Alphabet Soup of Bacteremias & Fungemias

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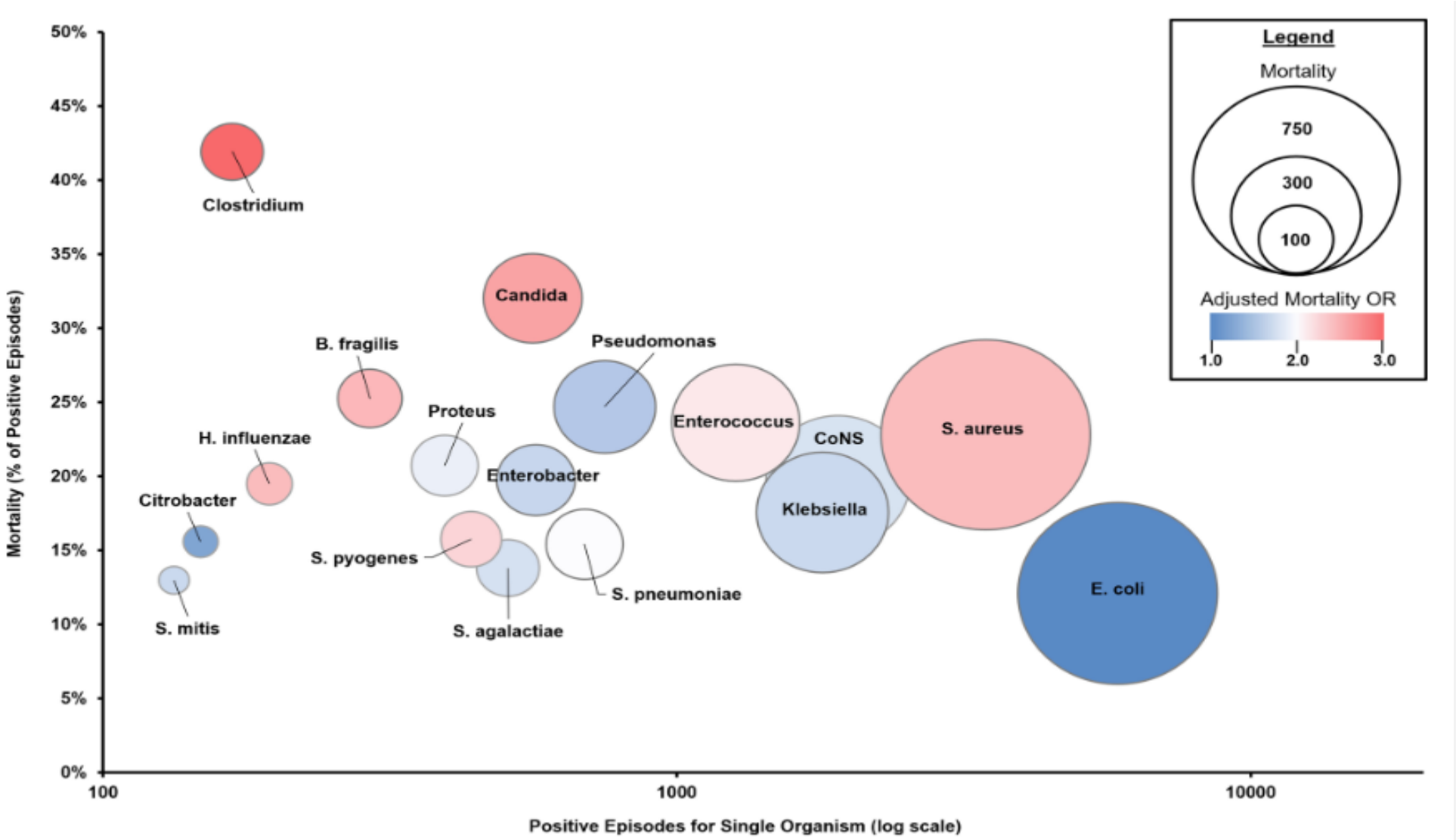
Learning Objectives

Describe the clinical significance, incidence, and mortality of bacteremia and fungemia.

Identify key stakeholders and summarize Moffitt's workflow for positive blood cultures.

Apply institutional guidance for the management of bacteremia/fungemia to a patient case.

Incidence and Lethality of Bacteremia



Verway M, et al. 2022. J Clin Microbiol 60:e02429-21

Clinical Significance of Bacteremia/Fungemia

Incidence of bloodstream infections

- Incidence of 150 per 100,000 population
- Approximately 30-70% of septic patients have bacteremia

Mortality associated with bloodstream infections

- 17% mortality at 30 days
- Ex: MRSA (22.8%) vs E. coli (12.1%) vs Candida spp (47%)

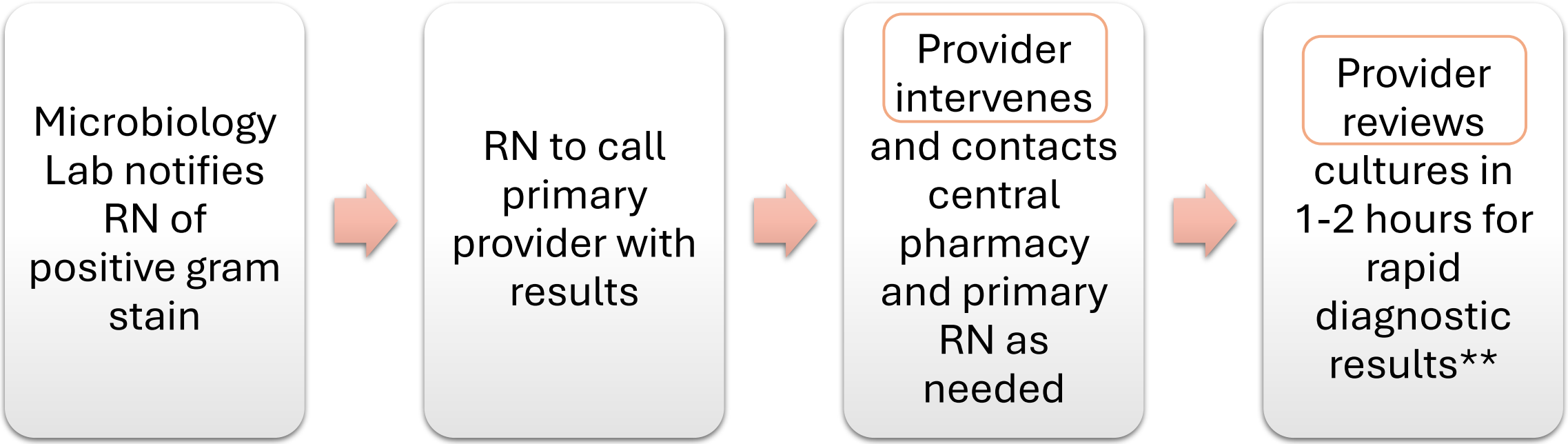
For patients with serious infections (bloodstream infections and sepsis), shortening time to effective therapy has been associated with decreased mortality

