Utilization Management in a Large Community Hospital

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Introduction

This chapter will review the numerous factors that influence laboratory test utilization in a large community hospital (Table 14.1). Assessment of laboratory test utilization usually relies on data compiled after a utilization review or analysis of the necessity, appropriateness, and efficiency of laboratory tests on a concurrent and/or retrospective basis. Most laboratory utilization studies have been reported from academic medical centers [1–8], however, there are often common findings in large community hospital settings [9–13]. The major difference between an academic center and community healthcare system is usually the number of hospital-employed physicians versus independent physicians with their own office practices. Some large community hospitals have only employed physicians on their medical staff like Kaiser Permanente, Henry Ford Hospital, and others. Generally, it will be easier to assemble a group of specialists to convene a laboratory utilization committee meeting, if the physicians are accustomed to leaving their practice responsibilities and going to a hospital-oriented committee meeting in the middle of the day. Since the focus of this committee is to review the evidence-based evaluation of a new or old laboratory test to rule in or out a specific disease, attendance and the quality of participation will vary depending on the physician's commitment to the project. In a large community hospital, it may "save time" during these meetings if homework is assigned beforehand. "This includes what do people need to read, think about, bring with them, or come prepared to discuss so the meeting will be more productive" [14].

One of the authors (FLK) has worked for 23 years directing the clinical laboratory and outreach laboratory at a large community hospital (William Beaumont Hospital) in Royal Oak, MI and for the past 9 years at a six hospital county healthcare system (Memorial Healthcare System) in Hollywood, FL with the co-author (RCA). We will review several of the issues listed in Table 14.1.

Current Trends

In preparation for the shift from fee-for-service to a value-based payment system [15] large community hospitals have been actively engaged in three enterprises which will impact laboratory test utilization: buying physician practices, increasing the use of hospitalists and consolidation of hospitals.

Buying Physician Practices

In the early 1990s during the initiation of health maintenance organizations (HMOs), hospitals purchased physician practices. In general, at that time, hospitals had a difficult time managing the physicians and their practices. During this second more recent phase of buying, contracts are designed to enhance physician productivity [16–19]. The "key motivation for hospital acquisition of physician practices is the ability to gain market share for inpatient admissions and outpatient services by capturing referrals from physicians employed by the owned practices" [16]. Carlin et al. [16] documented a shift in inpatient admissions, outpatient CT scans and MRI procedures from three large multispecialty clinic systems to a two hospital-owned integrated delivery

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Table 14.1 Factors that influence laboratory utilization in a large community hospital

Factor
1. Current trends
a. Hospitals buy physician practices
b. Hospitalists
c. Hospital consolidation
2. Regulations
a. CLIA'88 (laboratory test categories)
b. How laboratory tests are counted
3. Economics
a. Calculation of cost savings
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4. Technology
a. Disruptive innovations—Resource Table 14.4
b. Microbiology Laboratory: Shifting sands
Positive blood cultures
Respiratory pathogen testing
Infectious gastrointestinal illness testing
Matrix-Assisted Laser Desorption Ionization—Time of Flight (MALDI-TOF)
New methodologies
c. In vitro diagnostic companies
New equipment
Obsolete tests—Table 14.8

system (IDS) after the IDS purchased them. This same shift of referral patterns to the new hospital owner will also be true for laboratory tests ordered by newly acquired physician practices. In the USA 57 % of physicians were independent in 2000 compared to 39 % in 2012 [19] and 36 % of male and 23 % of female physicians in 2015 [17]. In 2004, 11 % of physicians were employed by hospitals compared to 64 % in 2014 [18]. A downside of this trend is the finding that hospitals charge more when the doctors work for them attributing the cause to higher overall costs [19]. This current trend should drive more laboratory testing from new hospital-based physicians to the hospital central laboratory with the consequence of potential utilization issues.

Hospitalists

The hospitalist model of inpatient care is one of the most rapidly growing forms of medical practice in the USA since its introduction in the mid-1990s [20, 21]. In 2006, there were more than 12,000 hospitalists in the USA [20] which has increased to 34,000 in 2014 [21]. Most hospitalists practice in hospitals with greater than 200 beds [20, 21]. Their average starting salary was greater than that for internal medicine or family practice physicians in 2014 [18]. Hospitalists work strictly in the hospital and oversee the care of complex patients with the goal of reducing the need of transferring patients from one physician to another [22]. Most large community hospitals use a voluntary hospitalist system in which primary care physicians can choose to admit to a hospitalist service or attend to their own patients [23]. Large community hospitals are more likely to adopt a hospitalist model if their case mix complexity was greater than the national average for Medicare's diagnosis rated group index, while high health maintenance organization market share resulted in lower interest in this model [22]. The hypothesis that the hospitalist model will lead to a reduction in the patient's length of stay and total hospital costs has been demonstrated [20, 22–24]. Hospitalists may order excessive diagnostic tests secondary to their lack of previous knowledge of the patient [20]. The Choosing Wisely campaign sponsored by the American Board of Internal Medicine Foundation, Consumer Reports, and more than 60 specialty societies have recommended reduction or elimination of inappropriate use of radiologic, laboratory, and therapeutic procedures [12, 25–27]. The first 25 societies provided five selections each, of which 12 % were related to laboratory tests or pathology [27]. One of these lists from the Society of Hospital Medicine recommended reducing the use of repetitive common laboratory testing when the patient is clinically stable [26]. In a quality improvement project focused on hospitalists, an effort was made through education to reduce the repetitive use of complete blood counts and basic metabolic panels [25]. These panels are often embedded in order sets established for specific diseases or for specific physicians to simplify computerized physician order entry [28]. There was a 10-month baseline period before the intervention followed by a 7-month intervention period [25]. The intervention resulted in a 10 % reduction of these two panels ordered per patient day associated with decreased direct costs of $16.19 per patient and annualized savings of $151,682 [25]. This study illustrates how a small segment of laboratory test ordering physicians can impact expenses through overutilization and by analogy underutilization of laboratory tests.

Hospital Consolidation

Like the first round of hospitals buying physician practices started in the early 1990s, so did the consolidation or mergers of hospitals [29]. There has been a recent increase in both horizontal and vertical consolidation [29, 30]. Horizontal consolidation involves hospitals merging with other hospitals that supply similar services in geographic proximity [29, 30]. These mergers are most likely to be investigated for antitrust violations [29]. Vertical consolidations involve hospitals consolidating with other health care provider entities [16, 29]. From 2007 to 2012, 432 hospital mergers and acquisitions were announced involving 835 hospitals [30]. Sixty percent of hospitals are now part of health systems. The downside to these mergers has been a 10–40 % increase in prices secondary to increased market share [30]. Strategies have been suggested for avoiding this market disequilibrium

[30, 31]. No US hospital markets were rated highly competitive [30] while the German market is competitive and the number of hospital systems decreased by 18 % from 2000 to 2007 [32]. There are myths associated with the latest hospital merger activity. The first myth is that consolidation is equivalent to integration [33]. The second is that higher quality is associated with size rather than leadership and competition [33, 34]. Evidence supports the suggestion that hospitals in competitive markets tend to have better administrative management [33]. The combination of hospital mergers and increased hospital-employed physicians [35] will lead to increase in laboratory test volumes and the need for robust utilization management practices.

Regulations

CLIA'88

The Clinical Laboratory Improvement Amendment of 1988 (CLIA'88) went into effect September 1, 1992. The regulations categorize laboratory procedures based on test complexity using well-defined criteria: waived, moderately complex, and highly complex or provider-performed microscopy. These regulations define the universe of tests that a large community hospital laboratory is directly or indirectly responsible for their utilization management. There are a variety of CLIA-tests that have been classified as waived by the FDA and a list of them from 2000 to present can be found at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/testswaived.cfm. The implementation of point-of-care testing (POCT) usually involves a desire to decrease the total turn-around time for an analytical test and improve patient outcome [36]. However, decreased turn-around time does not always equal improved patient outcome [37, 38]. Two prospective studies analyzed the effect of the POCT i-STAT device (Abbott, Abbott Park, IL) on length of stay in the emergency department after a control period when the central laboratory was used. The i-STAT cartridge that analyzed sodium, potassium, chloride, urea, glucose and calculated hemoglobin was used. Neither study revealed any change in the length of stay or clinical outcome for emergency department patients, although both showed a decrease in time required to obtain laboratory results for the six tests on the cartridge when the iSTAT was used. The blood test was not the rate-limiting step in the patient's length of stay [38]. In a similar study using five different testing cartridges for the iSTAT (INR, lactate, brain natriuretic peptide, troponin T and chemistry with hemoglobin and hematocrit), Singer et al. [39] reported a reduced turn-around time for POCT compared to the central laboratory which translated into a reduction in time to completion of IV contrast CT and the length of stay of those specific patients.

