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MINIREVIEW

Impact of Clinical Practice Guidelines on the Clinical Microbiology Laboratory

Peter H. Gilligan*

Clinical Microbiology-Immunology Laboratories, University of North Carolina Hospitals, and Departments of Microbiology-Immunology and Pathology-Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514

Evidence-based medicine is the application of a rigorous scientific framework to the ancient art of caring for a patient that is so central to medicine. Clinical practice guidelines are an important outgrowth of the concept of evidence-based medicine. They have been defined by the Institute of Medicine as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances" (16). The goal of these guidelines is the standardization of selected aspects of medical care to ensure both high quality and cost-effectiveness (29). A number of professional organizations have developed clinical practice guidelines that directly affect the practice of diagnostic microbiology and immunology. For example, guidelines promulgated by the Centers for Disease Control and Prevention (CDC), often in conjunction with professional societies such as the American Thoracic Society (ATS), the Infectious Disease Society of America (IDSA), or the American College of Obstetricians and Gynecologists (ACOG) (12–14), and guidelines published by the National Committee on Clinical Laboratory Standards are closely followed by most clinical microbiology laboratories. The reason for close adherence to these recommendations is that many are codified for purposes of laboratory accreditation and licensure by state laboratory licensing agencies, the College of American Pathology, or the Joint Commission on Accreditation of Healthcare Organizations. Reimbursement for laboratory testing is directly linked to laboratory accreditation, resulting in a clear incentive for adherence to the guidelines. It has also been shown that clinical practice guidelines have a medicolegal impact. One study reported that adherence to clinical practice guidelines could exonerate physicians in lawsuits and could also prevent lawyers from taking on lawsuits (19). Failure to adhere to clinical practice guidelines could also be used to show culpability on the part of the health care provider. It must be emphasized that, according to a survey of attorneys, clinical practice guidelines were cited in <10% of settled lawsuits and guidelines play an important role in less than one-third of cases (19). It should be noted that these data are almost a decade old and may not reflect the present legal environment as it relates to clinical practice guidelines.

This minireview discusses how practice guidelines are derived and what barriers exist that prevent laboratories from adopting guidelines that affect laboratory practices, reviews aspects of five recent guidelines and how they affect clinical laboratory practice, and finally, discusses what role the American Society for Microbiology (ASM) might take in the development of practice guidelines for clinical microbiology laboratories.

DEVELOPING CLINICAL PRACTICE GUIDELINES

There is a fairly extensive literature on the development of clinical practice guidelines (20, 28). One of the professional organizations with which ASM is closely aligned professionally is IDSA. IDSA has published a guide to the development of practice guidelines as well as over 25 guidelines covering various topics (20). The key points in guideline development are as follows: (i) choose a guideline topic that is of interest because there is a high workload, cost, or lack of consensus on how the specific issue should be addressed; (ii) select an expert panel which represents not only the interests of the professional organization (such as ASM) adopting the guidelines but also related, interested organizations or disciplines (such as IDSA, CDC, the American Society for Clinical Pathology, and the Association of Public Health Laboratories); (iii) review the evidence to be used in guideline development; (iv) grade the evidence to determine what will be used; (v) write the guidelines based on the currently available evidence; (vi) make the evidence available for outside review and make changes as necessary; (vii) publish the guidelines; and (viii) review and update the guidelines on a continuing basis.

One of the crucial issues in the development of guidelines in the spirit of evidence-based medicine is the quality of the data that are used. The evidence considered to be best is that derived from multiple randomized, controlled clinical trials (20, 28, 29). The development of clinical microbiology practice guidelines is challenging because this form of evidence is not available for this discipline. Rather, data from clinical evaluations and expert opinion are likely to be the basis for the development of clinical microbiology practice guidelines. In some cases, data for determining the best practices may be either absent or inadequate. Practice guidelines may then become dependent on "expert" opinion based on anecdotal experience rather than scientific data (29).

A new initiative called Standards for the Reporting of Di-

* Mailing address: Clinical Microbiology-Immunology Laboratories, UNC Hospitals, Rm. 1035, Chapel Hill, NC 27514. Phone: (919) 966-6313. Fax: (919) 966-0486. E-mail: pgilliga@unch.unc.edu.

agnostic Accuracy (STARD) has the goal of improving the quality of publications that report evaluations of diagnostic tests (5). The rationale for this is that poorly designed, biased diagnostic test evaluations may result in the use of a comparatively inaccurate test that ultimately results in misdiagnoses for patients and/or inappropriate clinical practice guidelines. The STARD guideline lists 25 items that should be present in any publication that reports on the evaluation of a diagnostic test. In addition, the STARD group has developed a flow diagram that explains how data should be analyzed from diagnostic accuracy studies. An expected outcome of the STARD initiative is the improvement of the quality of the data available to make clinical practice guideline decisions, including those that affect the clinical microbiology laboratory.

