Health care–associated infections (HAIs) continue to be one of the most critical burdens on the nation’s health care system, representing a significant source of patient morbidity and mortality. A multistate point-prevalence study of 183 acute care hospitals in the United States reported an estimated 648,000 inpatients with 721,800 HAIs during 2011. Although efforts to reduce the incidence of HAIs have grown in both scale and sophistication, thanks in part to multidisciplinary collaboration in the medical community, advances in technology, and implementation of and mandates for evidence-based HAI-specific safe practices, the battle against HAIs is far from over.

The ability to rapidly identify the pathogens causing HAIs has been an integral part of this battle. The development of polymerase chain reaction (PCR) testing of blood, sputum, urine, and stool specimens has been a critical step forward in this effort to increase the rapidity, sensitivity, and specificity of pathogen diagnosis. First developed in the 1980s, PCR is a method for amplifying specific sequences of DNA, which can, among other things, aid in the diagnosis of diseases and the identification of bacteria and viruses. Although batch PCR testing has been available for several decades for diagnostic purposes, on-demand PCR testing with results obtainable at the point of care and within 2 hours is a relatively new advancement that, unfortunately, has not yet been widely incorporated into the education and enrichment programs for many of those involved in infection control and prevention.

A recent survey of more than 200 infection preventionists (IPs) from across the country, of whom 75 responded, identified significant knowledge gaps among IPs with regard to PCR technology:

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Mycobacterium tuberculosis infection in today’s health care settings, it is imperative that those professionals at the forefront of the fight against HAIs understand the basics of PCR technology along with its potential impact on HAI rates, antimicrobial stewardship, patient isolation, and health care economics.

ON-DEMAND PCR TESTING

PCR testing of patient specimens involves harnessing the ability of the enzyme DNA polymerase to synthesize new DNA strands complementary to a template strand when exposed to short pieces of single-stranded DNA. These short pieces, called primers, are designed to be compatible with the template strand. In the detection of bacteria and viruses by PCR, specific primers, chosen based on the known gene sequences of particular bacterial and viral DNA, are added to the tested samples and will allow DNA polymerase to amplify numerous copies of the pathogen’s DNA if it is present.

In the early days of PCR testing, blood, sputum, urine, or stool samples were collected and run in batches in centralized locations. Although this PCR testing offered more expedient and, in some cases, more sensitive and specific results than other testing modalities, there remained some drawbacks. These included the need for highly skilled laboratory staff to run the tests (some states permit only licensed medical technologists or licensed professionals to run them), high vigilance for contamination given the requirement for highly skilled laboratory staff to run the tests (some states require the tests to be run in centralized locations), and the need for the tests to be run in a timely manner to ensure accurate results.

The on-demand PCR technology does not require specialized training for health care staff and allows for testing of patients at the point of care in numerous settings—emergency departments (EDs), satellite clinics, and ICUs, among others—with turnaround times of approximately 2 hours or less. Health care personnel are able to run the test samples in fully integrated and automated PCR testing units that can be placed in the setting of choice. Currently, on-demand PCR testing is available for methicillin-resistant Staphylococcus aureus (MRSA), methicillin-sensitive S. aureus, Clostridium difficile, Mycobacterium tuberculosis (MTB), Chlamydia trachomatis, Neisseria gonorrhoeae, vancomycin-resistant enterococcus, enteroviral meningitis, norovirus, and group B Streptococcus.

The question then becomes how does on-demand PCR testing impact health care delivery? The answer is that the impact is far-reaching: influencing HAI rates, health care outcomes, hospital length of stay (LOS), isolation days, patient satisfaction, antibiotic stewardship, and health care economics.

IMPACT OF ON-DEMAND PCR TESTING

HAI rates

Rapid and reliable identification of pathogens, particularly those that pose the most significant risks to patients, is an integral part of reducing HAI rates. As Sue Barnes, National Leader for Infection Prevention for Kaiser Permanente, says, “the critical first step in preventing transmission of communicable diseases in health care settings, such as CDI [Clostridium difficile infection], MRSA, pertussis, and TB [tuberculosis] is prompt diagnosis. This guides expedient isolation of the patient and PPE [personal protective equipment] use as indicated, as well as prompt treatment to minimize and optimize antibiotic use and reduce transmission risk.”