It is not clear whether relocating POCT tests to the patient's bedside increases [40, 41] or decreases [42] the test volume of that test in the central laboratory. It has been reported in both adult and newborn intensive-care units that patients with indwelling arterial lines have more blood drawn for laboratory studies than patients without arterial lines [43, 44]. The blood loss may be great enough to require a transfusion [43]. Certainly, utilization management of POCT programs will require investigations to determine the relationship between total laboratory turn-around time for results, patient outcome and hospital costs using cost effectiveness analyses [36].

There are at least 17 different sources of body fluids in a human [45]. Some of these are laboratory specimens that are examined under the bright-field or phase contrast microscope and are classified as provider-performed microscopy (PPM) by CLIA'88 [46, 47]. A separate CMS license is available for sites performing these assays which include KOH preparation, pinworm detection, fern test, microscope urinalysis, semen analysis for presence of sperm and motility, and eosinophils in nasal smears [46, 47]. It is wise for the laboratory POCT administrative committee to assist in the initiation of a PPM testing program in collaboration with the PPM license holder for that clinically defined program, like fern testing in the labor and delivery area under the direction of a staff OB/GYN physician. In this model, training and utilization management is not under the direction of the hospital POCT administrative committee [46, 47].

How Laboratory Tests Are Counted

In order to audit laboratory test utilization year to year it is "essential to understand how test volumes are actually counted" [1]. Are test panels bundled and counted as one test or are the test panels unbundled and each test in the panel counted separately. In an evaluation of the total inpatient test volumes from 1978 to 2000 for the Department of Clinical Pathology at William Beaumont Hospital, Royal Oak, MI, it was determined that the method for counting inpatient tests changed in 1992 and 1996 [36, Table 14.1]. These changes in counting methodology made it impossible to compare data from year to year. How it is done is not as important as it is done the same way year after year.

Economics

Calculation of Cost Savings

There are two categories for cost reductions: "hard" cost savings and "soft" cost avoidance. Tangible "hard" cost savings are often achieved by bringing reference laboratory tests in-house to the clinical laboratory (or eliminating the reference

laboratory test altogether) [4, 11]. The more intangible "soft" cost avoidance includes such things as decreases costs associated with the introduction of a new laboratory test with the intent to decrease costs in the future. It also can occur when a cost is lower than the original expense that would have otherwise been required if the cost avoidance exercise had not been undertaken. Since processes consume overhead and overheard costs money, any significant process improvement could represent significant cost avoidance for an organization. Total cost includes direct and indirect costs [48]. Direct cost includes personnel time to prepare and perform the test, reagents, quality control, proficiency testing, and equipment depreciation. Indirect costs including reporting costs (computer) and hospital overhead. Incremental or marginal costs include only variable direct costs and not the indirect costs [48–50]. Therefore, incremental costs demonstrate what it would cost to perform one more laboratory test, assuming the equipment and facility are already available. Neither total cost analysis nor incremental cost analysis includes an analysis of the defect rate or failure to achieve established goals, like turn-around time [50]. They are defined as internal or external failure rates. Internal failure costs are incurred by the testing center as a consequence of a defect in the testing system. The receiver of the test results incurs the external failure costs. Over utilization of laboratory tests incurs both internal and external failure costs in the excess time spent in the laboratory to generate the result and then excess insurance charges to the patient and nursing/physician time to evaluate the results.

To illustrate cost avoidance, consider the presentation of potential Enterovirus meningitis in the emergency department. Children and adults with detectable Enterovirus in the cerebrospinal fluid (CSF) may exhibit symptoms of meningitis including photophobia, stiff neck, acousticophobia, severe headache with vomiting, confusion, difficulty concentrating, seizure and sleepiness. A molecular test for Enterovirus detection will alter the patient's length of stay in the emergency department. If the patient is positive for Enterovirus in the CSF specimen, the patient will be discharged for home care until the viral meningitis resolves (Table 14.2). If the patient does not have Enterovirus in the CSF, they will need further hospitalization to rule out a bacterial source for the meningitis with culture and sensitivity studies (Table 14.2). Romero [51] has demonstrated the cost range for hospitalization related to Enterovirus testing/care of infection to be $4476–4921 with an average length of stay of 3–4 days. We used $4476 for the calculation in Table 14.2, which illustrates a cost avoidance of $187,992 for 20 patients with or without enteroviral detection by molecular methods.

Table 14.2 Enterovirus (EV) cost avoidance for 20 patients from May 2008 to May 2009

Population	EV positive	EV negative
Total patients	20	20
Total LOS days	26	68
Average LOS days for one patient	1.3	3.4
Literature-based cost for admission due to EV status	$116,376	$304,368

Estimated savings for cost avoidance $187,992 for 20 EV positive patients ($304,368 – $116,376 = $187,992). *LOS* length of stay

Economies of Scale

"Cost per unit went down if you could make longer and longer runs of identical products. This gave rise to the theory of economies of scale" [52]. The laboratory achieves economies of scale and lower unit costs per test by expanding the volume of laboratory tests it analyzes. In the early 1990s, the number of inpatient laboratory tests at William Beaumont Hospital began to decrease. To fill the gap, after a 3-year preparation period, we initiated an outreach program (Beaumont Reference Laboratory) expanding our laboratory testing services to non-patients from physician offices, nursing homes, and other hospitals [53, 54]. Several years later (1992) Beaumont Reference Laboratory joined a regional laboratory network of other hospital-based laboratory outreach programs in Michigan, Joint Venture Hospital Laboratories, to accommodate the wide geographic coverage required by third party payers [53, 54]. The participating laboratories are independently owned and operated. A central network administrator coordinates negotiations for managed care contracts. The volume of BRL specimens grew to half of the total volume of clinical pathology procedures of six million tests in 2004. This increased volume permitted an expansion of the test menu in each laboratory section. In 2002, we reviewed 2,976,494 procedures ordered by 2806 physicians in nine subspecialty areas (family practice, pediatrics, internal medicine, cardiology, endocrinology, gastroenterology, nursing home, OB/GYN, and urology). The requisitions for physician, procedures per requisition and procedures/physician were calculated for each of the nine groups of physicians [54]. Family practice (464 physicians) and internal medicine (831) ordered the greatest number of total procedures as well as procedures/physician while urology (126) ordered the least of these two categories [54]. The tests ordered by each of the nine groups were counted in seven laboratory sections. All nine groups ordered more chemistry tests than any other category but the percent varied from 34.5 % for OB/GYN to 90.2 % for internal medicine. The most popular individual tests in five laboratory sections (chemistry, hematology, immunology, microbiology, and molecular diagnostics) were calculated as an average number of a specific test ordered per physician per month. Using this data, a laboratory section could prepare themselves for the increased utilization from a six-member

internal medicine group that the Beaumont Reference Laboratory sales force just signed up as a new client. This type of deep dive into specific physician specialty ordering patterns is an invaluable resource for managing a growing outreach business [54]. The 20 million requests for chemistry, hematology, and microbiology tests were included for all physicians in Calgary, Canada who ordered a test in fiscal year 2013–2014 [55]. The physicians were divided into 30 subspecialties and the average yearly cost per group and average yearly cost per physician in each of the 30 groups was calculated. Family practice and internal medicine had the greatest average yearly cost per group while hematology and nephrology had the highest average yearly cost per physician per group secondary to utilization of more expensive laboratory tests [55]. This cost-based approach to utilization review requires the calculation of an average median cost for each test which in the USA would be much less than the price listed on the hospital's charge master.

