

education

FROM THE JOURNALS Edited highlights of weekly research reviews on <https://bit.ly/2PLtl8>

Thiazides and b blockers feel the pressure

“5 mm Hg, 11%.” I’m trying to commit these numbers to memory for consultations with patients at high risk of developing diabetes: lowering your systolic blood pressure by five points reduces the chances of getting diabetes by about a tenth. This was one of the conclusions of a meta-analysis of individual participant data from 22 studies conducted between 1973 and 2008.

The study also found that ACE inhibitors and angiotensin II receptor blockers reduce the risk of developing diabetes (relative risk of 0.84 for both drug classes), whereas thiazide diuretics and β blockers increase the risk (relative risks of 1.2 and 1.48 respectively). Calcium channel blockers sit in the middle refusing to get involved (relative risk 1.02). So we now have another factor to throw into the pot when discussing the choice of antihypertensive with patients.

• *Lancet* doi:10.1016/S0140-6736(21)01920-6

Glargine battles on as insulin turns 100

The *Lancet* is celebrating the 100 year anniversary of the isolation and purification of insulin by treating us to a head-to-head battle between insulin glargine and a new kid on the block: tirzepatide. And while there was no knockout blow from tirzepatide, it definitely won on points.

This was an open label study across 14 countries, of 2002 people with type 2 diabetes and inadequate glycaemic control who were already taking metformin, sulfonylureas, and/or a sodium-glucose cotransporter-2 inhibitor and were at high cardiovascular risk (such as already having had a cardiovascular event). They were randomly assigned to tirzepatide (a dual GIP and GLP-1 receptor agonist) or insulin glargine. After a year, average HbA_{1c} improvements with tirzepatide were 10.9 mmol/mol (0.99% in old money) greater than those seen with glargine. The HbA_{1c} changes were -24.5 mmol/mol (-2.24%) with 5 mg tirzepatide versus -15.7 mmol/mol (-1.44%) with insulin glargine. Upping the tirzepatide dose seemed to give only marginal extra benefit: -28.2 mmol/mol (-2.58%) with 15 mg. There was no difference in cardiovascular events or deaths between the two drugs.

• *Lancet* doi:10.1016/S0140-6736(21)02188-7

Plasma’s going home

Convalescent plasma from blood donors who have recovered from covid-19 was an early hope for an effective treatment. But, when given to high risk patients attending emergency departments within seven days of symptom onset, it doesn’t seem to prevent symptom progression, according to a single blinded, randomised placebo controlled trial in the US. The

study was halted early because the “stopping threshold for futility had been reached.” Sports fans will know this as the moment when your team is losing so badly you turn to your neighbour and say, “This is pointless, I’m going home.” But it might not be game over for convalescent plasma. The study’s authors suggest further research may find it can have a role if administered before the development of native antibodies, for preventing symptomatic covid-19 after exposure.

• *N Engl J Med* doi:10.1056/NEJMoa2103784

Sacubitril-valsartan swings again

Sacubitril-valsartan is back in another major journal after last week’s disappointing findings in patients with acute myocardial infarction complicated by heart failure. In the spotlight this week are patients with heart failure and a left ventricular ejection fraction >40%, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, structural heart disease, and reduced quality of life. The randomised controlled trial found no benefits in quality of life, mobility (six minute walk distance), or New York Heart Association classification after 24 weeks compared with controls (enalapril, valsartan, or placebo, depending on prior use of a renin angiotensin system inhibitor). Those in the sacubitril-valsartan arm did have lower NT-proBNP levels at 12 weeks, but it remains to be seen if this translates to improvements in symptoms or mortality over the long term.

• *JAMA* doi:10.1001/jama.2021.18463

The sound of silence

A research letter in *JAMA Internal Medicine* about inaudible heart sounds sent me down a Google rabbit hole that ended at chapter 42 of *Common Clinical Presentations in Dogs and Cats* (definitely one for the Christmas list). Apparently, quiet heart sounds in dogs are often due to neoplastic or idiopathic disease, whereas in cats congestive heart failure secondary to cardiomyopathy is more common. Returning to humans, the research letter presents an analysis of heart sound recordings from 200 hospitalised patients who were undergoing echocardiography. They found that “heart sounds were clinically undetectable at the aortic location in 30 (15%) patients and at the mitral location in 130 (65%) patients.” Of the 66 patients with mitral regurgitation, 62% had undetectable heart sounds. The numbers seem high, and there are various methodological limitations, but it’s good to read some research that seeks to question and advance the clinical value of examination findings.

• *JAMA Intern Med* doi:10.1001/jamainternmed.2021.6594

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Is cerclage safe and effective in preventing preterm birth in women presenting early in pregnancy with cervical dilatation?



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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme.

