Accuracy of negative dipstick urine analysis in ruling out urinary tract infection in adults

Report by Nick Ohly, Senior House Officer

Checked by Stewart Teece, Clinical Research Fellow

Abstract
A short cut review was carried out to establish whether negative dipstick urine analysis is sensitive enough to rule out urinary tract infection (UTI) in adults with urinary symptoms. Altogether 75 papers were found using the reported search, of which two presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Three part question
In [adults with symptoms of a urinary tract infection] does [negative dipstick urine analysis] rule out a [UTI]?

Search strategy
Medline 1966–04/03 using the OVID interface. [(exp Urinalysis OR exp Indicators and Reagents OR exp Reagent Strips OR stix.af OR urinalysis.af) AND (exp Urinary Tract Infections OR (urin$ adj5 infect$).af OR UTI.af OR exp Bacteriuria OR bacteriur$.af) AND (dysuria.af OR frequency.af OR haematuria.af OR hematuria.af OR stranguria.af OR urgency.af)]] LIMIT to human AND English language AND all adult <19 plus years>

Search outcome
Altogether 75 papers were found. Of these, two were identified as answering the three part question. One of these was a meta-analysis containing nine papers not identified by the original search as they did not consider dipstick urine analysis (table 1).

Comment(s)
The meta-analysis shows that the prevalence of UTI in patients who present with symptoms of UTI is around 50%. The probability of UTI is even higher (around 90%) with a convincing history. Dipstick urine analysis is a quick and inexpensive test however sensitivity (and therefore negative
predictive value) were found to be as low as 75%. Some studies included in the meta-analysis were of low quality and further studies need to be done in this field.

**CLINICAL BOTTOM LINE**

Dipstick urine analysis is of insufficient sensitivity to be used to rule out UTI in patients with one or more symptoms.


**Lammers RL. Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. Ann Emerg Med 2001; 38:5:505–12.**

**Bent S et al, 2002, USA**

**Venous blood gas in adult patients with diabetic ketoacidosis**

Report by Ziauddin Hassan, Devasena M Subramonyam, Registrars

Checked by Shobhan Thakore, Specialist Registrar

**Abstract**

A short cut review was carried out to establish whether venous blood gas measurement accurately demonstrates the degree of acidosis in patients with diabetic ketoacidosis. A total of 27 papers were found using the reported search, of which two presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

**Clinical scenario**

A 22 year old insulin dependent diabetic presents to our emergency department with a raised blood sugar and urine dipstick showing +++ of ketones. You suspect diabetic ketoacidosis and would like the know the degree of his acidosis, but the patient refuses arterial blood gas sampling due to a previous bad experience. You wonder whether venous blood would accurately show the degree of his metabolic acidosis.

**Three part question**

In [an adult patient with diabetic ketoacidosis] do [venous blood gases] accurately demonstrate [the degree of acidosis]?

**Search strategy**

Medline 1966–04/03 using the OVID interface. [(venous blood.mp OR exp blood specimen collection OR exp blood gas analysis) AND (exp diabetic ketoacidosis OR diabetic ketoacidosis.mp OR exp diabetic coma) AND (exp acidosis OR acidosis.mp OR exp hydrogen-ion concentration)] AND LIMIT to human AND English language.

**Search outcome**

Altogether 27 papers were found of which only two are relevant and of sufficient quality for inclusion (table 2).

**Comment(s)**

There are only a limited number of studies on this subject and these have involved small numbers of patients. Further studies with large series of patients are necessary.