In their 2008 Annals of Internal Medicine article, Robicsek et al reported implementing on-demand PCR testing followed by isolation and decolonization of patients who tested positive for MRSA. They subsequently saw a “reduction by more than half of health care–associated MRSA disease occurring during admission and in the 30 days after discharge” (12). Similar results have been seen in other institutions that switched to on-demand PCR testing for MRSA. Loyola University Medical Center reported a 68% reduction in MRSA infections (3) and New England Baptist Hospital reported a 60% reduction. After implementing an active MRSA high-risk patient screening program using on-demand PCR testing, J.T. Mather Hospital reported an 84% reduction in MRSA cases, an 84% cost reduction, and a decrease in average LOS in their ICUs and cardiac care units from 4.4 to 3.3 days between 2008 and 2014 (4). The Albert Einstein Health Care Network reported a 27% reduction in MRSA rates after initiating its Stop MRSA Acquisition and Spread in our Hospitals campaign involving on-demand PCR testing and new clinical protocols.

Awad et al reported an overall decrease in health care–associated MRSA infections from 2 to 1 per 1000 bed-days and a statistically significant overall decrease in surgical site infections (SSIs) at the Michael E. DeBakey Veterans Affairs Medical Center when universal on-demand PCR screening for MRSA (results obtained within 70 minutes) was implemented, along with contact precautions for infected or colonized patients, improved hand hygiene, a “cultural transformation campaign with staff and leadership,” and “ongoing monitoring of process and outcome measures.” This 5-pronged approach, referred to as the “MRSA bundle,” was later implemented across the Veterans Affairs health care system, resulting in a 62.2% decrease in health care–associated ICU MRSA infections and a 44.7% decrease in non-ICU health care–associated MRSA infections, as reported by Jain et al in their 2011 study (10). One study examining CDI incidence noted a decrease in health care onsets—health care facility–associated CDI rates from 52% to 16% in the 6 months after they implemented PCR testing instead of enzyme immunoassay testing (EIA) (7).

Antimicrobial stewardship

Prudent administration of antibiotics has become an issue at the forefront of the fight against HAIs in this era of multidrug-resistant organisms. The State of California has actually mandated that all...
general acute care hospitals implement “programs for monitoring the judicious use of antibiotics” with a “quality improvement committee” responsible for oversight. On-demand PCR testing represents a key opportunity to enhance antimicrobial stewardship. Studies have shown that more expedient receipt of bacterial identification and antimicrobial susceptibility results has a significant impact on physicians’ administration of antimicrobials. Trenholme et al demonstrated that the receipt of “rapid” results (within approximately 8 hours) had a statistically significant influence on antibiotic use with more effective and less expensive therapy initiated compared with when results were obtained at 48 hours. This is particularly relevant in the ambulatory care setting, where the opportunity to initiate optimal therapy is critical given the uncertainty of follow-up care. If a patient presents with an infected wound and the offending organism is identified within 2 hours, then the health care provider can initiate precise, targeted therapy, thereby avoiding the need for broader-spectrum antimicrobials. Patient satisfaction and compliance are likely to increase as patients leave armed with the knowledge that they are receiving ideal therapy. As Dr Jorge Parada, Medical Director of the Infection Control Program at Loyola University Medical Center, stated, “on-demand PCR testing allows for a switch from empiric therapy to directed therapy, which might be a game changer in the emergency department (J. Parada, personal communication, June 7, 2104).”

Pulia et al studied the use of on-demand PCR testing for MRSA in patients presenting to the ED with soft tissue abscesses and found that the observed ideal antibiotic selection rates improved by 45% in the PCR-tested group compared with the non–PCR-tested group. In addition, they were able to obtain results within 80 minutes, with no impact on LOS in the ED in the PCR group.

