Disclosure

I work for Cepheid as Director of Corporate Accounts

Cepheid.

Objectives

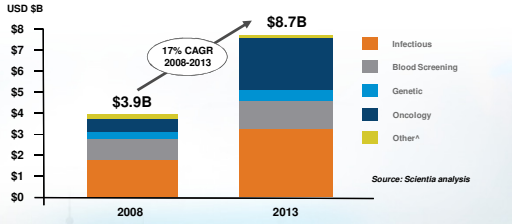
- Provide a brief overview of molecular PCR technology
- Learn about rapid applications available today
- Provide insight as to how rapid applications have impacted patient care based on current literature
- Provide an understanding of the impact on hospital costs related to rapid results.
- Discuss ways in which antibiotic stewardship can be influenced by rapid test results.

3

Cepheid.

MDx is Fastest Growing Segment of IVD Market

Significant growth is expected in oncology and portions of infectious disease in the critical care segment due to high value tests*



^Includes cardiology, CNS predisposition, theranostic tests, and other emerging tests.
*Tests that provide critical information to help physicians make clinically relevant decisions; as a result command a premium price

Molecular Diagnostics

- **Designated nucleic acid target (what are you looking for?)**
- **Sample type (where will you find the target?)**
- **Extract nucleic acid (how will you isolate the target nucleic acid?)**
- **Detection and results (how do you know if the target is there?)**

NAA (NAAT) – what does that mean? Nucleic Acid Amplification (Test)

Amplification Technology	Used By	Isothermal?	Level of Multiplexing (commercial product)	Quantitative CE IVD?
PCR	Cepheid, BD, Roche & most of Dx and research world	No	20-80 targets	Dozens
HDA	BioHelix	Yes	One target	0
SDA	BD	Yes	2-3 targets	0
NASBA	BioMerieux	Yes	One target (HIV viral load)	1
TMA	Gen-Probe	Yes	Three targets (HPV is an exception)	0
Loop Mediated Isothermal Amplification	Eiken, Illumigene, Quidel	Yes	One target	0
LDT	Laboratory Developed test	Currently FDA is reviewing how to better manage standards for this group of applications		

478 PRACTICE GUIDELINES nature publishing group

Am J Gastroenterol 2013; 108:478–498; doi:10.1038/ajg.2013.4; published online 26 February 2013

CME

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Christina M. Surawicz, MD[1], Lawrence J. Brandt, MD[2], David G. Binion, MD[3], Ashwin N. Ananthakrishnan, MD, MPH[4], Scott R. Curry, MD[5], Peter H. Gilligan, PhD[6], Lynne V. McFarland, PhD[7,8], Mark Mellow, MD[9] and Brian S. Zuckerbraun, MD[10]

Recommendations

2. Nucleic acid amplification tests (NAATs) for *C. difficile* toxin genes such as PCR are superior to toxins A+B enzyme immunoassay (EIA) as a standard diagnostic test for CDI. (Strong recommendation, moderate-quality evidence)
3. Glutamate dehydrogenase (GDH) screening tests for *C. difficile* can be used in two- or three-step algorithms with subsequent toxin A+B EIA testing, but the sensitivity of such strategies is lower than NAATs. (Strong recommendation, moderate-quality evidence)

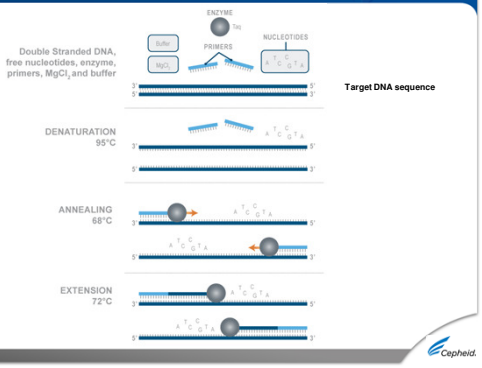
The sensitivity of GDH (EIA) antigen detection has led to its use as a screening test as part of CDI testing algorithms, although it should be noted that as many as 10 % of patients with toxigenic organisms can be missed by this method.

Evidence suggests that NAATs for toxigenic C. difficile are good stand-alone tests for toxigenic C. difficile . There are several Food and Drug Administration (FDA)-approved NAAT's, including PCR assays and isothermal amplification tests. PCR is an excellent confirmatory test, but data for isothermal amplification testing are not yet sufficient to recommend it.

7 | © 2010 Cepheid

Cepheid.

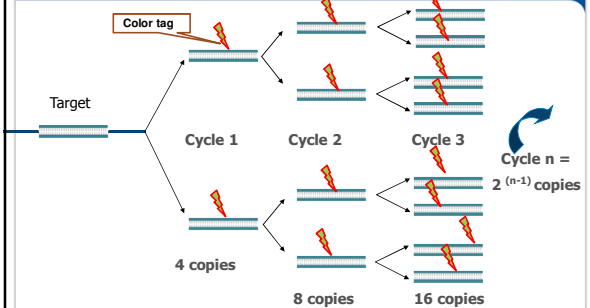
Polymerase Chain Reaction (PCR)



8 | © 2010 Cepheid

Cepheid.

PCR Cycles



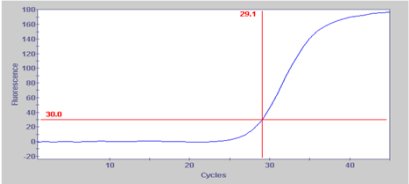
heating and cooling cycle is repeated several time and it is called thermal cycling

9 | © 2010 Cepheid

Cepheid.

How to Detect Amplified Target?

- Real-time PCR
- Continuous amplification and detection in one tube
- Use a target specific probe labelled with a fluorescent dye
- Instrument collects fluorescent data and provides result



No Specialized Training Required to Achieve Reliable, Reproducible Results

INTEGRATED PLATFORM AND TEST

1. Insert Swab into Elution Reagent Vial and Break at Score
2. Vortex and Dispense Sample into Port S
3. Insert Cartridge and Start Assay

Total Hands-On time <1 Minute

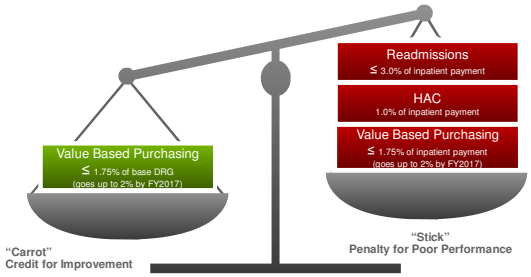
Random Access - Available 24-7

Trends in Healthcare Landscape

Focus is on value, performance & prevention

- Moving away from fee-for-service to fee-for-value
- Payments tied to quality and cost savings
- Increased accountability and transparency

CMS Quality Incentive Programs: A Carrot and a Stick



13 © Cepheid

Cepheid.

