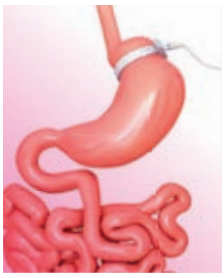
education

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

Safety and effectiveness of bariatric surgery technique



A 10 year retrospective observational cohort study in the US looked at bariatric procedures and compared their long term effectiveness. The three procedures were Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and adjustable gastric banding. Rates of major adverse events in the first 30 days were 5.0% for RYGB, 2.6% for sleeve gastrectomy, and 2.9% for adjustable gastric banding, all of which presumably need to be weighed up against the risks of ongoing obesity. Some people were lost to follow-up, the study design was non-randomised, and the outcome data incomplete, but at five years the study had data on 84% of those with RYGB, 68% sleeve gastrectomy, and 69% adjustable gastric banding. The RYGB group lost an average of a quarter of their total body weight, the sleeve gastrectomy group just under a fifth, and the adjustable gastric banding group just over a tenth. Patients who were less likely to lose as much weight were older, diabetic, less obese (BMI <50 kg/m^2), African American, and Hispanic. The more radical procedure, RYGB, is the most effective but also the riskiest.

Ann Intern Med doi:10.7326/M17-2786

Does obesity kill you?

The rise in bariatric surgery for obesity implies that we are all convinced that obesity is bad for health. However, a UK population based cohort study of nearly two million people who had never smoked found that BMI had a J-shaped association with mortality. Lowest overall mortality, including deaths from cancer, cardiovascular diseases, and respiratory diseases occurred in those with a BMI of 21-25 kg/m^2. Deaths from self harm or interpersonal violence showed an inverse linear association; the thinnest people were most at risk. Being obese shortened life expectancy by 4.2 years in men and by 3.5 years in women over 40.

Lancet doi:10.1016/S2213-8587(18)30288-2

Another nail in warfarin's coffin?

For more than 50 years, warfarin was the only option for stroke prevention. Since direct acting oral anticoagulants (DOACs) came on the scene in 2008, they've enjoyed a steady rise in popularity and now account for 31% of treated patients and around 93% of expenditure on anticoagulants. But which of the four DOACs commonly used is safest and most effective, and how do they each compare with warfarin? This review looks at 220 studies and found that all the DOACs are "at least as effective and safe as warfarin for patients with non-valvular atrial fibrillation (AF)." They have some minor differences: dabigatran and apixaban are better than rivaroxaban, edoxaban, and warfarin in stroke and embolism prevention. And apixaban and edoxaban are superior to rivaroxaban, dabigatran, and warfarin in terms of bleeding risk. Compared with warfarin, left atrial appendage closure is as effective at preventing stroke and all-cause mortality and it causes less major bleeding, but it has a higher (though still low overall) rate of adverse effects such as pericardial effusion. Is this study another nail in warfarin's coffin?

Ann Intern Med doi:10.7326/M18-1523

Viagra: does it reach the parts other drugs don't?

In theory, sildenafil (Viagra) could help treat Raynaud's phenomenon. It is sometimes prescribed off label for severe cases of the condition, but does it work? In this French study, on demand sildenafil was taken up to 90 minutes before conditions likely to trigger an attack, or within 5 minutes of the start of an attack and compared with placebo in a series of n-of-1 trials. The aggregated results did not show that on demand sildenafil was more effective than placebo from a clinical standpoint. The authors say "the use of n-of-1 trials allowed individual efficacy to be estimated, and on-demand sildenafil led to a clinically relevant benefit in a few patients. These findings may justify sildenafil use as a second-line treatment in patients who do not want daily, long-term therapy with calcium-channel blockers or PDE5 inhibitors and do not have digital ulcers."

Ann Intern Med doi:10.7326/M18-0517

Polycystic kidneys: seeking a solution

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disorder. It causes progressive cyst formation in both kidneys and loss of renal function, eventually leading to a need for kidney replacement. There's no definitive treatment, but a randomised clinical trial of 305 patients with later stage ADPKD were given the somatostatin analogue lanreotide to see whether it slowed the rate of decline in kidney function. Somatostatin—a peptide that is secreted by cells in the pancreas and thyroid—inhibits the enzyme that produces cyclic adenosine monophosphate (cAMP) in renal tubular cells. cAMP levels are raised in renal tubular cells in ADPKD, so the rationale behind this treatment is that somatostatin analogues may protect the kidneys. Alas, not all treatments that should work do, and this study couldn't show any slowing down in the rate of decline of kidney function in these patients over a 2.5 year period.