There was a synergistic relationship between the growth of Beaumont Reference Laboratory and test mix complexity in each laboratory section. In the molecular diagnostics laboratory started in 1992, *Chlamydia trachomatis* (CT) *Nisseria gonorrhoeae* (NG) were performed in urine using the ligase chain reaction in 1996 and PCR in 2002 [56, 57]. More than 75 % of the requests for these two assays are from BRL clients (Table 14.3). The increased volume of these two assays helped turn the molecular diagnostic section into a profit center in 4 years. Annual utilization review revealed that the outreach program contributed 33,019/43,814 = 75 % of the volume, Hospital A (8624/43,814 = 20 %) and Hospital B (2181/43,814 = 5 %). The multiplex assay using primarily urine specimens made a margin of $72.00 per assay billed (at that time) based on an average Medicare reimbursement ($83.00) and cost/test of $11.00. Why was there an exceptionally low NG volume from Hospital B? After an investigation it was learned that Hospital B chose to do the less sensitive NG culture assay [56] to retain laboratory test volume which was encouraged by their hospital administration. Also, a myth existed at hospital B that NG would not survive the transport time (40–60 min) to hospital A. The ordering physicians at hospital B prevailed and the request for molecular detection of NG at hospital B was followed. This case illustrates just how complex problem solving in utilization management issues can be in a large community hospital.

Table 14.3 CT/NG annual test volumes by site

Site	CT volume	NG volume	Total volume
Hospital A	1881	1613	8624
Hospital B	709	184	2181
Outreach clients	13,514	13,226	33,019
		Total	43,844

CT *Chlamydia trachomatis*, NG *Neisseria gonorrhoeae*

Technology

Disruptive Innovations

Some new technologies are defined as disruptive innovations, when they offer new paradigms in diagnostics (Table 14.4) [12, 83, 84]. All seven of the technologies listed in Table 14.4 share similar issues including clarification of the best applications for routine clinical use, paucity of evidence-based outcome literature to review, education of practitioners and physician users of the clinical information generated and software to convert big databases the method generates into useful information. The references in Table 14.4 will direct attention to these issues for the seven disruptive innovations [58–82]. As the paradigm shifts and these strategies become incorporated into daily clinical practice, the debate about appropriate utilization will diminish.

Microbiology Laboratory: Shifting Sands

This next section will devote time to describing the impact of current changes in microbiology (mass spectrometry for bacterial identification [12, 68, 69] and multiplex molecular panels for infectious agent detection for respiratory viral panels and gastric pathogen panels) and future changes (microscopy for antibacterial drug sensitivity).

Traditionally, the laboratory diagnosis of most infectious disease pathogens has relied on culturing and in vitro growth of the causative agent. Once culture growth has been achieved, then automated and/or manual biochemical tests can be performed to identify the microbial organism(s). These methodologies are dependent on skilled medical technologists to perform the manual tasks required to determine the bacterial identification (ID). The approach to ID and antimicrobial susceptibility testing (AST) has been dependent on testing a single pathogen at a time, regardless if the culture

Table 14.4 Current disruptive innovations for the laboratory

Technology	Reference
Next gen sequencing Whole genome sequence	[12, 58–60]
Targeted genome panels	[12, 61, 62]
Cell free DNA	
Fetal DNA	[63–65]
Tumor DNA	[66, 67]
Mass spectrometry in microbiology	[12, 68, 69]
Smartphone apps	
Laboratory tests	[70–72]
Physiologic parameters	[73, 74]
Wearable sensors	[75–77]
Bioinformatics	[78–80]
Digital pathology	[81, 82]

growth yielded multiple, significant pathogens. Although automated ID and AST systems can run multiple isolates to help streamline the workflow and maximize throughput, the basic testing is still individually performed for each isolate being analyzed. Another limiting factor for culture based detection methods is that some bacteria do not grow well or at all in vitro adding to the potential of missing a significant organism(s).

Viral cultures are time-consuming because cytopathic effects (CPE) must be observed before other methods can be used to determine the viral identification [85–87]. The development of viral antigen based testing [direct fluorescence antigen (DFA) and other rapid antigen testing devices] directly from the sample shortened the culture time to obtain a faster diagnosis. However, the reliable performance of the viral antigen based testing is highly dependent on the quality of the sample collected and is less sensitive than viral cultures [85]. A suboptimal specimen could lead to a false negative antigen/DFA result. Are viral cultures and antigen based testing truly needed in a clinical microbiology/virology laboratory since molecular methods are becoming the new gold standard? [85–87]. Many routine clinical microbiology/virology laboratories do not have the capabilities to perform viral cultures lacking the physical space and expertise to interpret the CPE [88].

As technology advances, the traditionally "agrarian society" of the laboratory is becoming more industrialized with the implementation of automation, molecular based testing, and use of mass spectrometry (MALDI-TOF—Matrix-Assisted Laser Desorption Ionization—Time of Flight). Many of these advances are revolutionizing how microbiology testing is performed and disrupting how traditional clinical microbiology workflows and processes are set up. However, all of these technological advances are shortening the time for a laboratory diagnosis and ultimately maximizing the impact to patient care and how physicians at a large community hospital will utilize the more rapid microbiology laboratory services.

Positive Blood Cultures

There is a trend in clinical microbiology to develop syndromic panels using molecular techniques. For example, positive blood culture panels have been developed to reduce time to start the most appropriate antibiotics in the patient. Once a blood culture bottle is flagged as positive, a Gram stained smear is prepared to determine the presence of bacteria (and potentially yeast) in the patient's blood sample. If any organism(s) are seen, a call is made to the patient's healthcare provider so that broad-spectrum antimicrobial therapy can be initiated until the confirmed microbiological ID is resulted. A caveat for the clinician is that s/he must make their best educated guess for determining which antibiotic treatment to use. Clinical microbiology laboratories typically publish an antibiogram so that clinicians and hospital pharmacists know the prevalence of susceptible and resistant phenotypes for their most common bacteria isolated. Although this provides a good start and useful reference, there is a heavy emphasis on antimicrobial stewardship and tailoring therapy as soon as possible so that there is less pressure for the development of antimicrobial resistance. Many institutions have developed or are in the process of developing formal antibiotic stewardship programs/committees in an effort to improve the utilization of antimicrobial treatments.

Molecular methods have been developed that will, within one test, identify a number of pathogens from a positive blood culture sample. These methods have decreased the amount of time to provide a more definitive ID and an abbreviated antimicrobial resistance genetic profile. AdvanDx/bioMerieux, Inc. utilizes PNA-FISH (peptide nucleic acid—fluorescent in situ hybridization) and detection of a positive fluorescent signal directly from a positive blood culture. Gram stained smear findings typically are resulted as "Gram Positive cocci in clusters" or "Gram Negative rods" (Table 14.5). This information is useful in deciding broad-spectrum therapy, but a more focused therapy is the ultimate goal to ensure that the pathogen is adequately treated. The PNA-FISH assays offer four basic assays [*Staphylococcus* (Gram Positive), *Enterococcus* (Gram Positive), Gram Negative, and *Candida*] that complements the Gram stain result so that clinicians at least have a presumptive genus identification. Additional PNA-FISH probes do have the ability to separate *S. aureus*/coagulase-negative *Staphylococcus* and a *mecA* probe for the identification of MRSA. Use of these PNA-FISH assays requires a fluorescent microscope to visualize the results. A number of studies have shown the clinical benefits of PNA-FISH implementation as part of the blood culture workup before the confirmatory culture growth and potentially identifying methicillin resistance genotype, in the example of *S. aureus*, before the full antibiotic susceptibilities can be performed [89–93]. Antibiotic therapy can, therefore, be tailored or deescalated as appropriate.

Similar to the PNA-FISH scenario, when utilizing Cepheid's Xpert MRSA/SA Blood Culture test the Gram stained smear prepared from the positive blood culture smear will determine whether Cepheid's assay should be run. Cepheid's methodology is real-time PCR based and does not require any subjective interpretation of the results by the laboratory staff. The cartridge for the Xpert MRSA/SA test houses all the reagents and is compartmentalized to accommodate the nucleic acid extraction, PCR amplification, and detection in one device. The testing is automated once the sample is loaded into the test cartridge and the software analyzes the PCR amplification curves to determine if a patient's blood sample is positive or negative for MRSA or MSSA [94–97].