Campaign to Prevent Antimicrobial Resistance in Healthcare Settings

Key Prevention Strategies

CDC

- Prevent infection
- Diagnose and treat infection effectively
- Use antimicrobials wisely
- Prevent transmission

CMS Issues Proposed Rule that Reduces Hospital-Acquired Conditions, and Promotes Antibiotic Stewardship in Hospitals

Under the proposed rule, hospitals and CAHs would be required to:

Have hospital-wide infection prevention and control and antibiotic stewardship programs for the surveillance, prevention, and control of healthcare-associated infections and other infectious diseases, and for the appropriate use of antibiotics;

Clinicians hold the solution!

14 | © 2010 Cepheid

Cepheid.

Infection Related Quality Metrics: Hospitals

Program (N) Infection Measures	2015	2016	2017	Lab Y/N
Value Based Purchasing (24)				
- Complications/patient safety	X	X	X	Y
- CLABSI	X	X	X	Y
- CAUTI		X	X	Y
- SSI (Colon, hysterectomy)		X	X	Y
- MRSA			X	Y
- CLABSI	X	X	X	Y
- C.difficile	X	X	X	Y
- Spending per beneficiary	X	X	X	Y
- Blood cultures	X	X	X	Y
- Patient Satisfaction	X	X	X	Y

15 | © 2010 Cepheid

Cepheid.

Two Areas to Measure When Considering PCR

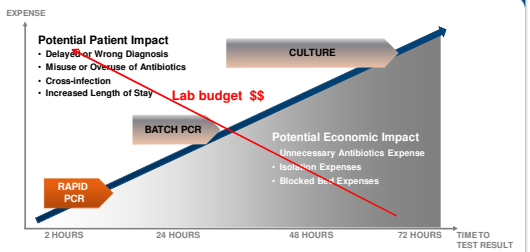
Understand current patient pathway and medical interventions around lab results.

Quantify impact on health system resources.

Quantify the total cost of diagnosis and patient management through the continuum of care.

Cepheid.

Economic and Medical Cost of Delayed Diagnosis



Time to Test Results Costs Money and Lives

Articles that look at time to result as crucial to maximizing diagnostic value:
1. Lance R. Peterson, M.D., Donna M. Hacek, M.T.(A.S.C.P.), Ari Robicsek, M.D., Case Study: An MRSA Intervention at Evanston Northwestern Healthcare, printed in The Joint Commission Journal on Quality and Patient Safety Volume 33 Number 12, December 2007

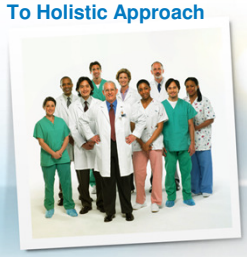
2. Lance R. Peterson, M.D., Rapid Diagnosis of Community-Acquired MRSA, printed in Clinical Updates in Infectious Diseases, Volume Issue 3, October 2008
3. Eli N. Perencevich, MD, MS et al., SHEA Guideline: Raising Standards While Watching the Bottom Line: Making a Business Case for Infection Control, Infection Control and Hospital Epidemiology, Volume 28, Number 10, October 2007

Cepheid.

Budgetary Headaches Move Toward Value-Based Medicine

From Silo

To Holistic Approach

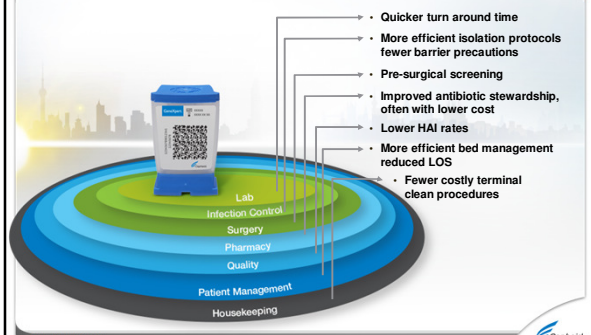


- **Moving away from the lowest cost per test to Total Cost of Care**
- **Focus on medical outcome, quality and prevention**

Cepheid.

Rapid Molecular: Institution Wide Impact

Potential to Improve Patient Outcomes and Reduce Costs



- Quicker turn around time
- More efficient isolation protocols fewer barrier precautions
- Pre-surgical screening
- Improved antibiotic stewardship, often with lower cost
- Lower HAI rates
- More efficient bed management reduced LOS
- Fewer costly terminal clean procedures

Cepheid.

Rapid Detection of Methicillin-Resistant *Staphylococcus aureus* using the Cepheid GeneXpert® Dx System and the Xpert™ MRSA Test

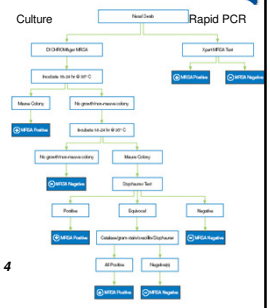
S. Lassiter2, G. Mayernick2, S.R. Patel1, T. M. Gannon1, P.R. Harris1 and **W.E. Phillips2**
Cepheid, Sunnyvale, CA1 and TriStar Health System, Centennial Medical Center, Nashville, TN2

Article highlights

1. Not isolated until tested positive
2. TAT
   - Culture – 35.8 Hrs
   - PCR – 6.9 Hrs
3. Culture is not as sensitive as PCR
4. Culture resulted in 7,584 fewer Potential Contact Precaution Hours (PCPH) which equates to an additional 44 potential HAI transmissions
5. Avoided 11 infections*

11 X $23,000 = $253,000 in cost avoidance over a 4 month period

*Davis, *et al*



Cepheid.

Veterans Affairs Initiative to Prevent Methicillin-Resistant *Staphylococcus aureus* Infections

Rajiv Jain, M.D., Stephen M. Kralovic, M.D., M.P.H., Martin E. Evans, M.D., Meredith Ambrose, M.H.A., Loretta A. Simbartl, M.S., D. Scott Obrosky, M.S., Marta L. Render, M.D., Ron W. Freyberg, M.S., John A. Jernigan, M.D., Robert R. Muder, M.D., LaToya J. Miller, M.P.H., and Gary A. Roselle, M.D.