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lammers RL et al, 2001, USA</td>
<td>331 adult women presenting to ED or intermediate care centre with more than one symptom of a UTI. Positive dipstick defined as detectable nitrite or leucocyte esterase. Prevalence 45.9%. Gold standard urine culture</td>
<td>Prospective observational study</td>
<td>Sensitivity</td>
<td>92%</td>
<td>Only women</td>
</tr>
<tr>
<td>NPV</td>
<td>83%</td>
<td>No sample size analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bent S et al, 2002, USA</td>
<td>Adult women from nine original studies involving patients with symptoms of an UTI presenting to outpatient clinics. Total number of patients 2331</td>
<td>Meta-analysis</td>
<td>Sensitivity</td>
<td>75%</td>
<td>Some studies only included women</td>
</tr>
<tr>
<td>Likelihood of UTI in presence of dysuria and frequency without vaginal discharge is high</td>
<td>&gt;90%</td>
<td>Only able to use data from some studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in cut off level for positive urine culture (range 100–100,000 CFU/ml)</td>
<td>Prevalence 48%</td>
<td>Some studies of poor quality</td>
<td></td>
<td></td>
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</tr>
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<td>Some studies of poor quality</td>
<td></td>
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<td></td>
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</tbody>
</table>

Table 1

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandenburg MA and Dire DJ, 1998, USA</td>
<td>38 patients with DKA presented to emergency department Venous v arterial pH</td>
<td>Prospective</td>
<td>Mean difference in pH</td>
<td>−0.03</td>
<td>Small numbers</td>
</tr>
<tr>
<td>No control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gokel Y et al, 2000, Turkey</td>
<td>152 samples, from 100 uraemic patients, 21 patients with DKA and 31 healthy volunteers Venous v arterial pH</td>
<td>Prospective</td>
<td>Mean difference in pH</td>
<td>−0.05</td>
<td>Small numbers</td>
</tr>
<tr>
<td>Unequal number of patients in each group</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Antithrombotic treatment of below knee deep venous thrombosis

Report by Kerstin Hogg, Clinical Research Fellow
Checked by Andrew Ashton, Senior Clinical Fellow

Abstract
A short cut review was carried out to establish whether oral anticoagulation is necessary to prevent pulmonary embolisation in patients with below knee deep venous thrombosis. A total of 425 papers were found using the reported search, of which 11 presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
A 50 year old man attends the emergency department with a plethoric, swollen left calf. Ultrasound examination reveals a posterior tibial vein thrombosis. You wonder what the risk of a pulmonary embolus is and whether he should be anticoagulated.

Three part question
In a patient with a below knee venous thrombosis, is oral anticoagulation necessary to prevent a pulmonary embolus?

Search strategy
Medline 1966–04/03 using the OVID interface. [{(DVT.mp OR exp venous thrombosis OR “deep vein thrombosis”).mp AND (“below knee”-mp OR calf.mp OR popliteal.mp OR exp popliteal vein OR fibular.mp OR peroneal.mp OR posterior tibial.mp) OR “deep calf venous thrombosis”.mp OR “calf vein thrombi”.mp)AND (therapy.mp OR exp therapeutics OR treatment.mp OR exp heparin OR exp heparin, low-molecular-weight OR heparin.mp OR exp warfarin OR warfarin.mp OR exp coumarins OR coumarin.mp)] LIMIT to human and English.

Search outcome
Altogether 425 papers were found, only 10 original papers and one literature review addressed the question. Some studies included other patients with PE or thigh DVTs—only the patients with calf thrombosis are described (table 3).

Comment(s)
All of these studies could have been more thorough in their diagnostic criteria and/or follow up. However, despite the flaws it is clear that pulmonary emboli do result from below knee thrombi.

CLINICAL BOTTOM LINE
All patients with calf thrombosis should receive oral anticoagulation.

Buccal nitrates in left ventricular failure

Report by Dhurga Gnanasegaram, Senior Clinical Fellow
Checked by Jon Argall, Senior Clinical Fellow

Abstract
A short cut review was carried out to establish whether buccal and intravenous nitrates are equally effective at preload reduction in patients with left ventricular failure. Seven papers were found using the reported search, of which one presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of this best paper is tabulated. A clinical bottom line is stated.

Clinical scenario
You are called to see a 60 year old man who has been increasingly breathless for a week. Examination reveals him to be mildly dyspnoeic at rest with a raised JVP and bibasal creps. There is evidence of ischaemia on his ECG. The chest radiograph shows upper lobe diversion and Kerley B lines. You wonder whether buccal succard would be an appropriate alternative to a GTN infusion.

