10** stopped, by median of 3 days

Negative T2Candida Results

- Reasons for continuing empiric antifungal therapy despite negative T2Candida result:
  - Standard-of-care antifungal prophylaxis for hematologic malignancy (**13**)
  - Positive blood culture results (**6**)
  - Continued empiric use for severe sepsis (**11**)

- Among **71** negative T2Candida/blood culture results who should not have routinely been on antifungal therapy, **60** were either not started or discontinued antifungals based on T2Candida result
- Among **36** surgical ICU patients, **19** were not given empiric antifungals

Rough Estimate of Cost Saving Implications

- Cost per test at RWJ= $220
- Estimated cost of micafungin = $70/day

- $220 x 90 patients = **$19,800**
- 14-day course of micafungin: ($980 x 50) + ($770 x 10) = **$56,700** cost saving on drug costs → $56,700 - $19,800 = **$36,900** total cost saving
- 7-day course of micafungin: ($490 x 50) + ($280 x 10) = **$27,300** cost saving on drug costs → $27,300 - $19,800 = **$7,500** total cost saving

Key Consideration in Clinical Practice

- T2Candida does not detect all pathogenic *Candida* species
  - Need for concomitant blood cultures
- Cases of negative T2Candida but positive blood cultures (before or after T2Candida result)
  - *C. albicans*, *C. glabrata*, *C. parapsilosis*
  - *C. lusitaniae*
  - *C. guilliermondii*
  - *C. auris*
- Most patients were admitted to the ICU or an oncology unit

Conclusions

- Clinical laboratories play an important role in antimicrobial stewardship and should be active participants in any ASP
- New molecular diagnostic assays that include susceptibility prediction components continue to enter the market and represent an important tool for antimicrobial stewardship
- While these assays almost always demonstrate excellent analytical performance characteristics, the optimization of clinical impact must be carefully considered, will require a team based approach in most cases and will likely vary significantly among institutions