Fast Diagnostics for Bloodstream Infections and their Role in Sepsis

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Disclosure

Maureen Spencer is employed by Accelerate Diagnostics, Inc.

Objectives:

- Describe 3 rapid molecular diagnostics systems that provide organism identification within a few hours
- Describe 3 methods for determining the antibiotic sensitivity of microorganisms
- Describe the role the Infection Preventionist can play in assuring rapid diagnostic results are provided to the clinicians for treatment of bloodstream infections and sepsis

Laboratory Results are Vital to Healthcare

70% of Medical Decisions are Based Upon a Laboratory's Results

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Laboratory Represents only 5% of Healthcare Costs

- While laboratory costs are a small part of a hospital operating budget, it has an substantial influence over the entire budget

Accurate and Timely Results from the Lab

Correct patient treatment executed quickly

- **Improve patient outcome**
- **No wasted medical/labor costs**
- **Increase patient satisfaction**

- **Higher patient throughput drive revenue**
- **Better resource utilization**
- **Improved hospital financials**

IDSA: Diagnostic Technology (2013)

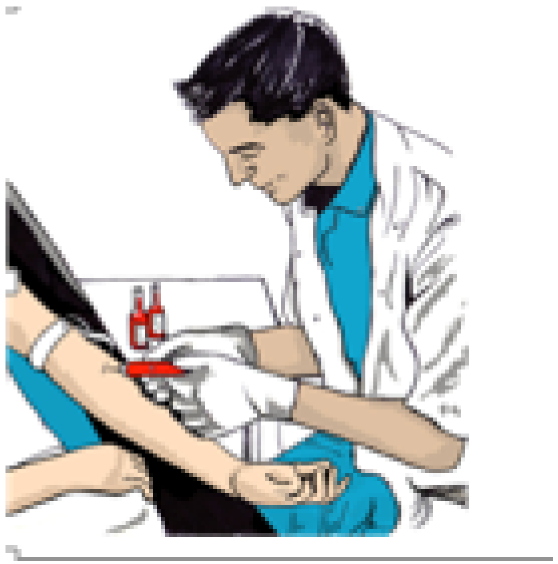
- Despite advances in diagnostic technology, there is an urgent need for tests that are:
  - easy to use
  - identify the microbe causing the infection
  - determine whether it is drug resistant
  - provide results faster than current tests
- **Faster, more accurate tests** would help ensure that patients are receiving:
  - the best treatment for a variety of infectious diseases
  - guide more effective infection control practices
  - improve the tracking of outbreaks.
- Better tests would also help protect our dwindling supply of effective antibiotics by reducing their misuse

Improved Infectious Diseases Diagnostics • CID 2013:57 (Suppl 3) • S139

Typical High Tech Lab Today

Molecular Lab – Labs of the Future

Blood Culture Journey



Evaluate Blood Cultures Procedures and Contamination Rates

Blood Culture – Key Elements - Competencies

- Selection of blood culture draw site
- Application of aseptic technique
- Collection of adequate volume of blood
- Collection of sufficient blood culture sets
- Appropriate timing of blood culture collection

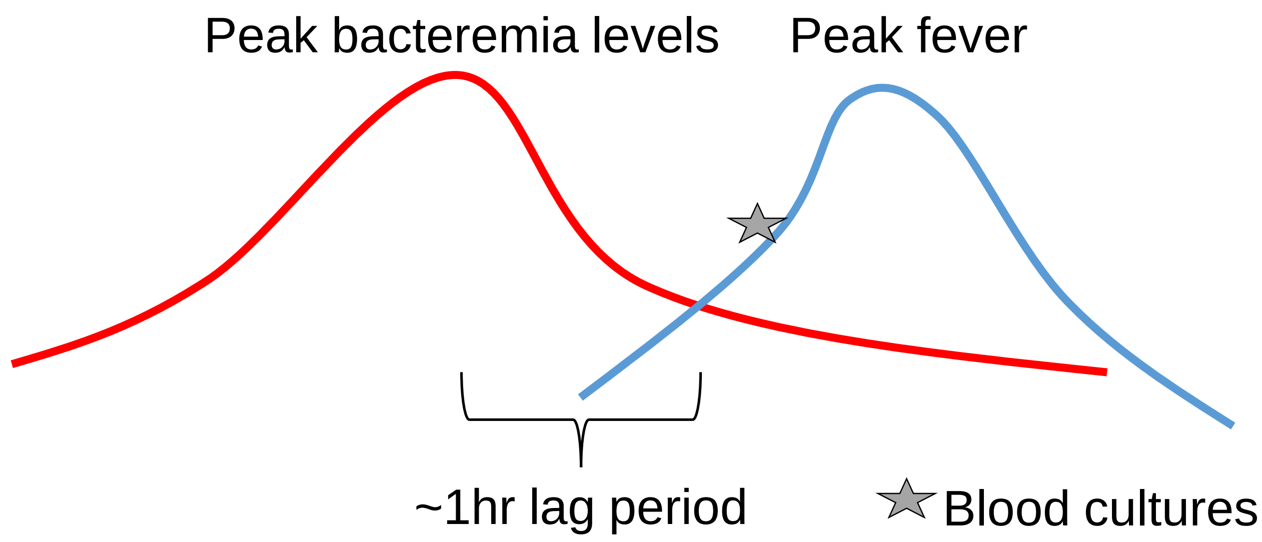
Blood Culture – Aseptic Technique

Aseptic technique is used to avoid contamination of blood culture bottles by normal skin bacteria

1. The skin is cleansed with 70% isopropyl or ethyl alcohol and allowed to air dry.
2. The skin is then cleansed with a 2% chlorhexidine solution and allowed to air dry.
3. Aseptic technique is used during venipuncture to prevent contamination of cleaned skin.
4. Finally, the blood culture bottle tops are cleansed with alcohol before blood is introduced.

Blood Culture – Timing of Culture

- Optimal timing of BC collection is just before the onset of a shaking chill
  - Symptoms of bacteremia lag ~1 hour behind peak bacteria levels in the blood
- Timing is difficult to anticipate, so common practice is to draw BC when fever is detected
  - Two blood culture sets obtained at this time
- Optimally, BC should be drawn before antimicrobial therapy is given



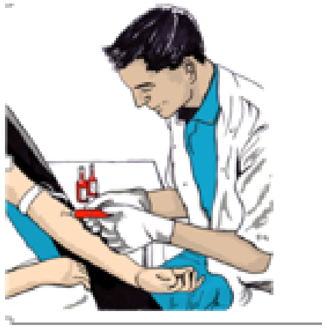
Blood Culture Contamination

Who draws them? Where are they obtained? Why contamination?

- BC contamination - clinically significant problem that results in extra expense and patient harm
- Case-control study in the UK found BC contamination was associated with 5.4 extra hospital days at a cost of approximately $7500 USD
- Similarly, in the US, Gander and colleagues observed excess charges of **$8720 per contamination event**
- Blood culture contamination is associated with **unnecessary antibiotic** treatment in approximately 30%–40% of patients – can lead to adverse outcomes

- Gander RM, Byrd L, DeCrescenzo M, Hirany S, Bowen M, Baughman J. Impact of blood cultures drawn by phlebotomy on contamination rates and health care costs in a hospital emergency department. J Clin Microbiol **2009**; 47:1021–4.
- Alahmadi YM, Aldeyab MA, McElnay JC, et al. Clinical and economic impact of contaminated blood cultures within the hospital setting. J Hosp Infect 2011; 77:233–6.
- Lee CC, Lin WJ, Shih HI, et al. Clinical significance of potential contaminants in blood cultures among patients in a medical center. J Microbiol Immunol Infect 2007; 40:438–44.

Cost of Contaminated BC



- Treatment with broad-spectrum IV antibiotics requiring hospital stay
- Delay in hospital discharge and longer Length of Stays (LOS)
- Additional bed, pharmacy and laboratory (micro, chemistry, radiology) costs
- Contaminated BC may meet the CLABSI surveillance definition and not be a true case - $$ CMS Penalties
- Est. >$8000 per case

TABLE 3. Patient charges associated with blood culture results[a]

Blood culture designation	No. of patient episodes	Median charge (25th quartile, 75th quartile)
Negative	960	$18,752 ($17,046, $20,315)
False positive	120	$27,472 ($21,063, $37,841)
True positive	153	$51,055 ($39,957, $69,459)

[a] All inpatient charges were tallied; 61 cost centers were surveyed, including laboratory, pharmacy, and radiology departments.

Δ $8,720

Calculate the cost of contaminated blood cultures for the Infection Control Committee each month

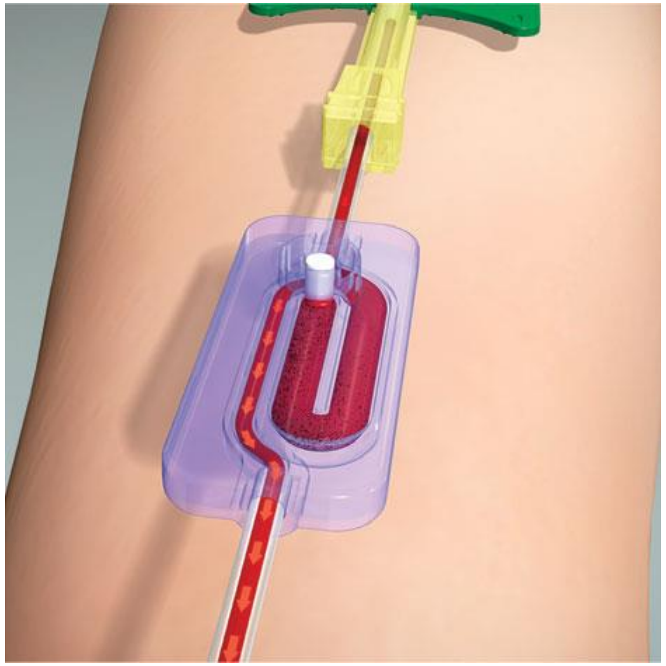
Gander et al. J Clin Microbiol. 2009 Apr;47(4):1021-4

Example of Contaminated Blood Culture Dashboard with Cost ($8720/case)

LABORATORY SERVICES:	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Total	Cost	Benchmark
BLOOD CULTURE CONTAMINATION															
# Blood Cultures Drawn		1677	1753	1662	1658	1359	1463	1482	1392	1548	1540		**15534**		
Total # of Contaminants		58	47	50	54	42	46	57	41	51	57		503	$4,386,160	
Blood Culture Contamination Rate		**3.5%**	**2.7%**	**3.0%**	**3.3%**	**3.0%**	**3.1%**	**3.8%**	**2.9%**	**3.3%**	**3.7%**			**3.2%**	≤ 2.5 %
# Blood Cultures Drawn by Lab		525	642	666	727	744	721	854	812	903	891		7485		
Total # of Contaminants		16	15	11	17	18	16	18	18	18	26		173	$1,508,560	
Lab Drawn Contamination Rate		**3.1%**	**2.3%**	**1.7%**	**2.3%**	**2.4%**	**2.2%**	**2.1%**	**2.2%**	**2.0%**	**2.9%**			**2.3%**	≤ 2.5 %
# Blood Cultures Drawn by ED		846	737	667	564	441	405	787	387	415	434		5683		
Total # of Contaminants		31	19	23	24	20	19	33	20	24	22		235	**$2,049,200**	
ED Drawn Contamination Rate		**3.7%**	**2.6%**	**3.5%**	**4.3%**	**4.5%**	**4.7%**	**4.2%**	**5.2%**	**5.8%**	**5.1%**			**4.4%**	≤ 2.5 %
# Blood Cultures Drawn by Nurses		51	62	41	60	1	131	13	48	37	4		448		
Total # of Contaminants		2	2	1	2	0	5	2	1	1	0		16	**$139,520**	
Nurse Drawn Contamination Rate		**3.9%**	**3.2%**	**2.4%**	**3.3%**	**0.0%**	**3.8%**	**15.4%**	**2.1%**	**2.7%**	**0.0%**			**3.7%**	≤ 2.5 %
# Blood Cultures Drawn by WFED		190	213	175	156	134	111	128	64	105	107		1383		
Total # of Contaminants		7	7	7	5	2	2	10	1	5	6		52	**$453,440**	
Weslaco FED Contamination Rate		**3.7%**	**3.2%**	**4.0%**	**3.2%**	**1.5%**	**1.8%**	**7.8%**	**1.6%**	**4.8%**	**5.6%**			**3.7%**	≤ 2.5 %
# Blood Cultures Drawn by FED		65	99	113	151	39	83	88	71	88	104		901		
		7	4	8	6	1	4	1	1	3	3		38	**$141,360**	
FED Contamination Rate		**3.1%**	**4.0%**	**7.1%**	**4.0%**	**2.6%**	**4.8%**	**1.1%**	**1.4%**	**3.4%**	**2.9%**			**3.4%**	≤ 2.5 %

