



INTERNATIONAL
SOCIETY
FOR INFECTIOUS
DISEASES

GUIDE TO INFECTION CONTROL IN THE HOSPITAL

CHAPTER 3:

Role of the Microbiology Laboratory in Infection Control

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KEY ISSUES

The microbiology laboratory plays an important role in the surveillance, treatment, control and prevention of nosocomial infections.

The microbiologist is a permanent and active member of the infection control committee (ICC) and the antimicrobial stewardship group (ASG). Since most of the infection control and antimicrobial stewardship programs rely on microbiological results, quality assurance is an important issue.

KNOWN FACTS

The microbiologist is a daily privileged interlocutor of the infection control team (infection control doctor and infection control nurse) and the antimicrobial stewardship working group.

The first task of the microbiology laboratory is to accurately, consistently and rapidly identify the responsible agents to species level and identify their antimicrobial resistance patterns.

Traditional microbiologic methods remain suboptimal in providing rapid identification and susceptibility testing. There is a growing need for more rapid and reliable laboratory results. Important progress made in the fields of instruments, reagents and techniques have made it easier to adapt to the important changes of the clinical microbiology context e.g. increasing use of microbiology tests, shortage of qualified personnel.

There is also a growing demand for quality in clinical laboratories and more and more countries are elaborating national regulations.

The microbiology processes are becoming increasingly more complex. Informatics are playing an increasing role in the improvement of these processes in terms of workflow, timeliness and cost.

Surveillance is a cornerstone for any infection control and antimicrobial stewardship program. The microbiology laboratory is a surveillance and early warning system. Laboratory based surveillance is efficient but incomplete because of the frequent lack of clinical and epidemiological data available in the laboratory and because specimens are not always collected from all cases of nosocomial infections. The laboratory must meet reportable diseases laws as mandated by countries.

The microbiology laboratory is also involved in the detection and investigation of outbreaks. Unusual events or trends (clusters apparition or multidrug resistant organism emergence) are usually first detected by the laboratory. Comparison (“typing” or “fingerprinting”) of epidemiologically related isolates helps to determine whether these organisms are related or not and thus essential to confirm the existence of an outbreak. The downside to the improvement of laboratory performances (detection and typing) is the extra investment needed. A special budget to participate in infection control activities is not always available, especially in the context of limited resources. The laboratory must collaborate with the ICC in the investigation of outbreaks. Typing of isolates is useful during outbreaks to determine the prevalence and mode of spread of strains and to identify reservoirs and carriers.

Antimicrobial resistance represents currently a worldwide threat, especially in hospital settings. On the other hand, the evolution of antibiotic resistance levels is a marker of the quality of infection control and prevention (ICP) and of antibiotic use in a hospital.

Surveillance and research, reduction of the incidence of infection and optimization of the use of antibiotics are among the strategic objectives of the WHO global action plan to combat antimicrobial resistance (1). The microbiology laboratory plays an important role in antimicrobial stewardship, which aims to optimize antibiotic prescribing to improve patient outcomes, minimize potential toxicity, prevent emergence of resistance and reduce healthcare costs.

SUGGESTED PRACTICE

- A representative of the microbiology laboratory staff must be an active member of the ICC (Infection Control Committee) and a consultant to the infection control and prevention (ICP) program. In many hospitals, the ICC is chaired by a microbiologist, and a key function is to improve collaboration between clinical, laboratory and ICC personnel.
- All healthcare institutions should have a committee / team responsible for antimicrobial stewardship (2). A non-limitative members list would be a clinician, a clinical pharmacologist, a clinical microbiologist and an infection preventionist, not to mention a nurse and all should serve as standing members of the ICC.
- If necessary, the microbiologist gives training in basic microbiology to ICC and antimicrobial stewardship members and provides expertise (e.g. quality of preanalytical phase, interpretation of culture and antimicrobial susceptibility results, ready to use microbiological strategies to deal with each specific infection control situation, evaluation of resources needed). This education could be conducted with classical lectures but could be improved by laboratory rounds for instance. Laboratory personnel should in turn engage in continuous education (e.g. rapid diagnostic techniques, detection of antibiotic

resistance phenotypes). Free education resources are now widely available on the internet.

