**Minocycline to prevent demyelination?**

Over a couple of decades, the tetracycline antibiotic minocycline has shown glimmers of promise in the treatment of multiple sclerosis. This is because it crosses the blood-brain barrier and exerts anti-inflammatory effects which have nothing to do with the drug’s action as an antibiotic. A recent Canadian trial should really have settled the question of whether it can usefully influence the very earliest clinical stage of MS, which is the transition from the first episode of symptomatic demyelination to the next. Tantalisingly, it falls just short. The 72 patients who were given minocycline after a first demyelinating event showed a 34% conversion to multiple sclerosis by six months, whereas in the 70 who received placebo, the rate was 61%. But as time went on, the difference became smaller, so that it was no longer statistically significant by two years. Something was happening, but this trial proved underpowered to show the true effect over time. So the use of minocycline to prevent progression to MS remains an experimental idea rather than a breakthrough.


**Capecitabine for residual breast cancer**

When I first started commenting on oncology trials each week in the late 1990s, I was inclined to be generous and regard each small success as part of an incremental process: helping to conquer one cancer at a time, by means of one advance at a time. Some cancer trials are still like that, i.e., designed to help patients, rather than bleed them dry with false promises of marginal benefit. I think this trial is a virtuous example, though I will leave the final judgment to my better informed friends Bishal Gyawali and Vinay Prasad. It was carried out with non-industry funding in Japan and South Korea, which is nice to see. The aim was to see if adding capecitabine to standard treatments might improve the otherwise poor prognosis of patients with residual invasive HER2-negative breast cancer after triple chemotherapy. At five years, there was a 4.6% overall survival advantage in the group given capecitabine, at the expense of a 7.3% rate of hand-foot syndrome. Someone needs to design a decision aid for patients faced with this choice.


**Avoiding readmission might not save money**

As a person who has a little job with Cochrane UK, I shouldn't say this too loudly, but I'm beginning to wonder if most meta-analyses of complex interventions are a waste of time. What the world needs to know about are successful models of care that are clearly defined, generalisable, and work over many years. What you usually get from an attempted meta-analysis is a muddy emulsion of different interventions that together don't show much effect and leave the reviewers calling for better studies. The authors of a recent systematic review concerning the cost effectiveness of quality improvement initiatives to reduce hospital readmission did the best they could. Here's the conclusion: “Multicomponent quality interventions can be effective at reducing readmissions relative to the status quo, but net costs vary. Interventions that engage general populations of patients and their caregivers may offer greater value to the health system, but the implications for patients and caregivers are unknown.”

Autoimmune bullous diseases are characterised by blistering of the skin or mucous membranes.1 Blisters form due to the antibodies against structural skin components. The two most common bullous diseases are bullous pemphigoid and pemphigus vulgaris. Estimates of the incidence of bullous pemphigoid range from 2.8 per 100 000 person years in the US2 to 4.28 per 100 000 person years in the UK,3 most commonly presenting in people over 80 years old. Pemphigus vulgaris is rarer and its geographic distribution more variable: whereas in Israel the incidence has been estimated at 5.3 per 100 000 person years, in the UK it was only 0.7.4

This article highlights the pathophysiology, investigations, and management of patients with bullous pemphigoid and pemphigus vulgaris.

Box 1 | Practical considerations before starting treatment with corticosteroids

- Baseline blood tests, including full blood count, urea and electrolytes, and liver function tests
- A proton pump inhibitor for gastric protection
- Osteoporosis baseline screening and bone protection
- Mycobacterium tuberculosis screening in high risk populations because of the risk of reactivation of latent tuberculosis

What causes bullous pemphigoid and pemphigus vulgaris?
The aetiology of bullous pemphigoid and pemphigus vulgaris is poorly understood. Possible triggers for bullous pemphigoid include trauma as well as administration of drugs such as furosemide, non-steroidal anti-inflammatory drugs (NSAIDs), or antimicrobials.5 Recently, an association with neurological conditions such as multiple sclerosis, dementia, and parkinsonism has also been demonstrated in case-control studies.6