Three part question
In a patient with left ventricular failure are [buccal nitrates equivalent to a nitrate infusion] for [preload reduction]?

Search strategy
Medline 1966–04/03 using the OVID interface. [{(exp nitrates OR nitrate.mp OR exp nitroglycerin OR nitroglycerin.mp OR exp vasodilator agents OR GTN.mp OR glyceryl trinitrate.mp OR exp isosorbide dinitrate OR isosel.mp OR Sustcard.mp) AND (buccal.mp OR exp mouth mucosa OR exp administration, buccal) AND (exp injections, intravenous OR intravenous.mp OR IVmp)) AND (exp heart failure, congestive OR heart failure.mp OR LVF.mp OR exp left ventricular failure.mp OR exp congestive cardiac failure.mp OR exp ventricular dysfunction, left OR exp ventricular dysfunction OR exp pulmonary oedema)] LIMIT to human AND English language.

Search outcome
Altogether seven papers were found, of which five were reviews of nitrates rather than comparative studies. The two...
Table 3

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
</table>
| Philbrick JT et al, 1988, USA | All studies of sufficient quality identified from literature search over years 1944 to 1986 | Literature review | Incidence PE | 6 of 163 patients receiving no anticoagulation (Strength of evidence weak). 9 of 208 patients receiving a range of anticoagulation (0 of 32 in only study with strong evidence, all other studies, weak) | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| Giachino A, 1988, Canada | 152 patients who died in Ottawa hospitals over a five year period, with PE listed as the cause of death. | Retrospective study | Source of thrombosis in fatal pulmonary emboli. | 82 had no postmortem examination. 23 postmortem examinations confirmed PE as the cause of death, and identified the source of the embolus. 3 of 23 postmortem examinations revealed the calf veins as the source of the thrombus. 15% propagated to involve the popliteal or larger veins. A further 17% propagated within the calf veins. | Publication bias—all of these patients may have been included in the study by Pellegrini V et al, 1993. 
No information regarding the length of follow up, or the effect of varying therapies Two of the PEs were diagnosed on the strength of sudden collapse and cardiac arrest—no postmortem examination carried out |
| Lohr J et al, 1991, USA | 75 patients with ultrasound diagnosed calf thrombosis. Treatment left to physician’s discretion. | Prospective study with follow up serial ultrasound examination. | Thrombus propagation | 4 of 13 untreated calf DVT patients were diagnosed with PE. 0 of 1 treated calf DVT patient and none of the superficial/muscular calf thrombosis developed PE | No information regarding exact criteria for diagnosing PE from VQ scan alone—probable over-estimation of incidence 
VQ scans were performed at 10 and 60 days, however no information regarding the breakdown of subsequent PEs between proximal and isolated calf DVT groups |
| Pellegrini V et al, 1993, USA | 25 patient with isolated calf DVT and 12 patients with superficial or muscular calf thrombosis, diagnosed by venography on postoperative screening of total hip arthroplasty patients. Only 12 calf DVTs and one superficial/muscular calf thrombosis were anticoagulated | Prospective study following up at 6, 12, 24 and 52 weeks | Incidence of PE | 53 of 139 thrombi propagated 
4 of 85 thrombi propagated | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| Nielsen HK et al, 1994, Denmark | 15 patients with venographically diagnosed calf DVTs. | Prospective study | VQ scan result at presentation | 5 of 15 had positive VQ scans | No information regarding exact criteria for diagnosing PE from VQ scan alone—probable over-estimation of incidence 
VQ scans were performed at 10 and 60 days, however no information regarding the breakdown of subsequent PEs between proximal and isolated calf DVT groups |
| Lohr JM et al, 1995, USA | 192 patients with ultrasound diagnosed below knee DVTs, Treatment left to physicians discretion | Prospective study with serial ultrasound for four weeks | Thrombus propagation | 53 of 139 thrombi propagated | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| O’Shaughnessy AM et al, 1997, Ireland | 50 patients with ultrasound diagnosed DVTs, 43 treated with anticoagulation and 7 without | Retrospective study | “Outcome” of isolated calf thrombosis | 3 patients presented initially with a “positive” VQ scan. One fatal PE within the first month. | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| Gottlieb RH et al, 1999, USA | 238 patients with ultrasound diagnosed below knee DVTs | Prospective study | Incidence of diagnosed PEs | 2 of 56 patients not receiving anticoagulant therapy had PE | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| Pindeo L et al, 2001, France | 105 patients with calf DVTs treated for six weeks with warfarin, 92 patients with calf DVTs treated for 12 weeks with warfarin | Prospective study | Incidence of PE | 1 of 197 (patient from 12 week warfarin group) had documented PE | No controlling of postmortem procedures—unclear if all legs veins thoroughly examined. 
Only 23 of 152 considered to die from PE actually had a PM and had the source of the embolus confirmed. |
| Schwarz T et al, 2001, Germany | 84 patients with isolated calf muscle thrombosis. 52 received LMWH for 10 days, 32 received no anticoagulation | Prospective cohort with serial ultrasound examinations | Progression to deep veins of calf PE | Study discontinued as 8 of 32 non-anticoagulated patients progressed to deep vein thrombosis, compared with 0 of 52 anticoagulated patients | Gold standard venography not used 
VQ scan results interpreted in isolation |
| Sharpe RP et al, 2002, USA | 85 trauma patients with below knee DVTs | Prospective cohort | Thrombus propagation PE | 4 of 155 thrombi propagated proximally. 1 of 85 did not propagate but had a PE | Gold standard investigations not applied for DVT or PE |
remaining publications consisted of a summary report and full article relating to the same trial. The results of this trial are shown in table 4.

