**Gabapentinoids: Less is (probably) more**

The widespread use of gabapentin as an analgesic is a classic tale of drug mission creep. Some of it was good. When it appeared as an anticonvulsant drug in the early 1990s, gabapentin offered little advantage over existing drugs for epilepsy. But gradually it was adopted for use in neuropathic pain, where its adverse effect profile and effectiveness gave it the edge over carbamazepine. General practitioners needed little encouragement to give it a try. But in the UK, use didn’t really shoot up until the 2000s. In the US, a research letter tells us that prescribing of gabapentin and pregabalin went up threefold between 2002 and 2015. People prescribed the “gabapentinoids” tend to be older and already on opioids and benzodiazepines. From my own experience, I suspect this is in part due to pain clinics and palliative care teams wanting to help patients with residual pain, by reclassifying it as “neuropathic.” We need to think of ways to reverse this trend. For every patient to benefit, there are probably 10 who end up fuddled and immobile. Every time you see one of these drugs on a chart (usually somewhere in the middle, as drugs accumulate geologically), think “don’t I need to check this with the patient?”

**Checking out checkpoint inhibitors**

Ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab. What do they have in common? Silly names: yes. Exorbitant prices: of course. Severe adverse effects related to inflammatory upregulation? Sadly, yes. Although they work by slightly different mechanisms, they are all called checkpoint inhibitors (don’t ask me, look it up on Wikipedia), and they do increase overall survival in some cancers. Next list: psoriasis, ulcerative colitis, Crohn’s disease, multiple sclerosis, myasthenia gravis, autoimmune thyroid disease, and sarcoidosis. What do these have in common? Yes, they are all nasty and incompletely understood. Yes, they have autoimmunity as part of the disease process. So, what happens if you give a checkpoint inhibitor to cancer patients with these diseases to prolong their overall survival? According to a mixture of observational evidence, their autoimmune diseases get worse, but they live a bit longer, especially if they have severe adverse effects. These effects can in turn be alleviated somewhat with anti-immune drugs (mostly steroids). This is a tricky area for shared decision making, but all the more necessary for that reason. Particularly in the USA, where the cost of treatment is likely to clear out your bank account and could lose you your home.

**Feeding statins to the herd**

Speaking of shared decision making, how about statins for primary prevention of cardiovascular disease? Well, it’s pretty clear. There are two opposing camps who begin from entirely different premises (or premises). Premiss One: If everybody took statins, there would be less cardiovascular disease in the population. Premiss Two: It is up to every individual to decide whether to take medication for life, based on their individual risk and informed preference.

If you put people randomly in a room to discuss statins for half an hour, the space will get hotter, its pressure will increase, and the two factions will end up at opposite sides of the room. It’s like Boyle’s Law of Gases in reverse.

Now throw in a guideline. The gases will explode, but then the same negative entropy will reassert itself and within half an hour every particle will be back in its original position. You can do this five times and the same thing will occur each time. Here’s the proof. Danish investigators looked at five European guidelines recommending that statins should be offered to anything between 44% (maximum) and 33% (minimum) of the adult population. They then modelled the likely incidence of cardiovascular events based on Danish whole-population statistics if statins were taken by these percentages of the adult population. Naturally, the more Danes taking statins, the fewer cardiovascular events predicted in Denmark. But what if the population would not deign (sorry) to take them?

Now here’s the natural experiment I would like to see carried out, in Denmark or anywhere else. Offer statins free of charge to the whole population, together with a cardiovascular risk assessment tool and a multi-layered decision aid. Keep doctors out of it. Observe the pattern of uptake and adherence. Introduce an element of proactive pharmacovigilance to detect hidden adverse effects, and test these with n-of-one trials in individuals. Publish observational data every five years.
EASILY MISSED?

Chronic limb threatening ischaemia

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A 72 year old ex-smoker with diabetes presents to his general practitioner with a four week history of increasing pain in his right foot, worse at night. He finds hanging the leg down provides some relief and he now sleeps in a chair. His leg is increasingly swollen. A cut on his foot has failed to heal and is now red and discharging. On examination, there are no pulses below the femoral artery. The right foot is cold and pale on elevation, and hyperaemic upon dependency. The GP diagnoses chronic limb threatening ischaemia (CLTI) and the patient is seen in the vascular clinic on the same day and admitted. He undergoes imaging and vein bypass surgery. He is discharged a week later free of pain with a healing foot wound.