- Quality assured results communicated in useful time are essential for decision making about patient care and preventive measures.
- The laboratory should follow good laboratory practices and guidelines from WHO, the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).
- The turnaround time for results obtained with conventional microbiological methods is 48-72h. Rapid diagnostic tests with non-molecular (e.g. immunochromatography) or molecular methods (e.g. PCR methods or mass spectrometry MALDI-TOF) allow rapid detection and identification directly in a sample (e.g. blood, cerebrospinal fluid, stools) or from the primary culture (e.g. blood culture or plate culture). The analytical microbiology process can be totally automated or in part (specimen inoculation, plate reading, blood culture or antimicrobial susceptibility testing) (3).
- In terms of quality assurance, the laboratory must follow national mandates. Accreditation according to the international ISO 15189 norm is suitable; in fact, this accreditation is already mandatory in many countries.
- Informatics are now an important component of the microbiology laboratory processes among which the information system, expert systems, equipment interfaces, automation, sequencing, surveillance and reporting (4).
- Laboratory based surveillance is an essential part of the hospital wide surveillance. Surveillance of healthcare associated infections can be active or passive and comprehensive or focused (patient units, specific sites of infections, selected pathogens). Active focused surveillance is the preferred method because it is more feasible and more efficient.

- Routine surveillance of nosocomial infections is based both on daily review and on periodic reports of microbiology records. These reports would be analyzed preferably during daily meetings between the IC team and the laboratory staff.
- Storage and analysis of information are usually computerized, and the laboratory information system is usually integrated in the hospital information system.
- Surveillance data are analyzed and reported promptly on a regular basis.
- The ICC and the antimicrobial stewardship working group and the microbiology laboratory should elaborate a reporting policy. To diminish the wait time to start optimum intervention (antibiotic treatment or preventive measures), the general rule is the early reporting, and the procedure will define which are the critical results and the reporting pathways. This communication may take several forms, including written or electronic reports but the best way to communicate important microbiology results is still a telephone call because it assures the rapid information of the person who needs to know and offers an opportunity to discuss these results.
- The microbiology laboratory is also a sentinel system. Prompt notification to clinical wards and to ICC initiate epidemiological investigation which may lead to preventive measures to halt the spread of causative microorganisms.
- The microbiology laboratory is responsible for the early detection of clusters of microorganisms with the same phenotypic characteristics. Laboratory and epidemiological studies of suspected outbreaks should be conducted in parallel. During outbreaks the microbiology laboratory collaborates with the ICC to elaborate case definitions, choose the specimens to collect, the isolates to fingerprint, and the relevant isolates to store. All this work should be done timely.

- Surveys of carriers, hospital personnel and environment should not be conducted routinely but only to address specific situations.
- Molecular biology techniques are more discriminatory than phenotypic methods (antibiotic resistance phenotypes, serotypes, biotypes, phage types).
- Various molecular methods have been used for bacterial typing and the chromosomal restriction patterns by pulsed field gel electrophoresis (PFGE) is considered the reference technique for typing most bacterial species (5); but this technique is costly, labor-intensive and require interpretation skills. Alternative methods (e.g., Arbitrarily Primed-PCR) lack reproducibility and standardized interpretative criteria.
- Whole genome sequencing (WGS) shows a higher discriminatory power in hospital outbreaks investigations than PFGE and MLST (6,7), and is likely to replace current molecular typing techniques in the future (5,8).
- To assess and improve antimicrobial usage, the antimicrobial stewardship working group should elaborate and implement an antimicrobial stewardship plan that can be adapted from the SHEA/IDSA (9) and Center for Diseases Control (2) models. Rapid diagnosis coupled to antimicrobial stewardship have positive impact on patient care and economical outcome
- The overall objective of the microbiology laboratory contribution to the AMS plan is to guide the antimicrobial choice to support successful patient outcome and minimize adverse impacts in terms of toxicity, antimicrobial selective pressure and costs. Antibiotic resistance levels vary widely depending on geographic location and even among hospitals from the same country. Hospital antibiotic policies can be generated only when local information is available.
- Monitoring the antibiotic susceptibilities of bacteria generates a database which is consulted when writing hospital antibiotic policies.

- Data on antimicrobial resistance should be periodically available to the medical staff, at least annually. These data are helpful for generating hospital treatment guidelines, which are useful in situations where empirical therapy is often given before the microbiology results are available.
- The laboratory contribution is multimodal from advice for appropriate sampling advice, to rapid diagnostic testing, selective reporting, early notification, antibiotic data compilation and feedback (10).

SUGGESTED PRACTICE IN UNDER-RESOURCED SETTINGS:

- The CML is a key actor of ICP. In the absence of a committee or healthcare worker especially dedicated to ICP, the CML can take the lead and develop a collaboration with the medical/nurse management of the clinical wards where are the patients the more at risk of healthcare associated infections (ICUs, neonatology, hematology, burns ...). This collaboration would then be extended to other patient categories whenever possible.
- The aim of this collaboration is to ensure a long-lasting working relationship with fluid communication, based on a clear definition of responsibilities between clinicians, clinical and laboratory staff.
- This partnership could adapt the WHO diagnosis stewardship model (11), to improve all the stages of the microbiological diagnosis starting by a pertinent indication for sampling, correct sampling and transport, quality assured analysis, to the timely report of results and interpretation of these results.
- This collaborative framework would also allow needs prioritization and elaboration of a list of essential diagnostics (12), based mainly on local epidemiology. This local list would be reviewed on a regular basis to parallel changes in technology, local epidemiology and available resources.

