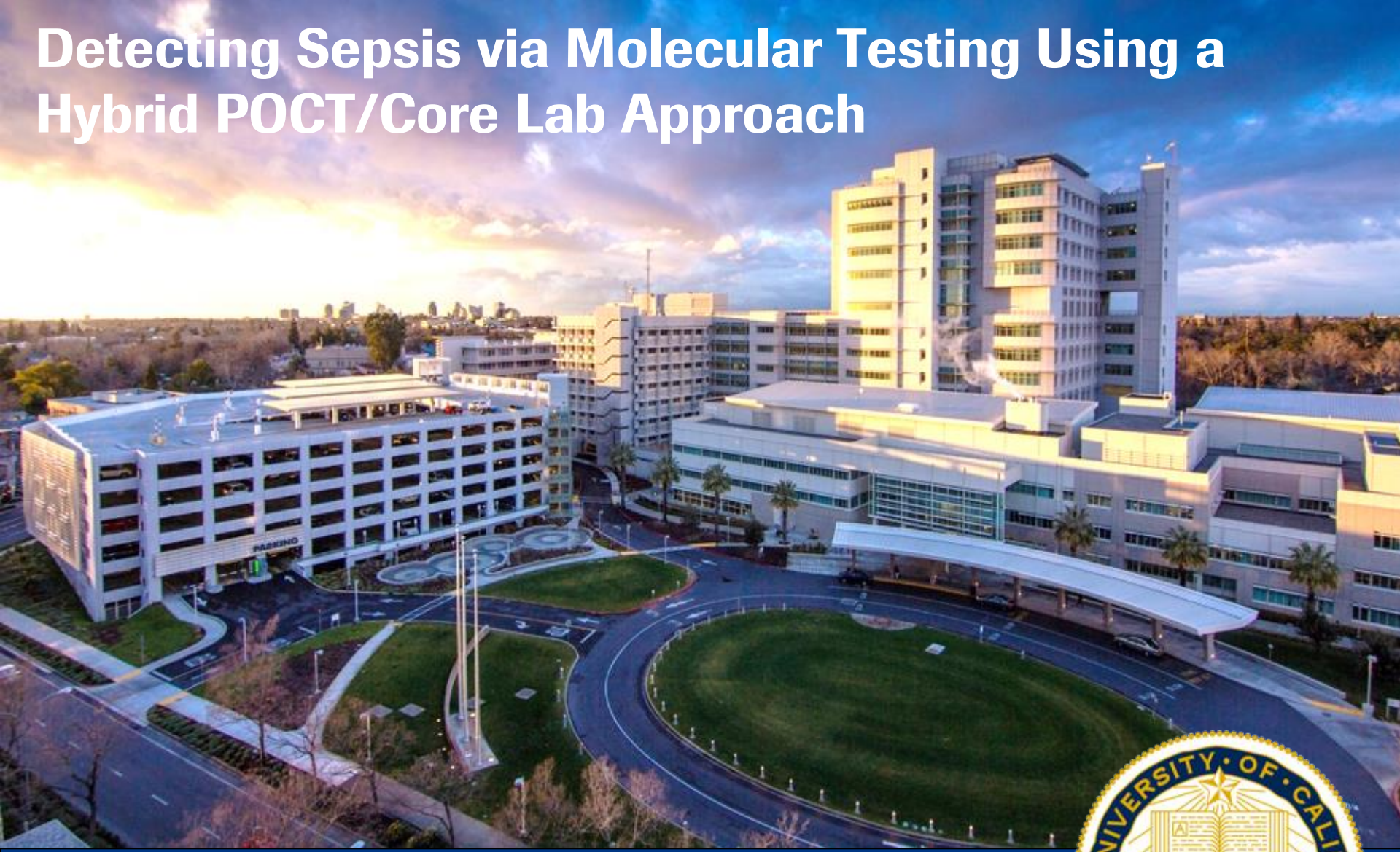
Detecting Sepsis via Molecular Testing Using a Hybrid POCT/Core Lab Approach



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Director of Clinical Chemistry, Special Chemistry/Toxicology, and POCT

Dept. of Pathology and Laboratory Medicine

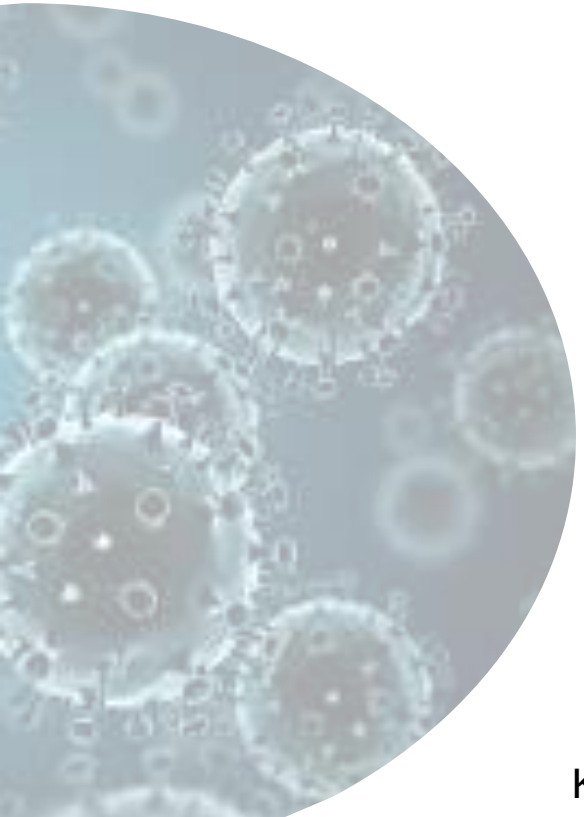
University of California, Davis Health

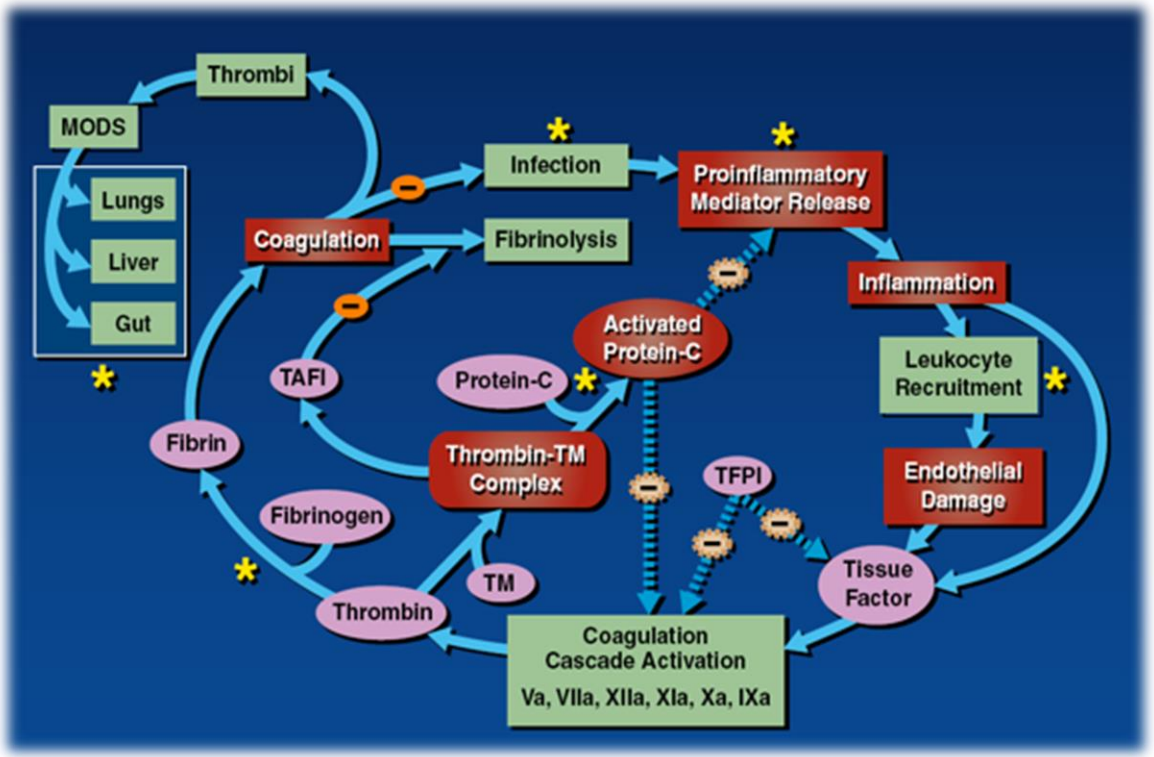
Learning Objectives

- Describe current challenges in sepsis recognition, pathogen detection, and management.
- Identify the strengths and weakness of microbiological techniques.
- Describe the types of rapid pathogen detection systems available.
- Identify potential roles for point-of-care molecular pathogen detection and the concept of the “hybrid” laboratory.

Sepsis: The Clinical Problem

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection





Kost GJ, Tang Z, Tran NK, et al. *Scand J Clin Lab Invest* 2003;63:15

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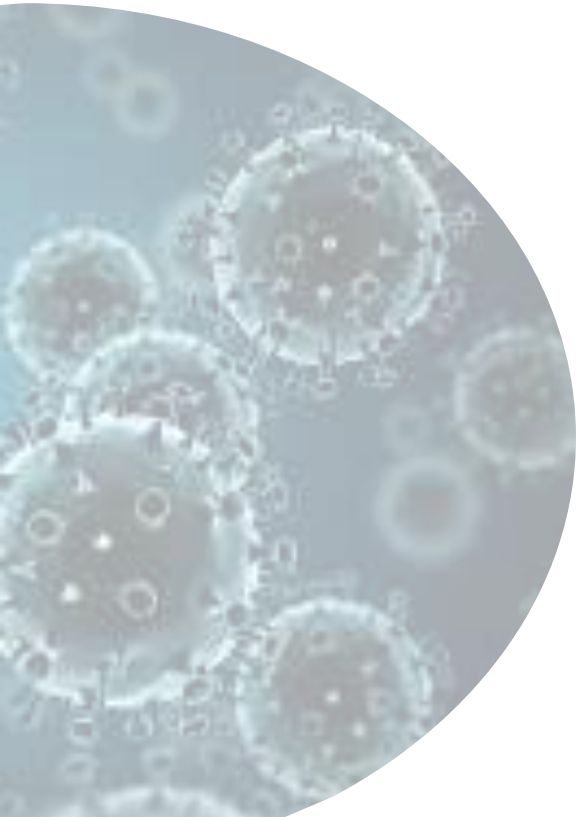