Comment(s)
There is very limited evidence available to allow direct comparison between intravenous and buccal routes.

CLA INICAL BOTTOM LINE
Buccal nitrates produce an immediate reduction in preload (comparable with intravenous GTN).


Oral methionine compared with intravenous n-acetyl cysteine for paracetamol overdose

Report by Walid Alsalam, Specialist Registrar
Checked by Mohamed Fadel, Specialist Registrar

Abstract
A short cut review was carried out to establish whether methionine was better than n-acetyl cysteine at reducing the severity of liver damage after paracetamol overdose. Thirty nine papers were found using the reported search, of which two presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
A 19 year old woman brought to the emergency department six hours after paracetamol overdose. She is fully conscious and admits ingestion of 32 tablets of paracetamol. She is complaining of abdominal discomfort but no nausea or vomiting. Her examination is unremarkable. You arranged blood investigations. Intravenous access and n-acetyl cysteine infusion started as per protocol. You wonder whether oral methionine would have been as effective as n-acetyl cysteine in her treatment.

Three part question
In a [patient with paracetamol overdose within eight hours] is [methionine as good as or better than n-acetyl cysteine] at [reducing liver damage]?

Search strategy

Search outcome
Altogether 39 papers were found, of which two were relevant (table 5).

Comment(s)
There have been no randomised controlled trials and only two prospective observational studies comparing these two drugs. However, patients in these two studies had the antidote within eight hours.

