

MINIREVIEW

Hunting Health Care-Associated Infections from the Clinical Microbiology Laboratory: Passive, Active, and Virtual Surveillance

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INTRODUCTION

We face an exciting future in modern health care. Advances have markedly prolonged the human life span, but accompanied by this increased life expectancy is the increasing challenge of controlling health care-associated infectious diseases. In order to manage this problem, timely and comprehensive surveillance is required so as to first detect and then intervene against these infections. The scope of surveillance activities can be either focused (by disease or nursing unit) or comprehensive (system-wide). It can also be passive (detection by fortunate chance observation) or active (planned monitoring of multiple data and infection event sources). The clinical microbiology laboratory has the information drawn from cultures performed for potentially infected patients, and cost-effective use of this data offers great potential for early detection of health care-associated infectious diseases.

Standardized practices for infection control arose in England early in the 19th century, when segregation of smallpox and fever patients was formalized (29). Later, when statistical analysis demonstrating the benefit of infection control practices was applied to an outbreak of typhus, it showed that a 10-fold reduction in nosocomial cases and a 42-fold decrease in associated deaths resulted from adherence to specific practices for contagious patients (16). Microbiologists began to play an important role in infection control, documenting microbial contamination of the operating room environment that resulted from surgeons' carrying on normal conversations, leading to the standard practice of wearing masks during surgery (28). Modern hospital epidemiology only began in the mid-1960s (15), and since that time the clinical microbiology laboratory has progressively demonstrated the critical roles it can serve for ongoing management and control of health care-associated infectious diseases.

SURVEILLANCE FOR MANAGEMENT AND CONTROL

The scope of monitoring activities is often confined to surveillance by objective, limited (targeted) monitoring, or hospital-wide surveillance. While the last type of surveillance is preferred, there are often too few resources available to accomplish this ideal. To undertake these differing activities, surveillance is often based on individual patient risk factors, focused on a hospital ward (nursing unit), or based on microbiology laboratory data (22). All methods have approximately the same sensitivity and specificity (9); however, surveillance from the laboratory has the advantage of measuring hospital-wide occurrences from a single, central data collection point. While current approaches to using laboratory data are thought to detect only approximately two-thirds of nosocomial infections (10), some have argued that the use of laboratory data is the most cost-effective surveillance approach (13).

Additionally, surveillance can be either passive or active. Passive surveillance refers to the strategy where problems are identified by those other than infection control professionals using data generated in the routine course of patient care. This method requires the fewest resources, but it is inherently unreliable and leads to underestimation of problems. Outbreaks are recognized at a much later stage, often when little can be done to contain them. Active surveillance, however, implies that trained practitioners use multiple data sources to detect problems at an early stage. It often includes routine patient screening for pathogens of concern and involves a multidisciplinary approach for the management and control of health care-associated infections. Ideally, it prevents single clones of infectious microbes from spreading within a population and thereby minimizes the number of persons affected (C. S. Price, S. Paule, G. A. Noskin, and L. R. Peterson, Abstr. 39th Annu. Meet. Infect. Dis. Soc. Am., abstr. 212, 2001).

CONTRIBUTION FROM CLINICAL MICROBIOLOGY

In 1998 a consensus report was published that set the current standard for required microbiology laboratory services as part of a comprehensive infection control program (26). The necessary contribution from the laboratory includes surveillance, providing for a systematic observance and measurement of disease, as well as molecular typing of microbial pathogens (26). Present and future needs for laboratory-based surveil-

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lance will require reliable detection of new pathogens that emerge as causes of important health care-associated infections, which implies accurate identification of microbial organisms; recognition of new or emerging antimicrobial agent resistance; and participation in active surveillance for outbreaks, including preparation of specialized media as well as molecular typing (25). This contribution dictates a strong collaboration between the hospital epidemiologist and the clinical microbiologist, with a consequent positive impact on both the infection control program and the diagnostic laboratory (23). Such cooperation will be needed as we move to a future where pathogens of concern not only spread within the hospital but have the potential to affect both inpatients and outpatients, health care workers, and their households (R. Kahtib, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. K-744, 1999).

