

# education

## THEBMJ.COM BLOGS

### Dogs that don't bark are the most difficult to hear

For decades patients in crowded outpatient clinics have sat in silence. Health systems worldwide have ignored the massive potential for patients to learn from each other; a case of dogs not barking if ever there was.

Ask why clinicians and managers don't promote mutual support between patients with the same condition and you hear the usual suspects—too busy, not enough money, “they” won't let us. The truth is more complex.

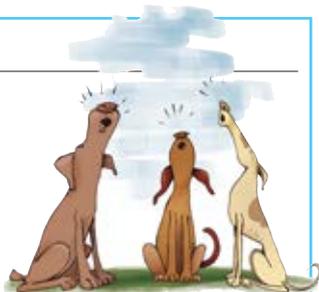
Sherlock Holmes explained, in *Silver Blaze*, that the dog didn't bark because the villain was its owner. In health systems the clinicians and managers are the villains. It is we who, in our hearts, don't want patients to bark, to engage with each other, to hunt in packs. Medicine is paternalistic. We “care for” patients, we “look after them,” we “nurture” them back to health. They are weak while we are strong. This is appropriate when people are vulnerable and in pain. But it also fills a deep need in us. We need to feel powerful because all that blood, pus, and shit; all that madness, ambiguity, uncertainty; all that pathology; and above everything, all that death—make us fearful that we will fail. Our own dark secret is that we are more invested in being the parent than we admit.

And then comes social media. Suddenly the dogs are barking and the patients are talking together anyway, about everything—including us. This new peer-to-peer world is profoundly flat, non-hierarchical, and powerful. Adult-adult relationships are becoming the norm in healthcare. Our psychological needs may still push our inner parent to the fore but “clinician-as-parent” is becoming something to be toggled into only at times of crisis.

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The full text of this blog can be found at: <http://bit.ly/1NtBdQD>

We welcome contributions to this column via our online editorial office: <https://mc.manuscriptcentral.com/bmj>.



## CLINICAL UPDATES

### Botulinum toxin for chronic migraine

The American Academy of Neurology now recommends botulinum toxin as a safe and effective treatment for chronic migraines. Several well designed studies since the 2008 guidelines found modest reductions in symptoms for those with  $\geq 15$  attacks a month—15% fewer days of headache in the four weeks after the first treatment when compared with dummy or placebo.

• <http://bit.ly/1NCVjTo>

### Asthma diagnosis simplified

Draft BTS-SIGN guidelines simplify the diagnosis of asthma for GPs. In high probability patients, asthma can be confirmed using patient symptom questionnaires or reversibility tests after a trial of corticosteroid therapy. Unlike current NICE guidelines, they favour use of forced expiratory volume in one second ( $FEV_1$ ) or serial peak expiratory flow to assess reversibility, avoiding referral for more complex tests such as fractional exhaled nitric oxide.

• <http://bit.ly/1VmkuBu>

### Scarlet fever on the rise

Numbers of group A streptococcal (GAS) infections have increased for the third year running. PHE figures show a 13% rise in incidence from last year, with 1319 cases from 21 to 27 March, the highest weekly total since records began in 1982. Invasive GAS infections, such as pneumonia or septicaemia, are also on the rise. PHE urges doctors to be mindful when assessing unwell patients and consider prompt antibiotic treatment if they suspect scarlet fever.

• <http://bit.ly/1VE3eGD>

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## FAST FACT—CONTRACEPTION AND DEEP VEIN THROMBOSIS

The use of combined hormonal contraceptives in women with a first degree relative aged under 45 years with a history of deep vein thrombosis is classified as UKMEC category 3—the theoretical or proved risks generally outweigh the advantages. Although not absolutely contraindicated, these contraceptives are not usually

recommended and should not be routinely started in primary care. Instead, expert opinion should be sought or the patient referred to a specialist contraceptive provider.

• For more information visit BMJ Learning (<http://ow.ly/YKycck>).