Peripheral arterial disease affects 10%-20% of patients over 60 and presents in several ways 1-3 (see table, right). A quarter of patients have symptoms, typically intermittent claudication, of whom 1%-2% progress to CLTI each year. However, many patients with CLTI do not have a history of intermittent claudication and present de novo with ischaemic rest (night) pain and/or a non-healing foot wound. This is either because they cannot, or choose not to, walk far enough to bring on the symptoms of intermittent claudication and/or because they have diabetic neuropathy. Patients with CLTI are at high risk of amputation and death, and all patients with suspected CLTI should be discussed immediately with a vascular surgeon.

WHAT YOU NEED TO KNOW

- Chronic limb threatening ischaemia (CLTI) is a more difficult diagnosis than acute limb ischaemia for the non-specialist because the clinical features can be more subtle and gradual
- It can be easy to mistake CLTI for other conditions, such as cellulitis, gout, or plantar fasciitis
- The affected foot might appear pink or red as a result of reactive hyperaemia when the patient is sitting with the leg down. It is often necessary to elevate the foot on the examination couch to elicit the ischaemic pallor.

HOW COMMON IS IT?

A vascular surgical unit serving a population of one million will typically see up to 250 new patients with chronic limb threatening ischaemia each year; a full time GP might see one each year (on the basis of as yet unpublished data from National Institute for Health Research.

Peripheral arterial disease affects 10%-20% of patients over 60 and presents in several ways 1-3 (see table, right). A quarter of patients have symptoms, typically intermittent claudication, of whom 1%-2% progress to CLTI each year. However, many patients with CLTI do not have a history of intermittent claudication and present de novo with ischaemic rest (night) pain and/or a non-healing foot wound. This is either because they cannot, or choose not to, walk far enough to bring on the symptoms of intermittent claudication and/or because they have diabetic neuropathy. Patients with CLTI are at high risk of amputation and death, and all patients with suspected CLTI should be discussed immediately with a vascular surgeon.

Features of chronic limb threatening ischaemia

These are
- Ischaemic rest pain, typically worse at night and relieved by hanging the leg down, and/or
- Tissue loss; typically:
  - ulceration, usually over pressure areas (toes, metatarsal heads, heel)
  - gangrene, usually of the toes.

The pain of CLTI is often worse at night because when asleep, blood pressure falls and the beneficial effect of gravity on lower limb circulation is lost. Typically, the person will be woken in the early hours with pain in the affected foot. Patients usually find that hanging their foot down provides some relief and so might take to sleeping in a chair. But this often leads to dependent oedema, a further reduction in perfusion pressure, and more pain. Next, a minor foot injury (often unrecognised) might lead to a non-healing foot wound that becomes infected.

Of the patients who present to vascular surgeons with a new diagnosis of CLTI, typically 15% are offered primary amputation, 20% are treated conservatively with non-surgical therapy only, and 65% will undergo revascularisation either by means of bypass constructed with a vein usually taken from the leg (25%) or endovascular intervention (40%). Of those who undergo an initially successful revascularisation, approximately 50% have undergone major limb amputation or die within five years.

It is important, therefore, to maintain a high index of suspicion in any patient presenting with foot symptoms. This is especially so in patients who have risk factors such as smoking or diabetes and/or who have a history of vascular disease (intermittent claudication, myocardial infarction, stroke).
Chronic limb ischaemia (onset ≥14 days)

### Intermittent claudication
- Atherosclerotic narrowing of a leg artery; most commonly the superficial femoral artery in the thigh but can be iliac arteries in the pelvis
- Gradual onset of pain in the leg upon walking which is relieved by rest. Pain returns when walking resumes. Pain is usually in the calf with superficial femoral artery disease but can affect the thigh with iliac artery disease
- Lifestyle modification (stop smoking and medical therapy (antiplatelets, statin)) to reduce cardiovascular risk. Supervised exercise programmes. Diagnosis and management of comorbidities such as diabetes and hypertension
- If patients are concordant with lifestyle modification, medical therapy, and supervised exercise, symptoms usually improve and very few require intervention. If patients are not concordant then the risks of progression to chronic limb threatening ischaemia greatly increase.

### Chronic limb threatening ischaemia (rest pain)
- Atherosclerotic narrowing of multiple arteries above and below the knee. Below knee disease is especially common in patients with diabetes
- Severe pain usually in the foot and toes that is present all the time and which is often worse with elevation leading to pain at night in bed
- Some patients can be managed conservatively like those with intermittent claudication. Most will require revascularisation
- If patients can be managed conservatively then the prognosis can be similar to intermittent claudication

### Chronic limb threatening ischaemia (tissue loss)
- Ulceration and/or gangrene often affecting toes and pressure points
- In addition to medical therapy, patients will require revascularisation by means of a bypass using a vein from the leg or endovascular intervention (angioplasty, stent)
- More than 50% of patients will undergo an initially successful revascularisation. However, about 50% of those patients have lost their leg or die within 5 years

