Journal of Hospital Infection (1999) **42**: 1–6

REVIEW

Laboratory role in the management of hospital acquired infections

M. P. Wilson and R. C. Spencer

Department of Microbiology, Level 8, Bristol Royal Infirmary, Marlborough Street, Bristol, BS2 8HW

Summary: The microbiology laboratory has many important roles. It must collaborate with the infection control team on the investigations of outbreaks. During outbreaks, it must save relevant samples, look for reservoirs and undertake typing techniques, all of which should be timely. New technology should be available to detect, identify and characterize micro-organisms. Molecular biological techniques have enhanced the speed and sensitivity of detection methods and have allowed the laboratory to identify organisms that do not grow or grow slowly in culture. Molecular techniques also enable the microbiologist to identify antibiotic resistance genes and to 'fingerprint' hospital organisms, thereby facilitating studies of nosocomial transmission.

Keywords: Microbiology laboratory; outbreaks; typing; 'fingerprint'; nosocomial

Introduction

The success of infection control in hospitals relies on the active involvement of the clinical microbiology laboratory.[1] The laboratory has always played a key role in controlling nosocomial infections. This role will continue to expand as antibiotic resistant organisms continue to cause an increasing proportion of infection in hospitalized patients. Traditionally, the function of the laboratory has been to identify pathogens and determine the in-vitro antibiotic susceptibility. However, it should and must also participate in surveillance and other tasks that aid infection control.[2]

Identification of pathogens

Probably the most important laboratory role is the ability to grow and detect microbial pathogens. It must be possible accurately to identify causative organisms to species level and to determine their antimicrobial susceptibilities in vitro.[3] This is especially true for resistant micro-organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), vancomycin-intermediate *Staphylococcus aureus* (VISA) and multiple drug-resistant tuberculosis (MDRTB). This particular task is becoming more difficult as the numbers and variety of pathogens that the laboratory must detect has dramatically increased.[2]

The microbiology laboratory must produce results that are correct and quality is a major issue. A variety of technical quality assurance (QA) procedures are performed because of this and external quality assessment (EQA) schemes participated in. Some laboratories also have internal quality assessment (IQA) schemes in operation.[4]

All laboratory results should be reported as quickly as possible. In most situations it is

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adequate to have the information on the hospital computer system and send out printed reports. However, some results have a higher priority and as such should be reported immediately. Examples of these are positive blood cultures and other usually sterile fluids, smears or cultures with acid-fast bacilli present or cultures that yield multiply-resistant organisms.[2] When a potentially, significant, infective agent is discovered it is then necessary to contact the clinician and members of the infection control team as it may be appropriate to advise on a change in antibiotic therapy or infection control measures.

Another function of the laboratory should be to liaise with clinicians and nursing staff to advise on the quality of specimens and appropriate use of laboratory investigations.[1]

Surveillance

The microbiology laboratory may be the first to notice an infection control problem and has been described as an 'early warning system' for infection control problems.[3]

Surveillance is defined as 'the systematic, active, ongoing observation of the occurrence and distribution of disease in a population'.[5] It has been stated that there are several areas essential to a surveillance programme. These are data collection, analysis, interpretation and the dissemination of these data to those who need to know.[6]

Surveillance can be done locally (looking at individual hospitals), nationally (looking countrywide) or internationally (looking at several countries). National surveillance programmes are useful for identifying general antibiotic resistance patterns of organisms whereas local surveillance identifies resistance patterns within an individual hospital and is a useful basis for infection control measures. Even within hospitals, it may be necessary to break down surveillance to ward level which would reflect the different clinical activity e.g., intensive care units (ICVs), organ transplant units. The data collected can be referred to when writing hospital antibiotic policies. This is especially true for ICU or neutropenic patients where empirical therapy is often given before microbiological culture results are available.[7] Not only is it helpful when advising on treatment of infections but also when considering what prophylactic antibiotics should be used.

