education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Cardiovascular risk in China

Lu et al report on a national cardiovascular screening project in China, where 1.7 million people aged 40 to 75 with no known cardiovascular disease were screened. As one might expect, 9.5% had high cardiovascular risk. The more pertinent finding was the incredibly low rates of statin and aspirin prescriptions. Less than 3% of those at high risk were receiving statins or aspirin. There was also substantial underuse of antihypertensives, although this was not nearly as notable as for aspirin and statins. This study makes a clear case for infrastructure to educate and offer primary prevention on a large scale, despite financial and cultural barriers.

Ann Intern Med doi:10.7326/M18-1932

VOT is the new DOT

Video observed therapy (VOT) for tuberculosis was compared with directly observed therapy (DOT) in a randomised controlled trial set up at 22 UK sites. Video observed therapy was done by a daily recording on a smartphone app, whereas directly observed therapy was three to five times a week with a healthcare or lay worker. Video observed therapy was found to be more effective and cheaper over a two month treatment period. These data are promising for the target population of what they refer to as "socially complex" patients. There is a caveat to this though. Although smartphones were provided free of charge by the study team, patients who did not have access to a place to charge a phone were excluded from the study. It is disappointing that this was an exclusion criterion as it is likely to discriminate against the very people this intervention is supposed to be for. Various creative solutions could have been implemented to address this, but never mind.

Lancet doi: 10.1016/S0140-6736(18)32993-3

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Anal incontinence and caesarean delivery

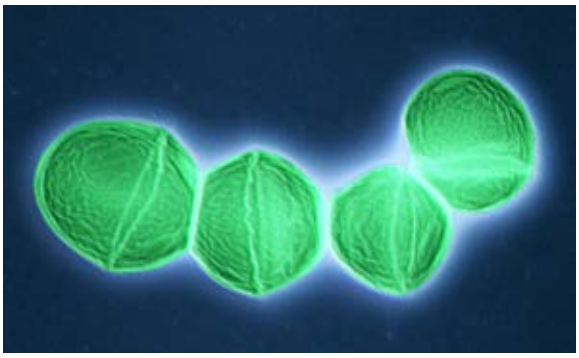
Using a Swedish nationwide registry, Larsson et al compared rates of anal incontinence between four groups: women who had had a caesarean delivery, women who had had a vaginal delivery, age matched nulliparous women, and age matched men. They included women who had given birth between 1973 and 2015 and excluded women who had had a multiple birth delivery, those who had four or more deliveries, and those who had had both vaginal and caesarean deliveries. This enabled them to make the best assessment of comparative risks. They found a lower risk of anal incontinence after caesarean delivery compared with vaginal delivery, although not as low as that of nulliparous women, which suggests aspects of the pregnancy other than the mode of delivery contribute to anal incontinence. Of the four groups, men had by far the lowest risk of anal incontinence.

Lancet doi:10.1016/S0140-6736(18)32002-6

Invasive Group B streptococcus

It is easy to become disillusioned about epidemiological studies because the findings can seem far removed from day to day clinical practice. This study of invasive group B streptococcus in non-pregnant adults in the US from 2008 to 2016 bucks the trend by being interesting and also concerning. Invasive group B streptococcus was defined as group B streptococcus isolated from a normally sterile site (blood, joints, and bones most commonly). Francois Watkins et al found that the incidence has been increasing. Invasive group B streptococcus was more common in men than women, in black people than white people, and in older age. In 2016, the incidence in people over 80 was more than 40 cases per 100 000 people. Antibiotic resistance rates are also increasing. Ninety five per cent of affected people had at least one underlying condition, usually obesity or diabetes. Perhaps understanding the characteristics of who is affected by this condition will provide insight into how group B streptococcus transfers. All in all, this important study provides an excellent basis for planning strategies for prevention and treatment of this condition.

JAMA Intern Med doi:10.1001/jamainternmed.2018.7269



CLINICAL UPDATES

Pertussis (whooping cough)

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Pertussis (whooping cough) is caused by the Gram negative bacterium *Bordetella pertussis*.[1] It is transmitted via airborne droplets and is highly infectious.[2] Diagnosis is often delayed or missed,[3] as pertussis mimics the presentation of a viral upper respiratory tract infection and can sometimes present atypically.[2]

CPD READING
0.5 HOURS

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How common is it?

Pertussis affects nearly 24 million children under the age of 5 years each year and causes 160 000 deaths in this age group.[4 5] Peak incidence is seen in infants up to 6 months of age.[6] This may be due to the timing of vaccination in the latter part of or after this 6 month period. In the United Kingdom and Australia, which have an accelerated primary vaccination schedule at 2, 3, and 4 months, higher incidence and hospitalisation rate is observed in those under 3 months old compared with older infants.[7] Mortality is high in this group,[1 8 9] possibly due to an immature immune system and incomplete primary immunisation.[10]

About 3% of adults presenting with acute cough in European primary care have pertussis.[3] Outbreaks of pertussis have been reported every 2 to 5 years, mainly in adolescents and adults.[11] Overweight or obese people and those with pre-existing respiratory conditions such as chronic obstructive pulmonary disease (COPD) or asthma are at increased risk.[12-14]

How do patients present?

After an incubation period of 4-21 days from exposure, patients present with symptoms of an upper respiratory tract infection such as coryza, low grade fever, and cough.[5 15] This is followed by the classic signs of pertussis: cough paroxysms followed by characteristic inspiratory whoop and vomiting[15] that can last for up to 10 weeks, followed by recovery. Coughing may be mild or severe. The illness can last up to 3 months and is colloquially termed "the 100 day cough."[16] Figure 1 presents the typical course of pertussis.

