

Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary

Edited by K Mackway-Jones

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Best evidence topic reports (BETs) summarise the evidence pertaining to particular clinical questions. They are not systematic reviews, but rather contain the best (highest level) evidence that can be practically obtained by busy practising clinicians. The search strategies used to find the best evidence are reported in detail in order to allow clinicians to update searches whenever necessary. The BETs published below were first reported at the Critical Appraisal Journal Club at the Manchester Royal Infirmary¹ or placed on the BestBETs web site. Each BET has been constructed in the four stages that have been described elsewhere.² The BETs shown here together with those published previously and those currently under construction can be seen at <http://www.bestbets.org>.³ Five BETs are included in this issue of the journal together with another five that inform the accompanying accumulator BET.

- ▶ Accuracy of negative urine analysis in ruling out urinary tract infection in adults
- ▶ Venous blood gas in adult patients with diabetic ketoacidosis
- ▶ Antithrombotic treatment of below knee deep venous thrombosis
- ▶ Buccal nitrates in left ventricular failure
- ▶ Oral methionine compared with intravenous n-acetylcysteine for paracetamol overdose

Accumulator BET

- ▶ Clinical probability scoring and pulmonary embolism
- ▶ Accuracy of combining clinical probability score and simpliRED D-dimer for diagnosis of pulmonary embolism
- ▶ IL D-dimer test in the diagnosis of pulmonary embolism
- ▶ Outpatient investigation of pulmonary embolism
- ▶ Outpatient treatment of pulmonary embolism

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- 1 **Carley SD**, Mackway-Jones K, Jones A, *et al*. Moving towards evidence based emergency medicine: use of a structured critical appraisal journal club. *J Accid Emerg Med* 1998;**15**:220–2.
- 2 **Mackway-Jones K**, Carley SD, Morton RJ, *et al*. The best evidence topic report: A modified CAT for summarising the available evidence in emergency medicine. *J Accid Emerg Med* 1998;**15**:222–6.
- 3 **Mackway-Jones K**, Carley SD. [bestbets.org](http://www.bestbets.org): Odds on favourite for evidence in emergency medicine reaches the worldwide web. *J Accid Emerg Med* 2000;**17**:235–6.

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.

Clinical scenario

A 20 year old student presents to the emergency department with a three day history of urinary frequency, dysuria, and lower abdominal pain. Examination is unremarkable and dipstick urine analysis is normal. You wonder whether normal dipstick urine analysis is sufficient to rule out a UTI or whether antibiotics anyway should be prescribed whatever the result.

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 UTL.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

Table 1

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

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.

Hurlbut T, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. *Am J Clin Pathol* 1991;**96**:582–8.

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, Nallamothu BK, Simel DL, et al Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 2002;**287**:2701–10.

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 to 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 2

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

► CLINICAL BOTTOM LINE

There is no clinically significant difference between arterial and venous pH estimates in patients with diabetic ketoacidosis.

Brandenburg MA, Dire DJ. Comparison of arterial and venous blood gases in the initial emergency department evaluation of patients with diabetic ketoacidosis. *Ann Emerg Med* 1998;**31**:459–65.

Gokel Y, Paydas S, Koseoglu Z, *et al*. Comparison of blood gases and acid-base measurements in arterial and venous blood samples in patients with uremic acidosis and diabetic ketoacidosis in the emergency room. *Am J Nephrol* 2000;**20**:319–23.

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.

Philbrick JT, Becker DM. Calf deep venous thrombosis. A wolf in sheep's clothing. *Arch Intern Med* 1988;**148**:2131–8.

Giachino A. Relationship between deep vein thrombosis in the calf and fatal pulmonary embolism. *Can J Surg* 1988;**31**:129–30.

Lohr JM, Kerr TM, Lutter KS, *et al*. Lower extremity calf thrombosis: to treat or not to treat? *J Vasc Surg* 1991;**14**:618–23.

Pellegrini VD Jr, Langhans MJ, Totterman S, *et al*. Embolic complications of calf thrombosis following total hip arthroplasty. *J Arthroplasty* 1993;**8**:449–57.