Gander et al. J Clin Microbiol. 2009 Apr;47(4):1021-4

Consider New Blood Culture Diversion Technology to Prevent Contamination

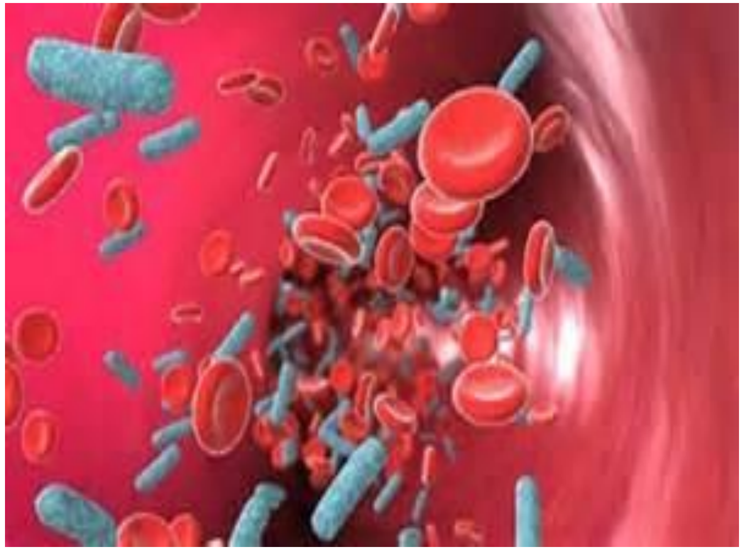


Device #1

Device #2

- Rupp M, et al. Reduction in Blood Culture Contamination Through Use of Initial Specimen Diversion Device. Clin Infec Dis Mar 2017
- Jared Sutton, MPH, CIC. Preventing Blood Culture Contamination using a Novel Engineered Passive Blood Diversion Device
  APIC. June 13-15, 2018 Minneapolis, MN
- Michael Allain, MS, RN, ACNS-BC, CCRN. A CNS-Led Project That Reduced Blood Culture Contaminations in One Emergency Department to Below Expected Levels. Clinical Nurse Specialist. May/June 2018

Blood Culture Organism Identification



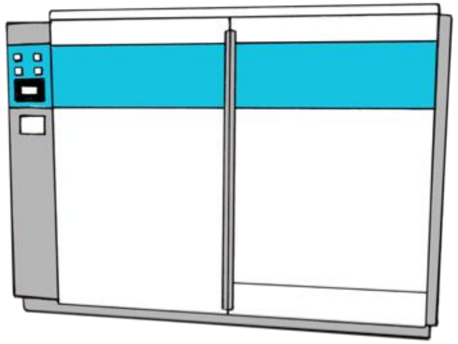
Challenges with Traditional Methods

- ✓ Slow – takes days to result
- ✓ Specimen processing
- ✓ Inexpensive $ for lab - **not for hospital**
- ✓ May have inferior performance

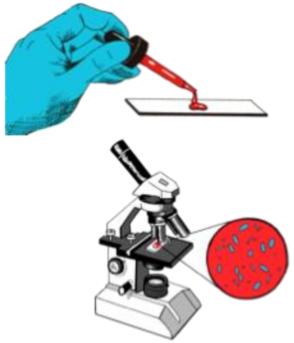
Blood culture Standard of care ID & AST workflow ~48-96 hours

1 patient blood draw

2 blood bottle incubation & screening



3 perform gram stain

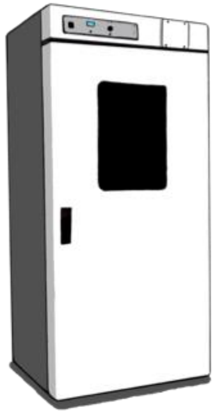


4 initial plate streaking

5 **OPTIONAL**: ID and resistance markers*

Incubation depends on the organism's growth –
typically from 6-18 hours

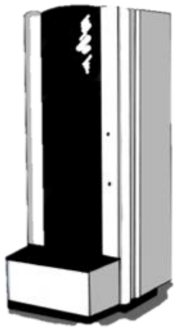
6 overnight incubation



8-12 hrs incubation

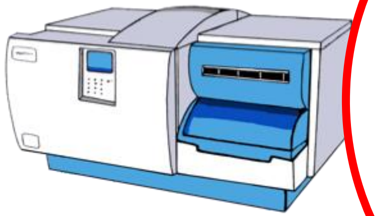
7 colony selection

8 **OPTIONAL**: MALDI-TOF ID



9 .5 McFarland

10 ID & susceptibility



11 Optimized Therapy

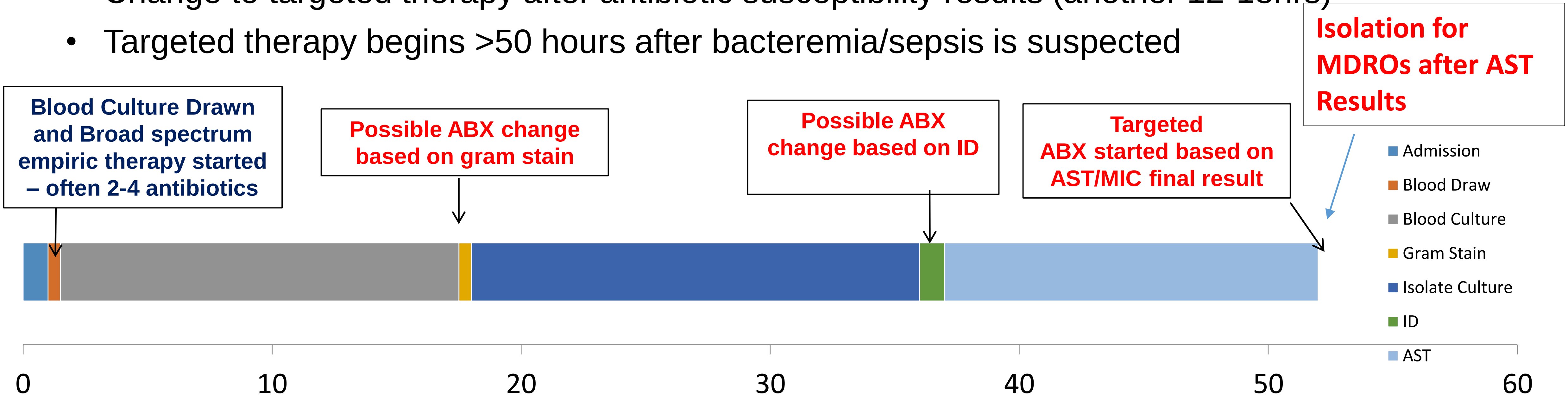
~48-96 hours

*ID only and resistance marker technologies are incremental to AST workflow.

Patient impact – Standard of Care Procedures

Antibiotic therapy workflow:

- If bacteremia or sepsis is suspected, empiric therapy started
- Wait on BC bottle positivity
- Next change of therapy at gram stain results (16-24hrs after BC drawn)
  - Gram stain informs on ID of organism only, no antibiotic susceptibilities – Resistance Markers may be available but does not assist with targeted therapy
- Change to targeted therapy after antibiotic susceptibility results (another 12-18hrs)
- Targeted therapy begins >50 hours after bacteremia/sepsis is suspected



Blood Culture Diagnostic Technologies

Identification

- Molecular genotypic PCR - <2 hr turn around time (TAT)
- 4 Molecular ID Systems - <2 hr TAT

Antibiotic Sensitivity Test (AST)

- 3 Manual traditional AST – Broth Dilution, Kirby Bauer, Etest
- 3 Standard Automated ID and AST – 2-4 day TAT
- 1 combined phenotypic ID and AST with MICs in <7hrs TAT

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journal homepage: www.ajicjournal.org

Brief report

A primer on on-demand polymerase chain reaction technology

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Practice Forum

Rapid diagnostics for bloodstream infections: A primer for infection preventionists

Charles E. Edmiston PhD, SM(ASCP), CIC [a], Robert Garcia BS, MT, CIC [b], Marsha Barnden RNC, MSN, CIC [c], Barbara DeBaun RN, MSN, CIC [d], Helen Boehm Johnson MD [e,*]

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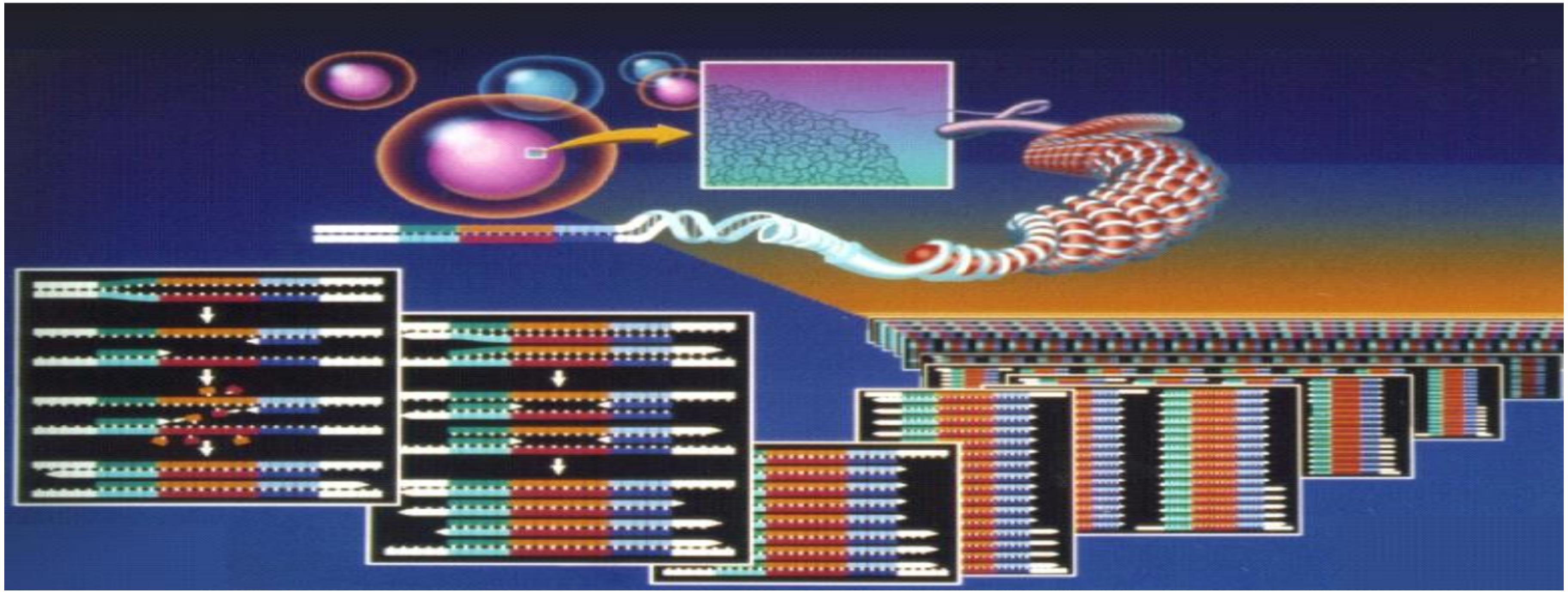
ID #1 Polymerase Chain Reaction (PCR)

A single or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence

- Offers accuracy & specificity
- Offers speed
- Offers detection at even very small amounts of organisms

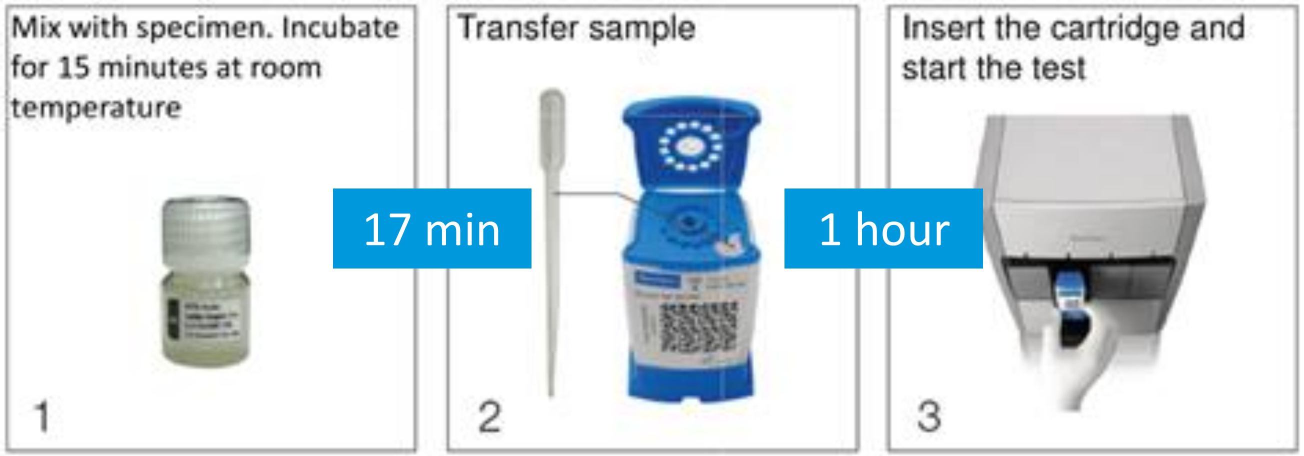


#1 Rapid PCR

#1 Rapid PCR

Workflow

Test



Differentiation

one, two, four, 16, 48, or 80-module configuration

#1 PCR Tests – One for Blood Cultures

Workflow

Test

Differentiation

Type of Infection	Test
Healthcare Associated $50-65 / test	MRSA
	SA Nasal Complete
	MRSA/SA SSTI
	Blood Culture MRSA/SA
	C. difficile
	C. difficile/Epi
	vanA
	Norovirus
	Carba-R