### Why is it missed?
- CLTI can be missed because
  - It can have a slow and insidious onset
  - Symptoms can be confused with other commoner causes of foot pain such as plantar fasciitis, arthritis, cellulitis, and gout
  - There is often no history of intermittent claudication as patients do not walk and/or they have diabetic neuropathy which obtunds the pain
  - Even tissue loss can be painless due to neuropathy
  - CLTI does not just affect older patients; for example, Buerger’s disease and other vasculitides can present in people in their 20s and 30s
  - Most patients with CLTI have absent foot pulses; however they can be palpable, at least initially, in cases of distal embolisation. It is important to remember that patients can, albeit infrequently, have potentially limb threatening distal ischaemia in the presence of pulses, although there are usually other obvious features of ischaemia, such as coldness and discoloration.
  - Palpation of foot pulses, even by vascular surgeons, is associated with a substantial false positive and negative rate.
  - There is a failure to perform Buerger’s test (the affected foot turns white on elevation as a result of ischaemia, and red on dependency because of reactive hyperaemia—the so called “sunset foot,” see figure). For this reason, do not just examine the patient sitting in a chair, as the dependent foot can look reassuringly pink with an apparently normal capillary refill time.

### Why does this matter?
- With prompt revascularisation through either vein bypass, angioplasty, or stenting, amputation can be avoided in most patients. It is our experience that if diagnosis is delayed and substantial tissue loss develops, the chances of limb salvage fall dramatically. Discuss all patients with suspected CLTI immediately with a vascular surgeon.

### How is chronic limb threatening ischaemia diagnosed?
- A diagnosis of CLTI can usually be made or excluded based on a high index of suspicion, a careful vascular history, and an appropriate vascular examination. If there is any doubt, err on the side of caution, and discuss the patient with a vascular surgeon. While measurement of the ankle to brachial pressure index (ABPI) can be useful in patients with intermittent claudication, it is much less useful in patients with suspected CLTI because:
  - It is technically difficult; the signals are often difficult to hear and might be coming from collaterals rather than the main pedal (foot) arteries
  - Pressure measurements will often be falsely elevated, especially in patients with diabetes, because of calcification of the arterial wall.
- Measurement of ABPI is potentially unreliable in CLTI. It should not be used in primary care to determine referral in patients in whom CLTI cannot be confidently excluded by vascular history and clinical examination.

### How is it managed?
- Management of CLTI involves urgent admission for:
  - Medical optimisation including (for example) antiplatelet agents, statins, control of hypertension and diabetes, optimisation of cardiac and renal function
  - Arterial imaging
  - Revascularisation by means of vein bypass, typically using the great saphenous vein, or endovascular intervention (angioplasty, stenting).

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Birth options after an earlier caesarean section include
- A trial of labour after caesarean: allowing spontaneous labour to occur, anticipating a vaginal delivery (known as vaginal birth after caesarean section, or VBAC)
- Planned elective repeat caesarean section (ERCS). Both are reasonable options for most women. The rates of serious maternal and neonatal adverse outcomes with either of the strategies are low. Pregnancy complications might alter the risks and benefits of each delivery strategy. ERCS is recommended in some scenarios (see box, facing page), but an exploration of the woman’s wishes and shared decision making is vital. Women attribute different values to the benefits and risks of either approach. Studies from the UK and US show that around 50% of women attempted a vaginal birth after one previous caesarean section. Initiate a formal discussion to make a final plan for delivery late in the third trimester.

What you should cover
Explore the woman’s circumstances, concerns, preferences, and plans for future pregnancies. Useful questions include
- How has your current pregnancy been so far? Have there been any problems?
- Have you had any illnesses or operations in the past? What was the reason for your first section?
- What was your first birth experience like, in terms of labour and the delivery? What was the recovery like? Was your baby OK?
- What are your plans for future pregnancies? This could influence choice of mode of delivery in this pregnancy. A systematic review (21 studies, 2,282,922 deliveries) showed that serious morbidity in future pregnancies (including hysterectomy, blood transfusions, adhesions, and surgical injury) increases as the number of previous caesarean deliveries increases. Adverse outcomes that will accrue in a future pregnancy, potentially consequent to ERCS in this pregnancy, are irrelevant for women who do not plan to have more children. By contrast, VBAC might have advantages for women who intend further pregnancies.
- Do you have any thoughts already about what you would prefer? Is there anything about either birth option that you are concerned about? What advice are your friends and family giving you?