JAMA doi:10.1001/jama.2018.15870

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CLINICAL UPDATES

Adverse drug reactions

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LEARNING MODULE

See http://learning.bmj.com for linked learning module

CPD READING

0.5 HOURS

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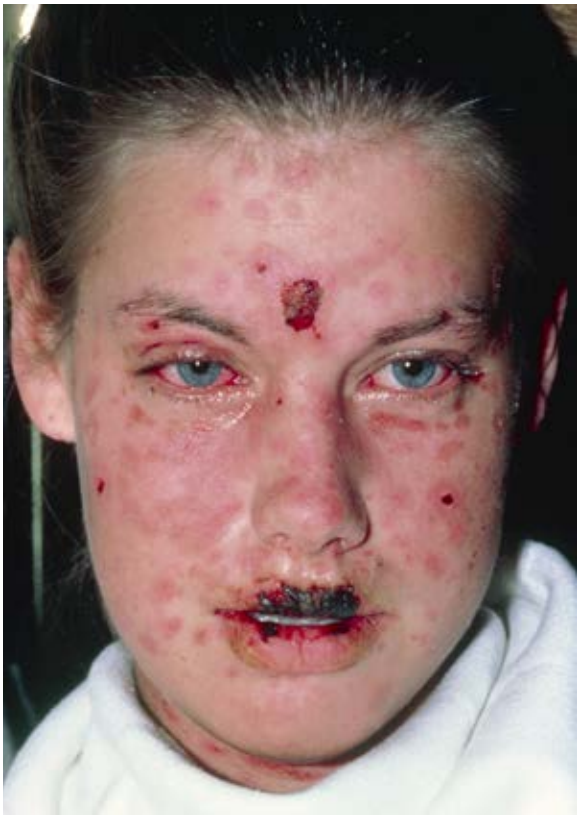
No medicine is entirely safe, so any therapeutic benefit needs to be balanced against the risk of an adverse drug reaction. The pharmacovigilance environment has changed in the past two decades, with biological therapies, complex multidrug regimens, genetic testing, "big data," and new regulation for drug safety.[1] In this clinical update we describe some principles that guide prevention, recognition, and response to adverse drug reactions.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked several patients' representatives on UK and European bodies for their views, and took into account the views of patient reviewers. They gave us advice on wording, made helpful suggestions on the flow chart, discussed information sources used by patients, and reminded us of the importance of registries. We thank the patients who read and advised on the content of this article, particularly Giulio Maria Corbelli of the European Community Advisory Board, François Houÿez of the European Organisation for Rare Diseases, and Phil Willan, patient representative on the Pharmacovigilance Expert Advisory Group of the Medicines and Healthcare products Regulatory Agency.

WHAT YOU NEED TO KNOW

- Prescribers need to balance the possibility of causing harm against the probability of benefit
- Some drugs cause characteristic adverse reactions, whereas others cause non-specific or bizarre effects
- Some adverse drug reactions occur within minutes of administration, whereas others can present years after treatment
- The dose of the drug, time since starting treatment, and potential susceptibility of the patient can help determine if adverse drug reactions enter the differential diagnosis
- Report suspected serious or unusual adverse drug reactions to the national medicines regulator; you don't have to be certain in order to report



P MARAZZI/SPL

A young girl with Stevens-Johnson syndrome, a rare, sometimes fatal form of erythema multiforme

What is an adverse drug reaction?

Medicines have unintended side effects, and if any of these is harmful, the patient has an adverse drug reaction.[2] The European Medicines Agency (EMA) defines an adverse drug reaction as "a response to a medicinal product which is noxious and unintended."[3] This definition now extends beyond the licensed use of a drug to include adverse reactions from off-label use, poisoning, and medication errors. The US Food and Drug Administration (FDA) defines an adverse drug reaction as any untoward medical occurrence associated with the use of a drug in humans "for which there is a reasonable possibility that the drug caused the adverse event."[4]

How common are serious adverse drug reactions?

Well established clinically serious[5] reactions to commonly prescribed drugs are uncommon: simvastatin probably causes rhabdomyolysis in one patient in 10 000.[6] However, adverse drug reactions are under-reported in most countries, making it difficult to assess the burden and take preventive action. In Europe, the proportion of acute hospital admissions caused by adverse drug reactions in 17 studies ranged from 0.5% to 12.8%, and the proportion of hospital patients developing an adverse drug reaction in 10 studies ranged from 1.7% to 50.9%.[7] Figure 1 depicts standard nomenclature in Europe for the likely frequency of adverse reactions.

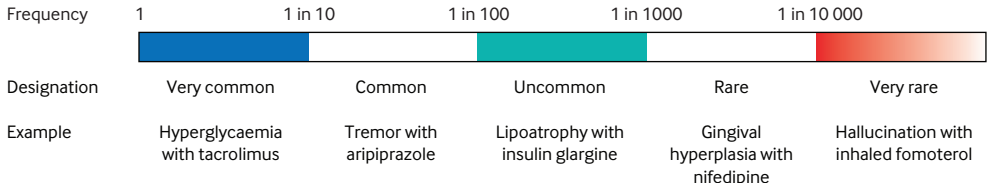


Fig 1 | The standard European nomenclature for the frequency of adverse drug reactions, with examples

How is an adverse drug reaction diagnosed?

