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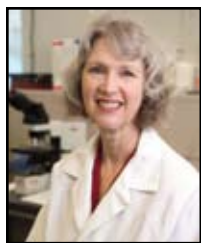
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## New England Baptist Hospital: Testing Patients for MRSA and *Staph aureus* Before Inpatient Surgery

*Patients asking for the lab test that “goes after the bad bug”*



Ellen Jo Baron, Ph.D.

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Professor, Dept. of Pathology, Stanford Med School

The New England Baptist Hospital (NEBH) in Boston is an orthopedic center of excellence, performing over 6,000 inpatient surgeries a year and another 4,000 outpatient cases. Surgeries

comprise 83% of their service, and 75% of that is orthopedics. Post-surgical infections in bones and joints are among the most difficult and costly to manage and patient morbidity rises dramatically if the organism reaches the bloodstream. The hospital has established a multidisciplinary infection control team with the audacious goal of achieving a zero surgical site infection rate. Part of the team's effort involves empowering patients to participate in an eradication program for methicillin-resistant *Staphylococcus aureus* (MRSA) and

methicillin-sensitive *Staphylococcus aureus* (MSSA). Since the team was formed in 2003, the overall infection rate has dropped from 0.7% to 0.4%.

In the summer of 2005, the infection control team, directed by Maureen Spencer, R.N., M.Ed, CIC, noticed an

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## Testing Patients for MRSA and *S. aureus*

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increase in secondary bacteremias due to MRSA and MSSA, associated with surgical site infections. This raised a red flag, since there is an increased risk of adverse outcomes with septicemia. This occurrence also coincided with national and international interest in rising rates of MRSA in the community and health-care settings.

Fortunately, Susan Cohen, MT(ASCP), S.M., Microbiology Supervisor, had saved the MRSA and MSSA isolates from orthopedic patients for more than a year. A large sample of isolates was sent to a reference lab for pulsed-field gel electrophoresis. Testing revealed that there was no point source outbreak or significant patient-to-patient transmission in the hospital. It became clear that the organisms causing the infections were from the patients' own skin flora. To test this hypothesis, the infection control team cultured 133 patients in the operating room searching for MRSA or MSSA in their noses. Results



The implementation team at NEBH (left to right): Susan Cohen, Maureen Spencer, and Diane Gulczynski.

initiated research on the problem. After educating herself about health-care-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA), she learned about active surveillance and prevention measures implemented in European hospitals and at the Evanston Hospital, Evanston, IL (read article in *On-Demand*, vol. 1, issue 1).

The overall national average infection rate for orthopedic surgery is 1.5%.  
NEBH's rate is 0.4%.

showed that 29% of the patients had MSSA and 4% had MRSA in their noses. This confirmed the team's suspicions, that many patients coming in for surgery were already colonized.

Maureen Spencer broached the topic at a Patient Care Assessment Committee meeting, saying, "we need to do something about this—bacteremia carries an increased risk of morbidity and mortality." Fortunately, someone with the ability to carry the momentum forward was listening. Diane Gulczynski, R.N., M.S., Senior Vice President for Patient Care Services,

Gulczynski realized that NEBH had a unique opportunity to go one step further. Why not perform active surveillance screens, using rapid test technology, in the pre-admission process? It would identify positive patients even before they arrived at the hospital and they could take appropriate measures to reduce colonization. She prepared a white paper on the eradication of MRSA and *S. aureus* prior to surgery and recommended opportunities for NEBH to meet the challenge. It had worked in other settings and she was sure it would work at NEBH. <sup>1-6</sup>

## at New England Baptist Hospital

She presented her research to the hospital's Board of Trustees and Administration in January, 2006 and requested the Board's support for her goal: "to identify strategies to eradicate HA-MRSA from New England Baptist Hospital's surgical patients." The program is now two years old, and has made substantial strides towards that goal, including upgrading the hospital's rapid testing technology (now Cepheid GeneXpert® System).

### Program Implementation

The three pillars of support necessary for implementation of a successful MRSA control program are:

- A strong administrator who advocates for the program (and sees to it that the necessary funding is provided)
- A proactive Infection Control Team
- An energetic and committed Microbiology Department

All three factors were poised for action at NEBH in February 2006. Gulczynski's report to the Board of Directors was convincing enough to secure the financial support needed to hire an additional Medical Technologist for the Microbiology Laboratory and a Patient Care Technician (PCT) for the Pre-Admission Screening Department. These positions were filled in the spring of 2006.