Although rapid pathogen identification is inarguably the critical first step in optimizing antimicrobial therapeutic choices, assessing antimicrobial susceptibilities is clearly an integral part of determining ideal treatment. Obtaining results from traditional susceptibility testing involving phenotypic methods often takes days, increasing the time during which patients might be placed unnecessarily on broad-spectrum antibiotics or jeopardizing those patients receiving an antibiotic to which their infecting pathogen is resistant (M. Spencer, personal communication, June 7, 2104). Rapid molecular antibiotic susceptibility testing (RAMAST), in which positive blood cultures are diluted and incubated with and without antibiotics and then subjected to quantitative on-demand PCR testing to examine for the presence or absence of growth, offers great potential for expediting the determination of antibiotic susceptibilities and promoting antimicrobial stewardship. In the case of MTB disease, multiple studies have shown that on-demand PCR testing for MTB and rifampin (MTB/RIF) resistance is highly sensitive and specific, which, as the World Health Organization stated, allows for “early and appropriate treatment initiation, as well as accelerating the implementation of MDR-TB [multidrug-resistant TB] control measures and ultimately reducing TB case incidence.” In fact, in 2010 the World Health Organization endorsed on-demand PCR testing for MTB/RIF and initiated a 3-year rollout of the technology in 2013 to 21 countries, primarily in Africa, Asia, and South America.

Isolation

The practice of implementing transmission-based precautions for patients with known infectious agents has become a mainstay of modern health care delivery. The Centers for Disease Control and Prevention has issued recommendations for isolating patients with a variety of different infectious agents, including active CDI and active MRSA infection, as well as those patients with a history of previous MRSA infection/colonization or CDI. A study published in 2013 from a California hospital documented that over a 1-year period, 18.1% of hospital days were isolation days, and that MRSA and CDI were responsible for 75.5% of all hospital isolation days in the hospital. Before the availability of on-demand PCR testing, if a patient’s MRSA status, for example, was not known, then isolation and contact precautions often were not initiated until culture or batch PCR testing results could be obtained. Depending on the testing modality used, receiving those results could take as many as several days. On-demand PCR testing, when implemented as part of a preadmission screening process, allows for the rapid diagnosis of a patient’s MRSA status so that the necessary isolation precautions can be instituted at the beginning of hospitalization, thereby preventing any potential exposures from the onset.

Although isolating patients with highly infectious pathogens is very effective infection prevention and control approach, it is a cumbersome practice for patients, practitioners, and health care facilities. Hospital rooms must be allocated for isolation patients, and practitioners and visitors must don PPE, such as gowns, masks, and gloves. Many infection prevention and control programs require a series of negative cultures to remove patients from isolation, and thus patients must wait days, sometimes even weeks, to receive laboratory results. Furthermore, the practice of implementing isolation precautions for a history of multidrug-resistant organisms and rule-out TB cases can adversely affect emergency room throughput, because the patient must wait in the ED for a private room that might not be ready until in-house discharges are complete.

Studies have shown that with increasing numbers of patients in contact isolation, health care worker (HCW) compliance with these precautions tends to decline. In a 9-month prospective cohort study conducted at 11 teaching hospitals, Dhar et al recorded an overall rate of compliance with contact precautions of just 28.9% and found that when the burden of isolation (ie, proportion of patients in contact isolation precautions) reached 40%, compliance rates began to decrease. The ability to obtain rapid results could help alleviate this problem. As Maureen Spencer, Corporate Infection Prevention Consultant at Universal Health Services, said, “If you can determine positive or negative results in a predictably effective time frame, you will increase human compliance and vigilance. Velocity and predictability drive patient workflow.”

On-demand PCR testing brings the potential to dramatically reduce both the number of patients placed in isolation and the number of days isolated patients must remain under precautions. In their 2009-2010 study, Catanzaro and Cirone demonstrated a significant decrease in isolation days, tests ordered, and metronidazole treatment in patients screened for CDI with PCR compared with those screened with EIA. In fact, they noted a decrease in the incidence of health care–associated CDIs from 4.4 per 10,000 patient-days to 0.9 per 10,000 patient-days when PCR testing was used.

Novak-Weekley et al compared the sensitivities and specificities of 2 different testing algorithms as well as on-demand PCR and found the following results: glutamate dehydrogenase (GDH)-EIA, sensitivity 86%, specificity 98.3%; GDH-EIA-cell culture cytotoxin neutralization (CCCN), sensitivity 83%, specificity 96.7%; on-demand PCR, sensitivity 95.1%, specificity 99.4%. At a time when as many as 13 in every 1000 in-patients have CDI and approximately 109,000 patients die annually from CDI, these differences are noteworthy.

