Football on the brain

American football is, I am told, a contact sport. I’ve tried to watch two matches on television with the help of American friends, but I was entirely unable to work out why people were running around in the directions they did, and generally failed to spot either the ball or (more importantly) the collisions of great importance that were taking place during the brief periods of play. Collisions between players lead to the presence of phosphorylated tau aggregates in brain cells: they have been found in 99% of deceased National Football League players who donated their brains to science. Such insoluble bits of material do not help brain function and are diagnostic of chronic traumatic encephalopathy. It’s possible that the same thing happens on a lesser scale among people who play proper football (soccer), since concussion in World Cup games is common and, according to a research letter (doi:10.1001/jama.2017.6204), poorly handled or ignored in 63% of cases.

Tocilizumab in giant cell arteritis

This week’s opening mab is tocilizumab, a humanised monoclonal antibody that targets the interleukin-6 receptor. As mab names go, this one is not too cili (I’m only doing this so you will remember it). In the UK, it costs about £12 000 per year. Here it is compared with placebo in a trial of steroid withdrawal in giant cell arteritis. What this trial tells us is that when you taper off prednisone (costing almost nothing) slowly over two years, giant cell arteritis will relapse in about 50% of people, whereas if you give them weekly subcutaneous tocilizumab, the figure is more like 20%. We are all familiar with the long term harms of corticosteroids (they add “sclerostin monoclonal antibody,” to let us know what it does. It’s not as arcane as you think: inhibiting sclerostin should increase bone production and reduce bone resorption. If a woman with postmenopausal osteoporosis can’t tolerate or doesn’t respond to a bisphosphonate, this might be a choice for her, if it is safe and effective over a long period of time. In this open label trial funded by Amgen, Astellas, and UCB Pharma, romosozumab was compared with teriparatide in such women. The mab increases hip bone density over one year, whereas teriparatide did not. So here’s an unblinded, short term trial of two very expensive long term agents using a surrogate endpoint. Not my favourite kind of evidence.

Resuming statins and cardiovascular events

Statins are a classic case of how hard it is to achieve a shared understanding of medicine. Primary prevention with drugs is a relatively recent and problematic idea, and what doctors think people should do may not accord with what healthy-feeling people wish to do. The evidence from double blinded randomised trials is pretty straightforward, whereas the observational evidence is often confusing. In this cohort study from China, based on electronic medical records, most people who were recorded as having had an adverse reaction to statins continued to receive prescriptions for a statin, including over 80% who were given a different statin and then had a further reaction to it. Over a mean of four years, people who continued their statins did slightly better than those who did not, judged by a composite outcome of myocardial infarction, stroke, or death. But the quality of the data is questionable, and this 1.7% difference could well be artefactual.

Dizziness and one minute hypotension

I recently had an experience of postural hypotension, and can confirm that a 50 mm Hg systolic drop from sitting to standing causes symptoms. In my youth, we were taught to measure it using a long rubber tube connected to a mercury sphygmomanometer, hopefully within one minute and ideally from a supine position. For some reason, the practice of measuring it after three minutes became favoured and is now hallowed by various guidelines. This is wrong. In a cohort of 11 429 middle aged Americans followed up over 20 years, the one minute rather than the three minute drop was most associated with dizziness on standing, falls, fractures, syncope, car crashes, and death.

Romosozumab

In the title of this paper about romosozumab, the Lancet kindly adds “sclerostin monoclonal antibody,” to let us know what it does. It’s not as arcane as you think: inhibiting sclerostin should increase bone production and reduce bone resorption. If a woman with postmenopausal osteoporosis can’t tolerate or doesn’t respond to a bisphosphonate, this might be a choice for her, if it is safe and effective over a long period of time. In this open label trial funded by Amgen, Astellas, and UCB Pharma, romosozumab was compared with teriparatide in such women. The mab increased hip bone density over one year, whereas teriparatide did not. So here’s an unblinded, short term trial of two very expensive long term agents using a surrogate endpoint. Not my favourite kind of evidence.
GUIDELINES

Parkinson’s disease: summary of updated NICE guidance

Gabriel Rogers,1 Debbie Davies,2 Joshua Pink,1 Paul Cooper3 4

1National Institute for Health and Care Excellence, Manchester M1 4BT, UK
2Aneurin Bevan Health Board, Newport, UK
3Greater Manchester Neuroscience Centre, Salford, UK
4University of Manchester, Manchester, UK
Correspondence to: G Rogers Gabriel.Rogers@nice.org.uk
Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

Parkinson’s disease is one of the most common neurological conditions, estimated to affect around 250 people per 100 000 in the UK.1 People with Parkinson’s disease classically present with motor symptoms including bradykinesia, rigidity, rest tremor, and postural instability; however, non-motor symptoms may also be prominent, including depression, cognitive impairment, and autonomic disturbances.