There is some evidence to suggest that the incidence of pemphigus vulgaris has a genetic component as there is variation between ethnic groups, with a higher prevalence having been reported in Ashkenazi Jews and in those of Mediterranean descent.7

What is the pathophysiology of pemphigus vulgaris and bullous pemphigoid?
In bullous pemphigoid, antibodies are directed against two basement membrane antigens, BP 180 and BP 230, which are responsible for dermal-epidermal adhesion (fig 1). The subsequent inflammatory response associated with eosinophil infiltration results in dermal-epidermal splitting.8

In pemphigus vulgaris, autoantibodies are directed against proteins desmoglein 1 and 3 (fig 1) that are involved in the function of desmosomes (cellular structures responsible for intercellular adhesion). Subsequent dysfunction of the desmosomes causes loss of cell adhesion in the epidermis, leading to intraepidermal lesions.9

How do pemphigus vulgaris and bullous pemphigoid present?
The peak age of presentation for patients with bullous pemphigoid is over 80 years, and it is rarely seen in those under 50 years old. Patients with bullous pemphigoid may complain of highly pruritic lesions initially. These lesions may last for several weeks to months, and often the lesions mimic eczema, delaying the diagnosis. In some patients, the disease may not progress beyond this stage.

Patients with pemphigus vulgaris tend to be aged between 40 and 60 years. They may complain of painful swallowing, oral pain, sore throat, or hoarseness, and they often first present to a dentist or oral surgeon.1

These two diseases are both characterised by blister-like skin lesions (bullae), which are tense in bullous pemphigoid and flaccid in pemphigus vulgaris. Figure 2 highlights the differentiating features on examination.
How is the diagnosis confirmed?
No formal diagnostic criteria exist for either of these diseases. Instead, the diagnosis is confirmed by the combination of clinical findings, direct immunofluorescence, and, on occasion, autoantibody testing. Direct immunofluorescence involving a perilesional biopsy taken from around 1 cm from the lesion is currently the gold standard for diagnosis of both bullous pemphigoid and pemphigus vulgaris.

Refer patients urgently to a dermatologist if you suspect a diagnosis of bullous pemphigoid or pemphigus vulgaris and consider contacting your local dermatology department by telephone if a patient presents with widespread disease. Although histology can support the diagnosis, it does not provide a definitive diagnosis. Serum ELISA kits, though not widely available in the UK, may become more common because of their high sensitivity, possible correlation with disease activity, and prognostic value.11 12

HOW THE NON-SPECIALIST CAN HELP
• Refer patients with widespread blistering suspected of having bullous pemphigoid or pemphigus vulgaris urgently to the dermatologist. Consider calling your local dermatology department to discuss the possibility of hospital admission
• After discussion with a dermatologist, be prepared to initiate oral corticosteroids in those strongly suspected to have either bullous pemphigoid or pemphigus vulgaris while awaiting a formal review
• Prescribe adequate quantities of potent topical corticosteroids on an ongoing basis for those with limited skin disease. Their use in extensive disease may be limited by practical factors (such as ability of patient or availability of carer to apply the treatment), and they may be associated with systemic absorption and adverse events
• Monitor patients taking oral corticosteroids long term for side effects by checking weight, blood pressure, and urine dipstick (for glucose) and review the risks of bone density loss
• Report any adverse events to the dermatologist where appropriate and any process for reporting adverse drug reactions (such as the MHRA yellow card scheme)
• Ensure compatibility with other concomitant medication and highlight any systemic medication on the patient’s electronic medical record in order to avoid any drug interactions
• Ensure patients taking immunosuppressants are offered annual flu vaccination and a once-only pneumococcal vaccination
• Ensure female patients taking immunosuppressants are up to date with their cervical screening

Fig 1 | Pathophysiology of pemphigus vulgaris and bullous pemphigoid. In pemphigus vulgaris, autoantibodies are directed against proteins desmoglein 1 and 3, which are involved in intercellular adhesion of epidermal cells. In bullous pemphigoid, antibodies are directed against basement membrane antigens BP 180 and BP 230, which are responsible for dermal-epidermal adhesion. (Adapted from MBL International. Autoimmune blistering diseases. https://www.mblintl.com/products/skin-blistering-diseases)
How are bullous pemphigoid and pemphigus vulgaris managed?