Nielsen HK, Husted SE, Krusell LR, *et al*. Silent pulmonary embolism in patients with deep venous thrombosis. Incidence and fate in a randomised, controlled trial of anticoagulation versus no anticoagulation. *J Intern Med* 1994;**235**:457–61.

Lohr JM, James KV, Deschmukh RM, *et al*. Calf vein thrombi are not a benign finding. *Am J Surg* 1995;**170**:86–90.

O'Shaughnessy AM, Fitzgerald DE. The value of duplex ultrasound in the follow-up of acute calf vein thrombosis. *Int Angiol* 1997;**16**:142–6.

Gottlieb RH, Widjaja J, Mehra S, *et al*. Clinically important pulmonary emboli: does calf vein US alter outcomes? *Radiology* 1999;**211**:25–9.

Pinede L, Ninet J, Duhaut P, *et al*. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf. *Circulation* 2001;**103**:2453–60.

Schwarz T, Schmidt B, Beyer J, *et al*. Therapy of isolated calf muscle vein thrombosis with low-molecular-weight heparin. *Blood Coagul Fibrinolysis* 2001;**12**:597–9.

Sharpe RP, Gupta R, Gracias VH, *et al*. Incidence and natural history of below-knee deep venous thrombosis in high-risk trauma patients. *J Trauma* 2002;**53**:1048–52.

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 suscard 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 Isoket.mp OR Suscard.mp) AND {(buccal.mp OR exp mouth mucosa OR exp administration, buccal) AND (exp injections, intravenous OR intravenous.mp OR IV.mp)} AND (exp heart failure, congestive OR heart failure.mp OR LVEF.mp OR left ventricular failure.mp OR 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

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Philbrick JT <i>et al</i> , 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)	
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 thrombi.	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.
Lohr J <i>et al</i> , 1991, USA	75 patients with ultrasound diagnosed calf thrombosis. Treatment left to physician's discretion.	Prospective study with follow up serial ultrasound examination.	Thrombosis propagation	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 Pelligrini V <i>et al</i> , 1993. No information regarding the length of follow up, or the effect of varying therapies
Pellegrini V <i>et al</i> , 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	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	Two of the PEs were diagnosed on the strength of sudden collapse and cardiac arrest—no postmortem examination carried out
Nielson HK <i>et al</i> , 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 <i>et al</i> , 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	Publishing bias—the cohort appears to include all of the patients included in the previous Lohr study (see study in this table) Paper does not establish rate of PE
O'Shaughnessy AM <i>et al</i> , 1997, Ireland	50 patients with ultrasound diagnosed DVTs, 43 treated with anticoagulation and 7 without	Prospective study, using repeat ultrasound at one week, one month, six months and one year.	"Outcome" of isolated calf thrombosis.	3 patients presented initially with a "positive" VQ scan. One fatal PE within the first month.	Venography not used to diagnose initial calf DVT. Apparently, no attempts were made to actively seek the diagnosis of PE throughout the follow up period. No adequate description of the positive VQ scans. 10 patients lost to follow up at six months. No account taken of the effect of treatment
Gottlieb RH <i>et al</i> , 1999, USA	238 patients with ultrasound diagnosed below knee DVTs	Retrospective study	Incidence of diagnosed PEs Incidence of extension into thigh DVT	2 of 56 patients not receiving anticoagulant therapy had PE 1 of 227 receiving anticoagulant therapy had documented extension to thigh DVT	Patients were not identified using venography. Retrospective study, therefore unable to detect silent PEs or those that did not present to medical services. One PE diagnosed on strength of high probability VQ scan alone. No description of frequency of follow up ultrasound scans. Therapy at the discretion of physician. No information regarding anticoagulant therapy for patient with extension to thigh DVT. 28 patients were not followed up for the full six months as they died
Pinede L <i>et al</i> , 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	Diagnosis did not always use venography No information regarding which symptoms would prompt investigations for PE. Method's description implies that a VQ scan result of intermediate probability would diagnose PE—no information as to how this PE was diagnosed
Schwarz T <i>et al</i> , 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 veins thrombosis, compared with 0 of 52 anticoagulated patients None	Gold standard venography not used VQ scan results interpreted in isolation
Sharpe RP <i>et al</i> , 2002, USA	85 trauma patients with below knee DVTs	Prospective cohort	Thrombus propagation PE	4 of 85 thrombi propagated proximally 1 of 85 did not propagate but had a PE	Gold standard investigations not applied for DVT or PE