Box 1 | National Institute for Health and Care Excellence (NICE) guidelines for management of preterm labour and birth (NG25)²

Women with a closed cervix

- For women with a history of spontaneous preterm birth or second trimester miscarriage, *plus* a cervical length of <25 mm on transvaginal ultrasound (TVUSS): offer a choice of prophylactic cervical cerclage or progesterone.
- For women with a history of spontaneous preterm birth or second trimester miscarriage, *or* a cervical length of <25 mm on TVUSS (but not both): consider progesterone.
- For women with a history of preterm premature rupture of the membranes (PPROM) or cervical trauma, *plus* a cervical length of <25 mm on TVUSS: offer prophylactic cervical cerclage.

*NICE guidance does not discuss any interventions other than emergency cervical cerclage (rescue cerclage) for women with cervical dilatation and exposed membranes.

Women with cervical dilatation and exposed unruptured fetal membranes*

- Do not offer “rescue” cerclage if there are signs of infection, bleeding, or uterine activity.
- Consider rescue cerclage for women between 16+0 and 27+6 weeks of gestation, taking into account gestational age and degree of dilatation, and in discussion with consultant obstetrician and paediatrician.
- Explain to women the risks of the procedure and that the aim is to delay birth to increase the likelihood of survival and decrease neonatal morbidity.

Preterm birth and its complications account for nearly one million neonatal deaths each year globally.¹ Women who present with a dilated cervix in the second trimester are at increased risk of pregnancy loss and preterm birth (fig 1). They generally have no or minimal preceding symptoms such as change in discharge or mild abdominal pain and are detected to have a dilated cervix on examination. Cervical dilatation may also be detected in the anomaly scan. International guidelines from the US, UK, and Canada suggest considering emergency cervical cerclage, or rescue cerclage, to prevent preterm birth in women presenting with cervical dilatation and exposed fetal membranes between 16 and 28 weeks of gestation if there are no signs of bleeding, infection, or uterine activity (see box 1).²

Asymptomatic women with a history of preterm birth or spontaneous miscarriage and a short cervix may be considered for prophylactic cervical cerclage (performed when the cervix is closed and the membranes are not exposed); this procedure is not the focus of this paper. Likewise, management of women presenting early in gestation with contractions, vaginal bleeding, or ruptured membranes is not part of this article.

Emergency cervical cerclage (ECC) tends to be complex as membranes must be replaced within the uterus and a stitch placed around any remaining cervix. The procedure carries a risk of complications such as membrane rupture, maternal or fetal infection, sepsis, and cervical trauma.

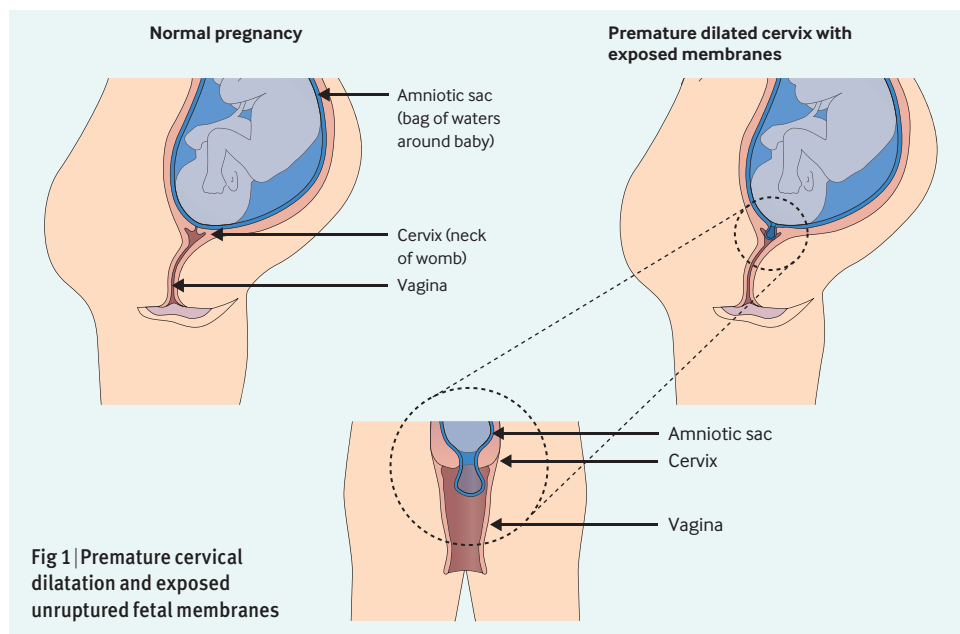


Fig 1 | Premature cervical dilatation and exposed unruptured fetal membranes

WHAT YOU NEED TO KNOW

- Emergency cervical cerclage is a potential treatment for women presenting with cervical dilatation and exposed unruptured fetal membranes before 28 weeks of pregnancy in the absence of bleeding, uterine activity, or infection
- There is limited low quality evidence mainly from retrospective studies that this may prolong pregnancy duration
- There is no evidence to support the use of progesterone, NSAIDs, pessary, prophylactic antibiotics, or tocolytics as independent treatments in these women