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## STATE OF THE ART REVIEW: HIGHLIGHTS

# Prevention of falls in older people living in the community

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This is an edited version of the state of the art review, full version is on thebmj.com

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CPD/CME

1 CREDIT

**According to the World Health Organization, 28-35% of older people (≥65 years) fall each year globally and prevalence increases with age.<sup>1</sup> A longitudinal study found that 68% of people who fell reported some injury; healthcare was needed in 24% of cases, functional decline was reported by 35%, and social and physical activities were impaired for more than 15%.<sup>4</sup> Close to 95% of all hip fractures are caused by falls.<sup>5</sup> After a first fall, people have a 66% chance of having another fall within a year.<sup>18</sup>**

### Assessing the risk of falls

#### History and examination

Patients may not spontaneously report falls for several reasons, including the perception that a fall event may not be relevant unless it resulted in injury. A recent fall, two or more falls in the previous 12 months, difficulty walking or balance problems, and lower limb pain indicate the need for a more detailed history and multifactorial assessment.<sup>44</sup>

### WHAT YOU NEED TO KNOW

- 28-35% of older people (≥65 years) fall each year globally and prevalence increases with age
- Falls result from interactions between multiple individual and environmental risk factors
- Antidepressants, sedatives and hypnotics, neuroleptics and antipsychotics, antihypertensives, and anticonvulsants have been linked to an increased risk of falls
- Evidence suggests that exercise based and tailored interventions are the most effective way to reduce falls and associated healthcare costs among older people in the community
- Guidelines recommend that healthcare providers ask all older people or their caregivers at least once a year about falls, frequency of falling, and difficulties in gait and balance



Previous falls are predictors of future falls, so asking about previous falls is an important first step. It is then essential to investigate what caused the fall (table 1). An assessment of the circumstances of fall events should be conducted.<sup>51</sup>

### Drug review

A drug review and reduction of the number or dose of drugs (or both) form part of the efforts to reduce falls.<sup>44,52</sup> Drug reviews should include evaluation of over-the-counter drugs such as those with anticholinergic effects (for example, allergy and sleep drugs) and those that can promote movement disorders.<sup>53</sup>

