RATIONAL TESTING

Investigating sepsis with biomarkers

Anthony S McLean,[1] Benjamin Tang,[1] Stephen J Huang[1 2]

[1]Department of Intensive Care Medicine, University of Sydney, Sydney, NSW, Australia
[2]Nepean Hospital, Sydney, NSW, Australia
Correspondence to: A S McLean Department of Intensive Care Medicine, Nepean Hospital, University of Sydney, Sydney NSW, Australia anthony.mclean@sydney.edu.au

Cite this as: *BMJ* 2015;350:h254
doi: 10.1136/bmj.h254

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College in Qatar; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

thebmj.com

Previous articles in this series

- Investigating asymptomatic invisible haematuria (*BMJ* 2014;349:g6768)
- Neutropenia in primary care (*BMJ* 2014;349:g5340)
- Ordering and interpreting ear swabs in otitis externa (*BMJ* 2014;349:g5259)
- Diagnosis of immediate food allergy (*BMJ* 2014;349:g3695)
- Investigation of suspected urinary tract infection in older people (*BMJ* 2014;349:g4070)

A 65 year old man presents with lethargy, fever, and rigors. On examination his arterial blood pressure is 120/50 mm Hg, he has a mild tachycardia (105 beats/min), and he is febrile (38.7°C), with no other abnormalities. His urine is cloudy and urinary dipstick test shows the presence of leucocytes and nitrate. There is no history of recent travel, urinary symptoms, or drug allergy (including antibiotic sensitivity) and no relevant findings on systems review (such as liver or kidney disease). You promptly establish intravenous access, draw blood for laboratory tests (including blood culture), send a urine sample for microbiology, and administer the first dose of an empirical broad spectrum antibiotic.

These clinical signs and symptoms strongly suggest sepsis. However, in a third of patients with sepsis, the causative pathogen cannot be identified.[1] The lack of confirmatory evidence of infection often makes the diagnosis of sepsis a challenge. This difficulty is reflected by the inclusion of the words "probable infection" in defining sepsis in the Surviving Sepsis Campaign guidelines (box 1).[2]

Box 1 | Definitions and classification of sepsis syndrome[2]

Systemic inflammatory response syndrome
An abnormal increase in two or more of the following parameters:
White cell count (>12×10^9)
Body temperature (>38°C)
Respiratory rate (>20/min)
Heart rate (>90/min)

Sepsis
The presence (probable or documented) of infection and the systemic inflammatory response syndrome (in response to an infectious process)

Severe sepsis
Sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion

Septic shock
Sepsis induced hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities

Box 2 | Non-septic conditions commonly associated with hyperlactataemia[6]

Impaired delivery (hypoxaemia, hypoperfusion, shock)
Excess catecholamine (salbutamol or adrenaline infusion, phaeochromocytoma)
Decreased clearance (hepatic dysfunction, renal failure)
Impaired gluconeogenesis (biguanides, alcohol intoxication)
Imbalance between ATP supply and demand (severe exercise, carbon monoxide poisoning)
Cancer
Metabolic problems (thiamine deficiency, pyruvate carboxylase deficiency)

What is the next investigation?

To gain more evidence to support your diagnosis of sepsis you request laboratory tests including full blood count, lactate, C reactive protein (CRP), and procalcitonin. His white cell count is 12×10^9/L (upper limit of normal 11×10^9/L), CRP is 123.8 nmol/L (reference value <19.05), and procalcitonin is 0.9 ng/L (<0.5 ng/mL). What do these results mean?

Role of white cell count in diagnosis of sepsis

Leucocytosis commonly accompanies infection, yet in sepsis of any severity the white cell count may be within or even below the normal range. Observational studies have found that increased leucocyte count (>12×10^9/L) does not significantly improve the post-test probability (positive likelihood ratio of 1.3-1.7, which is very low).[3] Furthermore, the white cell count can be raised in inflammation with non-infectious causes, making it rarely helpful as a sole diagnostic parameter.

Can CRP help diagnose sepsis?