Autoimmune bullous diseases are best managed by a dermatologist in secondary care. The British Association of Dermatologists (BAD) produced guidelines for the management of bullous pemphigoid in 2012. The evidence base for treatment of pemphigus vulgaris is less established, reflecting its rarity.

Advise patients who have bullous pemphigoid secondary to a particular drug to stop the suspected agent as this can reduce the risk of relapse.

In both conditions, the mainstay of treatment has been systemic or topical steroids. However, as these treatments may be associated with considerable adverse effects, the focus of attention has now moved towards steroid-sparing drugs and biological therapies. Box 1 outlines practical considerations before starting treatment with steroids.

The aim of treatment is to suppress disease activity to the point where new lesions stop forming and existing lesions begin to heal. Typically the disease begins to improve after two weeks of treatment. This is followed by a consolidation phase, when the optimum dose of the medication should be continued until most lesions have healed. During the maintenance period, medication doses are titrated down to a level sufficient to prevent disease recurrence with minimal side effects. In some patients, it may be possible to stop treatment altogether if disease remission occurs, although the risk of relapse remains.

Serum antibody testing may be useful at this stage (for antibodies to BP 180 and BP 230 in bullous pemphigoid and antidesmoglein 3 in pemphigus vulgaris) when considering stopping treatment, as immunological remission has been reported to be associated closely with clinical remission.

Topical corticosteroids

The use of both topical and systemic corticosteroids is supported by a strong evidence base, including a recent Cochrane review. In general, steroid creams such as clobetasol propionate are used first when disease is confined to a small area, as they have similar efficacy to that of systemic steroids. They are applied directly to the lesions and may be associated with cutaneous side effects, including the formation of striae and skin atrophy. In more widespread disease, application over the whole body is advised, excluding the face. However, the practical considerations of applying a cream in this way may limit this approach.

Systemic corticosteroids

Where disease is more widespread systemic treatment is preferred and effective. Usually oral prednisolone is preferred. Use of systemic steroids is limited by immunosuppressive and metabolic effects, which can lead to diabetes, osteoporosis, severe infections, and ischaemic heart disease. As these side effects are dose dependant, it is important to achieve remission with the lowest possible dose.

Prednisolone 0.75–1.0 mg/kg is effective in most patients within two to four weeks of initiation. At this point, the dose of steroid can be reduced. If, at four weeks, new lesions are still forming then an adjunct (see below) should be considered. Adjuvants may also be considered if the steroids are poorly tolerated.

Antibiotics and nicotinamide

Tetracycline antibiotics have long been used in the treatment of bullous pemphigoid and pemphigus vulgaris because of their anti-inflammatory effect, with little evidence to support their use until recently. In 2017 in a multicentre trial with 278 patients, after six weeks of treatment, doxycycline was shown to be non-inferior to oral prednisolone. Furthermore, the group treated with doxycycline had a lower incidence of adverse effects. Tetracyclines may therefore offer an alternative first line treatment in bullous pemphigoid: for example, in patients with pre-existing diabetes or hypertension. Trials on a similar scale have not looked at tetracycline use in pemphigus vulgaris, and no guidelines for pemphigus vulgaris routinely recommend using antibiotics.

Nicotinamide (also known as niacinamide or nicotinic acid amide) is the water soluble, active form of vitamin B3, and its anti-inflammatory properties are used for the treatment of blistering diseases. It is always combined with a tetracycline, and the dose is 500 mg three times a day.