WHAT YOU NEED TO KNOW

• Impulse control disorders can develop in a person with Parkinson’s disease who is receiving any dopaminergic therapy at any stage in the disease
• A wide range of non-motor symptoms are common in Parkinson’s disease, which may have modifiable causes (including antiparkinsonian medicines) and may be amenable to non-pharmacological management as well as some medicines
• Offer all people with Parkinson’s disease access to the services provided by Parkinson’s disease specialist nurses
• Offer access to specialist physiotherapy, occupational therapy, speech and language therapy, and cognitive behavioural therapy when relevant symptoms develop

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the creation of this summary. However, committee members involved in this guideline included lay members who contributed to the formulation of the recommendations summarised here. The views of multiple patient organisations were sought for both the original scope of the guideline and its draft recommendations.

This article summarises the most recent update to the National Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of Parkinson’s disease in adults.2 This NICE guideline provides an update on most aspects of managing Parkinson’s disease, reflects emerging experience in areas such as impulse control disorders, and provides recommendations on the use of treatments that may provide some relief from the distressing symptoms of advanced Parkinson’s disease. Recommendations, full details of evidence, and the NICE pathway are available via the NICE website (www.nice.org.uk/guidance/ng71).

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Diagnosis

Parkinson’s disease remains a clinical diagnosis based on the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria for Parkinson’s disease2 (box 1, see bmj.com).

Pharmacological management of motor symptoms

Involve the person with Parkinson’s disease and family members and carers (as appropriate) in all decisions. Take account of their clinical and lifestyle circumstances, their preferences, needs and goals, and how they view the potential benefits and harms of different drug classes.
First line treatment
Oral levodopa remains the preferred first line medicine for people with troublesome motor symptoms. When starting treatment, give information about adverse events. For dopamine therapy, these adverse events may include impulse control disorders (particularly dopamine agonists), excessive sleepiness, and hallucinations and delusions (all Parkinson’s disease treatments but particularly dopamine agonists). Table 1 lists the benefits and harms from first line drugs, and the infographic outlines the general strategy for managing Parkinson’s disease symptoms.

- Offer levodopa to people with early Parkinson’s disease whose motor symptoms affect their quality of life.
- Consider a choice of dopamine agonists, levodopa, or monoamine oxidase B inhibitors for people with early Parkinson’s disease whose motor symptoms do not affect their quality of life (see table 1).

Adjuvant treatment of motor symptoms
When a person with Parkinson’s disease develops dyskinesia or motor fluctuations (including “wearing off” episodes when effects of medication start to wear off in between medication doses) adjuvant therapy may be added, on advice from a healthcare professional with specialist expertise in Parkinson’s disease. Table 2 lists the benefits and harms of adjuvant drugs, and the infographic (p 245) outlines the general strategy for managing Parkinson’s disease symptoms.

- Offer a choice of dopamine agonists, monoamine oxidase B inhibitors, or catechol-O-methyl transferase inhibitors as an adjunct to levodopa for people with Parkinson’s disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy (see table 2).
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine.

Impulse control disorders as an adverse effect of dopaminergic therapy
People with impulse control disorders (ICDs) fail to resist the temptation to perform an act harmful to themselves or others such as compulsive gambling, hypersexuality, binge eating, and obsessive shopping. They are a recognised adverse effect of dopamine replacement therapies, and occur in 14–24% of patients with Parkinson’s disease who are taking these medications. ICD behaviours can cause distress for patients and carers, financial difficulties, and even criminal convictions. They may be difficult to recognise, particularly if patients conceal their behaviour from carers and family. ICD behaviours can develop in a person with Parkinson’s disease who is taking any dopaminergic therapy, particularly dopamine agonists, at any stage in the disease. They are also associated with previous impulsive behaviours and a history of alcohol consumption or smoking.