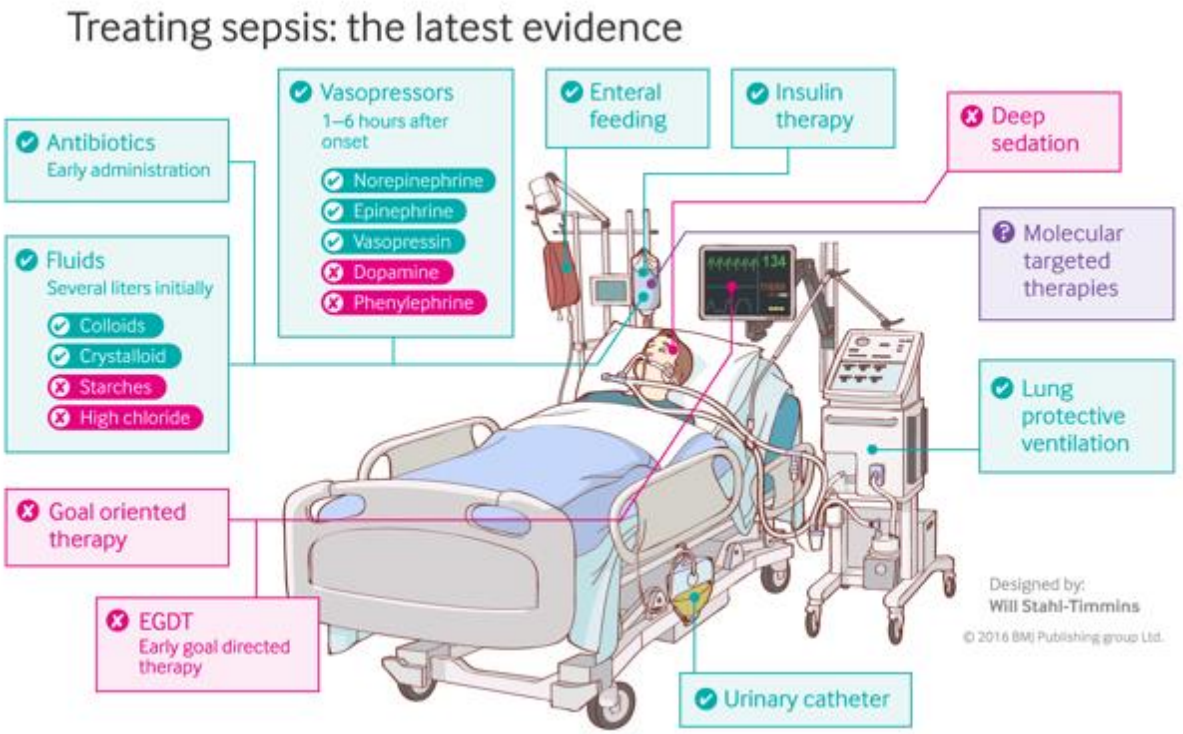

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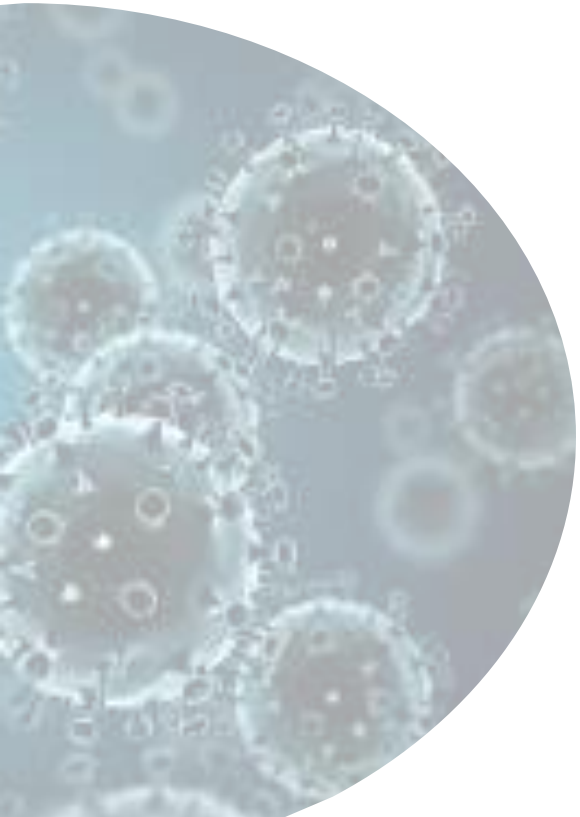
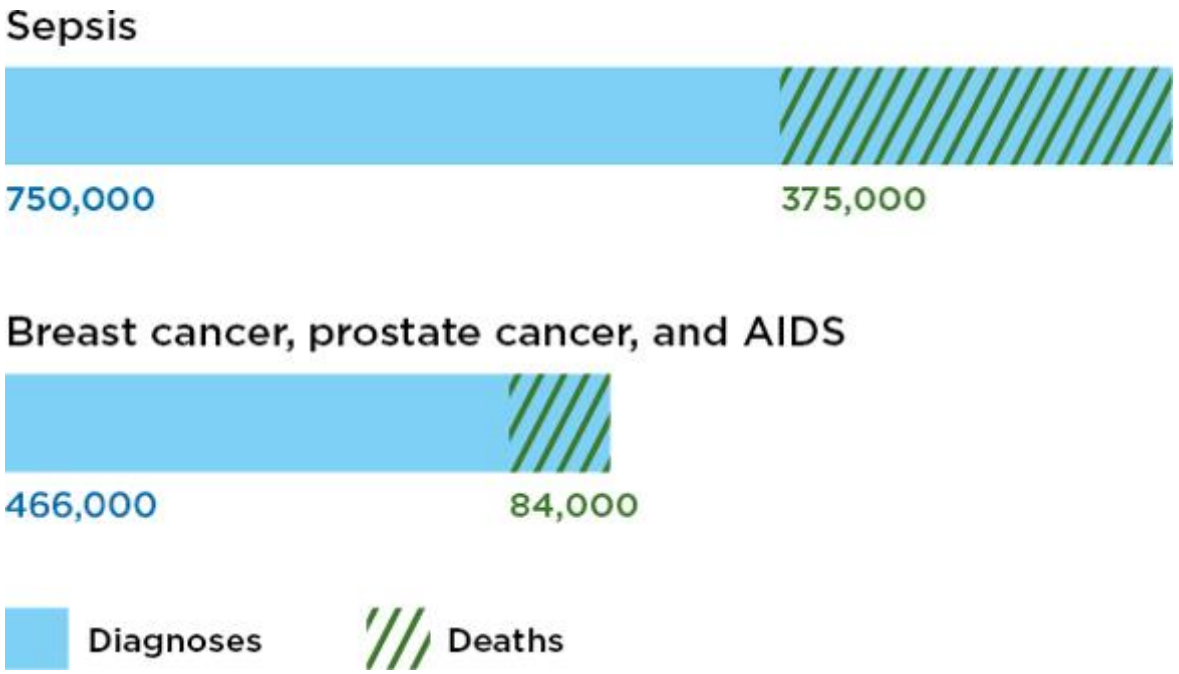
- Mortality ranges from 28-50% and can be as high as 90% in cases of septic shock.





https://business.kaiserpermanente.org/

Sepsis: The Definition Problem

- Sepsis definitions evolving – highlights the complexity of the disease process.

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	ESTABLISHED DEFINITIONS *(used by CMS)*	SEPSIS-3 DEFINITIONS
SEPSIS	Presumed/known infection + ≥2 systemic inflammatory response syndrome criteria	≥2 SOFA criteria (present or increased) Includes: hypotension + normal lactate (shock)
SEVERE SEPSIS	Sepsis + end organ dysfunction, lactate >2 mmol/L	Not a category
SEPTIC SHOCK	Sepsis + refractory hypotension (± lactate)	Vasopressors and lactate >2 mmol/L
MORTALITY RATIO = **OBSERVED MORTALITY** **EXPECTED MORTALITY**	Sepsis = low acuity Observed mortality low Expected mortality low	Sepsis = higher acuity Observed mortality higher Expected mortality low

https://www.acepnow.com/article/acep-endorses-latest-surviving-sepsis-campaign-recommendations/?singlepage=1&theme=print-friendly

Sepsis: Antimicrobial Problem

Empiric antimicrobials necessary since time matters in sepsis. Odds of non-survival increases by 7.6% for every hour delay in treating ”severe sepsis”.

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Unnecessary use of antimicrobials leads to:

- **Antimicrobial resistance, *C. difficile colitis*, ESBL, CRE**
- Toxicities and adverse drug events
- Increased morbidity and longer hospital stays
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UP TO

50%

of antimicrobial use in acute care hospitals is unnecessary

How Antimicrobial Resistance Spreads

Patient Demand Drives Antibiotic Overuse

Changing practices | Deadly hospital-acquired infections |

A lack of stewardship

About a third of Dr. Anna Julien's patients who come in with a cold ask for antibiotics, often saying they're too busy to be sick.

Overuse and non-judicious prescription exerts antimicrobial pressure to promote resistance!

- Realization that Urgent Care Centers lack any stewardship practices.
- Patients often ask for antimicrobials without medical background and physicians comply

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Microbiological culture remains the primary means for pathogen detection.

- Blood culture detection limits range from 3.2 to 3,000 CFU/mL
- In theory detects anything that grows in the specific media.
- Results may be affected by antimicrobial therapy.
- Median analytical turnaround time (TAT) not compatible with efforts for early recognition.
  - ✓ Collection → Gram Stain: 10.4 hours
  - ✓ Collection → Speciation: 26.4 hours
  - ✓ Collection → MIC: 43.7 hours

“Modern” Microbiology Laboratory

Microbiology hasn’t changed too much → concept remains the same up until recently. Grow the pathogen and determine the phenotype.

Biochemical Testing

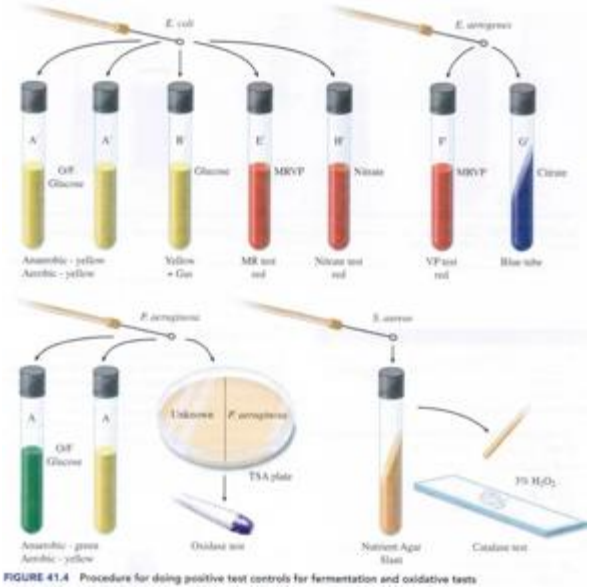

FIGURE 41.4 Procedure for doing positive test controls for fermentation and oxidative tests

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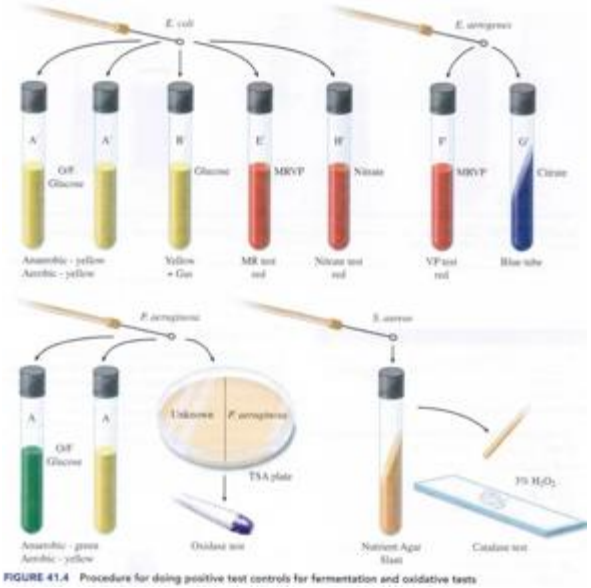

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Antimicrobial
Susceptibility Testing