Gestation calculator

At 24 weeks, 6 out of every 10 babies are expected to survive; at 28 weeks, 9 out of 10 babies will survive; and at 34 weeks, survival is equivalent to that of full term babies^{8,9}

Gestation at presentation	Prolongation required to reach gestation		
	24/40	28/40	34/40
16+0	56 days	84 days	126 days
18+0	42 days	70 days	112 days
20+0	28 days	56 days	98 days
22+0	14 days	42 days	84 days
24+0	0	28 days	70 days
26+0	0	14 days	56 days
28+0	0	0	42 days

- Mean pregnancy prolongation* for ECC and for bed rest are not expected to reach given gestation
- Mean pregnancy prolongation* for ECC, but not for bed rest, is expected to reach given gestation
- Mean pregnancy prolongation* for ECC and for bed rest are expected to result in reaching given gestation

* Trial by Althusius et al⁷ found mean prolongation of pregnancy of 54 days in ECC arm and 20 days in bed rest arm

Fig 2 | Prolongation of pregnancy with emergency cervical cerclage (ECC) or bed rest based on a single randomised controlled trial⁷

WHAT PATIENTS NEED TO KNOW

- Sometimes the neck of the womb can start to open early and the bag of waters around the baby can come through the neck of the womb (fig 1).
- If this happens too early in pregnancy (before 28 weeks), there are a limited number of options to prolong the pregnancy. These include expectant management or bed rest (combined sometimes with antibiotics, progesterone, or medicines to stop the womb contracting) or emergency cervical cerclage (ECC).
- An ECC is the placement of a stitch around the neck of the womb after replacement of the bag of waters.
- There is some evidence from small studies that ECC may prolong pregnancy, preventing some of the complications of being born too early. The evidence is of low quality, and there are no long term data on pregnancy outcomes in the mother and newborn.

EDUCATION INTO PRACTICE

- How would you discuss management options with pregnant women at risk of preterm birth?
- How would you ensure your practice is linked with local or regional maternity services that offer emergency cervical cerclage?

What is the evidence of uncertainty?

There is limited, low quality evidence that ECC prolongs pregnancy duration and reduces pregnancy loss in these women. Prolonging the pregnancy by even a few days can improve the chances of newborn survival. There is a lack of long term data if prolonging the pregnancy with ECC affects survival to childhood. It is unclear how variable presentations, gestation, infection, and add-on treatments influence outcomes with ECC and risks for mother and baby.^{3,4} Most studies do not report on complications with cerclage such as chorioamnionitis, maternal sepsis, rupture of membranes, and cervical trauma.

A systematic review and meta-analysis published in 2020 (12 observational studies, 1021 participants) found that ECC in singleton pregnancies decreased preterm birth (odds ratio 0.25 (95% confidence interval 0.16 to 0.39), 5 studies, n=392) and pregnancy loss (OR 0.26 (0.12 to 0.56), 8 studies, n=455) compared with expectant management.³ Emergency cervical cerclage was found to increase mean pregnancy duration by 47.45 days (95% CI 39.89 to 55.0). The evidence is of low to very low quality. Most studies were small,

retrospective, and at high risk of bias.

Unlike other options such as expectant management, the consequences of ECC may shorten the pregnancy (due to rupture of membranes or infection). Reported rates of rupture of membranes vary from 5% to 25% in observational studies.^{5,6} Depending on gestation, this may cause loss of the pregnancy or limit the chance of survival. It is also possible for ECC to prolong pregnancy without meaningful improvement in the chance of live birth or survival to childhood, particularly at earlier gestations of presentation (fig 2). Advances in neonatal care mean that many extremely preterm babies (22-27 weeks) will survive to neonatal unit admission, but overall mortality and morbidity in surviving infants remain high.¹⁰

A small randomised controlled trial (23 women (16 singleton and 7 twin pregnancies)), found that ECC led to a statistically significant improvement in time to delivery compared with bed rest (54 v 20 days, P=0.46) and composite neonatal outcome (risk ratio 1.6 (95% CI 1.1 to 2.3)) (fig 2).⁷ It lowered preterm birth before 34 weeks (7/13 in ECC group v 10/10 in bed

rest group, P=0.2). Both groups received antibiotic prophylaxis. Women in the cerclage group received indomethacin in addition. Results should be interpreted with caution because of fewer twin pregnancies and use of indomethacin in the cerclage group. There was no long term follow-up of mothers or babies. A trial of ECC compared with no cerclage in women with twin pregnancy (30 women) found similar reduction in preterm birth at <34 weeks (risk ratio 0.71 (95% CI 0.52 to 0.96)) and perinatal mortality.¹¹ All women in the cerclage group received indomethacin and antibiotics.

Progesterone, non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, pessaries, and prophylactic antibiotics have been variably used as adjuncts to ECC in small studies (box 2). There is little evidence to recommend their use as independent treatments for this condition. Urinary tract infection and bacterial vaginosis may cause cervical dilatation and increase the risk of preterm birth. Antibiotics may be used if infection is suspected or confirmed, but there is no evidence for prophylactic antibiotic use.