- When starting dopamine agonist therapy, give people and their family members and carers (as appropriate) oral and written information about the following, and record that the discussion has taken place:
  - The increased risk of developing ICD behaviours when taking dopamine agonist therapy, and that these behaviours may be concealed by the person affected
  - The different types of behaviour (such as compulsive gambling, hypersexuality, binge eating, and obsessive shopping)
  - Who to contact if ICD behaviours develop.
- If a person with Parkinson’s disease has developed a problematic ICD behaviour, discuss the following with the person and family members and carers (as appropriate):

Table 1 | Potential benefits and harms of first line medicines for management of Parkinson’s disease motor symptoms

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Dopamine agonists</th>
<th>MAO-B inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms</td>
<td>Greater improvement</td>
<td>Less improvement</td>
<td>Less improvement</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>Greater improvement</td>
<td>Less improvement</td>
<td>Less improvement</td>
</tr>
<tr>
<td>Motor complications</td>
<td>More complications</td>
<td>Fewer complications</td>
<td>Fewer complications</td>
</tr>
<tr>
<td>Adverse events*</td>
<td>Fewer events</td>
<td>More events</td>
<td>Fewer events</td>
</tr>
</tbody>
</table>

MAO-B = monoamine oxidase B. *Excessive sleepiness, hallucinations, and impulse control disorders.

Table 2 | Potential benefits and harms of medicines used as adjuvants to levodopa for management of Parkinson’s disease motor symptoms

<table>
<thead>
<tr>
<th></th>
<th>Dopamine agonists</th>
<th>MAO-B inhibitors</th>
<th>COMT inhibitors</th>
<th>Amantadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms</td>
<td>Improvement in symptoms</td>
<td>Improvement in symptoms</td>
<td>Improvement in symptoms</td>
<td>No evidence of improvement</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>Improvement in activities</td>
<td>Improvement in activities</td>
<td>Improvement in activities</td>
<td>No evidence of improvement</td>
</tr>
<tr>
<td>Off time*</td>
<td>Greater reduction of off time</td>
<td>Reduction of off time</td>
<td>Reduction of off time</td>
<td>No evidence</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Intermediate risk of events</td>
<td>Fewer events</td>
<td>More events</td>
<td>No evidence</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Greater risk of hallucinations</td>
<td>Lower risk of hallucinations</td>
<td>Lower risk of hallucinations</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

COMT = catechol-O-methyl transferase. MAO-B = monoamine oxidase B. *Periods of the day when levodopa is not working well, causing worsening of parkinsonian symptoms.
How the impulse control disorder is affecting their life

Possible treatments, such as reducing or stopping dopaminergic therapy

The benefits and disadvantages of reducing or stopping dopaminergic therapy.

When managing ICD behaviours, modify dopaminergic therapy by gradually reducing any dopamine agonist. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal.

Offer specialist cognitive behavioural therapy targeted at ICD behaviours if modification of dopaminergic therapy is not effective.

Box 2 | Recommended pharmacological management of non-motor symptoms of Parkinson’s disease

When modifiable causes and non-pharmacological treatments have been ruled out:

- **Excessive daytime sleepiness**—Consider modafinil
- **Rapid eye movement sleep behaviour disorder**—Consider clonazepam* or melatonin*
- **Nocturnal akinesia**—Consider levodopa or oral dopamine agonists
  - If neither is effective, consider rotigotine
- **Orthostatic hypotension**—Consider midodrine (taking into account the contraindications and monitoring requirements)
  - If midodrine is contraindicated, not tolerated, or ineffective, consider fluoroisocortisone* (taking into account its safety profile and potential interactions with other medicines)
- **Depression**—Identify and manage in accordance with NICE guideline on depression in adults with a chronic physical health problem
- **Hallucinations and delusions**—Do not treat if well tolerated
  - Consider quetiapine* in people without cognitive impairment
  - If standard treatment is not effective, offer clozapine in people without cognitive impairment (registration with a patient monitoring service is needed)
  - Lower doses of quetiapine and clozapine are needed for people with Parkinson’s disease than in other indications
  - Do not offer olanzapine
- **Dementia**—Offer a cholinesterase inhibitor for mild or moderate dementia (rivastigmine, donepezil,* or galantamine* capsules or rivastigmine patches*)
  - Consider a cholinesterase inhibitor* for severe dementia
  - Consider memantine* if cholinesterase inhibitors are not tolerated or contraindicated
- **Drooling**—Consider glycopyrronium bromide*
  - If glycopyrronium bromide is not effective, not tolerated or contraindicated, consider referral to a specialist service for botulinum toxin A*
  - Consider anticholinergic medicines other than glycopyrronium bromide only if the person’s risk of cognitive adverse effects is thought to be minimal

*Off-label use.