Occasionally patients present with atypical symptoms[2 18 19] such as breathlessness, wheeze,[20] fever, flushing, and stridor in children, and diarrhoea and breastfeeding difficulties in infants.[21] Adults may report sneezing attacks, sweating, hoarseness of voice, headache, sleep disturbance, weight loss, and fatigue.[22 23]

How is it diagnosed?

Making a clinical diagnosis is often difficult due to overlapping symptoms with an upper respiratory tract infection. Patients are often diagnosed after the 21 day window when antibiotics may be useful to prevent transmission. Pertussis may not be suspected in patients who have completed their vaccination schedule under the assumption that vaccination confers lifelong immunity.

Suspect pertussis in patients with characteristic features (see box on clinical criteria). The presence of symptoms for 2 weeks is helpful but not essential to make a diagnosis.[27 28] The presence of post-tussive vomiting and inspiratory whoop in adults increases the likelihood of pertussis (sensitivity 30-33%, specificity 78-80%).[29] Conversely, the lack of a paroxysmal cough or the presence of fever rules it out (sensitivity 82-93%, specificity 19-21%). In children, post-tussive vomiting was less helpful in making a clinical diagnosis (sensitivity 60%, specificity 66%).

WHAT YOU NEED TO KNOW

- Suspect pertussis in patients with 2 weeks of cough and coughing paroxysms, post-tussive vomiting, inspiratory whooping, no fever, or exposure to a person with confirmed pertussis
- Immunisation is no guarantee of protection as vaccine efficacy decreases with time
- Antibiotics within the first 21 days of illness can prevent transmission, but cough is likely to last up to 3 months and there are no recommended treatments for it
- Consider admission if patient is clinically unwell or less than 6 months old, when mortality is higher
- Report suspected and confirmed cases of pertussis to local public health agencies to initiate infection control measures
- Offer pertussis vaccination to pregnant women in the second or third trimesters of pregnancy as it can provide passive immunity to neonates and young infants

Clinical criteria for diagnosing pertussis[24-26]

Cough lasting for at least 2 weeks with at least one of the following symptoms:

- Coughing paroxysms or fits
- Inspiratory whooping
- Post-tussive vomiting without other apparent cause
- Apnoea with or without cyanosis for infants <1 year old

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We consulted a parent whose child was affected by pertussis at the article planning and completion stage, who suggested that we discuss long term sequelae of pertussis. The parent of a child with pertussis contributed the patient perspective on bmj.com. One of the authors who was affected by pertussis suggested discussing treatment of pertussis-associated cough.

thebmj Visual summary

Managing suspected pertussis

Diagnosis of pertussis, commonly known as whooping cough, is often delayed. This is because symptoms are similar to those of a viral upper respiratory tract infection, and may occur in children and adults with partial or even complete vaccination. Management is summarised below, and is dependent on whether diagnosis is made within the 21 day window in which antibiotics may be useful to prevent transmission.

1 History & examination

Consider pertussis if one or more of the following symptoms are present in anyone who has 14 or more days of symptoms:

- Cough and coughing paroxysms
- Inspiratory whooping
- Post-tussive vomiting
- Apnoea in infants

or recent exposure to a case of confirmed whooping cough

Consider admission if:

- Signs of complications such as apnoea or pneumonia
- Age is < 6 months

2 Chemoprophylaxis

Offer treatment before positive test results, such as:

- CLR — Clarithromycin — 7 days
- AZM — Azithromycin — 3-5 days

For pregnant women in the last month of pregnancy, consider:

- ERY — Erythromycin

3 Close contacts

Consider antibiotics for close contacts if index case disease onset < 21 days

- Partially immunised infants
- People with respiratory disease or immunodeficiency
- Pregnant women > 32 weeks' gestation

Also consider antibiotics for people who live or work with any of the above

4 Exclusion

Recommend not attending or working in:

- Nurseries
- Schools
- Health settings

Duration of exclusion

- 48 hours from commencement of antibiotics
- 21 days from onset of symptoms

5 Testing

Age 0-3 months	Age 4+ months
Culture	**Serology**
ONE OF: Throat swab; Nasopharyngeal aspirate	ONE OF: Blood test; Oral fluid swab; Throat swab
False negatives possible after 3 weeks of illness onset	To be performed if ≥ 1 year after immunisation

AND

Polymerase chain reaction (PCR)

ONE OF: Naso-pharyngeal swab; Nasal swab; Throat swab

Decreased sensitivity and increased false positive rate after 4 weeks of illness onset

6 Health protection

Inform local agencies for case notification or for advice if appropriate

7 Vaccination

Completion of unvaccinated and partially vaccinated close contacts and cases after full recovery

Pregnant women should be offered vaccination in the 2nd and 3rd trimesters

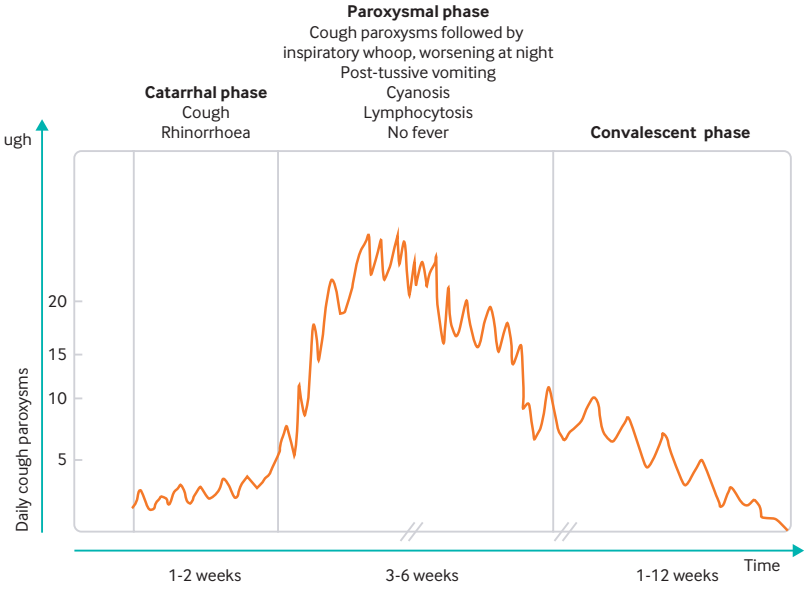

Fig 1 | Diagrammatic representation of the frequency of daily cough paroxysms against clinical course of pertussis.[17] Reproduced with permission from the World Health Organization

What other diagnoses should I consider?