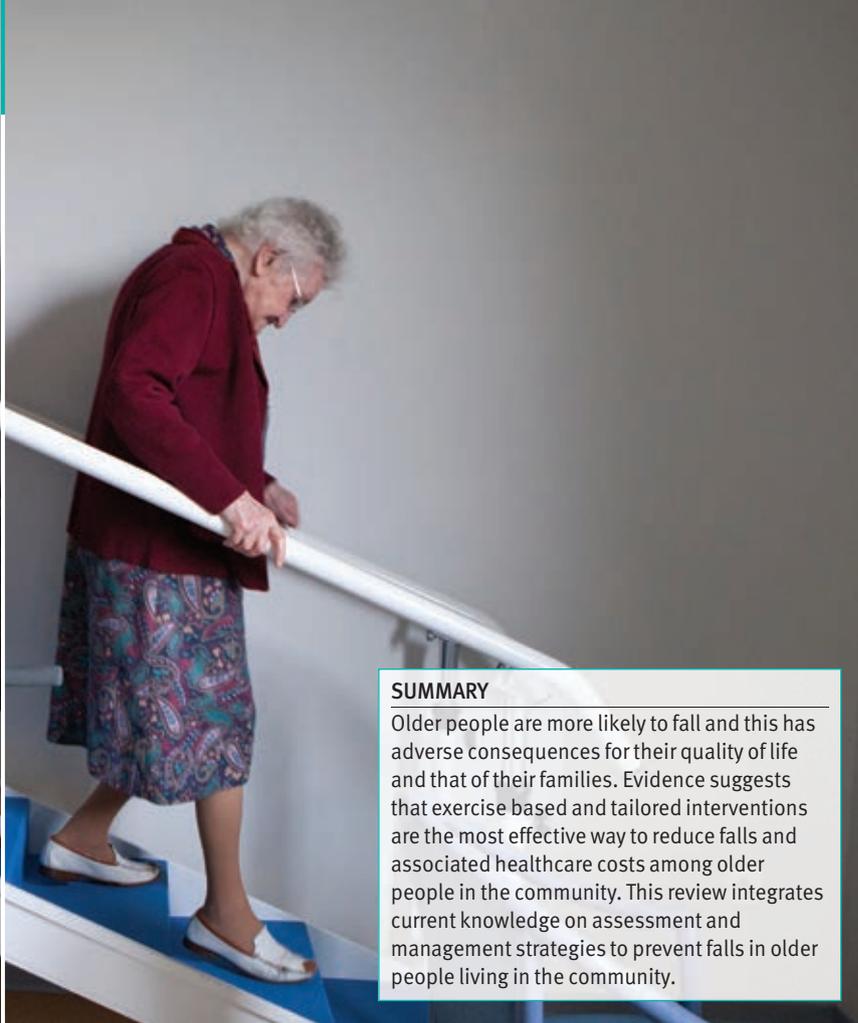
### Medical risk factors

#### Vision

Referral for ophthalmologic evaluation of visual acuity, depth, contrast sensitivity, and cataracts has been recommended by experts.<sup>53</sup>

#### Syncope

Older people whose falls are suspected to be caused by syncope or are unexplained should undergo syncope related investigation.<sup>54</sup> It can be difficult to determine whether syncope had occurred because falls are often unwitnessed.<sup>29,55</sup> An in-depth syncope investigation is guided by an initial evaluation, detailed history, physical examination, biochemical and hematologic tests, electrocardiography, and echocardiography.<sup>29</sup> In some cases, it may also include carotid sinus massage, tilt table tests, 24 hour Holter electrocardiography, and electrophysiological studies for arrhythmias. Referral to specialized interdisciplinary units may be required.<sup>56,57</sup>



**SUMMARY**  
 Older people are more likely to fall and this has adverse consequences for their quality of life and that of their families. Evidence suggests that exercise based and tailored interventions are the most effective way to reduce falls and associated healthcare costs among older people in the community. This review integrates current knowledge on assessment and management strategies to prevent falls in older people living in the community.

ABK/BSIP/SPL

Common risk factors for falls in older people in the community		
Risks	Examples	Reference
Previous falls	During the previous 12 months	<sup>22</sup>
Fear of falling	Low falls efficacy scale scores	<sup>12</sup>
Balance problems	Increased postural sway	<sup>25</sup>
Gait and mobility problems	Increased variability of step length, shorter single support time during dual task gait, timed up and go test time >12s	<sup>25 26</sup>
Pain	Lower limb and foot pain	<sup>27</sup>
Drugs	Polypharmacy (≥4), psychotropics, antidepressants, benzodiazepine	<sup>28</sup>
Cardiovascular conditions and syncope	Carotid sinus syndrome, vasovagal syncope, orthostatic and postprandial hypotension, arrhythmias	<sup>29</sup>
Cognitive impairment	Reductions in verbal ability, processing speed (executive function), and immediate memory	<sup>30</sup>
Urinary incontinence	Rushing to the bathroom at night	<sup>31</sup>
Stroke	Decreased paretic limb contribution to standing balance control, increased variability of step length, inability to step with the blocked limb	<sup>32</sup>
Diabetes	Peripheral neuropathy, as well as accelerated balance, somatosensory, visual, vestibular and cognitive function decline	<sup>33 34</sup>

#### Cardiovascular

A study found that 44% of older people treated at an emergency department over a 28 day period had experienced a fall.<sup>58</sup> Seventy seven per cent of those with unexplained falls, recurrent falls, or unexplained loss of consciousness had cardiovascular problems including orthostatic hypotension (19%), carotid sinus hypersensitivity (73%), vasovagal hypersensitivity (15%), and arrhythmia (8%).<sup>58</sup> Cardiovascular causes of falls include vasovagal syncope, carotid sinus syndrome, arrhythmias, other cardiac abnormalities (such as stenosis, cardiomyopathy, ischemia, and infarction), and postprandial or orthostatic hypotension.<sup>59</sup> Assessment of orthostatic hypotension is a component of the multifactorial assessment of falls risk in older people.<sup>60</sup> The use of blood pressure measurements in the seated and standing position is common. However, a substantial proportion of patients with orthostatic hypotension may be misclassified if supine blood pressure is not assessed.<sup>61 62</sup> The need for repeated measurements in different positions and minutes apart may be burdensome, particularly in time constrained clinical settings.