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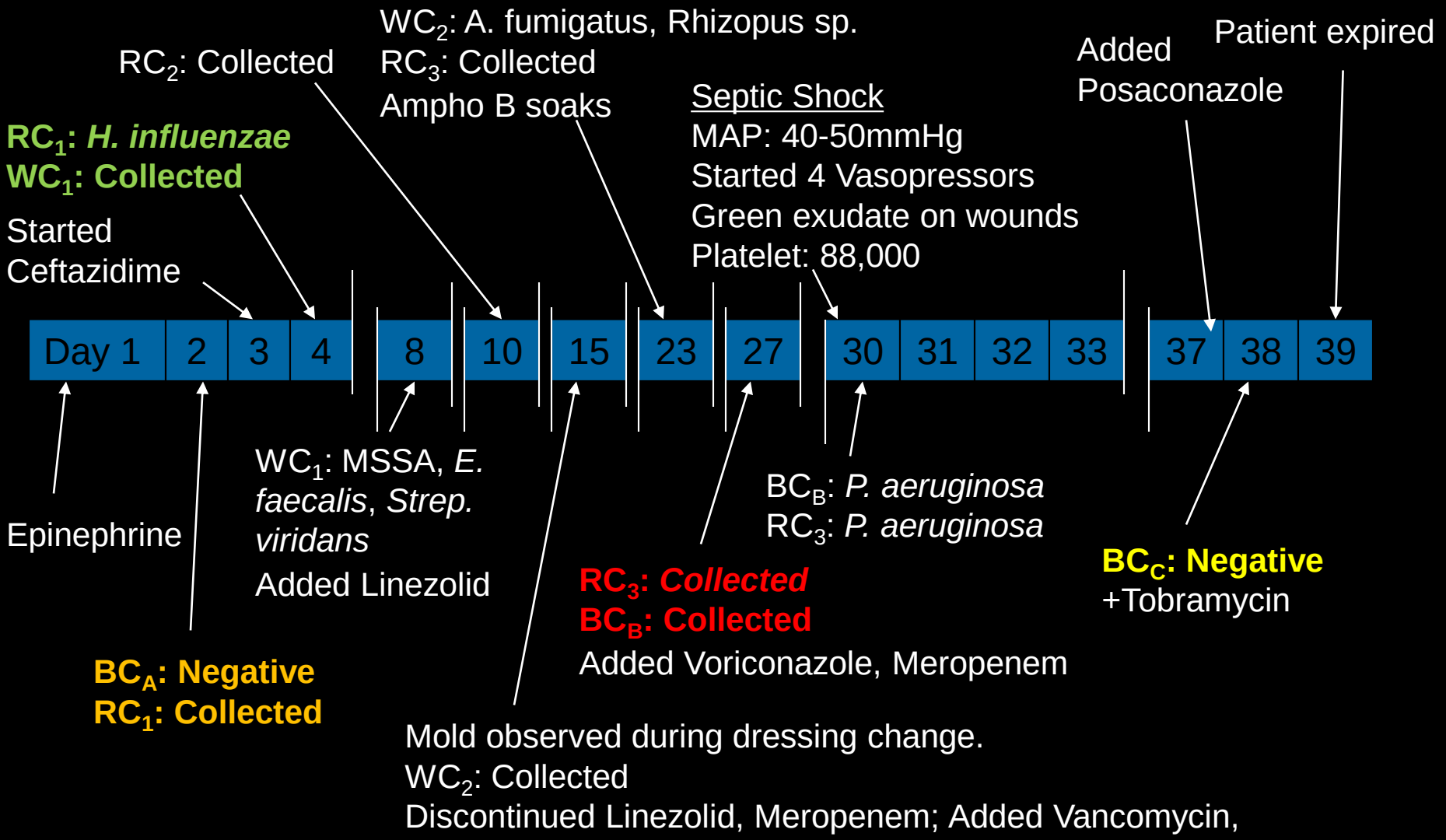

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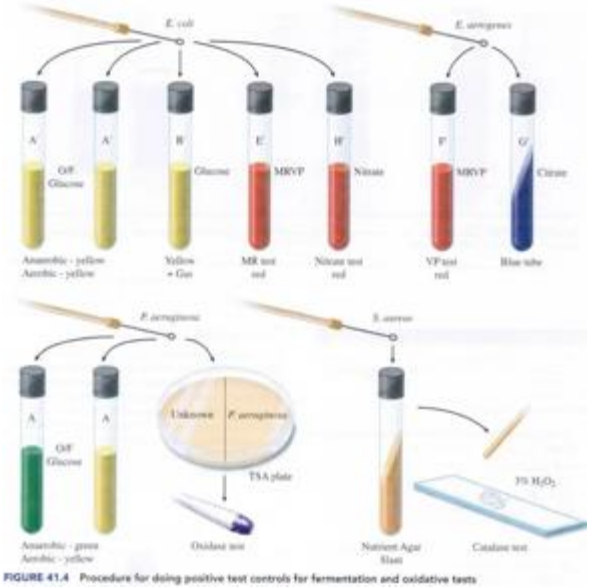

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Automated Culture Plating

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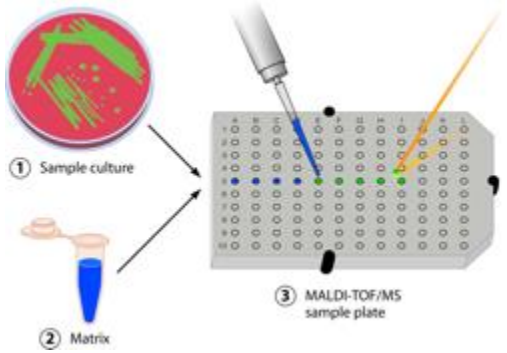

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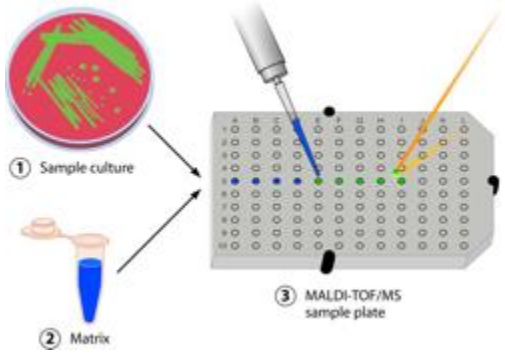

Molecular Dx

Species ID
Resistance (?)

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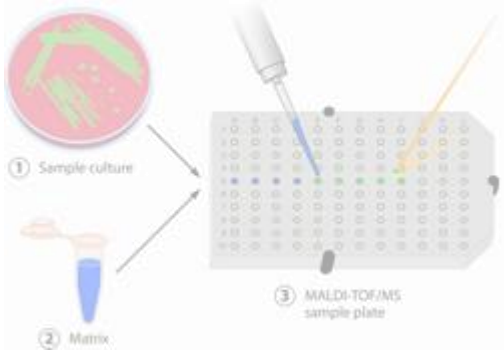

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Rapid Pathogen Detection: The Promise of Molecular Diagnostics

- Molecular approaches such as PCR offer highly sensitive and specific alternatives to existing microbiological tests.
- Provides potential to pick up certain resistance genes (e.g., mecA, kpc, NDM-1, etc)
- Multiplex system scan detect up to 22 viruses and bacteria in 45 mins to 60 minutes depending on the platform.

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Challenges:

- ✓ Current systems test directly from culture positive specimens rather than whole blood.
- ✓ Throughput limited and high upfront cost for individual instruments limit use at the enterprise-wide level.
- ✓ High cost per multiplex test: ~$100/test and billable to the patient could be thousands of dollars!
- ✓ Majority of pathogens are not needed.

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Molecular Enhanced Pathogen Detection

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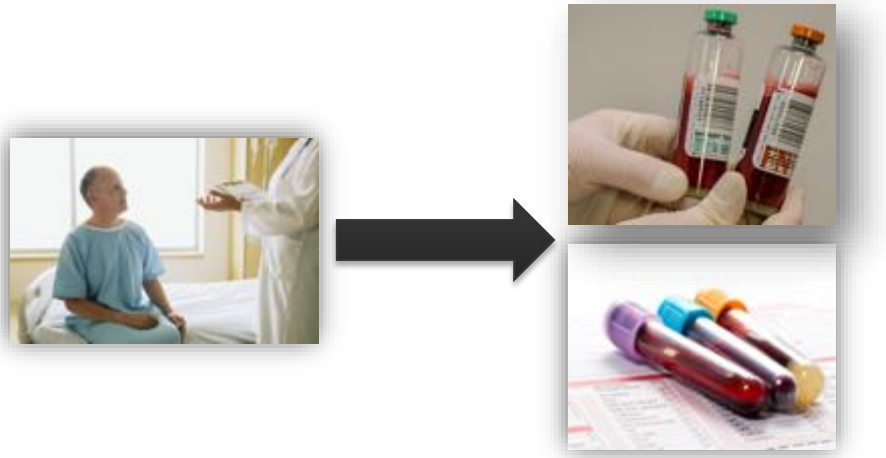

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Molecular Enhanced Pathogen Detection

Growth Time
(10.4 hrs)

PCT
Lactate
IL-6 (?)
CRP (?)

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Diagnostic Blind Zone

Species ID

Genotypic Resistance

Phenotypic Resistance

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We can conceivably get species ID and genetic resistance data for select targets within 24 hours now

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However genotypic resistance may not always = phenotypic resistance.

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IL-6 (?)
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A diagnostic blind spot still remains due to needing cultures to grow out as well

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Genotypic Resistance

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Is there clinical value getting faster than this?

ABA – MCTG
COMBAT CASUALTY GRANT:

"Rapid, Quantitative, PCR-Based Detection of Staphylococcus aureus in Burn Sepsis Patients"

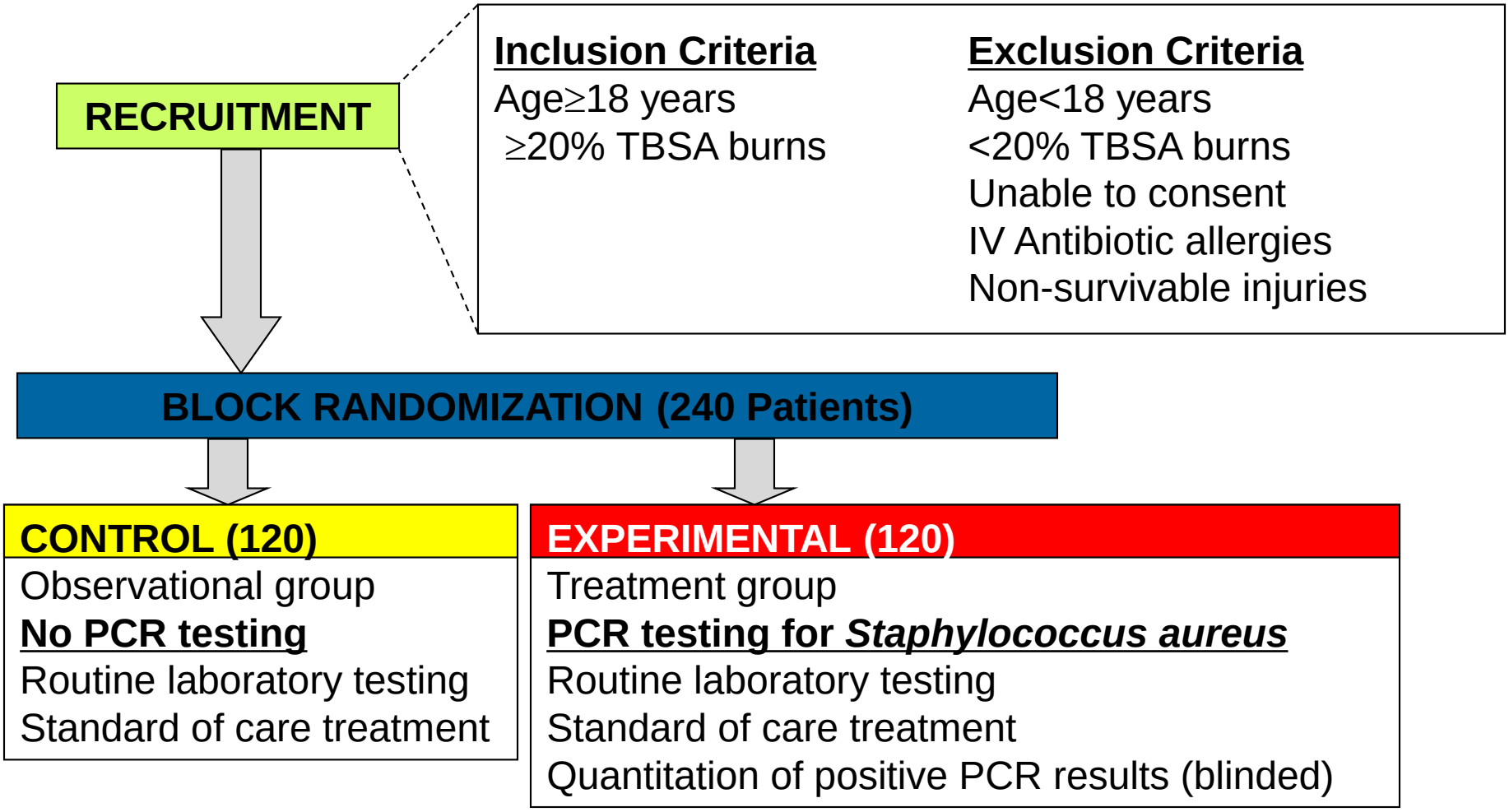
PI: Nam K. Tran, PhD

NIH Clinical Trials Registration Number: NCT01140269

UCD IRB Approval Number: 200918586

USAMRMC HRPO Log Number: A-15774.0 (Core Protocol)