Patients may not link symptoms to their medicines, so adverse drug reactions can go undiagnosed unless the prescriber specifically asks about them. Even then, the symptoms may be due to a cause other than the drug.[30] Since adverse drug reactions sometimes hide behind common presenting symptoms and sometimes present bizarrely, a good drug history will help to establish if they should figure in the differential diagnosis. The full version of this article on bmj.com describes how adverse drug reactions may be uncovered.

Does the presentation fit into a recognised pattern?

Some clinical presentations are characteristic. Patients will often attribute new symptoms or signs to medicines they have recently started. They are likely to be correct if they have developed common adverse effects such as sleepiness with the H_1-antihistamine chlorphenamine or nausea with the opioid analgesic oxycodone.

Adverse drug reactions can affect any part of the body (fig 2). Even rare reactions can be characteristic (see table 1 on bmj.com), so adverse drug reactions enter the differential diagnosis of unusual conditions.

Some conditions—Stevens-Johnson syndrome/toxic epidermal necrolysis, bone marrow aplasia, and acute dystonia—are commonly due to adverse drug reactions, so you should suspect a drug cause for these.

Are there any diagnostic clues?

In taking the patient's history, ascertain the dose (Do) of the drug, the time course (T) of the observed clinical event, and the potential susceptibility (S) of the patient (DoTS).[56] Remember that, occasionally, it is an excipient that causes the adverse drug reaction, not the active drug;[57] and that "herbal" remedies sometimes contain undeclared potent drugs.[58]

Dose-response

Toxic reactions, such as liver failure from paracetamol, usually occur only with high doses (or blood concentrations) in patients whose susceptibility is normal. If patients are hypersusceptible, only slight exposure to the drug (below therapeutic concentration) can cause adverse drug reactions, as happens when primaquine causes haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency or penicillin causes anaphylaxis.

Time course

Some adverse drug reactions, typically anaphylaxis to intravenous drugs, occur within minutes of administration. Others, such as the serious dermatological reaction toxic epidermal necrolysis, are due to delayed-type hypersensitivity and occur after days or weeks. Cytokine release syndrome following chimeric antigen receptor (CAR)-T cell therapies can appear several weeks after treatment.

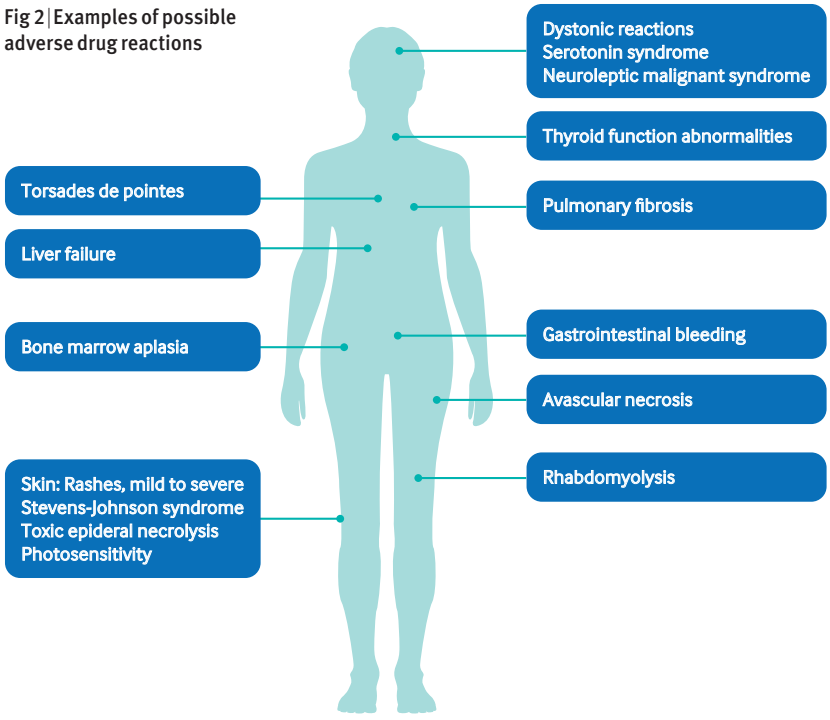
The risk of atypical femoral fractures from bisphosphonates increases with the duration of therapy, the odds increasing by about 1.3 per 100 days of treatment.[59]

Delayed reactions that become manifest months or years after exposure to the causative agent are especially hard to diagnose. It took nearly three decades to establish that diethylstilbesterol could cause a rare vaginal cancer in young women whose mothers had taken the drug in pregnancy.[60] Chemotherapy with alkylating agents for childhood lymphoma was introduced in the 1960s and dramatically improved survival, but it also increased the risk of second malignancies[61]: after 35 years, nearly half of those treated will develop a second malignancy.[62] It is still too early to define the long term effects of gene modification and other advanced therapies.