Table 14.5 FDA-approved molecular assays for positive blood cultures

Vendor	Assay name	Method	Panel composition
AdvanDx, Inc.	*Quick*FISH, PNA FISH	FISH[a]	*S. aureus*/CNS, *E. faecalis*/*Enterococcus* spp, Gram Negatives, *Candida* species
Cepheid	Xpert MRSA/SA blood culture	Multiplex real-time PCR	Methicillin resistant *S. aureus*/Methicillin sensitive *S. aureus*
Nanosphere, Inc.	Verigene Gram Positive blood culture test	Multiplex real-time PCR	*Staphylococcus* spp[b], *Streptococcus* spp[c], *Enterococcus* spp[d], *Micrococcus* species, *mecA* (methicillin), *vanA* and *vanB* (vancomycin)
	Verigene Gram Negative blood culture test		*E. coli*, *K. pneumonia*, *K. oxytoca*, *P. aeruginosa*, *S. marcescens*, *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp., CTX-M (ESBL), Carbapenemases (IMP, KPC, NDM, VIM)
	Verigene Yeast blood culture test		*Candida* spp[e]., *C. gattii*, *C. neoformans*
BioFire Diagnostics, Inc.	Blood Culture Identification Panel	Multiplex real-time PCR	Gram positive[f], Gram negative[g], Yeast[h], and Antibiotic Resistance genes[i]

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm (web page accessed July 13, 2015)
[a]Fluorescent in-situ hybridization
[b]*Staphylococcus* species identified (*S. aureus*, *epidermidis*, *lugdunensis*). Other species are identified as *S.* spp.
[c]*Streptococcus* species identified (*S. anginosus* Group, *agalactiae*, *pneumoniae*, *pyogenes*). Other species are identified as *S.* spp.
[d]*Enterococcus* species identified (*E. faecalis*, *faeceium*)
[e]*Candida* species identified (*C. albicans*, *dubliniensis*, *glabrata*, *krusei*, *parapsilosis*, *tropicalis*)
[f]*Enterococcus* spp., *L. monocytogenes*, *Staphylococcus* spp., *S. aureus*, *Streptococcus* spp., *S. agalactiae*, *S. pyogenes*, *S. pneumoniae*
[g]*A. baumanii*, *H. influenza*, *N. meningitides*, *P. aeruginosa*, *Enterobacteriacae* (*E. cloacae complex*, *E. coli*, *K. oxytoca*, *K. pneumonia*, *Proteus* spp., *S. marcescens*)
[h]*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*
[i]*mecA*, *vanA*/*B*, KPC

The Cepheid and AdvanDx tests must be added to the already existing workflow, and serves as another laboratory tool to more quickly determine the pathogen identification and a preliminary AST profile.

Nanosphere, Inc. and BioFire Diagnostics, Inc. approach testing from positive blood culture bottles by targeting the most common pathogens (bacteria or yeast) that can cause sepsis. This is a unique approach due to the overlap in patient symptoms for a specific syndrome or condition. When the symptoms overlap, clinicians have difficulty defining the causative pathogen(s) infecting their patient solely from the clinical picture, and delaying specific pathogen-based therapy. Use of these syndromic multiplex molecular panels streamlines the testing process to more of a "one-and-done" approach.

Nanosphere offers different panels: (1) Gram positive (BC-GP panel); (2) Gram negative (BC-GN panel); and (3) Yeast (BC-Y panel) and the organism(s) observed from the Gram stained smear will determine which panel(s) to run. Additional testing with the Gram Positive and Gram Negative panels also includes testing for certain antibiotic resistance genes encoding for methicillin (*mecA*) and vancomycin (*vanA* and *vanB*) resistance (Table 14.5). There are many studies showing overall good performance for the BC-GP panel [98–104], Gram negative species and *Candida* spp. panels [105, 106].

There are limitations with molecular testing as observed by Buchan et al. [101]. A positive *mecA* target was not able to be assigned due to the presence of a mixed infection. In this case the full antibiotic sensitivity testing is still recommended because the traditional methods test each bacterial pathogen individually. Beal et al. [102] noted that when blood culture infections were caused by one pathogen, there was good performance of the multiplex molecular assays. When polymicrobial blood culture infections were noted, there was only 33 % agreement with the routine cultures. Mestas et al. [103] also noticed a lower percentage agreement for polymicrobial infections when compared to monomicrobial infections. Polymicrobial bacteremia is relatively rare, but can potentially be severe [107]. Again, cultures are still required to identify the full antibiotic susceptibility profile, and to identify pathogens that are not included in the multiplex molecular panels.

The FilmArray Blood Culture Identification Panel (BCID) is another comprehensive panel that covers Gram positive, Gram negative, and yeast pathogens (Table 14.5) and a Gram stain is not required. However, it is still good routine practice to perform the Gram stain to correlate results with the molecular panel results and the eventual culture testing and antibiotic susceptibility testing. Altum et al. [105] observed that certain pathogens were detected in routine cultures that were not detected in the FilmArray panel because those pathogens

were not in the molecular panel. So although the comprehensive panel covers the most common pathogens, clinical intuition is still ultimately needed especially when clinical symptoms and other laboratory data point to a bacteremic process in the setting of a negative FilmArray panel. Overall, these assays show the potential for a decreased TAT and a preliminary susceptibility profile based on the antibiotic resistance genes tested [104, 105, 108, 109].

The ability to have a more rapid answer that is technically more sensitive and specific will have positive downstream effects on patient care and antibiotic stewardship. The impact of these rapid PCR blood culture assays on the clinical end users (infection control, pharmacy, length of stay, and overall hospital costs) is not well defined. One study by Bauer et al. [95] demonstrated clinical benefit after implementing the Cepheid Xpert MRSA/SA assay for positive blood cultures. A 4-month pre-PCR period was evaluated followed by a 4-month post-PCR period. There was an overall shorter length of stay (6.2 days shorter) and mean hospital costs were $21,387 less than what was observed in the pre-PCR period. Infectious disease pharmacists were more effective in deescalating or changing to more specific antibiotic therapies compared to the pre-PCR period. Benefits were gained by having a more rapid and sensitive test. When adopting newer molecular methods, the laboratory must work with their clinical counterparts to determine the clinical utility of a more rapid test. The cost and potential benefits of the newer tests may not be warranted if the clinical staff is not able to effectively utilize this information in their workflow.

Even though the downstream benefits have been documented and are almost inarguable from a clinical perspective, there are financial and workflow impacts to the microbiology/molecular laboratories that implement these assays. As mentioned prior, the Gram stain results from the positive blood cultures will help drive the culture workup. Thus, there is the time required for a blood culture bottle to alarm as positive, and then the culture time waiting for growth on the culture plates. The use of these molecular methods must be introduced into the workflow and will add additional work because culture ID and AST methods still must be performed. In the setting of having a continual decrease of incoming medical technologist graduates and an increasing number of laboratorians retiring, this puts the burden of additional testing on the existing staff.

Respiratory Pathogen Testing

Another example of a clinically beneficial, but disruptive test within the laboratory is the development of respiratory pathogen panels. Molecular multiplex panels have been developed to target the general syndrome of a respiratory illness. Table 14.6 shows that there are a variety of FDA-approved assays available with a varying number of pathogens offered

Table 14.6 FDA-approved multiplex molecular assays for respiratory pathogens

Vendor	Assay name	Method	Panel composition
Cepheid	Xpert Flu/RSV XC	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Verigene	Respiratory Virus *Plus*	Multiplex real-time PCR	Influenza A[a], Influenza B, RSV A, RSV B
GenProbe Prodesse, Inc.	Prodesse ProFAST Prodesse ProParaflu	Multiplex real-time PCR	Influenza A[a] Parainfluenza[b]
Quidel Corp	Quidel Molecular Influenza A + B	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B
Abbott Molecular Diagnostics, Inc.	IMDx FluA/B and RSV	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Focus Diagnostics, Inc.	Simplexa Flu A/B and RSV Direct	Multiplex real-time PCR	Influenza A (no subtyping), Influenza B, RSV (no subtyping)
Quiagen GmbH	Artus Infl A/BRGRT-PCR kit	Multiplex real-time PCR	Influenza A (no subtyping, Influenza B
Iquum/Roche	Liat Influenza A/B	Multiplex real-time PCR	Influenza A (no subtyping, Influenza B
Luminex	xTAG Respiratory Virus Panel (RVP)	Multiplex PCR, Bead Hybridization	RSV A, RSV B, Influenza A[c], Influenza B, Parainfluenza[b], Human Metapneumovirus, Adenovirus, Enterovirus/Rhinovirus
	xTAG Respiratory Virus Panel (RVP Fast)		RSV (no subtyping), Influenza A[c], Influenza B, Human Metapneumovirus, Adenovirus, Enterovirus/Rhinovirus
GenMark Dx	Respiratory Virus Panel	Multiplex PCR, Electrochemical detection	Influenza A[a], Influenza B, RSV A, RSV B, Parainfluenza, Human Metapneumovirus, Rhinovirus, Adenovirus B/E, Adenovirus C
BioFire Diagnostics, LLC	FilmArray Respiratory Panel	Multiplex real-time PCR	Adenovirus, Coronavirus[d], Human Metapneumovirus, Rhinovirus/Enterovirus, Influenza A[a], Influenza B, Parainfluenza[e]

www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm (webpage accessed on July 13, 2015)

[a]Influenza A and further subtyping (H1, H3, and H1-2009)

[b]Parainfluenza 1, 2, and 3

[c]Influenza A and further subtyping (H1 and H3)

[d]Coronavirus species (HKU1, NL63, 229E, OC43)

[e]Parainfluenza 1, 2, 3 and 4

within their respective multiplex assay. Each assay also requires varying levels of hands-on-involvement and molecular expertise required by the medical technologist.