Consider other conditions causing acute cough (<3 weeks) and chronic cough (>8 weeks). Respiratory infections present acutely and are often associated with other symptoms such as purulent sputum production and fever. Asthma, cough-variant asthma, cystic fibrosis, and *Mycoplasma* or adenovirus infection may cause chronic cough.[30 31] Non-respiratory causes such as allergic rhinitis and gastro-oesophageal or laryngo-oesophageal reflux may also present with cough.[30 31]

What investigation to request?

Pertussis can be diagnosed clinically, and diagnostic testing should not delay treatment.[32] Testing will allow confirmation of the diagnosis and is helpful for immunotyping and surveillance, especially during an outbreak. The infographic shows suggested investigations based on the duration of cough and patient's age.[33 34] Timing the tests in relation to the onset of symptoms is important as delay often decreases test accuracy, and a negative test result may be falsely reassuring (fig 2).

Culture

Nasopharyngeal bacterial culture from a throat swab or aspirate is the best method for diagnosis of pertussis[35] (sensitivity 58%, specificity 100%).[33 36 37] The sensitivity is lower beyond 2 weeks of illness and in older people because of lower bacterial loads.[33 38] Oral fluid samples are less reliable because of the risk of microbial contamination.[33] Culture generally takes 4-5 days[36] but may take up to 12 days,[33] making it the slowest diagnostic modality.

Polymerase chain reaction (PCR)

PCR testing of nasopharyngeal specimens provides a rapid diagnosis, usually within hours,[32] and has a high sensitivity (77-97%) and specificity (88-97%).[33 36 37 40] Testing is ideally done within the first 4 weeks of illness.[38] There have been concerns about cross reactivity with other *Bordetella* species and inability to differentiate between live or dead bacteria, which may cause a false positive diagnosis.[33 39 41]

Serology

Testing for IgG to the pertussis toxin can be performed 2 weeks after the illness and up to the eighth week.[26 43] The results with testing blood (sensitivity 88-92%, specificity 98-99%)[44] or oral fluid or a throat swab (sensitivity 80%, specificity 97%)[45] are comparable. Serology is not advised in infants and in patients vaccinated within the previous year, as the test cannot differentiate vaccine induced or maternal antibodies from infection induced antibodies.[33 48]

What are the risks?

Infants have a high risk of mortality due to pulmonary hypertension and resultant cardiac failure and shock.[1 8 40 50] Children are prone to dehydration and anorexia. Rarely, seizures and encephalopathy have been reported.[1 15 22 23] Acute cough-related complications include pneumothorax, aspiration, urinary incontinence, and increased risk of rib fractures, particularly in older adults.[23] Patients may develop sinusitis, secondary bacterial pneumonia, and otitis.

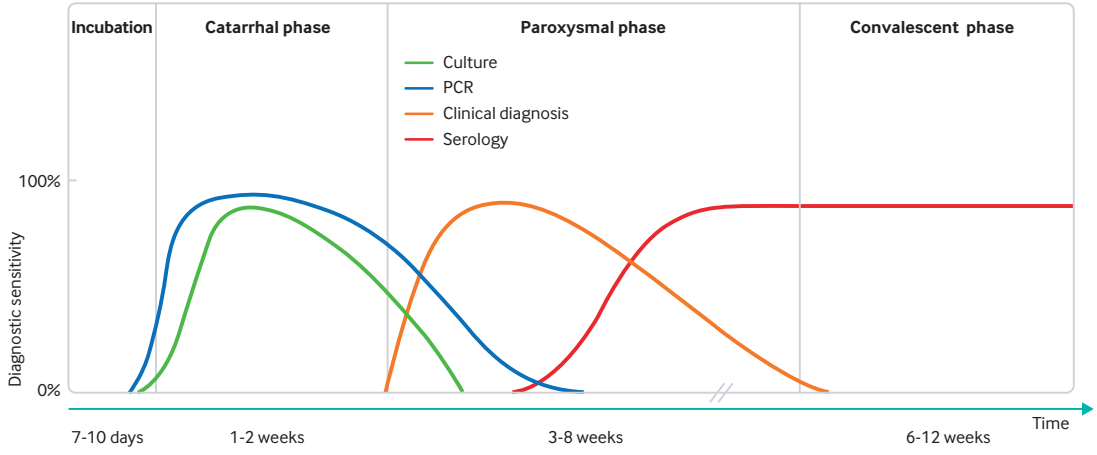

Fig 2 | Relative diagnostic sensitivities of culture (green), polymerase chain reaction (PCR) (blue), clinical diagnosis (orange), and serology (red) and during different stages of *B pertussis* infection. The represented sensitivities were idealised for clarity[33]
Reproduced with permission from the American Society of Microbiology

When to refer?