#### Cerebrovascular

Older people who have a stroke have an increased risk of falls because of sequelae such as decreased strength and balance, contralateral neglect (lack of attention and awareness of the side of the body opposite to the affected hemisphere of the brain), perceptual (for example, proprioception) and visual problems.<sup>63</sup> A study on the incidence and consequences of falls in older people with stroke found that 73% (n=79) fell at home within six months of discharge.<sup>64</sup>

**After a first fall, people have a 66% chance of having another fall within a year**

#### Diabetes

People with type 2 diabetes have an increased risk of falls compared with those without type 2 diabetes (odds ratio 2.0, 95% confidence interval 1.2 to 3.4).<sup>33</sup> Falls in older people with type 2 diabetes are often associated with diabetic peripheral neuropathy, as well as accelerated balance, somatosensory, visual, vestibular, and cognitive function decline.<sup>33 34</sup>

The prevalence of falls is directly associated with the number of chronic medical conditions such as cardiovascular problems, diabetes, chronic obstructive pulmonary disease, depression, and arthritis. Older women who have at least one chronic condition have an increased chance of having a fall compared with those with no chronic conditions (odds ratio 1.8, 1.4 to 2.3).<sup>65</sup>

#### Functional and mobility assessment

Evaluation of functional and mobility impairments can identify the need for referral and guide tailored rehabilitation interventions. In-depth evaluation of mobility requires appropriate expertise.<sup>52</sup> Several tests are available to assess function and mobility (eg, gait and balance), the most commonly used of which are summarized below.

#### Timed up and go test

The timed up and go (TUG) test involves timing how long it takes someone to get up from an armchair, walk 3 m, turn around, come back, and sit on the same chair.<sup>66 67</sup> The test is fairly easy to administer and takes less than five minutes.<sup>44</sup> It has been shown to be a reliable and valid indicator of falls risk.<sup>68 69</sup> In general, TUG times >12 seconds are associated with increased risk of falls. A study found that older

A 2013 systematic review and meta-analysis of randomized controlled trials evaluated the effect of fall prevention exercise programs on fall related injuries in community dwelling older people.<sup>100</sup> A total of 17 studies involving more than 4000 participants with data on injurious falls, serious falls, and fall related fractures were included. Data analyses of 10 trials showed a reduction in injurious falls in the groups that exercised compared with the groups that did not exercise (rate ratio 0.93, 0.51 to 0.77).<sup>100</sup> The figure shows a decision tree for referral to an exercise program aimed at reducing falls among older people in the community.

#### Pain, chronic conditions, and medication management

Pain is also a potentially modifiable risk factor for falls, but systematic assessment and management of pain are not explicit components of traditional assessment and management programs in primary medical care.<sup>27 111</sup>

Orthostatic hypotension may occur during transfers and exercise. Clinical management of orthostatic hypotension includes hydration and salt intake, positional related adaptive behavior, drugs (such as vasodilators), and elimination or reduction of drugs for cardiovascular disease.<sup>61 112</sup> All drugs—including sedative hypnotics, anxiolytics, antidepressants, and antipsychotics—should be reviewed with a view to reducing their number or dose.<sup>44</sup> It is essential to reduce psychotropics progressively to minimize withdrawal symptoms.<sup>113 114</sup>

#### Vision correction

It is unclear whether vision correction is an essential component of multifactorial interventions for falls prevention.<sup>117</sup> A systematic review for the US Preventive Services Task Force (USPSTF)<sup>35</sup> found that surgical and non-surgical vision correction did not reduce the risk of falling and raised concerns about an increased risk of falls.<sup>119</sup> As with improved mobility, improved vision may increase activity levels or reduce attention levels (or both) increasing opportunities for falls. Vision correction needs to be used in conjunction with other interventions to reduce the risk of falls.