Potential susceptibility

A patient's age, concurrent treatments, and pre-existing illnesses all affect susceptibility to adverse drug reactions. Renal impairment, hepatic impairment, and obesity[63] can increase exposure to drugs and make adverse drug reactions more likely. Genetics, including genetic heritage, can be important: patients described as "black" are three times more likely than "non-black" patients to develop angioedema with angiotensin converting enzyme (ACE) inhibitors.[64] Some reactions, such as cough with ACE inhibitors, affect women more often than men.[65]

Fig 2 | Examples of possible adverse drug reactions



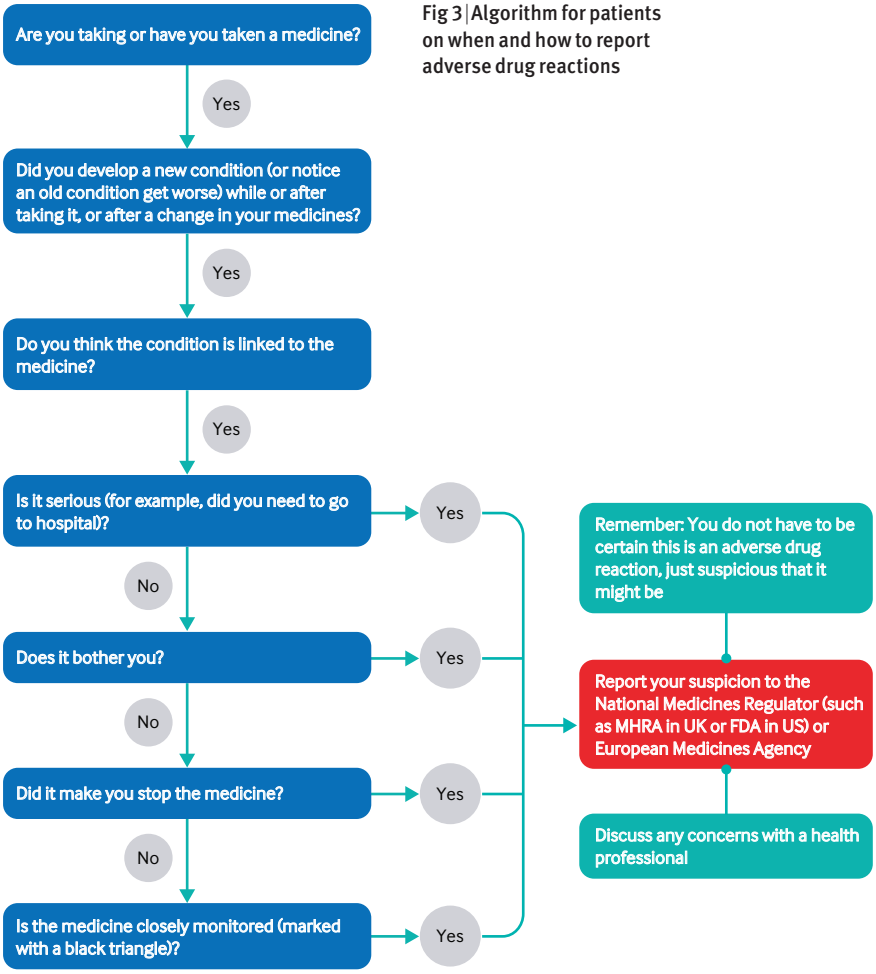
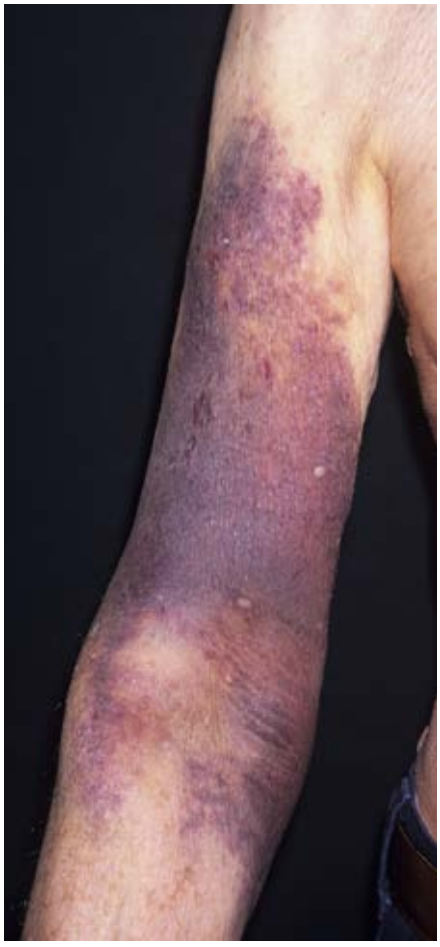


Fig 3 | Algorithm for patients on when and how to report adverse drug reactions



P MARAZZI/SPL

Bruising in the arm of a woman taking warfarin

How do you prevent or mitigate adverse drug reactions?

Prudent prescribing

When prescribing a drug, consider whether the potential benefits outweigh likely adverse drug reactions and whether the patient might be especially susceptible. Gradual up-titration of the dose of a drug, if possible, will increase the chances of reaching an adequate therapeutic dose before collateral or toxic adverse drug reactions become apparent, but it will not prevent hypersusceptibility reactions.