What you need to know
- Either vaginal birth or elective repeat caesarean section are reasonable options, and adverse outcomes are rare in most uncomplicated pregnancies in women with a previous caesarean section.
- Around 50% of women with one previous caesarean section attempt a vaginal birth in their second pregnancy, and of these nearly two thirds are successful.
- Explore the woman’s concerns, preferences, reasons for previous caesarean section, and plans for future pregnancies to inform the choice of mode of delivery.

Education into practice
- How do your own preconceptions and preferences about mode of delivery influence discussions about birth options after caesarean section?
- How can you minimise this and ensure you fully explore and support the woman’s preferences?
**What you should do**

Facilitate an informed choice

Provide information on the likelihood of a successful vaginal birth and the risks and benefits of either approach. Explain any reasons why ERCS might be recommended because of fetal or maternal conditions.

**VBAC success**

In a recent large UK series (143 970 women in their second pregnancy, with previous caesarean section), 52% of women attempted a VBAC, and 63% of these women had a successful vaginal delivery.1 The remaining third of women who attempted VBAC underwent an emergency caesarean section. Women who were young, white, and socioeconomically advantaged were more likely to have a vaginal delivery, as were those whose first caesarean section was elective. A systematic review shows that even with two previous caesarean sections, VBAC success rates remain high (4064/5666, 71.1%) and maternal morbidity is similar to that with ERCS.2 At least two validated prediction models for VBAC success are available,3,4 one of which is available as an online tool. Their predictive capability is moderate at best and these are not yet in common use.

**Benefits and risks of ERCS compared with VBAC**

ERCS is associated with a longer hospital stay and increased risk of complications such as hysterectomy for haemorrhage, cardiac arrest, and admission of the baby to the neonatal intensive care unit.2 Conversely, women having a vaginal delivery are more likely to have perineal and abdominal pain during birth and for up to three days post partum, injury to the vagina, haemorrhage, and obstetric shock.2 ERCS is likely to have fewer complications and recovery is likely to be faster than the woman’s original emergency caesarean section. A second labour is also likely to be faster than the first.11

There are no randomised controlled trials comparing the two approaches.12 In an Australian study, 2345 women with one previous caesarean section were assigned by patient preference to either VBAC or ERCS. The risk of fetal and infant death or serious infant outcome was lower with ERCS, and fewer women had major haemorrhage.13 A systematic review of observational studies examined maternal and neonatal outcomes after VBAC (200 studies, more than 400 000 women).1 Maternal mortality was lower following VBAC compared with ERCS (table). Importantly, the absolute risk of adverse outcomes in both groups was very low. Hence the woman’s preferences for a particular birth experience are likely to dominate decision making.

The impact of these birth options on longer term outcomes is less well studied. Systematic reviews suggest that babies born by caesarean section might have higher rates of food allergy (odds ratio 1.32, 95% confidence interval 1.22 to 1.55),14 hospitalisation for asthma (odds ratio 1.21, 95% confidence interval 1.12 to 1.31),14 and childhood obesity (relative risk 1.34, 95% CI 1.18 to 1.51).15

**Outcomes after ERCS or VBAC in women with previous caesarean section**

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Incidence per 1000 (95% confidence interval)</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCS</td>
<td>0.996 (0.021 to 0.432)</td>
<td>0.19 (0.004 to 0.995)</td>
</tr>
<tr>
<td>VBAC</td>
<td>0.945 (0.031 to 0.428)</td>
<td>1.46 (0.078 to 2.8)</td>
</tr>
<tr>
<td>Serious maternal morbidity†5</td>
<td>0.31</td>
<td>0.45</td>
</tr>
<tr>
<td>Uterine rupture (any gestation)†</td>
<td>0.26 (0.09 to 0.82)</td>
<td>4.7 (2.8 to 7.7)</td>
</tr>
</tbody>
</table>

**Fetal and neonatal outcomes**

<table>
<thead>
<tr>
<th>Neonatal mortality (term delivery)†</th>
<th>0.6 (0.2 to 1.5)</th>
<th>1.1 (0.6 to 2.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious neonatal morbidity, including birth trauma (subdural or intracerebral haemorrhage, spinal cord injury, basal skull fracture, other fracture, peripheral nerve injury present at discharge from hospital)††</td>
<td>9</td>
<td>23</td>
</tr>
</tbody>
</table>

†There were no maternal deaths in the Crowther patient preference study.
††There were two stillbirths in the Crowther patient preference study, both in the VBAC group, and both unexplained.