Study Model: Randomized Controlled Trial



PARTICIPATING SITES

U. Washington
Seattle, WA

Nathan Speare
Philadelphia, PA

UCDMC
Sacramento, CA

U. Cincinnati
Cincinnati, OH

Torrance Memorial
Torrance, CA

U. Miami
Miami, FL

GeneXpert PCR Near-Patient Testing

UCDAVIS HEALTH

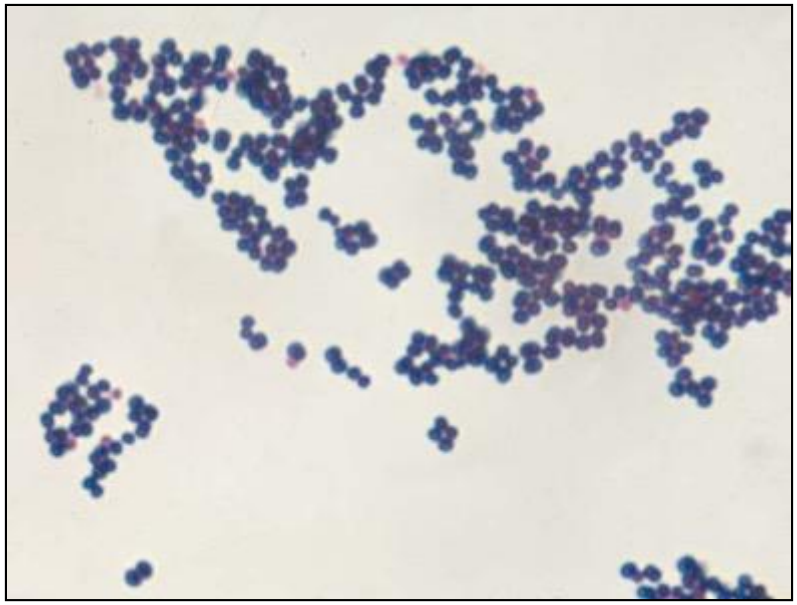
Nasal

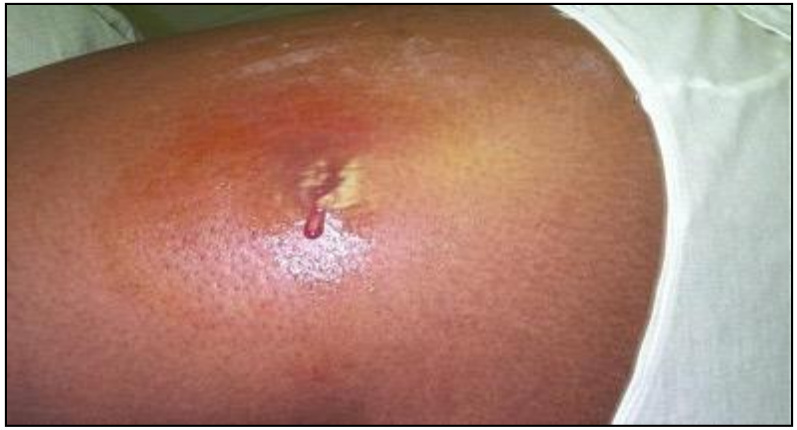
Wound

BC

Time (min)	2	60 - 70	RESULTS

Staphylococcus aureus



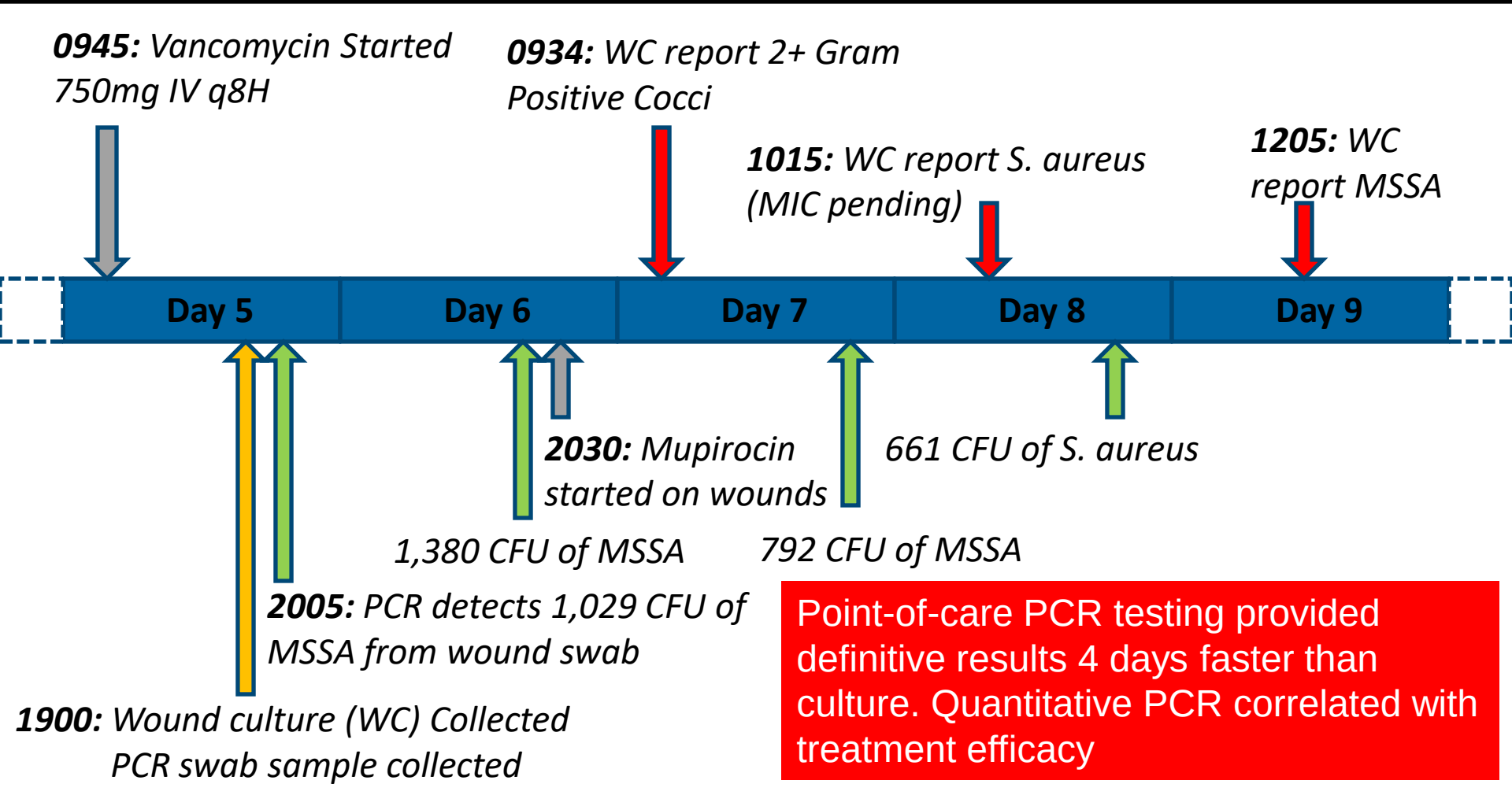


- Gram positive cocci found in groups.
- Coagulase and catalase positive
- Produces capsules (types 5 and 8 are common human pathogens)
- Expresses beta-lactamase to confer penicillin resistance
- Colonizes 10 to 20% of adults
- Methicillin resistant strains (MRSA) associated with higher mortality.

Lowy FD. *N Eng J Med* 1998;339:520-532.

Proof-of-Concept: Serial Quantitative PCR Testing

History: Patient is a 40 year old man with 20% total body surface area burns to the face, head, neck, left upper back, bilateral hands, and lower left extremity from a house fire. Blood cultures, respiratory cultures, and wound cultures were collected on day 5 for clinical suspicion of burn sepsis (*American Burn Association Sepsis Trial*)



Point-of-care PCR testing provided definitive results 4 days faster than culture. Quantitative PCR correlated with treatment efficacy

There's more than S. aureus

Gram Positive

CoNS
Enterococcus faecium
Enterococcus faecalis
Staph. aureus
Strep. pneumoniae
Strep. sp.
MRSA

Gram Negative

Acinetobacter baumannii
Enterobacter aerogenes/ cloacae
E. coli
Klebsiella pneumoniae/ oxytoca
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia

Fungi

Aspergillus fumigatus
Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis

SeptiFast (not available in US)

UCDAVIS HEALTH

Gram Positive

CoNS[1]
Enterococcus faecium
Enterococcus faecalis
Staph. aureus
Strep. pneumoniae
Strep. sp.[2]
MRSA[3]

Gram Negative

Acinetobacter baumannii
Enterobacter aerogenes/ cloacae[4]
E. coli
Klebsiella pneumoniae/ oxytoca[4]
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia

Fungi

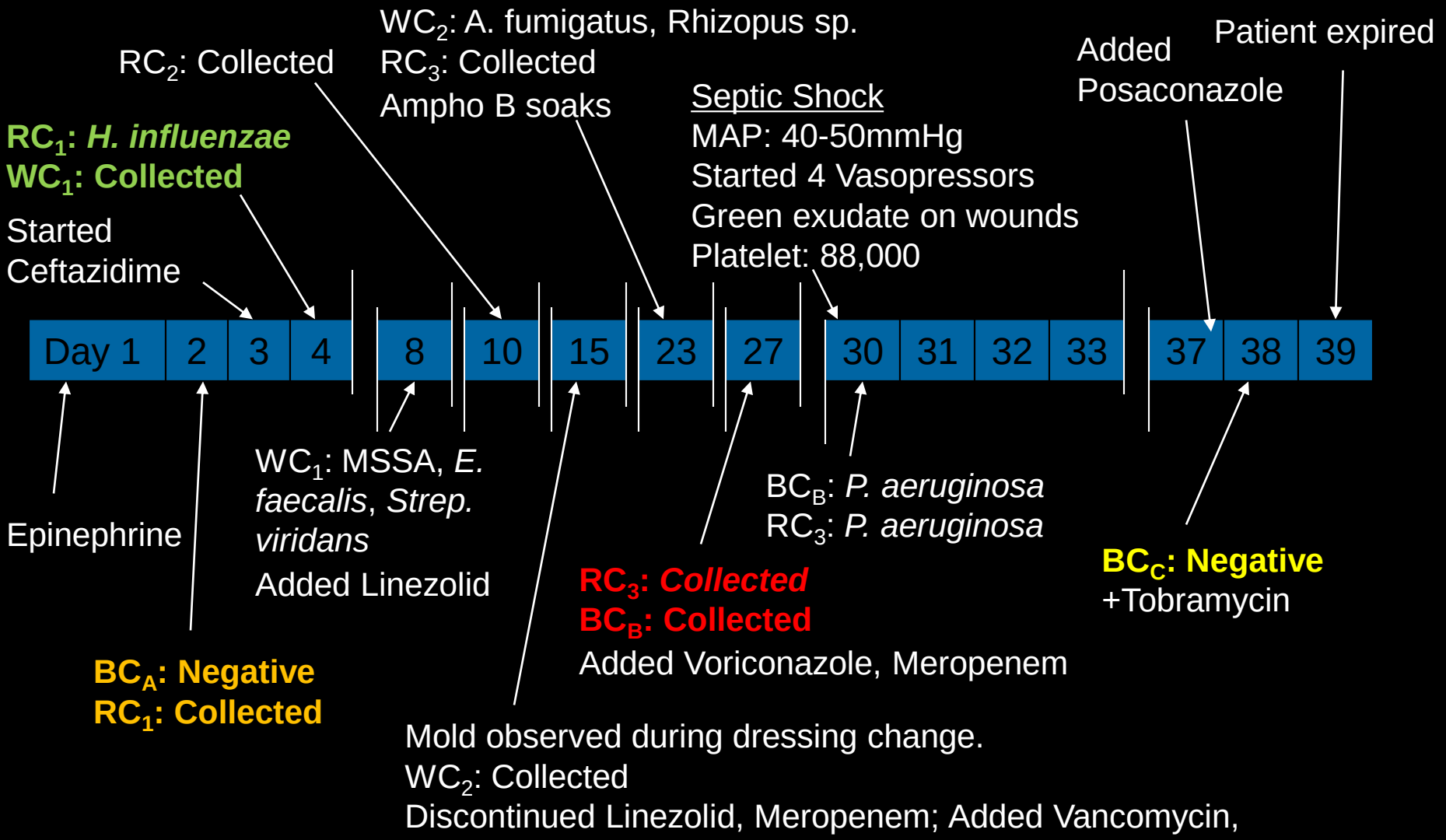
Aspergillus fumigatus
Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis

1-*Staphylococcus hemolyticus, epidermidis* = CoNS
2-*Streptococcus agalaciae, pyogenes, viridans* = Strep. Sp.
3-Separate test kit
4-No differentiation between these two subspecies

LAB BASED

Pathogen Detection in Burn Patients

Patient is a 20 year old man status post motor vehicle accident with 90% TBSA 3rd and 4th degree burns and C1 pedicle and C4 foraminal fracture.