Urgently refer infants under the age of 6 months with suspected pertussis for hospitalisation. There is no guidance on referring older children and adults with suspected or confirmed pertussis. It is prudent to refer patients with signs of cardiorespiratory compromise, including apnoea and cyanosis; those with pre-existing respiratory conditions; and signs of complications such as dehydration, pneumonia, or encephalopathy.[9]

How is it managed?

No medications provide symptomatic relief from pertussis-associated cough. Antibiotics eliminate *B pertussis* from the nasopharynx and reduce the risk of transmission. They have not, however, been shown to reduce the duration or severity of cough. A Cochrane systematic review found no benefit of treatments such as oral diphenhydramine, intravenous pertussis immunoglobulin, or inhaled salbutamol on the frequency of coughing paroxysms compared with placebo.[60]

Preventing transmission

Explain the role of antibiotics and initiate treatment in patients with suspected or confirmed pertussis within 21 days of symptom onset. Beyond the first 21 days of illness, or 2 days of antibiotic treatment, patients are no longer infectious.[26 57 58] Azithromycin taken for 3-5 days, or clarithromycin or erythromycin taken for 7 days are effective.[59] Be aware of potential drug interactions of macrolides in patients taking medications such as theophylline or warfarin.[58] Co-trimoxazole is recommended for patients allergic to macrolides.

Advise patients who attend or work in nurseries, schools, and healthcare settings to refrain from attending for 48 hours after initiation of antibiotics, or for 21 days from onset of symptoms.[26] Offer vaccination to unimmunised and partially immunised children under the age of 10 years after recovery.[26 43]

Report suspected cases to local public health agencies, even while diagnostic test confirmation is awaited, to facilitate tracing of contacts and timely chemoprophylaxis.

Pregnant women

Avoid antibiotics in the first trimester of pregnancy. They may be advised later in the pregnancy if there is risk of transmission to vulnerable close contacts. They have limited benefit for the affected woman. If the woman is affected in the last month of pregnancy, erythromycin is recommended to prevent neonatal transmission.[26]

What measures are needed in close contacts of the patient?

Offer antibiotics to household contacts within 21 days of disease onset of the index case.[43] Chemoprophylaxis is also advised for other close contacts of the patient who work or live with them and are at high risk (people with pre-existing health conditions such as asthma or immunodeficiency, unimmunised or partially immunised infants, and pregnant women over 32 weeks' gestation).[26 43]

Encourage unimmunised or partially immunised contacts less than 10 years of age to complete the course of primary immunisation, and offer a booster dose to contacts above 10 years old who have not received a dose in the past 5 years.[26]

EDUCATION INTO PRACTICE

- How would you ask about cough in patients with symptoms for 2 weeks or more?
- Review your clinic or practice records for women booked for antenatal care to see if vaccination during pregnancy is consistently discussed or offered.
- Think about the last time you talked to a parent (on behalf of child) or patient about declining vaccination based on research on the Internet. How would you provide a balanced view of the benefits of pertussis vaccination? What resources could you use?

How can it be prevented?

Primary immunisation

Vaccination is estimated to have prevented 78% of disease-associated mortality and 1.3 million deaths worldwide, presumably by reducing incidence of pertussis.[61] Most countries complete three primary vaccinations in the first 6 months of life with boosters given thereafter.[5 7]

Several high income countries have switched from whole cell to acellular pertussis vaccines because of their decreased reactogenicity and better adverse effect profile. The evidence on relative effectiveness and duration of active immunity of the vaccines is inconsistent.[5 62] The effectiveness of acellular pertussis vaccine decreases with time,[64] as reported in several case-control studies.[65-69] The short protection provided by vaccination suggests the possibility of repeated infections in both immunised and non-immunised individuals. The need for regular pertussis boosters throughout life must be explored.[70]

The World Health Organization recommends that countries using whole cell pertussis vaccine should continue to do so and consider a switch to the acellular vaccine only if additional periodic booster or vaccination in pregnant women can be assured and sustained.[5]

Vaccination in pregnancy

Pertussis vaccination in pregnancy may provide passive immunity to the infant via transplacental transfer of IgG, before primary immunisation.[72 73] Assure women that the vaccine is safe in pregnancy.

The optimal timing of maternal pertussis immunisation is not established. Observational studies indicate that pertussis vaccination in the third trimester reduced infection, hospitalisation, and mortality in infants compared with no vaccination in pregnancy.[74-78] Guidelines from Public Health England[26] and Centers for Disease Control and Prevention[84] recommend vaccination at 16-32 weeks and 27-36 weeks of gestation respectively. Immunisation in the second trimester may be preferred as it can protect preterm infants, allow more time for maternal antibody transfer, and can logistically be combined with a routine antenatal check.[85-87] Offer vaccination in every pregnancy as maternal antibody titres decrease rapidly after delivery.[88]

Competing interests: None declared.

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PRACTICE POINTER

Diabetes insipidus

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This Practice Pointer offers an approach to diagnosing suspected diabetes insipidus, and guidance on managing people with diabetes insipidus who have intercurrent illness or require hospital admission. Diabetes insipidus is a rare but treatable condition that typically presents with extreme thirst (polydipsia) together with the passing of large amounts of dilute urine (polyuria). Distinguishing these symptoms from those of primary polydipsia, diabetes mellitus, and causes of urinary frequency without polyuria can be challenging. Diabetes insipidus is caused by a problem with vasopressin production in the pituitary gland (central diabetes insipidus), or action of vasopressin in the kidneys (nephrogenic diabetes insipidus). Desmopressin, an analogue of vasopressin, is an effective treatment for cranial diabetes insipidus. Between 2009 and 2016 there were four reported deaths in England resulting from omission of desmopressin, and a further 56 reported incidents in which dosing errors resulted in harm.[1]

CPD READING
0.5 HOURS

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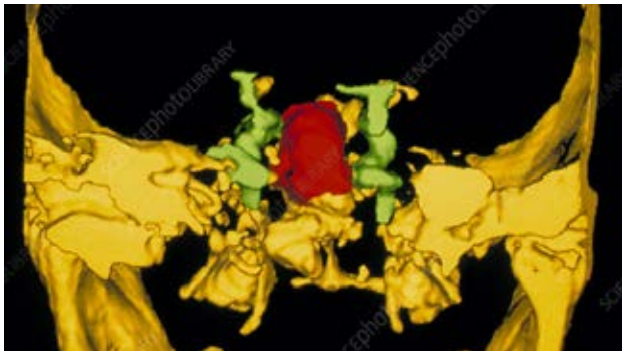
What is diabetes insipidus?