Another important issue is determining how frequently guidelines need to be updated. IDSA recommends that its guidelines be reviewed and updated every 2 years (20). The reality is quite different. For example, the pharyngitis management guidelines that IDSA initially published in 1997 were most recently updated and republished in 2002 (4). However, this 5-year period is well in keeping with the findings of a study that examined how frequently the clinical practice guidelines of the Agency for Healthcare Research and Quality needed updating on the basis of new evidence. In that study, it was recommended that clinical practice guidelines be updated every 3 to 6 years, with the specific update frequency dependent on the rapidity with which new, relevant data were accumulated (27).

BARRIERS TO THE ADOPTION OF CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines have several potential benefits, including better patient care at lower costs and, when applied properly, the potential to protect health care providers from legal claims. Why, then, are aspects of clinical practice guidelines as they relate to clinical microbiology laboratories not more universally applied? There are several potential reasons (10). The first is a failure to be aware of a clinical practice guideline. It is not surprising that clinical microbiologists might not be aware of a specific aspect of a clinical practice guideline. Currently, there are over 1,000 clinical practice guidelines in the National Guidelines Clearinghouse database (27). Over 40 different guidelines that relate to pneumonia diagnosis have been published in the last 25 years (17). As already mentioned, IDSA has published over 25 practice guidelines in the past 6 years, all of which make recommendations that directly affect laboratory practice (20).

The second reason may be the inability of the clinical microbiologist to determine the best practice based on conflicting guidelines. A prime example of this is the community-acquired pneumonia guidelines published by IDSA and ATS. IDSA advocates that direct Gram stains play an important role in the management of community-acquired pneumonia, whereas ATS puts little value in this procedure (2, 3). In the absence of compelling data, the guideline that actually results in a better patient outcome is unclear.

The third reason may be a laboratory decision maker's disagreement with a specific guideline that is based primarily on expert opinion rather than data. An example may be the insistence by the clinical microbiology laboratory that negative rapid group A streptococcal antigen tests be followed up by culture to avoid false-negative antigen test results for adults. Current IDSA guidelines for pharyngitis management suggest that follow-up cultures may not be necessary (4).

The fourth reason may be that the laboratory does not have the necessary resources, such as technology or staffing, to comply with the guideline. Other factors that may cause a failure to comply with guidelines may include inertia on the part of the laboratory, patient resistance, lack of reimbursement, and a perception that the guideline may increase legal liability (10).

FIVE RECENT CLINICAL PRACTICE GUIDELINES THAT DIRECTLY AFFECT THE CLINICAL MICROBIOLOGY LABORATORY

There are numerous guidelines that affect the practices within the clinical microbiology laboratory. Aspects of five guidelines published within the past 3 years that directly affect these practices are discussed because they represent important, common clinical problems and because barriers to the implementation of the portion pertinent to the clinical laboratory can be identified for each one.

Screening tests for *C. trachomatis* and *N. gonorrhoeae* infections. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* cause two of the most common sexually transmitted diseases in the United States. Screening for these organisms is an integral part of prenatal care during pregnancy as well as primary health care offered in sexually transmitted disease clinics. In the past decade, nucleic acid amplification techniques (NAATs) have been developed for the detection of both of these organisms. NAATs offer excellent turnaround times and sensitivities superior to those of culture (13). An additional advantage is that urine can be used to screen for *C. trachomatis* and *N. gonorrhoeae*, obviating the requirement for a cervical examination for women, although the sensitivity of urine is less than that of cervical swab specimens (13). Because of problems with false-positive assay results for both organisms, guidelines recommend that confirmatory testing be performed. Several strategies are recommended; the best strategy is to obtain a second specimen and test it by a different test. Because of the superior performance of NAATs, this would require the use of a second target sequence rather than a less sensitive test, such as culture or antigen detection. Because at present none of the Food and Drug Administration (FDA)-approved NAATs for these two organisms offers confirmatory testing by use of a second target, confirmatory testing would require that a second NAAT be available either on-site or at a reference laboratory. Alternatively, the original specimen could be retested by using an alternative amplification target or, less adequately, by repeating the original test with the original specimen or a newly obtained specimen. There are clear barriers to the implementation of what would be considered the best practices according to this guideline. The retrieval of an additional specimen is inconvenient for the patient, and the performance of a nonreimbursed confirmatory test is expensive and difficult to justify in a setting in which the results for a vast majority of positive specimens will in fact be confirmed. Confirmation should be limited to situations in which the patient and the physician make the joint decision that additional testing is important.