Co-prescription can mitigate some adverse drug reactions: folic acid will reduce the risk of bone marrow failure with methotrexate, mesna will make cyclophosphamide-induced cystitis less likely, and senna can prevent constipation with opioids. Unnecessary polypharmacy, however, makes harm more likely, especially if it represents a "prescribing cascade," when successive drugs are given to alleviate symptoms caused by drugs already prescribed.[66] Polypharmacy also increases the risk of drug-drug interactions.

Identify susceptible patients

Harm is less likely if susceptible patients can be identified before prescribing. Ask about previous drug reactions.

Skin-prick testing can help detect patients allergic to penicillin and prevent an anaphylactic reaction.[67] Genotyping to detect polymorphisms that alter drug metabolism or action can sometimes help to avoid adverse drug reactions.

For some drugs, it is standard practice to establish the patient's phenotype or genotype before treatment (see table 2 on bmj.com).

Discuss harms with the patient

Well informed patients are better able to distinguish between likely adverse effects and other symptoms. They will need to know of some rare but potentially serious adverse drug reactions, such as mouth ulcers with carbimazole or methimazole, which may indicate neutropenia. Sometimes specific advice on administration can minimise harm: oesophageal injury with alendronic acid is less likely if patients take tablets whole, on rising, with at least 200 mL of water, and on an empty stomach and then remain upright for at least 30 minutes.[69]

The recent UK Supreme Court judgment in *Montgomery v Lanarkshire Health Board* requires that patients should be informed of risks, however small, that are important to them: "a patient should be told whatever they want to know, not what the doctor thinks they should be told."[70] Brief consultations and a patient information leaflet (package insert) may no longer suffice.

The internet can be a useful source of information (see Additional Educational Resources box on bmj.com) but can also carry alarmist or over-optimistic stories. Physicians, pharmacists, and other healthcare professionals can provide patients with a more realistic picture of the benefits and harms of medicines.

Box 2 | Diagnostic tests for CDAD in acute healthcare settings

- Full differential blood count typically shows leucocytosis. If the white blood cell count is very high (30 000 to 50 000/mm^3) the patient is at risk of fulminant colitis
- Perform radiography of the abdomen in patients with abdominal distension or symptoms and signs suggestive of infection. This may show dilation of the colon[5]
- Check stool samples for presence of occult blood
- Test stool for *C difficile* infection in patients with unexplained, new onset diarrhoea (defined as three or more unformed stools in 24 hours) who are not taking laxatives
- Stool polymerase chain reaction (PCR) can be used alone or as part of a multistep algorithm
- Immunoassays for glutamate dehydrogenase and toxins are recommended as part of a multistep algorithm
- Sigmoidoscopy or colonoscopy is indicated if treatment fails, or in patients for whom enzyme immunoassay was negative, or if other causes are suspected (eg, ischaemic colitis)
- A computed tomography scan of the abdomen is indicated in patients with abdominal distension, worsening pain, or absent bowel sounds

Who is at risk?

Typically, older adults with a recent history of antibiotic use—particularly broad spectrum antibiotics—are at risk of CDAD. Other key risk factors are given in box 1.

Risk factors for recurrent infection include female sex, increasing age, chronic kidney disease, nursing home patients, immunosuppression, and recent use of corticosteroids or proton pump inhibitors.[20]

How should you diagnose CDAD?

Consider CDAD in patients with a history of recent exposure to antibiotics who present with diarrhoea. Diagnosis is based on taking an accurate history, physical examination, and confirmation by appropriate tests (box 2).

Physical examination may reveal anything from little or no abdominal tenderness to signs of an acute abdomen.

Systemic symptoms of shock, including hypotension and tachycardia with severe abdominal pain and tenderness, suggest life threatening fulminant colitis.

Updated US guidance[4] advises limiting stool testing for *C difficile* infection to patients with unexplained new onset diarrhoea (defined as three or more unformed stools in 24 hours) who are not taking laxatives. In institutions that adopt this policy, stool PCR tests (nucleic acid amplification tests) alone are an acceptable test for confirming the diagnosis. However, if there are no such policies in place, a testing algorithm (stool immunoassays for glutamate dehydrogenase (GDH) plus toxin; GDH plus toxin, arbitrated by stool PCR; or stool PCR plus toxin) is recommended.

European guidelines recommend a two step algorithm, starting with a highly sensitive test (stool PCR or GDH enzyme immunoassay) and, if positive, confirmation with a highly specific test (toxin A/B enzyme immunoassay). Alternatively, samples can be screened with both a GDH and toxin A/B enzyme immunoassay.[21]

What are the latest recommendations for management?

Most recommendations in this section are based on guidelines from the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America, which were updated in early 2018.[4]

Patients not already hospitalised should be admitted unless they have no systemic symptoms and no organ dysfunction, in which case they can be treated as outpatients.