Diabetes insipidus is rare, with a prevalence of 1 in 25 000.[2] Central diabetes insipidus usually results from pituitary pathology,[3] either as a result of infiltrative or inflammatory pathology, or following surgery for a pituitary tumour (below left), but may also be due to a congenital defect in the production of arginine vasopressin.[3] Nephrogenic diabetes insipidus is usually caused by electrolyte disturbance, renal disease, or drug toxicity (commonly lithium[2]).

Arginine vasopressin causes water reabsorption at the collecting ducts of the kidney. Deficiency of or resistance to the hormone, as seen in diabetes insipidus, leads to excessive water loss resulting in polyuria. Typically, the compensatory drive for thirst will provide adequate rehydration, but in severe cases when there is not ready access to water, someone with diabetes insipidus can become rapidly dehydrated, which may lead to hyperosmolality, hypernatraemia, and potentially death.[1]



Coloured three dimensional computed tomography (CT) scan of a tumour (red) of the pituitary gland

How is diabetes insipidus diagnosed?

Presenting symptoms

Extreme thirst and passing large quantities of pale urine are typical presenting symptoms of diabetes insipidus. It may be difficult to distinguish diabetes insipidus from differential diagnoses with these symptoms, but there are pointers in the history and investigation that can help (table). A particular challenge is primary polydipsia, which refers to a psychologically driven increase in fluid intake rather than impaired vasopressin regulation and is often seen in patients with severe mental illness and/or developmental disability,[4 5] although it may simply be behavioural and occur in healthy individuals in the absence of psychiatric disease. Polyuria should be distinguished from urinary frequency in the history, the latter suggesting a urological problem.

In central diabetes insipidus, the history of polyuria and polydipsia is usually abrupt, presenting within weeks or months of onset.[3] In nephrogenic diabetes insipidus, the onset is more insidious and patients have often had symptoms for months or years before the diagnosis is made.[2]

Symptoms suggestive of pituitary disease may include fatigue, dizziness, irregular periods, and galactorrhoea in women, or loss of libido and reduced secondary sexual characteristics in men.

Ask about a history of pituitary disease, major head injury, or neurosurgery, which are risk factors for central diabetes insipidus. Several genetic mutations have been identified for the condition, so a family history of central or nephrogenic diabetes insipidus may be highly relevant.[2 3]

Look carefully at medication history. Patients taking loop diuretics and nephrotoxic drugs are at risk of developing nephrogenic diabetes insipidus.[7] Nephrogenic diabetes insipidus occurs in approximately 15% of patients taking lithium.[7]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were directly involved in the writing of this article. A person with diabetes insipidus wrote the *Patient perspective*.

WHAT YOU NEED TO KNOW

- In patients with polyuria, diabetes insipidus is very unlikely if urine osmolality is >700 mOsmol/kg
- Patients with central diabetes insipidus who are admitted to hospital should have specialist input and safeguards in place to ensure that desmopressin is not omitted
- Intercurrent illness with hypernatraemia in a patient with diabetes insipidus should be managed as a medical emergency

Clues to help distinguish diabetes insipidus from primary polydipsia			
	Primary polydipsia	**Central diabetes insipidus**	**Nephrogenic diabetes insipidus**
Comorbidities	History of psychiatric disease[4 5]	History of pituitary disease, brain injury, or neurosurgery	History of lithium therapy or renal disease
Timing of symptoms	Longstanding symptoms.[6] Symptoms worse in daytime.Patient wakes with thirst rather than need to pass urine	Rapid onset Symptoms[3] bad day and night. Patient wakes with need to pass urine as well as thirst	Insidious onset Symptoms day and night, and may have been present for months or years[2]
Response to reduced intake of fluid	Polyuria may improve with reduced fluid intake	Polyuria does not improve with reduced fluid intake	Polyuria does not improve with reduced fluid intake

Initial investigation

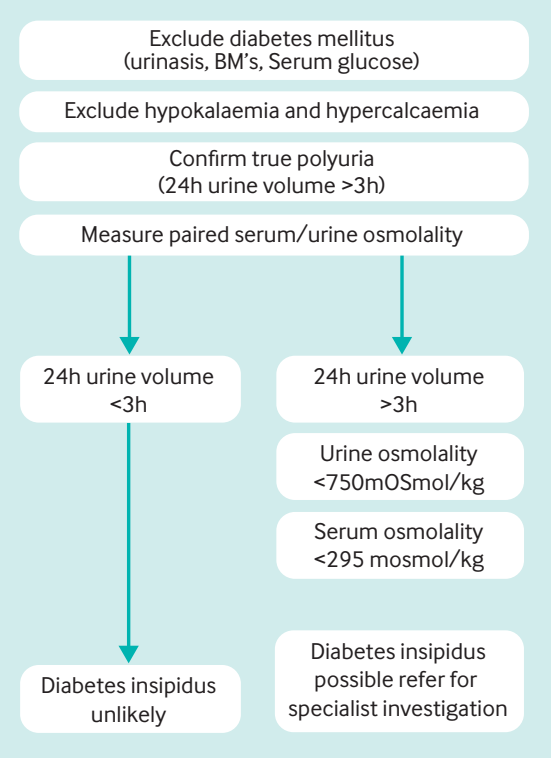
The initial investigation of a patient presenting with polyuria and polydipsia is summarised in the figure.