Immunosuppressants

For pemphigus vulgaris, immunosuppressants such as azathioprine, mycophenolate, dapsone, methotrexate, chlorambucil, and cyclophosphamide are often used off-label in conjunction with steroids for their steroid-sparing effect as first line treatment. However, in a Cochrane review, there was no clear benefit from using combination therapy of corticosteroid and immunosuppressive agents compared with corticosteroid alone. In bullous pemphigoid these agents are used as second line therapy after treatment with steroids has failed or the side effects were not tolerated. There is no conclusive evidence of superiority of any one of these agents over another. Adverse effects differ between drugs but can include myelosuppression and hepatotoxicity, and so full blood count and liver function need to be monitored.

Useful information and support is available for patients (box 2).

Box 2 | Information resources for patients

- International Pemphigus and Pemphigoid Foundation (www.pemphigus.org/) — Provides free and up to date information about blistering diseases as well as hosting an online chat
- Pemphigus Vulgaris Network (http://pemphigus.org.uk/) — A similar support group for the UK
- PEM Friends (http://pemfriends.co.uk/) — UK based support organisation, affiliated with the International Pemphigus and Pemphigoid Foundation
**Examination findings**

**Bullous pemphigoid**
- Tense, fluid-filled blisters may form, 1-3 cm in diameter
- These tend to be stable as the lesions are subepidermal and hence unlikely to erode
- If they do burst, the exudate is usually clear, and they heal with post-inflammatory hyperpigmentation
- Lesions are most commonly on the flexures, but may be symmetrically distributed over the trunk and extremities
- Involvement of the oral mucosa and mucosal surfaces is rare

**Pemphigus vulgaris**
- Mucosal erosions are an early sign, often preceding the cutaneous changes
- Cutaneous lesions typically affect the chest and back in addition to the scalp
- Erythematous macules appear first, only later evolving into flaccid blisters
- As the blisters are intraepidermal, they are weak and rupture easily, resulting in painful erosions

**Nikolsky sign***

- Typically negative
- Often positive and frequently cited as a diagnostic aid. It is a somewhat specific, but not very sensitive, diagnostic aid

**Differential diagnoses**

**Bullous pemphigoid**
- Mucous membrane pemphigoid
- Pemphigoid gestationis
- Linear IgA disease
- Epidermolysis bullosa acquisita
- Bullous systemic lupus erythematosus
- Dermatitis herpetiformis

**Pemphigus vulgaris**
- Acute herpetic stomatitis
- Erythema multiforme
- Aphthous ulcers
- Bullous lichen planus

*A positive Nikolsky sign is when application of tangential pressure to the skin adjacent to a lesion causes separation of the dermis from the epidermis.


**Fig 2** Differentiating features of bullous pemphigoid and pemphigus vulgaris on examination. (Images reproduced from Rook’s *Textbook of Dermatology* (9th edition, 2016), courtesy of John Wiley & Sons. Images of pemphigus vulgaris are also courtesy of Dr RJ Pye, Addenbrooke’s Hospital, Cambridge, UK)

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**What is the prognosis of bullous pemphigoid and pemphigus vulgaris?**

Bullous pemphigoid is often self-limiting but may last from months to years. During its active stage, bullous pemphigoid can lead to considerable morbidity, and older age and use of high-dose steroids have been identified as risk factors for increased mortality.

Before the introduction of corticosteroids, pemphigus vulgaris was also almost universally fatal, but there has been a subsequent decline in mortality. Though the duration of disease varies, pemphigus vulgaris is thought to have a more chronic course than bullous pemphigoid, with few patients achieving complete remission.

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**EDUCATION INTO PRACTICE**

- Would you consider autoimmune diseases when confronted with a blistering rash?
- When should the generalist refer urgently to a dermatology clinic?
- What is the role for shared care between specialists and GPs for long-term stable patients on systemic immunosuppressant therapy?

Contributors: MK and AMA both contributed to the concept and design of the review. MK created the first draft and AMA revised the content and approved the final version to be published. Both authors act as guarantors

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UNCERTAINTIES

What treatment can reduce the need for caesarean section in nulliparous women with prolonged labour?