Type of Infection	Test
Critical Infectious Disease	MTB/RIF
	Flu
	Flu/RSV XC
	EV
	Ebola

Type of Infection	Test
Sexual Health/Woman's Health	CT/NG
	GBS LB
	GBS
	TV

#2 Rapid Organism Identification Blood Culture Identification (BCID)

BCID Panel tests for a comprehensive set of 24 gram positive, gram negative and yeast pathogens and 3 antibiotic resistance genes associated with bloodstream infections. The BCID Panel detects and identifies the most common causes of bloodstream infections

#2 Rapid ID

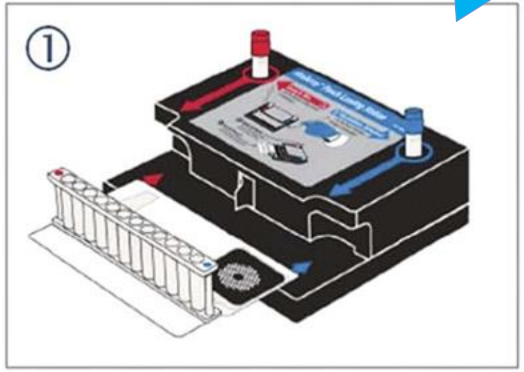
5 min+
Hands-On
1.25h TAT

Workflow

Menu

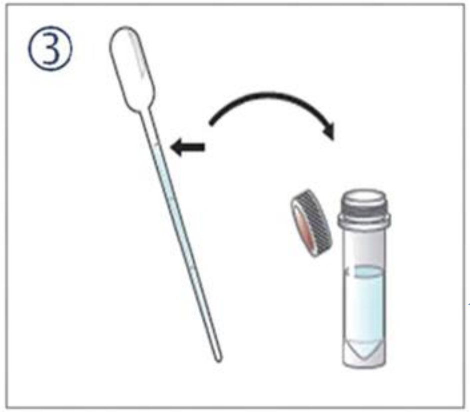
Differentiation

Pouch

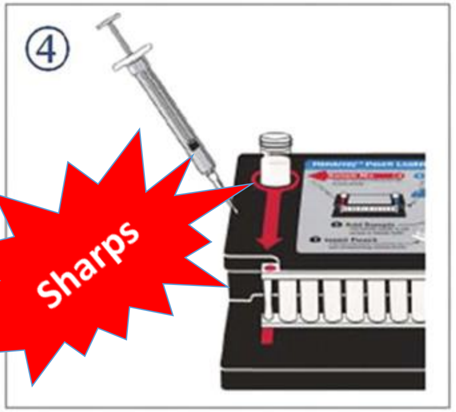


Load pouch into loading block

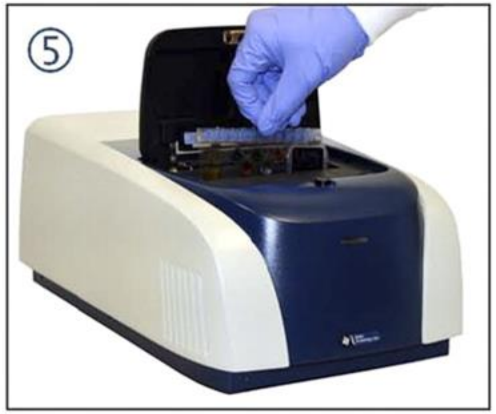
Inject hydration solution



Add patient sample to buffer



Inject sample



Load pouch

#2 Rapid ID Panels

Workflow

Menu

Differentiation

Gram Pos. Bacteria ID & Resistance Markers	Gram Neg. Bacteria ID & Resistance Markers
• **Bacterial ID** • Enterococcus • *Listeria monocytogenes* • Staphlococcus • Staph. aureus • Streptococcus • *Strep. agalactiae* • *Strep. pyogenes* • *Strep. pneumoniae* • **Resistance markers** • vanA (vancomycin) • vanB (vancomycin) • mecA (MRSA indicator)	• **Bacterial ID** • *Acinetobacter baumannii* • *Haemophilus influenzae* • *Neisseria meningitidis* • *Pseudomonas aeruginosa* • Enterobacteriaceae • Enterobacter cloacae complex • *Escherichia coli* • *Klebsiella oxytoca* • *Klebsiella pneumoniae* • Proteus • *Serratia marcenscens* • **Resistance markers** • KPC – carbapenem resistance

#3 Rapid ID

Results in ~ 2.5 hrs

System enables clinicians to rapidly identify the pathogens responsible for some of the most complex, costly, and deadly infectious diseases

#3 Rapid ID

10 min+
Hands-On
~2.5 hr TAT

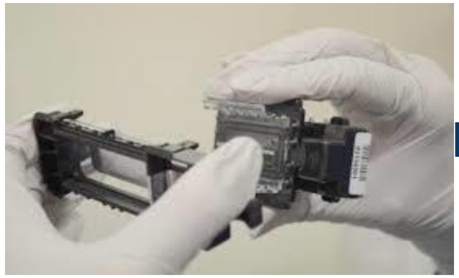
Workflow

Menu

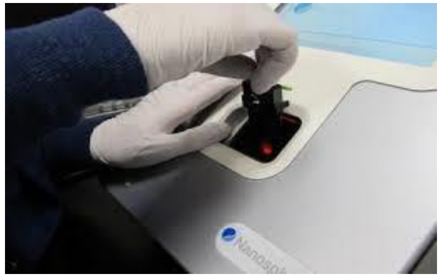
Differentiation

Load each consumable into the Processor *SP*

Remove the cartridge



Disassemble test cartridge



Scan barcode on slide, then place in Reader

#3 Rapid ID Panel

Workflow

Menu

Differentiation

Gram Pos. Bacteria ID & Resistance Markers

- **Bacterial ID**
  - *Enterococcus faecalis*
  - *Enterococcus faecium*
  - Listeria spp.
  - Staphylococcus spp.
    - *Staph. aureus*
    - *Staph. epidermis*
    - *Staph. lugdunensis*
  - Streptococcus spp.
    - Strep. anginosus Group
    - *Strep. agalactiae*
    - *Strep. pyogenes*
    - *Strep. Pneumoniae*
- **Resistance markers**
  - vanA (vancomycin)
  - vanB (vancomycin)
  - mecA (MRSA indicator)

  - **Respiratory Panel**
  - Identification of a broad panel of viruses and bacteria commonly responsible for respiratory infections from
  - nasopharyngeal swabs (NPS)

Gram Neg. Bacteria ID & Resistance Markers

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

  - **Gastrointestinal Panel**
  - *C. difficile*
  - Enteric Pathogens

#4 Rapid Biosystem – for Yeast and Bacteria – direct from blood specimen)

Fastest species identification of major bacteria directly from whole blood *without the wait for blood culture*

#4 Rapid Biosystems

Workflow

Technology

Menu

Blood Culture Assay

(1) Build Cassette
(2) Remove cap on blood
(3) Invert into Cassette

Load purple top tube

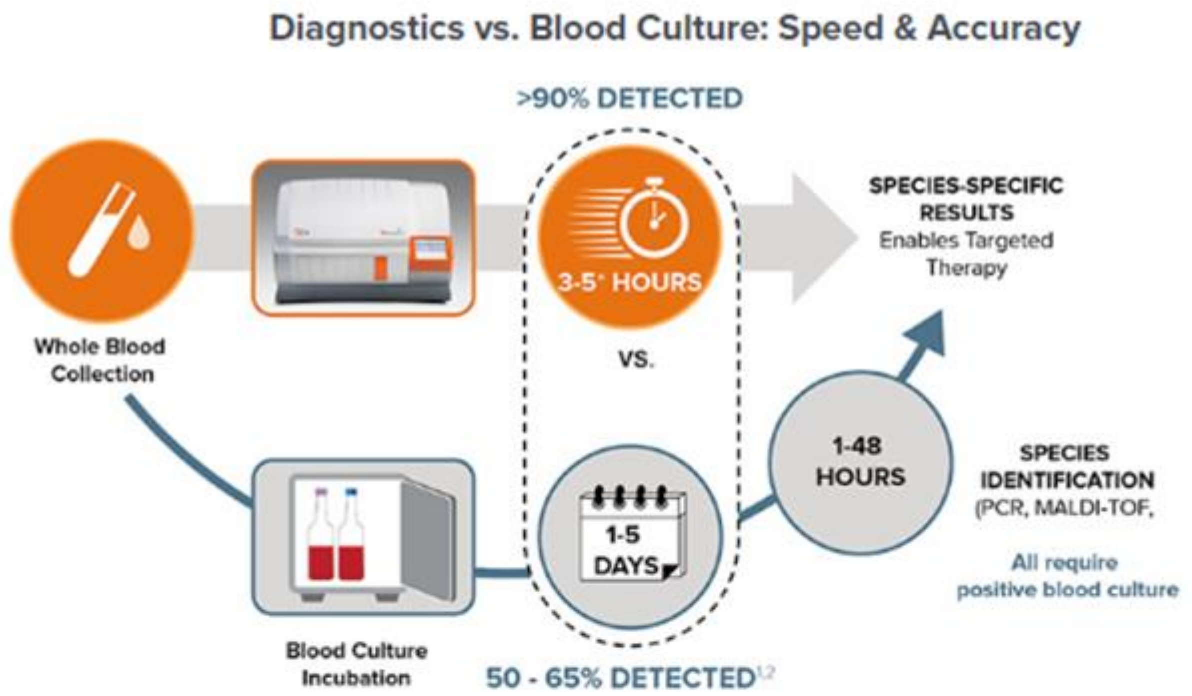
#4 Rapid Biosystem Technology

Workflow

Technology

Menu

Blood Culture
Assay



#4 Rapid Biosystem Menu and Cost

Workflow

Technology

Menu

Blood Culture Assay

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

Bacteria Panel
- *E. faecium*
- *S. aureus*
- *K. pneumoniae*
- *P. aeruginosa*
- *E. coli*

$200-250 / test

#4 Direct Diagnostics utilize proprietary **Magnetic Resonance** technology to enable faster and more accurate identification for pathogens that cause sepsis

#5 Rapid ID

#5 Rapid ID - MALDI-TOF MS

- Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry
- ID of bacteria, yeast and fungi
- Identification by *signature* high-abundance proteins (primarily ribosomal proteins)
- Signature protein patterns are compared / matched to an extensive open database

#5 ID MALDI-TOF

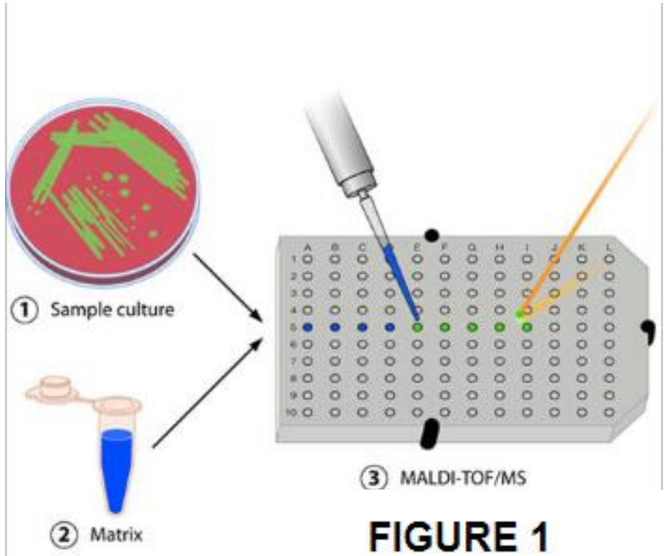
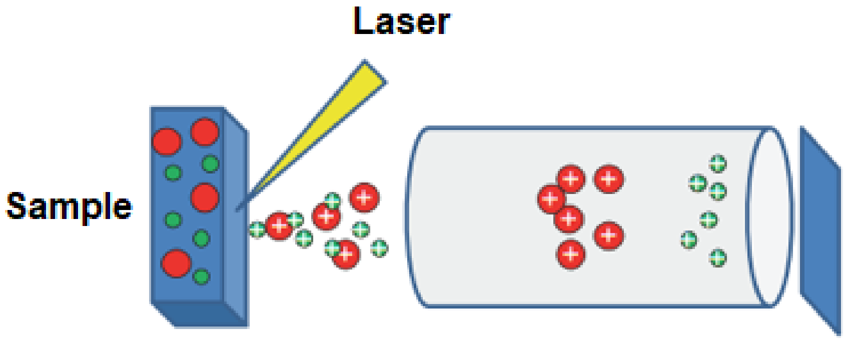
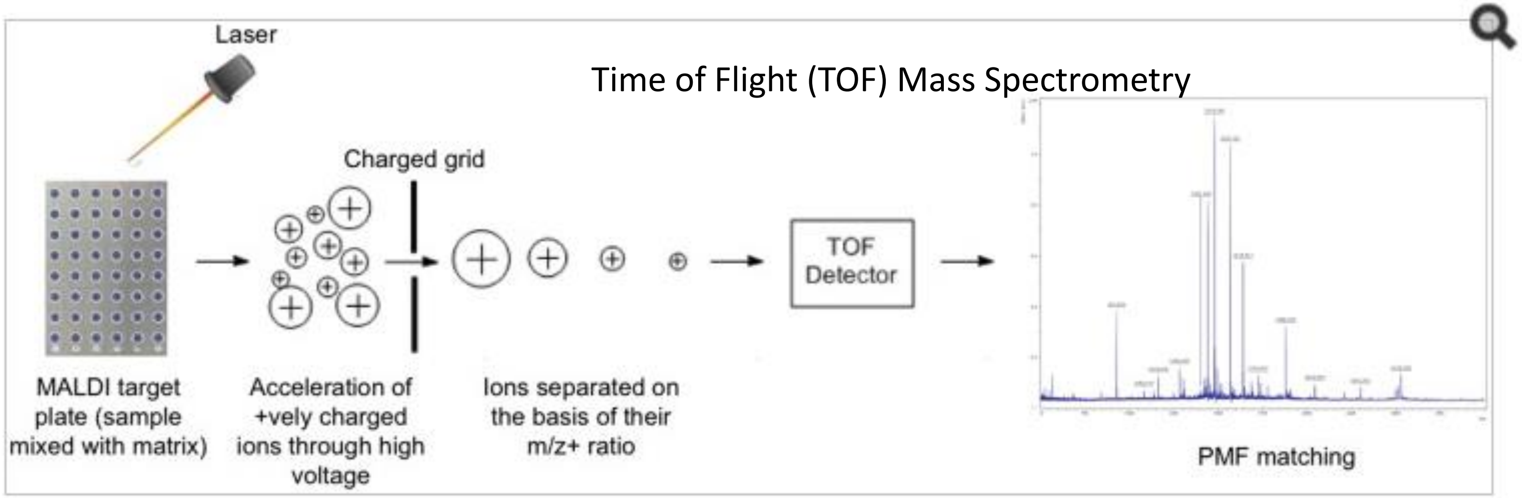