Cheng MP. Ann Intern Med. 2019 Oct 15;171(8):547-554.
Coburn B. JAMA. 2012 Aug 1;308(5):502-11.
Rhee C. JAMA Netw Open. 2024 Jun 3;7(6):e2418923
Verway M, et al. 2022. J Clin Microbiol 60:e02429-21

Key Stakeholders

- RNs
- Microbiology technicians
- Providers (APPs, MDs)
- Pharmacists

Workflow for Positive Blood Culture Results



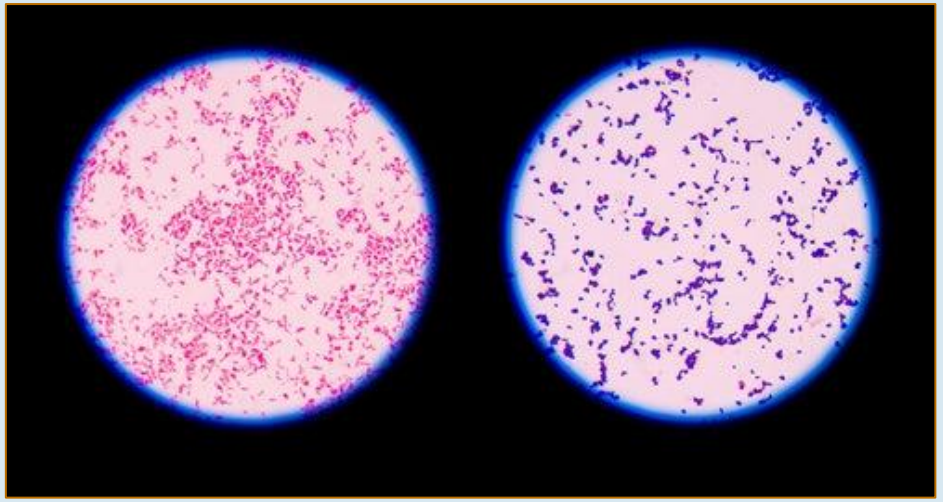
**Please note the rapid diagnostic result may be delayed if the culture was drawn at Moffitt McKinley Hospital (MMH) due to courier time constraints.

WHAT IS THE FIRST STEP ONCE THE SAMPLE REACHES THE MICRO LAB?

BACT/ALERT® VIRTUO®
bioMerieux

aerobic blood culture incubator that detects growth by monitoring carbon dioxide production using fluorescent substrates

10^8 – 10^9 CFU/mL



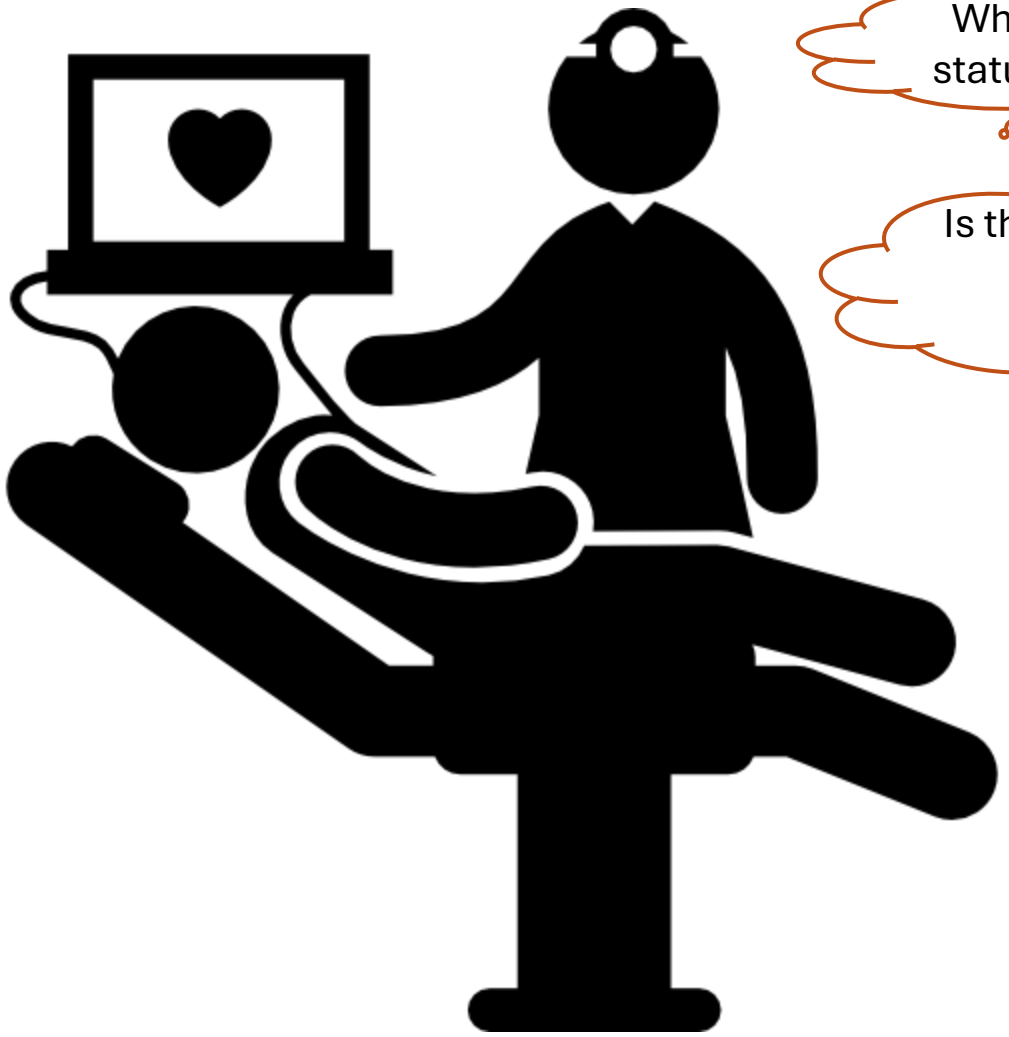
Gram stain

Safranin (pink) vs crystal violet (purple)

Gram - vs Gram + organisms

*Time: 5-10 minutes

At the Time of Positive Gram Stain



What is the clinical status of the patient?