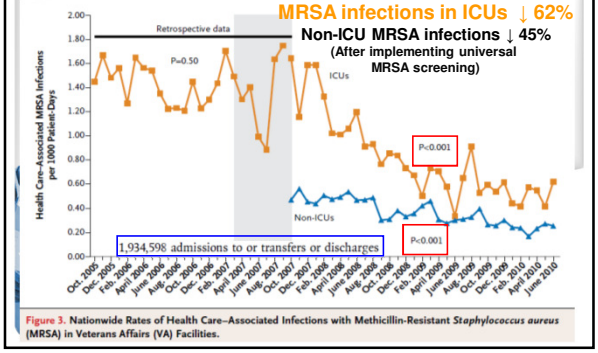


Figure 3. Nationwide Rates of Health Care–Associated Infections with Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Veterans Affairs (VA) Facilities.

Title: Discontinuation of Contact Precautions for Methicillin-Resistant *Staphylococcus aureus* (MRSA): A Randomized Controlled Trial Comparing Passive and Active Screening with Culture and Polymerase Chain Reaction

Erica S. Shenoy, MD, PhD, JiYeon Kim, MD, MPH, Eric S. Rosenberg, MD, Jessica A. Cotter, MPH, Hang Lee, PhD, Rochelle P. Walensky, MD, MPH* and David C. Hooper, MD*

Table 3. Single First PCR Test Performance Compared to Three Sequential CA in Intervention Arm Population.

1 negative Xpert MRSA PCR test = 3 negative cultures

	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
All subjects, series of 3 swabs completed (N=191)	93.9 (85.4 to 97.6)	92.0 (85.9 to 95.6)	86.1 (75.9 to 93.1)	96.6 (91.6 to 99.1)

Gets MRSA-negative patients out of costly isolation rooms

Cepheid.

Title: Discontinuation of Contact Precautions for Methicillin-Resistant *Staphylococcus aureus* (MRSA): A Randomized Controlled Trial Comparing Passive and Active Screening with Culture and Polymerase Chain Reaction

Erica S. Shenoy, MD, PhD, JiYeon Kim, MD, MPH, Eric S. Rosenberg, MD, Jessica A. Cotter, MPH, Hang Lee, PhD, Rochelle P. Walensky, MD, MPH* and David C. Hooper, MD*

Estimated Effect on Unnecessary Contact Precaution Days Avoided and Costs Saved

Strategy	Passive cultures	Active surveillance cultures	PCR screening (1 Xpert MRSA)
Discontinuation rates of contact precautions	6.6%	26.2%	63.8%
Fewer contact precaution days	104	418	1841
Cost savings	$86,950	$349,472	$1,539,180

Cepheid.

Culture: Missed MRSA (pos) Results

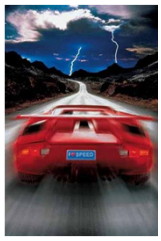
Studies indicate that culture may miss MRSA (pos) results up to 1/3 of the time

Study 1	Study 2	Study 3
33%-36% Missed Positives[1]	25%-32% Missed Positives[2]	16%-24% Missed Positives[3]

[1] Comparison of Bio-Rad MRSA Select Agar with BBL ChromAgar for MRSA Nares Swab Surveillance Cultures in VISN 12. Wisniewski et. al (64% to 67% Sensitivity)
[2] Current trends in Rapid Diagnostics for MRSA and Glycopeptide-Resistant Enterococcus Species. Malhotra-Kumar et. al (68% to 75% Sensitivities)
[3] Evaluation of three chromogenic media (MRSA-ID, MRSA-Select and CHROMagar and ORSAB for surveillance cultures of MRSA. Nahimana et.al (broth enrichment needed to increase detection rate of MRSA by 16-24%)

Cepheid.

The Need for Laboratory Speed

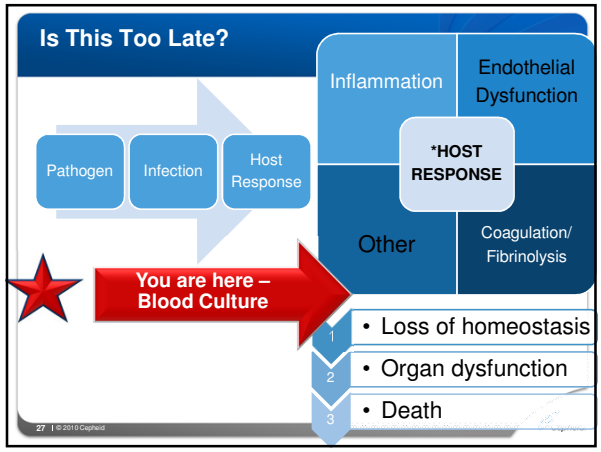


- Rapid Antibiotic Therapy Saves Lives
  - **Targeted antibiotic therapy increases survival by ~ 25-45%**
  - **For every hour appropriate antibiotic is delivered sooner, survival increases by ~ 7-10% [1]**

In the U.S., sepsis kills nearly 600 patients each day!

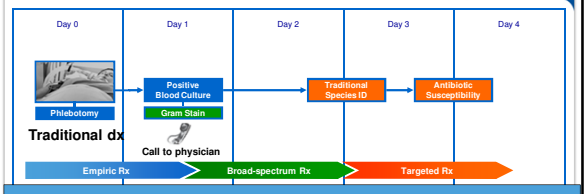
1. Kumar et. al, 2006. Crit. Care Med. (34)

Is This Too Late?



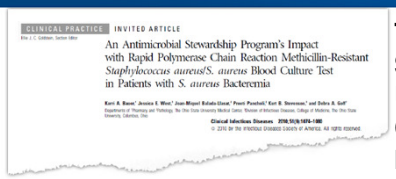
Traditional vs. Rapid Identification

Active role of Microbiology: improved integration with patient care



Rapid Detection of MRSA & SA – Blood Culture

On-Demand Results Reduces LOS and Cost



CLINICAL PRACTICE INVITED ARTICLE

An Antimicrobial Stewardship Program's Impact with Rapid Polymerase Chain Reaction Methicillin-Resistant *Staphylococcus aureus*/*S. aureus* Blood Culture Test in Patients with *S. aureus* Bacteremia

The Ohio State University College of Medicine

- **Implementation of the Xpert® MRSA/SA BC test coupled with an infectious disease pharmacist's consultation resulted in:**
  - **Mean time of switch from vanco to cefazolin/nafcillin (optimal antibiotic therapy) occurred 1.7 days sooner (for MSSA bacteremic patients)**
  - **Mean length of stay was 6.2 days shorter (for both MRSA and MSSA bacteremic patients)**
  - **Mean hospital costs were $21,387 less (for both MRSA and MSSA bacteremic patients)**

Cepheid.