The new PCT's title was MRSA Coordinating Technician, with responsibilities to collect the nasal swabs, communicate with the patients and caregivers, and manage the paperwork. The other PCTs in the Pre-Admission Screening Department were then cross-trained to perform the same functions.

Initiation of the program required extensive and continuous communication

among the healthcare team. Coordination included Information Systems, which developed a special test code that automated immediate results reporting to the patient's unit and the pre-admission clinic. At the beginning, weekly meetings were held with Infection Control, Microbiology, Operating Room nurse managers and pre- and post-surgical services representatives, Housekeeping (which assists with patient room disinfection and maintaining isolation), Pre-Admission Services, and Information Services. Now, says Cohen, the system is running so smoothly that they rarely need to meet anymore.

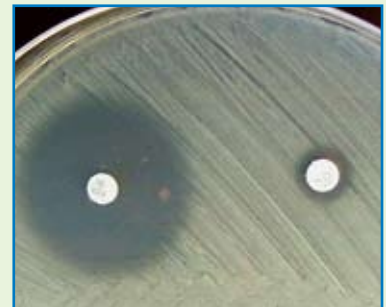
Susan Cohen initially chose to validate the GeneOhm (BD, Cockeysville, MD) system performed on the Cepheid SmartCycler PCR instrument. The initial validation consisted of the laboratory running 150 patient nares swabs in parallel with culture on a colistin-nalidixic acid agar and a regular sheep blood agar plate. Initially no proficiency testing (P.T.) survey was available, and samples were shared with two other facilities using the SmartCycler. The College of American Pathologists now offers P.T. for MRSA surveillance and sharing samples is no longer necessary.

Due to staffing and method requirements, the Microbiology Laboratory initially tested samples twice a day, Monday through Friday. Because patients were tested approximately 10 days before their surgery date, this testing schedule provided adequate turnaround times. However, patients admitted for emergency surgery and those who could only visit the pre-admission clinic on weekends were excluded. Nevertheless, the lab was ready and the program was formally launched for a pilot trial on spinal

### Culture-testing for *Staph aureus*



*Staphylococcus aureus* on blood agar plate showing beta hemolysis.



*In vitro* tests for methicillin resistance can be misleading. This *S. aureus* isolate exhibits oxacillin resistance by disk diffusion, but the cefoxitin disk (on the right) correctly reveals that the organism is not MRSA.



Selective culture on mannitol salt agar is only relatively sensitive for detection of *Staphylococcus aureus*.

*Continued on next page*

## Testing Patients for MRSA and *S. aureus*



Microbiology technologists Scott Shurlow, MT(ASCP) and Martha Hedman, MT(ASCP) ready to place a cartridge into the GeneXpert instrument at New England Baptist Hospital.

surgery patients in July 2006 using Cepheid's SmartCycler test.

### Testing Process

The Pre-Admission Screening Department collects nasal swabs, which are sent to the Microbiology Lab. The swabs are plated for a standard culture to detect MSSA with results available the next day and are then processed for MRSA by PCR with results available in hours. Patients are given a decolonization protocol that includes a prescription for 2% mupirocin nasal ointment (Bactroban) and 2% chlorhexidine (Hibiclens).

If the tests show colonization with either MRSA or MSSA, the patient is called at home by the MRSA Coordinating Technician and instructed to begin the decolonization protocol. A prescription is called to the pharmacy and the patient is instructed to purchase the bottle of Hibiclens. The topical decolonization protocol has shown a 78% eradication of *S. aureus* at the time of surgery<sup>7</sup>. Patients positive for MRSA are re-tested at time of admission. If test results are still positive for MRSA, contact precautions are used in the operating room and throughout

the hospitalization. All patients who initially tested positive for MRSA receive vancomycin for surgical prophylaxis. Prior to active surveillance for MRSA, patients would have received cefazolin, which would have been ineffective. Most impressively, overall MRSA infections at NEBH have dropped dramatically, more than 50%, from previous years. The overall national average infection rate for orthopedic surgery is 1.5%. NEBH's rate is 0.4%.

### Introducing the GeneXpert® System

The GeneXpert test replaced the SmartCycler test in May 2007, allowing universal patient testing whenever the patient




The GeneXpert family.

arrives, including weekends. In addition, the moderate complexity allows the Microbiology specimen processor (their Planter) to perform the test, speeding up results to the patient and freeing the Microbiology Technologists to concentrate on other more complex testing. The GeneXpert System has made it feasible to entertain moving the testing to all admissions, not limiting it to inpatient surgical patients as initially practiced.