**Plan timing of delivery**

ERCS is safest for the baby if scheduled after 39 weeks’ gestation,1 and the National Institute for Health and Care Excellence recommends that planned caesarean section should not be performed before this because of the increased incidence of adverse neonatal outcomes.2 Women opting for VBAC will normally not be offered any intervention to accelerate delivery until after 41 weeks. If labour has not started by 41 weeks, or if there are indications (or maternal request) for induction of labour before 39 weeks, women should be advised that there is a recognised risk of uterine rupture with a previous caesarean section. A UK population database study in more than 45 000 women with one previous caesarean section reports that induction of labour after 39 weeks was associated with reduced rates of caesarean section (adjusted odds ratio 0.81 (95% confidence interval 0.71 to 0.91)) but higher rates of neonatal unit admission compared with expectant management.16

**Indications for elective caesarean section**2,13

**Fetal complications**

Breech presentation at term; offer elective caesarean section if external cephalic version is unsuitable or unsuccessful

Other non-vertex presentations, including transverse lie

Twin pregnancy if the first twin is breech

**Maternal complications**

Placenta praevia (covering or less than 2 cm from the internal orifice)

Maternal viral infections:

- Primary genital herpes simplex virus infection occurring in the third trimester
- HIV: if the woman is on any antiretroviral therapy and the viral load is 400 copies per ml or more, OR if the woman is not on antiretroviral therapy

Obstruction to pelvic outflow such as a pelvic fibroid, or a bony pelvic deformity

Maternal conditions rendering labour unsafe, such as substantial dilation of the aortic root (eg, >4 cm with Marfan’s syndrome)

Women with uterine scars other than those associated with lower segment caesarean section, such as women with a myomectomy or classic caesarean section scar

Find the full version with references at http://dx.doi.org/10.1136/bmj.j5737

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Competing interests: None declared.
A 78 year old man is brought to the emergency department after collapsing. He is drowsy with signs of a left hemiparesis. Computed tomography of the brain shows an intracranial bleed. He has a history of atrial fibrillation, and he has been taking warfarin (INR target 2-3) for several years. His wife says he started a course of antibiotics for a chest infection a week before. His INR is 8.

Warfarin is the most commonly used vitamin K antagonist in the world.1 The main uses for vitamin K antagonists (fig 1) are prevention of stroke in patients with atrial fibrillation, and prevention of thrombosis in those with previous venous thromboembolism or with mechanical heart valves.

In patients taking a vitamin K antagonist and presenting with a serious or life threatening haemorrhage, urgent anticoagulation reversal is recommended by current national guidelines (see table 1 on bmj.com).2,3 Each clinical situation requires a careful assessment of the benefits and risks of reversing anticoagulants1 by considering the indication for the antithrombotic agents and the bleeding risk.

The biochemical reversal of vitamin K antagonists can be achieved quickly. Guidelines on warfarin use, such as those produced by the British Society for Haematology,4 advise rapid restoration of a normal international normalised ratio (INR), although evidence that this reduces intracranial haematoma growth or improves clinical outcome in those with an intracranial haematoma is limited to case series.4,5 Intracranial haematoma is the most devastating complication of vitamin K antagonist use, accounting for 90% of deaths or permanent disability (fig 2).6

**WHAT YOU NEED TO KNOW**

- There are three options for urgent reversal of anticoagulant effects of vitamin K antagonists such as warfarin: vitamin K, prothrombinase complex concentrate, and fresh frozen plasma
- Monitor reversal of vitamin K antagonists with the international normalised ratio (INR) to measure clotting time
- Prevention of bleeding is key: keep the patient’s INR in the desired therapeutic range and provide extra INR checks during illness and when starting a new medication that may interfere with warfarin’s effect

**HOW PATIENTS WERE INVOLVED IN CREATING THIS ARTICLE**
The executive team of Thrombosis UK (some of whom have taken or are taking warfarin) advised on a summary of the article for patients (see bmj.com). Thrombosis UK is a charity aiming to increase awareness of, and improve care and research in, thrombosis.

**PREVENTING BLEEDING IN PATIENTS RECEIVING VITAMIN K ANTAGONISTS**

- Prevention is key: keeping the patient’s INR in the desired therapeutic range is important
- Dietary intake of vitamin K should be consistent
- It is particularly important to perform extra INR checks during intercurrent illness
- Since many drugs interfere with the action of warfarin, recheck INR after changes in other medication (in particular antibiotics)
- Management by dedicated anticoagulation clinics or patient self management with access to medical advice is recommended
- NICE guidance9 recommends reassessment of anticoagulation for patients with poor anticoagulation control, shown by any of the following:
  - Two INR values >5 or one INR value >8 within the past six months
  - Two INR values <1.5 within the past six months
  - Time in therapeutic range (duration of time in which patient’s INR values were within the desired range) <65%
WHAT REVERSING AGENTS ARE AVAILABLE?

The reversing agents available can directly replace the missing coagulation factors intravenously either by giving concentrates of the missing factors, which work immediately (prothrombinase complex concentrates (PCC)), or enabling regeneration of the missing coagulation factors by giving vitamin K. The third option is fresh frozen plasma, which contains the missing coagulation factors alongside all the other plasma proteins.