At the first suggestion of diagnosis, the inciting antibiotic(s) should be discontinued as soon as possible. If antibiotics cannot be withdrawn, an agent less likely to cause *C difficile* infection should be substituted. Hospitalised patients with confirmed or suspected infection should be isolated under contact precautions to reduce the risk of infection to other patients.

Evaluate patients for fluid status, especially if they are hospitalised. If necessary, start hydration and electrolyte replacement. Avoid giving antimotility agents, including opioids and loperamide, although there is no evidence to support this recommendation.[4]

Antibiotic therapy

First episode

Updated US guidelines now recommend either oral vancomycin or fidaxomicin as a first line agent for an initial episode of *C difficile* infection. This recommendation is based on evidence that treatment with vancomycin or fidaxomicin results in greater cure rates and decreased risk of recurrence compared with metronidazole.[22]

Recommended treatments for different disease severities are given in box 3. Previously, oral metronidazole was the antibiotic of choice; however, it is now only recommended in settings where access to first line agents is limited.[4]

Evidence from systematic reviews and meta-analyses suggests that fidaxomicin is better than vancomycin at reducing recurrence.[22-31] Fidaxomicin might therefore be a better treatment option than vancomycin, except for patients with severe infections.

Box 3 | Recommended drug treatments for a first episode of CDAD[4]

Non-severe

- Supportive clinical data: leucocytosis with white blood cell count of ≤15 000 cells/mL and serum creatinine <0.13 mmol/L (<1.5 mg/dL)
- First line treatment: oral vancomycin or fidaxomicin for 10 days
- Alternative treatment: oral metronidazole for 10 days

Severe

- Supportive clinical data: leucocytosis with white blood cell count of ≥15 000 cells/mL and serum creatinine >0.13 mmol/L (>1.5 mg/dL)
- First line treatment: oral vancomycin or fidaxomicin for 10 days
- Fulminant (severe, complicated infection)
- Supportive clinical data: hypotension, shock, ileus, or megacolon
- First line treatment: oral vancomycin (at a higher dose than the dose for non-fulminant infection). If ileus is present, consider rectal application of vancomycin. Intravenous metronidazole can be given with oral or rectal vancomycin, particularly if ileus is present as this may impair delivery of oral vancomycin to the colon
- Alternative treatments: tigecycline or immunoglobulins have been used in symptoms that do not respond to first line treatments, but no controlled trials have been performed.

Box 4 | Recommended antibiotic options for recurrence[4]

First recurrence

- A prolonged tapered and pulsed dose regimen of oral vancomycin (if oral vancomycin was used for the initial episode), or
- A standard 10 day course of fidaxomicin (if oral vancomycin was used for the initial episode), or
- A standard 10 day course of oral vancomycin (if metronidazole was used for the initial episode)

Subsequent recurrences

- A prolonged tapered and pulsed dose regimen of oral vancomycin, or
- A standard 10 day course of oral vancomycin followed by rifaximin for 20 days, or
- A standard 10 day course of fidaxomicin

European guidelines recommend metronidazole as a first line agent for non-severe disease (with vancomycin or fidaxomicin as alternatives), and vancomycin as the first line agent for severe disease.[32] Public Health England also supports these recommendations.[33] Publication of these guidelines precedes the updated guidelines published by the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America in 2018.

Recurrent episodes

Recurrence rates vary from 5% to 50%. Approximately 25% of patients treated with vancomycin for an initial episode experience at least one recurrent episode.[24 34] A small number of patients have repeated relapses, necessitating several courses of treatment.

Antibiotic options depend on the treatment used for the initial episode.Box 4 gives the latest recommendations.[4]

Surgery

Surgical evaluation for colon resection may be warranted in fulminant disease or in patients whose infection does not respond to antibiotic treatment.[4-36] Fulminant disease is underappreciated as a life threatening disease because of a lack of awareness of its severity and its non-specific clinical syndrome. Early diagnosis and treatment are essential for a good outcome, and early surgical intervention should be considered in patients whose condition does not respond to medical treatment or who have rising white blood cell count or lactate levels.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is recommended as an option in patients with at least two recurrences and where antibiotic therapy has failed.[4] This is based on evidence of higher cure rates with FMT compared with antibiotic treatment (70% to 80% for FMT compared with 45% to 50% for antibiotic treatment) and favourable short term safety. The procedure involves implanting processed stool collected from a healthy donor into the intestinal tract of infected patients to correct intestinal dysbiosis.

There is insufficient evidence to recommend FMT for severe disease (as opposed to recurrent disease).[37] Further research on this treatment is needed, as key components of FMT interventions are poorly reported.[38]

What other treatments are on the horizon?

Bezlotoxumab, a human monoclonal antibody that binds to *C difficile* toxin B, is approved in the US and Europe to reduce recurrence in adults who are receiving antibacterial treatment for *C difficile* infection and who have a high risk of recurrence. However, its place in treatment is currently unclear.