Studies have shown that infection control measures together with microbiological surveillance can significantly reduce infection rates and hospital costs.[7] An active surveillance programme of surgical wound infections with feedback to surgeons can reduce subsequent infection rates by 30–40%.[8]

A number of different surveillance methods for detecting hospital-acquired infection have been reported. Namely ward-notification surveillance, laboratory-based surveillance, ward-liaison surveillance, laboratory-based ward-liaison surveillance and temperature and treatment chart surveillance.[9]

However, because of problems with staffing levels this may not be possible and many hospitals practice targetted surveillance of patient units e.g., ICU or neutropenic patients or alternatively the detection of 'alert' organisms for example *Clostridium difficile*, MRSA, VRE, penicillin-resistant pneumococci and MDRTB.

The problems with surveillance lie in the lack of uniformity of identification of microorganisms and in the determination of antibiotic susceptibility. In addition one has to consider the accuracy of denominator data, the diversity of the case mix and which surveillance programme to adopt.

Other areas of surveillance include environmental testing, for example air sampling looking for aspergilli on bone marrow transplant units.[10] Water sampling can be appropriate, for instance, active surveillance of water looking for Legionella in high-risk patient areas such as transplant units.[11]

Role in detection, investigation and control of outbreaks

The laboratory must collaborate with the infection control team in the investigation of outbreaks.

During outbreaks, relevant isolates must all be saved so that they can be further investigated as required. In this situation it may be necessary to look for potential reservoirs of infection which may involve supplementary cultures, for example from food, environmental sources such as water or screening other patients or staff.[2] This should be performed in a timely fashion. Advice may be required as to appropriate samples and specific testing may be necessary for example using selective media.

One of the most important roles of the laboratory is accurate identification and sensitivity testing of suspected outbreak organisms. This also includes typing potentially related isolates. All laboratories should have access to typing facilities even if these are not provided locally. When deciding whether to rely upon on site testing or whether to use a reference laboratory for typing, the issues to consider are number of isolates that will require testing and whether it is worth the cost of equipment and reagents. Also, the training and the cost of adequately skilled staff have to be considered.[12]

New technology

Molecular biological techniques have enhanced the speed and sensitivity of detection methods and have allowed the laboratory to identify organisms that do not grow or grow slowly in culture, therefore increasing the laboratory's ability to identify pathogens.

Molecular techniques also enable the microbiologist to identify antibiotic-resistance genes and to 'fingerprint' hospital organisms, thereby facilitating studies of nosocomial transmission. They may detect pathogens quicker and hence reduce the likelihood of spread in hospital.[1] Using molecular methods to look for organisms or resistance genes has the advantage of speed and may reduce the unnecessary use of antibiotics in patients who are not going to benefit from them. In theory, if bacteria are rapidly identified, targeted or narrow-spectrum rather than broad-spectrum antibiotics can be given which should help reduce drug resistance.[13] An example of this would be the rapid detection of the *mec*A gene in *Staphylococcus aureus* looking for methicillin resistance.[14] In this way vancomycin need only be used in patients with *mec*A positive strains and so reduce unnecessary use of glycopeptide antibiotics.

Typing of isolates

This is useful for surveillance or during outbreaks. The laboratory needs to be able to determine whether organisms are related or not and hence be able to define an outbreak, find an environmental source or likely method of spread.[1] In many cases reliable fingerprinting of isolates can be a critical factor in the direction, extent and success of an epidemiological investigation.[12]

Typing of isolates is useful as an aid in the control of infection and can exclude sources or reservoirs of infection, identify carriers of infection, determine the prevalence of strains of organisms and identify their patterns of spread and therefore influence preventative programs.

Pseudo-outbreaks

Typing can help differentiate a pseudo-outbreak from a true one and hence save unnecessary work for the infection control team. There have been many causes of pseudo-outbreaks described which can be related to the clinician, the laboratory, case-finding or just chance clustering of infections.[3] Those related to the clinician include the wrong diagnosis of a clinical entity,[15] colonization rather than infection, failure to distinguish community-acquired from nosocomial infections and contamination of specimens during collection.[16] Laboratory related causes include contamination of specimens during transport or processing[17,18] and using inadequate methods or techniques.[19] Other causes are better surveillance, improved identification of the organism or simply a chance clustering.

The principle of epidemiological typing is that organisms that are part of the same chain of transmission are clonally related because they are the progeny of the same ancestor cell. There is extensive genomic and phenotypic variation within populations of bacteria within the same species. Clonally related isolates have significantly more similar characteristics than unrelated ones.[20] Typing methods can distinguish that which is different but are not confident in saying that two isolates are the 'same'.

