

Avoiding laboratory pitfalls in infectious diseases

T S Lo, R A Smego

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In today's medical care environment, clinicians are challenged to order clinically relevant, cost effective laboratory tests and antibiotic therapy. Together, physicians and laboratories must have guidelines and strategies that can provide quality patient care, while minimising costs and preventing further emergence of antimicrobial drug resistance. Five clinical vignettes that demonstrate these principles are presented.

Numerous studies and review articles have been published that emphasise the importance of appropriate antibiotic use to reduce the increasing incidence of antimicrobial drug resistance and to curtail medical costs. However, little has been written about the significance and impact of the inappropriate ordering of laboratory tests for infectious diseases.^{1, 2}

Inappropriate and redundant laboratory testing is not only cost ineffective, but more importantly it may lead to unwarranted and potentially toxic drug treatment.³ The following short cases illustrate some of the common pitfalls of laboratory medicine in the field of infectious disease that clinicians should be aware of.

CASE REPORTS

Case 1

A 45 year old alcoholic male was admitted to an alcohol abuse treatment programme. Fourteen days later while in the hospital he developed diarrhoea. Apart from alcoholism, the patient had no other underlying medical illnesses, and he had not been given antibiotics before the development of diarrhoea. As part of the diarrhoea work-up, the resident in charge ordered a test for fecal leucocytes, a stool culture for enteric pathogens, a test for ova and parasites, and a *Clostridium difficile* stool toxin assay. Fecal leucocytes and *C difficile* toxin were found to be present, while the remainder of the work-up was negative.

Comment

The above case illustrates the validity of the "three day rule" when ordering stool study in a hospitalised patient who develops loose stools. The detection rate for bacterial pathogens such as salmonella, shigella, campylobacter, and yersinia and for enteric parasites is less than 0.5% for persons who have been in hospital for greater than 72 hours.^{4, 5} The "three day rule" advises clinicians to avoid ordering tests for enteric bacteria and stool parasites for patients

who have been hospitalised for more than three days, unless there is an ongoing nosocomial outbreak of food poisoning, or unless medical sleuthing determines that patients have been eating ethnic or other take-out food brought into the hospital by a family member or friend. Patients seropositive for HIV, neutropenic patients, and patients more than 65 years of age with immunosuppressive co-morbid illnesses can be considered exceptions to the "three day rule".⁶ In this present case, the resident appropriately sent a stool specimen to the laboratory for *C difficile* toxin assay; *C difficile* is the most common enteric pathogen causing diarrhoea in hospitalised patients, and pseudomembranous colitis can occur in patients who have not been recently exposed to antibiotics.⁷

Case 2

A 68 year old diabetic man on haemodialysis was admitted with nausea, vomiting, and fever. Blood cultures were drawn and methicillin resistant *Staphylococcus aureus* (MRSA) was isolated from four of four bottles. Intravenous vancomycin was begun, and the patient's PermCath (Kendall, Mansfield, MA 02048, USA) was removed three days later. The catheter tip was sent for culture and subsequently grew MRSA and rare *Escherichia coli*, and gentamicin was added to the regimen because of this culture result.

Comment

It has been shown that qualitative intravenous catheter cultures have minimal value as predictors of catheter related bacteraemia and such culturing of catheter tips should be discouraged.^{8, 9} A semiquantitative culture technique (the "technique of Maki") provides more interpretive results; catheter segments are aseptically submitted to the microbiology laboratory where technicians roll them across the surface of a sheep blood agar plate. After 24–48 hours of incubation, colonies of bacteria or fungi growing on the plate are counted: the presence of >15 colonies per plate suggests a true catheter related infection, while <15 colonies generally represent clinically insignificant catheter colonisation or contamination.¹⁰ Some laboratories will not process a catheter tip sent for culture if a concurrent blood culture has not been submitted within a 24 hour period either before or after the catheter removal, or if a recent (≤24 hours) blood culture is negative.¹¹ In this patient, qualitative culturing of the catheter tip led to an incorrect conclusion that the patient was not responding to antibiotic therapy, and unnecessary exposure to a potentially toxic aminoglycoside.

See end of article for authors' affiliations

Correspondence to:
Dr Tze Shien Lo,
Department of Medicine,
University of North
Dakota, School of
Medicine and Health
Sciences, 1919 Elm Street,
Fargo, ND 58102, USA;
tshienlo@medicine.nodak.
edu

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Using simultaneous selective cultures drawn from central venous catheter and peripheral vein sites, Raad and colleagues demonstrated that the recovery of micro-organisms from catheter site cultures ≥ 120 minutes sooner than from peripheral blood cultures was highly suggestive of catheter related bacteraemia.¹² Thus, it may be possible to detect catheter related infection without initially removing the catheter, although once a diagnosis is made catheter removal is indicated in most instances.

Case 3

An 85 year old diabetic woman was hospitalised for treatment of worsening right foot ulcers. Physical examination of the right foot revealed three discrete ulcers on the great toe, the second toe, and the heel, respectively. All three ulcers were draining yellowish material; the ulcers were swabbed and MRSA, *Enterococcus faecalis*, and corynebacterium species were isolated from one or more of these cultures.

Comment

While swab culturing the surface of an open ulcer can identify wound colonisation that may help determine appropriate isolation precautions (for example, as in the case of MRSA, vancomycin resistant enterococcus, or other multidrug resistant bacteria), it frequently leads to an uninterpretable result that does not accurately reflect the true underlying pathogen.¹³⁻¹⁶ Micro-organisms recovered from the surface of a wound do not reliably predict the causative pathogens to be found deep within underlying soft tissue or bone. Cultures of material obtained from curettage of the ulcer or from deep tissue biopsy will be less contaminated and provide cultural information more useful in guiding antimicrobial therapy.