FIGURE 1

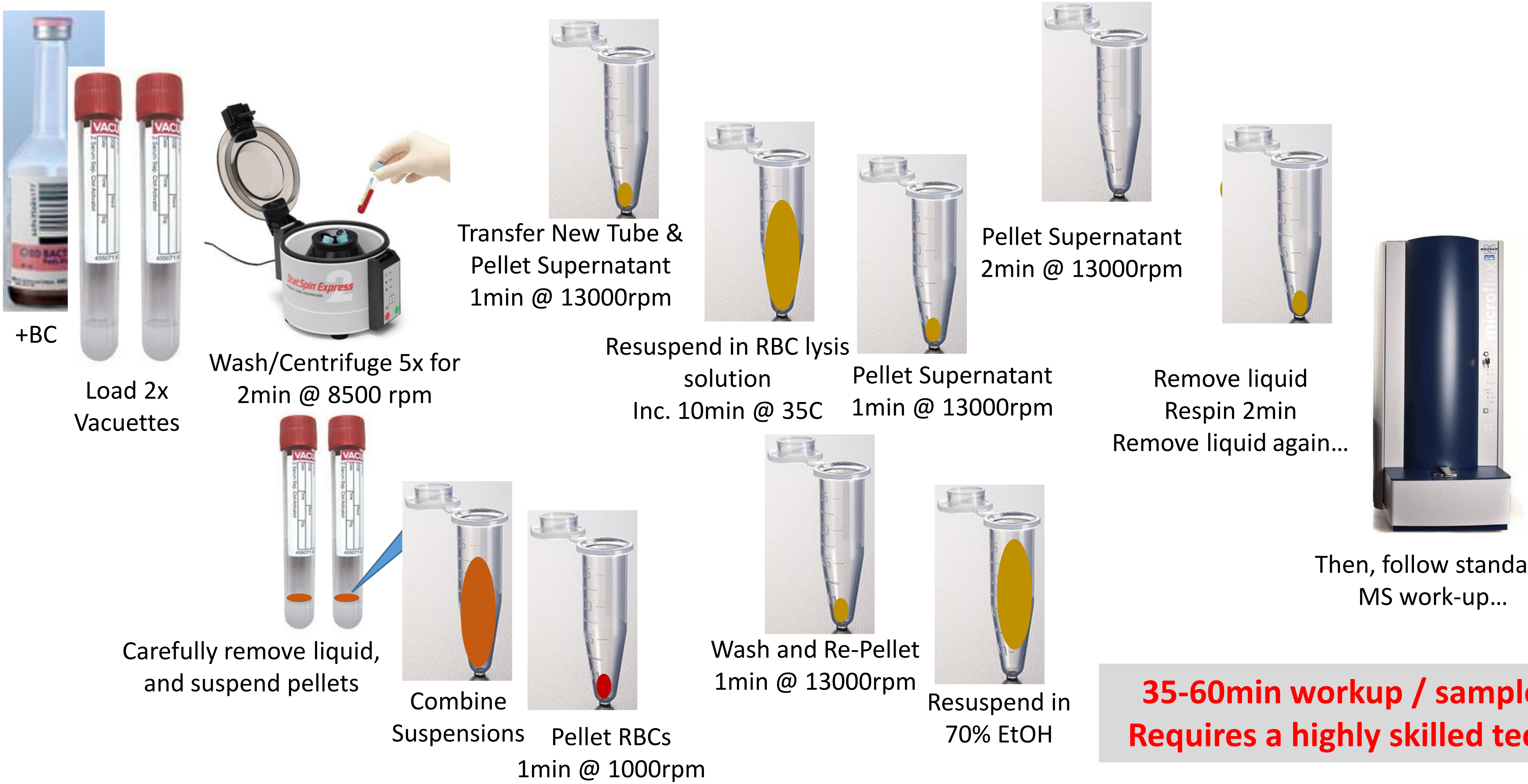




Schematic diagram showing the work-flow in a MALDI-TOF MS.

Peptide mass fingerprinting

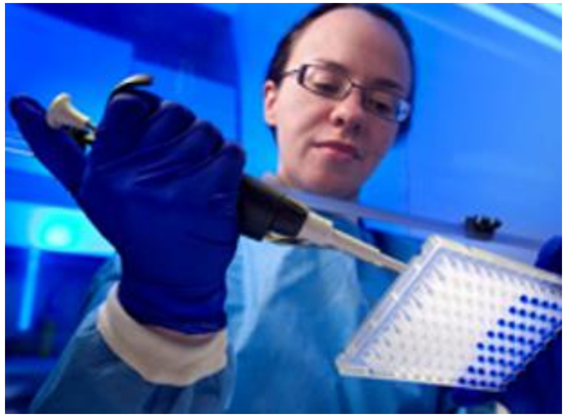
#5 “Rapid” Direct MALDI Workflow



35-60min workup / sample
Requires a highly skilled tech

Stevenson, et al. Rapid Identification of **Bacteria** in Positive Blood Culture Broths by MALDI-TOF MS. JCM, Feb. 2010, p. 444–447.

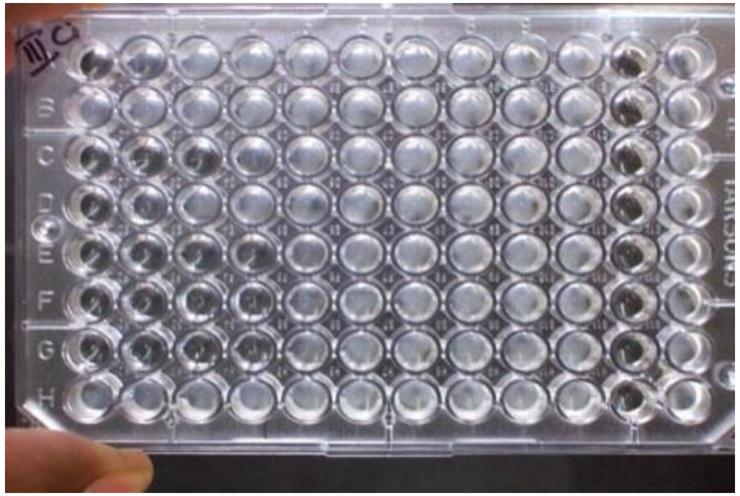
Antimicrobial Sensitivity Tests (AST)

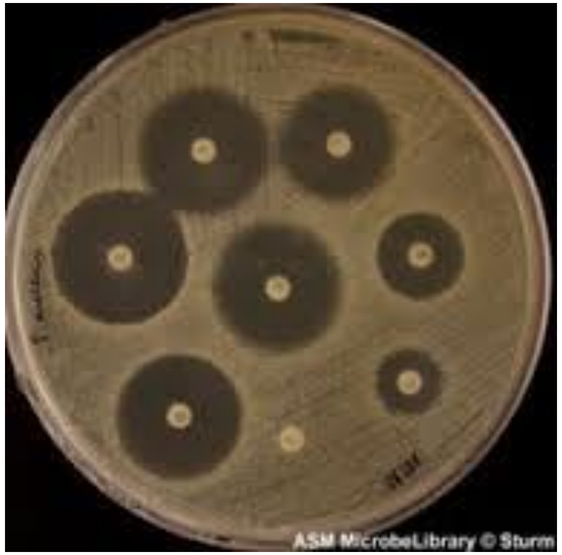


3 Manual AST

Three Common Methods

- Broth Microdilution (BMD)
- Disc Diffusion (DD)
- Etest





#1 Manual AST – Broth Micro Dilution (BMD) Workflow

A serial dilution of antibiotic is made in broth (growth media)

- Concentrations halve with each dilution
  i.e. 32, 16, 8, 4, 2, 1

Antibiotic dilutions are placed into wells of 96-well microtiter plate with concentration gradient going left to right

Bacteria are inoculated into each well of BMD plate

Inoculated BMD plate is placed in an incubator for 16-24 hours

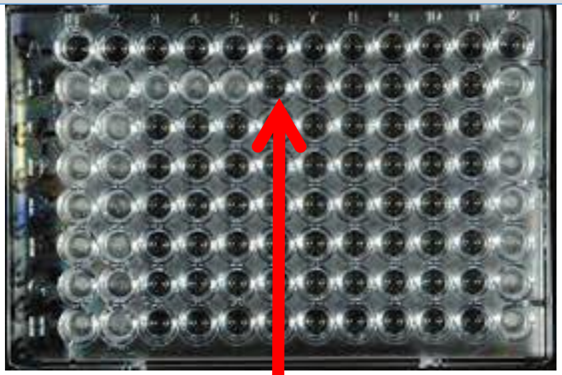
Post-incubation, BMD plate is read for results by looking for growth in the wells across the antibiotic dilution. The Minimum Inhibitory Concentration (MIC) is the first well with no growth – the lowest concentration of antibiotic that stopped bacterial growth.

Sample BMD

Antibiotic Gradient

Concentration per column

0.25 0.5 1 2 4 8 16 32 64 128 256



Growth inhibited here, so this is the MIC

#2 Manual AST – Disc Diffusion Workflow

1

Select isolated bacterial colonies

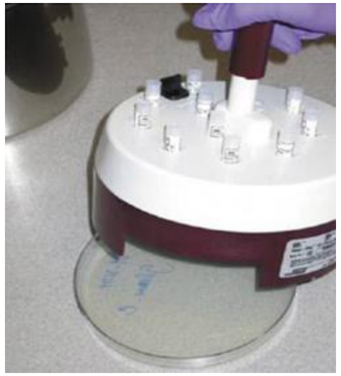
2

Make a 0.50 McFarland (Bacterial suspension)

3

Inoculate the agar plate

4

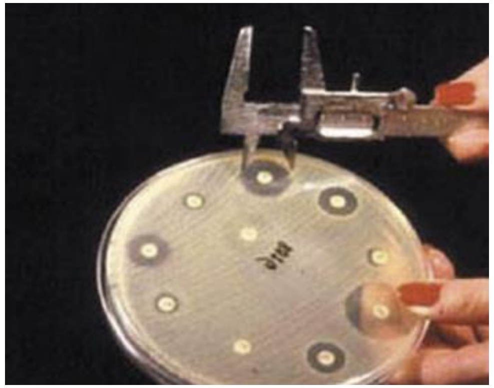


Place discs containing antibiotic on plate

5

Incubate the agar plate overnight

6



Measure the zone of inhibition

#3 Manual AST – Etest workflow

1

Select isolated bacterial colonies

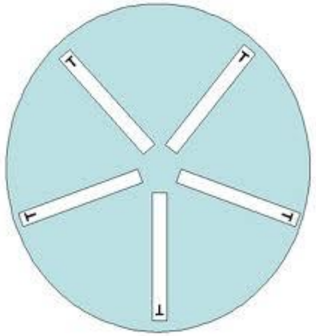
2

Make a 0.50 McFarland (Bacterial suspension)