GUIDELINES INTO PRACTICE

- Do you feel confident providing oral and written information about adverse events including impulse control disorders when starting dopaminergic medicines?
- Are you aware of local pathways to refer people with Parkinson’s disease for physiotherapy, occupational therapy, and speech and language therapy when they develop relevant symptoms?
- Have you discussed palliative care preferences with your Parkinson’s disease patients?

Management of non-motor symptoms

Rule out possible pharmacological and physical causes of any new non-motor symptoms, and think about non-pharmacological treatments (for example, speech and language therapy for saliva management) before prescribing medicines.

Non-pharmacological management

Consider referral for assessment and advice from specialist physiotherapists, occupational therapists, speech and language therapists, and dietitians early in the disease. Always offer these therapies under the following circumstances:

- Offer Parkinson’s disease-specific physiotherapy for people who are experiencing balance or motor function problems.
- Offer disease-specific occupational therapy for people who are having difficulties with daily living activities.
- Offer speech and language therapy for people with Parkinson’s disease who are experiencing problems with communication, swallowing, or salivation.

NICE has not updated its guidance that people with Parkinson’s disease should have regular access to the services provided by a Parkinson’s disease nurse specialist.

Pharmacological management

Box 2 summarises the medicines recommended for persistent symptoms. Some of these recommendations represent off-label use of the medicine in question; follow GMC advice when prescribing.

Management of advanced Parkinson’s disease

Deep brain stimulation may be considered for people with advanced Parkinson’s disease, but only when symptoms are not controlled with best medical therapy (which may include intermittent apomorphine injection or continuous subcutaneous apomorphine infusion). Analysis undertaken for the guideline showed that levodopa-carbidopa intestinal gel is not cost effective in people with advanced Parkinson’s disease.

Consider referring people at any stage of Parkinson’s disease to the palliative care team to give them and their family members or carers (as appropriate) the opportunity to discuss palliative care and care at the end of life.

Competing interests: See bmj.com.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j1951
Managing symptoms of Parkinson’s disease (PD)

**Ongoing care and support**

- **Specialist nursing**
  - People with PD should have regular access to the services provided by a PD nurse specialist

- **Physiotherapy**
  - Offer PD specific physiotherapy for people who are experiencing:
    - Balance problems
    - Motor function problems

- **Occupational therapy**
  - Offer PD specific occupational therapy for people who are having:
    - Difficulties with daily living activities

- **Speech and language**
  - Offer speech and language therapy for people with PD who are experiencing:
    - Communication problems
    - Problems with swallowing or saliva

- **Palliative care**
  - Consider referring people at any stage of PD to the palliative care team to discuss their priorities for care at the end of life

**Managing non-motor symptoms**

While the non-pharmacological management strategies listed above are first line treatments for non-motor symptoms, consider treating refractory problems with the following drugs:

- **Excessive daytime sleepiness**
  - Modafinil

- **REM* sleep behaviour disorder**
  - Clonazepam / Melatonin

- **Orthostatic hypotension**
  - Midodrine
    - If contraindicated, not tolerated or not effective
      - Fludrocortisone

- **Hallucinations and delusions**
  - Quetiapine
    - If not effective
    - Clozapine
    - Lower doses needed for people with PD than in other indications
    - Do not offer olanzapine

- **Drooling**
  - Glycopyrronium bromide
    - If contraindicated, not tolerated or not effective
      - Specialist referral for Botulinum toxin A

- **Dementia**
  - Mild–moderate
  - Severe
    - Offer Cholinesterase inhibitor
    - If not tolerated or contraindicated
      - Memantine

- **Advanced Parkinson’s disease**
  - Offer best medical therapy which may include:
    - Interim intermittent apomorphine injection
    - Continuous subcutaneous apomorphine infusion
    - Consider deep brain stimulation
    - If symptoms are not adequately controlled