This requires that physicians or other health care providers be educated regarding the performance characteristics of these NAATs.

Screening for GBS. One of the great success stories of clinical practice guidelines is their use in reducing the incidence of early-onset neonatal group B streptococcal infections (12). The most recent recommendations have three major points directly related to clinical microbiology laboratory practices (12). (i) Screening for group B streptococci (GBS) should be done by using a vaginorectal swab cultured in enrichment broth. (ii) Due to potential drug resistance, susceptibility testing of isolates from patients who are allergic to penicillin should be performed with the second-line antimicrobials, erythromycin and clindamycin. (iii) Women with bacteriuria caused by GBS during pregnancy should be offered intrapartum antimicrobial prophylaxis.

These guidelines seem straightforward and easily implemented. However, there are, in fact, barriers to each one of these. Specimen collection is crucial to the first recommendation. What if the physician collects only a vaginal swab specimen? Because tests with a vaginal swab specimen are not as sensitive as those with a vaginorectal swab specimen, the former specimen should be rejected (12). However, is that the current practice in your laboratory? Certainly, the requirement to obtain an additional specimen would be very inconvenient for the patient, and this inconvenience is likely to create a barrier to the collection of an additional specimen.

Testing of susceptibility to alternative agents for patients who are allergic to penicillin is straightforward. However, the barrier here is identifying the patient allergic to penicillin. Alternatively, reflex susceptibility testing could be done with all isolates but requires written agreement between the medical staff and the laboratory. This is not cost-efficient, since the vast majority of patients are not allergic to penicillin and isolates from these patients do not require such testing.

The third guideline also presents challenges to the laboratory. Urine specimens are most commonly sent for culture for diagnostic purposes for the same general population that is likely to become pregnant, women between 15 and 45 years of age. Because the guideline does not specify the quantitative definition of GBS bacteriuria, laboratories are left to determine the approach that they will use. My institution reports any amount of GBS seen, including those seen in cultures of urine with mixtures of organisms. Whether this is the best practice could be debated, but it is in keeping with a strict interpretation of the guidelines.

HPV. Human papillomavirus (HPV) is now recognized as the etiologic agent of squamous cell carcinoma of the cervix, having been detected in 90% of women with cervical cancer (22). Fifteen genotypes have been characterized as "high-risk types," with an additional three genotypes classified as "probable-high-risk types." Genotypes 16 and 18 are the most common types found in women with cervical cancer, with >70% of women with cervical cancer being infected with these types (22). Cervical cancer rates have been declining in the industrialized world, in large part due to cervical cytology screening. The performance of cervical cytology has undergone several refinements since its introduction. A recent technical improvement has been the introduction of liquid-based, thin-layer preparations. Placement of specimens in a liquid-based system facilitates the application of molecular diagnostic techniques to the detection of high-risk HPV genotypes. ACOG has recently published new guidelines (1) for cervical cytology screening that incorporate the use of HPV detection as an important adjunct. Key issues as they relate to the use of HPV testing for women being screened are as follows: (i) reflex testing for HPV high-risk genotypes for women over age 30 who have atypical squamous cells of unspecified significance (ASCUS) is recommended. (ii) HPV testing is not recommended for women under age 30, women with low- or high-grade intraepithelial lesions, or those with a history of sexually transmitted diseases, because all are likely to be infected with HPV (1, 18). (iii) Women who have a negative cytologic examination as well as a negative HPV test need to undergo cervical cytology testing only at 3-year intervals instead of the currently recommended 1-year interval (1).

There are two advantages to the first guideline. First, women with a negative HPV test do not require diagnostic colposcopy (an examination of the vagina and cervix for early-stage precancerous lesions referred to as cervical intraepithelial neoplasia [CIN]). Between 40 and 60% of women with ASCUS are negative by HPV testing and would not require this procedure (1). Cytological screening would be performed at a 1-year interval rather than at the 6-month interval that would be required if HPV screening was not used (1). Second, between 78 and 96% of women positive for ASCUS and HPV DNA are positive for CIN (1) and can be managed appropriately.