Sara Kenyon,1 Julia Sanders,2 Lee Middleton,3 Tracey Johnston4

1Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT, UK
2Healthcare Sciences, Cardiff University, Cardiff CF24 0AB, UK
3Birmingham Clinical Trials Unit, School of Cancer Sciences, Robert Aitken Institute, University of Birmingham, Birmingham B15 2TT
4Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham

Correspondence to: S Kenyon s.kenyon@bham.ac.uk

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. This paper is based on a research priority identified and commissioned by the National Institute for Health Research’s Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com.

WHAT YOU NEED TO KNOW

• Prolonged labour is associated with adverse outcomes for mother and fetus, and intravenous oxytocin is the mainstay of treatment
• There is uncertainty as to the optimal regimen of oxytocin to decrease the chances of caesarean section with minimal adverse effects, and there is some evidence that high dose regimens may be effective
• Administer oxytocin in hospital where the mother and baby can be closely monitored

Labour is commonly divided into three stages. The duration of the first and second stages of labour vary, dependent on parity. The figure depicts the stages of labour and expected duration as defined by the National Institute for Health and Care Excellence (NICE). Nulliparous women tend to have a longer labour than multiparous women. Delay can result from poor uterine contractions or the relationship between size, presentation, and position of the fetus and the maternal pelvis that obstructs vaginal delivery. Uterine contractile dysfunction affects between 11% and 30% of nulliparous women and is the focus of this paper.

Delayed labour—There is some variation worldwide in the definition of delayed labour (table, see bmj.com). The World Health Organization considers delay as a rate of cervical dilation of less than 0.5-1 cm in four hours once labour is established, whereas NICE recommends waiting a further two hours with cervical dilation of less than 1 cm before delay is confirmed. Prolonged labour is associated with higher rates of chorioamnionitis9 with risk of neonatal sepsis and of unplanned caesarean section with associated risks of infection and bleeding.10-12

Oxytocin—Treatment for a confirmed delay in labour is with intravenous oxytocin15 to re-establish effective uterine contractions. The dose is titrated against the strength and frequency of uterine contractions by means of a variable rate infusion pump and taking into account fetal wellbeing through electronic fetal heart monitoring. Adverse effects include uterine tachysystole and uterine hyperstimulation (see box 1 for definitions), which are associated with hypoxic ischaemic encephalopathy and neonatal death. Mother and baby therefore need to be intensively monitored during treatment with oxytocin. Injudicious use of oxytocin and inappropriate management during labour have resulted in cases of fetal hypoxia and resultant controversy around its use.13 There is no consensus on the optimal dose regimen of oxytocin for delay in the first stage of labour in nulliparous women at term (37-42 weeks’ gestation) to reduce unplanned caesarean section and increase vaginal birth with minimal adverse events. Recommendations are lacking apart from in the UK (table 1), and the regimens used vary widely even within the same country,14 despite calls for a standardised regimen.15

Box 1 | Definitions of terms used

Nulliparous—Woman who has not given birth before
Uterine tachysystole—Increased uterine contractions; >5 uterine contractions in 10 minutes for 20 minutes
Uterine hyperstimulation—Tachysystole with abnormal features of the fetal heart rate suggestive of hypoxia
What is the evidence of uncertainty?
Limited evidence from randomised trials suggests that use of oxytocin at a low dose shortens labour but does not affect whether the baby is born normally, by means of instruments (forceps or ventouse), or by caesarean section.1,16

With respect to the effectiveness of high dose regimens of oxytocin, a Cochrane review17 published in 2013 (including 644 women, three randomised controlled trials, and one quasi-randomised trial) compared high dose oxytocin regimens with low dose regimens in women delayed in normal labour. Because of variation in the dose regimens in the trials, the authors defined high dose oxytocin as starting dose and increments >4 mU/minute and low dose oxytocin as starting dose 1-4 mU/minute and increments of 1-2 mU/minute. High dose regimens were associated with a decrease in the rate of caesarean section (risk ratio 0.62; 95% confidence interval 0.44 to 0.86), although there was some doubt about this estimate because of heterogeneity of treatment effect estimates (risk ratio 0.67; 0.38 to 1.18) under alternative model assumptions. The only trial reporting length of labour17 included only 40 women and reported a reduction with high dose of oxytocin (mean difference −3.50 hours; 95% CI −6.38 to −0.62). Two of the trials included both nulliparous and multiparous women, which limits interpretation of findings. No differences were noted in other maternal and neonatal outcomes or adverse effects.