Whole-Blood PCR-Based Pathogen Detection

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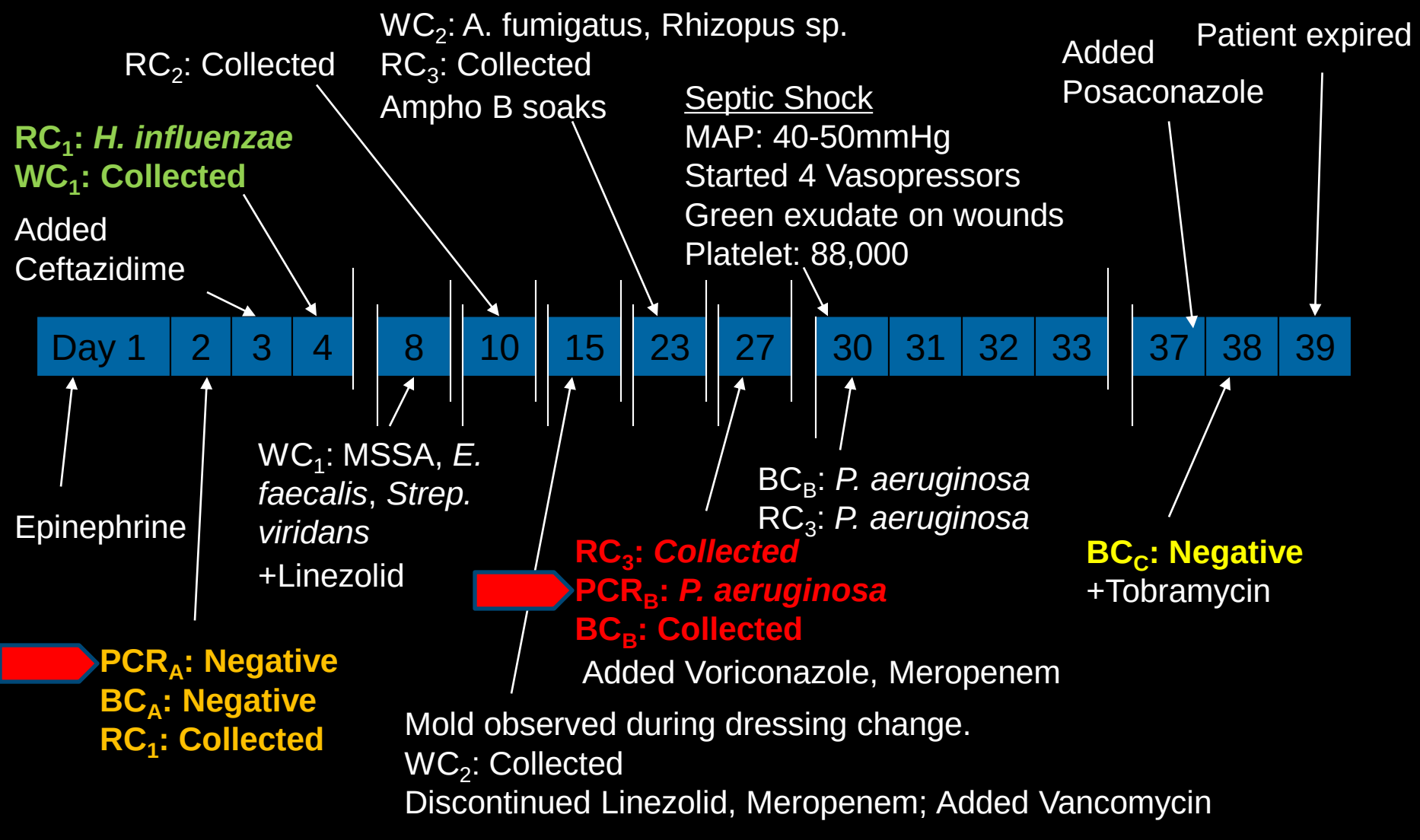

Where are the whole blood PCR tests?

Blood Culture Sample

As noted, the majority of pathogen detection systems today for septicemia relies on blood culture as the specimen type. Reason:

- Integrates into microbiology workflow.
- Don’t have to worry about amplifying the signal.
- Less questions about what you’re detecting is “real” or not.

FDA-approved

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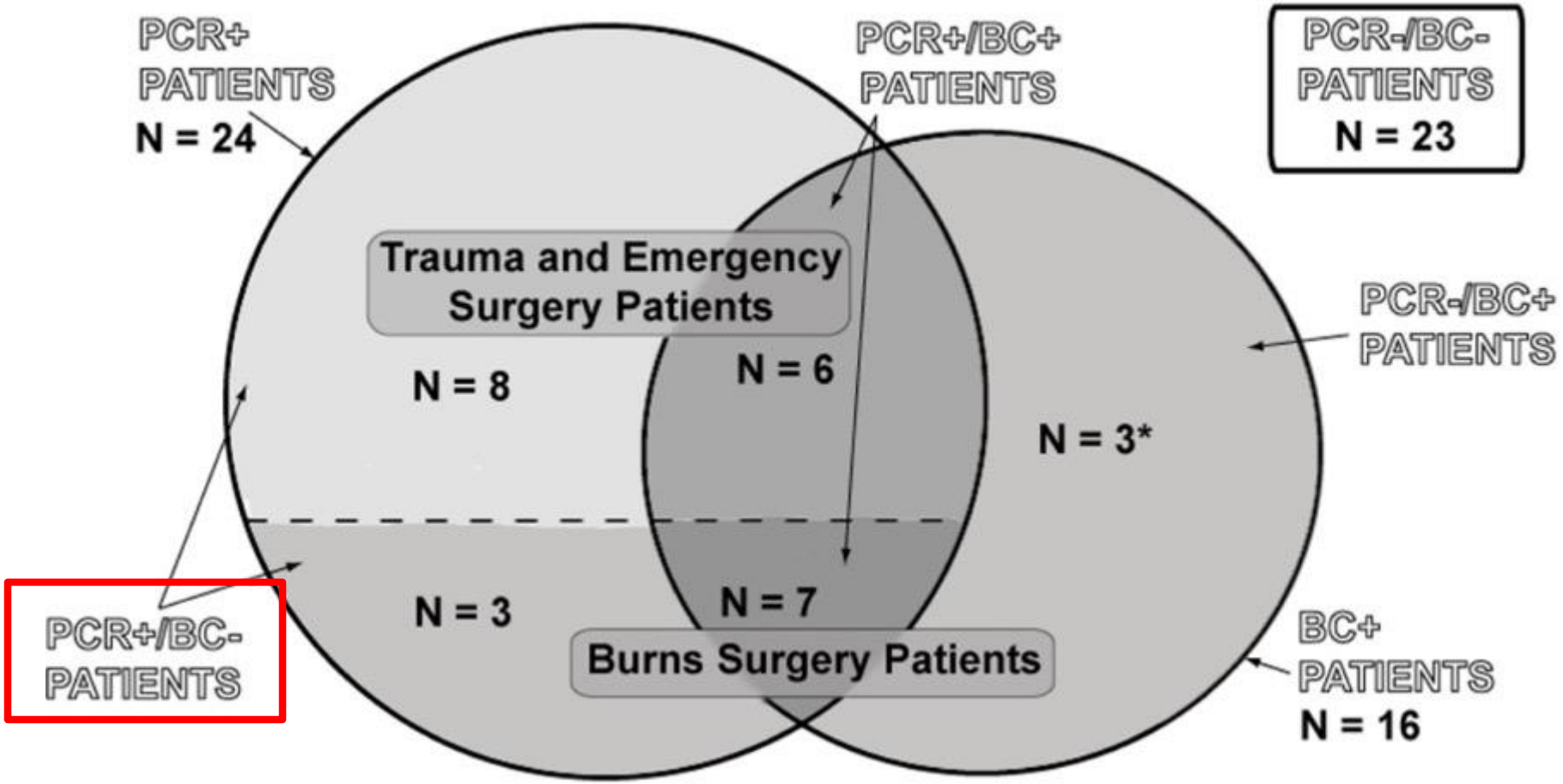
What to do with PCR+/BC– Cases: Is ”DNAemia” Real?



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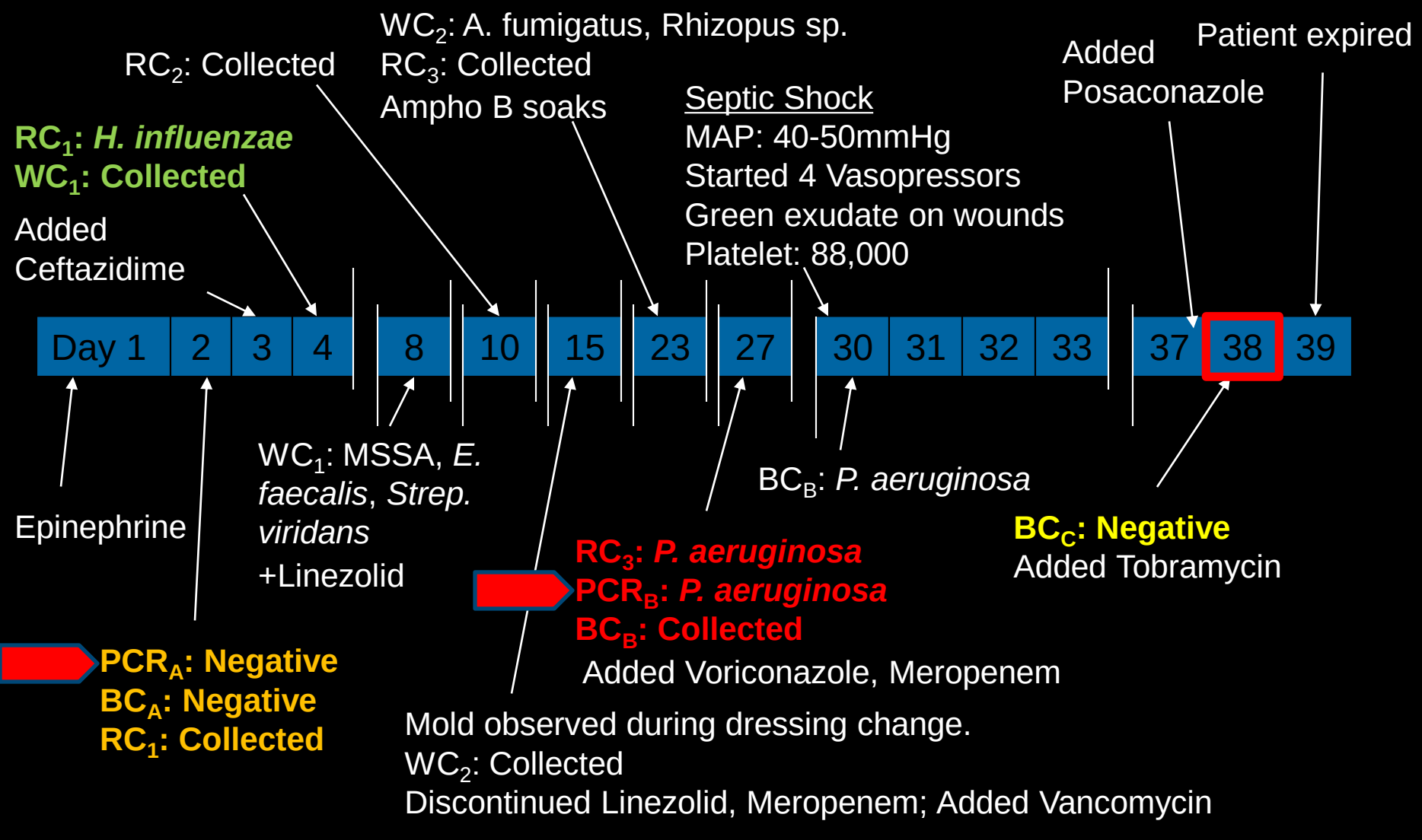