- To ensure a relevant use of the limited resources, and in agreement with the local list of diagnostics, when implementing a new test, the laboratory staff will take into consideration its sensitivity, specificity, necessary skills, turnaround time to results and cost. Furthermore, a plan to educate clinicians to ensure accurate interpretation and appropriate use of results should be implemented.
- Achieving, maintaining and improving accuracy, timeliness and reliability are major challenges for health laboratories (WHO). For any laboratory, ISO 15189 accreditation is the ultimate mid or long-term goal. To achieve this goal, the laboratory can use the WHO stepwise approach (13) with phases, roadmaps and tools to improve the essential quality management processes according to the norm ISO 15189 and the Clinical Laboratory Standards Institute (14).
- At a minimum, the microbiology laboratory staff should implement internal quality control. Quality control strains for antibiotic susceptibility testing are well defined isolates from international culture collections (American Type Culture Collection or Collection Institut Pasteur). For reagents, media and equipment quality controls, a set of well identified isolates recovered in the laboratory itself may be used. The laboratory must participate in his country national external quality assessment and if non-applicable, voluntary laboratories may organize and participate in an interlaboratory comparison of samples and isolates. Quality advanced laboratories may consider serving other hospitals / laboratories.
- Concerning the laboratory information system, for laboratories with limited resources, the WHONET software from WHO is a powerful tool which is free of charge, well documented, easy to learn, user friendly and can be customized to each laboratory needs (15).
- WHONET allows for data structure design, data entry (with standardization, rapidity and consistency of repetitive texts), analysis, reporting, printing and archiving of laboratory data. Most of these tasks can be automated. WHONET has an expert system - a set of

pre-defined microbiological rules – which makes data validation easier. It is also possible for an individual laboratory to add new rules. WHONET provides data encryption which ensure confidentiality.

- Social media via smartphones have proven useful in health and healthcare (16). In settings with limited access to computers and/or internet, social media may be helpful for professional communication between groups of specialists, for resources sharing, small groups education, or for information campaigns. Nevertheless, a special attention should be paid to confidentiality.
- The surveillance system is part of the already discussed collaborative project between clinical wards and microbiology laboratory. The type and domains of surveillance, the responsibilities, communication channels and quality indicators are formalized in an annual surveillance program.
- Laboratory records are an important source of information for the ICC.
- The microbiology laboratory must issue daily reports of significant microbiology results, sorted by ward, pathogen or site of infection. These repetitive tasks are easily automated with WHONET. The reports include patient's identification, date of hospitalization, type and date of collection of specimen, culture results and antibiotic susceptibility data. Reports that focus on selected pathogens (e.g. methicillin resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, extended spectrum β -lactamase producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae or *Acinetobacter baumannii*) can also be issued. The list of selected pathogens which include bacteria with known epidemic potential and multi-resistant bacteria is established by the collaborative project participants and is revised periodically following the epidemiological situation at the institution.
- The microbiology laboratory is responsible for dissemination of this information. All significant laboratory results should be reported as

quickly as possible e.g. the reports are communicated daily or better discussed with the ward medical/nurse management. Some of these results (isolation of *Salmonella*, *Shigella* or *Neisseria meningitidis*, smears showing acid-fast bacilli, cultures with multi-resistant bacteria) have a high priority and should be notified immediately by phone.

- Periodic reports (e.g. weekly reports focused on multidrug resistant bacteria) are also useful in that they monitor trends. Data from various time periods should be analyzed to study the patterns of infections.
- Biochemical and antibiotic resistance phenotypes are less reliable epidemiological markers than molecular markers, but can represent a first alert and suggest more epidemiological and laboratory investigations. Early and broad detection of possible outbreaks / clusters is made easier with WHONET (17-19)
- Whether to fingerprint the isolates locally or to send the strains to reference laboratories depends on laboratory staffing and skills, the number of isolates and available budget.
- The microbiology laboratory plays a central role in the hospital antimicrobial stewardship. Laboratory data are an essential source for treatment guidance.
- The sample quality (appropriate site, timing, frequency, volume) has a direct impact on the quality of the laboratory results. Procedures for proper collection and storage should be elaborated and made easily available. This effort should be completed by continuous education, assessment and feedback.
- Final results of standard microbiological techniques require at least 48-72h. Rapid diagnosis tests provide results more quickly – sometimes within hours- and their combination with antimicrobial stewardship has shown improvements in antimicrobial use and clinical outcome. In settings with limited resources, rapid diagnostic testing may be of interest e.g. urine strips use to avoid unnecessary

urine cultures or rotavirus detection by immunochromatography. Chromogenic culture media are useful for presumptive bacterial identification (e.g. bacteria from urines samples or *Clostridium difficile* from stools) or for screening of drug resistant bacteria (methicillin resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended spectrum beta-lactamase producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae, carbapenem resistant *Acinetobacter baumannii*). These screening methods for antibiotic resistant bacteria have a comparable sensitivity to PCR methods (20).