Cadazolid and ridinalazole are new antibiotics under investigation. Both have completed phase II testing. One phase III trial of cadazolid is ongoing.

Teicoplanin is a semi synthetic glycopeptide antibiotic. One review found that sustained symptomatic cure was improved with teicoplanin compared with vancomycin[39]; however, the quality of evidence is low, and the drug is not available in the US.

Surotomycin is an orally administered, minimally absorbed, selective bactericidal cyclic lipopeptide that is being investigated for the treatment of *C difficile* infection. Surotomycin and vancomycin had similar clinical cure rates, and recurrence rates were lower with surotomycin in one phase II randomised controlled trial.[40]

Resins that bind *C difficile* toxin have been used in recurrent disease with or without vancomycin. These medications also bind vancomycin, and they have not been well studied.[7]

Vaccines against *C difficile* are in development, and one—VLA84—has completed phase II trials.

What's the prognosis?

The expected response to treatment is rapid resolution of fever and diarrhoea within four to six days. Most patients see an improvement in symptoms after initial treatment. No specific follow-up is required and repeat stool testing is not routinely recommended.

Recurrence rates vary depending on the presentation, immune function, severity of disease, and treatment type and duration. One study found at least one recurrence in 21% of healthcare associated infections and 14% of community associated infections.[9] A small number of patients have repeated relapses, necessitating several courses of treatment.[7] The annual incidence of multiply recurrent infection has increased in recent years.

Complications of *C difficile* infection include ileus, perforation, and toxic megacolon. All are rare. An epidemic strain that emerged in the 2000s (North American pulsed field gel electrophoresis type 1) led to more serious disease that is more refractory to treatment and carries a higher mortality. The NAP1 strain has been decreasing in prevalence since it was first isolated but remains a problem in the US.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k4369

EDUCATION INTO PRACTICE

- To what extent did you consider the possibility of *C difficile* last time you prescribed antibiotics to a patient at risk?
- How might you reduce the risk next time?

CASE REVIEW

Hypercalcaemia with undetectable parathormone levels

A 54 year old woman had unintentional weight loss of 12-19 kg with nausea, abdominal discomfort, and constipation over 2-3 months. She presented acutely with profuse vomiting for three days. She was taking venlafaxine 150 mg/day for bipolar disorder, she smoked (40 pack years), consumed little alcohol, and had no family history of disease. On examination, she was dehydrated, her blood pressure was 106/74 mm Hg, pulse 122 beats/min and regular, and her temperature was 37.2°C. She had a smooth symmetrical goitre with no retrosternal extension or lymphadenopathy, and mild abdominal tenderness. Systems examination was normal. She underwent blood tests, the results of which were normal for renal function, alkaline phosphatase, total protein, globulin, and protein electrophoresis. Abnormal blood test results are shown in the table.

Chest radiography and computed tomography scans of the abdomen and pelvis were normal.

1 What are the possible causes of this patient's hypercalcaemia?

2 What is the most likely diagnosis?

3 How would you treat this patient?

Abnormal blood test results

Test	Result	Reference range
Potassium	3.0 mmol/L	3.5-5.3
Adjusted calcium	3.02 mmol/L	2.20–2.60
Phosphate	1.06 mmol/L	0.8-1.5
Parathyroid hormone (PTH)	‹0.4 pmol/L	1.3-9.3
Alanine transaminase (ALT)	256 IU/L	‹50
Free thyroxine (FT4)	63.3 pmol/L	9.2-21
Free triiodothyronine (FT3)	›46.1 pmol/L	2.6-5.7
Thyroid-stimulating hormone (TSH)	‹0.02 mU/L	0.3-4.4
TSH receptor antibody (TRAb)	›40 IU/L	‹0.9
Vitamin D	37 nmol/L	›50
Angiotensin-converting enzyme (ACE)	64 U/L	8-52

Submitted by Ilaria Muller and Lakdasa D Premawardhana

Patient consent obtained

Cite this as: *BMJ* 2018;363:k4074

If you would like to write a Case Review or Spot Diagnosis for Endgames, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

answers

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

CASE REVIEW

Hypercalcaemia with undetectable parathormone levels

1 This patient has non-PTH mediated hypercalcaemia (low PTH, high adjusted calcium).

Causes include:

- Malignancy (eg lung, breast, kidney, skin, multiple myeloma, lymphoproliferative disorders)
- Granulomatous disorders (eg sarcoidosis, tuberculosis)
- Drugs (eg vitamin A, vitamin D, thiazide diuretics, calcium supplements causing milk alkali syndrome)
- Endocrine disorders (eg, thyrotoxicosis/hyperthyroidism, phaeochromocytoma, hypoadrenalism, VIPoma)
- Immobilisation

2 Hyperthyroidism due to Graves' disease, causing non-PTH mediated hypercalcaemia.

Classical features of Graves' disease include tachycardia, weight loss, a smooth symmetrical goitre, and high TRAb levels. The patient also presented with relatively uncommon features of Graves' disease: hypercalcaemia with normal serum phosphate, and biochemical evidence of hepatitis. The hypercalcaemia of Graves' disease is caused by FT3 mediated osteoclast activation, increasing bone turnover and transfer of calcium from bone to serum.