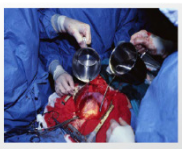
Institute *for* Healthcare Improvement

Project JOINTS: Joining Organizations IN Tackling SSIs

Screen patients for Staph aureus (SA) carriage and decolonize SA carriers with five days of intranasal mupirocin and at least three days of CHG soap prior to surgery

---

MRSA/MSSA - Rapid detection of MSSA and/or MRSA nasal colonization in 1 hour



Cardiac Surgery

- Cardiovascular operations represent the 2nd most frequent surgical procedure in the US
- SSIs in cardiac surgery patients represent a serious complication leading to higher morbidity, mortality and prolonged hospital stay
- Infective endocarditis (infection of the inner heart tissues) can occur after valve replacement or pacemaker implant

CHALLENGES

- **Patients colonized with Staph aureus and/or MRSA not accurately identified prior to surgery create opportunities for:**
  - Increase risk of SSI
  - Spread of infection to other patients
  - Less than optimal antibiotic prophylaxis

Rapid and Accurate detection of MRSA/SA colonization in 66 minutes or less

- Enables Surgeon to choose appropriate prophylaxis antibiotic
- Ability to implement targeted decolonization prior to surgery
- Quickly identify patients requiring contact precautions
- Allows for better patient management after surgery

Cepheid.

Low culture sensitivity can miss MRSA – no vancomycin ordered

MRSA	Sensitivity[1]	Specificity[1]
Culture with selective media (24-hour test)	62%	99.5%
Culture with selective media (48-hour test)	78%	98%
Same-day PCR	98%	98%

MSSA[2]

- Bathe with CHG for 5 days prior to surgery
- Administer intranasal mupirocin decolonization treatment
- Administer antibiotic prophylaxis (cefazolin)

MRSA[2]

- Bathe with CHG for 5 days prior to surgery
- Administer intranasal mupirocin decolonization treatment
- Administer antibiotic prophylaxis (cefazolin + vancomycin)

1. Dykewicz, M. et al. Infect Control Hosp Epidemiol. 2013;(2):205-7.
2. Optimizing Pre-Operative Antibiotic Prophylaxis for Elective Joint Orthopedic Procedures Study Protocol (STOP-IT® Project).

Cepheid.

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

Case Studies: Methicillin-resistant *Staphylococcus aureus*

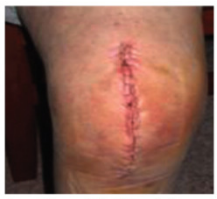


Figure 2. Successful Total Knee Replacement in Patient colonized with MRSA

- Age of patient: Mid 50s
- Modifiable risk factors: Yes - colonized with MRSA
- Screened for MRSA: Yes
- Preoperatively Decolonized: Yes
- Prophylaxis given: Cefazolin

Outcome

This patient successfully completed a Total Knee Replacement, with no complications from post-operative surgical site infections.

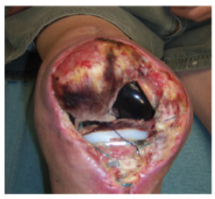


Figure 3. Unsuccessful Total Knee Replacement in Patient colonized with MRSA

- Age of patient: Mid 50s
- Modifiable risk factors: Yes - colonized with MRSA
- Screened for MRSA: No
- Preoperatively Decolonized: No
- Prophylaxis given: Cefazolin

Outcome

This patient underwent a Total Knee Replacement, and developed a postoperative MRSA SSI. The antibiotic given did not cover MRSA. The patient's leg was amputated after several surgical attempts to salvage his leg. Preop screening and decolonization may have prevented the infection.

What's the Impact?

- As a result of this post-surgical complication, the site may be subject to associated reimbursement penalties:
  - ☑ Surgical site infection
  - ☑ Readmission after total knee replacement
- The average cost of a MRSA surgical site infection is $42,300 and the average length of stay is 23 days
- CMS does not reimburse hospitals for additional costs associated with a surgical site infection following certain orthopedic procedures

One Infection Avoided Can Pay for Over 1200 PCR Tests!

Zimlichman E., et al. JAMA Intern Med. 2013;(173):2039-46.

Cepheid.

Preventing Surgical Site Infections

- *Staphylococcal aureus* represents 30% of surgical site infections[1]
- Perioperative screening to identify colonization + active decolonization prior can help reduce rates
- On-demand PCR testing has high sensitivity and specificity to ensure the correct organism is identified so appropriate treatment/measures can be administered
- Effective decolonization
  - Nasal decolonization
  - CHG body washes

MRSA Nasal Screening - NEBH

Eradication of Methicillin Sensitive Staphylococcus aureus and Methicillin Resist… Staphylococcus aureus Before Orthopedic Surgery

18… …the Society for Healthcare E… …2008 … …rida S…

$573,000 savings after the cost of implementing the program

Key points:

- Rapid Screening utilized to detect M… …gery
- Rapid screening allowed for more effective patient education
- Mupirocin and CHG used to decolonize prior to surgery
- Appropriate prophylaxis antibiotic utilized at time of surgery
- Appropriate patient management after surgery
- Reduced SSI by 61% the first year

Clin Orthop Relat Res. 2013 Mar 6. [Epub ahead of print]

Staphylococcus aureus Screening and Decolonization in Orthopaedic Surgery and Reduction of Surgical Site Infections.

Chen AF, Wessel CB, Rao N. Department of Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA, USA.

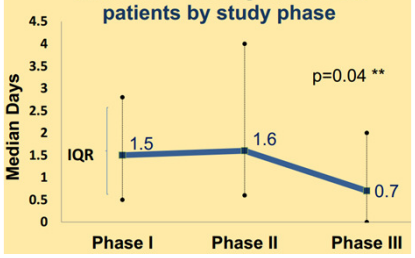
QUESTION: The purposes of this study were to determine (1) whether S. aureus screening and decolonization reduce SSIs in orthopaedic patients and (2) if implementing this protocol is cost-effective.

RESULTS: **All 19 studies** showed a reduction in SSIs or wound complications by instituting a S. aureus screening and decolonization protocol in elective orthopaedic (total joints, spine, and sports) and trauma patients. The S. aureus screening and decolonization protocol also saved costs in orthopaedic patients when comparing the costs of screening and decolonization with the reduction of SSIs.

CONCLUSION: Preoperative screening and decolonization of S. aureus in orthopaedic patients is a cost-effective means to reduce SSIs.

Xpert MRSA/MSSA SSTI in the ED

Figure 2. Days of inappropriate antibiotics* among non-MRSA patients by study phase



Talan et al, IDSA 2011

- Retrospective blinded review
- Admitted adults with complicated SSTI
- Phase I: Baseline
- Phase II: ED use of rapid test, MD education
- Phase III: PharmD direction

***treatment with vancomycin, linezolid, daptomycin and TMP/SMX were considered inappropriate for non-MRSA**

Cepheid.