CRP, used for many years as a marker of inflammation, may be useful in monitoring the patient's course through a chronic illness, but it lacks specificity to diagnose sepsis. It is an acute phase plasma protein synthesised by hepatocytes, so its plasma concentration rises in response to infection or systemic inflammation. CRP was only mildly raised in our patient, adding little diagnostic information to refine the initial diagnosis. Its long half life also means that changes in CRP values may reflect physiological challenges that occurred more than 36 hours earlier,[4] further limiting its use in the acute care setting. A recent meta-analysis showed a low sensitivity and specificity (0.75 and 0.67).[5] Given its limited diagnostic performance, current sepsis guidelines do not recommend CRP as a sepsis biomarker.[2]

What is the role for lactate in sepsis diagnosis?

Hyperlactataemia has many causes (box 2), so lactate has no role in the diagnosis of sepsis. However, lactate can be used as an indicator of tissue hypoxia in patients with sepsis. This has led to some observational studies suggesting that lactate has value as a companion test to monitor the adequacy of fluid resuscitation in resolving tissue hypoxia in sepsis.[7 8] Consequently, current sepsis guidelines recommend reduction of serum lactate by timely fluid resuscitation as a therapeutic endpoint.[2] However, this recommendation was not confirmed by a recent randomised controlled trial.[9] Consequently, the role of lactate monitoring remains controversial and further studies are needed.

THE BOTTOM LINE

- The diagnosis of sepsis is a challenge, and the causative pathogen is not always identified
- Clinical assessment remains the mainstay of diagnosis of sepsis, with tests such as white cell count, C reactive protein, lactate, and procalcitonin being adjunctive
- Biomarkers such as lactate and procalcitonin have only moderate diagnostic performance and are also raised in non-infectious conditions

Box 3 | Non-septic conditions associated with increased procalcitonin[10]

- Trauma
- Surgery
- Burns
- Cardiogenic shock
- Prolonged severe organ perfusion anomalies
- OKT3 antibodies or drugs that stimulate the release of proinflammatory cytokines
- Small cell lung cancer
- Medullary C cell carcinoma of the thyroid

What is the role of procalcitonin in sepsis diagnosis?

Procalcitonin is a 116 amino acid precursor of calcitonin with largely unknown biological function, and its concentration is stable up to three hours after blood is drawn. The surviving sepsis guidelines included procalcitonin as a biomarker for sepsis diagnostic criteria.[2] The test is more expensive but more accurate than CRP testing (as shown by a meta-analysis).[5] However, it is raised in non-infectious conditions as well as in bacterial sepsis (box 3). Normal serum values are below 0.5 ng/mL, and a value of 2.0 ng/mL suggests a significantly increased risk of sepsis, whereas values of 0.5-2.0 ng/mL suggest an intermediate likelihood of sepsis.[2] In a recent meta-analysis, the sensitivity and specificity of procalcitonin to discriminate sepsis from non-infectious causes were 77% (95% confidence interval 0.72 to 0.81) and 79% (0.81 to 0.88), respectively.[11] This indicates a modest diagnostic performance. Our patient has a procalcitonin level of 0.9 ng/mL. Although this is a "positive" result, it falls within the intermediate range, so it is not particularly useful in making the final diagnosis. Procalcitonin has limitations and should always be interpreted carefully in the context of medical history and other clinical information.

Are there any other clinically useful sepsis biomarkers?

Many proposed alternative markers of sepsis (including interleukins (IL-6, IL-8), lipopolysaccharide binding protein, adrenomedullin, endotoxin activity assay, and pentraxin-3) have been found not to be suitable for regular clinical use. Molecular diagnostic techniques (pathogen specific nucleic acid amplification tests and gene expression of the patient's circulating white cells) offer promise of more accurate diagnosis of infection, but have yet to be realised in everyday practice.[12]

Conclusion

Evidence shows that current biomarkers have only moderate diagnostic performance and have a limited role. International sepsis guidelines therefore recommend their use only as an adjunct to clinical assessment, which remains the mainstay of sepsis diagnosis.[3]

Outcome

Gram negative septicaemia (*Escherichia coli*), mostly likely from urinary tract infection. He responded well to antibiotic and fluid therapy, and a follow-up urological consultation excluded predisposing factors for urinary tract infection.