Table 4

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Verma SP <i>et al</i> , 1989, UK	36 male patients with acute LVF secondary to recent MI (<10 hours) in CCU IV v buccal v transdermal GTN Average doses over 90 min: IV 12.9 mg, buccal 5 mg, dermal 20 mg	PRCT	Left heart filling pressures Cardiac output BP	All three groups reduced No reduction in any group 3 patients had BP falls in buccal group but with no clinical deterioration	Only 36 patients Different doses of buccal, IV and dermal GTN (based on previous studies) IV dose individually titrated; buccal and dermal doses predetermined

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.

► CLINICAL BOTTOM LINE

Buccal nitrates produce an immediate reduction in preload (comparable with intravenous GTN).

Verma SP, Silke B, Reynolds GW, *et al*. Nitrate therapy for left ventricular failure complicating acute myocardial infarction: a haemodynamic comparison of intravenous, buccal and transdermal delivery systems. *J Cardiovasc Pharmacol* 1989;14:756–62.

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

Medline 1966–04/03 using the OVID interface. [exp methionine OR methionine\$.mp] AND [exp acetaminophen OR acetaminophen\$.mp OR paracetamol.mp] AND [exp acetylcysteine OR acetylcysteine\$.mp OR parvolex.mp] LIMIT to human AND English.

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.

Table 5

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

Table 6

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

► CLINICAL BOTTOM LINE

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

Vale JA, Meredith TJ, Goulding R. Treatment of acetaminophen poisoning. The use of oral methionine. *Arch Intern Med* 1981;141:394–6.

Prescott LF. Treatment of severe acetaminophen poisoning with intravenous acetylcysteine. *Arch Intern Med* 1981;141:386–9.

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 exp Thromboembolism OR PE.mp OR pulmonary infarct\$.mp OR Pulmonary Embol\$.mp) AND (exp Risk Assessment OR risk assessment.mp OR risk stratification.mp OR probability.mp) LIMIT to human AND English language.

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

Clinical risk stratification is a potentially useful method of identifying low risk patients in whom PE may be safely excluded by simple non-invasive tests.

Wells PS, Anderson MR, Ginsberg JS, *et al*. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416–20.

Wicki J, Perneger TV, Junod AF, *et al*. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med* 2001;161:92–7.

Kline JA, Nelson RD, Jackson RE, *et al*. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study. *Ann Emerg Med* 2002;39:144–52.

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 are

Table 7

Author, date and country	Patient group	Study type (levels of evidence)	Outcomes	Key results	Study weaknesses
Ginsberg JS <i>et al</i> , 1998, Canada	1250 consecutive referred patients to teaching hospital thromboembolic clinic with putative diagnosis of PE (73 lost to follow up)	Cohort	Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with –ve SimpliRED D-dimer	Negative predictive value of 99%	Exclusion criteria “lost” 484 of original 1881 patients screened then further 147 excluded because of non-consent
Wells PS <i>et al</i> , 2000, Canada	1211 patients with presumptive diagnosis of PE broken into derivation and validation set	Diagnostic test	Sensitivity of clinical decision rule with addition of SimpliRED latex agglutination test E	87.8%–88.3% (validation-derivation)	Actual methodology not fully demonstrated, for example, gold standard definition predictive values and likelihood ratios not given
Farrell S, 2000, USA	198 patients presenting to US ED with suspected thromboembolic disease	Diagnostic test	Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with –ve SimpliRED D-dimer	Negative predictive value 97% Sensitivity 84%	Estimation of clinical probability was with implicit not explicit methods 12% patients “lost” in study
MacGillavry MR, 2001, Netherlands	404 adults, both in and outpatients in teaching hospitals with putative diagnosis of thromboembolic disease	Diagnostic test	Sensitivity and specificity of using a clinical probability and SimpliRED D-dimer test	Sensitivity 98% Specificity 11%	Over 50% exclusion rate for entry into study. Implicit methods only for determining clinical probability
Wells P, 2001, Canada	946 adult patients referred for assessment of ? PE	Cohort	Diagnostic utility of a combination of low clinical probability of PE on clinical assessment with –ve SimpliRED D-dimer	Negative predictive value 99.5%.	Investigation protocol violations occurred in nearly 10% of the patients

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 simpliRED.mp OR whole blood.mp] AND [exp thromboembolism OR exp pulmonary embolism OR PE.mp OR pulmonary embol\$.mp OR pulmonary infarct\$.mp] AND [exp“sensitivity and specificity”.mp OR sensitivity.tw OR di.xs 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.