There is uncertainty as to women’s views of the use of oxytocin, with most trials focusing on clinical outcomes.18 Limited qualitative evidence from interviews with women who experienced prolonged labour suggests that intervention is acceptable to women19 and that, in case of a delay, women preferred to defer decision making to professionals.20

Is ongoing research likely to provide relevant evidence?
No further trials have been reported since publication of the Cochrane review, but several are ongoing. We searched the WHO International Clinical Trials Registry Platform and Clinicaltrials.gov in January 2017 and identified three ongoing trials comparing low dose and high dose oxytocin for delay in the first stage of labour in nulliparous women (see box 2 on bmj.com for details).

These studies are likely to provide evidence on effectiveness and safety of a high dose oxytocin regimen in delayed labour to reduce duration of labour and improve chances of spontaneous vaginal birth. The trials are taking place in America, Sweden, and the UK.

Box 3 lists recommendations for further research.
What should we do in light of the uncertainty?
Nulliparous women and women with a higher body mass index have higher risk for slow progress in labour. At the antenatal visit close to term, discuss with the woman and her partner the expected duration and stages of labour and the possibility of prolonged labour. Emphasise the importance of remaining mobile and hydrated during labour. Explain that, if labour progresses more slowly than expected, there is an increased chance of infection and of requiring a caesarean section. At the start of labour, inform the woman that progress of labour and wellbeing of the fetus will be monitored throughout. Regular vaginal examinations will be done to assess cervical dilatation. As there is variation in the definitions of delay in labour, rely on the relevant guidelines to make a diagnosis (table, see bmj.com).

Women with prolonged labour can opt to wait and see how labour progresses without augmentation by oxytocin. Intravenous oxytocin may be offered to strengthen uterine contractions and accelerate progress, but there is only limited evidence that this will increase the likelihood of spontaneous delivery.

In case of a delay, offer pain relief and intravenous oxytocin until the woman gives birth. Further evidence is required before offering high dose oxytocin outside of a research setting. Oxytocin should be given only where close monitoring of the mother and fetus is possible and where adequate pain relief can be given. If the woman is in labour outside an obstetric unit, timely referral to a hospital for assessment and appropriate intervention is recommended.

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BMJ OPINION

Teaching compassionate communication

Work environments that support caring and compassionate communication with patients provide foundations on which high quality, patient centred care can flourish.

Nothing tests communication skills so much as breaking bad news. Emotions are often running high for both patient and doctor. Compassionate behavioural skills—using the right words expressed in the right way—can help minimise patient distress and offer reassurance to accompanying relatives.

It is, however, common for younger medical graduates to find it difficult to initiate respectful and compassionate dialogue with their patients while working in a crowded outpatient department. Many struggle to provide optimum care in such a stressful working environment.

Some of these new doctors report that they didn't have the opportunity as students to develop professional communication skills in real life scenarios. They have not been exposed to local communities for supervised learning of the doctor-patient relationship, and they struggle to develop compassionate relationships with unknown patients in a limited time period.

Coursework on taking case histories and classroom teaching of communication skills remain incomplete until medical students are exposed to interactions with real patients.

Well designed training in behavioural science builds confidence and self respect and often includes content to develop students’ humanity. However, some medical school curricula still hinder the effective progression of this teaching into routine care.

Integrative teaching models that allow students to gradually introduce this training into their practice offer a greater potential for improving critical-reflective learning in real life situations.