Box 2 | Summary of evidence for other interventions in women with cervical dilatation and exposed fetal membranes before term (in the absence of uterine contractions)

Antibiotics

A Cochrane review of prophylactic antibiotics in women in spontaneous preterm birth with intact membranes found no significant reduction in birth within 48 hours (relative risk 1.02 (95% CI 0.89 to 1.18), 4 trials, n=6800) or preterm birth <36 weeks (RR 0.98 (0.92 to 1.04), 8 trials, n=7185). Antibiotic use was associated with increased risk of harm to neonates.¹² There was an increased risk of neonatal death with any antibiotic compared with placebo (RR 1.57 (1.03 to 2.40), 9 studies, n=7248).

One randomised controlled trial¹³ (RCT) (n=84) in women with painless cervical dilatation and exposed membranes found no significant difference in preterm birth <34 weeks (25.6% in antibiotic group v 40% in placebo group, P value not significant, not otherwise specified) or in composite neonatal outcome (2.6% v 17.5%, P value not significant). There was also no evidence of benefit of antibiotics in preventing preterm birth or neonatal outcome in the subgroup with confirmed microbial invasion of the amniotic cavity (preterm birth <34 weeks 50% in antibiotic group v 100% in placebo group, P value not significant).

One small single centre RCT (n=53) randomised women undergoing emergency cervical cerclage (ECC) to either ECC alone or ECC plus indomethacin and antibiotics.¹⁴ Adjunctive use of indomethacin and antibiotics were associated with a significant increase in the percentage of women with an ongoing pregnancy at 28 days (92.3% (n=24) v 62.5% (n=15), P=0.01). There was no difference in gestation at delivery overall or neonatal outcomes.

Arabin pessary

Low quality evidence from one retrospective observational study comparing pessary, ECC, and expectant management in women with an open cervix (n=112) suggests no significant difference in gestation at delivery between pessary and expectant management.¹⁵ ECC was associated with a significant increase in gestational age at delivery (mean 22.9 (SD 4.5) weeks with pessary, 25.6 (6.7) weeks with expectant management, and 29.2 (7.5) weeks with cerclage, P=0.015). There is no RCT or meta-analysis evidence for the use of cervical pessaries in women with an open cervix.

Indomethacin

Indomethacin is an NSAID and potential uterine muscle relaxant sometimes used at the time of ECC. There is no role for indomethacin as a stand-alone treatment for women with cervical dilatation.

One small single centre RCT (n=53) randomised women undergoing ECC to either ECC alone or ECC plus indomethacin and antibiotics.¹⁴ Adjunctive use of indomethacin and antibiotics were associated with an increase in the percentage of women with an ongoing pregnancy at 28 days (92.3% (n=24) v 62.5% (n=15), P=0.01). There was no significant difference in gestation at delivery overall or neonatal outcomes.

A retrospective observational study (n=222) of women undergoing ECC compared women who received indomethacin (31%) with those who did not and found no significant difference in risk of preterm birth <32 or <35 weeks.¹⁶

Progesterone

There is no RCT or meta-analysis evidence for the use of progesterone in the prevention of preterm birth or late miscarriage in women with an open cervix and exposed fetal membranes.

A small observational study (n=69) which included women with a short cervix or an open cervix (22% of study population) undergoing cerclage found no difference with progesterone and cerclage (prophylactic or emergency) compared with cerclage alone (odds ratio 2.83 (95% CI 0.58 to 13.89)).¹⁷

Tocolysis

There is no role for tocolysis alone in women with an open cervix and exposed membranes in the absence of uterine activity.

Tocolytics have been given as an adjunct to ECC, but their role as an intervention has not been individually assessed.⁷

Unlike other options, ECC may shorten the pregnancy (due to rupture of membranes or infection)

Is ongoing research likely to provide relevant evidence?

We searched ISRCTN, PROSPERO, and NIHR registries for ongoing studies on emergency cervical cerclage. We found two ongoing randomised controlled trials, both in the United Kingdom and expected to report in 2024. Recruitment tends to be difficult, and the studies are small. The findings may apply to other high income settings, but not across other practice settings.

We are conducting the C-STICH2 trial to assess effect of ECC on pregnancy loss in singleton pregnancies (50 women), the risks of ECC, and maternal and neonatal outcomes over a two year follow-up. An accompanying prospective observational cohort study (120 women) will inform on the incidence of the condition.

ENCIRCLE aims to assess the effect of ECC on time to delivery, preterm birth, pregnancy loss, and maternal and neonatal outcomes in (a) women with a twin pregnancy with an open cervix and exposed fetal membranes and (b) women with a short cervix after laser treatment for twin-to-twin transfusion syndrome. ENCIRCLE aims to recruit 31 women.