Shenoy et al conducted a randomized controlled trial comparing the impact of passive and active screening with culture and PCR for
MRSA on the discontinuation of contact precautions. They demonstrated a 55% reduction in patient-days on contact precautions with active PCR screening, with an estimated annual savings of $1,539,180.27 They noted that a single PCR assay compared with 3 cultures had a sensitivity of 93.9% and specificity of 92.0%, and found that, “with regard to averted CP [contact precaution] days and their associated costs...the most substantial impact is appreciated when active screening using single PCR is implemented”.27

Having the ability to obtain highly sensitive and specific diagnostic results either at the time of admission or before admission not only can shorten the isolation period, but also can prevent unnecessary isolations.

**Health care economics**

Reducing unnecessary isolation days has far greater implications than simply increasing HCW compliance and patient satisfaction, just as reducing HAI rates and improving antimicrobial stewardship have ramifications beyond improving patient outcomes. All of these factors carry significant economic consequences. Even in the pre-on-demand PCR era, studies have shown that the ability to obtain more expedient pathogen identification has significant cost-saving consequences.14,28

**HAI costs**

The direct annual hospital cost of treating HAIIs has been reported to range from $28.4 billion to as high as $45 billion, depending on whether the figures are adjusted for the consumer price index for all urban consumers or for inpatient hospital services.29 Although these total numbers are staggering, it is important to look at the impact of drug-resistant organisms and difficult-to-treat organisms like CDI on these costs. Zimlichman et al conducted a meta-analysis of the literature covering a 27-year period to assess the financial impact of HAIIs on the US health care system and reported average costs (in 2012 US$) of $20,785 for a non-MRSA SSI and $42,300 for a MRSA SSI.30 Similarly, another study found an average cost of $45,814 for a non-MRSA central line–associated bloodstream infection (CLABSI), compared with $58,614 for a MRSA CLABSI.31 In a retrospective analysis of the New York state Department of Health data from 2007-2008, Lipp et al estimated an annual cost of health care—associated CDI of $55 million.32

Numerous studies have performed cost–benefit analyses of screening patients for resistant pathogens like MRSA. Nyman et al studied the cost of screening ICU patients with standard culture, chromogenic agar, and PCR and imposing contact precautions on those colonized with MRSA compared with no intervention.33 They noted that for all 3 testing modalities, “when the cost of the intervention is netted against the cost reduction from reduced MRSA infection treatment costs, screening of ICU patients produces a net cost savings to the hospital”.34 Huben et al studied the costs and effects of selective and universal hospital admission screening for MRSA using a simulation model and found that in high MRSA-prevalence settings, selective screening with PCR was the most cost-saving strategy, particularly when the cost of single room isolation was factored in.35 In fact, they estimated a net benefit of averted MRSA infection when using selective PCR screening of $28.7 million over a 15-year period for the 3-hospital health care system model in their study.33 In their 2005-2007 randomized, double-blind, placebo-controlled study conducted at 5 hospitals in The Netherlands, Bode et al demonstrated a significant reduction in the risk of SSIs caused by *S aureus* in patients screened with on-demand PCR and then decolonized with mupirocin nasal ointment and chlorhexidine gluconate soap.34 This screening and decolonization also was associated with a reduction in the mean hospital LOS of almost 2 days.34 The debate over universal versus targeted MRSA screening is ongoing and beyond the scope of this article, but omission of screening may be associated with risk.32,33,35

Similar trends have been seen with the use of on-demand PCR testing for MTB.36 In 2013, Millman et al performed a cost–benefit analysis of on-demand PCR testing compared with smear microscopy for MTB.36 They reported a 48% reduction in total annual isolation bed use and an average savings of $2278 per admission with the use of on-demand PCR versus smear microscopy.36 The authors noted that a number of intangible cost savings, such as “decreased risk of health care–associated complications while hospitalized because of decreased time in the hospital...and faster return to work and family,” could potentially add additional savings for both health care facilities and individual patients.36

