The clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient specific culture and susceptibility data to optimize individual antimicrobial management and by assisting infection control efforts in the surveillance of resistant organisms and in the epidemiologic investigation of outbreaks. Intensive care units are an area of particular importance, as the control of resistance in these units can affect other areas of the hospital.

Speaking of the clinical microbiology laboratory, the culture and sensitivity reports remains the mainstay for the successful recovery of the infected patient. Annual antibiograms made can help in the initial empiric treatment of the patient; these antibiotics can later be de-escalated based on the sensitivity reports. But how does one confirm that the reports are truly authentic? Validation of reports is the answer. This applies to not only for the microbiological, but also for the other departments of the laboratory as well.

Validationfor laboratory reports involves positive comparisonof results with an already approved method provided by a body or organization[1].

- Performance check of consumables: This check used for consumablesand instruments validates them while performing the test confirms to the basic standards. Ex: ATCC (American Type Culture Collection) strain checks of each and every prepared media and stains;temperature & calibration checks for centrifuge machines, refrigerators, incubators etc
- Method & reporting checks: Method used for the culture & reporting should be in strict adherence to the approved CLSI (Central Laboratory Research Institute) guidelines.
- Interlaboratorycomparison of results (ILC): Periodically, the reports of a lab should be compared to government approved laboratory (NABL); a quality improvement procedure.
- External quality assurance scheme (EQAS): There are certain government approved bodies which conduct exams for laboratories which are willing to maintain the quality of their reports. They send patient samples to these laboratories which they process and report back to them. Based on these results, they are given marks and are judged on the national (or international) scale. For microbiology in India, this body is at Sir Ganga Ram Hospital, New Delhi.

What if inspite of all the quality checks, the clinician is still at doubt with the reports?

- Disparity between the in vitro and in vivo results: This is the most common cause involved. In such a situation, the clinician must delve into its finer details.
    - Firstly, the immune mechanism where even though a sensitive antibiotic is administered, the patient deteriorates[2]. Ex: Results of in vitro susceptibility testing cannot be expected to predict the clinical response to penicillin therapy in patients with group A streptococcal infection when the clinical outcome may be greatly influenced by TSS[3]. A similar disconnect can be seen with necrotizing pneumonia caused by community-acquired methicillin-resistant *Staphylococcus aureus* having the Panton-Valentine leukocidin (PVL) gene where patients may die of necrotizing pneumonitis despite receiving appropriate antimicrobial therapy[4].
    - Secondly, the site of infection[5]: Certain antibiotics are more favorable to penetrate certain areas of the human body more than the others. For ex: 3rd generation cephalosporin have excellent CSF penetrability[6].
    - Thirdly, the intrinsic factors[7,8,9]:

1. A) Pharmacodynamicfactors such as beingbacteristatic or bactericidal; minimal inhibitory concentration; the relationship between the concentration of the drug and its antimicrobial effects and the post antibiotic effect (PAE)

and B) Pharmacokinetic parameters such as peak concentration (Cmax), the serum half-life (t1/2), and cumulative exposure to an antibiotic (areaunder-the-concentration-time curve [AUC]).

Bactericidal antibiotics are defined as being either concentration dependent (eg, aminoglycosides) or time dependent (eg, cephalosporins). These effects may depend on the Cmax:MIC ratio (aminoglycosides) or the AUC:MIC ratio (eg, fluoroquinolones). The goal of antimicrobial therapy with an aminioglycoside is to achieve a very high peak concentration, while that for a fluoroquinolone is to maximize drug exposure by achieving both a high peak and trough concentration. Other concentration-dependent antibiotics includeazolides (ie, azithromycin), ketolides (ie, telithromycin), and vancomycin. Therefore, dosing becomes a critical factor in achieving the proper concentration-dependent bactericidal effect.Antimicrobial agents with time-dependent killing include beta-lactam agents (ie, penicillins, cephalosporins, carbapenems, and monobactams), macrolides, clindamycin, and oxazolidinones (ie, linazolid). Because these agents have minimal post antibiotic effect, the goal is to optimize the duration of exposure of the

microorganism to antimicrobial concentrations above its MIC. On the other hand, there are some agents that appear to exhibit both concentration-dependent killing and time-dependent killing ; these include azithromycin, tetracyclines, vancomycin, and linezolid. For these agents, the AUC/MIC seems to be the primary parameter that correlates with clinical efficacy.

Prolonged in vivo PAEs are seen with antimicrobial agents that inhibit protein and nucleic acid synthesis such as aminoglycosides and fluoroquinolones and they may be administered less frequently than would be predicted based on elimination half-life.

- Lastly, when the hesitation still remains on the validity of the reports , the clinician can, at best, send the samples can do an inter-laboratory comparison of the results. Care should be taken that both the samples are to be collected at the same time and source.

Validation of reports is primary for the better clinical outcome. The forementioned are just a few of the pillars of good quality practice in the laboratory. Without them, the reports are just as good as being invalid. For this purpose, in India, bodies like National Accreditation Board for Testing and Calibration Laboratories (NABL) have been established to assist the quality practicing laboratories. Therefore, the clinician should also be aware of these basic quality parameters being exercised in the laboratories whose reports they frequently refer to.

References:

1. Specific Criteria of Accreditation of Medical Laboratories (NABL 112; Issue No: 03, Issue Date: 01.02.2008, Amendment No: 03, Amendment Date: 16.10.2012). Available from: http://www.nabl-india.org/nabl/index.php?c=publicaccredationdoc&m=index&docType=both
2. Weinstein L, Dalton AC. Host determinants of response to antimicrobial agents. N Engl J Med 1968;279(9):467–73. McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial super-antigens: an update. Annu Rev Microbiol2001;55:77–104.
3. Norrby-Teglund A, Thulin P, Gan BS, et al. Evidence for superantigen involvement in severe group A streptococcal tissue infections. J Infect Dis 2001;184(7):853–60.

4. Tseng MH, Wei BH, Lin WJ, et al. Fatal sepsis and necrotizing pneumonia in a child due to community-acquired methicillin-resistant Staphylococcus aureus: case report and literature review. Scand J Infect Dis 2005;37(6–7):504–7.
5. Kastenbauer S. Pneumococcal meningitis: a 21st century perspective. Lancet Neurol 2006; 5(2):104–5.
6. John CC. Treatment failure with use of a third-generation cephalosporin for penicillin-resistant pneumococcal meningitis: case report and review. Clin Infect Dis 1994;18(2):188–93.
7. Finch RG. Introduction: standards of antibacterial performance. ClinMicrobiol Infect 2004;10(Suppl 2):S1–5.
8. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, gycopeptides, and linezolid. Infect Dis Clin North Am 2003;17:479–501.
9. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of ‘‘bug and drug.’’ Nat Rev Microbiol 2004;2(4):289–300.

Author:

Dr. Vicky Lahkar, Consultant Microbiologis (Narayna Superspeciality Hospital, Amingaon,Guwahati,Assam)

Author

- CCEM Journal

View all posts