Prior to the implementation of a Respiratory Virus Panel (RVP) in our institution, the only viral testing offered were the rapid antigen immunochromatographic devices for Influenza A/B and Respiratory Syncytial Virus (RSV). With the addition of offering RVP testing, we are now able to provide our clinicians with a more comprehensive answer of which virus(es) are occurring in their patient. This benefits transplant, immunocompromised, and oncology patients who have more frequent respiratory viral infections [110–112]. We had serendipitously brought in the RVP before the 2009 H1N1-Influenza A outbreak which demonstrated the poor performance of the rapid antigen testing [113]. Because of this observation, many laboratories have discontinued their rapid antigen test offerings and now only offer molecular tests. In our laboratory, we have observed a decline in rapid influenza and RSA antigen testing (Fig. 14.1). The spike in volumes in 2008–2009 was related to the 2009 H1N1 Influenza A outbreak. We will eliminate these rapid antigen tests in favor of a rapid molecular test for Influenza and RSV. An algorithm will reflex a negative rapid molecular Influenza A/B and RSV test to a more comprehensive viral and/or bacterial panel.

When compared to the DFA and/or shell vial culture, a molecular multiplex respiratory virus panel saved time and lowered costs to the patient [114, 115]. Despite the clinical benefits observed, a limitation of molecular based methodologies is that they are batched and can take hours to perform in the laboratory. For example, in our laboratory the testing time is 6–7 h as compared to the 20-min it takes to run the rapid antigen testing. That trade off in time to result is offset by the increase in sensitivity, specificity, and breadth of viral pathogens discovered. This can be a challenge for clinicians because many times they will want a fast answer for the purposes of triaging or taking action on a patient. However, the question that should be asked of them is whether they want a bad quality, rapid answer or a good quality, not-so-fast answer.

BioFire Diagnostics, Inc. has attempted to solve the testing time problem by offering a comprehensive respiratory pathogen panel that tests directly from the respiratory specimen. Only one patient can be run on one instrument and the assay time is approximately 1 h. There will be certain institutional settings where this technology will have benefits such as an urgent care clinic, smaller community hospital, or within a laboratory that has minimal molecular testing experience. However, for those institutions with a higher volume where batch testing is more optimal, the BioFire may not be the best solution. There are other commercial panels that differ in the number of pathogens offered as well as various levels of medical technologist involvement (Table 14.6). The decision to implement one of these panels is driven by a myriad of factors such as cost, workflow, physician demand, and the technical capabilities of the laboratory staff. Whatever respiratory pathogen panel is introduced, remember that the sample testing volume is highly dependent on seasonal variations. Figure 14.2 shows a graph of our volumes over two respiratory virus seasons (August 2013 through April 2015) with our peak volumes occurring over the winter months. This variability can have a significant impact to how microbiology/molecular laboratories are staffed. Physician demand, coupled with an increase in testing volumes, may be high enough to warrant increasing the number of runs per day as the staffing levels allow, potentially leading to an increase in employee overtime hours. Interestingly during

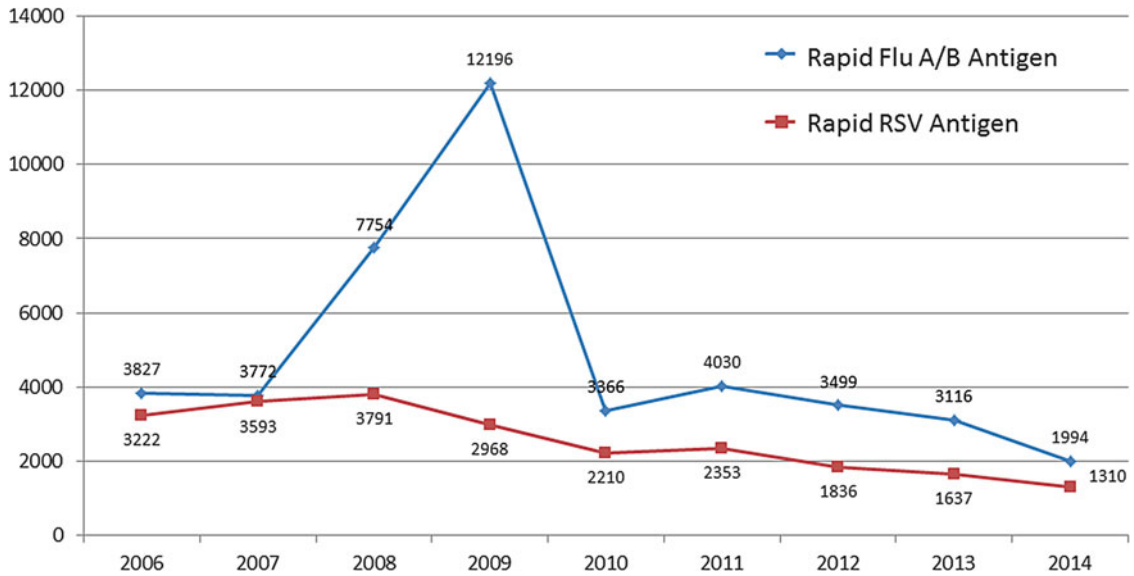

Fig. 14.1 The decline in the rapid antigen influenza and RSV testing volumes in response to the introduction of RVP testing in conjunction with the 2009 H1N1/Influenza A outbreak

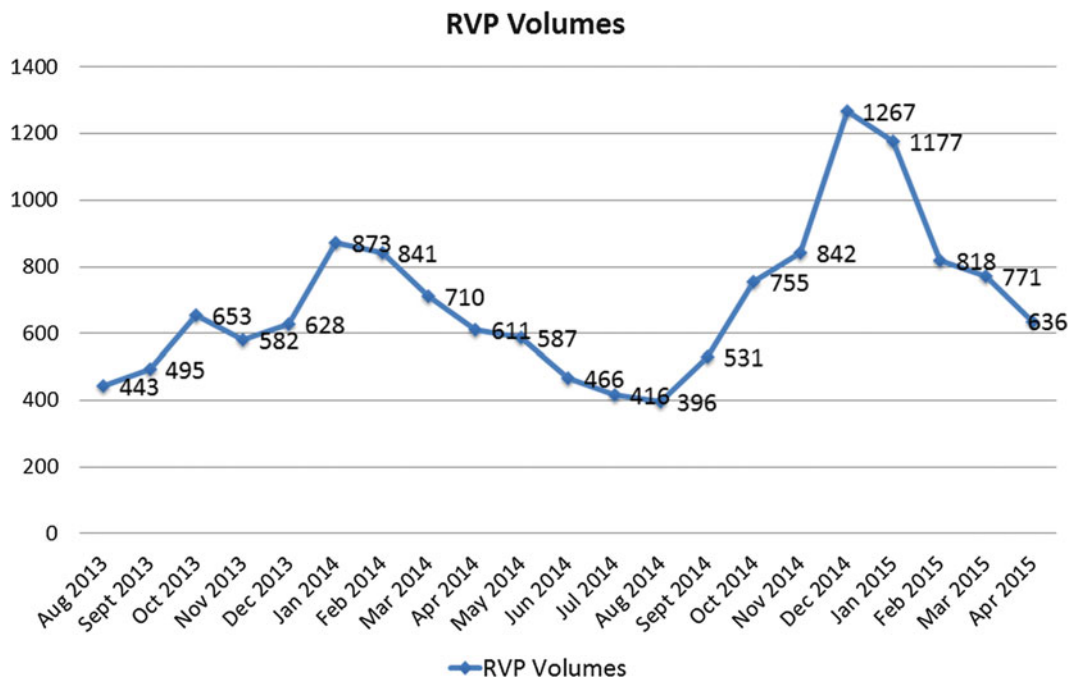

Fig. 14.2 Respiratory virus panel (RVP) testing volumes at Memorial Healthcare System. This figure shows the impact of seasonal variations on the testing volumes experiences by our molecular laboratory