Diabetes mellitus—Exclude diabetes mellitus either by urinalysis or point of care testing, confirmed by formal measurement of fasting or random glucose.

Electrolyte disturbance—Take blood to exclude hypercalcaemia and hypokalaemia as these can cause nephrogenic diabetes inspidus.[2]

Urine volume—If 24 hour urine volume is less than 2.5 L, diabetes insipidus is highly unlikely and other causes of urinary symptoms should be considered. Urine volume can be measured by the patient themselves (eg, with a measuring jug), or a 24 hour collection bottle can be given and sent to the laboratory for measurement of volume only.

Paired urine and plasma osmolality—If 24 hour urine volume exceeds 2.5 L, paired serum and urine osmolalities can help to distinguish diabetes insipidus from polyuria caused by primary polydipsia. If baseline urine osmolality is >700 mOsmol/kg, diabetes insipidus is very unlikely as the ability to concentrate urine adequately has been demonstrated. Diabetes insipidus is likely if serum osmolality is high (>295 mOsmol/kg) and urine osmolality low (<300 mOsmol/kg). Because patients with diabetes insipidus compensate by drinking according to thirst, it can be difficult to distinguish diabetes insipidus from primary polydipsia on the basis of a one-off paired urine and plasma osmolality measurement.[6] In this situation it may be necessary to perform more complex investigations in the specialist setting.



Biochemical assessment of polyuria and polydipsia

Referral and specialist management

Patients with suspected diabetes insipidus should be referred for specialist investigation and treatment. The urgency of referral depends on the severity of symptoms. If thirst and polyuria are extreme and serum osmolality >295 mOsmol/kg, refer patients within days or a few weeks at most. Patients with known diabetes insipidus who have hypernatraemia should be seen as an emergency the same day.

Specialist investigations

Water deprivation test—Currently, in equivocal cases where the diagnosis of diabetes insipidus is not clear cut, the water deprivation test is the most common confirmatory test used in specialist care.[6] In this test, the person is deprived of water for several hours while their urine output, urine osmolality, and serum osmolality are monitored over time. In patients with severe diabetes insipidus, water deprivation can be highly unpleasant and should be supervised by the endocrine team with continued measurement of serum and urine osmolality, urine volume, and weight. In people with diabetes insipidus there is continued polyuria and low urine osmolality despite water deprivation. If urine output falls and urine osmolality exceeds 750 mOsmol/kg, diabetes insipidus is excluded. In such cases primary polydipsia is more likely. In the second part of the water deprivation test, desmopressin is given to those with confirmed diabetes insipidus. Patients with central diabetes insipidus respond to desmopressin with a rise in urine osmolality and fall in urine volume. There is no response to desmopressin in patients with nephrogenic diabetes insipidus.

Other specialist investigations—There is an increasing move to measure copeptin, a marker of arginine vasopressin levels,[8] in response to hypertonic saline infusion. Detailed pituitary imaging such as magnetic resonance and positron emission tomography may help to differentiate between inflammatory and infiltrative pituitary disorders.

PATIENT PERSPECTIVE—THE WATER DEPRIVATION TEST

The test begins with the words "YOU WILL NOT DRINK ANY FLUIDS FOR THE NEXT EIGHT HOURS." If you do have suspected diabetes insipidus, you'll now be in a total panic! I would typically have at least five litres in eight hours—often much more. You are then told that all trips to the toilet will be escorted—just in case you find a dripping tap, or (bliss) a can of icy coke on the way. Half hourly blood tests will break the monotony and you'll carry a measuring jug at all times. After several hours of the test, any hope of a trickle of saliva has long gone—your tongue is firmly welded to the roof of your mouth. Can these doctors and nurses possibly imagine what you are going through? Why do they remark on your grey pallor and shuddering body—this is dehydration! Even with no fluids going in, your bladder will still twinge, like an annoying buzzing wasp urging you to empty it yet again. Where on earth is all this pee coming from? Finally, the doctor approaches with a cheery "the test is now over, you are free to drink." You'll gulp any fluid in sight—the entire ward's water jugs, the domestic's dirty water bucket! On completion of the test and if diagnosed, you'll receive an injection of desmopressin—the most wonderful medicine ever produced for a person with diabetes insipidus. That injection gives you back a normal bladder output, and the raging thirst is quelled. Temporarily, of course, but heaven while it lasts.

Management

Central diabetes insipidus—adequate fluid replacement, treatment of the underlying condition, and desmopressin administration are the mainstays of management. Desmopressin can be taken orally or via an intranasal spray.

Empowering patients to manage their own condition is an important part of management, and the endocrine specialist nurse plays a key role in this regard. The Pituitary Foundation produces a diabetes insipidus card and booklet for patients to carry, to alert the treating physician to the diagnosis in the event of an emergency.[10]

Nephrogenic diabetes insipidus—is managed with fluid replacement and cause specific treatment, under the care of a renal specialist.[2] Other treatments include diets low in salt and protein, diuretics, and non-steroidal anti-inflammatory drugs.[2]

Management of diabetes insipidus for the non-specialist

Inpatient care

The Society for Endocrinology has recently produced guidance for inpatient management of acutely unwell patients with diabetes insipidus.[11] These guidelines suggest that all patients admitted to hospital with central diabetes insipidus are identified on admission and that the endocrinology or alternative appropriate clinical team is alerted. Any patient with central diabetes insipidus who is admitted to hospital needs close monitoring of fluid replacement as well as appropriate administration of desmopressin.