- Hemodynamically stable
- Septic vs septic shock

Is the patient currently on therapeutic antibiotics?

- If yes, how long have they been on current antibiotics?
  What agent are they on?

Does the patient have a history of infections (any positive culture data) within the last 3 months especially?

Do I need to make changes now or is the patient stable enough to wait for more information from rapid diagnostics and make changes then?

Introducing our patient, RV

34 YOM PMH poorly differentiated carcinoma with spinal mets. The patient presents to Urgent Care with complaints of fatigue, shortness of breath, and cough. The patient had a recent hospital admission and therefore was empirically started on hospital-acquired pneumonia coverage by the admitting team with vancomycin and cefepime.

The overnight RN calls you to notify you they received a critical result from microbiology that blood cultures are growing gram positive cocci in clusters.

Pre - February 28, 2024 11:20 EST -
Blood culture bottle gram stain shows: Gram Positive Cocci in clusters
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Positive Blood Culture Gram Stain
Called report to and read back by RN name (location) on 2/28/2024 11:19:49 by Micro tech

Gram Positive

Potential for contaminant

Acid fast bacilli (AFB) --> Consult ID

Could be a contaminant if any of the following are true:

- Clinically stable without signs/sx of infection
- Growth in only one set
- Prolonged time to growth > 48 hours

- If suspected contaminant, consider holding off on antibiotics and **follow-up rapid diagnotic result** (see below for guidance).

Any history of gram positive infections?

Consider **vancomycin** as the general drug-of-choice

Gram Negative

Should never be considered a contaminant

Any history of resistant gram negative infections in last 3 mos?

- Prior *Proteus, E. coli,* or *Klebsiella oxytoca/pneumoniae* with ceftriaxone non-susceptibility (ESBL) --> meropenem
- Prior *Enterobacter cloacae, Citrobacter fruendii,* or *Klebsiella aerogenes* (AmpC) --> cefepime

Is the patient neutropenic?

- If neutropenic, consider higher possibility of *Pseudomonas* spp --> cefepime, piperacillin-tazobactam, or meropenem

Is the patient septic?

- If patient is septic or in septic shock, consider addition of tobramycin to core beta-lactam

See decision tree for further guidance

Fungal

Should never be considered a contaminant

Any history of fungal infections?

Has the patient been on antifungal prophylaxis?

- If yes, consider consulting Infectious Diseases on call.
- If yes, do not use the same agent the patient was receiving as prophylaxis for treatment given the potential for breakthrough.

Consider **micafungin** as the drug-of-choice for yeast; **liposomal amphotericin B** for mold

Gram Positive

Potential for contaminant

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Consider **vancomycin** as the general drug-of-choice

Common Blood Culture Contaminants

Gram Positive Cocci in Clusters	Gram Positive Rods

• Coagulase-negative *Staphylococcus* species (not including *lugdunensis*)
  • *Staphylococcus capitis*
  • *Staphylococcus caprae*
  • *Staphylococcus epidermidis*
  • *Staphylococcus haemolyticus*
  • *Staphylococcus hominis*
  • *Staphylococcus pseudintermedius*
  • *Staphylococcus simulans*
  • *Staphylococcus warnei*
  • Etc
• *Micrococcus luteus*
	• *Bacillus* species (not including *anthracis*)
	• *Corynebacterium* species
	• *Cutibacterium (Propionibacterium) acnes*

Bekeris LG, et al. 2005. *Arch Pathol Lab Med* 129:1222–1225.
CLSI. 2022. In *CLSI guideline M47*, 2nd Edition.
Doern G, et al. 2019. *Clin Microbiol Rev* 33:00009–00019
Leber AL, Burnham C-AD. 2023. *Clinical Microbiology Procedures Handbook*, 5th ed.

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Any history of resistant gram negative infections in last 3 mos?

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- Prior *Enterobacter cloacae, Citrobacter fruendii,* or *Klebsiella aerogenes* (AmpC) --> cefepime

Is the patient neutropenic?

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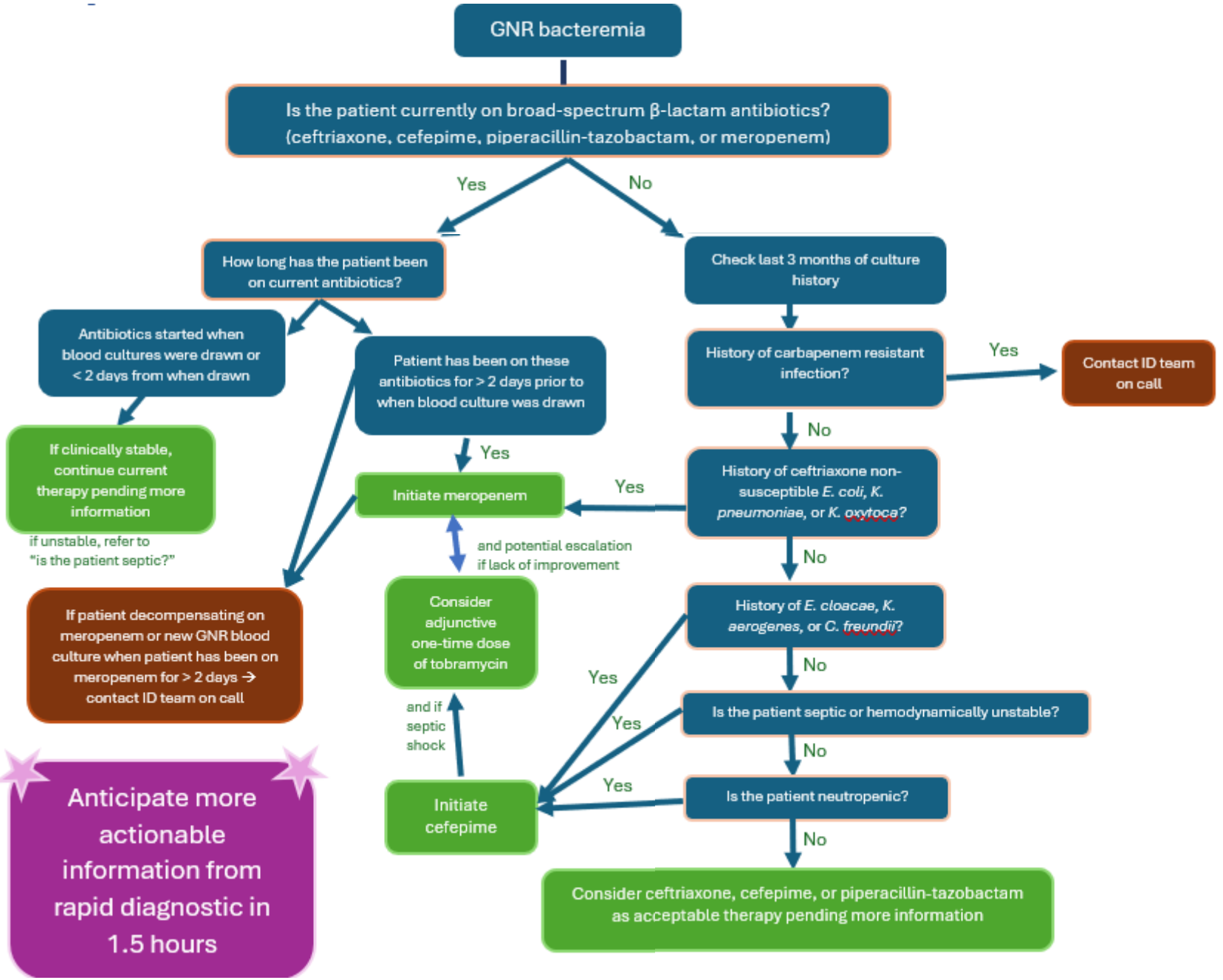