Tanu Pramanik, associate professor, All American Institute of Medical Sciences, St Elizabeth, Jamaica
TP originally posted her views in a rapid response to The BMJ article Humanising healthcare www.bmj.com/content/355/bmj.i6262.
Competing interests: TP has been teaching behavioural science at medical schools since 2006.

SOURCES AND SELECTION CRITERIA
We searched the websites of English speaking colleges of obstetricians and gynaecologists internationally for definitions of normal and delayed labour and treatment. We also searched WHO Guidelines and in the UK NICE guidelines (detailed in the table (see bmj.com)).

For evidence of effectiveness of oxytocin, we searched the Cochrane Database of Systematic Reviews and Clinical Evidence in January 2017 with search terms “delay in labour,” “augmentation,” “spontaneous vaginal birth,” and “caesarean section.” We found one Cochrane review.
CASE REVIEW
A young goalkeeper with buttock pain and fever

A previously healthy 13 year old boy presented to the emergency department with pain in the right buttock and fever. Five days earlier he had fallen diving to catch a ball during a football match, and two days later had a fever of up to 39°C and had started to complain of buttock pain. Physical examination on presentation was unremarkable except for pain on abduction of the right hip, with limited range of motion. Radiography of the pelvis was normal. Oral ketoprofen was prescribed for pain and he was discharged. Three days later the pain had worsened and he was still feverish. He returned to the emergency department. Physical examination was unchanged from the previous visit. Ultrasonography was performed on the right hip, which was normal. Laboratory findings included elevated C reactive protein (155.4 mg/L, normal values <5) and erythrocyte sedimentation rate (56 mm/h, normal values <20), and leucocytosis (leucocyte count 17 × 10⁹/L, normal range 4.0-10.5 × 10⁹/L), with 88% neutrophils (normal range 50-65%), with normal haemoglobin and platelet count. Creatine kinase levels were within the normal range and blood cultures were negative. Magnetic resonance imaging (MRI) of the pelvis was performed (fig 1).

1. What is the most likely diagnosis?
2. What complications can arise?
3. How is this condition managed?

Submitted by Valentina Moressa, Serena Pastore, Samuele Naviglio, and Alessandro Ventura

Parental consent obtained.

Cite this as: BMJ 2017;357:j2400

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

SPOT DIAGNOSIS
A Brazilian child with a nodule in the foot

A 2 year old girl from the north coast of Brazil presented on arrival in the UK with a day's history of a painful and mildly pruritic nodule on the sole of her right foot (figure). Seven days later, the nodule had grown in size and had become more tender. What is the diagnosis?

Submitted by Khuen Foong Ng and Stephen Owens

Parental consent obtained.

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Fig 1

1 Pyomyositis of the right gluteus maximus muscle (fig 2, arrow). There are no specific laboratory tests for pyomyositis; MRI is the gold standard for diagnosis.

2 Complications of pyomyositis include spread of infection to surrounding structures (arthritis, osteomyelitis) and distant sites (endocarditis, septic emboli). Untreated pyomyositis can lead to septic shock.

3 Prompt intravenous antibiotic therapy targeted on Staphylococcus aureus is generally effective for early infections. Adjunctive immunosuppressive and biologic therapies may be considered for resistant cases.

4 Immunomodulating preparations can lead to specific complications of pyomyositis, including spread of infection to surrounding structures, anaphylaxis, aseptic meningitis, or septic shock.

1 Pyomyositis of the right gluteus maximus muscle (fig 1).

2 Pyomyositis of the right gluteus maximus muscle (fig 2, arrow).
**Acute lymphocytic leukaemia optic nerve infiltration**

A 27 year old white man undergoing chemotherapy for acute lymphocytic leukaemia was referred for ophthalmic observation after experiencing sudden loss of vision in the left eye. He had no associated headaches or nausea. Left eye best corrected visual acuity was counting fingers at 1 m. Fundus examination revealed optic disc oedema with associated flame shaped haemorrhages and clinical macular oedema (figure). The right eye was unremarkable. Lumbar puncture showed normal cerebrospinal fluid opening pressure, and blood tests excluded any infectious aetiology. AT2 weighted orbital magnetic resonance scan showed enhancement in the left optic nerve. A diagnosis of leukaemic optic nerve infiltration was made, and the patient was started on hyperfractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone and local radiotherapy. After treatment his vision fully improved (20/20 on Snellen scale) and anatomical resolution was achieved.