The NEBH team has tested more than 10,000 patients for MRSA and MSSA to date. Judging from both the community's response and in 2007, the prestigious Betsy Lehman Award, given annually to the Boston area hospital with the best new program for innovations in patient care, NEBH has succeeded magnificently.

In addition to the obvious success in lowering the rate of MRSA infections in their patients, Maureen Spencer, R.N., is also enthusiastic about broader aspects of the program. Testing and reporting results on colonization gives the MRSA Coordinating Technician the opportunity to provide patient education on hand hygiene and risks for transmission both inside and outside of the hospital, regardless of whether the patient is actually colonized with MRSA, MSSA, or neither. She points out, "even if we only focus on inpatients, imagine the patient care education we can accomplish. And the patients have loved it." The program has been so successful that patients are now actively seeking out NEBH for their surgeries because it is the hospital that "looks for the bad bug."

Susan Cohen is also extremely satisfied, especially now that the hospital can offer two-hour turnaround 24/7 with much less labor and effort using the GeneXpert test. She concludes "If we have access to a better technology, aren't we obligated to provide that for our patients? We should feel a responsibility to provide the best care that we can for our patients. Our entire hospital team never lost sight of that." 

# Celebration of the 30th Anniversary of *Clostridium difficile*

## A summary of selected presentations from the 9th Biennial Congress of the Anaerobe Society of the Americas

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Ellen Jo Baron, Ph.D.

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More than 300 participants from 30 countries gathered in Long Beach, California from June 24–27 to hear the latest on anaerobe-related topics, ranging from probiotics for prevention and treatment of infections to the possibility that autism is due to an infectious disease. Special tribute was bestowed to **Dr. Sherwood Gorbach** (Tufts University School of Medicine, Boston, MA) and **Dr. John Bartlett** (Johns Hopkins University School of Medicine, Baltimore, MD) for their seminal roles in delineating the association between pseudomembranous colitis and *Clostridium difficile* colonization of the gastrointestinal tract. Their now-classic paper, published in the *New England Journal of Medicine* in 1978 (Bartlett, et al.), also established the cytotoxic cell culture system as the gold standard method of testing for presence of the etiological agent in stool.

**Dr. Bartlett** began the *C. difficile* portion of the program with an historical perspective on the early years of initial detection of the organism and subsequent changes in diagnostic methods and treatment. After its discovery, epidemiological studies soon revealed that numerous infants less than one year old could be asymptomatic carriers of toxigenic *C. difficile*, hence the recommendation to avoid testing for *C. difficile* in children less than one year old. He stated that enzyme-immunoassay has largely replaced cytotoxin assays for diagnosis in most U.S. laboratories not because it was better, but because it was easier to perform, cheaper and yielded faster results. Interestingly, vancomycin

was originally the treatment of choice but over the next decade metronidazole gained favor similarly because it was cheaper and because of fears of encouraging vancomycin resistance in other organisms. Recent experience however, suggests that vancomycin is indeed the preferred treatment. Finally, Bartlett mentioned that new data from David Relman's laboratory at Stanford University (Dethlefsen, et al.; Eckburg, et al.) illuminating the length of time that the bowel flora are perturbed by antibiotics has prompted him to create a unique new treatment regimen using pulsed dosing of vancomycin for six weeks.

The next two speakers explored virulence factors of *C. difficile*. **Dr. Gayatri Vedantam** from Loyola University in Chicago, IL reported that the recently emerged hypervirulent NAP1 (North American Pulsed-Field type 1), also called PCR ribotype 027 or restriction endonuclease analysis type BI ("bee-eye") strains, have 100% higher adherence to human intestinal epithelial cells than related non-hypervirulent strains. This adherence is mediated by surface protein A. This information could serve as the basis for development of new therapies. Because of increasing numbers of the hypervirulent strains, from 5.7% in 1999 to 23% in 2007 (Redelings, Sorvillo, and Mascola), there has been expanding interest in virulence factors. **Dr. Dena Lyris** from Monash University, Victoria, Australia, described the role of Toxins A (enterotoxin) and B (cytotoxin). New genetic tools have allowed better dissection of the toxin genes, and her studies revealed unequivocally that Toxin B is the major virulence factor. In conventional strains, toxin production results from starvation conditions

in the stationary phase of growth. The BI strains produce 16 and 23 times the normal levels of Toxins A and B respectively, in all growth phases. These strains also produce a binary toxin, whose role in virulence is not yet known. In response to the question of why this strain has spread so rapidly, she mentioned that other studies point to increased spore production, and thus to an increased environmental reservoir as one factor in the rapid spread of the hypervirulent strains throughout western Europe and the U.S.