ANSWERS TO ENDGAMES, p 35

For long answers go to the Education channel on thebmj.com

ANATOMY QUIZ

Neonatal chest and abdominal radiograph: identification of tubes and lines

A: Endotracheal tube with its tip lying at the level of the thoracic inlet (clavicles)

B: Umbilical venous catheter positioned at the junction between the right atrium and the superior vena cava

C: Nasogastric tube with its tip lying in the gastric fundus

D: Umbilical arterial catheter positioned with the distal end in the thoracic aorta at the level of the T7 vertebral body. Positioning between T6 and T10 is acceptable

E: Proximal portion of the umbilical arterial catheter in the right internal iliac artery. This allows for differentiation from the umbilical venous catheter, particularly in unclear and rotated radiographs

STATISTICAL QUESTION

Bias in observational study designs: case-control studies

Answers *b*, *c*, *d*, *e*, *f*, and *g* are true, whereas *a* is false.

PICTURE QUIZ An elderly woman with chest pain and constipation

1 The radiograph shows a large round shadow behind the heart with an air-fluid level. The right lung appears displaced and compressed. Differential diagnoses include cardiomegaly, huge pneumomediastinum and oesophageal perforation, epiphrenic oesophageal diverticulum, large pulmonary hydatid cyst, huge diaphragmatic hernia, delayed presentation of a large traumatic rupture of the diaphragm, paralysis of the left hemidiaphragm, mediastinal abscess, pulmonary tuberculosis, and gastrointestinal perforation with air migration above the diaphragm.

2 The easiest way is to look at previous imaging if available. A definitive diagnosis is needed before making treatment decisions. Computed tomography of the chest and abdomen with intravenous contrast medium is most useful for confirming the diagnosis of a hiatus hernia and for differential diagnosis. The introduction of multi-slice computed tomography with sagittal, coronal, and three dimensional reformatted images has greatly increased sensitivity. Use of both intravenous and oral contrast improves diagnostic accuracy, especially in the case of cephalad migration of the gastro-oesophageal junction or gastric fundus through the hiatus, or to rule out perforation and extraluminal leaks.

3 Paraoesophageal hernias (PEHs) may evolve into potentially life threatening complications, such as incarceration and obstruction, and may acutely evolve into strangulation with ischaemia, gangrene, and perforation of the stomach, small bowel, or colonic loops (if type IV PEHs).

4 Fluid resuscitation, electrolyte replacement, oxygen administration, and nasogastric decompression.

5 Emergency surgery is mandatory for complicated PEHs, whereas symptomatic uncomplicated ones should be considered for elective repair if the operative risks are acceptable. Routine elective repair for completely asymptomatic hiatus hernias may not be indicated.

6 Symptoms of acid reflux should initially be managed by behavioural changes and lifestyle measures and then the addition of drugs. When conservative management of a large PEH is thought to be the most suitable option, long term treatment should be aimed at preventing the potentially life threatening complications.

CPD/CME

Link to this article online for CPD/CME credits

10-MINUTE CONSULTATION

Pain at the base of the thumb

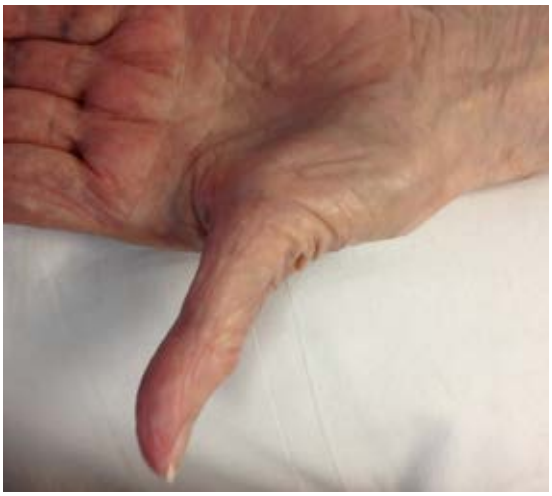
David Robin Dickson,[1] Claire C L Dickson,[2] Robert Farnell[1]