There are no registered trials assessing progesterone, antibiotics, or bed rest for women with an open cervix and exposed fetal membranes.

What should we do in light of the uncertainty?

Women, their partners, and families must be offered counselling by a consultant obstetrician and paediatrician, taking into consideration the woman's wishes, to choose between expectant management or bed rest and emergency cervical cerclage. It is important that they receive information about possible outcomes of the condition, interventions, and potential adverse effects for mother and baby.

Antibiotics may be used if urinary tract infection or chorioamnionitis is suspected or confirmed. Women with exposed membranes may have increased risk of subclinical infection within the amniotic fluid (microbial invasion of the amniotic cavity). This is thought to cause some cases of painless cervical dilatation,¹³ but it is not routinely investigated (by amniocentesis) or treated.

Competing interests: See bmj.com.

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Find the full version with references at doi: 10.1136/BMJ-2021-067470

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked a patient representative on our trial group to contribute to this paper. She contributed extensively in the context of the trial regarding use of language and what parents wish to know, and reviewed the manuscript. We are grateful for her contribution.

GPs may help people at risk of self-harm by asking open questions and acknowledging distress



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The study | Asking about self-harm and suicide in primary care: moral and practical dimensions

Ford J, Thomas F, Byng R, McCabe R
Patient Educ Couns 2020;104:4

Why was this study needed?

In 2018, more than 6500 suicides were recorded across the UK. The number of deaths by suicide is rising; during 2018, it increased by 10%.

Conversations about self-harm and suicidal thoughts can be difficult for both patients and doctors. But GPs play an important role in discussing mental health concerns, self-harm, and suicidal thoughts with their patients.

Simple changes to the way doctors ask questions about self-harm and suicidal thoughts could improve conversations with vulnerable patients and enable access to help and support.

In this study, researchers wanted to explore real life consultations to see how patients respond and how the conversation unfolds.

What did this study do?

As part of the DeSTRESS Project on mental health, researchers sought to explore how these conversations unfold by analysing real life recordings of primary care consultations. They wanted to identify ways of improving the communication between doctor and patient.

Researchers searched the One in a Million database of video recorded consultations between GPs and people from diverse backgrounds. They identified 18 consultations for mental health conditions in which doctors asked patients about self-harm or suicide and carried out an in-depth analysis of how these discussions unfolded.

What did it find?

This small, detailed study found that the way doctors asked questions could make it difficult for patients to talk freely. Patients' responses were often hesitant or ambiguous, downplaying the seriousness of their thoughts or behaviours.

Doctors usually initiated the discussion about self-harm but they often inadvertently limited it. Unhelpful aspects of conversations included:

- Closed questions framed for a "no" response, that made it difficult for patients to answer "yes." When asked, "But you've not had any thoughts of harming yourself or suicide or anything like that?" even patients who answered "yes" downplayed their response: "I have in some ways."
- A change of topic after an ambiguous "no" response (such as a long pause before the patient said "no") and not referring to self-harm again in the consultation.
- One tightly coupled question addressing both self-harm and suicide: "Sometimes when people feel low and stressed, they think of harming themselves—is that ever something that crosses your mind?"
- A focus on prevention without acknowledging distress: "So do you ever get far enough that you think of making plans to harm yourself?"
- Moral issues around suicide: "It rebounds on other people... a terrible thing to leave other people with."

Why is this important?

Given the vital role of GPs in offering help to these people, the researchers suggest many doctors could do more to seek clarity and encourage discussion from those who seem hesitant or reluctant to discuss their feelings.

They suggest that

- Adopting a more open questioning style and asking about self-harm and suicide separately could encourage patients to talk about self-harm and suicidal thoughts
- Acknowledging suicidal thoughts as distressing in themselves could help patients get the most suitable help
- Exploring patients' positive reasons for wanting to stay alive.

What's next?

This was a small exploratory study, but the findings could help improve the way in which doctors ask patients about self-harm and suicidal thoughts. They could be used to develop a new standard of questions to open up discussions. A larger, more long term study would be needed to influence policy. This kind of research could

follow people with mental health problems over time to explore the outcomes of consultations. This study was based on GP consultations that took place between 2014 and 2015. Further research could use more recent data to reflect the changes to general practice during covid-19.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. Further details of other interests, disclaimers, and permissions can be found on bmj.com

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CASE REVIEW

Unexplained metabolic acidosis

A man in his 20s was found to be unresponsive after experiencing headache and vomiting for two days. His medical history included depression, paracetamol (acetaminophen) overdose on several occasions, and an episode of unexplained encephalopathy five months earlier. He experienced two generalised tonic-clonic seizures during initial assessment in the emergency department. Clinical examination revealed a Glasgow coma scale score of 3/15, with global hypotonia, areflexia, and size 6 pupils that were unresponsive to light.

A systematic ABCDE approach was taken, with a focus on securing the airway because of the patient's decreased level of consciousness.