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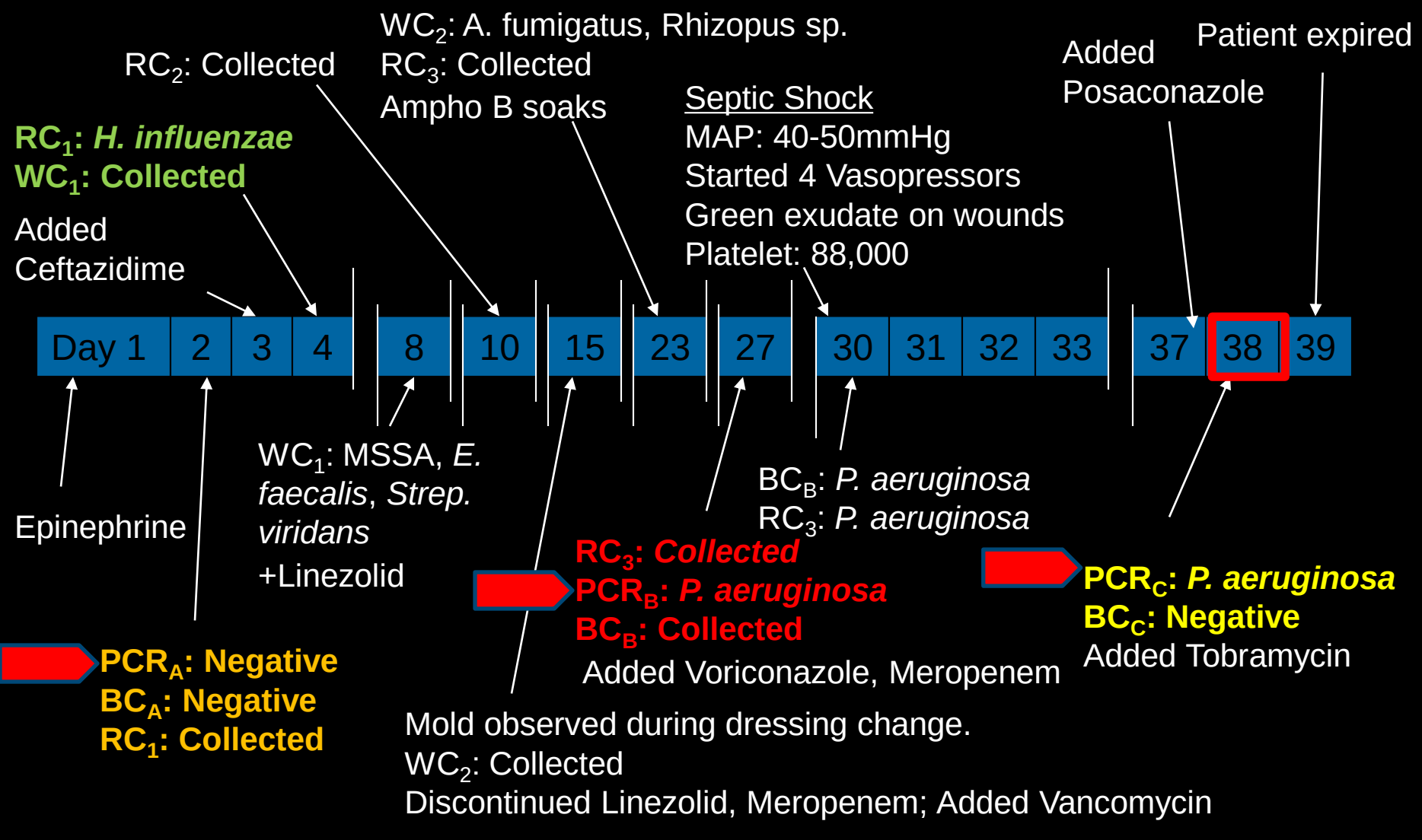

Whole-Blood PCR-Based Pathogen Detection

Patient is a 42 year-old woman with a perforated jejunum status post exploratory laparotomy and small bowel resection, who developed septic shock 24-hours later.

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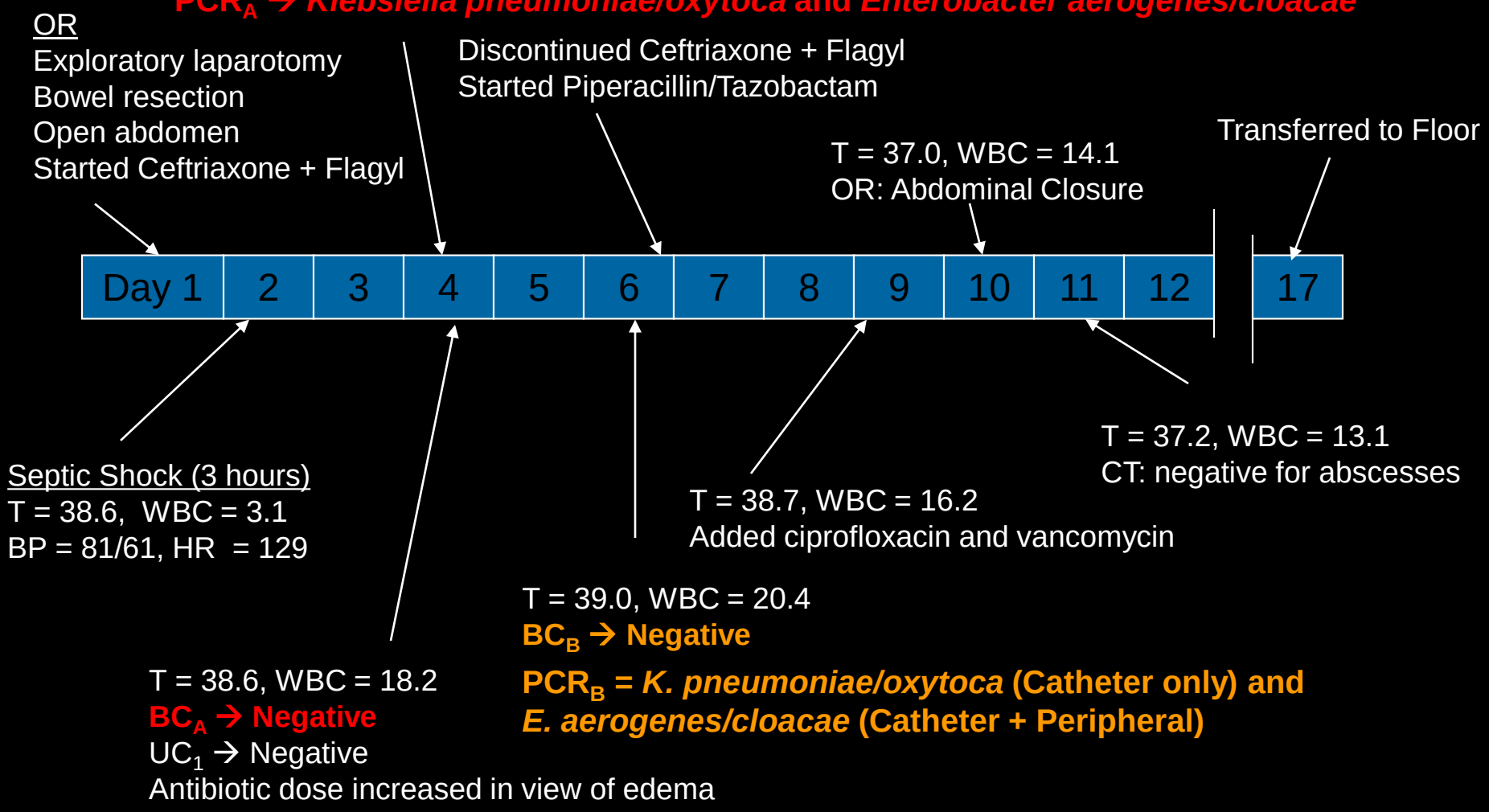


Where are the whole blood PCR tests?

Whole Blood Sample

Blood Culture Sample

Quite a few whole blood-based systems exist, but are not FDA approved (SeptiFast CE Marked)

7 Gram pos
8 Gram neg
6 Fungi

In Development

Not FDA-approved

FDA-approved

Where are the whole blood PCR tests?

UCDAVIS HEALTH

Whole Blood Sample

Candida sp. (5 species)
E. faecium
E. coli
K. pneumoniae
P. aeruginosa
S. aureus

FDA-approved

7 Gram pos
8 Gram neg
6 Fungi

In Development

Not FDA-approved

Blood Culture Sample

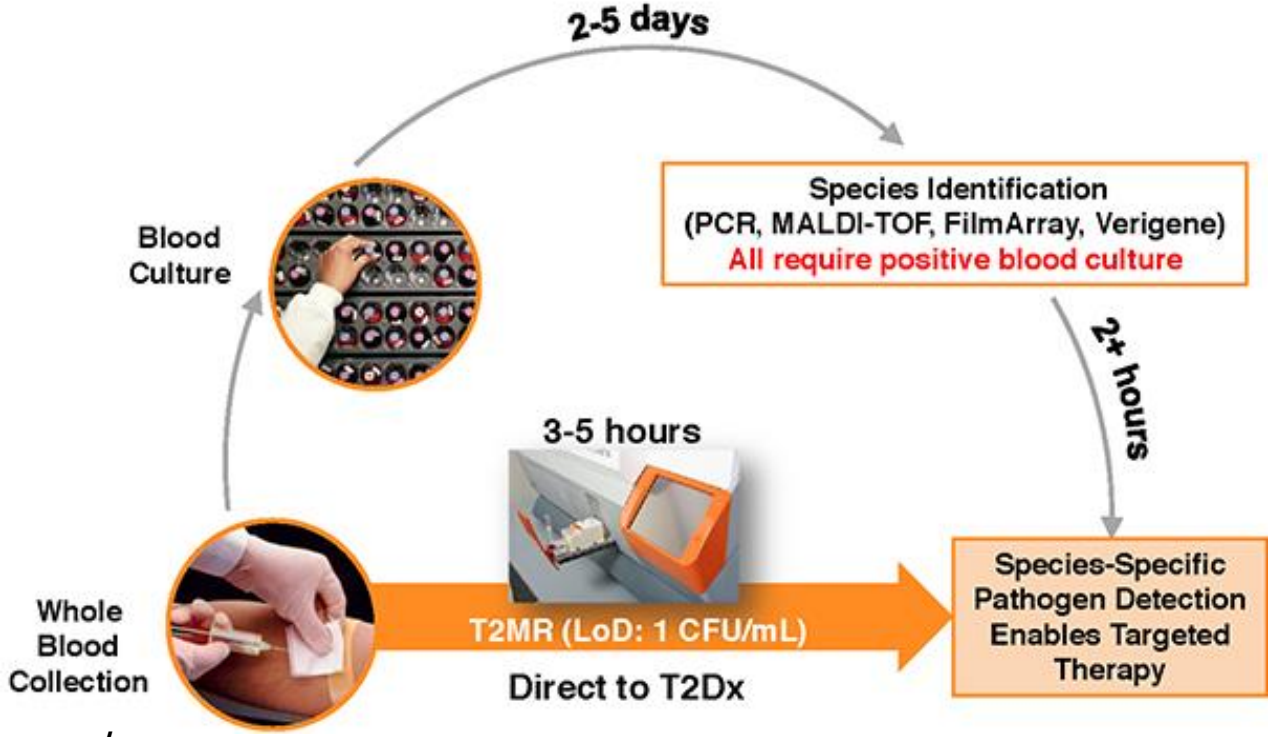
FDA-approved

Small, but growing number of molecular tests available that can assay from whole blood. However, test menu remains limited.