**Exergaming (videogame based exercises) is now being evaluated for its ability to reduce falls in older people**

#### Vitamin D and calcium supplementation

In 2009 a meta-analysis of seven randomized controlled trials with about 1900 participants linked 700-1000 IU of vitamin D supplementation to a lower risk of falls compared with those who did not take vitamin D (pooled relative risk 0.81, 0.71 to 0.92).

The USPSTF reviewed nine vitamin D supplementation randomized trials and found that a median oral daily dose of 800 IU of vitamin D with or without calcium was associated with a 17% (11% to 23%) reduced risk of falling in the intervention group (6-36 months of follow-up), and the USPSTF recommended vitamin D supplementation to prevent falls in community dwelling older adults.<sup>96</sup>

By contrast, a systematic review and meta-analysis in 2012 reported that in general vitamin D supplementation was not associated with lower fall rates in community dwelling older people (rate ratio 1.0, 0.90 to 1.11), but it reduced the rate of falls and risk of falling in subgroups with low vitamin D levels at baseline compared with those who did not receive vitamin D supplementation.<sup>36</sup> Analyses of 804 participants with low vitamin D levels at baseline from four trials showed that fewer people fell in the group who received vitamin D supplements than in the group who did not received vitamin D supplements (relative risk 0.70, 0.56 to 0.87).<sup>120-123</sup> The review concluded that vitamin D supplementation reduced falls only in people with lower vitamin D levels.<sup>36</sup>

#### Emerging treatments

The use of technology to reduce the risk of falls is increasing. One such technology, exergaming (videogame based exercises), is now being evaluated for its ability to reduce falls in older people. Exergames are games with remote controls and motion sensors that require the players to move while playing a video game.

#### Guidelines

The American Geriatrics Society/British Geriatrics Society (AGS/BGS) guidelines recommend that healthcare providers ask all older people or their caregivers at least once a year about falls, frequency of falling, and difficulties in gait and balance.<sup>44</sup> A gait and balance evaluation should be conducted in those with a history of falls in the past 12 months.<sup>44</sup> Examinations should include:

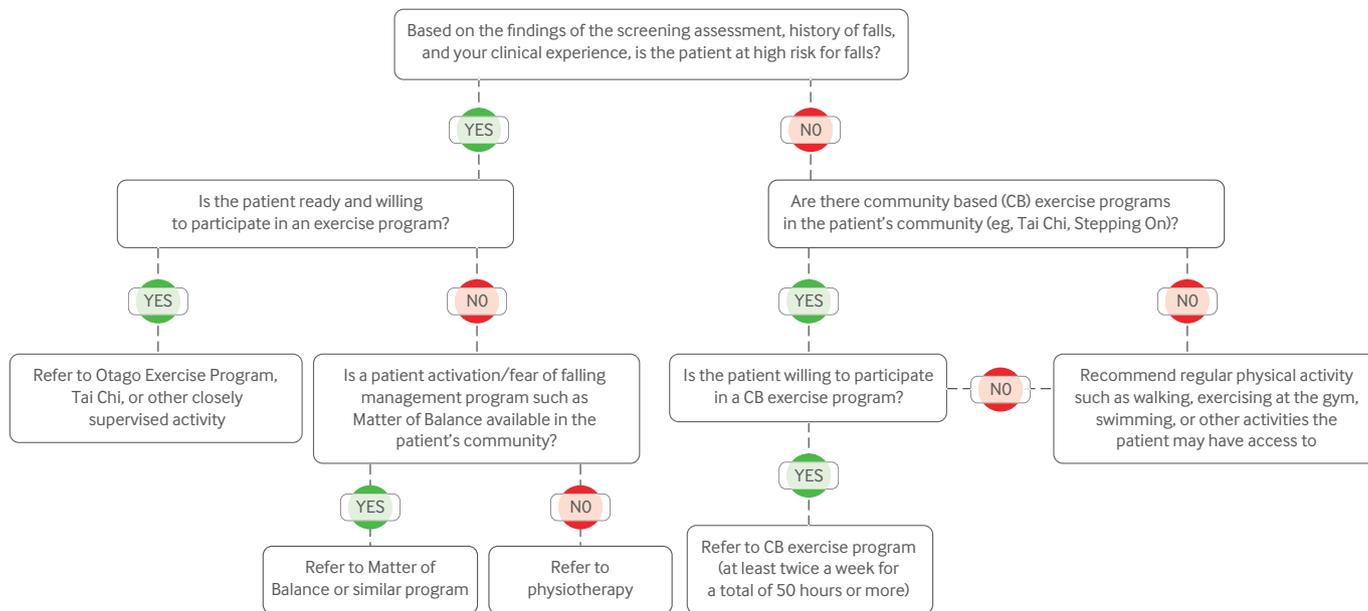
- A detailed assessment of gait, balance, mobility, and the function and muscle strength of the lower extremity joints
- Evaluation of neurological and cognitive function
- Assessment of lower extremity peripheral nerves, proprioception, reflexes, cortical, extrapyramidal and cerebellar function, and cardiovascular status
- Assessment of visual acuity
- Examination of the feet and footwear
- Assessment of activities of daily living including use of adaptive equipment and mobility aids
- Assessment of current activity levels, perceived functional ability, and fear of falls.<sup>44</sup>