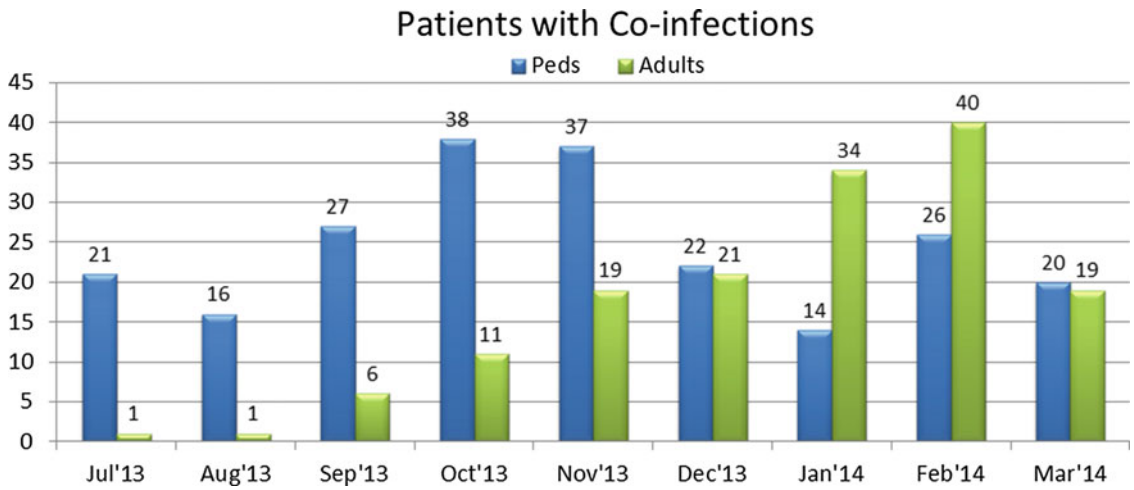

Fig. 14.3 Numbers of co-infections observed for RVP testing for pediatric and adult patients

the 2014 respiratory virus season, amidst reports of the Influenza vaccine having suboptimal efficacy [116], we observed a large increase in RVP testing volumes compared to the prior season. Thus, one factor that is virtually impossible to control is the antigenic drift/shift of the Influenza A virus affecting the effectiveness of the current vaccine in use. Assay performance may also be affected due to genetic mutations being introduced into the PCR targeted gene regions.

With the limitations of culture and antigen based testing, co-infections were greatly under-appreciated for respiratory viral infections. One can expect an increased incidence of co-infections with multiplex molecular panels. Figures 14.3 and 14.4 show our experiences with co-infections among pediatric and adult patients. The clinical significance of these co-infections is not completely understood in relationship to modulation of disease severity [117–119]. Research is needed to fully understand virus–virus and bacteria–virus co-infections and their interactions with the other pathogens present as well as the pathogen–host interactions. Every respiratory virus season, our laboratory publishes a "Virogram" that shows the prevalence of viruses currently circulating among the patient population (Fig. 14.5a, b).

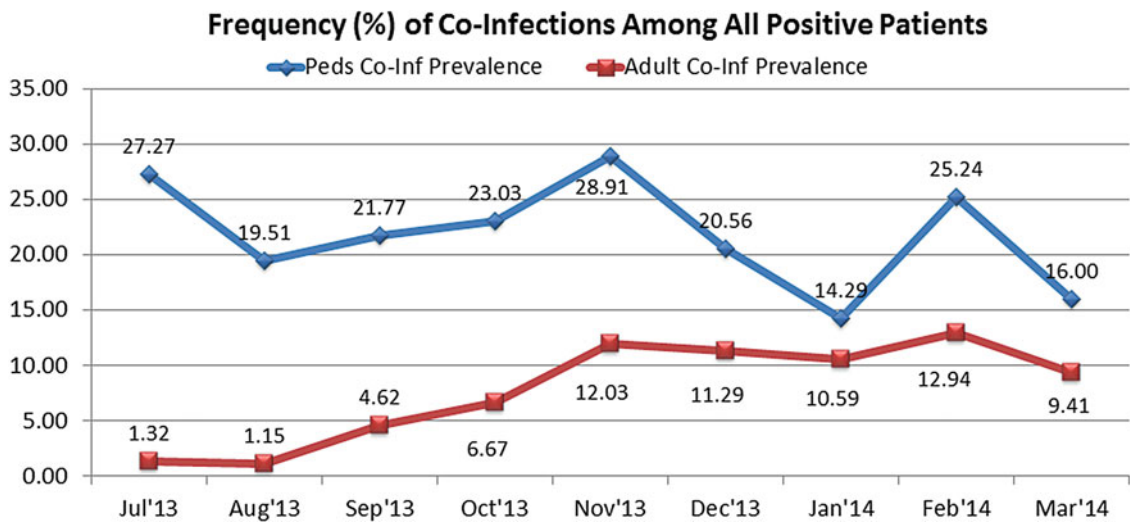

Fig. 14.4 Percent of co-infections observed among pediatric and adult patients. This figure shows that pediatric patients are more likely to have co-infection when compared to adult patients

Infectious Gastrointestinal Illness Testing

Infectious gastrointestinal illness is another syndrome targeted by commercial vendors. As of this writing, there are a number of FDA-approved assays from Luminex, Inc., BioFire Diagnostics, Inc., Becton Dickinson Diagnostics, Inc., Nanosphere, Inc., and GenProbe-Prodesse (Table 14.7). Clinicians are often unaware of what pathogens are actually included when they order a stool culture and Ova & Parasite (O&P) testing [120]. Similar to respiratory illness symptoms, the symptoms of an infectious gastrointestinal (GI) illness overlap also making it difficult to ascertain the true pathogen(s) causing the disease.

The development of an infectious GI panel that targets bacterial, viral, and parasitic pathogens, provides a more efficient approach to diagnosis compared to standard practices. The appeal to the clinical microbiology laboratory is the consolidation of culture, antigen, biochemical, and single-molecular analyte testing into one comprehensive panel. The implications to the state and public health laboratories that rely on culture isolates for epidemiological typing and characterization may not be immediately recognized when considering these molecular stool panel tests. Because of the improved ability to detect a pathogen(s) with molecular methods as compared to culture, there will be scenarios when the molecular test is positive and the culture growth is negative. It is imperative that clinical laboratories communicate with their state/public health laboratory counterparts to come up with an amenable solution given that there will be discordant molecular and culture results if an isolate is required to be sent to the state/public health laboratory.

Similar to respiratory co-infections, GI co-infections are also an under-appreciated aspect of disease and pathogenicity. What potentially makes GI co-infections more confusing and would require some additional clinical scrutiny is that some bacteria can be colonizers (i.e., *C. difficile*) and so the burden of determining clinical significance is left to the clinician.

Matrix-Assisted Laser Desorption Ionization: Time of Flight

MALDI-TOF is another technology that shortens the time to result for determining the microbial identification of clinically significant pathogens. The reader is referred to a number of reference review articles on the technology itself [121–126]. Recently, MALDI-TOF systems have been made commercially available for use in the clinical microbiology laboratory. How this technology compares with the currently available testing (culture/biochemical and DNA sequencing) is outside the scope of this chapter [127–132]. MALDI-TOF does outperform the conventional methods in overall accuracy and time to result.

Our laboratory has implemented MALDI-TOF as an identification tool. Results are available in approximately 1 day earlier when compared to our traditional culture based testing. Branda et al. [88] found that MALDI-TOF reduced turn-around time by 1.45 days compared with their traditional testing. A side effect that we have observed is an increased number of calls from clinicians asking for the antimicrobial susceptibility results. These results are available the next day from our automated AST system. In addition laboratories will need to adapt their workflow processes when MALDI-TOF testing is implemented.