Early diagnosis and effective treatment for both drug-susceptible and drug-resistant cases are essential for improving patient health, preventing the spread of disease to others, and ultimately, achieving our goal of TB elimination in the U.S.

FDA Press Release, July 25, 2013

Cepheid.

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

Morbidity and Mortality Weekly Report (*MMWR*)

Availability of an Assay for Detecting *Mycobacterium tuberculosis*, Including Rifampin-Resistant Strains, and Considerations for Its Use — United States, 2013

1. Perform NAA testing on at least one (preferably the first) respiratory specimen from each patient suspected of pulmonary TB before a diagnosis has been established
2. NAA testing does not replace the need for culture
3. Because NAA testing, including Xpert MTB/RIF, is significantly more sensitive and specific for the detection of MTBC than microscopy alone, substitution of Xpert MTB/RIF assay results that are negative for MTBC for microscopy results increases the negative predictive value for MTBC.
4. For patients with a diagnosis of TB, decisions regarding discontinuation of ALL precautions should be based on microscopy (i.e., three consecutive negative smears) and other clinical criteria.

October 18, 2013 / 62(41);821-824

MMWR Xpert MTB/RIF update 2015

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 64 / No. 7 February 27, 2015

Morbidity and Mortality Weekly Report

Revised Device Labeling for the Cepheid Xpert MTB/RIF Assay for Detecting *Mycobacterium tuberculosis*

Division of Microbiology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, Food and Drug Administration

- 638 U.S. patients, 14.4% TB+, 37.6% HIV+
- Negative Predictive Value 1 Xpert = 99.6 %
- Negative Predictive Value 2 Xperts = 100 %

Cepheid.

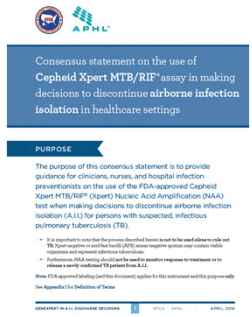
Key US publications

Consensus Statement on the Use of Xpert MTB/RIF

- NTCA/APHL* recommends:
  - Negative Xpert MTB/RIF results: Consider release from respiratory isolation
  - Positive Xpert MTB/RIF result: Diagnosis of TB is highly likely; continue respiratory isolation
  - Xpert MTB/RIF is the only nucleic acid amplification test, cleared by FDA, that can help support decisions to discontinue respiratory isolation for persons suspected of infectious pulmonary tuberculosis

Note: LDT NAA test ≠ Xpert MTB/RIF

*NTCA = National TB Controllers Association APHL = Association of Public Health Laboratories


Consensus statement on the use of **Cepheid Xpert MTB/RIF**® assay in making decisions to discontinue **airborne infection isolation** in healthcare settings

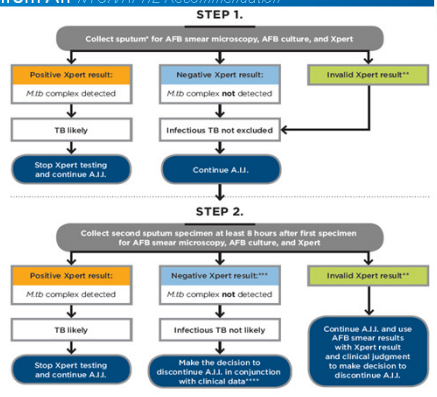
PURPOSE

The purpose of this consensus statement is to provide guidance for clinicians, nurses, and hospital infection preventionists on the use of the FDA-approved Cepheid Xpert MTB/RIF® (Xpert) Nucleic Acid Amplification (NAA) test when making decisions to discontinue airborne infection isolation (A.I.I.) for persons with suspected, infectious pulmonary tuberculosis (TB).

Source: Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings. April 2015

Cepheid.

Use of 2 Xpert Mtb/Rif for Removing patients from All *NTCA/APHL Recommendation*



Cepheid.

Key points in the document

- **Specimen quality is important. Document contains detailed guidance for proper specimen collection.**
- **Once diagnosed with TB, Xpert test results should not be used to remove patients from isolation.**
- **For any laboratory test, physician judgement based on risk factors, physical exam, chest X-ray, other factors, should be used along with the Xpert result to decide whether to remove patients from All.**

(Note: 3 smears much less sensitive [60.4% vs 85.2%] than 1 Xpert)

- **At least 2 smears and cultures on samples collected at least 8 hours apart should be performed, even if Xpert is being used.**
- **Note: positive smear and negative Xpert = Non-TB mycobacterium**

Rapid Molecular Testing for TB to Guide Respiratory Isolation in the U.S.: A Cost-Benefit Analysis

Alexander J. Millman[3,5], David W. Dowdy[6], Cecily R. Miller[4], Robert Brownell[3], John Z. Metcalfe[1,2,3], Adithya Cattamanchi[1,2,3], J. Lucian Davis[1,2,3]*

PLOS ONE | www.plosone.org 1 November 2013 | Volume 8 | Issue 11 | e79669

Results: Among a hypothetical cohort of 234 individuals undergoing evaluation for presumed active TB annually, 6.4% had culture-positive TB. Compared to smear microscopy, Xpert reduced isolation bed utilization from an average of 2.7 to 1.4 days per patient, leading to a 48% reduction in total annual isolation bed usage from 632 to 328 bed-days. Xpert saved an average of $2,278 (95% uncertainty range $1582–4570) per admission, or $533,520 per year, compared with smear microscopy.

Conclusions: Molecular testing for TB could provide substantial savings to hospitals in high-income countries by reducing respiratory isolation usage and overall length of stay.

Impact of Xpert MTB/RIF on Antibiotic Stewardship

Impact of GeneXpert MTB/RIF on Patients and Tuberculosis Programs in a Low-Burden Setting
A Hypothetical Trial

J. Lucian Davis[1,2], L. Masae Kawamura[3], Lelia H. Chaisson[1], Jennifer Grinsdale[3], Jihane Benhammou[4], Christine Ho[5], Anna Babst[6], Houmpheng Banouvong[3], John Z. Metcalfe[1,2], Mark Pandori[6], Philip C. Hopewell[1,2], and Adithya Cattamanchi[1,2]

Am J Respir Crit Care Med Vol 189, Iss 12, pp 1551–1559, Jun 15, 2014

Conclusions:

- Xpert could greatly reduce the frequency and impact of unnecessary empiric treatment, contact investigation, and housing

Clinician Decision

TB Therapy?	TB (n=13)	Not TB (n=143)
Initiate (n=59)	12	47
Withhold (n=97)	1	96

Xpert Reclassification

TP	FP
1 → 1	1 → 45
FN	TN

Xpert-guided Decision

TB Therapy?	TB (n=13)	Not TB (n=143)
Initiate (n=15)	12	3
Withhold (n=141)	1	140

CDC Antimicrobial Resistance Recommendations

In general, threats assigned to the urgent and serious categories require more monitoring and prevention activities, whereas the threats in the concerning category require less. Regardless of category, threat-specific CDC activities are tailored to meet the epidemiology of the infectious agent and to address any gaps in the ability to detect resistance and to protect against infections.