Nuno Pinto Ferreira (ngcpferreira@gmail.com), Filipa Teixeira, Hospital de Santa Maria, Ophthalmology, Lisbon

Patient consent obtained.

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**Loneliness and death**

“Be not solitary, be not idle” was Robert Burton’s advice in *The Anatomy of Melancholy* (1621). This applies beyond melancholia: the association between premature death and loneliness has long been recognised. Not to mention the benefits of activity. The UK Biobank Study includes 466 901 men and women with enough social information to examine the connection between isolation and loneliness and death rate over 6.5 years (*Lancet* doi: 10.1016/S2468-2667(17)30075-0). There is a definite association (hazard ratio 1.38) but this is completely mediated by known risk factors, many of them modifiable by more activity and better support and care.

**Gliflozins and cardiovascular protection**

Plenty of drugs lower blood glucose in people with type 2 diabetes, and produce millions in revenue for their manufacturers. But it came as a surprise even to the trialists when one drug, empagliflozin, produced a clear signal of benefit in reducing cardiovascular events as well as sugar (*Lancet* doi: 10.1161/CIRCULATIONAHA.117.029190). Most trials of other drugs in the sodium-glucose co-transporter-2 inhibitor (SGLT-2i) class were not powered to show a similar effect, but an observational study based on registry data from more than 300 000 patients in Europe and the United States suggests a reduction in heart failure and cardiovascular death from all drugs in the SGLT-2i class.

**Sex differences in inpatient outcomes**

“The association of sex with daily risk of rehospitalisation varies across conditions” is a perfectly correct use of words, though it could be misconstrued as referring to pleasures which Minerva, the chaste goddess, has little knowledge of. In a survey of three million Medicare admissions, US researchers explored differences between men and women in three common causes of hospital readmission (*Circ Outcomes* doi:10.1161/CIRCOUTCOMES.116.003271). Women were more at risk for rehospitalisation (but not death) after myocardial infarction and heart failure, but not pneumonia.

**Discordant preferences**

Shared decision making with patients has been advocated for the past 30 years, and since the Montgomery v Lanarkshire case it is now a legal requirement. This raises thorny issues about how well the preferences of patients match those of clinicians, and how such differences can be resolved. One way to study the problem is by discrete choice experiments, and a recent review identified 38 of these exploring 16 interventions in 26 diseases/indications (*BMJ Open* doi: 10.1136/bmjopen-2016-014719). They showed a variety of discordances, highlighting the need for better skills and better tools for clinicians in their dialogue with patients.

**Parent delivered CBT for anxious kids**

Mental health services for children in the UK are unable to match demand, especially for one to one cognitive therapy. Could parents help by being trained to deliver cognitive behavioural therapy (CBT) to their offspring? A randomised trial in Oxfordshire produced mixed results (*Lancet* doi:10.1016/S2215-0366(17)30149-9), but showed that parental CBT might be as good as solution focused, brief therapy for anxious children. Minerva wonders if it works worse or better if the parent is the source of anxiety.

**Population oral steroid use**

Oral corticosteroids always carry some risk. For example, a recent *BMJ* paper (doi:10.1136/bmj.j1415) showed a fivefold increase in the risk of sepsis after short courses, as well as an increased risk of thromboembolism and fractures. All the more alarming, then, to read a survey showing that about 3% of the Danish population redeemed at least one prescription for a systemic steroid annually between 1999 and 2015 (*BMJ Open* doi: 0.1136/bmjopen-2016-015237). In the oldest age groups, who are at highest risk of harm, this approached 10%.

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