Prothrombinase complex concentrate

For immediate reversal of vitamin K antagonists, the missing coagulation factors should be replaced directly with PCC. PCCs are derived from human plasma and contain coagulation factors II, IX, and X, but the factor VII content varies considerably between different formulations. Modern PCC formulations contain substantial amounts of factor VII and can completely reverse the effect of vitamin K antagonists as it is infused. A few countries have access only to three-factor PCCs, which produce poor correction of the INR and are therefore not recommended if four-factor PCCs are available.

The half-life of administered factor VII is only six hours, thus vitamin K should be given with the PCC if interruption of anticoagulation is required for longer than six hours.

Vitamin K

Reversing vitamin K antagonists for planned procedures may be achieved in hours, by giving phytomenadione (vitamin K$_1$) to restart the production of vitamin K-dependent coagulation factors (II, VII, XI, and X). Factor VII has the shortest rate of synthesis, at six hours, whereas the other factors have synthesis times of 25-50 hours. As the INR is most affected by factor VII levels, the INR should return to normal in six hours after vitamin K administration.

Fresh frozen plasma

The alternative to PCC is fresh frozen plasma (FFP) which contains the missing coagulation factors diluted among all the other constituents of plasma.

HOW WELL DO THEY WORK?

Prothrombinase complex concentrate

Table 2 (see bmj.com) gives details of two randomised trials comparing PCC versus FFP in reversing warfarin with clinical endpoints of mortality and safety. PCC was significantly superior to FFP in terms of speed of effect and risk of fluid overload. A recent systematic review and meta-analysis (19 studies, 18 cohort and 1 randomised controlled trials (n=2878)) suggests that PCC provides more rapid and complete factor replacement than FFP (odds ratio 0.64, 95% confidence interval 0.27 to 1.5).

Vitamin K

Immediately after administration of vitamin K, the synthesis of active vitamin K-dependent coagulation factors will recommence, with restoration of adequate factor VII levels in about six hours after intravenous vitamin K and 12 hours after oral vitamin K. An intravenous dose of 2 mg or an oral dose of 5 mg is usually adequate. The reversal of vitamin K antagonists can be monitored with the INR, which is very sensitive to factor VII levels. A recent meta-analysis of 21 studies (n=983) suggested that oral and intravenous vitamin K had similar efficacy, but that subcutaneous vitamin K was inferior and similar to placebo. In the four trials using oral vitamin K (n=75), the proportion of patients with a target INR at 24 hours was 82% (95% confidence interval 70% to 93%), which was similar to that with intravenous vitamin K (six trials, n=69; target INR 77%, 95% CI 60% to 95%).

Fresh frozen plasma

If FFP is used, the amount required to replace the missing coagulation factors in an adult is about 1500 mL (six units) and is not as rapid acting as PCC and will not necessarily fully correct the INR. It also takes time to thaw and transport, whereas PCC can be stored locally and therefore can be reconstituted in minutes. For all these reasons guidelines recommend PCC over FFP in life threatening bleeding although we suggest that if FFP is immediately available pre-thawed (as is recommended in trauma centres) it can be used for a patient needing volume restoration as well as warfarin reversal.
WHAT ARE THE HARMS OF REVERSING AGENTS?

It is important to consider the risk and benefit of reversing anticoagulation in each case individually, and to consult specialist haematologists for advice. For example, in a patient with prosthetic mitral and aortic valves who presents with moderately severe gastrointestinal bleeding (that can probably be managed endoscopically), interruption of vitamin K antagonist may increase the risk of valve thrombosis and cerebral or systemic embolism, and this should be offset against the risk of sustained anticoagulation.

Prothrombinase complex concentrate

Early forms of PCCs were associated with thromboembolism, ascribed to the presence of activated coagulation factors in the concentrate. With modern manufacturing processes, this risk has been greatly reduced.15 Currently thromboembolic complications such as stroke in those with atrial fibrillation after reversal of anticoagulant treatment are mainly ascribed to a patient’s pre-existing thromboembolic risk in the absence of anticoagulation.15 This risk may be amplified by the prothrombotic state induced by the specific clinical settings that require reversal (such as trauma). A meta-analysis of 18 cohort studies and one randomised controlled trial (n=2878) found that thromboembolic complications were observed in an average of 2.5% of PCC recipients and in 6.4% of FFP recipients. The same meta-analysis found no significant difference in mortality between PCC versus FFP (odds ratio 0.64, 95% CI 0.27 to 1.3) or between PCC versus no treatment (odds ratio 0.41, 0.13 to 1.3), suggesting that, even with treatment, clinical outcome was poor.11

Vitamin K

The most important side effect of intravenous vitamin K is an unpredictable anaphylactoid reaction (characterised by dyspnoea, hypotension, shock, and in some cases cardiac arrest), which has an incidence of 3 per 100 000 doses.16 There is a danger of overdose, as large doses of vitamin K (such as 10 mg) will prevent vitamin K antagonists from working for days.