HAZARD LEVEL URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (*C. difficile*), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

- ***Xpert C diff/EPI***
- ***Xpert Carba-R*** *Now FDA approved for rectal screening*
- ***Xpert CT/NG***

HAZARD LEVEL SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or inaccessible availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumoniae*, Drug-resistant tuberculosis (MDR and XDR)

- ***Xpert VAN-A***
- ***Xpert MRSA, SSTI and Blood Culture, Pre-surgical***
- ***Xpert MTB/RIF***

HAZARD LEVEL CONCERNING

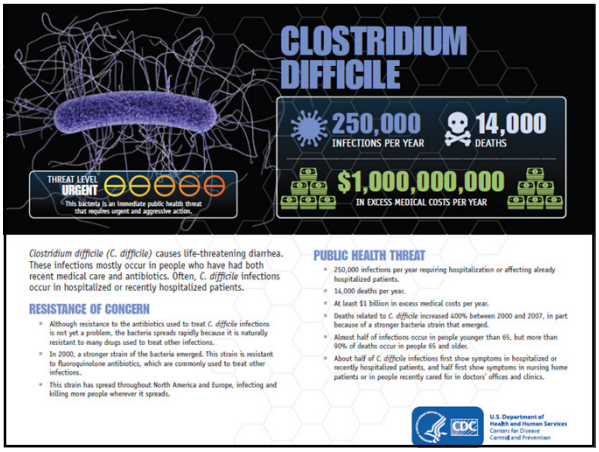
These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

- ***Xpert GBS***

Although *C. difficile* is not currently significantly resistant to antibiotics used to treat it, it was included in the threat assessment because of its unique relationship with resistance issues, antibiotic use, and its high morbidity and mortality.

Cepheid.



Clostridium difficile (*C. difficile*) causes life-threatening diarrhea. These infections mostly occur in people who have had both recent medical care and antibiotics. Often, *C. difficile* infections occur in hospitalized or recently hospitalized patients.

RESISTANCE OF CONCERN

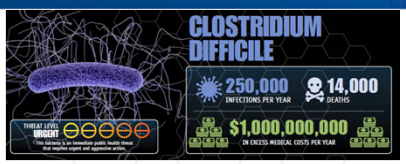
- Although resistance to the antibiotics used to treat *C. difficile* infections is not yet a problem, the bacteria spreads rapidly because it is naturally resistant to many drugs used to treat other infections.
- In 2000, a stronger strain of the bacteria emerged. This strain is resistant to fluoroquinolone antibiotics, which are commonly used to treat other infections.
- This strain has spread throughout North America and Europe, infecting and killing more people wherever it spreads.

PUBLIC HEALTH THREAT

- 250,000 infections per year requiring hospitalization or affecting already hospitalized patients.
- 14,000 deaths per year.
- At least $1 billion in excess medical costs per year.
- Deaths related to *C. difficile* increased 400% between 2000 and 2007, in part because of a stronger bacteria strain that emerged.
- Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older.
- About half of *C. difficile* infections first show symptoms in hospitalized or recently hospitalized patients, and half first show symptoms in nursing home patients or in people recently cared for in doctors' offices and clinics.

CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

CDC Recommendations



WHAT YOU CAN DO

CEOs, Medical Officers, and other Healthcare Facility Leaders Can:

- Support better testing (nucleic acid amplification tests), tracking, and reporting of infections and prevention efforts.
- Ensure policies for rapid detection and isolation of patients with *C. difficile* are in place and followed.

50 | © 2010 Cepheid

Cepheid.

Real-time polymerase chain reaction correlates well with clinical diagnosis of *Clostridium difficile* infection

N. Berry [a,*], B. Sewell [b], S. Jafri [c], C. Puli [c], S. Vasia [a], A.M. Lewis [a], D. Davies [d], E. Rees [a], C.L. Ch'ng [c]
J Hosp Infect 87:109-14, 2014

Table I
Comparison of test algorithms with clinical diagnosis of *Clostridium difficile* infection (CDI)

(a) Polymerase chain reaction (PCR) test vs clinical diagnosis of CDI

PCR	Clinical diagnosis		
	Negative	Positive	
Negative	912	1	913
Positive	10	111	121
Total	922	112	1034

(b) Culture cytotoxin neutralization assay (CCNA) vs clinical diagnosis of CDI

CCNA	Clinical diagnosis		
	Negative	Positive	
Negative	917	55	972
Positive	5	57	62
Total	922	112	1034

(c) Glutamate dehydrogenase (GDH) alone vs clinical diagnosis of CDI

GDH	Clinical diagnosis		
	Negative	Positive	
Negative	832	17	849
Positive	48	88	136
Total	880	105	985

	Sens (%)	Spec (%)	PPV (%)	NPV (%)
(a)	99.1	98.9	91.9	99.9
(b)	51.0	99.4	91.9	94.3
(c)	83.8	94.5	64.7	97.9

n=1034 patient episodes

New Epidemic Strain of *C. difficile*

- **Name: BI/NAP1/027, toxinotype III**
  - Historically uncommon (particularly in U.S. strain collections), now epidemic
  - Current strain more resistant to fluoroquinolones
  - Carries extra toxin known as **binary toxin**
  - Mutations in **toxins A and B regulatory gene (*tcdC*)** and increased toxin production *in vitro*
  - Shows increased spore production

Xpert C. difficile/Epi - *FDA approved*

Product Profile:
- Rapid detection of toxigenic C. difficile in stool
- Identification of the 027/B1/NAP1 strain
- **Detection of three targets plus control:**
  - **toxin B**
  - **Binary toxin**
  - **tcdC mutation**
- Specific call-out of potential epidemic strains
- <50 minutes for a result
- Rapid enablement of antibiotic or other treatment selection
- PCR results available on-demand, 24/7 (even your night crew can do this test)

Overview
Title: Diagnosis of Clostridium difficile Infections: The Latest Poop
Ferric C. Fang, MD
Professor of Laboratory Medicine, Microbiology, and Medicine
University of Washington School of Medicine
http://portal.on24.com/view/channel/index.html?showId=1112689&showCode=cepheid

The Society for Surgery of the Alimentary Tract

Back to SSAT Site | 53rd Annual Meeting • May 18 – 22, 2012 •

Predicting Recurrence of C. difficile Colitis Using Bacterial Virulence Factors: Binary Toxin Is the Key

David B. Stewart, Arthur Berg, John P. Hegarty*
Surgery/Division of Colon and Rectal Surgery, Penn Sta... Medical Center, Hershey, PA

70%

Conclusions:

1) ***Binary toxin*** is an independent predictor of CDC recurrence, which has not previously been reported.
2) The combination of ***binary toxin and tcdC mutation*** is associated with the highest number of CDC recurrences, such that their combined presence is associated with a 70% recurrence rate.
3) C. difficile which produces binary toxin may require longer antibiotic regimens to prevent disease recurrence.