T2-Time Magnetic Resonance Pathogen Detection

Innovative technology that mitigates the challenges of whole blood matrix by using T2-time magnetic resonance.

- Providers faster results compared to contemporary blood culture enhanced molecular / mass spec testing.
- Limits of detection are reasonable and down to 1 CFU/mL.
- However limited panel.



https://www.t2biosystems.com/

Where are the whole blood PCR tests?

UCDAVIS HEALTH

Whole Blood Sample

Candida sp. (5 species)
E. faecium
E. coli
K. pneumoniae
P. aeruginosa
S. aureus

FDA-approved

7 Gram pos bacteria
8 Gram neg bacteria
6 Fungi

In Development

Not FDA-approved

Blood Culture Sample

FDA-approved

Also some novel technologies are on the horizon!

Not FDA-approved

Smart Particle Technology

Another innovative technology with the potential benefit to accelerate in vitro susceptibility results and speciation

- Utilizes “smarticles” bioparticles to specifically bind to target bacteria.

https://diagnostics.roche.com/global/en/article-listing/smarticles-technology.html

Smart Particle Technology

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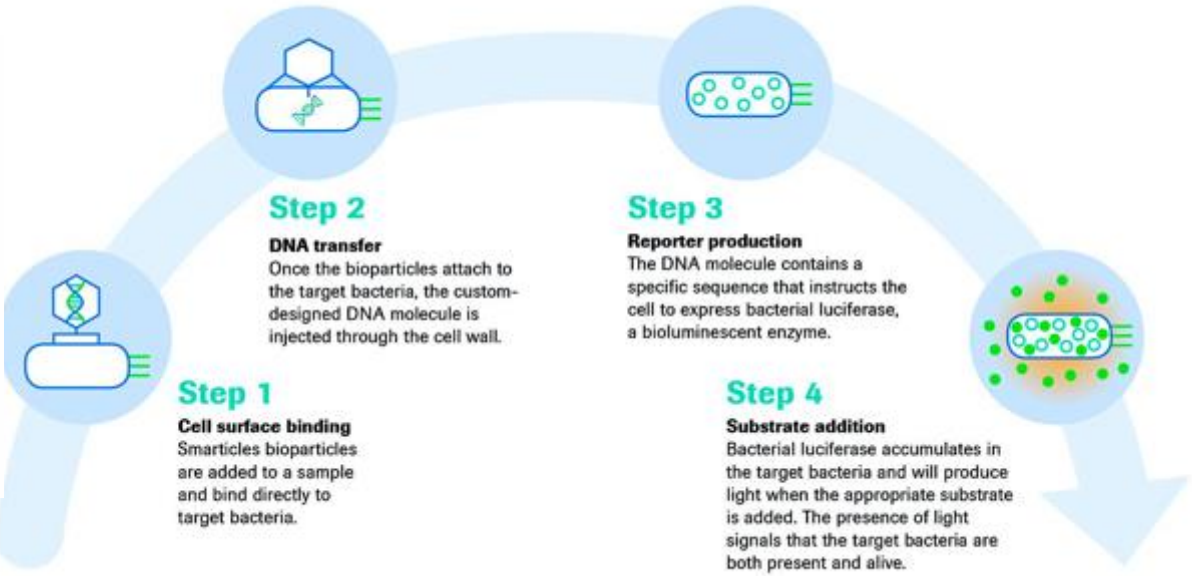
- Effectively a “live-cell” molecular test.



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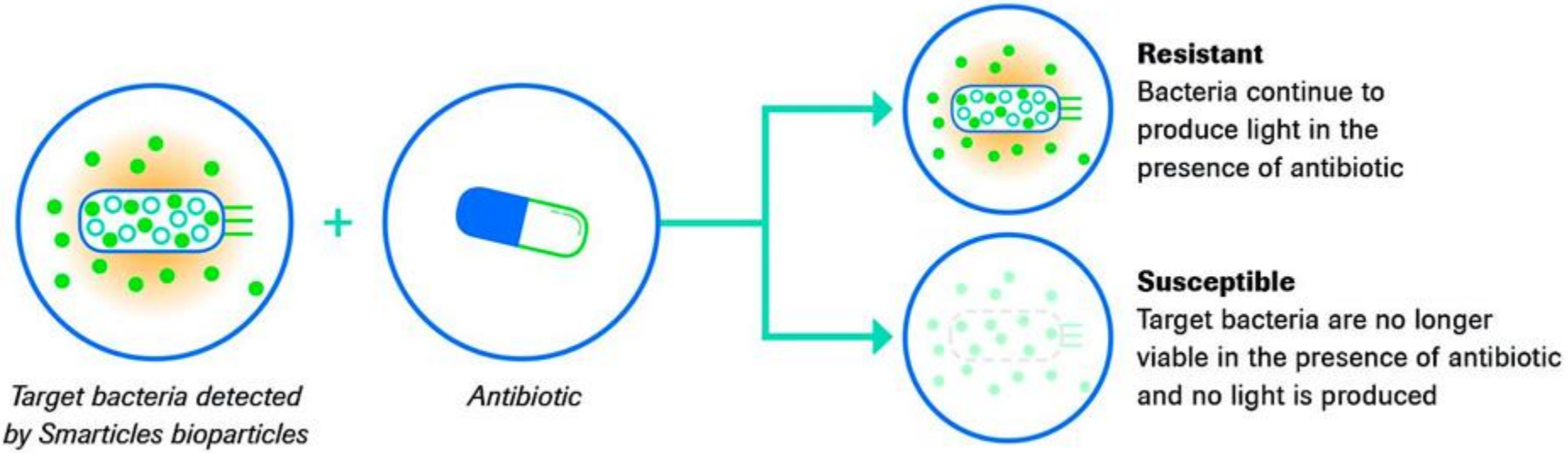
Smart Particle Technology

Another innovative technology with the potential benefit to accelerate in vitro susceptibility results and speciation

- Utilizes “smarticles” bioparticles to specifically bind to target bacteria.
- Effectively a “live-cell” molecular test.
- Can also detect phenotypic drug resistance in vitro.



https://diagnostics.roche.com/global/en/article-listing/smarticles-technology.html

Current Lab-Centric Solutions

So most molecular pathogen detection remains in the central laboratory space.

Laboratory-based testing

- Lab keeps revenue
- Demand on lab staff
- Ensures consistency
- Minimizes regulatory oversight of waived users
- However impacts ED/ ICU workflow
- Not all detectable pathogens are needed

Current Lab-Centric Solutions

Constrained to the laboratory due to their complexity (CLIA) or reliance on blood culture samples. Good for the laboratory!

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Current Lab-Centric Solutions

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Hybrid Laboratory: Molecular

Could we exist as a “hybrid lab” incorporating both centralized diagnostics and point-of-care testing?

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ED and ICU

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Bedside Testing

- Options limited to mainly respiratory panels.
- ”True” POCT (waived) solutions typically tests for Flu A/B and RSV.
- RN workflow?
- $$$$

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ED and ICU

Hybrid Laboratory: Molecular

Could we exist as a “hybrid lab” incorporating both centralized diagnostics and point-of-care testing? Can we leverage multiple platforms to optimize clinical impact?

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Near-patient testing?

- Lab keeps revenue
- Demand on lab staff
- Intermediate turnaround time – some ED/ICU workflow issues
- New space / new operators?

ED and ICU

Challenges Remain for POCT

Significant technological and regulatory barriers in the way of POCT molecular pathogen detection for sepsis.

Bedside Testing

- Options limited to mainly respiratory panels.
- ”True” POCT (waived) solutions typically tests for Flu A/B and RSV.
- RN workflow?
- $$$$

- Whole blood remains a challenging matrix.
- Bloodstream pathogen concentrations may be low (0.5 – 1.0 CFU/mL) in early sepsis.
- Molecular panels remain limited (can only detect what you assay is designed to detect).
- Flu A/B, RSV, Strep A is easier to diagnose versus sepsis.

ED and ICU

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- RN workflow?
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- Costs for molecular tests remain relatively high.
- Costs associated with POCT operators poorly defined.
- Over utilization of molecular assays is a known problem → need mechanisms to optimize use.

ED and ICU

Hybrid Laboratory: Immunoassays with Molecular Creates Value

Case Example:
Diagnosis of Respiratory Tract Infections (RTI) in the ED during Flu Season

SIRS
RTI

POCT

Leveraging chemistry tests to enhance molecular performance and cost-effectiveness

Linkage of molecular diagnostics with chemistry / immunoassays offers other options and may optimize utilization of expensive molecular tests.

Hybrid Laboratory: Immunoassays with Molecular Creates Value

Case Example:
Diagnosis of Respiratory Tract Infections (RTI) in the ED during Flu Season

SIRS
RTI

POCT

Procalcitonin
Lactate
CRP(?)
IL-6(?)

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Bacterial vs. Non-Bacterial Sources

Antibiotics vs. Antivirals vs. Non-Antimicrobials

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LAB

Improves BOTH antimicrobial and diagnostic stewardship!