[1]Hand Unit, Leeds General Infirmary, Leeds LS1 3EX, UK
[2]Wetherby Surgery, Wetherby, UK
Correspondence to: D R Dickson
davidrdickson@hotmail.com

Cite this as: *BMJ* 2015;350:h182
doi: 10.1136/bmj.h182

This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

A woman in her 60s presents with progressive pain at the base of her thumb, which is exacerbated by writing, lifting pans, and turning door handles.



Typical thumb with basal osteoarthritis

What you should cover

Osteoarthritis at the base of the thumb (the carpometacarpal joint) is common, usually idiopathic, and mostly affects postmenopausal women. The joint is subjected to considerable forces, particularly during pinching and gripping, making it prone to osteoarthritis.

Take a focused pain history:

- Site: typically spread over a broad area around the base of thumb.
- Onset: pain has usually progressed over a long period.
- Exacerbating factors: activities requiring thumb pinch with twisting such as opening jars and doors, turning keys, and lifting pans.
- Severity and effect on activities of daily living: ascertain the impact on the patient's function, quality of life, occupation, mood, relationships, and leisure activities.[1]

Alternative or concomitant diagnoses to consider

- Carpal tunnel syndrome (usually idiopathic but can be associated with basal thumb arthritis owing to compression of the median nerve by bony spurs and synovitis in the carpal tunnel): numbness in the hand, particularly at night, and in the thumb, index, middle, or radial half of the ring finger (median nerve distribution).
- Trigger thumb (differential diagnosis): patients often present with pain and a palpable nodule over the palmar aspect of the metacarpophalangeal joint, with clicking on flexing the thumb.
- De Quervain's tenosynovitis (a differential diagnosis, with pain from irritation of two thumb tendons where they run through a fibrous sheath): pain is typically over the radial styloid rather than the base of the thumb.
- Other diagnoses: atypical features such as a history of trauma may suggest a fracture; prolonged morning stiffness is typical of an inflammatory arthropathy; rapidly worsening symptoms with severe pain and swelling may indicate cancer; and a hot swollen joint points towards a septic joint or gout.

THE BOTTOM LINE

- Encourage patients to self manage the condition with simple analgesics, joint protection, and activity modification
- Refer patients with a history or recent trauma or a red hot swollen joint for an urgent orthopaedic opinion

What you should do

Examination

- Look (see figure):
  - The thumb is usually held in an adducted position. There may be compensatory hyperextension of the metacarpophalangeal joint
  - The thenar eminence may be wasted, either from disuse or carpal tunnel syndrome.
- Feel: the carpometacarpal joint should be tender to palpate.
- Movement: movement of the carpometacarpal joint and the "grind test" should reproduce pain. This test loads the base of the thumb by applying pressure towards the wrist joint and twisting.
- Assess for other diagnoses—for example:
  - Carpal tunnel syndrome: altered sensation to light touch in the median nerve distribution and reproduction of symptoms by tapping over the nerve (Tinel's test) or direct pressure (Durkan's test). The nerve lies in the proximal palm between the thenar and hypothenar eminences in line with the webspace between the middle and ring fingers.
  - Trigger thumb: tenderness and a palpable nodule over the palmar metacarpophalangeal joint, clicking on thumb flexion
  - De Quervain's tenosynovitis: tenderness over the radial styloid.

Investigations

- Osteoarthritis can be diagnosed without investigations in patients aged over 45 years who have activity related joint pain and no more than 30 minutes of morning stiffness.[1]
- Radiological imaging may be helpful if the diagnosis is in doubt or other conditions, such as a fracture, are suspected.

thebmj.com
Previous articles in this series
- The drooling child (*BMJ* 2014;349:h38)
- Breast lumps (*BMJ* 2014;349:g5275)
- Eyelid lumps and lesions (*BMJ* 2014;348:g3029)
- Eustachian tube dysfunction in adults (*BMJ* 2014;348:g1647)
- Diagnosis and management of chronic heart failure (*BMJ* 2014;348:g1429)

- Similarly, investigations for carpal tunnel syndrome, De Quervain's tenosynovitis, or trigger thumb are not needed routinely.