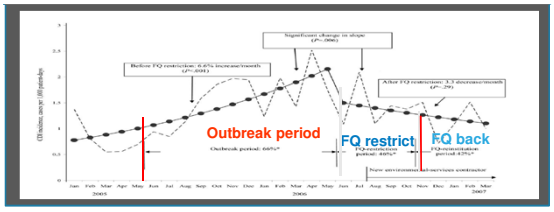
The need for hospital admission for CDC recurrence was strongly associated with tcdC mutation (p=0.04), binary toxin (p=0.02) and ribotype 027 (p=0.02). The combination of toxins A, B and binary toxin exerted an additive effect by increasing risk of readmission three-fold when all three toxins were present (p=0.02).

Cepheid.

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MARCH 2009, VOL. 30, NO. 3

ORIGINAL ARTICLE

Complete Restriction of Fluoroquinolone Use to Control an Outbreak of *Clostridium difficile* Infection at a Community Hospital



- Over 27 months, 319 cases of CDI, predominately 027, multiple interventions
- Started stewardship program; 22% decrease in DDDs of antimicrobials
  - 66% decrease in use of FQs (complete restriction)
- Effect: 22% decrease in *C. difficile* infections
- After CDI declined, gradually added some FQ use back

Cepheid.

Value of 027/NAP1/BI call out; Hospital A Data (Northeast US)

Month 1 CDI Results	Month 4 CDI Results
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 negative
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 positive	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 negative
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive
• C.diff tox B+; 027 negative	• C.diff tox B+; 027 positive

Wouldn't infection control want to know this?

Cepheid.

The Value of 027/NAP1/BI Identification in Xpert C diff/Epi

- **Identifies one of the most virulent and difficult to control *C. difficile* strains immediately without the need for culture and the expense of sending multiple isolates for strain typing**
- **Can provide early indications of an outbreak in the hospital that may require changes in environmental disinfection or other infection control practices to stop transmission, such as restriction of fluoroquinolones**
- **Can provide evidence for effectiveness of infection control interventions when 027/NAP1/BI outbreaks occur**

Cepheid.

Implementation of Polymerase Chain Reaction to Rule Out *Clostridium difficile* Infection Is Associated With Reduced Empiric Antibiotic Duration of Therapy

William J. Peppard, PharmD, BCPS, and Nathan A. Ledeboer, PhD, D (ABMM)†,‡*

Moving from batch test to a rapid test resulted in:

Table 2. Primary and secondary clinical and economic outcomes

Clinical and economic outcomes	EIA (n = 79)		PCR (n = 87)	P
Duration of antibiotic therapy in days, mean (CI)	2.31 (1.48-3.15)	↓	0.88 (0.45-1.33)	.007
Diagnostic test performed per patient, mean (CI)	2.73 (2.64-2.83)	↓	1.16 (1.04-1.28)	<.001
Duration of contact isolation in days, mean (CI)	1.46 (0.61-2.32)	↓	0.62 (0.08-1.32)	.131
Total treatment cost per patient* (CI)	69.54 (43.36-95.73)	↓	65.97 (46.61-85.34)	.828
Diagnostic test cost* (CI)	13.67 (13.08-14.26)	↑	37.15 (32.51-41.79)	<.001
Antibiotic therapy cost* (CI)	36.95 (12.70-61.20)	↓	20.64 (5.08-36.20)	.262
Contact isolation cost* (CI)	19.39 (8.07-30.71)	↓	8.19 (1.14-17.52)	.131

Note: CI = 95% confidence interval; EIA = enzyme immunoassay; PCR = polymerase chain reaction.
*Costs are reported in US dollars.

The rapid reporting of PCR test results was associated with a reduced empiric CDI antibiotic duration of therapy. When combined with fewer diagnostic laboratory tests performed per patient, shorter length of empiric antibiotic therapy, and briefer duration of contact isolation, the higher acquisition cost of the PCR test was offset and resulted in cost neutrality. These findings provide additional data to support the routine use of the PCR test.

Hosp Pharm 2014;49(7):639–643 2014 © Thomas Land Publishers, Inc.

Cepheid.

Rapid Molecular Flu/RSV

*Unmet Need**

- An ability to detect and differentiate influenza A and B and RSV accurately will provide additional value to the management of patients presenting with Influenza-Like Illness (ILI) as symptoms for Flu and RSV are very similar to common cold and pneumonia.
  - Prescription drug is available and widely used for influenza, but there is no available antiviral treatment for RSV.
- Overwhelming evidence now shows that rapid influenza and RSV tests lack adequate clinical performance and, therefore, clinical usefulness.[1,2]
- Respiratory viruses, especially influenza, mutate rapidly and novel strains can emerge with little notice making reliable diagnostics challenging.

1. Harper et al., Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America, Clinical Infectious Diseases 2009.
2. http://www.cdc.gov/rsv/about/faq.html

Cepheid.

FDA Re-classification of the FLU rapid tests

Summary

Due to the public health implications of influenza virus infections and the wide use of RIDTs in US medical practice, FDA proposes:

- To reclassify rapid influenza detection devices from Class I into Class II with special controls
- To implement special controls, along with design controls to significantly improve the reliability of influenza tests over their TPLC and reduce the likelihood of false negative results

Improved and reliable influenza diagnostic devices would:

- Aid physicians to make accurate patient diagnosis and appropriate treatment decisions
- Allow for effective infection control during influenza outbreaks

FDA Re-classification of the FLU rapid tests

What are the Issues?