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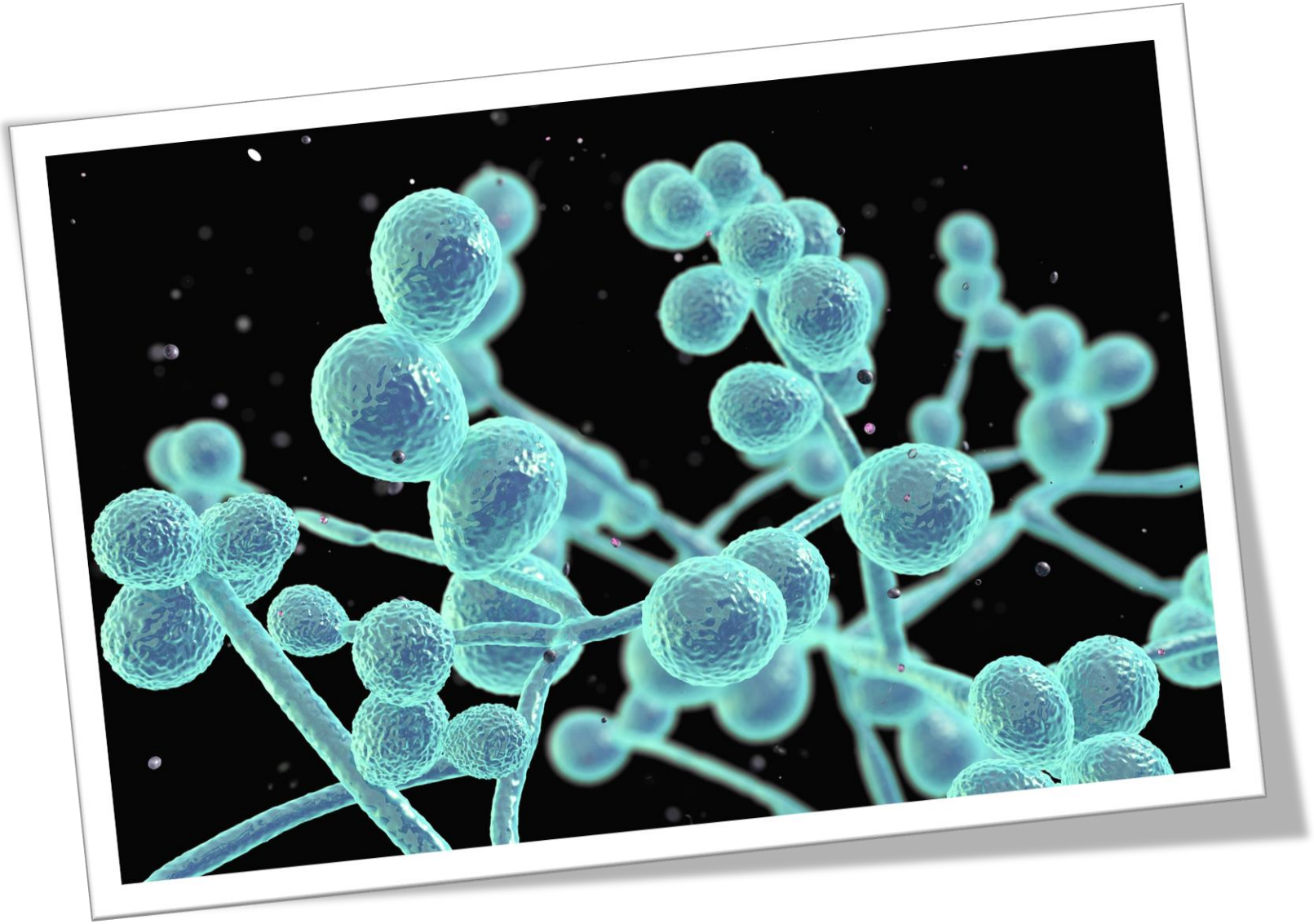


BACT/ALERT® VIRTUO®
bioMerieux

BIOFIRE® BCID2 Panel

*Time: 60-90 minutes

BioFire BCID2 Panel Targets

BioFire BCID2 Panel Targets		
Gram Positive	**Yeast**	**Gram Negative**
Enterococcus faecalis *Enterococcus faecium* *Listeria monocytogenes* *Staphylococcus* spp.* *Staphylococcus aureus* *Staphylococcus epidermidis** *Staphylococcus lugdunensis* *Streptococcus* spp. *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	*Candida albicans* *Candida auris* *Candida glabrata* *Candida krusei* *Candida parapsilosis* *Candida tropicalis* *Cryptococcus* spp *(C. neoformans/C. gattii)*	*Acinetobacter calcoaeceticus-baumannii* complex *Bacteroides fragilis* *Enterobacterales* *Enterobacter cloacae* complex *Escherichia coli* *Klebsiella aerogenes* *Klebsiella oxytoca* *Klebsiella pneumoniae* group *Proteus* spp *Salmonella* spp *Serratia marcescens* *Haemophilus influenzae* *Neisseria meningitidis* *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*
Antimicrobial Resistance Genes: *mecA/C* *mecA/C* and MREJ *vanA/B*	**No Antifungal Resistance Genes**	**Antimicrobial Resistance Genes:** CTX-M IMP KPC OXA-48-like NDM VIM
*Assess for contaminant with consideration for time to growth, number of sets/bottles, source of culture (central line vs peripheral), and clinical status of patient		

At the Time of Rapid Diagnostic Results

Identification and resistance genes result in **1.5 hours** after positive gram stain

It is imperative to <u>check back</u> for rapid diagnostic results

There will <u>NOT</u> be an additional page from micro with the rapid diagnostic result unless positive detection of resistance genes

Do <u>NOT</u> forget to click the **"Next" button** in cases where multiple blood cultures sets were documented as being drawn at the same time

RV Patient Case Continued

You check back and see that the gram positive cocci in clusters has updated now as *Staphylococcus aureus* – by PCR – mecA/C and MREJ not detected.