<p>| Table 4 |</p>
<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verma SP et al, 1989, UK</td>
<td>36 male patients with acute LVF secondary to recent MI (&lt;10 hours in CCU)</td>
<td>PRCT</td>
<td>Left heart filling pressures</td>
<td>All three groups reduced</td>
<td>Only 36 patients</td>
</tr>
<tr>
<td></td>
<td>IV v buccal v transdermal GTN</td>
<td>Cardiac output</td>
<td>No reduction in any group</td>
<td>3 patients had BP falls in buccal group but with no clinical deterioration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average doses over 90 min: IV 12.9 mg, buccal 5 mg, dermal 20 mg</td>
<td>BP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| Table 5 |</p>
<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vale JA, 1981, UK</td>
<td>158 patients with paracetamol overdose. Mean age: 26 y: 1:2 M: F ratio High risk patients defined as paracetamol level: &gt;300 mg/l at 4 h.</td>
<td>Prospective observational</td>
<td>Liver damage:</td>
<td>NRD</td>
<td>No randomisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methionine within 10 h (n=96)</td>
<td>7%</td>
<td>Small study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV n-acetyl cysteine within 10 h (n=62)</td>
<td>2%</td>
<td>2 of 7 vomited the first dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In high risk patients methionine within 10 h (n=43)</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In high risk patients IV n-acetyl cysteine within 10 h (n=33)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Prescott LF, 1981, UK</td>
<td>104 patients with paracetamol overdose. Mean age 33 y: 1:1.5 M: F ratio High risk patients defined as paracetamol level: &gt;300 mg/l at 4 h.</td>
<td>Prospective observational</td>
<td>Liver damage:</td>
<td>NRD</td>
<td>No randomisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methionine. Within 10 h, (n=42) 57% of them were high risk</td>
<td>7%</td>
<td>Small study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV n-acetyl cysteine within 10 h (n=62)</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33 of 62 (53%) of them were high risk</td>
<td></td>
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</tbody>
</table>
Clinical probability scoring and pulmonary embolism

Report by Ged Brown, Specialist Registrar
Checked by Kerstin Hogg, Clinical Research Fellow

Abstract
A short cut review was carried out to establish the diagnostic utility of clinical probability scoring in stratifying the risk of pulmonary embolus. A total of 938 papers were found using the reported search, of which three presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
A 30 year old man presents to the department with a spontaneous onset of atraumatic pleuritic chest pain. He has no previous medical history and has no shortness of breath or haemodynamic compromise. You wonder whether his clinical features and risk factors can help to safely exclude a pulmonary embolus.

Three part question
In [a patient presenting with features suggestive of pulmonary embolus] what is [the diagnostic utility of clinical probability scoring] in [stratifying risk of pulmonary embolus]?

Search strategy
Medline 1966–04/03 using the OVID interface. (exp Pulmonary Embolism OR esp Thromboembolism OR PE.mp OR pulmonary infarct8.mp OR Pulmonary Embol8.mp) AND (exp Risk Assessment OR risk assessment.mp OR risk stratification.mp OR probability.mp) LIMIT to human AND English language.

Table 6

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells PS et al, 2000, Canada</td>
<td>964 (derivation) and 247 (validation) patients referred for V/Q scan from earlier cohort</td>
<td>Retrospective clinical decision rule study</td>
<td>% of patients with PE in low risk</td>
<td>7.8% (5.9–10.1) in derivation set, 5.1% (2.3–9.4) in validation set</td>
<td>Use of previous cohort of patients includes inpatients</td>
</tr>
<tr>
<td>Wicki J et al, 2001, Switzerland</td>
<td>1090 emergency ward patients with suspected PE</td>
<td>Prospective clinical decision rule study</td>
<td>Pre-test probability of PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decision rule developed which divides patients into low medium and high risk groups</td>
<td></td>
<td>Low</td>
<td>10%</td>
<td>Reference standard included nondiagnostic scan</td>
</tr>
<tr>
<td></td>
<td>Decision rule developed which divides patients into high and low risk groups</td>
<td></td>
<td>Medium</td>
<td>38%</td>
<td>No validation study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Kline JA et al, USA, 2002</td>
<td>Convenience sample 934 patients presenting to 7 EDs, who underwent pulmonary vascular imaging for PE</td>
<td>Prospective clinical decision rule study</td>
<td>Pretest probability of PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decision rule developed which divides patients into high and low risk groups</td>
<td></td>
<td>Low</td>
<td>13.3% (10.9–15.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>42.1% (35.3–49.6)</td>
<td>The authors suggest that the decision rule would determine a low risk group suitable for application of a d-dimer test—this has yet to be validated.</td>
</tr>
</tbody>
</table>

Search outcome
Altogether 938 papers were found of which 935 papers were irrelevant to the question, of insufficient quality or did not report a mathematically derived scoring systems. The remaining three are included in table 6.