All patients undergoing elective surgery should be highlighted in the pre-assessment process with a clear perioperative plan. They recommend hospitals develop an alert system to highlight all patients requiring ongoing desmopressin therapy to ensure doses are not missed.

A Society for Endocrinology survey of UK based endocrinologists suggests that the problem of delayed administration of desmopressin and fluids when patients are admitted to hospital is widespread.[12] Fifty-five per cent of respondents had concerns about management of patients with diabetes insipidus in their hospital, and 47% reported at least one patient coming to harm because of delayed administration of desmopressin or insufficient fluid replacement. An NHS patient safety alert has reported a series of critical incidents occurring in patients with central diabetes insipidus.[1] Between 2009 and 2016, four inpatient deaths caused by desmopressin omission were reported in England.[1] One was a 22 year old man with a benign pituitary tumour who died after a routine orthopaedic procedure. This safety alert identified several themes from these incidents, including a lack of awareness of the critical nature of desmopressin among medical, pharmacy, and nursing staff; poor availability of desmopressin within inpatient clinical areas; and omission due to nil-by-mouth status or acute illness. A small survey of non-specialist nursing staff found that some were not aware that diabetes insipidus was a different condition from diabetes mellitus.[1]

Intercurrent illness

Central diabetes insipidus—In those who are unwell with intercurrent illness, it is important to assess fluid status accurately and measure serum electrolytes. Patients with hypernatraemia should be managed as a medical emergency in a high dependency setting. Monitor serum sodium every four hours during fluid resuscitation. In patients who have impaired consciousness, it may be necessary to administer desmopressin by the intravenous, subcutaneous, or intramuscular route.

Nephrogenic diabetes insipidus—Patients are similarly at risk of hypernatraemia and severe dehydration. Seek specialist input ideally from the renal team. Treat the cause of the intercurrent illness, consider withdrawal of drugs which may be causing diabetes insipidus, as well as fluid resuscitation.

Competing interests: None declared.

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EDUCATION INTO PRACTICE

- Do your patients with diabetes insipidus have alerts on their electronic patient record that highlight the risk of desmopressin omission?
- How might you offer training to staff to highlight the difference between diabetes insipidus and diabetes mellitus?
- Do you offer safety cards to patients with diabetes insipidus?

CASE REVIEW

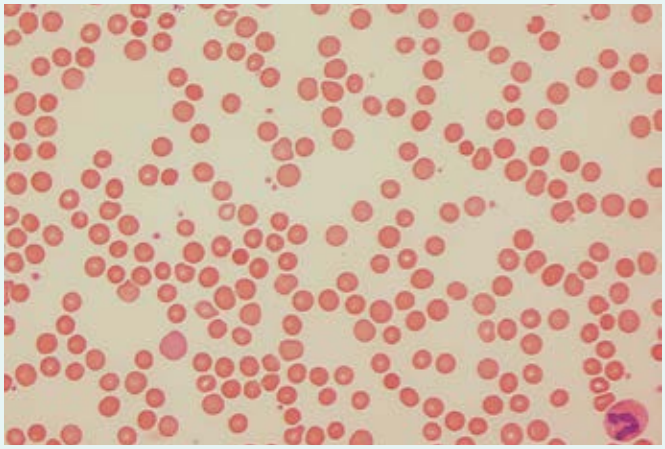
A woman with recurrent anaemia and jaundice

A 41 year old white woman presented to the emergency department. She described fever, cough, and exercise intolerance, yellowish discolouration of her eyes, and pain in the left upper quadrant that had been ongoing for three days. She had experienced three similar episodes in the past five years. Each episode resolved completely after treatment with antibiotics prescribed by her general practitioner. She had no other notable medical conditions or family history.

She appeared pale and had scleral icterus. Her spleen was enlarged and palpable below the left costal margin, firm in consistency, and mildly tender on palpation. Results of laboratory investigations are shown in the table.

Results of laboratory investigations

	Result	Reference range
Haemoglobin concentration	96 g/L	130 to 180 g/L
Mean corpuscular volume	87 fL	80 to 100 fL
Mean corpuscular haemoglobin concentration	368 g/L	320 to 360 g/L
White cell count	14.5 × 10^9/L	4.0 to 11.0 × 10^9/L
Absolute reticulocyte count	354 × 10^9/L	50 to 100×10^9/L
Lactate dehydrogenase	540 U/L	125 to 240 U/L
Indirect bilirubin	64 µmol/L	0 to 18 µmol/L
Haptoglobin	<0.01 g/L	0.3 to 2.0 g/L
Liver enzymes	Normal	
Direct antiglobulin	Negative	
Platelet count	Normal	



Blood film

Examination of peripheral blood film revealed abnormalities in red blood cell morphology (figure).

Ultrasonography of the abdomen confirmed splenomegaly with spleen size of 16 cm.

1 What is the most likely diagnosis?

2 How can you diagnose this condition?

3 How is this condition managed?

Submitted by Muhajir Mohamed and Wan Danial Noor

Patient consent obtained.

Cite this as: *BMJ* 2019;364:k5168

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answers

For extra material, including patient outcome, go to bmj.com/endgames

CASE REVIEW **A woman with recurrent anaemia and jaundice**

1 What is the likely diagnosis?

Hereditary spherocytosis presenting with haemolytic crisis.

There is marked spherocytosis and polychromasia on peripheral blood smear. The negative direct antiglobulin test and splenomegaly are suggestive of hereditary spherocytosis. In patients with hereditary spherocytosis, development of anaemic symptoms and jaundice in association with a rapid drop in haemoglobin and increase in indirect bilirubin and lactate dehydrogenase are suggestive of haemolytic crisis.