The patient is on vancomycin and cefepime – would you like to make changes to therapy?

A. Discontinue vancomycin, continue cefepime
B. Discontinue cefepime, continue vancomycin
C. Discontinue vancomycin and cefepime; initiate cefazolin 2g IV Q8H
D. Discontinue vancomycin and cefepime; consider consistent with contamination

GRAM POSITIVE GENOTYPIC RESISTANCE

Gene	Applies to which organisms?	Mechanism	Drug of Choice if Detected
mecA	*Staphylococcus aureus, epidermidis,* and *lugdunensis*	Confers methicillin resistance via encoding expression of penicillin binding protein 2a (PBP2a)	Vancomycin
mecC			
MREJ	*Staphylococcus aureus* only	MRSA; Staphylococcal cassette chromosome mec element (SCCmec) right extremity junction	Vancomycin
vanA	*Enterococcus faecium* >>>>> *Enterococcus faecalis*	VRE; Confers vancomycin resistance by building new precursors of the peptidoglycan cell wall to prevent glycopeptides from acting on the bacterial cell	Linezolid, Daptomycin
vanB			

Other Gram-Positive Examples

Vancomycin-resistant *Enterococci* (VRE)

BioFire →

Gram stain →

```
Pre - February 15, 2024 4:45 EST -
Enterococcus faecium by PCR - vanA/B     Detected - Susceptibility to follow
-----------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by:  RN name (location)        on  2/15/2024 02:23:48 by  Micro tech


Pre - February 15, 2024 2:24 EST -
Blood culture bottle gram stain shows: Gram Positive Cocci in pairs & chains
-----------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by: RN name (location)        on  2/15/2024 02:23:48 by Micro tech


Pre - February 14, 2024 18:01 EST -
No Growth < 24 Hours
```

Initiate linezolid or daptomycin ASAP

Management of *Enterococcal* Bacteremia

E. faecalis is 99.8% sensitive to ampicillin
vs.
E. faecium is 29% ampicillin sensitive, 52% vancomycin sensitive
Genotypic data can further guide us…

Gram Positive Organisms		
Target Detected	**Optimal Empiric Therapy***	**Acceptable Empiric Coverage Overnight***
*Enterococcus faecalis*** *vanA/B* NOT detected	Ampicillin	Ampicillin-sulbactam, daptomycin, linezolid, piperacillin-tazobactam, vancomycin
*Enterococcus faecalis*** ***vanA/B* detected**	Daptomycin, Linezolid	
*Enterococcus faecium*** *vanA/B* NOT detected	Vancomycin	Daptomycin, linezolid
*Enterococcus faecium*** ***vanA/B* detected**	Daptomycin, Linezolid	

Other Gram-Positive Examples

Streptococcus spp

- In our patient population at Moffitt, this is most commonly viridans group *Streptococci* like *Streptococcus mitis/oralis*

ID

BioFire

Gram stain

```
Pre - February 23, 2024 10:09 EST -
Streptococcus mitis/Streptococcus oralis - Susceptibility to follow
------------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by RN name (location)        2/22/2024 11:38:29 by  Micro tech


Pre - February 22, 2024 13:02 EST -
Streptococcus species - not S. agalactiae, S. pneumoniae, or S. pyogenes by PCR
------------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by RN name (location)        2/22/2024 11:38:29 by  Micro tech


Pre - February 22, 2024 11:38 EST -
Blood culture bottle gram stain shows: - Gram Positive Cocci in pairs & chains
------------------------------------------------------------
```

Moffitt's 2025 *Streptococcus mitis/oralis* Susceptibility Trends

Organism Name ▲	Streptococcus mitis/Streptococcus oralis		
Drug Name ▲	% Susceptible	Isolate # (Susceptible)	Test by Group
Ampicillin	68%	41	60
Cefepime	91%	51	56
Cefotaxime	91%	53	58
Ceftriaxone	93%	56	60
Clindamycin	72%	42	58
Daptomycin	100%	1	1
Levofloxacin	30%	18	60
Linezolid	100%	59	59
Meropenem	100%	1	1
Moxifloxacin	54%	31	57
Penicillin	50%	30	60
Tetracycline	45%	26	58
Tigecycline	100%	57	57
Vancomycin	100%	60	60

Data extracted from Clarion ®

Other Gram-Positive Examples

Staphylococcus spp

- Because it was not further identified as *aureus*, *epidermidis*, or *lugdunensis*, this means this is some other coagulase-negative *Staphylococcus* species (CONS).
- Assess for possible contaminant.

ID →

```
Pre - November 06, 2025 12:39 EST -
Staphylococcus hominis (coagulase negative) - Susceptibility to follow
```

BioFire →

```
Pre - November 05, 2025 12:22 EST -
Staphylococcus species - not S. aureus, S. epidermidis or S. lugdunensis by PCR
```

Gram stain →

```
Pre - November 05, 2025 11:04 EST -
Blood culture bottle gram stain shows: Gram Positive Cocci in clusters
------------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by: K. Knight, RN (5S) on  11/5/2025 at 11:03:49 by AMQ
```

Most CONS are methicillin-resistant

Introducing our patient, KS

50 YOM PMH invasive muscle bladder cancer s/p nerve sparing radical cystoprostatectomy and b/l pelvic lymph node dissection and ileal neobladder formation on 12/27/2023 who presented to the Urgent Care with complaints of chills and rigors x 3 days.

The patient is admitted to MMH IHM A.

The RN calls you to notify you they received a critical result from microbiology that blood cultures are growing gram negative rods.