Competing interests: None declared.

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### Exercise referral decision tree for patients

adults who had had a previous fall took 22 s (standard deviation 9) to complete the TUG, while non-fallers took 8 s (2) to complete the test ( $F=23$ ;  $P<0.001$ ).<sup>70</sup> Using a cut-off value of 13.5 s, TUG had a sensitivity of 80% and specificity of 100%. However, the test does not provide in-depth gait information, and cut-off values indicative of an abnormal result vary. Reference values are available for different age groups and for people with certain health conditions.

#### Short physical performance battery

The short physical performance battery (SPPB) involves a timed 4 m walk at usual pace, a timed repeated chair sit to stand test, and balance tests with feet side by side, semi-tandem, and full tandem for 10 seconds.<sup>73</sup> The test takes about 10 minutes to complete. The SPPB has been found to be a reliable and valid measure of mobility that is predictive of falls, physical disability, hospital admission, nursing home admission, and mortality.<sup>73,74</sup> SPPB scores  $\leq 9$  indicate mobility impairment.<sup>73</sup> The SPPB can be used to identify older people with mobility limitations who are likely to benefit from moderate intensity physical exercise programs.<sup>75,76</sup>

#### Usual or preferred walking speed

This is an item in the SPPB score, a determinant of the TUG time and of the six minute walking test, and it is a frailty phenotype.<sup>77</sup> The association between walking speed and falls is non-linear, with a greater risk of outdoor falls among faster walkers, and greater risk of indoor falls among slow walkers.<sup>78</sup>

#### Home and environmental assessment

A cluster randomized trial (842 households) in 2015 reported that home modification reduced the rate of injuries from falls by 39% compared with a waiting list control group.<sup>87</sup> Home environment assessment checklists are available,<sup>88,90</sup> to identify:

- Environmental hazards that can be removed or avoided, including tripping obstacles such as cords, rugs, and furniture; slippery surfaces; and poorly illuminated areas
- Accessories that can be installed and furniture that can be modified to facilitate transfer or walking including ramps, proper height toilet seats and beds, grab bars next to the toilet and shower, and railings along walking pathways
- The need and opportunities for use of assistive gadgets and devices, such as extended reaching gadgets, falls monitoring devices, medical staff or rescue alert systems.