NB The clinical scoring systems have not been represented in the table. Please refer to the individual papers for these details.

Comments
There is evidence to suggest a variety of clinical models can be used to stratify patients into different levels of risk for PE. It is possible that these may be combined with other tests to give an acceptably low post-test probability of PE.

Clinical Bottom Line
Intravenous acetylcysteine (parvolex) is more effective than methionine in preventing liver damage in patients after paracetamol overdose.


Accuracy of combining clinical probability score and simpliRED d-dimer for diagnosis of pulmonary embolism

Report by Russell Boyd, Consultant
Checked by Kerstin Hogg, Clinical Research Fellow

Abstract
A short cut review was carried out to establish whether bedside clinical examination and simpliRED d-dimer
sufficiently sensitive to rule out pulmonary embolus. A total of 272 papers were found using the reported search, of which five presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
A 34 year old woman presents with a two day history of pleuritic chest pain. There are no abnormal physical signs and her only risk factor is that she is taking oral contraceptives long term. You wonder if a combination of clinical examination and the available d-dimer test (SimpliRED) would be suitable to rule out pulmonary embolism.

Three part question
In [suspected PE] is [bedside clinical examination and simpliRED d-dimer] sufficiently sensitive at [ruling out PE]?

Search strategy
Medline 1966–04/03 using the OVID interface. [D-dimer.mp OR simplified.mp OR whole blood.mp] AND [exp thromboembolism OR exp pulmonary embolism OR PE.mp OR pulmonary embolis.mp OR pulmonary infarc5.mp] AND [exp"sensitivity and specificity".mp OR sensitivity.tw OR di.xx OR du.fs OR specificity.tw] LIMIT to human AND English.

Search outcome
Altogether 272 papers were identified of which five were relevant and of sufficient quality. These are shown in table 7.

Comment(s)
Use of a bedside clinical decision rule for PE probability with the additional use of latex agglutination d-dimer testing results in high levels of sensitivity and high negative predictive values in the low PE risk groups. It is this group of patients that makes up the bulk of patients with a putative diagnosis of PE. However, latex agglutination d-dimers do not perform well in high or even moderate risk groups.

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (levels of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsberg JS et al, 1998, Canada</td>
<td>1250 consecutive referred patients to teaching hospital thromboembolic clinic with putative diagnosis of PE (73 lost to follow up)</td>
<td>Cohort</td>
<td>Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with -ve SimpliRED d-dimer</td>
<td>Negative predictive value of 99%</td>
<td>Exclusion criteria “lost” 484 of original 1881 patients screened then further 147 excluded because of non-consent</td>
</tr>
<tr>
<td>Wells PS et al, 2000, Canada</td>
<td>1211 patients with presumptive diagnosis of PE broken into derivation and validation set</td>
<td>Diagnostic test</td>
<td>Sensitivity of clinical decision rule with addition of SimpliRED latex agglutination test E</td>
<td>87.8%–88.3% (validation-derivation)</td>
<td>Actual methodology not fully demonstrated, for example, gold standard definition predictive values and likelihood ratios not given</td>
</tr>
<tr>
<td>Farrell S, 2000, USA</td>
<td>198 patients presenting to US ED with suspected thromboembolic disease</td>
<td>Diagnostic test</td>
<td>Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with -ve SimpliRED d-dimer</td>
<td>Negative predictive value 97%</td>
<td>Estimation of clinical probability was with implicit not explicit methods</td>
</tr>
<tr>
<td>MacGillavry MR, 2001, Netherlands</td>
<td>404 adults, both in and outpatients in teaching hospitals with putative diagnosis of thromboembolic disease</td>
<td>Diagnostic test</td>
<td>Sensitivity and specificity of using a clinical probability and SimpliRED d-dimer test</td>
<td>Sensitivity 98%, Specificity 11%</td>
<td>Over 50% exclusion rate for entry into study. Implicit methods only for determining clinical probability</td>
</tr>
<tr>
<td>Wells P, 2001, Canada</td>
<td>946 adult patients referred for assessment of PE</td>
<td>Cohort</td>
<td>Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with -ve SimpliRED d-dimer</td>
<td>Negative predictive value 99.5%</td>
<td>Investigation protocol violations occurred in nearly 10% of the patients</td>
</tr>
</tbody>
</table>