**Managing motor symptoms**

If symptoms affect daily life, offer levodopa

- **Levodopa**
  - Symptoms
  - Activities
  - Motor comp
  - Adv Evts

- **Dopamine agonists**
  - Symptoms
  - Activities
  - Motor comp
  - Adv Evts

- **MAO-B inhibitors**
  - Symptoms
  - Activities
  - Motor comp
  - Adv Evts

- **COMT inhibitors**
  - Symptoms
  - Activities
  - Off-time
  - Adv Evts
  - Hallucinat

- **Amantadine**
  - (no evidence of benefit or harms)

**Adjuvant therapy**

If dyskinesia or motor fluctuations develop, adjuvant therapy may be added to a levodopa regimen, under specialist advice

- **Dopamine agonists**

- **MAO-B inhibitors**

- **COMT inhibitors**

If dyskinesia is not adequately managed by the above, consider amantadine

**Impulse control disorders (ICDs)**

ICDs are common adverse effects of dopaminergic therapy. They are a group of psychiatric conditions linked by a failure to resist the temptation to perform an act harmful to either oneself or others

- **Ensure patients and carers are aware of ICD types**

- **Compulsive gambling**

- **Hypersomnia**

- **Compulsive eating**

- **Obsessive shopping**

- **Also inform them who to contact if ICDs develop**

**Managing ICDs**

- **Adjust dopaminergic therapy gradually, to balance motor symptoms and ICDs**

- **If not effective**

- **Offer specialist CBT targeted at ICDs**

**Disclaimer:** This infographic is not a validated clinical decision aid. This information is provided without any representations, conditions or warranties that it is accurate or up to date. BMJ and its licensors assume no responsibility for any aspect of treatment administered with the aid of this information. Any reliance placed on this information is strictly at the user’s own risk. For the full disclaimer wording see BMJ’s terms and conditions: [http://www.bmj.com/company/legal-information/](http://www.bmj.com/company/legal-information/)
**Penicillin allergy: getting the label right**

**WHAT YOU NEED TO KNOW**

- Penicillin allergy is the most commonly reported drug allergy.
- It is estimated that between <10% and up to 20% of those reporting penicillin allergy are truly allergic.
- Prescription of a penicillin to patients with a previous allergy-like event after penicillin treatment is common and could result in serious harm or death.
- The diagnostic workup for penicillin allergy includes clinical history, skin tests, in vitro testing, and drug provocation tests.
- Some cephalosporins with a different side chain to the reacting penicillin can be considered under specialist management for life-threatening infections when non-cephalosporin antibacterial drugs would be suboptimal.

**WHO SHOULD NOT RECEIVE A PENICILLIN?**

- Those with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration— who are at risk of immediate hypersensitivity to a penicillin.
- People with a positive skin test.
- People with severe non-immediate reactions to penicillin (eg, toxic epidermal necrosis or Stevens-Johnson syndrome), who should be advised to avoid penicillins under all circumstances.

Penicillin allergy is a potentially serious adverse reaction that alters and reduces the options for antibacterial treatment, and which can be life threatening. It is the most commonly noted drug allergy in the UK, reported by about 10% of the population. It is estimated, however, that only around 20% of those reporting penicillin allergy are truly allergic. It is important that the term “penicillin allergy” is correctly applied to avoid adverse effects or inappropriate treatment.

Here, we discuss key features that help to distinguish patients at low or high risk of having a true penicillin allergy, summarise what is known about the risk of allergic reactions to other β-lactam antibacterials in patients with penicillin allergy, and discuss the steps to consider when assessing a label of penicillin allergy.

**Who is at risk of penicillin allergy?**

Repeated exposure to antibacterials, for example in medical conditions that require frequent antibacterial use such as cystic fibrosis, is recognised as a clinical risk factor for penicillin allergy. Female sex has been identified as a risk factor in adults for both self reported and confirmed penicillin allergy, possibly related to greater antibacterial use in women. The prevalence of penicillin allergy appears to increase with age and might be partly explained by higher rates of antibacterial exposure in older age groups.

A family history of penicillin allergy has been found to be associated with self reported penicillin allergy; however whether there is a genetic component to penicillin allergy is not clear. There does not appear to be a major relationship between atopy and the incidence of penicillin allergy. However, the British National Formulary advises that people with atopic...
Allergies could be at greater risk from anaphylactic reactions to penicillins. No specific risk factors have been identified in children and it has been suggested that many rashes attributed to penicillin allergy might be viral in origin.

**What are the different types of reaction to penicillin?**

Reactions can be classified as immediate or non-immediate based on the timing of appearance of symptoms.