► CLINICAL BOTTOM LINE

Patients at low clinical risk with a negative bedside D-dimer can have pulmonary embolus ruled out.

Ginsberg JS, Wells PS, Kearon C, *et al*. Sensitivity and specificity of a rapid whole blood assay for D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med* 1998;**129**:1006–11.

Wells PS, Anderson DR, Rodger M, *et al*. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;**83**:416–20.

Farrell S, Hayes T, Shaw M. A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep venous thrombosis or pulmonary embolus in emergency department patients. *Ann Emerg Med* 2000;**35**:121–5.

Mac Gillavry MR, Lijmer JG, Sanson BJ, *et al*. Diagnostic accuracy of triage tests to exclude pulmonary embolism. *Thromb Haemost* 2001;**85**:995–8.

Wells PS, Anderson DR, Rodger M, *et al*. Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model. *Ann Intern Med* 2001;**135**:98–107.

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.

Table 8

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Legani C <i>et al</i> , Italy 1999	105 consecutive outpatients ?DVT	Prospective cohort	ROC curve to define max sensitivity of IL test	230 ng/ml cut off sensitivity 100% specificity 77.2%	Patients ?DVT not PE High prevalence DVT. Would not reflect an average emergency department population
van der Graaf F, 2000	99 ?DVT outpatients. Comparison of 13 different D-dimer tests	Prospective cohort	IL test Sensitivity specificity	90% 78%	Patients ?DVT not PE High prevalence of DVT
Villa P <i>et al</i> , Spain 2000	86 patients with a moderate or high clinical suspicion DVT	Prospective cohort	Sensitivity Specificity Iltest using 255 ng/ml cut off Sensitivity Specificity Iltest using 292 ng/ml cut off Sensitivity Specificity Gold EIA ELISA test	98.4% 33.3% 95.2% 41.7% 90% 57.1%	Patients suspected of having DVT not PE Cohort had high prevalence DVT Venography not used
Harper P <i>et al</i> , New Zealand 2001	235 patients presenting to emergency department with ?DVT	Prospective cohort	Sensitivity IL test (250 ng/ml cut off) and SimpliRED Specificity IL test and SimpliRED	94.1% 66% 51.5% 75.6%	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
Kovacs MJ <i>et al</i> , Canada 2001	All patients with suspected DVT (468 patients) or PE (525 patients), presenting to four hospitals	Prospective cohort	Sensitivity of SimpliRED, IL test and Accuclot Specificity of SimpliRED, IL test and Accuclot	80% 91% 91% 79% 74% 76%	Results combined for ?DVT and ?PE patients Cut off level of 200 ng/ml was used for IL test (much lower than most labs)

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 and wonder whether a normal result would be sufficiently sensitive to rule out a pulmonary embolus.

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 Degredation 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.

Legani C, Pancani C, Palareti G, *et al*. Performance of a new, fast D-dimer test (IL test d-dimer) for the management of outpatients with suspected deep vein thrombosis in emergency situations. *Fibrinolysis and Proteolysis* 1999;13:139–41.

van der Graaf F, van den Borne H, van der Kolk M, *et al*. Exclusion of deep venous thrombosis with D-dimer testing—comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thromb Haemst* 2000;83:191–8.

Villa P, Ferrando F, Serra J, *et al*. Quantification of D-dimer using a new fully automated assay: its application for the diagnosis of deep vein thrombosis. *Haematologica* 2000;85:520–4.

Harper P, Marson C, Grimmer A, *et al*. The rapid whole blood agglutination d-dimer assay has poor sensitivity for use as an exclusive test in suspected deep vein thrombosis. *N Z Med J* 2001;114:61–4.