3 Immediate management involves rapid rehydration with intravenous normal saline infusion (to increase glomerular filtration and calcium excretion) and intravenous bisphosphonates (to inhibit osteoclast activation.)

Next, treat the hyperthyroidism with oral thionamides after warning the patient about side effects, especially neutropenia and liver toxicity. If thionamides are unsuitable or there is relapse, consider radioiodine or thyroidectomy with lifetime levothyroxine.

LEARNING POINTS

- In non-PTH mediated hypercalcaemia, PTH is below the reference range or undetectable. In PTH mediated hypercalcaemia, PTH levels are inappropriately raised, ie, detectable, and within or above the reference range.
- In Graves' disease, hypercalcaemia with normal serum phosphate results from absent PTH and phosphate conservation by thyroid hormones.

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.

MINERVA

Extreme cardiomegaly induced by rheumatic heart disease

A 62 year old woman presented with a 10 month history of progressive dyspnoea and peripheral oedema. She had a 40 year history of rheumatic heart disease and a 20 year history of exertional dyspnoea, but had declined valve surgery when it had been offered in the past.

Chest radiography showed extreme cardiomegaly (cardiothoracic ratio 0.95) and heavily calcified mitral and aortic valves (figure).

Transthoracic echocardiography revealed bilateral atrial enlargement (with a giant left atrium), severe mitral and aortic valve stenosis and regurgitation, and severe tricuspid regurgitation. The patient had mitral and aortic valve replacement, tricuspid annuloplasty, and left atrium plication. Giant left atrium is rare and mostly occurs with rheumatic pancarditis.

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Patient consent obtained

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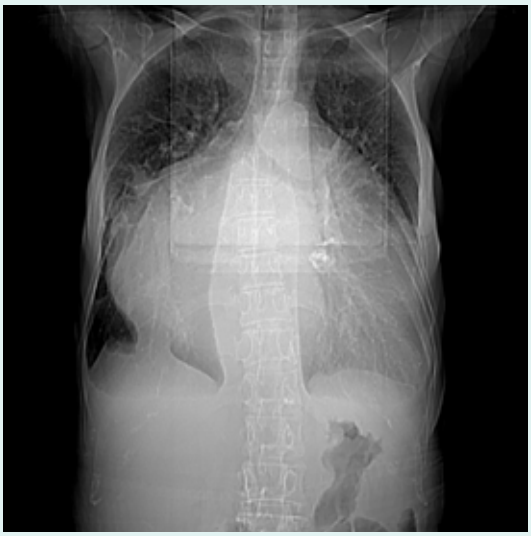

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Egg consumption

A study from China, with data on more than half a million adults, reports that higher consumption of eggs was associated with a lower risk of heart disease. People who ate an egg daily had an 18% lower risk of death from cardiovascular causes than people who never ate eggs (*Heart*). Does this mean that everything we've believed about dietary cholesterol is wrong? Perhaps not, since it's possible that the large differences in average levels of education, household income, and blood pressure between people in the different categories of egg consumption weren't fully adjusted for.

Unrecognised myocardial infarction

Cardiac magnetic resonance imaging in nearly a thousand community dwelling older people in Iceland found that around 17% had evidence of a previously unrecognised myocardial infarction. Followed up over 10 years, the mortality risk in this group was similar to that in people who had survived a recognised infarction and considerably higher than in people without evidence of infarction (*JAMA Cardiol*). But they won't be an easy group to reach for secondary prevention.

Emergency triage

The emergency department of a hospital in New Zealand compared its routine system of triage carried out by trained nurses with a quick assessment of clinical urgency made by phlebotomists and medical students who hadn't had any specific training for the task. Over a period of four months, more than 6000 patient visits were evaluated, and the findings are rather astonishing (*Emerg Med J*). The quick assessment turned out to be much better than formal triage at predicting short term mortality.

Surgery for essential tremor

Several different surgical approaches can be used to treat essential tremor, including deep brain stimulation, radiofrequency ablation, gamma knife radiosurgery, and most recently, focused ultrasound. All target the ventral intermediate nucleus of the thalamus. A systematic review reckons that all are moderately effective, although all have considerable rates of adverse effects, including dysarthria, gait instability and paraesthesiae (*J Neurol Neurosurg Psychiatry*). Most of the information on outcomes was derived from unblinded assessment of case series, which may have led to an overestimation of the benefits

Happy people live longer

Nearly 5000 participants in a longitudinal study of people aged over 60 in Singapore rated how happy they were on a 7 point scale over six years. All cause mortality tended to be lower in those whose happiness scores were higher (*Age Ageing*). An increase of one point on the happiness scale was roughly equivalent to a 9% reduction in mortality. The investigators suggest that interventions to improve happiness would be beneficial for older people. However, it's also possible that poorer health makes people feel less happy.

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