3

Inoculate the agar plate

4

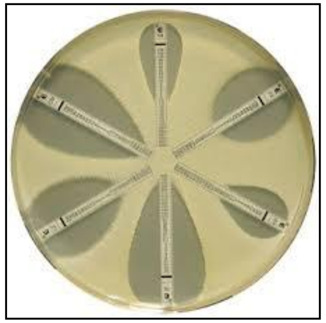


Place Etest strips on agar plate

5

Incubate the agar plate overnight

6



Measure the zone(s) of no growth

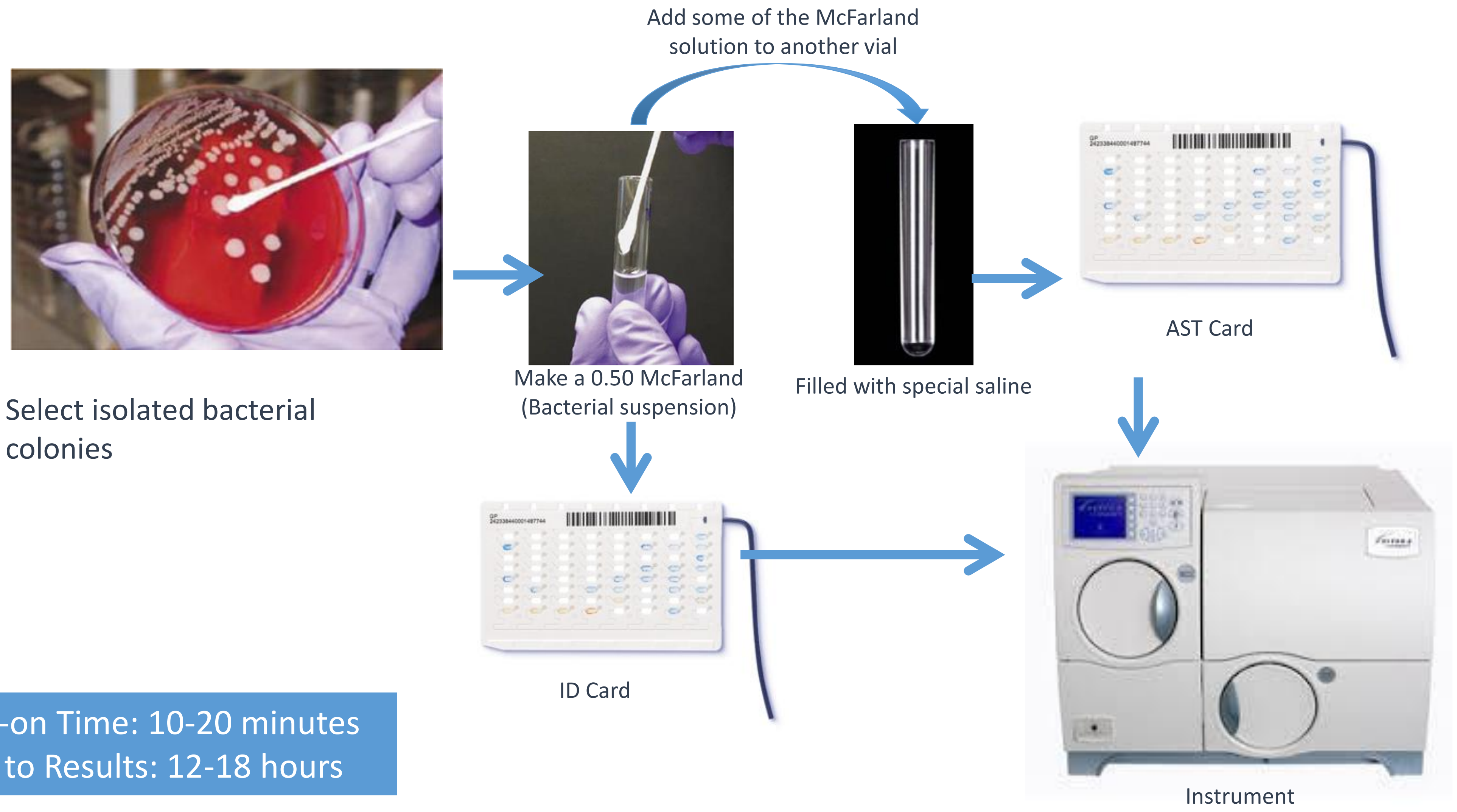
Automated AST - Standard of Care (SOC)

System #1

System #2

System #3

Automated AST– #1 workflow

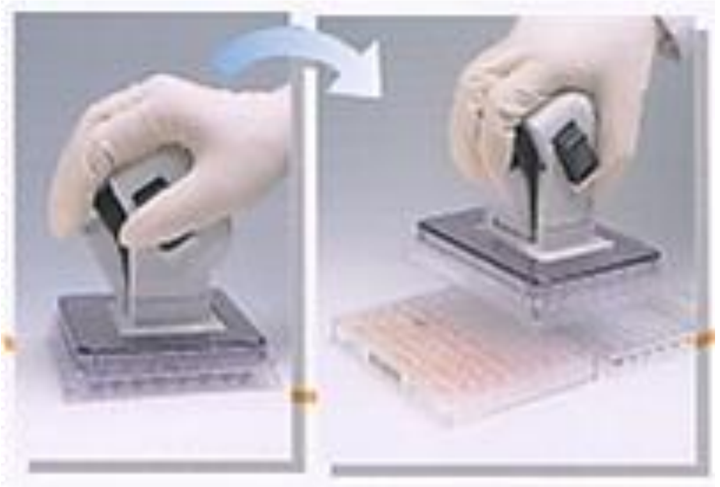


Hands-on Time: 10-20 minutes
Time to Results: 12-18 hours

Automated AST #2 Workflow

Select isolated bacterial colonies with PROMPT Inoculation System

Suspend bacteria in inoculum solution



Use system to inoculate 96-well panel

Place panel in instrument

Hands-on Time: 10-20 minutes
Time to Results: 12-18 hours

Automated AST #3 Workflow

Select isolated bacterial colonies

Make a 0.50 McFarland (Bacterial suspension)

Add some of the prepared ID Broth solution to AST Broth

Add drop of indicator fluid to AST Broth before adding ID Broth solution

Inoculate panel with ID Broth

Inoculate panel with AST Broth

AST Panel

AST Instrument

Hands-on Time: 10-20 minutes
Time to Results: 12-18 hours

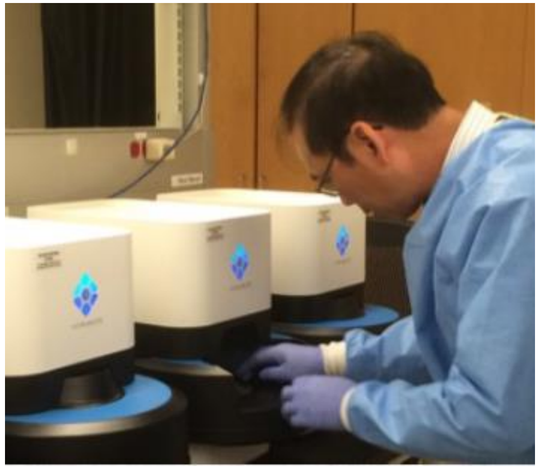
#4 – New Fast Antibiotic Sensitivity System that provides ID and AST ~7hrs

Direct from Positive Blood Culture (does not require colony isolation)

Direct from Positive Blood Culture

Fast Results

- Identification in under 90 minutes using Fluorescence In-situ Hybridization (FISH)
- Susceptibility reported ~5 hours after ID
- **~7 hours to microbiology report**

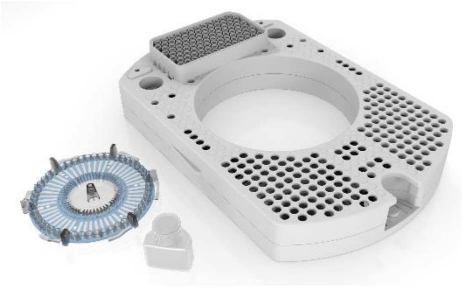


Easy to Use

- <2 min hands-on time
- Bring testing closer to the patient

FDA cleared February 23, 2017

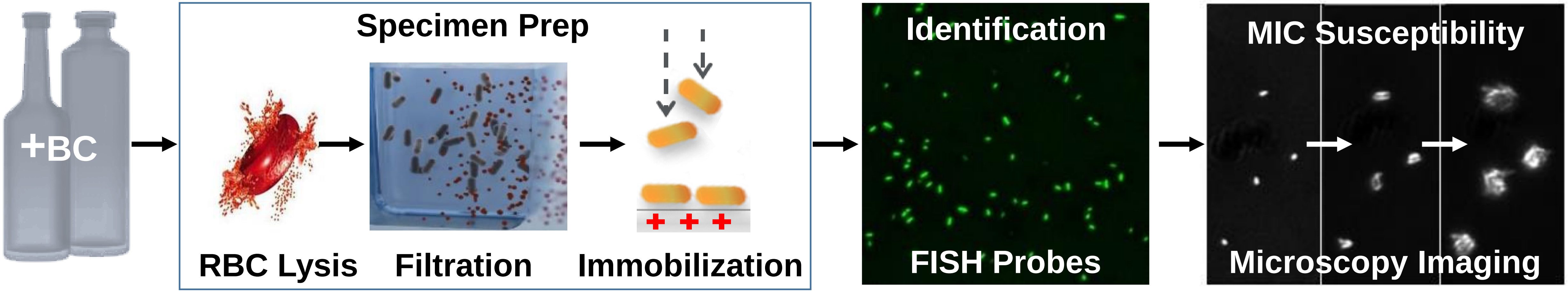
Fast ID and AST BC System



System
- 1-4 module(s)
- Control & Analysis PCs
- Touchscreen monitor

Module
- Automated pipetting robot
- Digital camera
- Custom microscope

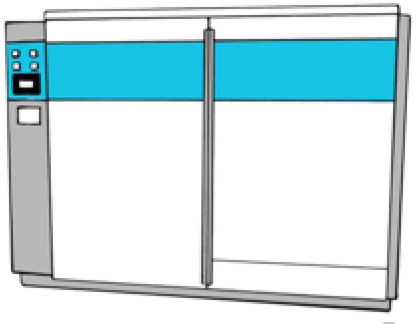
Kit
- 48 flow-channel cassette
- Reagent cartridge
- Sample vial



Accelerate Pheno™ System = FAST Workflow

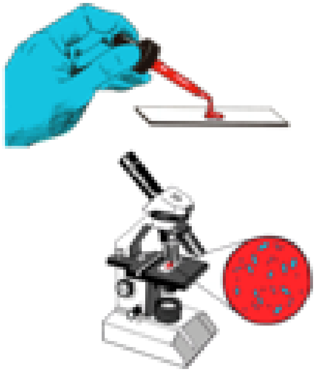
1 patient blood draw

2 blood bottle incubation & screen



Incubation depends on the organism's growth – typically from 6-18 hours

3 perform gram stain



4 **ID & susceptibility with MICs in ~ 7hrs**

5 Optimized therapy: de-escalate or escalate

De-escalate or escalate empiric antibiotic therapy

Place patients with MDROs on isolation precautions at ~7 hours

Research Article

iMedPub Journals
http://www.imedpub.com/

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A Comprehensive Review of the Present and Future Antibiotic Susceptibility Testing (AST) Systems

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Table 1 Summary of the current, emerging and future AST technologies.

System	Methodology	Time taken for AST	Direct from sample
Manual systems			
Broth microdilution	Media (in ml) containing different antibiotics tested against pathogen of interest	24 hours	No
Broth microdilution	Media (in µl) containing different antibiotics tested against pathogen of interest	24 hours	No
Agar dilution	Antibiotic incorporated into agar plates and bacteria inoculated on surface	16-20 hours	No
Disk Diffusion	Antibiotic impregnated filter discs placed on agar surface pre-inoculated with pathogen	16-24 hours	No
Etest	Plastic strip impregnated with gradually decreasing concentrations of antibiotic placed on agar surface pre-inoculated with pathogen	24 hours	No
Automated systems			
Vitek system	Measures light attenuation by optical scanner for growth/no growth detection in micro-wells with different antibiotics	6-36 hours	No
BD Phoenix system	Uses redox indicator for detection of growth in micro-well panels containing various antibiotics at different concentrations	4-16 hours	No
Sensititre	Fluorescence technology used to monitor activity of enzymes produced by test organism emitting fluorescence	18-24 hours	No
Microscan Walkaway	Colorimetric readings using photosensors for optical detection of bacteria	4.5-7 hours	No
Emerging Technologies			
BacterioScan FLLS	Uses laser light source with scattered intensity measurements for accurate OD readings in the presence of antibiotics	6-18 hours	Yes
Smarticles Technology	Detects increase in luciferase activity due to bacterial growth from plasmids containing DNA probes inside phages	< 4 hours	Yes
Accelerate Pheno system	Dark-field microscope used to image cells to record growth vs no growth vs cell lysis	~ 7 hours	Yes
LifeScale system	Changes to cantilever vibration changes measured by sensor and correlated to biomass can determine MIC	~ 3-4 hours or longer	No
Future Technologies			
AFM Cantilever	Measures changes in amplitude of cantilever fluctuations based on immobilized bacteria on the surface of cantilever	< 1 hour	No
MAC system	Bacteria immobilized in agarose and monitored using real-time time-lapse microscopy	4-10 hours	Unsure
SERS-AST	Uses silver nanoparticles in nano-channels to identify SERS spectroscopic patterns to determine MIC	2 hours	No
fASTest	Uses microfluidic channels into which bacterial cells are trapped and monitored for growth with microscopic imaging	< 1 hour	Yes (urine)
Isothermal microcalorimetry (IMC)	Measures heat flowrate of bacterial samples in the presence or absence of antibiotics	~ 24 hours	Yes
m-EIS system	Uses microfluidic impedance measurements to determine capacitance changes in presence of different concentrations of antibiotics	< 4 hours	Yes

Only one that is commercially available and FDA cleared

Future Applications
Severe pneumonia

- 2 million severe pneumonia cases in the US and EU each year would benefit[1]
- Current workflow is complicated and lengthy, 68 hours to AST on average[2]
- Mortality rate of 28-69% in the US[3]
- Cost per US case ranges from $10-40k per patient[4]
- Mortality rate of 29-48% in the EU[5]

EU: CE marked for *in vitro* diagnostic use with the Accelerate Pheno™ system
US: For research use only, not for use in diagnostic procedures.