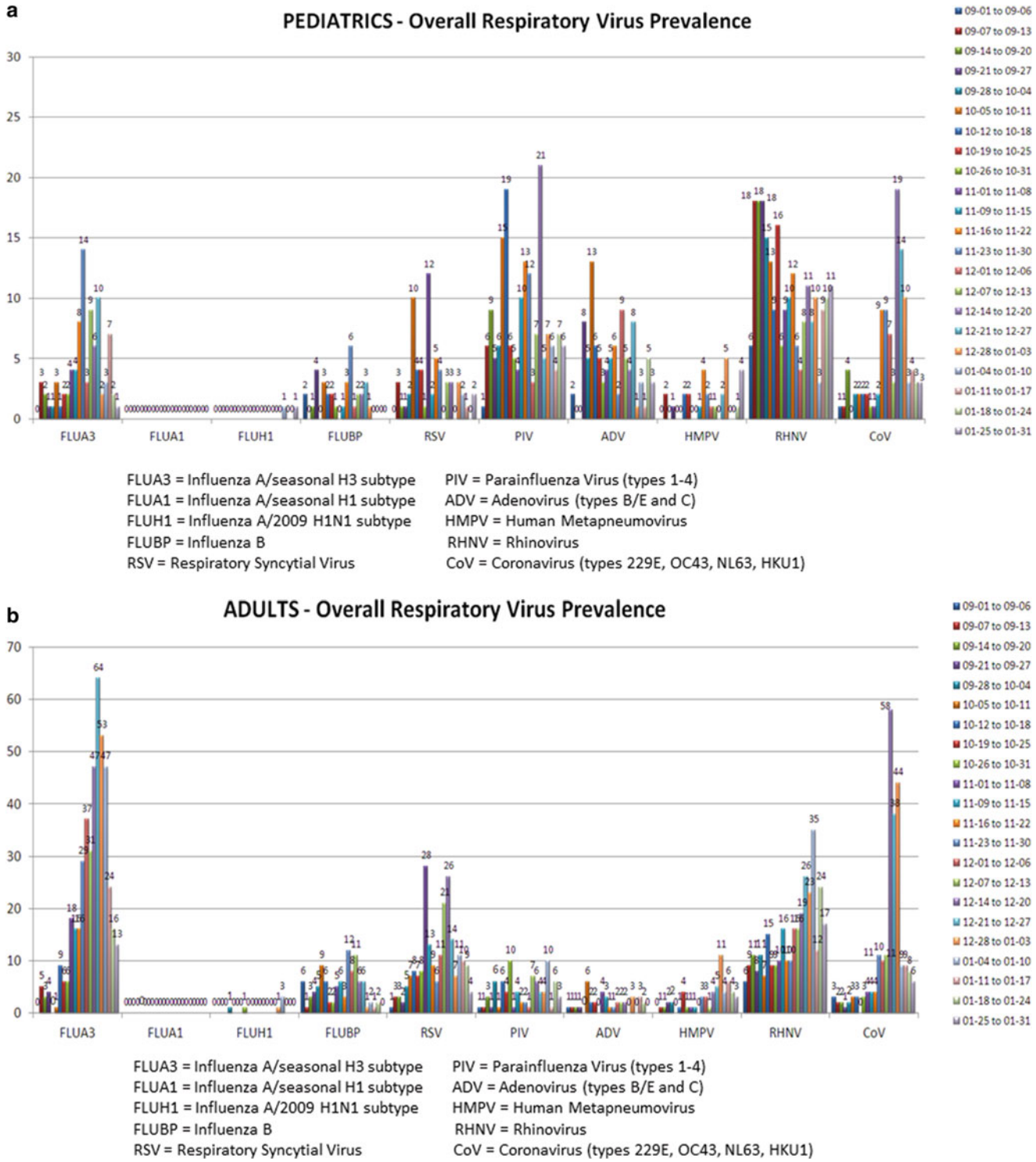

Fig. 14.5 (**a**) Pediatric Virogram showing the overall prevalence of the viruses tested within the RVP assay by week (September 2014 through January 2015). (**b**) Adult Virogram showing the overall prevalence of the viruses tested within the RVP assay by week (September 2014 through January 2015)

The upfront cost of instrumentation is high (approximately $200,000), resulting in delayed implementation in some clinical microbiology laboratories. The financial savings are realized in the cost per isolate of running the MALDI-TOF compared to the cost per isolate for a traditional work-up [127, 133, 134]. There can be reductions in the reagent and laboratory costs when compared to culture/biochemical methodologies [134, 135]. Despite the initial

Table 14.7 FDA-approved molecular assays for gastrointestinal pathogens

Vendor	Assay name	Method	Panel composition
Gen-Probe Prodesse, Inc.	ProGastro SSCS	Multiplex real-time RT-PCR	*Salmonella*, *Shigella*/EIEC1 *Campylobacter*[a], Shiga Toxins 1/2, Shiga Toxin *E. coli*
Nanosphere	Enteric Pathogens Test	Multiplex real-time RT-PCR	*Campylobacter*, *Salmonella*, *Shigella*/EIEC[b], *Vibrio*, *Y. enterocolitica*, Shiga Toxins 1/2 (*stx*1/*stx*2), Norovirus, Rotavirus
BD Diagnostics	BD Max Enteric Panel	Multiplex real-time RT-PCR	*Salmonella*, *Shigella*/EIEC[b], *Campylobacter*[a], Shiga Toxins 1/2 (*stx*1/*stx*2), Shiga Toxin *E. coli*
Luminex Molecular Diagnostics	GastroPathogen Panel	Multiplex PCR, Bead Hybridization	*Campylobacter*, *C. difficile*, *E. coli* O157, ETEC[c], Shiga Toxin 1/2 (*stx*1/*stx*2), *Salmonella*, *Shigella*/EIEC[a], *V. cholerae*, Adenovirus 40/41, Norovirus GI/GII, Rotavirus, *Cryptosporidium*, *E. histolytica*, *G. lamblia*
Biofire Diagnostics	Gastrointestinal Panel	Multiplex real-time RT-PCR	*Campylobacter*, *C. difficile*, *P. shigelloides*, *Y. enterocolitica*, *Vibrio* spp., *V. cholerae*, EAEC[d]EPEC[e], ETEC[c], STEC[f] *Shigella*/EIEC[a], *Cryptosporidium*, *Cyclospora*, *E. histolytica*, *G. lamblia*, Adenovirus 40/41, Astrovirus, Norovirus GI/GII, Rotavirus, Sapovirus

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm (web page accessed July 13, 2015)
[a]Only *C. jejuni* and *C. coli* are detected
[b]*EIEC* enteroinvasive *E. coli*. Assay cannot differentiate due to cross reactivity
[c]*ETEC* enterotoxigenic *E. coli*
[d]*EAEC* enteraggregative *E. coli*
[e]*EPEC* enteropathogenic *E. coli*
[f]*STEC* Shiga toxin *E. coli*

capital expenditure to obtain the instrumentation, there are cost-savings after MALDI-TOF is implemented.

If the organism is not in the MALDI-TOF database, it will need to be confirmed by traditional methods and/or DNA sequencing. Another potential limitation is that the definitive speciation by MALDI-TOF can confuse clinician end users when they see a new bacterial genus/species name that they do not readily recognize and may pose challenges in deciding what antibiotics to prescribe. This new definitive identification is a result of technological advancements that have a greater ability to further speciate bacteria when only a genus answer may have been given with traditional techniques (i.e., coagulase-negative *Staphylococcus* or *Enterobacter cloacae* complexes). From the laboratory perspective, changes in nomenclature must be updated in the Laboratory Information System as appropriate when microorganisms undergo taxonomic reclassifications.

Future advancements with MALDI-TOF technology also will affect the clinical microbiology laboratory workflow. Studies have preliminarily shown the ability to detect the pathogen directly from a patient sample (i.e., positive blood cultures [92, 135, 136] and urines [137–139]), bypassing the current requirement for testing on a culture isolate. However, it should be stressed that direct sample testing is in the very early stages of development. Antibiotic susceptibility testing has also been examined and Hrabak et al. [140] provide an in-depth review of using MALDI-TOF for these purposes. Interestingly, this technology has also been described in identifying the species of ticks potentially minimizing the ectoparasite experience normally required [141].