Criteria for typing methods

The criteria for evaluating a typing method are its typeability, reproducibility, discriminatory power, ease of performance and ease of interpretation.[21,22] Typeability refers to the ability of the method to obtain an unambiguous result for each isolate analysed. Reproducibility is the ability of a technique to yield the same result when same strain is tested repeatedly. This is influenced by both technical (reflected in run-to-run variations among replicate aliquots of a single sample) and biological factors ('the biological clock'). The discriminatory power of a method is the ability to differentiate between unrelated strains. Ease of performance is important – it should be technically simple, rapid and economical. Ease of interpretation refers to the effort and experience required to obtain useful, meaningful, reliable results.

Typing methods are either phenotypic or genotypic. Phenotypic methods detect characteristics that are genetically expressed by the micro-organism. The disadvantage with this is that these can change depending on growth conditions, growth phase and spontaneous mutation. Genotypic methods are direct DNA based analysis of chromosomal and extra chromosomal genetic material. These methods have higher discriminatory power than phenotypic ones, a broader application to more bacterial species and sometimes have the advantage of speed.[21,22]

Surveillance versus outbreak

Different typing systems are appropriate for different uses. Most molecular typing methods available are comparative. They can only distinguish between closely related or markedly different genomes of isolates. This is appropriate for outbreak investigations, determining clonal spread of organisms or identifying a potential source. However, these may not be the best methods for long term surveillance.[23]

When deciding on the appropriate typing system, the time and scale of investigation and

Table 1 *Methods for typing nosocomial pathogens*

Phenotypic methods:
Traditional:
Antibiotic sensitivity patterns
Biotyping
Serotyping
Bacteriophage and bacteriocin typing
Protein-based
Polyacrylamide gel electrophoresis (PAGE) of cellular or membrane proteins
Multilocus enzyme electrophoresis (MLEE)
Immunoblot fingerprinting
Genotypic methods:
Plasmid fingerprinting
Restriction endonuclease analysis of chromosomal DNA with conventional electrophoresis
Restriction fragment length polymorphism (RFLP) analysis of chromosomal DNA, supplemented with nucleic acid probes
Pulsed field gel electrophoresis (PFGE)
Random amplification of polymorphic DNA (RAPD) and other PCR based methods

the stability of markers over this period have to be considered.[23,24]

The validity of a typing method will depend upon the bacterial evolution of the isolates. There are three evolutionary levels. Micro-epidemiology refers to short duration of days or months during the infectious cycle in the host. This occurs in localized areas and therefore is relevant for outbreaks. Macro-epidemiology is national or international and occurs in an infected population over a time scale of years. Evolutionary refers to change over millions of years and is worldwide.

'Library typing systems' are used for ongoing surveillance over extended periods. It is vital that the methodology is reproducible and terminology must be uniform and standardized. Examples of these are serotyping of *Salmonella* or *Streptococcus pneumoniae* which is done by reference laboratories and is internationally standardized. Other suitable methods for this purpose include multilocus enzyme electrophoresis or randomly amplification polymorphism DNA performed with a large set of primers.[24]

The disadvantages of phenotypic methods

Phenotypic characteristics involve gene expression that can be influenced by environmental, selective pressure. For example resistance patterns are strongly influenced by antibiotic treatment. Other problems include the presence of unstable antigenic traits and the fact that bacteria will predictably alter the expression of the characteristic being assessed. Also, the differences may not be sufficient to distinguish each strain of a species.[25]

The disadvantages of genotypic methods

These methods are generally highly discriminatory and have a broader application to a variety of bacterial species. They can also, in some cases, have the advantage of speed.[22]

The disadvantages are that they can be too specific and the discrimination of different methods varies. They usually need good technique and are low volume tests. When used over long periods of time, mutation and stability can be a problem.

Whatever typing method is used should be appropriate and scientifically valid for each organism investigated.[24]

Conclusion

The laboratory has always played a key role in controlling nosocomial infections. Its function has always been to identify pathogens and determine the in-vitro antibiotic susceptibility. However, it should also participate in other tasks that aid infection control such as taking a role in detection, investigation and control of outbreaks, surveillance and typing of isolates. The availability of new technology may enable the laboratory to do this more effectively.

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