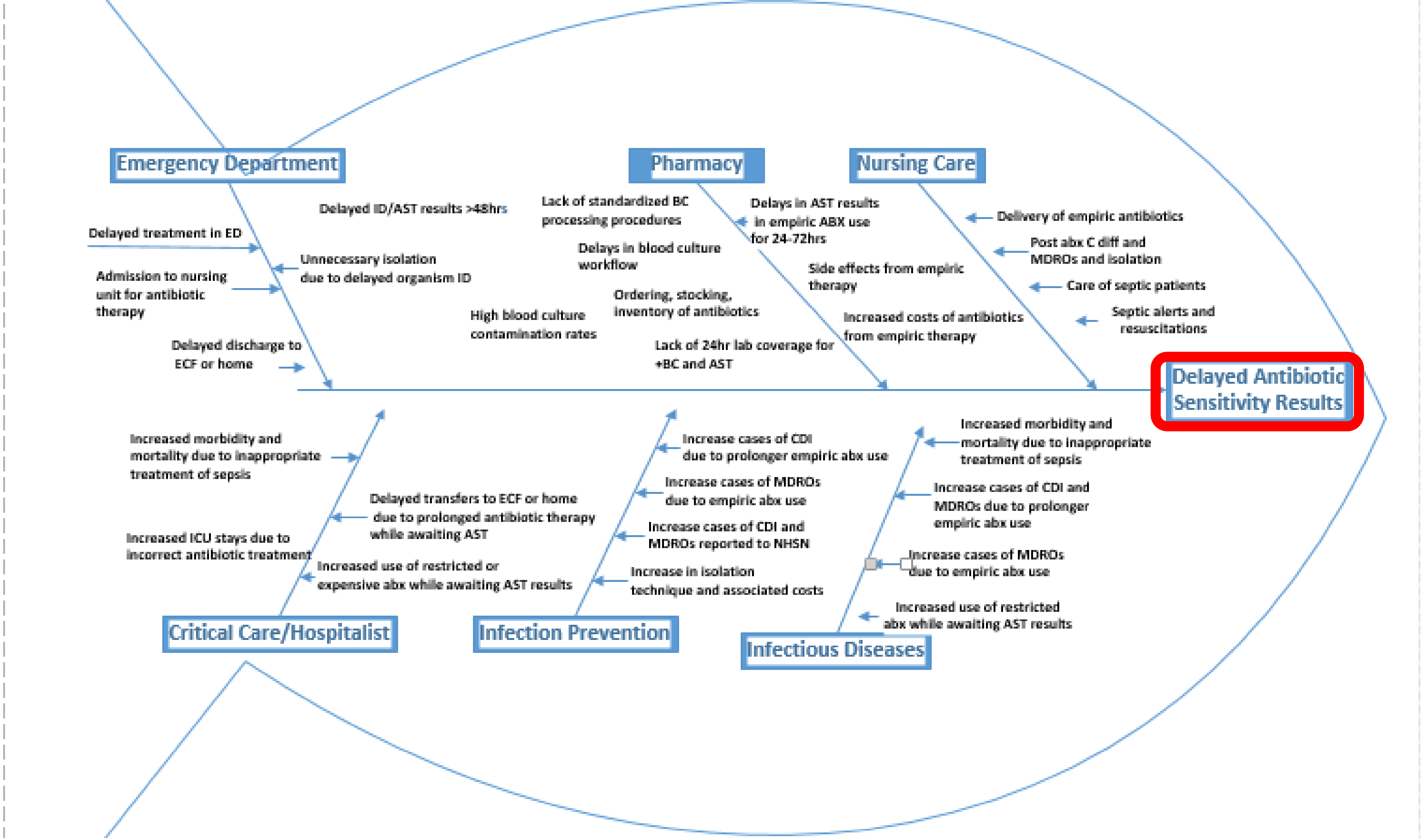
[1] Company estimates (in millions) of total test opportunities based on an accumulation of various third party community and HAI infection sizing market studies
[2] Retrospective chart review of current respiratory standard of care time to result at a large U.S. hospital
[3] Iregui MG, Kollef MH. Ventilator-associated pneumonia complicating the acute respiratory distress syndrome. Semin Respir Crit Care Med 2001; 22(3): 317-326
[4] Safdar N, et al. Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. Critical Care Medicine. 2005
[5] Koulenti D, et al. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis. 2016

Antibiotic Side Effects:

1) Antibiotic Resistance

2) Effects of Delayed Antibiotic Sensitivity Tests

A Myriad of Factors from Delayed Antibiotic Sensitivity Tests

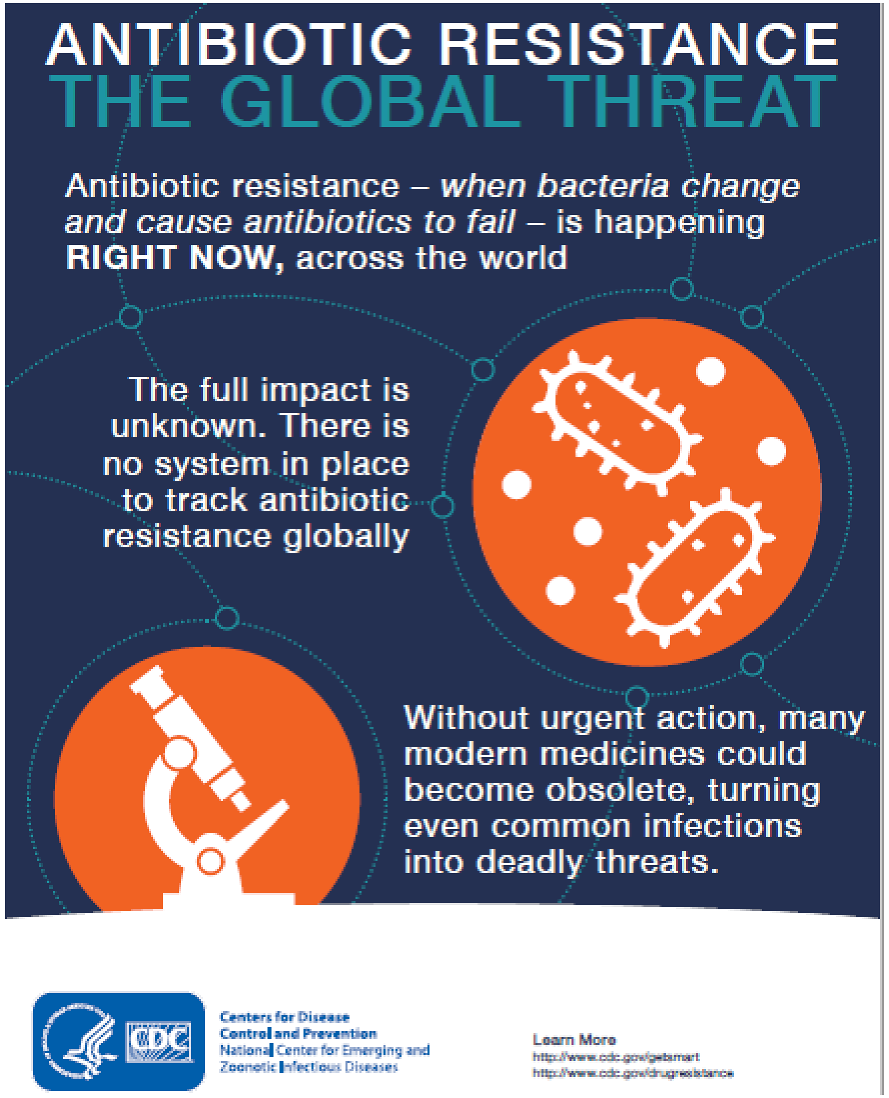


Antimicrobial Resistance

1) Spread from delays in Isolation Precautions
2) Overuse of Antibiotics

"The CDC estimates that the direct costs of antimicrobial resistance on the U.S. economy is $20 billion annually. When you factor in the economic consequences of lost productivity, it adds an additional $35 billion in costs"

Resistance is Spreading Across Countries



A real global crisis

December 2015

Pan-Resistant Enterobacteriaceae seen in 19 countries

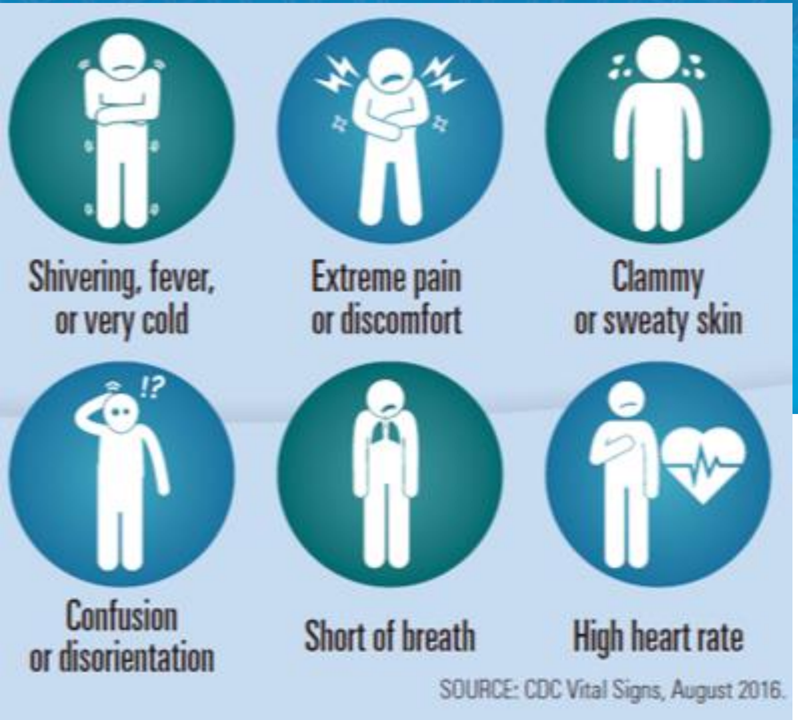
mcr-1 >> Colistin resistant

- Plasmid mediated
- Easily passed between organisms (E. coli/Klebsiella)
- Pan Resistance = No drugs work

CDC - Pathogen Distribution and Antimicrobial Resistance 2011-2014 infection control & hospital epidemiology January 2018, vol. 39, no. 1