In the population under 30, HPV infection rates have been reported to be as high as 43% (18), with the overwhelming majority of these infections resolving spontaneously, including those due to high-risk genotypes (1). Therefore, HPV testing is not of use for this population. Additional misuse of HPV testing occurs when women with low- and high-grade intraepithelial lesions are tested (25). These women should be positive for HPV, and a positive result adds little to patient management beyond additional expense (1).

The third guideline is becoming understood by savvy medical consumers who desire less frequent screening without sacrificing test reliability. "Patient request" is second only to an ASCUS diagnosis as the most common reason that physicians order HPV testing (25).

There are at least two barriers to the widespread application of HPV detection for screening for precancerous lesions. First, approximately 20% of gynecologists surveyed believed that HPV detection did not contribute information that was valuable for clinical management, although the data would clearly argue otherwise (25). This is an example of misinterpretation of the current data upon which this guideline is based. The second barrier is the cost and the availability of the test, which was cited by approximately 10% of the respondents to the survey. There are currently no data on the number of clinical laboratories that are offering HPV testing, although it is available at many reference laboratories and large medical centers. At present there is only one FDA-approved test for HPV DNA detection, the Hybrid Capture 2 test (Digene Corporation, Gaithersburg, Md.) (11). Implementation of this test requires investment in a technology that may not have as many applications as other amplification methods, such as PCR. Individ-

uals in clinical microbiology laboratories planning on implementing HPV testing need to collaborate with their cytology colleagues to develop strategies for HPV testing in their institutions. This testing is expensive and is frequently used inappropriately, suggesting that the clinical microbiologist should serve a gatekeeper role to ensure that the ACOG clinical practice guidelines are being appropriately applied.

Screening for MRSA and VRE. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are important nosocomial pathogens and a major target of infection control practices in the industrialized world. The Society for Healthcare Epidemiology of America (SHEA) has recently published guidelines for the prevention of transmission of these two organisms in health care institutions (23). These guidelines argue that surveillance and the use of contact precautions for colonized individuals decrease the rates of hospital infections due to these organisms and the accompanying morbidity and mortality. Despite the increased cost associated with these activities, it is estimated that reductions in VRE and MRSA infection rates will yield significant overall savings for the institution (23). Active surveillance for these organisms can be accomplished by either culture or molecular detection. The paramount questions as they relate to these guidelines are (i) Who should be screened? (ii) When should they be screened? and (iii) How should they be screened?

The guidelines state that patients who are at high risk of carriage of VRE and MRSA should be screened. At least one study (26) suggests that this might mean all patients who are to be admitted to a health care institution. This kind of surveillance is being done in some institutions in the United States. Less stringent surveillance aimed at identifying those who have specific risk factors, such as prior hospitalization (23), may be an alternative approach; but with the increasing number of community-acquired cases of MRSA infection (24), this might not be optimal.

For surveillance and implementation of barrier precautions to be successful, screening cultures should be done at admission (23). For patients who are initially negative for MRSA and VRE by screening, if they are at high risk for colonization with these organisms, they should be screened at some interval during their hospitalization. The frequency of this screening is dependent on a myriad of factors, such as where the patients are located within the institution, what antibiotics they have received, what procedures they may have undergone, and their underlying disease. Given the multiple factors that may influence the likelihood of a patient becoming colonized, institution-specific guidelines are likely to provide the most successful and cost-effective approach to this problem.

Finally, the specimens from the patient that should be cultured have been only broadly defined. For MRSA, a combination of throat and nasal swab specimens is recommended (23). There are no recommendations for the type of medium that should be used, although both mannitol salts and CHROMagar (BD Microbiology Systems, Cockeysville, Md.) appear to work well as screening media (21). Anal or rectal swab specimens are the specimens of choice for VRE surveillance; but no specific recommendations for the type of culture, the use of enrichment broth versus direct plating, or what type of selective medium should be used are given.