Kovacs MJ, MacKinnon KM, Anderson D, *et al*. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. *Br J Haematol* 2001;115:140–4.

Table 9

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Bauld DL <i>et al</i> , Canada, 1999	128 emergency department patients—50 with suspected PE, the rest suspected DVT. All given one dose of dalteparin and discharged overnight before investigations	Prospective cohort	Adverse events	6% had bruising at injection site No other adverse events relating to outpatient investigation	Small study numbers

Outpatient investigation of pulmonary embolism

Report by Kerstin Hogg, *Clinical Research Fellow*

Checked by Debbie Dawson, *Clinical Research Nurse*

Abstract

A short cut review was carried out to establish whether outpatient investigation of suspected pulmonary embolus is a safe strategy. A total of 198 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 are tabulated. A clinical bottom line is stated.

Clinical scenario

A 38 year old man presents to the emergency department with left posterior pleuritic chest pain. He had a DVT eight years ago and his D-dimer levels are raised. He is haemodynamically stable with normal oxygen saturations, ECG, and chest radiograph. You would like to rule out a pulmonary embolism, but it is 8 pm. You wonder whether it would be safe to discharge the patient home overnight before his VQ scan tomorrow.

Three part question

In a [patient with suspected pulmonary embolism] is [outpatient investigation] [safe]?

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 (diagnosis.mp OR exp Diagnosis) AND (outpatient.mp OR exp Outpatients OR clinic.mp OR exp Outpatient clinics, hospital)] LIMIT to human AND English.

Search outcome

Altogether 198 papers were found, one of which looked at outpatient investigation of patients with suspected PE. This is shown in table 9.

Comments

This is the only published study looking at outpatient investigation of PE and is small. Further research is needed.

► CLINICAL BOTTOM LINE

It may be safe to investigate selected patients with suspected pulmonary embolus at home.

Bauld DL, Kovacs MJ. Dalteparin in emergency patients to prevent admission prior to investigation for venous thromboembolism. *Am J Emerg Med* 1999;17:11–15.

Outpatient treatment of pulmonary embolism

Report by Kerstin Hogg, *Clinical Research Fellow*

Checked by Debbie Dawson, *Clinical Research Nurse*

Abstract

A short cut review was carried out to establish whether outpatient treatment of patients with pulmonary embolus is a safe strategy. Sixty six papers were found using the reported

Table 10

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Wells PS <i>et al</i> , 1998, Canada	184 patients with either DVT or PE (34 had PE) deemed at low risk of complications randomised to self administration dalteparin or homecare nurse administration. All treated at home	Prospective cohort	Recurrent thromboembolic event in three month follow up Major haemorrhage Minor haemorrhage Death	3.6% 2.0% 5.1% 7.2% — 11 died of metastatic carcinoma, one of sepsis and one MI	Small number of patients with PE
Kovacs MJ <i>et al</i> , 2000, Canada	81 patients treated at home for pulmonary embolism. Further 27 managed at home after average 2.5 days in hospital.	Prospective cohort	Recurrent thromboembolic event in three month follow up Major haemorrhage Death	5.6% 1.9% 3.7%—none due to PE or bleed	Comparatively small numbers
Labas P <i>et al</i> , Slovakia, 2001	28 patients diagnosed with concurrent PE and DVT treated at home	Prospective cohort	Death	None	No details given regarding diagnostic criteria for PE