https://www.cdc.gov/drugresistance/

Progression of Bacteremia to Sepsis due to Inappropriate Antibiotic Therapy

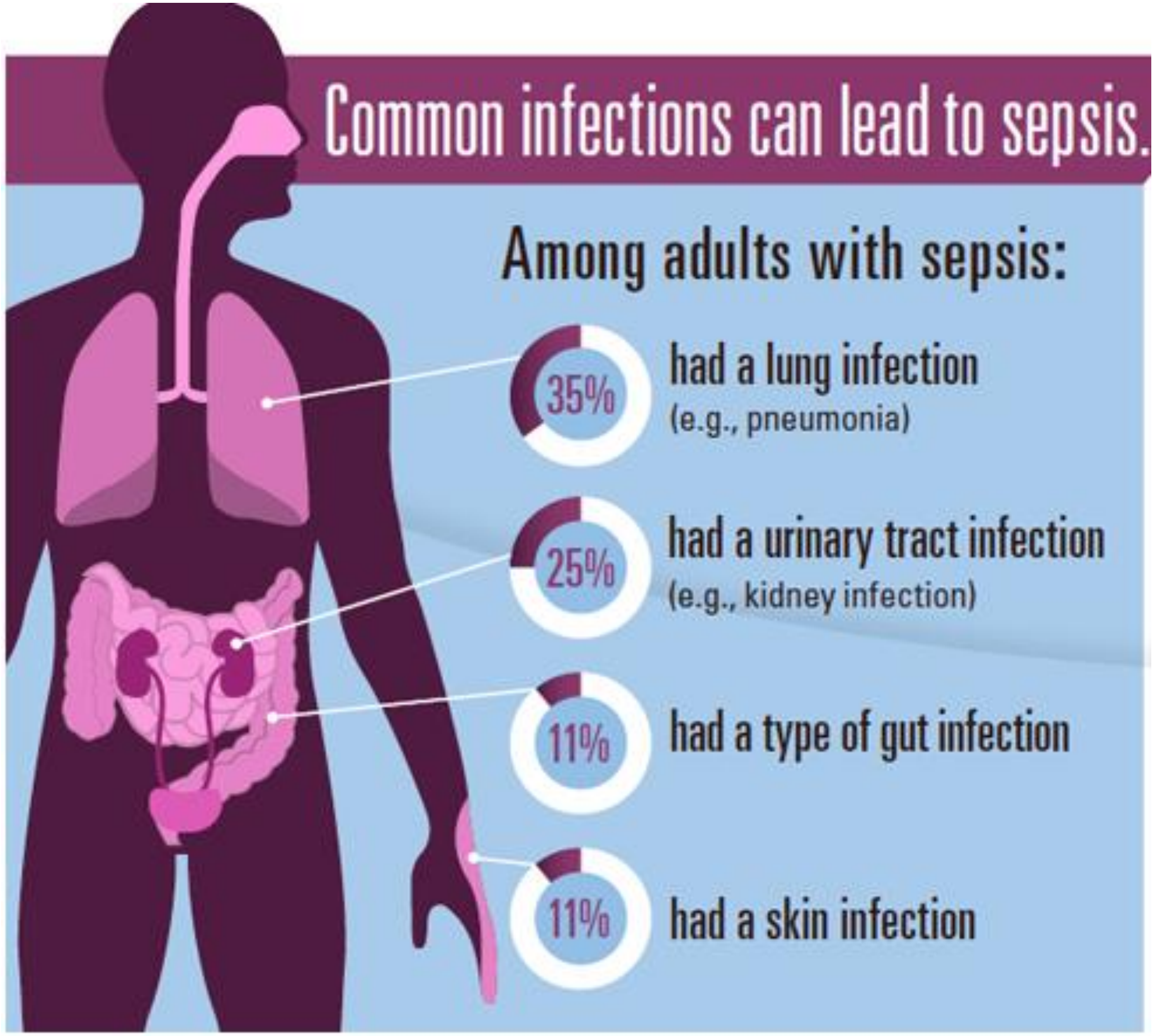


Epidemiology of Sepsis

- Sepsis affects over 26 million people worldwide each year
    - Largest killer of children – > 5 million each year
- > 1.6 million people in the U.S. are diagnosed with sepsis each year – one every 20 seconds and the incidence is rising 8% every year
- **258,000 people die from sepsis every year in the U.S. – one every 2 minutes**
- > 42,000 children develop severe sepsis each year
    - 4,400 of these children die, more than from pediatric cancers
- **Every day, 38 sepsis patients require amputations**

https://www.sepsis.org

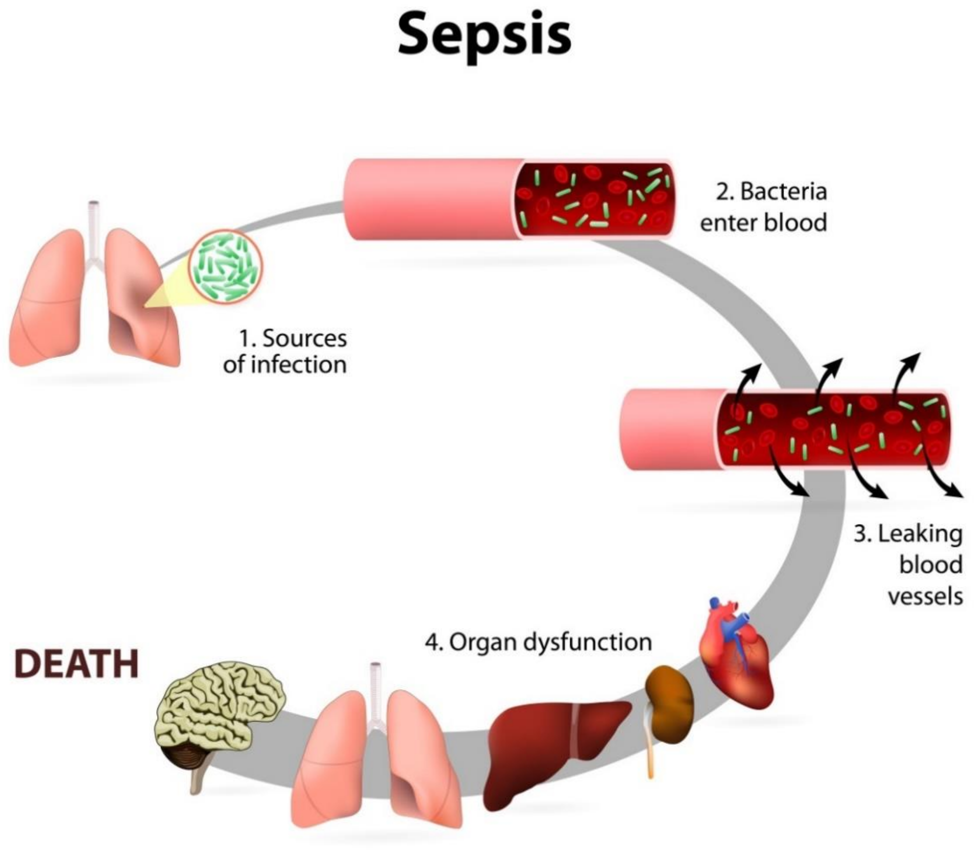
Infections Associated with Sepsis



Sepsis-3 Definitions

Sepsis is the body's overwhelming and life-threatening response to infection that can lead to tissue damage, organ failure, and death[1]

- ***Sepsis***: Life-threatening organ dysfunction caused by dysregulated host response to infection[2]
- ***Septic Shock***: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality[2]
- Approx 50% of patients with sepsis have positive blood cultures[3]
- Fatality rate for severe sepsis is about 40%, and treatment costs over $16 billion annually[3]



1. www.cdc.gov/sepsis
2. JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287
3. Proc (Bayl Univ Med Cent). 2015 Jan; 28(1): 10–13.

Post Sepsis Syndrome (PSS)

- **Post Sepsis Syndrome (PSS)**
  - Sepsis survivors have a shortened life expectancy
  - More likely to suffer from an impaired quality of life
  - 42% more likely to commit suicide
- **~50% of survivors suffer from post-sepsis syndrome**
  - Insomnia, difficulty getting to sleep or staying asleep
  - Nightmares, vivid hallucinations and panic attacks
  - Disabling muscle and joint pains
  - Extreme fatigue
  - Poor concentration
  - Decreased mental (cognitive) functioning
  - Loss of self-esteem and self-belief

Sepsis Treatment

If sepsis is suspected:

- Draw lactate
- Draw 2 sets of blood cultures (prior to antibiotic administration, if possible)
- Culture suspected site of infection (urine, wound, lower respiratory tract, etc.)
- Begin empiric antibiotic therapy

Gram positive coverage

\+

Gram negative coverage

or

or

+/- aminoglycoside

+/-

Yeast (*Candida*) coverage

Clinicians Need Fast ID and AST for Effective Antibiotic Therapy

38 people a day have amputations due to Sepsis

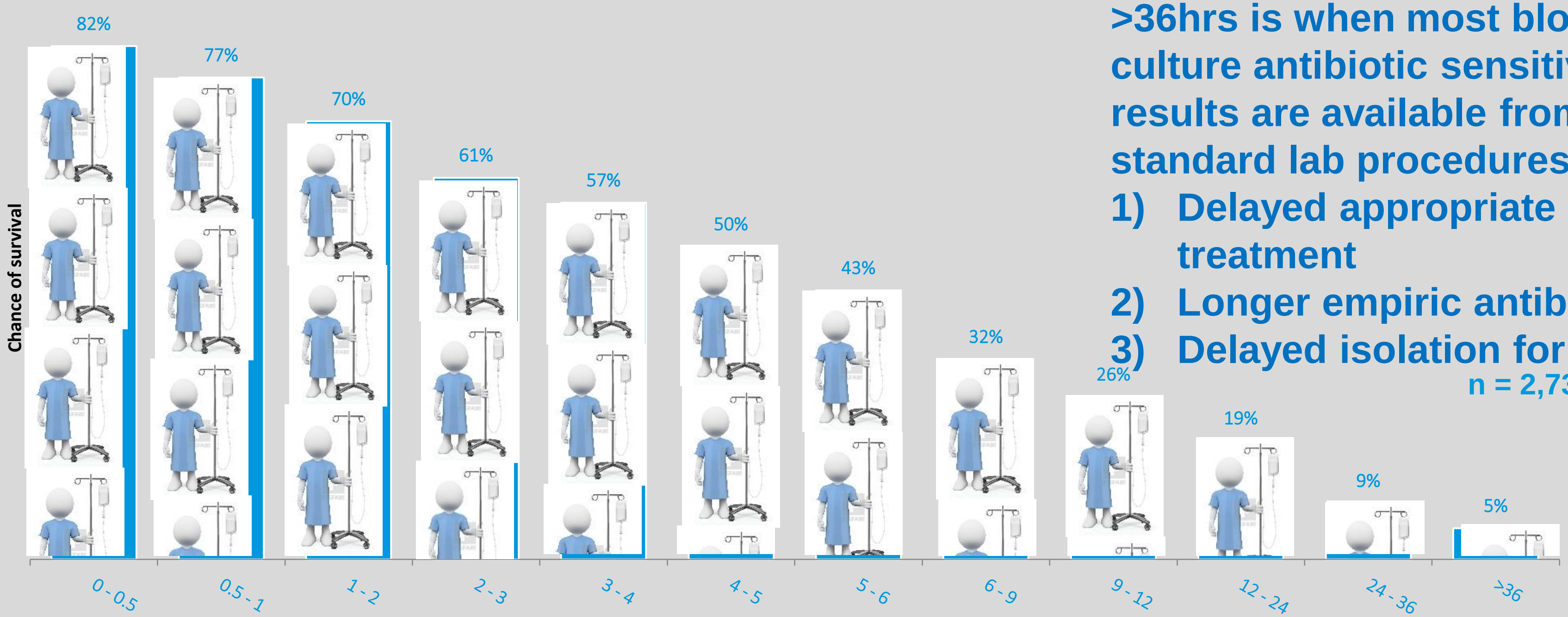
A

B

Clinical Urgency: Surviving Sepsis

Time to Appropriate Antimicrobial Rx following Onset of Hypotension

Every hour of delay to appropriate antimicrobial therapy for patients with severe sepsis decreases the chances of survival by 7.6%[1]

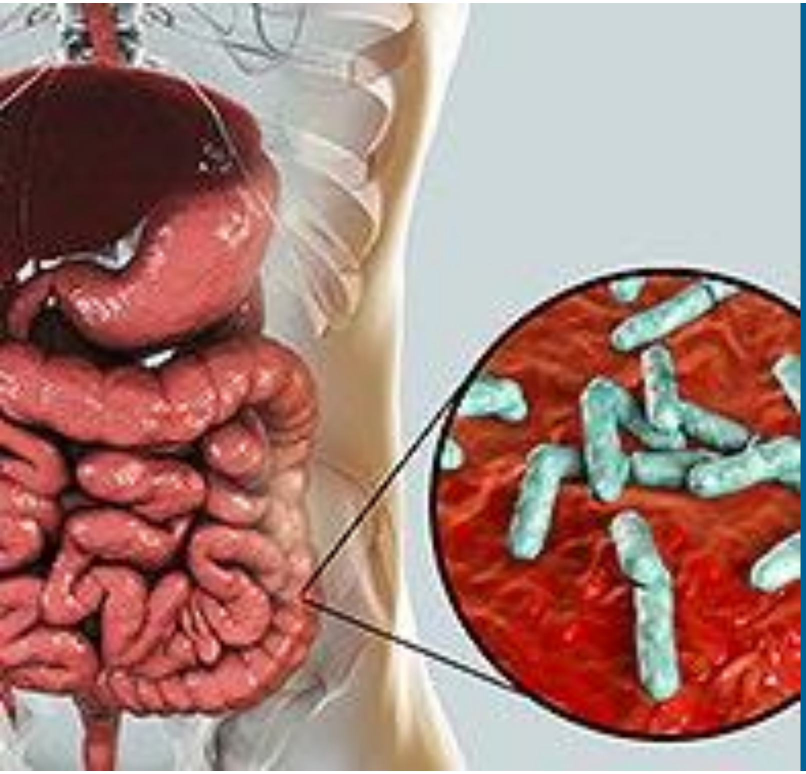


>36hrs is when most blood culture antibiotic sensitivity test results are available from standard lab procedures:

1) **Delayed appropriate treatment**
2) **Longer empiric antibiotic use**
3) **Delayed isolation for MDROs**

n = 2,731

[1]Kumar *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006 Jun; 34 (6):1589-96.