| Table 7 |

**IL d-dimer test in the diagnosis of pulmonary embolism**

**Report by Kerstin Hogg, Clinical Research Fellow**

**Checked by Russell Boyd, Consultant**

**Abstract**
A short cut review was carried out to establish whether a negative IL d-dimer test alone could be used to rule out a diagnosis of pulmonary embolus. Six papers were found using the reported search, of which four presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.
Clinical scenario
A 30 year old woman presents to the emergency department with distressing, left sided pleuritic chest pain. She may have had a pulmonary embolism and you request a D-dimer test. You know the laboratory in your hospital uses the IL D-dimer test. Of note, there is almost no research looking relevant. One further paper was found from hand searching where between 90% and 100%. It is worth noting that all of these studies used a comparatively low cut off level and it is worth being aware what the cut off level is in your hospital laboratory.

Table 8

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legani C et al, Italy 1999</td>
<td>105 consecutive outpatients ?DVT</td>
<td>Prospective cohort</td>
<td>ROC curve to define max sensitivity of IL test</td>
<td>230 ng/ml cut off sensitivity 100% specificity 77.2%</td>
<td>Patients ?DVT not PE High prevalence DVT. Would not reflect an average emergency department population</td>
</tr>
<tr>
<td>van der Graaf F, 2000</td>
<td>99 ?DVT outpatients. Comparison of 13 different D-dimer tests</td>
<td>Prospective cohort</td>
<td>IL test Sensitivity specificity</td>
<td>90% 78%</td>
<td>Patients ?DVT not PE High prevalence of DVT</td>
</tr>
<tr>
<td>Villa P et al, Spain 2000</td>
<td>86 patients with a moderate or high clinical suspicion DVT</td>
<td>Prospective cohort</td>
<td>Sensitivity Specificity IliS test using 255 ng/ml cut off</td>
<td>98.4% 33.3%</td>
<td>Patients suspected of having DVT not PE Cohort had high prevalence DVT Venography not used</td>
</tr>
<tr>
<td>Harper P et al, New Zealand 2001</td>
<td>235 patients presenting to emergency department with ?DVT</td>
<td>Prospective cohort</td>
<td>Sensitivity IL test (250 ng/ml cut off) and SimpliRED Specificity IL test and SimpliRED</td>
<td>94.1% 66% 51.5% 75.6%</td>
<td>All patients presented as ?DVT not PE The gold standard venogram not used in diagnosis DVT All patients underwent ultrasound (USS), but not all underwent more than one. Probable under-estimation of DVT prevalence Patients were simply advised to return to the department if symptoms did not settle</td>
</tr>
<tr>
<td>Kovacs MJ et al, Canada 2001</td>
<td>All patients with suspected DVT (468 patients) or PE (525 patients), presenting to four hospitals</td>
<td>Prospective cohort</td>
<td>Sensitivity of SimpliRED, IL test and Accuclot Specificity of SimpliRED, IL test and Accuclot</td>
<td>80% 91% 91% 79% 74% 76%</td>
<td>Results combined for ?DVT and ?PE patients Cut off level of 200 ng/ml was used for IL test (much lower than most labs)</td>
</tr>
</tbody>
</table>

Three part question
In a [patient with suspected pulmonary embolus] does a [negative IL D-dimer test] adequately [rule out the diagnosis]?

Search strategy
Medline 1966–04/03 using the OVD interface. ([D-dimer.mp or exp Fibrin Fibrinogen Degradation Products or FDP.mp] AND [IL test.mp] AND [exp Thromboembolism or exp Pulmonary Embolism or pulmonary embol$.mp or PE.mp or pulmonary infarct$.mp or exp venous thromboembolism]).