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

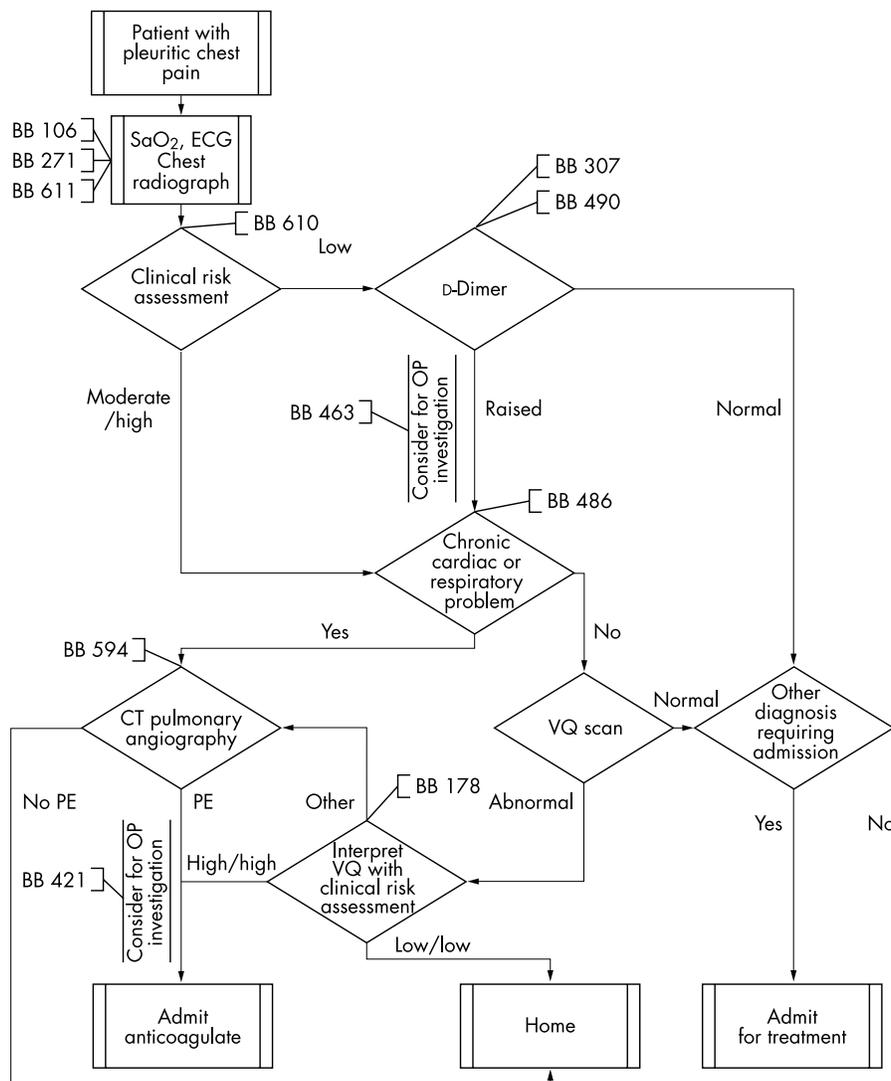
It may be safe to treat a low risk group of patients with pulmonary embolic disease at home.

Wells PS, Kovacs MJ, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with homecare injection. *Arch Intern Med* 1998;**158**:1809–12.

Kovacs MJ, Anderson D, Morrow B, et al. Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* 2000;**83**:209–11.

Labas P, Ohradka B, Cambal M. Could deep vein thrombosis be safely treated at home. *Bratisl Lek Listy* 2001;**102**:458–61.

Accumulator BET: a traumatic pleuritic chest pain



BB 106. Diagnostic utility of arterial blood gases for investigation of pulmonary embolus.

<http://www.bestbets.org/cgi-bin/bets.pl?record=106>

BB 178. Combining clinical probability and ventilation-perfusion scan for diagnosis of pulmonary embolism. <http://www.bestbets.org/cgi-bin/bets.pl?record=178>

BB 271. Diagnostic utility of ECG for diagnosing pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=271>

BB 307. Accuracy of combining clinical probability score and simpliRED D-dimer for diagnosis of pulmonary embolism. <http://www.bestbets.org/cgi-bin/bets.pl?record=307>

BB 421. Outpatient treatment of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=421>

BB 463. Outpatient investigation of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=463>

BB 486. CT pulmonary angiogram versus ventilation-perfusion scan for the diagnosis of pulmonary embolism in patients with cardiorespiratory disease.

<http://www.bestbets.org/cgi-bin/bets.pl?record=486>

BB 490. IL D-dimer test in the diagnosis of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=490>

BB 594. Accuracy of CT pulmonary angiogram in the diagnosis of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=594>

BB 610. Can clinical probability score estimate the probability of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=610>

BB 611. Diagnostic utility of chest xray for investigation of pulmonary embolism.

<http://www.bestbets.org/cgi-bin/bets.pl?record=00611>

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