Pre - September 22, 2025 16:47 EDT -
Blood culture bottle gram stain shows: Gram Negative Rods

Positive Blood Culture Gram Stain
Called report to and read back by: RN name (location) 9/22/2025 at 1645 by Micro tech

KS Patient Case Continued

BioFire →

```
Pre - September 22, 2025 19:07 EDT -
Escherichia coli by PCR - CTX-M Detected. Suggestive of +ESBL resistance mechanism.  Recommend
initiation of carbapenem therapy, such as meropenem, and Infectious Diseases consult.
```

Gram stain at MCC →

```
Pre - September 22, 2025 17:51 EDT -
Blood culture bottle gram stain shows: Gram Negative Rods
-------------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by: RN R. Fabijanczuk. ICU. 9/22/2025 at 1645 by DD.
```

Gram stain at MMH →

```
Pre - September 22, 2025 16:47 EDT -
Blood culture bottle gram stain shows: Gram Negative Rods
-------------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by: RN R. Fabijanczuk. ICU. 9/22/2025 at 1645 by DD.
-------------------------------------------------------------
To be reviewed.
```

GRAM NEGATIVE GENOTYPIC RESISTANCE

Gene	Mechanism	Drug of Choice
CTX-M	ESBL (extended spectrum beta-lactamase); Confers resistance to penicillins, cephalosporins, and monobactams	Meropenem
IMP, NDM, VIM	Metallo-beta-lactamase (carbapenemase) – confers resistance to penicillins, cephalosporins, and carbapenems	Ceftazidime-avibactam + aztreonam Cefiderocol
KPC	Carbapenemase – Confers resistance to penicillins, cephalosporins, monobactams, and carbapenems	Meropenem-vaborbactam
OXA (OXA-23 and OXA-48)		Ceftazidime-avibactam

Extended-Spectrum β-lactamases (ESBLs)

Common Pathogens	
P	*Proteus mirabilis*
E	*Escherichia coli*
K	*Klebsiella pneumoniae*
	Klebsiella oxytoca

DRUG OF CHOICE: Carbapanems (ertapenem, meropenem)

ESBLs hydrolyze…
All penicillins
✗ Ampicillin
✗ Amoxicillin
✗ Penicillin
✗ Piperacillin-tazobactam
All cephalosporins
✗ 1st generation (cefazolin, cephalexin)
+/− 2nd generation (cefoxitin)
✗ 3rd generation (ceftriaxone, cefdinir)
✗ 4th generation (cefepime)
✗ 5th generation (ceftaroline)
All monobactams
✗ Aztreonam

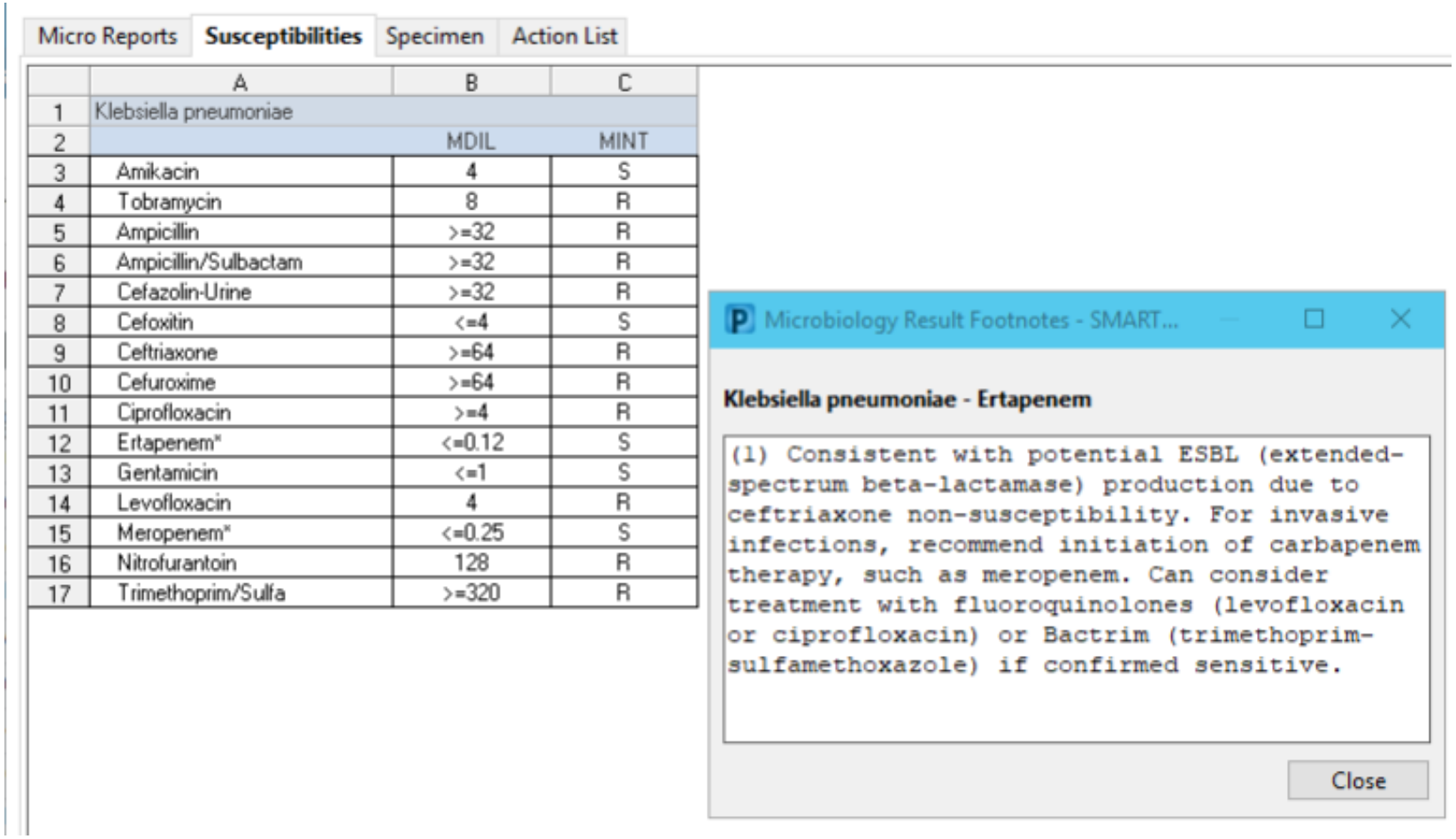
KS Patient Case Continued

- Use ceftriaxone non-susceptibility as a surrogate for ESBL production in *Proteus mirabilis, E. coli, Klebsiella pneumoniae,* and *Klebsiella oxytoca*.
- When these “PEK” organisms are ceftriaxone non-susceptible, our micro lab will now hide susceptibility results for cefepime and piperacillin-tazobactam
- Most ESBL organisms will remain susceptible to cefoxitin (helpful double check) whereas AmpC producing organisms tend to be cefoxitin resistant.