Arterial blood gas test results showed a metabolic acidosis with raised levels of lactate. Table 1 summarises the patient's laboratory test results on presentation to the emergency department.

The patient was intubated and transferred to the intensive care unit.

1 What laboratory investigations are required for patients with metabolic acidosis?

2 What do the laboratory test results in table 1 show?

3 What are the differential diagnoses in this case?

Submitted by James McCaffrey and Kieren Allinson

Patient consent obtained.

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Table 1 | Laboratory test results on presentation to emergency department

Investigation	Result	Normal range
Arterial blood tests		
pH	6.89	7.35-7.45
Partial pressure of oxygen	15.2 kPa	10.7-13.3 kPa
Partial pressure of carbon dioxide	7.6 kPa	4.7-6.0 kPa
Bicarbonate	10.5 mmol/L	22-26 mmol/L
Base excess	-22.5 mmol/L	-2-2 mmol/L
Lactate	11.1 mmol/L	0.5-2.2 mmol/L
Venous blood tests		
Haemoglobin	154 g/L	135-169 g/L
White cell count	23.4 cells×10 ⁹ /L	4.5-13 cells×10 ⁹ /L
Neutrophil count	13.7 cells×10 ⁹ /L	2-7.5 cells×10 ⁹ /L
C reactive protein	51 mg/L	0-80 mg/L
Glucose	5.8 mmol/L	3-6 mmol/L
Urea	5.7 mmol/L	2.5-7.8 mmol/L
Creatinine	112 µmol/L	64-110 µmol/L
Estimated glomerular filtration rate	≥90 ml/min/1.73m ²	90-120 ml/min/1.73m ²
Adjusted calcium	2.3 mmol/L	2.2-2.6 mmol/L
Chloride	112 Mmol/L	95-108 Mmol/L
Serum anion gap	27.5 mmol/L	8-16 mmol/L
Serum osmolal gap	15.5 mmol/kg	-10-10 mmol/L
Troponin I	<2 ng/L	0-34 ng/L
Paracetamol (acetaminophen)	<10 mg/L	-
Salicylate	<10 mg/L	-
Alcohol	<10 mg/dL	0-50 mg/dL
Microbiological culture	No growth	-
Urine toxicology screen		
Opioids	Negative	-
Amphetamine	Negative	-
Benzodiazepines	Negative	-
Cocaine metabolites	Negative	-
6 Mono acetyl morphine	Negative	-
Methadone metabolites	Negative	-

answers

CASE REVIEW Unexplained metabolic acidosis

1 What laboratory investigations are required for patients with metabolic acidosis?

When patients present with metabolic acidosis, perform investigations for the following urgently:

- Lactate: a high lactate level in critically unwell patients is a marker of poor prognosis
- Serum electrolytes and creatinine: to assess kidney function and to calculate the anion gap
- Serum osmolality: to calculate the osmolal gap
- Serum ethanol: to exclude alcoholic ketoacidosis
- Serum glucose: to investigate the possibility of diabetic ketoacidosis
- Serum calcium: to exclude hypocalcaemia, which is an uncommon finding in patients with ethylene glycol poisoning.

Evaluation of the anion gap (calculated by subtracting serum concentrations of bicarbonate and chloride anions from concentrations of sodium and potassium cations) helps to delineate the possible causes of metabolic acidosis. Metabolic acidosis with a normal anion gap (eg, with diarrhoea) results from loss of bicarbonate with retention of chloride.

Evaluation of the osmolal gap (calculated by subtracting the calculated serum osmolality from the measured serum osmolality) helps to identify the presence of exogenous osmotically active substances such as ethylene glycol and methanol.

Consider cerebrospinal fluid analysis if infectious meningitis is suspected and urine toxicology screen if there is reduced consciousness of unknown aetiology.

answers

2 What do the laboratory test results in table 1 show?

A raised serum anion gap, increased serum osmolal gap, severe metabolic acidosis, reduced bicarbonate level, and high lactate level.

Raised anion gaps most commonly result from increases in “unmeasured anions” (ie, anions except for sodium and potassium), which reduce bicarbonate concentrations.

Increased osmolal gaps occur in the presence of abnormal, unmeasured osmotically active molecules, which can be exogenous (eg, methanol, ethylene glycol) or endogenous (eg, hypertriglyceridaemia). In ethylene glycol poisoning this gap might decrease with time as the toxin becomes metabolised. The presence of ethylene glycol metabolites can also affect the measurement of lactic acid.

The normal ethanol concentration ruled out alcoholic ketoacidosis.

The normal salicylate concentration excluded aspirin ingestion as a cause of the high anion gap metabolic acidosis. The normal venous blood glucose concentration suggested that diabetic ketoacidosis was unlikely.

3 What are the differential diagnoses in this case?

Infectious meningitis can cause headache with lactic acidosis and raised white cell count.