Ultimately, when a decision is made regarding adopting new technology, particularly when it requires budgetary changes, a hospital’s or health care system’s corporate leaders must be on board with the decision. It thus becomes imperative to look at the financial impact of averted HAIIs from the hospital administration perspective. Shepard et al did this in a retrospective study published in *JAMA Surgery* in 2013.37 They examined data from a 3-year period at 4 Johns Hopkins Health System acute care hospitals and reported some very noteworthy findings, including a total increase in profits for the health system of $2,268,589 if all SSIs were eliminated and $12,164,457 if 30-day readmissions were not reimbursed.37 They noted that patients with an SSI had on average significantly longer LOS compared with patients without an SSI (10.56 vs 5.64 days), as well as a significantly higher 30-day readmission rate (51.94 vs 8.19 readmissions per 100 procedures).37 They also found a significantly higher total cost for patients with an SSI compared with those without an SSI but, interestingly, lower daily costs for patients with an SSI.37 They posited that a patient with an SSI occupying a room for an extended period represents a lost opportunity for hospital revenue, given the fact that at least 1, if not more, patients without an SSI patients with shorter LOS but higher daily charges could be housed in that room.37

**Reimbursement**

An added dimension to these costs is how HAI rates and readmission rates drive hospital performance and thus reimbursement. Several programs implemented by the Centers for Medicaid and Medicare Services stand to have a significant impact on hospital finances. In 2008, the Present on Admission policy began to restrict payment for certain secondary diagnoses that were not present on admission and are considered preventable.38 With institution of the value-based purchasing program in 2010, hospitals began to see their health care outcomes linked to payment by receiving greater reimbursement for better health care outcomes and lower reimbursement for inferior outcomes. The more recent Hospital-Acquired Condition (HAC) Reduction Program will penalize the quartile of hospitals with the highest HAC rates by 1% of their inpatient Medicare revenue. The qualifying HAC conditions are a composite of a number of patient safety indicators (PSI-90), along with catheter-associated urinary tract infections and CLABSI.39 These conditions will expand to include 2 SSIs (colony surgery and abdominal hysterectomy) in fiscal year 2016 and then MRSA and CDI in fiscal year 2017.39 With all 3 programs operating at 100% by 2017, a hospital could face a worst-case scenario of losing 6% of its inpatient Medicare reimbursement.40 Health care facilities are essentially being called to task for the fact that evidence suggests as many as 70% of HAIIs are preventable.41
One final financial consideration is the potential for hospitals to reduce their outbreak insurance policy costs. Health care institutions insure themselves against the numerous consequences associated with an infectious disease outbreak—business interruption costs, patient relocation costs, and cleanup costs among them. It is well known that the insurance industry’s goal is to reduce their risk exposure. A facility with access to the most accurate and rapid diagnostic capabilities certainly stands to mitigate that risk exposure and potentially lead to outbreak policy reductions.

**Implications**

The evidence supporting the potential for on-demand PCR testing to significantly impact HAI rates, health care delivery, and hospital economics is strong, yet—as our IP survey indicates—basic knowledge of on-demand PCR technology and its impact appears to be suboptimal among a critical group of health care workers. Filling these knowledge gaps will require an emphasis on education, communication, collaboration, and standardization in the medical community at large:

- **Education.** Infectious disease physician directors and IPs need to partner with laboratory scientists to educate hospital executives about the savings and revenue opportunities associated with on-demand PCR testing. Similarly, larger organizations, such as APIC, need to partner with laboratory organizations, such as the American Society for Clinical Laboratory Scientists, to provide educational support to regional and local chapters and smaller institutions that might not have access to or familiarity with on-demand PCR.
- **Communication.** It is commonly felt that physicians often have the best success in persuading a health care facility’s C-suite leaders to adopt new technology. As such, physicians involved with antibiotic stewardship programs and infection prevention and control need to be educated on the economics of on-demand PCR testing so that they are better equipped to communicate not just the health care benefits, but also the financial benefits to these leaders. Similarly, IPs also must be educated on the economics if they are to successfully communicate with C-suite executives.
- **Collaboration.** Institutions must take a multidisciplinary approach to on-demand PCR testing. Departments such as Infectious Diseases, Microbiology/Laboratory, Infection Prevention and Control, Nursing, Surgical Services, Anesthesiology, and Ancillary Services need to collaborate both in their efforts to obtain access to on-demand PCR testing and in the consideration of sharing the budget burden and return on investment. These departments need to work together to develop a business plan demonstrating the return on investment to present to C-suite executives.
- **Standardization.** Facilities using on-demand PCR testing must establish evidence-based guidelines for integrating PCR testing. Process improvement teams should be established during the implementation of on-demand PCR testing to study cost avoidance, cost savings, improved workflow, increased throughput, and other outcome measures in an effort to support the increased budgetary impact in the microbiology laboratory.