Immediate reactions have their onset in 1 to 6 hours (generally within 60 minutes) after exposure to a dose of an antibacterial, and often involve symptoms of an immunoglobulin E mediated allergic reaction, ranging from urticaria or pruritus to angioedema and anaphylaxis.

Non-immmediate reactions, occurring more than 60 minutes (commonly several days) after exposure to penicillin, mainly result from the release of specific cytokines by activated T cell subsets. The most common non-immmediate reactions are maculopapular or morbilliform and urticarial rashes. Less commonly, severe reactions can occur, including Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis.

**How is penicillin allergy confirmed?**

For some people, the label of penicillin allergy might have few clinical consequences if their need for antibacterials is infrequent. However, a full diagnostic investigation by specialist allergy services is recommended for people with specific anticipated treatment requirements.

There is no single validated test to diagnose or exclude hypersensitivity to β lactam and a combination of tests is required. The protocol in the European Network for Drug Allergy (ii) guidelines (2003) includes clinical history, skin tests, in vitro testing, and, when required, drug provocation tests. Guidelines produced by the British Society for Allergy and Clinical Immunology omit the routine use of in vitro testing.

**Clinical history**

Although clinical history alone is an unreliable basis for diagnosing penicillin allergy, it forms an essential first step in assessing the diagnosis. When a patient presents with suspected penicillin allergy, the following data should be collected:

- A label of “multiple antibacterial allergy,” or
- A personal history of hypersensitivity to beta lactam in people who require frequent antibacterial treatment (eg, people with cystic fibrosis, diabetes, immunodeficiencies), or
- A personal history of hypersensitivity to beta lactam in people who require treatment with a specific beta lactam, or
- A history of an anaphylactic reaction during general anaesthesia, when penicillin was one of several drugs administered.

**Skin testing**

Skin testing provides useful diagnostic information for reactions that are immunoglobulin E and T cell mediated, and should be the first line of investigation in adults. Testing should be carried out in specialist allergy centres, as experience is required to interpret the results and to manage any potential adverse systemic reactions. It should be performed shortly after a reaction has occurred, as positive responses are less likely after a long interval. Skin testing for penicillin allergy is useful in children with a history of anaphylaxis. The diagnostic value of skin testing is lower in non-immmediate reactions.

**In vitro testing**

The sensitivity of bioassays for Immunoglobulin E in penicillin allergy is low. Advice should be sought from a specialist.
Oral provocation testing
For people with negative skin test results, drug challenge is required to confirm or exclude both immediate or non-immediate drug allergy. Oral provocation testing is not used in people with a positive skin test and is not recommended for people at high risk of delayed life threatening reactions (eg, those who have had a severe cutaneous systemic reaction) or for people with unstable asthma or those taking β blockers. Oral provocation tests should be undertaken only by specialist centres and typically involve administering incremental doses of the suspect drug under supervision.

Is there cross reactivity with other antibiotics?
Penicillin and cephalosporin cross reactivity appears to have been overestimated, in part because first generation cephalosporins were contaminated with penicillin. In patients allergic to penicillin, cross reactivity between penicillin and first and early second generation cephalosporins has been reported to occur in up to 10% of patients, and between penicillin and third generation cephalosporins in 2%-3% of patients. Cefadroxil, cefadine, cefaclor, cefalexin, and ceftaroline should be avoided in patients who have a confirmed reaction to a penicillin, as cross reactivity can result from similarities in the side chains of the molecules. Other second and third generation cephalosporins with a different side chain to the reacting penicillin can be considered, under specialist management, for life threatening infections when non-cephalosporin antibacterials would be suboptimal. Guidelines from the British Society for Allergy and Clinical Immunology for patients with a history of penicillin allergy requiring cephalosporin treatment recommend skin tests for both penicillin and cephalosporin followed, depending on the results, by oral provocation and, if necessary, desensitisation.

The British National Formulary advises that patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin.

What are the antibacterial choices for people with a label of penicillin allergy?
If there is a specific or regular requirement for treatment with penicillin, people with suspected immunoglobulin E mediated allergy should be formally re-evaluated for penicillin allergy in a drug allergy clinic. For patients with confirmed immunoglobulin E mediated penicillin allergy, drug desensitisation under expert supervision leads to a temporary tolerance of a single course of penicillin, but should be carried out only if this is felt to be clinically important and no alternative drug is available. However, expertise in drug desensitisation is limited to a relatively small number of specialist allergy centres in the UK.