Recurrent encephalopathy with lactic acidosis could be caused by a mitochondrial disorder—differentiating tests are serum creatinine kinase, cerebrospinal fluid lactate measurements, and skeletal muscle biopsy.

The patient’s history of depression and paracetamol overdose increased the possibility of an ingested toxic substance.

In patients with altered mental state and a high anion gap metabolic acidosis, consider the mnemonic CAT MUDPILES (Cyanide/Carbon monoxide, Alcoholic ketoacidosis Toluene, Methanol, Uraemia, Diabetic ketoacidosis, Paraldehyde, Isoniazid/Iron, Lactic acidosis, Ethylene glycol, Salicylates).

The following investigations can also help to elicit the cause of a high anion gap metabolic acidosis: blood glucose, ketones, lactate, methanol (if available), salicylate concentrations, and blood ethylene glycol concentration (if available), and urinalysis to assess for the presence of calcium oxalate crystals (which are present in about half of patients with ethylene glycol poisoning).

PATIENT OUTCOME

Treatment for presumed infectious meningitis was started. Serum creatinine kinase and cerebrospinal fluid lactate measurements were obtained (table 2) and the plan was to perform a skeletal muscle biopsy.

On day 2 of admission, magnetic resonance imaging showed evidence of tonsillar herniation and cerebral global hypoxic changes, and the patient developed acute kidney injury (table 2). The patient died on day 3.

Glycolic acid and oxalic acid were found on post mortem urinalysis, and calcium oxalate crystals were identified on histology of the leptomeninges. The coroner considered ethylene glycol overdose to be the most likely cause of death.

The high cerebrospinal fluid protein level might have been related to breakdown of the blood-brain barrier after a period of seizure activity before death, with cerebral hypoxic changes and tonsillar herniation. Noticeably high protein cerebrospinal fluid levels have been documented in patients with ethylene glycol poisoning.

LEARNING POINTS

- For critically unwell patients with no clear cause, seek early intensivist advice.
- Check venous blood for electrolytes, ethanol, glucose, calcium concentration, and osmolality when patients present with metabolic acidosis
- Consider the mnemonic CAT MUDPILES for acutely unwell patients with a high anion gap metabolic acidosis
- Undertake urinalysis for calcium oxalate crystals if ethylene glycol poisoning is suspected.

Table 2 | Laboratory test results on admission to intensive care unit (day 0) and day 2 after admission. Relevant venous blood test results on presentation to the emergency department (day 0) are included for comparison

Investigation	Results		Normal range
	Day 0	Day 2	
Cerebrospinal fluid tests			
Protein	11822 mg/L	-	150-400
Glucose	3.1 mmol/L	-	60-80% of plasma value
Lactate	11.8 mmol/L	-	0.9-1.8 mmol/L
White cell count	250 cells×10 ⁶ /L	-	0-5 cells×10 ⁶ /L
Microscopy	No organisms	-	
Polymerase chain reaction:			
<i>Neisseria meningitidis</i>	Negative	-	
Pneumococcus	Negative	-	
Enterovirus	Negative	-	
Parechovirus	Negative	-	
Herpes simplex virus	Negative	-	
Varicella-zoster virus	Negative	-	
Microbiological culture			
Creatinine kinase	144 U/L	-	40-320 U/L
Haemoglobin	154 g/L	95 g/L	135-169 g/L
Venous blood tests			
White cell count	23.4 cells×10 ⁹ /L	11.5 cells×10 ⁹ /L	4.5-13 cells×10 ⁹ /L
Neutrophil count	13.7 cells×10 ⁹ /L	10.0 cells×10 ⁹ /L	2-7.5 cells×10 ⁹ /L
C reactive protein	5.1 mg/dL	244 mg/dL	0-8 mg/dL
Glucose	5.8 mmol/L	7.4 mmol/L	3-6 mmol/L
Urea	5.7 mmol/L	7.4 mmol/L	2.5-7.8 mmol/L
Creatinine	112 μmol/L	226 μmol/L	64-110 μmol/L
Estimated glomerular filtration rate	≥90 ml/min/1.73m ²	33 ml/min/1.73m ²	90-120 ml/min/1.73m ²
Adjusted calcium	2.3 mmol/L	2.6 mmol/L	2.2-2.6 mmol/L
Chloride	112 Mmol/L	112 Mmol/L	95-108 Mmol/L
Serum anion gap	27.5 mmol/L	32.9 mmol/L	8-16 mmol/L
Serum osmolal gap	15.5 mmol/kg	-3.0 mmol/kg	-10-10 mmol/kg



You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.



Articles with a “learning module” logo have a linked BMJ Learning module at <http://learning.bmj.com>.

Hemichorea in non-ketotic hyperglycaemia

This is a brain magnetic resonance image (MRI) of a woman in her 70s with hemichorea associated non-ketotic hyperglycaemia (HC-NKH) because of poorly controlled diabetes (white arrowhead).