As the medical community continues to battle HAIs and adapt to the changing landscape of health care reimbursement and economics, taking advantage of new technology with proven health care outcome and economic benefits is imperative. As Benjamin Franklin so aptly stated, “By failing to prepare, you are preparing to fail.”

**GLOSSARY OF TERMS**

**PCR**

PCR is a biomedical technology in which multiple copies of a segment of DNA can be produced. The technique involves the use of 2 short DNA sequences called primers, which are designed to bind to the beginning and end of a targeted DNA segment. The targeted DNA segment, the primers, free nucleotides, and the enzyme DNA polymerase are combined and placed into a PCR machine. The mixture is initially heated to denature and separate the double-stranded DNA into single strands. This is followed by cooling, which facilitates binding of the primers to the single DNA strands. DNA polymerase then synthesizes new strands of DNA from the single-stranded templates beginning with the primers, resulting in a double-stranded DNA molecule consisting of 1 old DNA strand and 1 new DNA strand. Each new DNA molecule can serve as a template for repetitions of this cycle, such that millions of copies can be produced.

**Batch PCR**

Batch PCR refers to the processing of a group or batch of collected samples intended for PCR testing. Different samples are collected over a set period and processed collectively at a set time during, typically after an optimal number of samples are received. Depending on the time of collection and the time of the batch PCR processing, receipt of results can take multiple hours to days.

**On-demand PCR**

On-demand PCR testing refers to the ability to process samples for PCR testing at any location and at any time. Samples can be run individually as soon as they are collected. Results are available in less than 2 hours, and there is no need to amass a group of samples before testing can be initiated. The rapid turnaround time enables expeditious initiation of results-driven patient management strategies.

**RAMAST**

In RAMAST, a 2-step process for assessing the antibiotic susceptibility of a positive blood culture, the blood culture is diluted and incubated with and without antibiotics and then subjected to rapid PCR testing to detect the presence or absence of growth. Susceptibility results can be available within as few as 9 hours from when the culture is identified as positive.

**EIA**

EIA is a group of techniques that use an enzyme linked to an antibody or antigen as a marker for the detection of a specific molecule of interest (the analyte), which is often a protein. The antibody or antigen attached to the enzyme is designed specifically to bind to the analyte and not to any other substance in the sample. EIA can be used to detect the presence of bacteria or viruses in body fluid samples; for example, they are used to detect the presence or absence of *C. difficile* toxins A and B. Results are typically available within 24 hours; however, given EIA’s high specificity but lower sensitivity, it is not considered diagnostic on its own. EIA is often used in combination with testing for GDH.
**GDH**

GDH is an enzyme produced by *C. difficile* as well as many other bacteria. As a result, testing for the presence of GDH must be combined with a *C. difficile* toxin A and B assay, given the high sensitivity but low specificity of GDH testing alone.

**C difficile culture**

*C. difficile* is cultured by placing an enteric sample in either a blood-enriched cycloserine-cefoxitin-fructose agar or a taurocholate-cycloserine-cefoxitin-fructose agar under anaerobic conditions, which allows for the isolation of *C. difficile* colonies from other enteric microorganisms. It is considered to have relatively high sensitivity but lower specificity, because asymptomatic patients (ie, those not considered to have CDI) may carry both the toxigenic and non toxigenic strains. Turnaround time for results is typically 48-96 hours.

**CCCN**

The CCCN assay was developed as a means of identifying *C difficile* toxin B. A dilute fecal eluate is added to a monolayer of mammalian or human cells. In the presence of *C difficile* toxin B, the mammalian cells will round up and slough off the monolayer. If antitoxin is then added, this phenomenon or effect is reversed, thereby confirming the presence of *C difficile* toxin B. The CCCN assay requires relatively sophisticated laboratory expertise and resources, including the ability to maintain cell lines for the cytotoxic assay. Turnaround time for results ranges from 24 to 72 hours.

**References**