Escherichia coli		
	MDIL	MINT
Amikacin	4	S
Doxycycline	8	I
Minocycline	<=0.5	S
Tobramycin	<=1	S
Ampicillin	>=32	R
Ampicillin/Sulbactam	4	S
Cefazolin	>=32	R
Cefepime	2	S
Cefoxitin	<=4	S
Ceftriaxone	>=64	R
Cefuroxime	>=64	R
Ciprofloxacin	>=4	R
Ertapenem	<=0.12	S
Gentamicin	<=1	S
Levofloxacin	>=8	R
Meropenem	<=0.25	S
Piperacillin/Tazobactam	<=4	S
Trimethoprim/Sulfa	>=320	R

Clinical Decision Support

- When these “PEK” organisms are ceftriaxone non-susceptible, our micro lab will now hide susceptibility results for cefepime and piperacillin-tazobactam
- Footnotes appear in Powerchart by double clicking the ertapenem or meropenem result that has an associated asterick (*)



KS Patient Case Summarized

KS' blood cultures with CTX-M resistance gene detected signaled ESBL resistance was likely (genotypic data)

48 hours later -- KS' blood cultures susceptibilities showed ceftriaxone resistance confirming this concern (phenotypic data)

Carbapenems (meropenem, ertapenem) are the drug-of-choice for ESBL resistance mechanisms

Does not necessarily apply to *Enterobacter cloacae* complex or *Klebsiella aerogenes* if detected on BioFire since these organisms more consistently harbor AmpC resistance

Amp-C β-lactamases

Common Pathogens	
H	*Hafnia alvei*
E	*Enterobacter cloacae*
C	*Citrobacter freundii*
K	*Klebsiella aerogenes*
Y	*Yersinia enterocolitica*
E	
S	

DRUG OF CHOICE: Cefepime

AmpCs hydrolyze…
All penicillins
✗ Ampicillin
✗ Amoxicillin
✗ Penicillin
✗ Piperacillin-tazobactam
All cephalosporins **EXCEPT** cefepime
✗ 1st generation (cefazolin, cephalexin)
✗ 2nd generation (cefoxitin, cefuroxime)
✗ 3rd generation (ceftriaxone, cefdinir)
★ 4th generation (cefepime) ★
✗ 5th generation (ceftaroline)
All monobactams
✗ Aztreonam

Target Detected (assuming no resistance genes detected)	Optimal Empiric Therapy*	Acceptable Empiric Coverage Overnight*
Acinetobacter calcoeceticus-baumanii complex	Ampicillin-sulbactam (high dose) + minocycline	
Bacteroides fragilis	Metronidazole	Ampicillin-sulbactam, piperacillin-tazobactam, ertapenem, meropenem
Enterobacterales, not further delineated	Cefepime, piperacillin-tazobactam	Meropenem
Enterobacter cloacae complex	Cefepime	Meropenem
Escherichia coli	Ceftriaxone, cefepime, piperacillin-tazobactam	Meropenem
Haemophilus influenzae	Ceftriaxone, ampicillin-sulbactam	Cefepime, levofloxacin, piperacillin-tazobactam, meropenem
Klebsiella aerogenes	Cefepime	Meropenem
Klebsiella oxytoca	Ceftriaxone	Cefepime, piperacillin-tazobactam, meropenem
Klebsiella pneumoniae group	Ceftriaxone, cefepime, piperacillin-tazobactam	Meropenem
Neisseria meningitidis	Ceftriaxone	Cefepime, meropenem
***Proteus* spp**	Ceftriaxone	Cefepime, piperacillin-tazobactam, meropenem
Pseudomonas aeruginosa*	Cefepime, piperacillin-tazobactam	Meropenem
***Salmonella* spp**	Ceftriaxone	Ampicillin, piperacillin-tazobactam
Serratia marcescens	Ceftriaxone	Cefepime, piperacillin-tazobactam, meropenem
Stenotrophomonas maltophilia*	Trimethoprim-sulfamethoxazole + levofloxacin, cefiderocol	Trimethoprim-sulfamethoxazole + minocycline, Levofloxacin + minocycline, ceftazidime-avibactam + aztreonam
Gram negative, no targets detected*	Piperacillin-tazobactam +/- trimethoprim-sulfamethoxazole	Meropenem +/- trimethoprim-sulfamethoxazole

***Ensure appropriate treatment dose: Refer to Antimicrobial Guide for dose recommendations**
***Infectious Diseases consultation strongly recommended per policy for *Pseudomonas aeruginosa* and should be strongly considered *for Acinetobacter baumanii, Stenotrophomonas maltophilia*, if no targets are detected, or if resistance genes are detected.**