For people with allergy to a particular penicillin side chain, it might be possible to select a β lactam with a different side chain. For patients in whom all β lactams are contra-indicated, alternative non-β lactam antibacterials include tetracyclines, metronidazole, macrolides, aminoglycosides, quinolones, and glycopeptides. National antimicrobial prescribing guidelines include suggested alternatives for people with penicillin allergy. The British National Formulary suggests that patients with a history of a minor rash (ie, non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin. In these individuals, a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other β lactam antibiotics (including cephalosporins) can be used in these patients.

What are the risks of inappropriate labelling?
Guidelines highlight the need to check for hypersensitivity and outline treatment options for people with penicillin allergy. Prescription of a penicillin to patients with a previous allergy-like event following penicillin treatment is common and could result in a severe allergic reaction if there is a true penicillin allergy. People with suspected but unverified penicillin allergy are likely to be treated with alternative antibacterials that have a broader spectrum of activity, which might impact on microbial resistance patterns. In addition, alternative antibiotics might have more adverse effects and be more expensive.

In case control studies, people with a history of suspected penicillin allergy spent more time in hospital and had poorer clinical outcomes than controls without such a history. In a retrospective study of patients in hospital in the USA, those with a label of penicillin allergy were exposed to substantially more fluoroquinolones, clindamycin, and vancomycin (P<0.0001) and had higher rates of Clostridium difficile, meticillin resistant Staphylococcus aureus, and vancomycin resistant enterococcus infections than matched controls.

**Drug allergy notification**
Penicillin allergy notification is important for the prevention of further episodes. People with suspected or confirmed penicillin allergy should have their allergic status documented in their medical records and in all correspondence between primary and secondary care. This information should be disseminated to other healthcare professionals to reduce the risk of re-exposure. If the suspected allergy has been excluded by allergy testing, details should be added to the medical record and all interested parties informed in writing.

Competing interests are in line with Drug and Therapeutics Bulletin’s policy on conflicts of interests.

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**EDUCATION INTO PRACTICE**
- Do you take a full history of previous reactions when a patient reports that they are allergic to penicillin?
- Do you refer patients to specialist allergy services if they are labelled penicillin allergic and have specific anticipated treatment requirements?
- Do you ensure that people with suspected or confirmed penicillin allergy have their allergic status documented in their medical records and in all correspondence between primary and secondary care?
CASE REVIEW
Epstein Barr virus, abdominal pain, and jaundice

A 22 year old man presented to the emergency department with abdominal pain, jaundice, itching, and fever. His urine was dark and stools pale. His temperature was 38.7°C and he was icteric with abdominal tenderness, worst in the right upper quadrant with a negative Murphy’s sign. The gall bladder was impalpable. The oropharynx was inflamed with cervical and axillary lymphadenopathy.

Liver function tests (alkaline phosphatase 327, aspartate aminotransferase 358, bilirubin 109) suggested cholestasis. White cell count was high (20.8) and C reactive protein raised (17). Platelets were low (168).

Monospot test was positive (Epstein Barr virus), confirmed by positive Epstein Barr virus serology. Hepatitis A, B, and C serology were negative.

Ultrasound revealed splenomegaly with normal hepatopetal flow and a markedly thickened (10 mm) gallbladder wall but no gallstones or sludge (figure). The common bile duct was not dilated.

1. What is the most likely diagnosis?
2. What further imaging might be useful?
3. How is this condition managed?

Submitted by Alexandra Khoury, Francois Porté, Masud Haq
Patient consent obtained.
Cite this as: BMJ 2017;358:j3386

Imaging of the head: (A) axial CT image, (B) axial T2 weighted magnetic resonance cholangiopancreatography sequence, (C) axial fluid attenuated inversion recovery MRI image, (D) coronal T2W MRI image showing subdural haematoma (arrows)

SPOT DIAGNOSIS
An incidental finding on computed tomography scan

A 10 year old girl was referred for a computed tomography (CT) scan of the head (figure) after having had intermittent headaches for two months following a head injury. On examination, she had bilateral papilloedema. The main finding on the CT scan was a left subacute subdural haematoma. What else is shown in the images?