**Dr. Cliff McDonald** from the Centers for Disease Control and Prevention in Atlanta, GA, discussed the changing epidemiology of *C. difficile* infection. Data from hospital discharge summaries suggest that there were 100,000 cases in 1992, and around 300,000 in 2006. More than half of reported cases occur in long-term care facilities. If more reliable data from an Ohio-based study are extrapolated to the entire U.S., there are 500,000 cases/year and 23,000 deaths. Costs including 180 day follow-up after hospitalization are estimated to be from \$3800 to \$7200 per patient, or more than \$1 billion/year in the U.S. *C. difficile* infection accounts for a 2.8 day average increased length of stay (Dubberke, et al.). The attributable mortality is 5.7%, but those who survive are more likely to be discharged to a nursing home.

Another factor that is likely contributing to the rapid spread of the BI strain is its increasing resistance to fluoroquinolones (FQs) in a time of increasing use of FQs worldwide. Substitution of one FQ for

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another (from levofloxacin to gatifloxacin, for example) is unlikely to control an outbreak (Gaynes, et al.). Some improvement has been noted when FQs were removed from the formulary altogether (Dubberke, et al.). Dr. McDonald stated that the risk of acquisition rises four-fold if more than one patient on a ward has *C. difficile* infection. Both infection control measures and antibiotic restrictions are needed for optimal control. Although the expanded use of alcohol gel hand washes has been postulated to contribute to the increase in *C. difficile* infections, institutions have not shown an increase in *C. difficile* rates coinciding with alcohol gel use. According to Dr. McDonald, the use of alcohol gel and increasing *C. difficile* cases are probably unrelated. **Dr. Brandi Limbago** from CDC

next discussed the changing mix of strains in the U.S. after the hypervirulent strains suddenly erupted in six states starting in 2005. Her most recent study revealed that 83% of cases were healthcare related and 17% community related. Approximately half of both groups were NAP<sub>1</sub> or hypervirulent strains. Dr. Limbago also reported that strains associated with outbreaks affecting pigs in pork production facilities are moving into the human population.

The keynote address by **Dr. Abraham Sonenshein** from Tufts University began with an explanation of the mechanics of spore formation and germination. One characteristic that is exploited in culture methods is the encouragement of vegetative growth from spores by taurocholate

or by thioglycolate and lysozyme. Taurocholate is now a component of the most sensitive media formulations used for cultivation of *C. difficile* from stool. In the bowel, the normal flora produces compounds from bile that are inhibitors of germination. Antibiotic therapy lowers the formation of such secondary bile compounds, leading to increased *C. difficile* germination in the gut.

**Dr. Peter Gilligan**, University of North Carolina, Chapel Hill, NC, presented a summary of current laboratory testing options and his recommendations for laboratories today. Recent data from College of American Pathologists proficiency testing surveys showed that

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## From the Editor: Sputum, the Final Frontier: PCR from the Research Bench to the Diagnostic Trench

Some readers of this newsletter may have had the experience of actually performing PCR as it was first described in 1985. The procedure involved pipetting new aliquots of Klenow polymerase after each PCR cycle because the temperatures required for denaturation of the target and amplification products also denatured the enzyme. Most memorably, the procedure required sequential steps of floating small plastic tubes in water baths kept at three different temperatures, with no time for bathroom breaks. The advent of a thermostable DNA polymerase was a huge improvement, but the novelty of the water baths quickly wore off, even for the most dedicated graduate student.

I recall the great excitement at the University of California on the day when a prototype Perkin-Elmer thermal cycler was delivered to Dr. Jane Gitshier's lab; one thermal cycler was made available for the entire university. The sign-up list quickly filled up as eager graduate students filed into and out of the lab at all hours of the day and night. The inconvenience of a midnight PCR run was a much-preferred alternative to standing, lock-kneed, pipettor in hand, in front of three water baths.

Needless to say, times have changed. Two decades of technological improvement have now made the field of molecular diagnostics barely recognizable. Clumsy, contamination-prone techniques have been largely replaced with real-time detection technology performed in closed systems. DNA sequencing and microarray technologies developed under the auspices of the Human Genome Project are making steady inroads into clinical laboratories. Diagnosticians have taken a great leap forward in their level of overall sophistication and familiarity with these technologies. Phylogenetic analysis and identification of bacteria, fungi and viruses by direct DNA sequencing are quickly entering the mainstream, and will require us to add a few new words such



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as “bootstrapping” and “parsimonious” to our vocabulary.