Newer Methodologies

Technological advancements are focused on shortening the time of pathogen detection so that clinical action can be taken much more quickly. Two relatively new companies have been working on methodologies that will further disrupt clinical microbiology practices. T2 Biosystems, Inc. has recently received FDA approval for the detection of five *Candida* species (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glaboratoryrata*) direct from the patient's blood sample without prior incubation within a blood culture bottle. The T2 Biosystems assay claims to detect these *Candida* species within 5 h. This technology shortens start time for appropriate Candidemia treatment. Patient mortality is decreased, the earlier treatment is started [142]. Having the ability to identify the particular *Candida* species is critical since *C. glaboratoryrata* and *C. krusei* have significant rates of azole resistance [143, 144]. Similar to the other blood culture tests mentioned above, this technology will not eliminate the need for culture/PCR and antimicrobial susceptibility testing after a blood culture bottle becomes positive. The technology allows for processing of the whole blood sample, since a thermostable mutated DNA polymerase that is not affected by inhibitors in whole blood detection is used to amplify DNA. Detection of any PCR product is done via T2 Magnetic Resonance technology. (www.t2biosystems.com). Clinical trials data show an overall sensitivity of 91.1 % with a mean time of 4.4 h for detection and species identification [144]. The limit of

detection was between 1–3 CFU/ml. Knowing a patient's blood sample is positive can be just as important as knowing the sample is negative and the T2 Candida assay was observed to have a 99–99.5 % negative predictive value. Other studies have demonstrated earlier detection and its effect on antimicrobial stewardship [145, 146]. Because this is a relatively new technology, hospitals and other healthcare institutions are currently determining the most optimal and cost effective way to utilize this technology. This test is not intended as a screening tool, but should be used in a more targeted patient population where Candidemia is more significant and more likely to occur.

Accelerate Diagnostics, Inc. has developed a methodology for both rapid pathogen identification and antimicrobial susceptibility testing that can purportedly be performed within 5 h (www.accerlatediagnostics.com). The company is conducting clinical trials on blood culture pathogen panel at the time of this writing. The technology utilizes FISH DNA probes to identify the panel pathogens that may be present. The antimicrobial susceptibility testing results are determined by single-cell microbiological analysis via time-lapse computerized images of the pathogen's growth characteristics in the presence of a particular antibiotic. The blood culture pathogen panel assay is intended to be the company's first FDA-approved assay with other sample type panels in their assay pipeline.

Automation in the microbiology laboratory has been a slow to make an impact unlike the other laboratory sections (i.e., chemistry, urinalysis, etc.) attributable to the inherent manual process of specimen preparation required. Vendors are developing automated plate streakers for more consistent yields with culture plating. Also, companies are developing automated specimen processors that can be programmed to inoculate a battery of plates. One can imagine the advantages to be gained with high volume sections of the laboratory such as urine cultures [147–153]. The implementation of microbiology automation is in its infancy and there is debate on the utility of automation and its widespread adoption. The potential is there for a large impact on the manual workflow and disruption of how clinical microbiology laboratories function. Obviously, there is a financial aspect to the implementation of automation and the estimated total cost of a total automated microbiology solution can be in the millions of dollars [149]. It is not out of the realm of possibilities for further advancements for a total microbiology laboratory automated technological solution where clinical microbiologists may be able to function from a "virtual" bench able to work up cultures and set-ups for other downstream tests from a computer touchscreen/tablet eliminating the potential hazard of being exposed to pathogenic and/or bioterrorism organisms.

In Vitro Diagnostic Companies

New Equipment

The arrival of new equipment in a large community hospital laboratory, chemistry automation [154] for example, creates a lot of stress on the staff to complete the performance verification of the new quantitative analytical systems [155, 156]. The practicing physician and healthcare system depend on this equipment to perform well. The assays will require verification of calibration, linearity, analytic measurement ranges, accuracy, precision, appropriateness of the reference range and quality control requirements [155–157]. A variety of POCT and main chemistry laboratory methods for HbA1C have been evaluated to see if that meets the total allowable error goal set by the CAP proficiency testing program and the National Glycohemoglobin Standardization Program (NGSP) [158–160]. "Clearly, many methods, including a few POC methods, do perform well in laboratories, as seen by data from the CAP proficiency surveys" [160], our new system was not one of those good performers. We replaced immunoassays for HbA1C (Roche Diagnostics method, Siemens Medical Solutions Diagnostics—potential new method) with a capillary electrophoresis method (Sebia) [161–163]. During the evaluation of these three HbA1C methods, the Roche immunoassay reported HbA1C values (3.7–4.8 %) for four patients with no HbA but had HbSC. During the screening of 231 random patients, 13 % had homozygous or heterozygous variants [163]. Hb N-Baltimore comigrates with HbA1C on capillary electrophoresis while Hb Silver Spring and 17 other Hb variants did not [162]. In this case, a method for HbA1C had to be quickly evaluated to replace the immunoassay originally planned for implementation to prevent repeated proficiency testing failures and potential discontinuation of the HbA1C assay.

Obsolete Tests

An obsolete test is a test that is no longer in use or no longer useful (Table 14.8) [12, 164–171]. An effective way to evaluate whether a test has become obsolete is to review it at the Laboratory Utilization Committee that is responsible for the laboratory formulary [172]. The formulary concept comes from the play book of the Pharmacy and Therapeutics Committee that approve medication for use by medical providers and under what circumstances. When a newer more effective drug is FDA approved it may replace an older less effective drug in the formulary. In the laboratory, the perfect obsolete test cannot be ordered by a medical provider

Table 14.8 Partial list of obsolete tests

Test	Reference
Creatine kinase MB	[164–166]
Amylase isoenzymes	[164]
Lactate dehydrogenase isoenzyme	[12]
Myoglobin	[164]
Prostatic acid phosphatase	[164]
Qualitative serum human chorionic gonadotropin	[164, 167]
Chromium, blood	[168]
T3 uptake	[12]
Free Thyroxine index	[12]
Protein bound iodine	[169]
Myelin basic protein, CSF	[170]
Lecithin/Sphingomyelin ratio, amniotic fluid	[164]
C1Q binding	[168]
Bleeding time	[164]
Most viral cultures	[12]
Group B *Streptococcus* antigen	[12]
Bacterial antigen detection	[12]
HIV-1 Western blot	[12]
Gliadin antibodies, IgA and IgG	[171]

because the reagents are no longer provided by the in vitro diagnostics industry. For example, protein bound iodine (PBI) [169] is no longer available at any reference laboratory because the test reagents are no longer manufactured. However, T3 uptake is just as obsolete and useless; however, its reagents are still manufactured by many vendors and still offered by reference laboratories [12]. In a utilization review of our hospital's send out test volume, it was asked by the reference laboratory why physicians ordered so many T3 uptake assays from them. I said it is not on our formulary just like CK MB [164–166], but both of these obsolete tests and others are still ordered and performed by your reference laboratory. The response was "we offer the test because physicians order the test," however, if the reagents were not available from the manufacturer, it is unlikely the reference laboratory would develop a laboratory developed test to support obsolescence. The workaround for removal of the obsolete tests from the hospital laboratory formulary usually involves the use of an EMR that has reference laboratory test ordering built for the convenience of the medical providers. If this feature is not inactivated for inpatients the hospital laboratory formulary develops a leak from which a flood of abuse can originate. Until locally defined obsolete tests are universally accepted and eliminated from the test lists of hospitals, manufacturers, and reference laboratories, the discovery of ingenious work-arounds will occupy the time of the medical providers who by habit are accustomed to having the obsolete test results by their side.

Conclusion

The utilization management of laboratory tests in a large community hospital is similar to academic and smaller community hospitals. There are numerous factors that influence laboratory utilization (Table 14.1). Outside influences like hospitals buying physician practices, increase in the placement of hospitalists and hospital consolidation will influence the number and complexity of test menu that will need to be monitored for over and under utilization in the central laboratory and reference laboratory. The Laboratory Utilization Committee and laboratory formulary stewardship are key to a successful beginning. There are numerous excellent suggestions and reports of the successful implementation of remedies that have been reviewed and arranged in generic toolkits or tool boxes [1, 173, 174] or with solutions for specific laboratory sections like microbiology [12, 88], toxicology [5], chemistry [175], transfusion medicine [176], and molecular diagnostics [177–180]. This useful approach provides a resource for the exploration of laboratory test utilization management issues and their potential resolution using a method that is successful in your local geographical environment.

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