- For antimicrobial resistance surveillance, and depending on the resources available, the laboratory can participate in the starting WHO network called GLASS (global antimicrobial resistance surveillance system) or set up a more comprehensive system.
- The Glass project (21) covers hospital and community settings. In its early implementation phase, it targets data from four priority specimen types (bloodstream, urinary tract, gastrointestinal tract and genital tract) and eight priority bacterial pathogens (*S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *Salmonella* spp, *Shigella* spp and *Acinetobacter baumannii* and *Neisseria gonorrhoeae*).
- In settings with more favorable resources, an important task will be a pertinent choice of drugs to evaluate. Guidelines have been published by the CLSI (22) and EUCAST (23) with first and second line choices based on bacteria – antibiotic groups considering sites of infection and particular patient conditions as well. The laboratory list should be adapted to its hospital formulary. In addition to antibiotics used for patient treatment, molecules useful for identification can be tested as well.
- Disk diffusion method is the most adapted to these settings. Certain antibiotic - bacteria interactions can be evaluated only with a quantitative method (e.g. MIC determination by Etest methodology or by a dilution method).

- Susceptibility testing results should be validated by a daily internal quality control and by an expert system (e.g. WHONET). The expert system will alert on possible laboratory errors (e.g. *Klebsiella pneumoniae* susceptible to amoxicillin), unusual results to investigate more thoroughly (e.g. *Staphylococcus aureus* resistant to vancomycin or *E.coli* resistant to imipenem), important results that should be confirmed at the local or national level, isolates to save or send to a reference laboratory, findings that should be communicated to the ICC or communicated to the health authorities.
- CLSI (22) and EUCAST (23) expert rules include recommendations on inferring susceptibilities to other agents from one results (e.g. *Staphylococcus aureus* if resistant to isoxazolyl-penicillins - as determined with oxacillin, ceftaxime, or by detection of *mecA*-gene or of PBP2a - THEN report as resistant to all beta-lactams except those specifically licensed to treat infections caused by methicillin-resistant staphylococci owing to low affinity for PBP2a) or editing results from susceptible to intermediate or resistant (Enterobacteriaceae -mostly *Klebsiella* spp. and *Escherichia coli* – if resistant to ticarcillin but susceptible to piperacillin, THEN edit piperacillin to resistant). These rules can be added to WHONET rules database.
- To promote judicious use of antibiotics, the most recommended approach for antibiotic susceptibility results reporting is the selective or cascade method, in which the results of the second line choices are reported only if the isolate is resistant to first line drugs (e.g. susceptibility results of imipenem are not reported for cefotaxime, ceftriaxone, ceftazidime susceptible *E. coli*). Nevertheless, the second line results must be readily available to the clinicians and the infection control team upon request. This approach can be handled with WHONET.
- Apart from the susceptibility results, the reports may comprise different types of comments (10,23): therapy related comments (e.g. *Enterobacter* spp., *Citrobacter freundii*, *Serratia* spp., and *Morganella*

morganii. If susceptible in vitro to cefotaxime, ceftriaxone or ceftazidime, THEN note that the use in monotherapy of cefotaxime, ceftriaxone or ceftazidime should be discouraged, owing to the risk of selecting resistance, or suppress the susceptibility testing results for these agents), diagnostic issues or culture interpretation.

- Monitoring the antimicrobial susceptibilities of bacteria generates a database, that is useful for elaboration of hospital formulary or hospital antibiotic treatment guidelines (e.g. first choice and alternative treatment organized by sites of infection). Laboratories are encouraged to aggregate these data and generate “cumulative antimicrobial susceptibility reports” (24) on a regular basis and at least once a year. Before aggregating the data, and to ensure their accuracy, the data should be validated; when running a standard report, WHONET will edit statistics about the percentage of completion and of invalid data for each data field, allowing editing and corrections.
- Another recommendation of importance, is to include in the final report, only the first isolate of a given species recovered from a given patient during an analysis interval. The data should be summarized for each ward or clinical specialty, by anatomic site of infection or type of pathogen.

SUMMARY

The clinical microbiology laboratory is an important resource for the infection control and the antimicrobial stewardship programs.

The laboratory should comply with regulatory mandates, provide quality assured results, promptly notify and be available for patient care and preventive measures decisions.

Current microbiology context has changed. The laboratory has to adapt to new quality mandates and to technical evolution (rapid diagnostic testing, automation, increasing importance of informatics, new communication tools).

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