#### Managing risks and interventions to reduce falls

Multidisciplinary risk assessment followed by tailored multifactorial interventions including exercise has been shown significantly to reduce falls among older people in the community.<sup>19-92</sup>

#### Exercise based interventions

A systematic review of randomized trials of interventions to reduce falls in older people living in the community published in 2012 supported the beneficial effect of exercise interventions in reducing the number of falls and the number of participants who fell.<sup>36</sup> Data from more than 3500 participants from 16 trials showed that group exercise classes with multiple components (such as balance retraining and muscle strengthening) reduced the rate of falls (prevalence) in the groups that exercised compared with the groups that did not exercise (rate ratio 0.71, 0.63 to 0.82). Tai Chi—an exercise intervention that involves movements that emphasize weight shifting, balance, postural alignment, and coordination—was associated with a 28% (0% to 48%) reduction in the rate of falls and a 29% (13% to 43%) reduction in the risk of falling.<sup>36</sup> Home based exercises containing multiple exercise categories also resulted in a significant reduction in the rate of falls (rate ratio 0.68, 0.58 to 0.80) and risk of falling (risk ratio 0.78, 0.64 to 0.94).<sup>36</sup>

## UNCERTAINTIES

# How big a problem is heart failure with a normal ejection fraction?

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### WHAT YOU NEED TO KNOW

- There is variation in the thresholds for diagnosing heart failure with a normal ejection fraction
- Treatment of heart failure with normal ejection fraction does not improve survival: however, offer symptom relief with diuretics and treat hypertension and other comorbidities
- Further research is needed to characterise normal echocardiography in the ageing heart and to understand better the natural history of heart failure with a normal ejection fraction

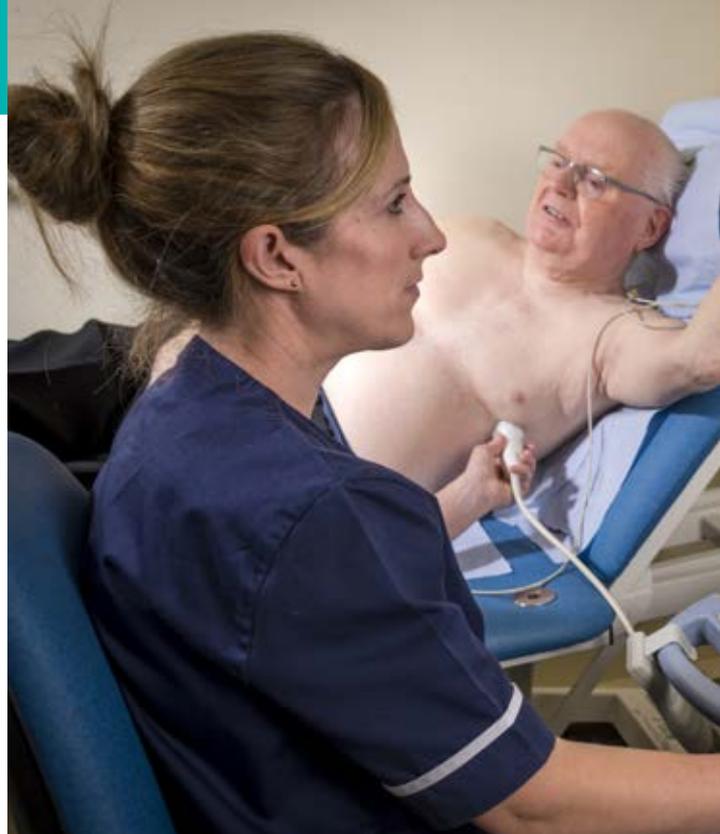
**Much uncertainty exists around heart failure with a normal ejection fraction, beginning with its diagnosis; there are no clinical features that distinguish it from heart failure with reduced ejection fraction.<sup>1,2</sup> On echocardiography the filling capacity of the left ventricle can at best be measured only indirectly. Estimates of the prevalence of heart failure with a normal ejection fraction and its prognosis vary. Doubt exists about the clinical relevance of the diagnosis of heart failure with a normal ejection fraction because no treatment to date has substantially improved prognosis. Management is focused on symptom reduction and blood pressure control.<sup>1,2</sup>**

### What is the evidence of the uncertainty?

#### How is heart failure with normal ejection fraction diagnosed?

A diagnosis of heart failure requires a combination of clinical features—such as breathlessness, fatigue, and ankle oedema—together with a structural or functional abnormality of the heart that impairs its ability to pump on echocardiography.<sup>1</sup> Pump failure is typically caused by reduced contraction of the left ventricle, measured as a reduced ejection fraction. Reduced ejection fraction is almost always accompanied by impaired filling of the left ventricle, but in some patients reduced filling dominates whereas the ejection fraction is normal, and that is heart failure with normal ejection fraction.