Hybrid Laboratory: Immunoassays with Molecular Creates Value

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LAB

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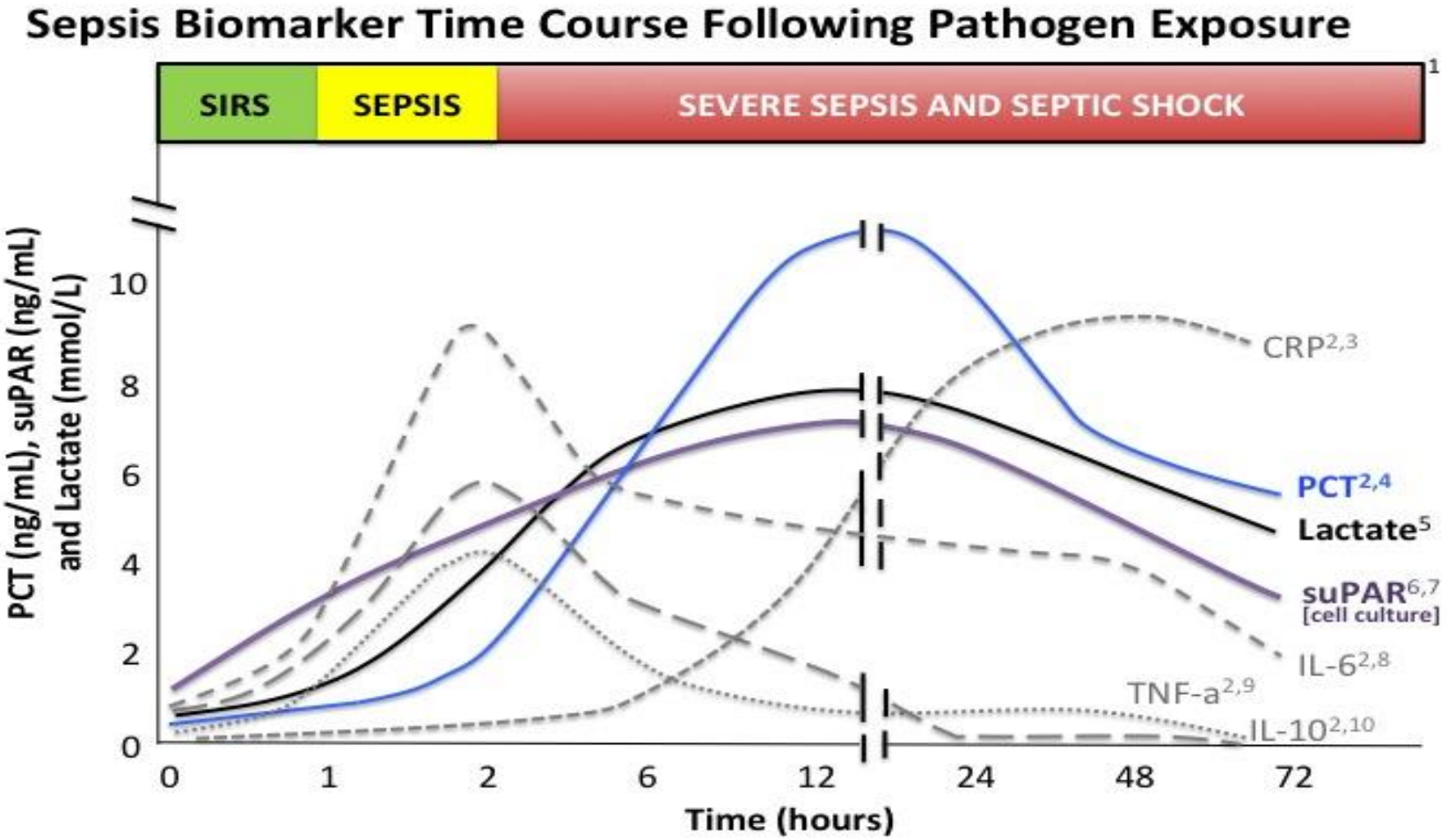
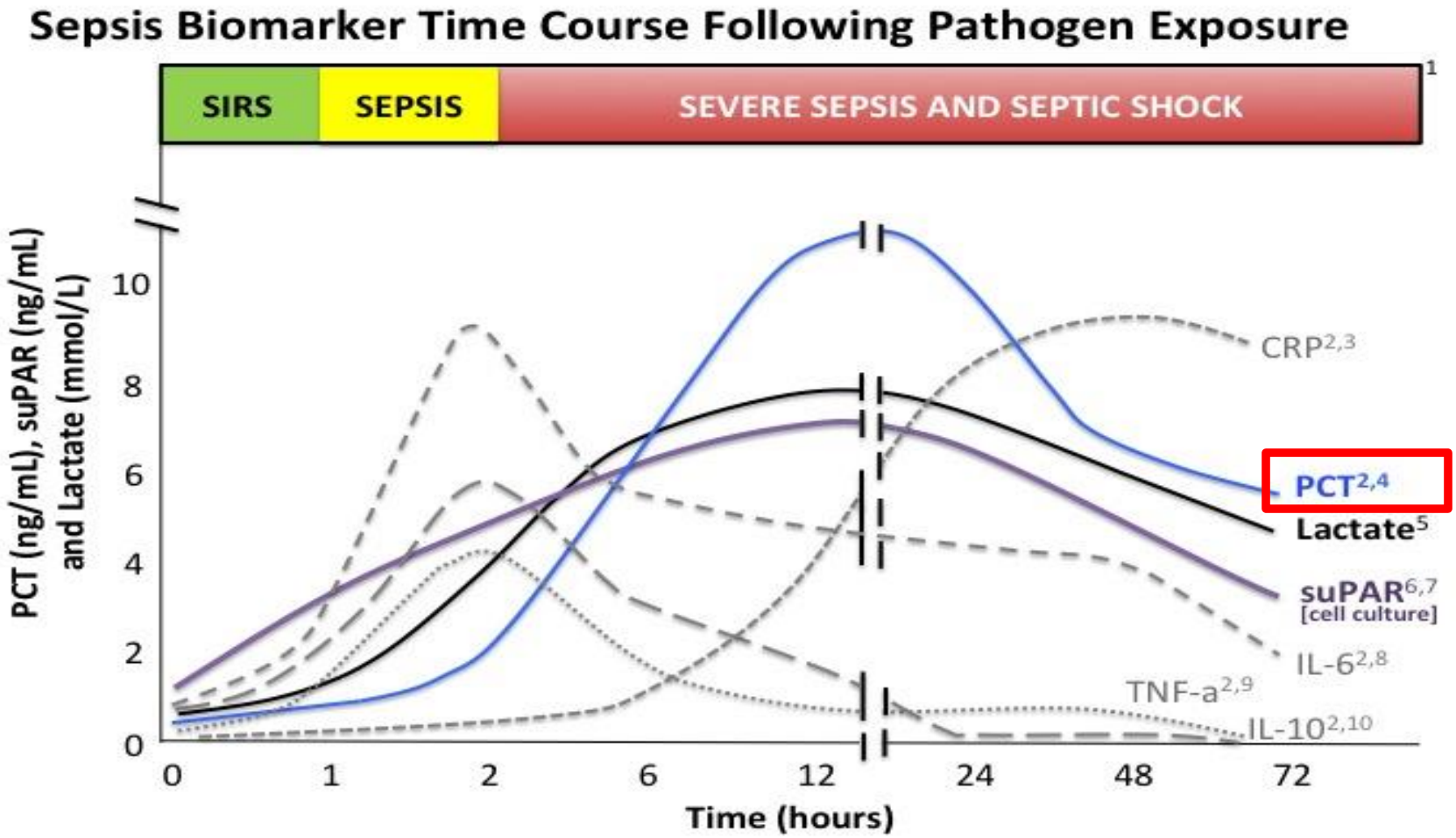
Hybrid Laboratory: PCT and IL-6



References: [1]Meisner M, et al. *Clin Chem Lab Med* 2000;38:989-995. [2]Meisner M. J Lab Med 1999;23:263-272. [3]Schmit X, et al. *Infection* 2008;36:213-219. [4]Gibot S, et al. *Crit Care Med* 2005;33:792-796. [5]Bakker J, et al. *Am J Surg* 1996;171:221-226. [6]Dekkers PE, et al. *Infect Immun* 2000;68:2156-2160. [7]Donadelo, et al. BMC Medicine 2012;10:2. [8]Damas P, et al. *Ann Surg* 1992;215:356-362. [9]Damas P, et al. *Crit Care Med* 1989;17:975-978. [10]Wu H, et al. *Inflam Res* 2009;58:385-393.

Hybrid Laboratory: PCT and IL-6



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Procalcitonin (PCT) Basics

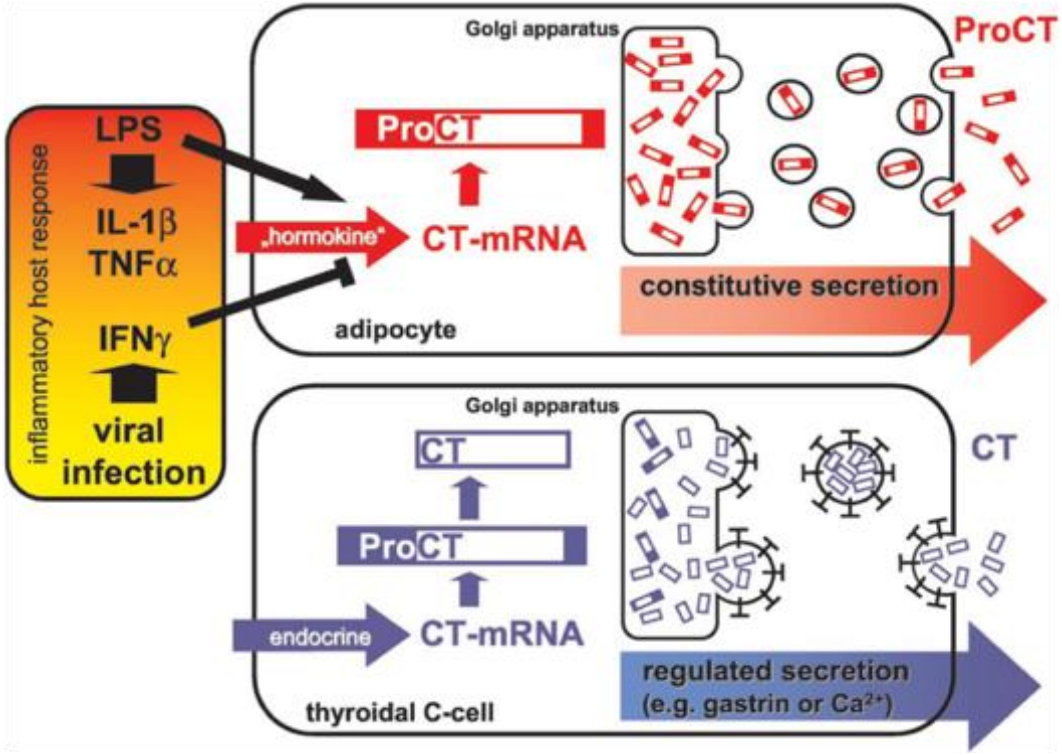


FIG. 5. Schematic diagram of CALC I expression in adipocytes and thyroidal C cells. In the classical neuroendocrine paradigm, the expression of CT mRNA is restricted to neuroendocrine cells, mainly C cells of the thyroid. Initially, the 116-amino acid prohormone ProCT is synthesized and subsequently processed to the considerably smaller mature CT. In sepsis and inflammation, proinflammatory mediators induce CT mRNA. In contrast to thyroidal cells, adipocytes and other parenchymal cells lack secretory granules, and hence, unprocessed ProCT is released in a nonregulated, constitutive manner.

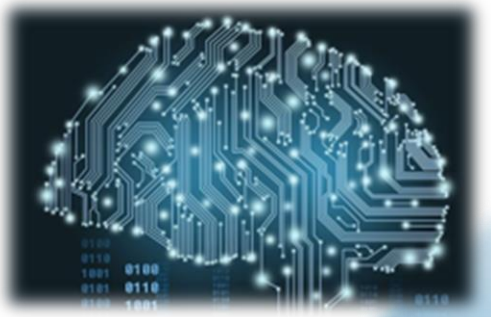
Linscheid et al. Endocrinology 144(12):5578–5584

- Pro-hormone to calcitonin
- Normally produced in C-cells (normal serum levels <0.05 ng/mL)
- Bacterial infections: PCT released into bloodstream uncleaved
- Viral infections: PCT suppressed by IFNγ
- Low in non-specific inflammation, neutropenia, viral/fungal infections

Future of the Hybrid Laboratory for Sepsis Prediction, Detection, and Management

Future Directions

Integrating Molecular Testing, Microbiology, Chemistry/Immunoassay, POCT and Data Sciences

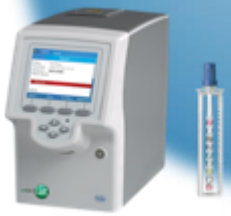


Artificial Intelligence

High-Throughput Automated Molecular Diagnostics

Proteomics

Point-of-Care Molecular



Automated Chemistry / Immunoassay

Conclusions

Clinical Performance	Molecular provides superior performance versus microbiology for detectable pathogens.
Value	Early appropriate and targeted anti-infective therapy improves outcomes.
Speed	Molecular diagnostics and potentially POC pathogen detection reduces “diagnostic blind spot”.
Diagnostic Stewardship	Diagnostic stewardship is needed to optimize molecular testing due to the relatively high cost.
Workflow Optimization	Integration of molecular POCT and laboratory methods with chemistry/immunoassay techniques.
Future	Future will involve integrating multiple test modalities (hybrid lab) with electronic decision support to optimize value and care.