Gram-Negative Treatment Recommendations

Yeast blood cultures

BioFire

Gram stain

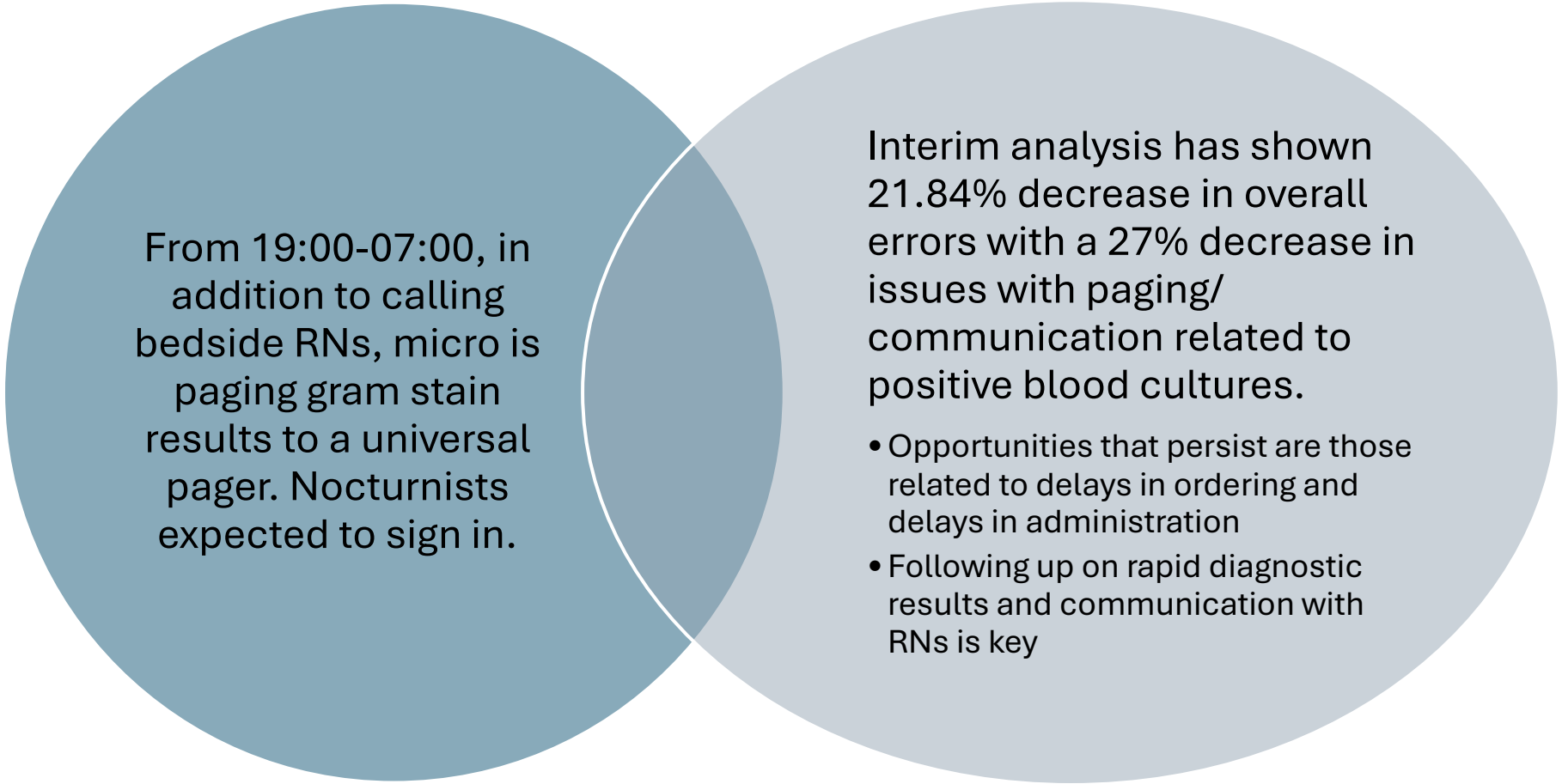
```
Pre - February 01, 2024 11:10 EST -
Candida glabrata - by PCR
----------------------------------------------------------
Positive Blood Culture Gram Stain
Called report to and read back by: RN name (location)    on 2/1/2024 at 09:48:53 by Micro tech


Pre - February 01, 2024 9:50 EST -
Blood culture bottle gram stain shows: Yeast
----------------------------------------------------------
```

Yeast		
Target Detected	**Optimal Empiric Therapy***	**Acceptable Empiric Therapy***
Candida tropicalis	Micafungin	Fluconazole
Candida albicans, Candida parapsilosis	Fluconazole	Micafungin
Candida auris, Candida glabrata, Candida krusei	Micafungin	
Cryptococcus (C. neoformans/C. gattii)	Liposomal amphotericin B + flucytosine	
Yeast, no analytes detected	Liposomal amphotericin B	

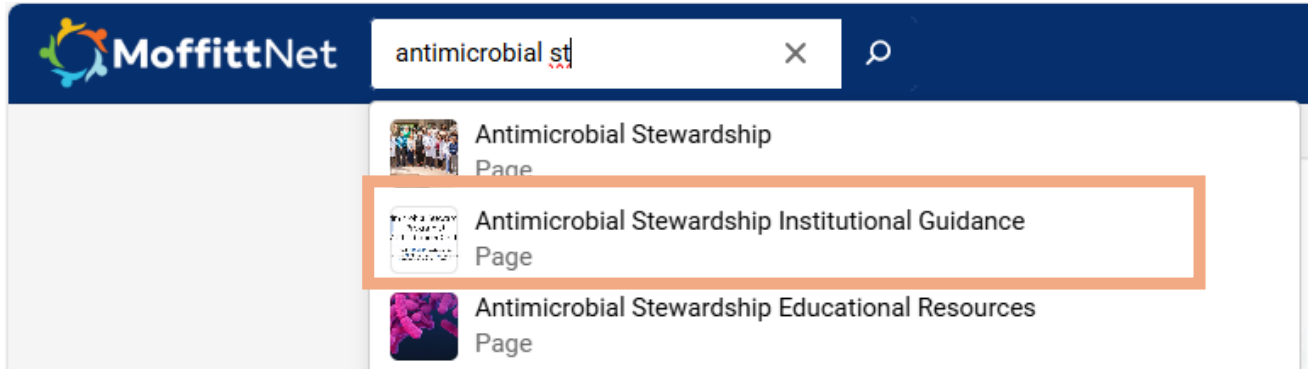
*Ensure appropriate treatment dose: Refer to Antimicrobial Guide for dose recommendations

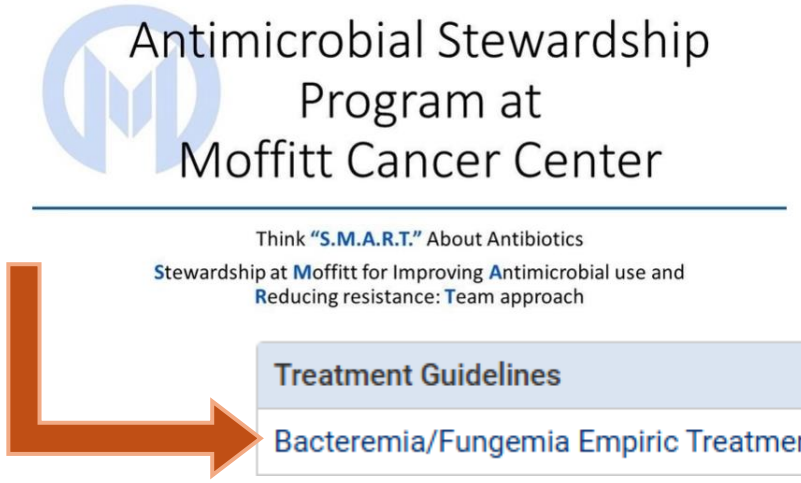
**Infectious Diseases consultation strongly recommended per policy for all fungemias

Quick Plug for Positive Blood Culture Pager



Locate Guidance on MoffittNet





Key Takeaways

#1: time zero	#2: 1.5 hours later	#3: 48 hours later
Gram stain	Rapid diagnostic (identification and resistance genes)	Susceptibility data

- NEW gram-negative decision tree (prior to rapid diagnostic result)
- All blood cultures – gram positive, gram negative, and yeast – will be run on the BioFire BCID2
  - Expect actionable information with identification and resistance genes in 1.5 hours after gram stain
  - Most common gram-negative resistance gene to be aware of is CTX-M = ESBL resistance mechanism → meropenem drug-of-choice
- Susceptibilities will take 48 hours from gram stain

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Questions?