Case 4

A 75 year old man with multiple sclerosis and an indwelling urinary catheter for many years because of a neurogenic bladder came to the emergency room when he noticed his urine had recently turned darker and had a strong smell. The patient denied fever, chills, dysuria, suprapubic discomfort, nausea, or vomiting and his physical examination was unremarkable. A urinalysis was performed and revealed 10-12 white blood cells/low power field, trace leucocyte esterase, and 1+ bacteria. A diagnosis of urinary tract infection was made and the patient was prescribed oral levofloxacin for 10 days.

Comment

There is no evidence demonstrating that odorous or dark urine is, by itself, diagnostic of urinary tract infection.¹⁷ Furthermore, the presence of pyuria does not necessarily indicate a urinary tract infection. Indwelling urinary catheters are among a number of non-infectious causes of urinary white blood cells including calculi, malignancies, stents or other foreign bodies, interstitial nephritis, and papillary necrosis. In our patient, the unimpressive results of the urinalysis did not indicate a urinary tract infection requiring antimicrobial therapy, although they may have been supplemented with a urine culture. It is important to note, however, that almost all patients with bladder or suprapubic catheters in place for more than two weeks will become colonised with micro-organisms, and asymptomatic bacteriuria without associated pyuria does not require treatment. Studies have shown that administration of systemic antibiotics in such patients, with the catheter still in place, will not eradicate bacteria or yeast in the urine.¹⁸ Also, in the absence of pregnancy, neutropenia, urological procedures, or anatomic abnormalities of the urinary tract such as calculi, strictures, malignancy, and stents or other foreign bodies, antimicrobial treatment is not necessary. Prescribing antibiotics exposes

such patients to potential adverse drug reactions and increased selective pressure leading to the development of antimicrobial resistance.

Case 5

An 87 year old woman had a convulsion at home and was admitted for work-up of new onset seizure disorder. On the day of admission, she spiked a fever to 39°C; meningitis was suspected and a lumbar puncture was performed.

The cerebrospinal fluid was clear and colourless and microscopic examination of the cerebrospinal fluid revealed only a few red blood cells and no white blood cells. Gram stain of the cerebrospinal fluid revealed no organisms and protein and glucose levels were within normal limits. The spinal fluid was also sent for cryptococcal antigen, *Herpes simplex* polymerase chain reaction testing, cerebrospinal fluid Venereal Disease Research Laboratory test, and acid-fast bacilli and fungi smear and culture. As expected, all these tests were subsequently found to be negative.

Comment

It has become the standard practice in the United States to have four test tubes ready for collection of cerebrospinal fluid when performing a spinal tap: tube 1 for cell counts and differential; tube 2 for Gram stain bacterial culture, India ink smear and acid-fast bacilli and fungal smear and cultures; tube 3 for protein, glucose, Venereal Disease Research Laboratory test, cryptococcal antigen, and cytology; and tube 4 for viral and other serologies.¹⁹ However, it can be predicted that if the initial basic tests such as cell counts/differential, protein and glucose, and Gram stain and bacterial culture are within normal limits, the likelihood of a positive result from additional cerebrospinal fluid testing is negligible (exception: frequently in AIDS patients and occasionally in others, there are minimal or no cerebrospinal fluid abnormalities but cryptococci grow in cultures).²⁰ Thus, clinicians should order only basic tests when initially submitting cerebrospinal fluid. An extra tube of cerebrospinal fluid should be submitted to the laboratory that is dated and labelled, "hold for three days". If basic studies are abnormal, then further laboratory testing is warranted and can be performed on this held tube.

DISCUSSION

The above cases illustrate the importance of minimising unnecessary laboratory tests or tests that have no clinical relevance. Cases 2 and 4 clearly demonstrate how such testing may lead to inappropriate antimicrobial treatment that can be expensive and associated with potential adverse effects. In this era of increasing antibiotic resistance, it is crucial to educate medical students, residents, and staff physicians about the deleterious consequences of misusing both antimicrobial agents and laboratory tests.²¹ The use of computerised reminders for ordering physicians is an educational tool that holds promise for decreasing unnecessary laboratory testing.²² Furthermore, microbiology laboratories should develop and implement specific guidelines that allow them to reject inappropriate specimens.

QUESTIONS (TRUE/FALSE; ANSWERS AFTER REFERENCES)

1. Tests for stool enteric pathogens, ova, and parasites should be sent for a patient who developed diarrhoea a week after admission.
2. Intravenous catheter tip should be cultured qualitatively whenever the catheter is removed.
3. Swab culturing the surface of an open ulcer should be discouraged.

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4. If the urine from an asymptomatic patient with indwelling catheter grows *Escherichia coli*, the patient should be treated for urinary tract infection.
 5. If the initial tests for cerebrospinal fluid such as cell count/differential, Gram stain, protein, and glucose are within normal limits, no further tests should be sent.

Authors' affiliations

T S Lo, R A Smego, Department of Medicine, University of North Dakota, School of Medicine and Health Sciences, Fargo, North Dakota, USA

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ANSWERS

1. *False.* The detection rate for bacterial pathogens and for enteric parasites is less than 0.5% for patients who have been hospitalized for >72 hours.
2. *False.* Qualitative intravenous catheter cultures have minimal value as predictors of catheter related bacteremia.
3. *True.* Swab culturing the surface of an open ulcer usually does not accurately reflect the true underlying pathogen.
4. *False.* Clinicians generally need not treat asymptomatic bacteriuria except in pregnant women, patients with neutropenia, those with urinary abnormalities, or before urological procedures.
5. *True.* It can be well predicted that if the initial cerebrospinal fluid tests are normal, the likelihood of a positive result from additional testing is negligible.