2 How can you diagnose this condition?

Initial investigations include full blood counts, reticulocyte count, peripheral blood smear, bilirubin, lactate dehydrogenase and direct antiglobin test. Haemoglobin, reticulocyte, and bilirubin levels are used to determine severity. Anaemia is typically mild to moderate and haemoglobin concentration may be within normal range (reticulocyte count remains high).

Diagnosis is usually confirmed by flow cytometric analysis of eosin-5-maleimide (EMA) labelled intact red blood cells (EMA binding test).

3 How is this condition managed?

There is no specific treatment for hereditary spherocytosis. If the patient is asymptomatic, no treatment is required. In more severe cases supplementation with folic acid and splenectomy are required to minimise complications of chronic haemolysis and anaemia. Infections can precipitate haemolytic crises in people with the condition, so investigate and treat any infection as necessary.

LEARNING POINTS

- Hereditary spherocytosis is an inherited disorder commonly manifesting as mild or moderate haemolytic anaemia.
- This condition is diagnosed by the presence of spherocytes in blood smear, negative direct antiglobulin test, along with a positive family history.
- Moderate to severe cases require treatment with folic acid and splenectomy.

CPD READING 0.5 HOURS

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

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

Giant bilateral pulmonary arteriovenous malformations with refractory hypoxaemia

A 63 year old woman with alcoholic cirrhosis presented with a two week history of platypnoea (dyspnoea worse on sitting up). She had a history of upper gastrointestinal bleeding six months earlier and on examination she had ascites, suggesting portal hypertension. Oxygen saturation on room air was 70-75% on sitting and 80-85% on lying, suggesting orthodeoxia. Arterial blood gas showed an elevated alveolar-arterial gradient of 65 mm Hg. Echocardiography revealed right to left shunt. Pulmonary computed tomography angiography showed bilateral pulmonary arteriovenous malformations (figure, arrows).

Hepatopulmonary syndrome is characterised by hypoxaemia, platypnoea-orthodeoxia, pulmonary arteriovenous malformations in the presence of liver disease, and portal hypertension. Platypnoea occurs because of a ventilation-perfusion mismatch when deoxygenated blood flows through arteriovenous shunts in the lung bases.

This patient's hypoxaemia improved with embolotherapy, making liver transplantation possible. Early diagnosis of hepatopulmonary syndrome reduces morbidity and mortality.

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Patient consent obtained.

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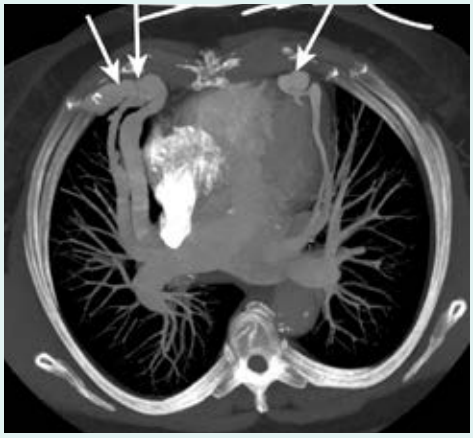

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Mortality among homeless people

A survey from Dublin finds that deaths among homeless people are shockingly common. Counting only those deaths verified by death certificate or coroners' records, age standardised mortality was six times higher than in the general population and the median age at death was 42 years (*BMJ Open*). Alcohol and drugs, particularly opioids, were implicated in more than a third of deaths. Surveys of homeless people in other parts of the world have found similarly appalling figures.

Gut bacteria and depression

It's easy to believe that colonic micro-organisms might influence aspects of human health beyond the gastrointestinal tract. But who would have predicted correlations between the composition of gut microbiota and mood or quality of life? It turns out that, among people taking part in the Flemish Gut Flora Project, two genera of faecal bacteria, *Coprococcus* and *Dialister*, were depleted in people with depression (*Nat Microbiol*). By contrast, participants with higher numbers of *Coprococcus* and *Faecalibacterium* in their large bowel tended to score higher on a questionnaire about quality of life.

Exercise after concussion

Symptoms such as headache, blurred vision, and dizziness are common after mild traumatic brain injury and they are often made worse by exercise. Conventional wisdom has it that patients should rest until symptoms resolve. A trial among adolescents who sustained sports related concussion suggests moderate physical activity might be a better option (*JAMA Ped*). Those randomised to a progressive regimen of aerobic exercise became symptom free faster than those allocated to a stretching programme that didn't raise heart rate.

Functional B12 deficiency

Nitrous oxide is used as a propellant in the catering industry to decorate food with whipped cream, and small pressurised canisters of the gas (whippits), are easily available. Without much extra equipment it's possible to open the canisters, inhale the gas, and enjoy its euphoric effects. But it's important not to let this become a habit because nitrous oxide irreversibly oxidises the cobalt in vitamin B12, leading to a functional vitamin deficiency and a myeloneuropathy that resembles subacute combined degeneration of the spinal cord. A 17 year old boy who presented with a short history of progressive sensory disturbance and limb weakness is a case in point (*BMJ Case Reports*).

Unsafe sex in films

According to an analysis in the *Scottish Medical Journal*, James Bond had sexual relations with 58 women in 24 films. The investigators claim to be horrified that contraception is never discussed, although they undermine their argument by suggesting that Bond is probably infertile as a result of testicular trauma early in his career. What's more, they point out that Bond's sexual partners go on to experience such a high mortality that an unplanned pregnancy or a sexually transmitted disease may not be top of their list of concerns.

Cite this as: *BMJ* 2019;364:l799