C. difficile from Antibiotics

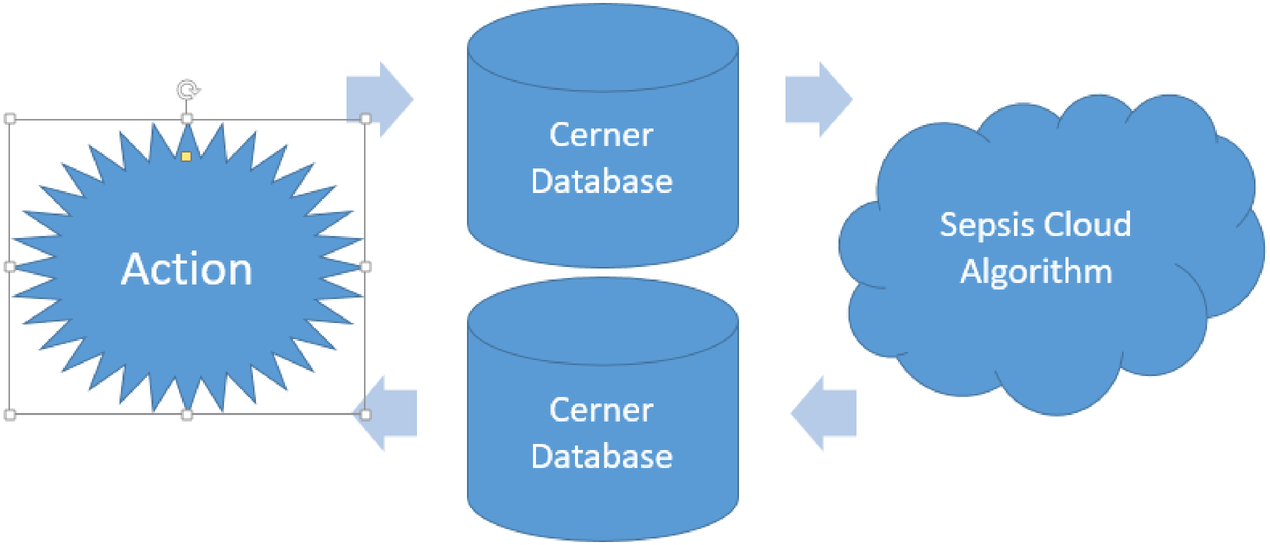
Antibiotic Classes and Risk for *C. difficile* Infection

- Two meta-analyses found risk to be greatest with clindamycin, fluoroquinolones or cephalosporins
  - 465 studies and included 5 published between 1994 and 2011 (total, 26,435 patients) in their meta-analysis[1]
    - Risk for CDI to be more than **tripled after any antibiotic exposure** (odds ratio, 3.55).
    - Treatment with clindamycin showed the strongest association with subsequent CDI (OR, 16.80)
  - 910 studies and included 8 published between 2005 and 2011 (total, 30,184 patients)[2]
    - Risk for CDI to be **increased nearly sevenfold after antibiotic treatment** (OR, 6.91)
    - Risk was greatest with clindamycin (OR, 20.43), followed by fluoroquinolones (OR, 5.65), cephalosporins (OR, 4.47)

1. Brown KA et al. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. Antimicrob Agents Chemother 2013 May; 57:2326
2. Deshpande A et al. Community-associated Clostridium difficile infection and antibiotics: A meta-analysis. J Antimicrob Chemother 2013 Apr 25

Sepsis Alert For Faster Diagnosis of Potential Sepsis

Interdisciplinary Sepsis Management Advisor – “Sepsis Alerts”



Electronic Sepsis Initiative Increases CDI

- Studied over 127,346 total patient days
  - increased antibiotic use and hospital onset (HO) CDI during sepsis care bundle implementation
  - period directly following the implementation phase accounting for the highest rate of antibiotic use

Sepsis Bundle Implementation	CDI Rate Per 10,000 Patient Days
Pre-implementation of sepsis care bundle	1.4
During implementation	1.6
After Implementation	10.8
3 yrs. After Implementation	**14.4**

- Cefepime was the most commonly used antibiotic
- Levofloxacin, which was not part of the sepsis care order set, was the main driver of increased antibiotic use

Hiensch R, et al. Impact of an electronic sepsis initiative on antibiotic use and health care facility-onset Clostridium difficile infection rates. American Journal of Infection Control, Volume 45, Issue 10 (October 2017)

IP Challenges:

1) Preventing HAIs
2) Delays in Isolation Precautions due to Delayed AST Results

IP Role – Preventing HAIs that Could Progress to "Bloodstream infection"

Rate of microorganism multiplication

Rate of microorganism's removal by immune system

Bloodstream infection (BSI)

1.6 million cases of BSI annually in the US with a 20-50% mortality rate[1]

Sources of bloodstream infections:

- Percutaneous Catheters (central and peripheral)
- Genitourinary tract
- GI or Biliary tract
- Respiratory tract
- Skin and soft-tissue infection (SSTI)

1. Elixhauser, A. et al. *Septicemia in U.S. Hospitals, 2009.* HCUP Statistical Brief #112. October 2011

Challenges with Isolation Precautions

- Delays obtaining antibiotic sensitivity test results 24-96hrs
- Patients not giving a complete history on admission
- Communication problems cause delays with housekeeping services, delivery of PPE, other equipment necessary to “put up barriers,” and isolation signs for doors
- Deciding to isolate and the ability to sustain isolation depends on patient-related factors in addition to the risk of spreading infection
- Patients with complex care that need to be moved out of their specialty area to get an isolation room brings safety risks
- Clinicians’ adherence to isolation precautions once initiated
- Isolation imposes “costs” on patients in terms of liberty and human rights for the public health benefit

D.J. Gould et al. / American Journal of Infection Control (2018)

Direct Costs of a Contact Isolation Day: A Prospective Cost Analysis at a Swiss University Hospital

- Additional mean costs per patient day were calculated for extra materials used, increased workload, and one-off isolation activities
- Cost of contact precautions was **$158.90** (95% confidence interval, $124.90–$192.80) per patient day

TABLE 1. Cost Items and Respective Direct Costs of Contact Precautions per Patient Day on Medical and Surgical Wards (N = 10 Patient Days)

	Direct Costs per Patient Day, $	
(Direct) Cost Item	Mean (95% CI)	Median (IQR)
Isolation materials[a]	43.10 (33.80–52.40)	
Cleaning and disinfection materials[a]	5.30 (4.00–6.60)	
Extra workload[a,b]		
Nurses, assistant nurses and trainee nurses	64.40 (45.30–83.40)	
Physicians (all categories)	8.50 (5.50–11.50)	
All other hospital staff categories	16.00 (11.80–20.20)	
Total (all hospital staff categories)	88.80 (67.70–110.00)	
One-off costs[a,c]	21.70 (2.60–40.70)	11.90 (4.40–16.70)
Total (all cost items)	158.90 (124.90–192.80)	

Roth, J., Hornung-Winter, C., Radicke, I., Hug, B., Biedert, M., Abshagen, C., . . . Widmer, A. (2018). Direct Costs of a Contact Isolation Day: A Prospective Cost Analysis at a Swiss University Hospital. *Infection Control & Hospital Epidemiology, 39*(1), 101-103. doi:10.1017/ice.2017.258

Study: Isolation Outcomes at Three Academic Tertiary Care Hospitals in Toronto

- Researchers included 17,649 control patients, 737 patients isolated for methicillin-resistant *Staphylococcus aureus* and 1,502 patients isolated for respiratory illnesses:
- Patients on contact precautions for MRSA:
  - higher 30-day readmission rate than did controls (19% vs. 14.7%)
  - longer average length of stay (11.9 days vs. 9.1 days)
  - higher direct costs ($11,009 vs. $7,670)
- Patients on contact and droplet precautions for respiratory illnesses had
  - longer average length of stay (8.5 days vs. 7.6 days)
  - higher direct costs ($7,194 vs. $6,294)

Tran K et al. The effect of hospital isolation precautions on patient outcomes and cost of care: A multisite, retrospective, propensity score-matched cohort study. J Gen Intern Med. 2017;32(3):262-8.

CDC – MRSA Colonized and Infected Patients

- Based on the current evidence CDC continues to recommend the use of contact precautions (CP) for MRSA-colonized or infected patients
- CDC will continue to evaluate the evidence on CP as it becomes available
- CDC continues to work with partners to identify and evaluate other measures to decrease transmission of MDROs in healthcare settings

- https://www.cdc.gov/mrsa/healthcare/clinicians/index.html

One Challenge from IP Perspective: Surveillance

- Surveillance system for bacteremia and sepsis?
  - NHSN MRSA bacteremia surveillance
  - Primary and secondary bacteremia may be on HAI dashboards
  - Secondary bacteremia due to HAIs may be on HAI dashboards
  - Sepsis readmissions reported as a healthcare acquired condition (HAC)
  - Progression from sepsis to septic shock reported as a HAC

- What Additionally Should be Collected: Epidemiology of Bacteremia and Sepsis
  - Lab: unique positive blood cultures, bacteremia types, locations, organisms
  - Demographics
  - Risk
  - Antibiotic therapy
  - Length of stay
  - Mortality rate due to bacteremia/sepsis
  - Sepsis readmissions
  - Progression from septic shock to sepsis
  - C difficile in bacteremia patients on long-term empiric antibiotic therapy
  - MDROs in bacteremia patients
  - Adverse side effects
  - Cost and loss in revenue due to HACs

Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level

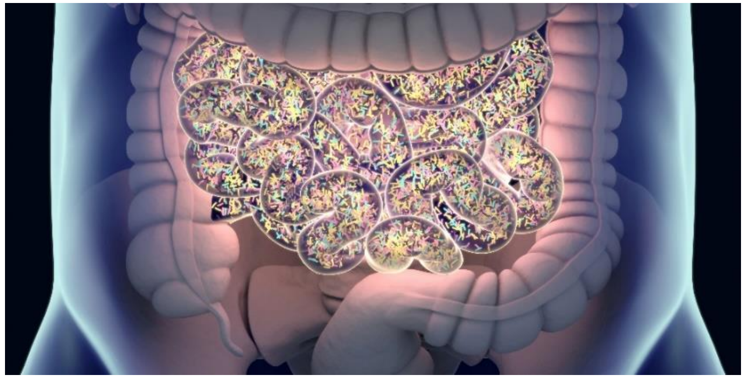
- Characterize the current burden, outcomes, and costs of managing sepsis patients in U.S. hospitals
- Retrospective observational study was conducted using the Premier Healthcare Database
- Patient demographics, characteristics, and clinical and economic outcomes for the index hospitalization and 30-day readmissions.
- Sepsis patient hospitalizations (2010-2016) including inpatient, general ward, and ICU (intermediate and/or step-down)
  - **2,566,689** sepsis cases (mean age of 65 years (50.8% female)
  - **Overall mortality was 12.5%**
    - sepsis without organ dysfunction 5.6% Cost:$16,324
    - severe sepsis 14.9% Cost: $24,638
    - septic shock 34.2% Cost: $38,298
- **Cost of sepsis not present at admission ($51,022)**

Paoli et al. Crit Care Med. 2018 Jul 25

In Conclusion

Due to Delays in Standard Lab Procedures there is an Increased Use of Empiric Antibiotics, Adverse Side Effects, Delayed Treatment of Sepsis, Delayed Isolation of MDROs

- Disruption in microbiome in GI tract from empiric antibiotics
- Results in overgrowth of *C. difficile* and progression to infection
- Development of resistant strains to unnecessary antibiotics
- Adverse side effects, such as acute kidney injury and skin rashes, which make the patient prone to other healthcare associated infections and conditions
- High risk antibiotics: Cephalosporins, Fluoroquinolones, Clindamycin



Role of IPs, Pharmacists, Microbiologist, Infectious Disease Physicians in Collaboration with Nurses and ASP

- ✓Microbiology education and training on how to both obtain cultures and interpret the results
- ✓Education about infection versus colonization
- ✓Assertiveness training to engage in discussions with the health care team
- ✓Information on IV-PO switch criteria
- ✓Joint Commission's Medication Management standard and CMS Condition(s) of Participation on antimicrobial stewardship to guide antibiotic stewardship tools and products
- ✓Engage C-Suite in stewardship issues and support of fast diagnostics for antibiotic sensitivity tests

Our Potential Impact On the Continuum of Care

Micro Lab
- Standardized blood culture procedures
- Improved bench workflow
- Improved turnaround time to ID/AST/MIC

Information Technology
- Improved drug/bug orders and standardized order sets

C-Suite and Administration
- Improved services and staff utilization
- Improved patient satisfaction
- Reduced cost of care

Infectious Disease Physicians
- Eliminates broad-spectrum ABX use
- Reduced use of restricted ABX
- Reduced side effects of antibiotics

FAST ID & AST

Infection Prevention
- Lower rates of MDROs, CDI, cross infection
- Reduction in isolation beds and PPE
- Fewer outbreaks
- Improved bed utilization
- Fewer cases reported to NHSN and CMS Penalties

Nursing Staff and Sepsis Coordinators
- Reduced RN lab draws and drug admin
- More efficient use of ICU beds/staff
- Expedited transfers of +BC patients back to LTACs
- Reduced adverse effects of sepsis
- Reduced cost of care

Pharmacy and ASP
- Rapid transition to targeted therapy
- Escalation or de-escalation
- Reduced ABX cost
- More efficient ABX Stewardship Program

Critical Care
- Faster optimal therapy
- Reduced use of restricted ABX
- More efficient use of ICU beds
- Reduced adverse effects of sepsis


THANK YOU