It must be remembered that emerging and reemerging infectious disease problems develop locally and then spread globally if not contained. National surveillance based on laboratory data has been particularly useful for detecting rising antimicrobial agent resistance in key human pathogens, and it is becoming increasingly clear that careful monitoring of individual clinical microbiology laboratories is the key to recognizing regional differences as well as to being alert to new organisms or resistance patterns with the potential to disseminate far from their point of origin. Monitoring the results of local laboratories permits early response for needed changes in infection control policy as well as implementation of additional surveillance strategies to interdict new health care-associated infections at an early stage. At times, even unit-specific monitoring may be needed, since just as national surveillance data can inadvertently hide problems apparent in isolated laboratories, so, too, can hospital-wide surveillance data obscure emerging problems within individual nursing units (1, 2, 14, 19). It seems clear from the accumulated information that the optimal approach for the management and control of health care-associated infections is hospital-wide surveillance as recommended by the Centers for Disease Control and Prevention (6). Viewing the global data set, particularly if analyzing data from individual units is also possible, provides the opportunity to identify problem clusters at an early stage. The principal hindrances to this approach are that it is very labor and resource intensive if historical surveillance tools are used and that the amount of data collected is overwhelming with contemporary computer analysis (12).

Passive surveillance. Passive surveillance, as noted earlier, requires personnel untrained in epidemiology or infection control to detect a pattern of unusual infections as part of their (unrelated) health care duties. There is no attempt to systematically monitor any type of available data, including that from the laboratory, in an effort to detect emerging or reemerging infectious disease problems. A dramatic example of this is the current epidemic of human immunodeficiency virus infection. This epidemic was recognized in 1981, when clinicians in Los Angeles noted a cluster of young males with pneumonia due to *Pneumocystis carinii* (4). However, by then the epidemic had already spread worldwide. The passive approach is the least desirable form of infection control surveillance.

Active surveillance. Optimally, active surveillance includes using trained infection control professionals and information

from multiple sources, including from the microbiology laboratory, to detect changing patterns of microbial pathogens and health care-associated infections. Surveillance cultures (usually nasal, pharyngeal, or rectal) to determine the epidemiology of potentially dangerous infections are often included as part of this approach. An elegant use of active surveillance applied to an entire region of the United States was recently reported by Ostrowsky and colleagues (20). In 1996, vancomycin-resistant enterococci (VRE) were detected in the 32 health care facilities of the Siouxland region (Iowa, Nebraska, and South Dakota) of the United States. Once this problem was recognized through laboratory surveillance, an intervention strategy that included both laboratory monitoring and patient isolation was planned. Active infection control surveillance with swabs was instituted for all newly admitted patients, with approximately 2,000 patients being screened each year and VRE-colonized patients being isolated. Sustaining this surveillance and accompanying intervention over 3 years lowered the prevalence of VRE from 2.2 to 0.5% ($P < 0.001$) in patients in health care facilities for the entire region (20).

Active surveillance combined with a multidisciplinary infection control program also has been shown to be effective at a single facility, Northwestern Memorial Hospital in Chicago, Illinois (11, 24). In a 5-year sustained program, workers achieved a reduction in morbidity, mortality, and overall hospital care cost (24). Overall, nosocomial infections fell 13 to 23% (depending on how measurements were taken), and some 1,400 fewer patients developed any adverse outcome, with approximately 50 deaths avoided during the 5-year observation. From an economic standpoint, for each dollar spent, approximately \$5 less was expended for treating patients with hospital-acquired infections (24).

Virtual surveillance. Application of mathematical models to detect outbreaks of infection has been proposed as a novel strategy to optimize available laboratory information in the fight for control of health care-associated infections. Threshold limits and cluster analysis have both been proposed (8, 21). Hacek and colleagues have used a 3-month rising trend model as well as an analysis of variance (ANOVA) model (D. M. Hacek, R. Cordel, G. A. Noskin, and L. R. Peterson, Abstr. 4th Decen. Int. Conf. Nosocom. Healthcare-Associated Infect., abstr. P-T1-29, 2000). Applying their methods to clinical microbiology data has shown both to be superior to simple visual screening for trends. Use of these models on clinical microbiology data from 1999 identified three nosocomial infection outbreaks not initially recognized by the Infection Control and Prevention Department of Northwestern Memorial Hospital. However, the overall sensitivities and specificities for the 3-month trend and ANOVA models were 44 and 91.8% and 37.5 and 95.9%, respectively, indicating a significant margin for improvement.