Fresh frozen plasma

FFP, like any other unpasteurised blood product, carries a risk of rare adverse events of about 1:1700 units.17 These risks include transfusion related lung injury, circulatory overload, allergic reactions, and, less commonly, transfusion associated infection.

HOW ARE THEY ADMINISTERED AND MONITORED?

Either PCC or prethawed FFP is given to reverse the anticoagulant effects immediately. Vitamin K should be given simultaneously to cover the period after the effects of PCC have worn off: vitamin K will allow an endogenous regeneration of the missing factors.

Prothrombinase complex concentrate

Give four-factor PCC (examples are Octaplex, Beriplex, Cofact, KCentra) intravenously. The dose of PCC is 25-50 units/kg, and algorithms are available to calculate the most appropriate dose based on body weight and INR level (such as http://beriplex.co.uk/home/dosing-and-administration/). A stepwise increase in dose is recommended with INR prolongation (for example, 25 units/kg if INR is 2-4.0, 35 units/kg if INR 4-6.0, and 50 units/kg if INR >6.0). Thus, in an adult weighing 80 kg with an INR of 8, you should give 4000 units PCC. Overuse of PCC (giving further PCC when INR is in normal range) will produce a prothrombotic state which may lead to further thrombosis.

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Give four-factor PCC (examples are Octaplex, Beriplex, Cofact, KCentra) intravenously. The dose of PCC is 25-50 units/kg, and algorithms are available to calculate the most appropriate dose based on body weight and INR level (such as http://beriplex.co.uk/home/dosing-and-administration/). A stepwise increase in dose is recommended with INR prolongation (for example, 25 units/kg if INR is 2-4.0, 35 units/kg if INR 4-6.0, and 50 units/kg if INR >6.0). Thus, in an adult weighing 80 kg with an INR of 8, you should give 4000 units PCC. Overuse of PCC (giving further PCC when INR is in normal range) will produce a prothrombotic state which may lead to further thrombosis.

Vitamin K

Give vitamin K intravenously and not intramuscularly in an anticoagulated patient because of the risk of muscle bleeding. After reversal of the vitamin K antagonist effect, check INR regularly for at least the next week, as a minority of patients take over a week to clear warfarin. It may be necessary to give further vitamin K. Do not “overcorrect” reversal with more than 10 mg vitamin K as it can prevent “rewarfarinisation” for days.

Fresh frozen plasma

FFP is given intravenously, and a blood transfusion bedside checklist must be followed to ensure positive patient identification and that the blood unit is compatible, and the blood unit number is recorded. The blood unit must also be checked for leaks, discolouration, and expiry date.

Generally, restarting anticoagulation needs daily monitoring—especially for patients at high risk of thrombosis.

EDUCATION INTO PRACTICE

• How would you explain to a patient taking warfarin the benefits and harms of the three agents used to reverse vitamin K antagonists?
• Which agents are used in your department or organisation to reverse warfarin? Does their use adhere to the guidelines presented in this article?
• How can you ensure all patients you see taking warfarin are being assessed regularly for their time in therapeutic range of INR?

COST EFFECTIVENESS

In a cost effectiveness analysis of UK practice in 2010,18 the cost of warfarin reversal with either PCC or FFP was estimated to be ≥15% of the total cost of managing a patient after a life threatening intracranial, gastrointestinal, or retroperitoneal haemorrhage, and PCC was more cost effective than FFP.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j5424
A 2 year old boy was referred to the emergency department by his general practitioner with a non-pruritic, erythematous, papular rash on his knees (figure), elbows, buttocks, and face for 10 days. He had experienced a recent viral upper respiratory tract infection, but was clinically well.

What is the diagnosis and with which viral infections is it associated?

Submitted by Lyndon Wells and Satveer Mahil
Parental consent obtained.

Cite this as: BMJ 2018;360:j5547

Gianotti-Crosti, also known as “infantile papular acrodermatitis,” is associated with several viral infections, including Epstein Barr virus, adenovirus, human herpesvirus 6, cytomegalovirus, enterovirus, and rarely hepatitis B.