Low sensitivity and failure to detect emerging influenza viruses

- Sensitivity reported in the labeling for devices cleared since 1998:

Flu A 73.8% (95% CI: 64.4%-81.9%) - 94.2% (95% CI: 91.0%-96.3%)

Flu B 60.0% (95% CI: 45.2%-73.6%) - 97.8% (95% CI: 88.7%-99.6%)

- Tests not used as intended; negative results frequently not followed up by culture or molecular test as indicated in labeling
- Insufficient post-market monitoring to ensure that tests continue to detect newly emerging influenza virus strains
- Risk to Health
  - False negative results may lead to non-use/delay of antiviral therapy and failure to institute proper infection control procedures

Both CDC and RIDT test manufacturers recommend confirming negatives

A Case Study

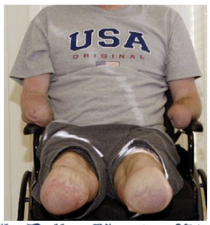
A Texas jury awarded $17.5 million to a man (Mr. F.) who lost both arms and legs

developed an infection known as MRSA, or methicillin-resistant *Staphylococcus aureus*, after surgery for ulcers

A doctor who failed to properly treat the infection with the right type of antibiotic. Dr. P treated the plaintiff with eight different antibiotics, but the infection was known to be resistant to all of them, and the doctor failed to prescribe the one that treats MRSA

Dr P's attorney said: There were no less than seven doctors from seven specialties, all board-certified, who saw this guy over the crucial time period, and nobody knew what it was

As a result of the failure to properly treat the infection, patient developed gangrene and required both of his arms to be removed below the elbows and both of his legs to be removed below the knees



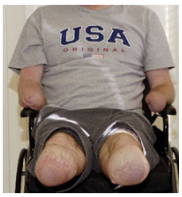
The Dallas Morning News

Pre-surgical Work-up:

MRSA/SA Nasal surveillance – Detects MRSA and SA colonized patients from nasal swabs at the time of admission or during pre-surgical work-up and is used in active surveillance programs to prevent the SSI associated with MRSA and SA.

Mr F. could have been screened prior to surgery and then decolonized with mupirocin and chlorhexidine and if MRSA positive, Vancomycin prophylaxis could have been considered during surgery

A Texas jury awarded $17.5 million to a man who lost both arms and legs



The Dallas Morning News

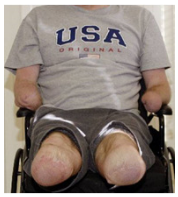
Cepheid.

If the infection did develop after surgery then:

MRSA/SA Skin and Soft Tissue - In less than one hour, Cepheid's Xpert MRSA/SA SSTI test processes specimens from suspected skin and soft tissue infection swabs to determine if a patient is infected with MRSA or SA, giving physicians and surgeons a powerful new tool to aid in selecting the most effective antibiotic therapy to improve patient management. The ability to detect MRSA or SA in less than one hour, versus two to three days with current culture methods, will enable clinicians to make real-time decisions as to the best course of treatment or management.

Mr F. surgical site infection could have been swabbed and results would have been available in one hour. Appropriate antibiotics could have been administered within an hour.

A Texas jury awarded $17.5 million to a man who lost both arms and legs



The Dallas Morning News

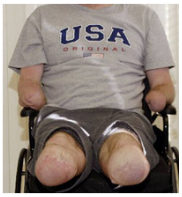
Cepheid.

If the infection goes onto sepsis and blood cultures turn positive for GPCC:

MRSA/SA blood culture - for the detection of Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA, typically Methicillin susceptible) in blood culture bottles showing gram-positive cocci — in less than one hour. Cepheid's Xpert MRSA/SA BC test processes positive blood culture specimens to determine if a patient's blood is infected with MRSA or SA, which are frequent causes of sepsis in hospitalized patients. This may enable physicians to quickly de-escalate from broad-spectrum antibiotic treatment to a more effective targeted therapy, thus reducing risk of resistance and improving patient outcomes and cost.

Mr F. could have gotten to a targeted therapy days quicker.

A Texas jury awarded $17.5 million to a man who lost both arms and legs



The Dallas Morning News

Cepheid.

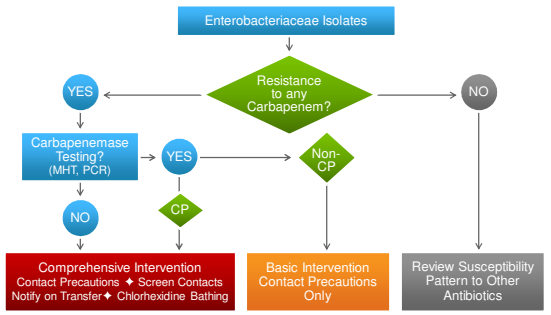
What Does CDC Recommend That Hospitals Do About CRE?

Healthcare CEOs, Medical Officers, and Other Healthcare Facility Leaders Can:

- Require and strictly enforce CDC guidance for CRE detection, prevention, tracking, and reporting.
- Make sure your lab can accurately identify CRE* and alert clinical and infection prevention staff when these bacteria are present.
- Know CRE trends in your facility and in the facilities around you.
- When transferring a patient, require staff to notify the other facility about infections, including CRE.
- Join or start regional CRE prevention efforts, and promote wise antibiotic use.

* The more information you have about which types of CRE are in your hospital, the better your infection prevention measures will be

CDC Recommendations for CRE Management



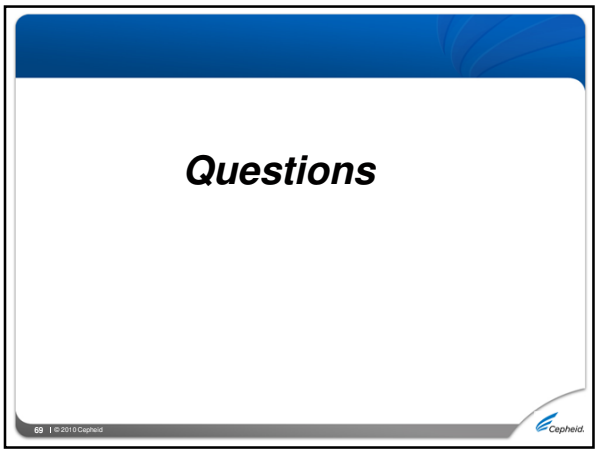
Workflow courtesy of CDC

Xpert® Carba-R

Key Features for Isolate Confirmation....And now rectal swabs

The On-Demand PCR test for confirmation of the most prevalent carbapenem-resistant gene families from cultured isolates and rectal swabs

- **48 Minutes to results**
- **>90 genes reported as 5 common CPE families**
  - **KPC, NDM, VIM, OXA-48, IMP**
- **Screening Rectal Swabs**
- **Isolates cultured from many specimen sources**
  - **Urine**
  - **Blood**
  - **Sputum**


Questions
69 | © 2010 Cepheid
Cepheid.