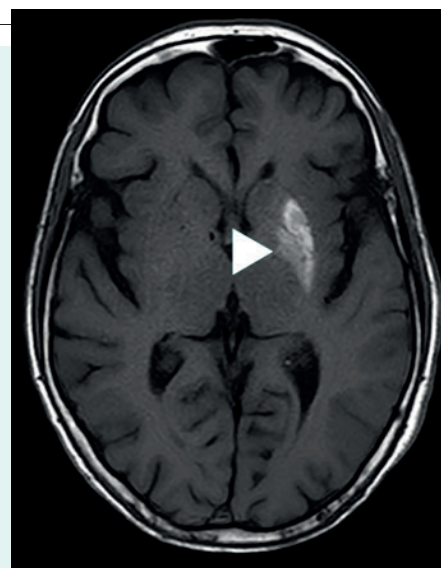
The patient had experienced involuntary choreatic movements on her right side for seven days. Neurological examination was normal. Her blood glucose level was 18.6 mmol/L (normal range 3.9-6.1 mmol/L) and haemoglobin A_{1c} concentration was 77 mmol/mol (normal range 20-42 mmol/mol). No ketones were found in urine or blood.

Computed tomography, the initial choice of imaging, suggested hyperdensity in the left lenticular nucleus. Subsequent MRI confirmed T1 hyperintensity, which, although not always present in HC-NKH, is diagnostic of the disorder.

HC-NKH is a rare and reversible hyperkinetic movement disorder predominantly seen in older women with poorly controlled diabetes. It should be considered in patients presenting with hemichorea (acute onset of unilateral, random, irregular contractions of distal extremities face, and trunk) and non-ketotic hyperglycaemia. MRI is the imaging modality of choice, and in 87% of patients visible T1 hyperintensity confirms the diagnosis.

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If you would like to write a Minerva picture case, please see our author guidelines at <http://bit.ly/29HCBAL> and submit online at <http://bit.ly/29yyGSx>

Suicides during the covid-19 pandemic

Covid-19 has had a deleterious effect on the mental health of many people. However, an analysis of national data reports that suicides in Finland are no more frequent than would be expected from pre-pandemic rates (*Br J Psych* doi:10.1192/bjp.2021.136). Indeed, numbers of suicides have declined for every consecutive month during the pandemic period.

Eating disorders

By contrast, eating disorders have become commoner during the pandemic. According to a study from the US based on electronic health records of 5 million people, diagnoses of eating disorders were around 15% higher in 2020 than in previous years (*Br J Psych* doi:10.1192/bjp.2021.105). The increase occurred mainly as anorexia nervosa in teenage girls.

No health benefits from low and moderate alcohol consumption

The J shaped curve obtained when mortality is plotted against alcohol intake seems to suggest that total abstinence is associated with a lower life expectancy than low or moderate alcohol consumption. However, in a population sample from northern Germany, most abstainers were former consumers of alcohol and had risk factors that increased the likelihood of early death. Mortality in abstainers who lacked these

risk factors was no higher than in those who consumed low to moderate amounts of alcohol (*PLoS Med* doi:10.1371/journal.pmed.1003819).

Machine learning to target covid-19 testing of travellers

So far, the performance of machine learning models for diagnosing covid-19 has been disappointing. An exception is the application of artificial intelligence to the targeting of testing in travellers. The approach has been highly successful in Greece, where the algorithm doubled the number of cases detected per test and allowed the country to keep its borders open (<https://www.nature.com/articles/d41586-021-02556-w>).

Fish oils and atrial fibrillation

A couple of years ago, a Cochrane review concluded that long chain omega 3 fats had no benefits on mortality or the incidence of cardiovascular events. It now looks as if they may be harmful—at least as far as arrhythmias are concerned. A systematic review of randomised controlled trials of supplements of marine omega 3 fatty acids discovered an increase in rates of atrial fibrillation (*Circulation* doi:10.1161/CIRCULATIONAHA.121.055654). The risk was greatest in trials testing supplementary doses of more than 1 g/d.

Diagnoses of eating disorders were around 15% higher in 2020 than in previous years

Measuring blood pressure

Guidelines stipulate a rest period of 3 to 5 minutes before blood pressure is measured—a rule that is ignored more often than it is followed in clinical practice. However, a crossover trial finds that this probably doesn't matter much. In people with systolic pressures below 140 mm Hg, differences in pressures after 0, 2, and 5 minutes of rest were nugatory (*Hypertension* doi: 10.1161/HYPERTENSIONAHA.121.17496).

More on measuring blood pressure

The recommendation that an interval of 1 to 2 minutes should be left between repeated blood pressure measurements may not be justified either. Among a group of people whose blood pressure had already been characterised by 24 hour ambulatory monitoring, half the participants had three blood pressure measurements separated by 30 seconds and the other half had measurements separated by 60 seconds. Using a 30 second interval between measurements gave as accurate a result as a 60 second interval (*Hypertension* doi:10.1161/HYPERTENSIONAHA.121.17876).

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