Due to their complexity, as the above-mentioned results suggest, many significant patterns in microbiology data go undetected by standard surveillance activities (S. E. Brossette, B. D. Taylor, B. Warren, K. C. Avent, and S. A. Moser, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1215, 2001; P. A. Hymel, and S. E. Brossette, Abstr. Soc. Healthcare Epidemiol. Am., abstr. 201, 2001). Manual review of positive microbiology test results is resource consumptive, as duplicate isolates must be removed, results must be correlated

with patient charts, patient locations within the hospital must be tracked, and related events must be correlated and monitored. In order to improve patient outcomes by reducing nosocomial infections and antibiotic resistance, it is now recognized that sophisticated, active, and timely hospital-wide surveillance is needed (18, 27). In fact, ideal surveillance systems of the future will include analysis tools that automatically identify, on different time and geographical scales, unusual and interesting patterns from time slices of raw data (5).

For this discussion, we will define data about an isolate and the patient from whom it was obtained as describing one infection event. A typical hospital may have 20 common clinically significant organisms, 20 hospital locations, 10 specimen sources, 10 physicians and/or services, and 12 antibiotics tested for each bacterial isolate, each with an interpreted result of susceptible, intermediate, or resistant. Consequently, a staggering 21,257,640,000 ($20 \times 20 \times 10 \times 10 \times 3^{12}$) potential events exist from bacteriology culture data alone. The manual review of this event space using traditional surveillance methods is prohibitive. Additionally, patterns of events develop over time and geography, increasing the complexity of pattern discovery. As a result, searching for significant occurrences is often limited to focused surveillance of a small subset of events (e.g., VRE, methicillin-resistant *Staphylococcus aureus* [MRSA], and National Nosocomial Infection Surveillance events), serendipitous observations by hospital staff, and the manual review of culture data for outliers. Thus, it is not surprising many small infection outbreaks that are potentially amenable to intervention are not suspected and go undiscovered. This is the current state of traditional hospital epidemiology.

The ultimate goal of surveillance is to reduce the rate of nosocomial infections by automatically detecting patterns in the large event space described above. Virtual surveillance must begin with the cleaning and normalization of electronic data. Data in paper-based patient charts and those collected by labor-intensive counting methods are not amenable to virtual surveillance. However, laboratory data are available electronically and are sufficient for such use.

Replicate isolates should be removed. Patients cultured more than once with the same pathogen identified in more than one culture produce multiple distinct laboratory records describing the same microbe. As much as 30 to 40% of antimicrobial susceptibility results from selected organisms are from replicate isolates (17; H. Horowitz, M. Agresta, and K. Van Horn, Abstr. 89th Annu. Meet. Am. Soc. Microbiol., abstr. C-58, 1989). Such results, if not removed, may lead to false patterns and skewed antibiograms (3, 17). Allowing one isolate per patient (or per organism, 30 days, or phenotype) (± 2 changes) in the data set is an effective criterion for eliminating replicate isolates in pattern detection (Hymel and Brossette, Abstr. Soc. Healthcare Epidemiol. Am.).

Mapping free-text terms to meaningful data elements (e.g., blood, urine, and wound) is also desirable for pattern detection. For example, the term specimen source is commonly a free-text field in laboratory data. Additionally, classifying isolates from specimens taken on hospital day 1, 2, or 3 as community-acquired those obtained from specimens on or after hospital day 4, as well as those obtained in clinic or on readmission from patients recently discharged (e.g., within the last

5 days), as nosocomial, allows for the identification of nosocomial and community-acquired outbreaks (3; Brossette et al., 41st ICAAC). One analysis suggests that approximately 75% of non-duplicate nosocomial isolates are from true nosocomial infections (Hymel and Brossette, Abstr. Soc. Healthcare Epidemiol. Am.). Due to the time delay from the onset of infection to the appearance of signs and symptoms, the probable location of acquisition of a nosocomial infection is the patient's location 2 to 3 days prior to appearance of symptoms and, therefore, prior to the collection of diagnostic specimens. The location of a patient prior to specimen retrieval can be obtained from electronic hospital census data and should be considered in virtual surveillance strategies.