A 39 year old woman presented with an asymptomatic ulcer on her left nipple. The ulcer had been present for five weeks. She also reported malaise. She denied any travel history in the past three months, but recalled a history of breast bites and breast-genital contact during sexual intercourse, which had occurred two weeks before the skin lesion appeared. Physical examination revealed demarcated ulceration with a border that was slightly elevated, crusted, and indurated (figure). Left axillary lymphadenopathy was noted.

1 What are the clinical differential diagnoses of nipple ulceration?
2 What investigations would be helpful to confirm the diagnosis?
3 How would you manage the main differentials?

Submitted by Jianjun Qiao, Sha Zhou, and Hong Fang
Patient consent obtained.

Cite this as: BMJ 2018;360:j5850

If you would like to write a Case Review for Endgames, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx
Leonine facies as a sign of leukaemia cutis

A 46 year old woman was referred for investigation of deranged blood counts. She had a white blood cell count of 20×10^9/L (normal range 4-10×10^9/L), haemoglobin 6.8 g/dL (11.5-16 g/dL), and platelets 79×10^9/L (140-450×10^9/L). Progressive facial disfigurement over six months had resulted in her social isolation, but she only sought medical attention when she became lethargic because of anaemia. Clinically, she had coarse “leonine-like facies” (figure, left). Differentials for such an appearance include lepromatous leprosy, systemic amyloidosis, cutaneous lymphoma, and leukaemia.

Uric acid and lung function

Uric acid has antioxidant properties, and Danish investigators wondered if it might protect against impaired pulmonary function. In fact, the reverse seemed to be true since, in two longitudinal studies in Copenhagen, people with high plasma urate levels tended to have poorer lung function and more respiratory symptoms. However, genotyping of participants showed that genetic variants known to be linked to high plasma urate levels were not associated with respiratory outcomes, which suggests that there is no causal relation operating in either direction (Thorax doi:10.1136/thoraxjnl-2017-21027).

The President’s Malaria Initiative

It’s too soon to know how history will judge President G W Bush. However, the way in which he channelled US foreign aid into measures to control malaria will surely weigh in his favour. A modelling study in PLoS Medicine reckons that since 2005, when the President’s Malaria Initiative began, the combination of nets treated with insecticide, indoor spraying, and artemisinin combination therapy has prevented around 200 million cases and saved a million lives (PLoS Med doi:10.1371/journal.pmed.1002448). The investigators judge the interventions to be highly cost effective and argue that funding should be continued.

Bone marrow aspiration confirmed acute monocytic leukaemia. A punch biopsy of the cheek showed dense infiltration of malignant cells, corresponding to extramedullary involvement by leukaemia. She started induction therapy with cytarabine and daunorubicin. By day 5, the patient had recovered her pre-morbid appearance (figure, right).

Unusual facial eruptions, such as leonine facies, can be a sign of leukaemia cutis; a rare manifestation of acute monocytic leukaemia. It is a rapidly reversible cause of facial disfigurement, and readily diagnosed on skin biopsy.

Marriage and dementia

A systematic review finds that married people have a slightly lower risk of dementia than either people who are single throughout their lives or people who are widowed (J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2017-316274). Divorce, on the other hand, makes no difference. It’s well known that married people have a healthier way of life than single people and, since the differences between the groups were reduced after adjusting for poor health, this might be the explanation rather than marriage having any direct cognitive benefit.

Green leafy vegetables

On the subject of cognitive decline, a longitudinal study of nearly 1000 elderly people in the US suggests that a diet rich in green leafy vegetables has a useful preventive effect (Neurology doi:10.1212/WNL.0000000000004815). The rate of decline among those who consumed 1–2 servings per day was the equivalent of being 11 years younger when compared with those who rarely or never consumed green leafy vegetables. Folate, phylloquinone, and lutein seemed to be the most active nutrients.

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Appendicitis in children

Compared with appendicectomy, conservative treatment of appendicitis is less efficacious and more likely to require readmission, according to a systematic review of five studies of children with acute uncomplicated appendicitis (Arch Dis Child doi:10.1136/archdischild-2017-313127). Unfortunately, only one of the five studies was randomised. The others allowed patients, parents, or doctors to choose between treatments. What’s more, the studies used different antibiotic regimens, so this is unlikely to be the final word on the subject.

Maternal diet and asthma in children

The idea that exposure to ω-3 long-chain fatty acids in the womb protects against atopic conditions in childhood gets no support from an analysis of pooled data from more than 60 000 mother-child pairs from 18 birth cohorts (Int J Epidemiol doi:10.1093/ije/dyx007). Fish consumption by mothers during pregnancy varied from less than once every two weeks in the Netherlands, to more than four times a week in Spain. But there was no association between maternal fish intake and symptoms of wheeze in their offspring at any age, nor with risk of asthma or allergic rhinitis at school age.

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