Search outcome
Six papers were found from the above search. Four were relevant. One further paper was found from hand searching journals and references. These five papers are shown in table 8.

Comments
To date there have been few studies measuring the accuracy of this d-dimer test. Of note, there is almost no research looking in particular at patients presenting with symptoms of PE. The sensitivity of the IL test for ruling out DVT seems to lie somewhere between 90% and 100%. It is worth noting that all of these studies used a comparatively low cut off level and it is worth being aware what the cut off level is in your hospital laboratory.

CLINICAL BOTTOM LINE
The IL d-dimer test alone is not sufficiently sensitive to rule out pulmonary embolus. It must be used in conjunction with another test.

Table 9

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauld DL et al, Canada, 1999</td>
<td>128 emergency department patients—50 with suspected PE, the rest suspected DVT. All given one dose of dalteparin and discharged overnight before investigations</td>
<td>Prospective cohort</td>
<td>Adverse events</td>
<td>6% had bruising at injection site</td>
<td>Small study numbers relating to outpatient investigation</td>
</tr>
</tbody>
</table>

Table 10

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells PS et al, 1998, Canada</td>
<td>184 patients with either DVT or PE (44 had PE) deemed at low risk of complications randomised to self administration dalteparin or homecare nurse administration. All treated at home</td>
<td>Prospective cohort</td>
<td>Recurrent thromboembolic event in three month follow up</td>
<td>3.6%</td>
<td>Small number of patients with PE</td>
</tr>
<tr>
<td>Kovacs MJ et al, 2000, Canada</td>
<td>81 patients treated at home for pulmonary embolism. Further 27 managed at home after 2.5 days in hospital.</td>
<td>Prospective cohort</td>
<td>Recurrent thromboembolic event in three month follow up</td>
<td>5.6%</td>
<td>Comparatively small numbers</td>
</tr>
<tr>
<td>Labas P et al, Slovakia, 2001</td>
<td>28 patients diagnosed with concurrent PE and DVT treated at home</td>
<td>Prospective cohort</td>
<td>Death</td>
<td>None</td>
<td>No details given regarding diagnostic criteria for PE</td>
</tr>
</tbody>
</table>
search, of which one presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of this best paper are tabulated. A clinical bottom line is stated.

Clinical scenario
A 40 year old woman presents to the emergency department with pleuritic chest pain. She comments that she has had “cramp” in her left leg since discharge from the surgical ward after hysterectomy. Her ventilation-perfusion scan shows a high probability of pulmonary embolism. You have scored her as a high clinical probability of PE and therefore diagnose pulmonary embolic disease. She is comfortable, has normal oxygen saturations and is keen to return home to her family. You wonder whether treating her as an outpatient would be a safe option.

Three part question
Is it [safe] to treat a patient with [pulmonary embolic disease] as an [outpatient]?

Search strategy
Medline 1966–04/03 using the OVID interface. [(pulmonary embol$.mp OR exp Pulmonary Embolism OR PE.mp OR exp Thromboembolism OR pulmonary infarct$.mp) AND (treatment.mp OR exp Therapeutics OR LMWH.mp OR exp Heparin, Low-Molecular-Weight OR low molecular weight.mp OR exp Anticoagulants) AND (outpatient.mp OR exp Outpatients OR clinic.mp OR exp Outpatient clinics, hospital)] LIMIT to human AND English.

Search outcome
Altogether 282 papers were found, of which three were relevant (table 10).

Comment(s)
There are no large studies validating this approach to the treatment of pulmonary embolism.

CLINICAL BOTTOM LINE
It may be safe to treat a low risk group of patients with pulmonary embolic disease at home.


Accumulator BET: a traumatic pleuritic chest pain

Prepared by K Hogg, G Brown, K Mackway-Jones


Prepared by K Hogg, G Brown, K Mackway-Jones