Pattern identification and data mining. The ideal surveillance system would perform both hospital and outpatient surveillance by automatically searching for patterns in event spaces. Data mining processes are appropriate for this task. It should be noted that data mining differs from query-based or hypothesis-based knowledge discovery. Any surveillance methodology that requires that a pattern be suspected before it is tracked really does not involve data mining. Data mining methodologies employ techniques from computer science and statistics to search large event spaces for interesting patterns that would likely have gone undetected by traditional analysis (7).

Data mining has been successfully applied to the analysis of electronic microbiology and patient demographic information (3). In one study, the Data Mining Surveillance System (DMSS) (S. Brossette, S. Moser, A. Sprague, W. Jones, J. M. Hardin, 5 October 2000, U.S. Patent and Trademark Office) was shown to increase pattern detection 10-fold with 95% of pattern isolates coming from cases of nosocomial infections ($P < 0.01$) (Hymel and Brossette, Abstr. Soc. Healthcare Epidemiol. Am.). In the same study, the DMSS identified three outbreaks that were confirmed by infection control (e.g., it identified an outbreak of VRE infection 2 months earlier than traditional surveillance) and 40 additional patterns that merited investigation. In a separate study at a smaller facility, the DMSS identified an outbreak of infection with highly resistant *Pseudomonas* 1 month before infection control, not to mention its identification of unknown patterns of MRSA and novel resistance phenotypes in gram-negative bacilli (Brossette et al., 41st ICAAC). It appears clear that such computerized approaches to rapidly assessing the total universe of microbiology laboratory data currently offer the best potential for dramatically enhancing our ability to detect potential new and unrecognized problems associated with infectious diseases in our health care system.

DISCUSSION

The 20th century saw the dawning of the antibiotic era and the age of modern infection control, as well as plagues of emerging and reemerging infectious diseases. Medical microbiology has played pivotal roles in all these exciting frontiers. While the debate continues over what may be the most cost-efficient and necessary approach for prospective monitoring of health care-associated infections, it is clear the surveillance is the first step to understanding and management. Infection control surveillance can be passive or active, focused or comprehensive. In contemplation of an ideal world, where active,

comprehensive surveillance is carried out, the resources required to accumulate the data and then interpret them in a timely fashion seem to appear overwhelming.

The clinical microbiology laboratory sits as the centerpiece of attempts to monitor the global data set of infection events that can be clues to the emergence of a new microbial plague as well as an outbreak of nosocomial infection. Initial statistical assessments, such as those using a rising 3-month trend or ANOVA, of microbiology data have shown promise but still lack sufficient sensitivity to serve as primary surveillance tools. The cutting-edge application of data mining to electronic results contained within microbiology laboratory information systems has shown considerable promise for dramatically increasing our ability to detect infectious disease patterns of concern at a very early stage and to do so with very modest resource consumption.

Should the process of data mining, or some other novel approach for accessing microbiology computerized data, live up to its potential, there are other pressing needs that could be addressed by such a tool. On a national level, a central agency such as the Centers for Disease Control and Prevention could monitor data from microbiology laboratories for rapid outbreak detection of foodborne illness, either intra- or interstate. Similarly, individual laboratories could monitor their affiliated emergency departments for an unexpected increase in the numbers of sputum samples collected or chest X rays performed, which may signal a bioterrorist event associated with a pathogen like *Bacillus anthracis*.

Whatever the future holds for health care, it is clear that high-quality diagnostic microbiology laboratories are needed to support the infrastructure requirements to assist the health care providers for the ongoing management and control of infectious diseases.

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