Treatment options

Encourage and support self management by patients.[1] Explain to the patient that this is a common condition of wear and tear of the thumb joint that can usually be treated with painkillers and simple adjustments to normal activities, although some people will require more specialist treatment from hand surgeons. Patient information sheets on an array of hand conditions can be found and downloaded for free from the British Society for Surgery of the Hand website (www.bssh.ac.uk). Many respond to non-operative measures:

- Approaches to joint protection[2]:
  - Avoid repetitive thumb movements
  - Avoid prolonged gripping
  - Avoid heavy objects
  - Use as large a grip as possible.
  - Use assistive devices for specific activity problems.[1] These include electric potato peelers and devices to remove jar lids. These reduce the repetitive high loads to the thumb joint and thus reduce the pain caused by these activities.
  - Use splints to reduce the load and ease pain.
  - A trained hand therapist may be beneficial both in patient education and exercises.
- Analgesia[1]:
  - Paracetamol and topical non-steroidal anti-inflammatory drugs (NSAIDs) are first line analgesics
  - When paracetamol and topical NSAIDs prove ineffective, consider oral NSAIDs. Because of the risk of side effects, these drugs should be used at the lowest effective dose for the shortest possible time
  - Use topical capsaicin as an adjunct
- Steroid injections provide at least short term benefit in 76% of patients,[3] so consider as an adjunct to non-operative management in patients with moderate to severe pain.[1] Referral to a hand surgeon may be needed for this.

A combination of hand therapy, splints, and simple analgesics removed 70% of patients from a waiting list for surgery.[4]

Refer patients for surgery only after they have been offered and remain refractory to non-surgical treatment.[1] The mainstay of operative treatment is excision of the trapezium, although joint fusion is often preferred in young labourers.

An article published in *The BMJ* in 2011 provides further information.[5]

ALL THINGS CONSIDERED

A surgeon's hands

I remember when I was a young and budding doctor; people would look admiringly at my hands, smile knowingly, and say "you have the hands of a surgeon." This was a wonderful compliment; it generally meant you had elegant hands, long nimble fingers, and soft, unblemished skin. They were not heavy labourer's hands—surgeon's hands were for delicate work, they were for making art . . . or so I thought.

Yesterday, five years later, after I had finished operating for the day, I felt a twinge on the side of my right thumb. I removed my surgical gloves and inspected this new source of physical aggravation. Lo and behold, there it was. A callus, on the inner side of my thumb, exactly where my needle holders sit, and exactly where they have sat for the past five years. I was horrified. I took a closer look at my hands, and I was shocked by what I saw: the skin was dry and flaky, the cuticles were red and inflamed, even my nails had lost their lustre. My once beautiful surgeon's hands had started to look more like a bricklayer's.

I rushed to a computer to find out how this problem could be remedied. I read up on pumice stones, moisturisers, and callus plasters. Then I thought about what I had put my hands through over the past five years. Operating on most weekdays with an average of four patients a day: that's roughly 1040 scrubs a year or 5200 in five years. That's not even counting all the alcohol rubs and hand washing outside of operating. Reflecting on this, I was actually

quite impressed that my hands had not dissolved into a waxy mess.

I sighed deeply and resigned myself to this fate: a knobbly thumb and sandpaper palms. They certainly don't tell you that in medical school.

Every cloud has a silver lining, so although my hands may look a bit worse for wear, these calluses show how hard I've worked. Surgeons may be artists but they're also manual labourers, and I will wear the signs of my labour with pride.

Mai Rostom specialist trainee year 3 plastic surgery, Aberdeen Royal Infirmary, Foresterhill Road, Aberdeen AB25 2ZN, UK
motsar@gmail.com

Cite this as: *BMJ* 2014;349:g1892