There are several barriers to the implementation of these guidelines. The most obvious one from the laboratory perspective is increased workload. My institution has approximately 30,000 admissions/year. Even if we eliminate low-risk patients such as psychiatric and obstetric admissions, we are still left with 20,000 to 25,000 "at-risk" individuals, if we use the broadest definition in the SHEA guidelines. Assuming a minimum of two cultures per admission, we estimate that we will require an additional 50,000 cultures/year. An additional barrier is determining what is the best method for detection of these two organisms when factors such as cost and accuracy are considered.

Platelet contamination. By March 2004, the American Association of Blood Banks will require that all platelet units be assessed to determine whether they are contaminated with bacteria (9). The College of American Pathologists has similar requirements in its Transfusion Medicine Checklist. Failure to determine if platelets are contaminated with bacteria is a phase 1 deficiency (9). These requirements are based on solid evidence. Unlike other commonly used blood products, platelets are stored for 5 days at 20 to 24°C with agitation, allowing amplification of contaminating organisms. Platelet contamination is the most common cause of death due to transfusion-associated infections in the United States (6). The most common contaminants are skin microflora organisms and enteric gram-negative rods from donors with asymptomatic bacteremia (8, 15). It is estimated that these infections are responsible for between 67 and 333 deaths annually, with death largely being due to septicemia caused by enteric gram-negative rods (6, 8). Data suggest that culture is the best method for detecting this contamination (6, 7).

This recommendation has been controversial in some quarters of the clinical microbiology community. First, in institutions with apheresis platelet programs, it will require in-house monitoring of those units. At the University of North Carolina Hospitals, we began culturing platelets in February 2003 and are doing approximately 300 cultures/month. However, this increased workload is not the major reason for the controversy. FDA has approved only two automated culture systems, BccT/ALERT (bioMérieux, Durham, N.C.) and BDS (Pall Corporation, East Hills, N.Y.), for this purpose (9). Since 4 million platelet units are transfused annually in the United States (6), this would seem to be a fairly valuable market. At the core of the controversy was the decision by bioMérieux not to extend its licensing agreement with BD Microbiology Systems to allow it to seek FDA approval for this application with its current BACTEC technology. A similar agreement exists between bioMérieux and TREK Diagnostics, Inc. (Westlake, Ohio), the manufacturer of the ESP automated blood culture system. The use of the automated blood culture system of either BD Microbiology Systems or TREK Diagnostics for platelet testing would be an infringement of bioMérieux's patents and may place laboratories that use the BACTEC or ESP system to monitor platelet contamination at risk for patent infringement. An additional barrier is that laboratories that decide to use either the BACTEC or the ESP system to detect bacterial contamination of platelets must validate those systems, which adds significant additional cost to this process.

ASM'S ROLE IN DEVELOPING CLINICAL MICROBIOLOGY GUIDELINES

Unlike IDSA or the American Association of Clinical Chemistry, ASM currently does not have a formal structure for the development of clinical guidelines related to practices within the disciplines of clinical microbiology and immunology. However, ASM has in place both the experience and the resources that could be applied to the development of discipline-appropriate guidelines.

In response to the anthrax attacks in the fall of 2001, ASM, through the auspices of the Public and Scientific Affairs Board, brought together a team of experts from ASM, the Association of Public Health Laboratories, and the CDC to develop sentinel laboratory protocols for bioterrorism agents. This group of experts has developed nine different protocols for all category A organisms and selected category B ones. This information is available to the general public online at http://www.asm.org/Policy/index.asp. Although protocols are not practice guidelines per se, the process used for protocol creation is similar to that used by IDSA and other organizations for the development of practice guidelines (20).

Within the American Academy of Microbiology is the Committee for Laboratory Practices in Microbiology. The development of clinical practice guidelines is consistent with the aims of that committee, which includes "review and comment on proposed legislation, rules, guidelines, and standards." Clinical microbiology and immunology laboratory guidelines could be developed with this group's input and oversight.

ASM has an ideal forum for the publication of practice guidelines: the Cumitech series. Cumitechs are publications that have many of the characteristics and goals of practice guidelines. Unlike IDSA, there has not been a concerted effort by ASM to develop Cumitechs as practice guidelines. For example, there are currently 39 published Cumitechs, but only 5 have been published in the past 5 years, a time period that would be considered "up to date" for practice guidelines (10). ASM and the American College of Microbiology have a system in place for the development of clinical practice guidelines for the clinical microbiology laboratory. It is incumbent on the Society, the College, and the diplomates of the American Boards of Medical Microbiology and Clinical Laboratory Immunology to develop practice guidelines that can be used to improve the quality of health care in this country.

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