Much of Cepheid's current focus revolves around the detection and characterization of infectious agents that cause healthcare-associated infections (Methicillin-resistant *S. aureus*, Vancomycin-resistant enterococci, and *C. difficile*). Although these pathogens come from entirely different branches of the prokaryotic phylogenetic tree, they are all similar in that they harbor genetic signatures that can be used to identify them, quantify their infectious burden, determine their virulence, and assess their susceptibility or resistance to available drugs.


From a diagnostic test development standpoint, the major hurdles to be overcome are now related less to the nucleic acid detection technology itself than to sample processing. Indeed, the main challenges for many procedures involve determining: the appropriate quantity of specimen, how to eliminate inhibitors of enzymatic reactions that exist in these specimens, and how best to efficiently release the target from its often impermeable microbial shell. To paraphrase a well-known opening line, “sputum, the final frontier”. For the molecular diagnostician, it truly is.

As real-time PCR technology continues to evolve, so should our focus on delivering real-time patient results. Most diagnostics manufacturers have focused heavily on development of batch-based commercial tests, for which the rapid turnaround requirements are not as stringent as for acute infectious processes. Choices about when and how to run the batches are usually decided according to test volume. The end result is that the very technology once touted for its speed is

reporting results in days or even weeks, depending on when batches are run. Cepheid has taken a fundamentally different approach to molecular diagnostic testing, creating the GeneXpert for rapid turnaround and quick response to patient test requests.

Each GeneXpert cartridge is a virtual laboratory in itself, containing specimen-specific preparation instructions, target-specific reaction components and controls that allow specimens to be tested, irrespective of specimen type or test request, on-demand and in the order received. By accomplishing all of this in an easy-to-use format, the GeneXpert allows testing to be performed at any time and in almost any laboratory. At Cepheid, the enthusiasm fueled by making extraordinary technology incredibly easy to perform has taken on infectious proportions of its own.

The case study of New England Baptist Hospital presented in this issue is an example of how rapid MRSA test results delivered by the GeneXpert can be used to determine the most effective care options for surgery patients, lowering the overall risk of infection. The success of the NEBH program speaks for itself, with the reward of lower transmission pressure in the hospital, reduced infectious complications and increasing patient demand for NEBH services.

Ultimately, we at Cepheid believe that all patients, in or out of the hospital, will benefit from molecular diagnostics technology that is well-practiced and accessible to patients where and when they need it most. 

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use of immunochromatographic tests for toxin has increased from 26% of laboratories in 2004 to 46% in 2008, whereas enzyme immunoassays for toxin A alone usage has dropped from 18% to 2%. Unfortunately, the gold standard test, cytotoxicity and neutralization in cell culture is performed by only 1% of all U.S. laboratories. After the cytotoxicity test, the next most reliable results are derived from toxigenic culture. Unfortunately, the results take at least 48 hours, too late for clinical decision-making. According to Dr. Gilligan, the most cost-effective algorithm today is to perform an initial screening test with the *C. diff* Quik Chek® (TechLab, Blacksburg, VA) glutamate-dehydrogenase (GDH) test and reflex all positives to a reference test such as cytotoxin. The source of the GDH

test does make a difference, with certain products yielding unacceptably low sensitivities. Studies published by Ticehurst and colleagues from Johns Hopkins University Medical Center showed that compared to an immunoassay for toxins A and B with sensitivity of only 38%, the GDH screen had a sensitivity of 100%, so no potential cases were missed with this system (Ticehurst, et al.).

**Dr. Lance Peterson**, Northwestern University in Evanston, IL, highlighted current and future molecular methods for detection toxigenic *C. difficile*. With the newly developed GeneOhm system (Becton Dickinson), two pre-clinical trials have shown better sensitivity than the GDH screening methods (average 96% vs. 79% for GDH). Dr. Peterson stated that

once excellent and rapid PCR tests are available, it is imperative for the physician to be educated as to which patients to test (those with  $\geq 3$  loose stool per day) and then to use the most sensitive test first. He noted, "PCR appears to be that technology."

Additional presentations followed by **Dr. Dale Gerding**, VA Hospital, Hines, I.L. on antimicrobial therapeutic options and **Dr. Johan Bakken**, St. Luke's Infectious Disease Associates, Duluth, M.N. on non-traditional therapies, particularly the controversial but highly effective fecal transplant therapy. Finally, **Dr. Sherwood Gorbach** summarized the state of the art and outlined the continuing challenges faced in order to respond to the rising epidemic of CDI. 



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