Submitted by Anan Shtaya, Bassam Dabbous
Parental consent obtained.
Cite this as: BMJ 2017;358:j3500

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CASE REVIEW
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MINERVA  A wry look at the world of research

Headache in a case of β thalassaemia

A 17 year old boy with transfusion dependent β thalassaemia presented with a six year history of a mild, dull headache. He had undergone blood transfusions but at varying intervals because of financial constraints, and this had led to persistent anaemia. On examination he had massive splenomegaly, and neurological examination was unremarkable. A radiograph of the skull showed a “hair on end” appearance (figure). Inadequate frequency of blood transfusion in patients with β thalassaemia can result in this classic appearance, which is caused by excessive haematopoiesis of the skull marrow, sometimes 25 to 30 times greater than normal. The patient received six months of regular transfusions, after which he had a pre-transfusion haemoglobin of 92 g/L (previously 60-80 g/L).

Aditya Jandial, Kundan Mishra
Subhash Varma, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Patient consent obtained.

Cite this as: BMJ 2017;358:j3482

Recovery from mild head injury

Mild head injury (defined as a Glasgow Coma Score of 13 to 15, loss of consciousness for less than 30 minutes, and post-traumatic amnesia lasting less than 24 hours) turns out to be anything but mild for many victims. Half of those affected still have symptoms six months later, and some never make a full return to health. Data from three trauma centres in the Netherlands show that emotional distress and difficulty coping early after the injury, and pre-injury mental health problems are predictors of a delayed recovery (Lancet Neurol doi:10.1016/S1474-4744(17)30117-5).

Head impact velocities in snowboarders and skiers

On the related subject of preventing head injury, a study in the British Journal of Sports Medicine analysed video footage of head injuries sustained during World Cup snowboard and freestyle skiing events (Br J Sports Med doi:10.1136/bjsports-2016-097086). Four videos were clear enough to allow pre-impact velocity of the head to be estimated. In all cases it exceeded 7.0 m/s. Rather worryingly, the International Ski Federation currently requires ski helmets to be safety tested to an upper limit of 6.8 m/s.

Screening for lung cancer

There has been anxiety that people at high risk of lung cancer might be falsely reassured and de-motivated to stop smoking if they test negative when screened. The behaviour of smokers taking part in the UK Lung Cancer Screening trial suggests the opposite (Thorax doi:10.1136/thoraxjnl-2016-209690). All participants were given smoking cessation advice and a list of local Stop Smoking services. But those randomised to computed tomography were about 50% more likely to have quit two years later.

Prescription medicine use by pedestrians

French investigators asked whether prescription drugs that impair ability to drive also affect the ability to walk safely. Not surprisingly, the answer is yes. Several classes of drug, including benzodiazepines, antihistamines, and anti-inflammatory drugs, were associated with an increased risk of a pedestrian being injured in a road traffic incident, (PLOS Med doi:10.1371/journal.pmed.1002347). Most of the injuries occurred while crossing a street.

Vitamin D supplementation for diabetes

Although observational studies suggest links between low levels of vitamin D and impaired glucose metabolism and type 2 diabetes, a randomised controlled test finds no signs of benefit from supplementation. Sixty two men and women with type 2 diabetes and low levels of vitamin D were allocated either to a large dose of vitamin D3 or to placebo (Diabetes Care doi:10.2337/dc16-23). After six months, insulin secretion was measured by an intravenous glucose tolerance test, and insulin sensitivity by euglycaemic-hyperinsulinaemic clamp. There were no differences between the groups.

Tremor stability index

The tremor of advanced Parkinson’s disease is unmistakable, but that’s not true in the early stages when it can easily be confused with essential tremor. Analysis of accelerometer recordings from patients with the two conditions, using some fancy mathematics, showed that shake-to-shake variation in the frequency of the tremor is less in people with Parkinson’s disease than in those with essential tremor (Brain doi:10.1093/brain/awx104). Only a short period of recording is necessary, so it might be possible to develop a useful diagnostic test.

Deaths from firearms in children

Every year, nearly 1300 children die of gunshot wounds in the United States, according to an analysis in Paediatrics. Firearm related deaths are now the third leading cause of death among children aged 1 to 17 years (Paediatrics doi:10.1542/peds.2016-3486). Boys, older children, and minorities are affected disproportionately, and more of the deaths are from homicide or suicide than are caused unintentionally. The report calls these deaths an important public health problem, which seems something of an understatement.

Cite this as: BMJ 2017;358:j3629