Heart failure with reduced ejection fraction is better understood: it typically develops after myocardial infarction, when myocyte loss results in left ventricle dilation and diminished contraction (fig 1).<sup>3</sup> Heart failure with normal



ejection fraction often develops after longstanding hypertension.<sup>3</sup> Compensatory left ventricular hypertrophy leads to myocardial stiffening, with reduced filling capacity of the normal sized or even small left ventricle. This leaves a ventricle with an ejection fraction in the normal range but a reduced stroke volume. Patients with heart failure with normal ejection fraction may have particularly bothersome symptoms during exercise.<sup>3</sup>

#### *Misdiagnosis of mild disease is problematic*

In the early stages, heart failure with normal ejection fraction causing breathlessness (a key symptom of heart failure) may be confused with chronic obstructive pulmonary disease (COPD), obesity, or deconditioning.<sup>1,4</sup> Fluid overload may be absent, particularly in patients receiving diuretics for hypertension. This may lead to underdiagnosis of heart failure with normal ejection fraction. On the other hand, age related breathlessness is common, which may cause overdiagnosis of heart failure with normal ejection fraction.<sup>5-7</sup>

#### *Debate about cut-off levels for natriuretic peptides suggestive of heart failure*

UK guidelines recommend that the diagnosis of heart failure is ruled out in patients in primary care with B-type natriuretic peptide (BNP) levels below 100 ng/L or N-terminal BNP (NTproBNP) below 400 ng/L.<sup>2</sup> Although, NTproBNP below 400 ng/L has a high negative predictive value (about 97%), some of those with low levels will have heart failure with normal ejection fraction.<sup>8</sup>

Natriuretic peptides are produced by myocytes in response to increased wall tension, which is generally lower in heart failure with normal ejection fraction than in heart failure with reduced ejection fraction, in line with Laplace's law, because the diameter of the ventricle is smaller and wall thickness higher. Thus natriuretic peptide levels are lower in heart failure with normal ejection fraction than in heart failure with reduced ejection fraction and can even be in the normal range.<sup>9</sup>

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at [uncertainties@bmj.com](mailto:uncertainties@bmj.com)



Fig 1 | Echocardiogram of an elderly man with previous myocardial infarct and heart failure with reduced ejection fraction. The left ventricle is dilated (upper limit of normal for minor axis is 5.5 cm) and globular (arrow). Left ventricular ejection fraction was 24%



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#### HOW PATIENTS WERE INVOLVED IN THE CREATION OF THE ARTICLE

We discussed drafts of the paper with two elderly patients with heart failure with normal ejection fraction who provided input. They stressed that, by knowing the cause of their shortness of breath and how to cope with episodes of breathlessness, they felt able to manage their symptoms in daily life and avoid being hospitalised.

P

Lowering the natriuretic peptide threshold for referral for echocardiography to avoid missing heart failure with normal ejection fraction would result in more testing with echocardiography. For example, based on a prospective cohort study, lowering cut-off points to 35 ng/L for BNP and 125 ng/L for NTproBNP would result in a negative predictive value of over 99%, but at the cost of many more echocardiograms.<sup>8</sup>

#### Variation in the cut-off levels on echocardiography

The description and cut points of abnormality of function in heart failure with normal ejection fraction is defined by expert consensus. It includes (a) a (nearly) normal ejection fraction, (b) left atrial enlargement, (c) increased left ventricular mass or wall thickness, and (d) raised left ventricle filling pressures (fig 2).<sup>10</sup> The European Society for Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE) define the cut-off point for a “normal” ejection fraction as 50%,<sup>12</sup> but others suggest 45%. There is some support for introducing an “in between” category with an ejection fraction of 40-50%.<sup>4,11</sup> Assessing diastolic function in patients with atrial fibrillation is even more unclear as measuring left ventricle filling is particularly difficult.

#### What is the prevalence of heart failure with normal ejection fraction?

There is uncertainty about the prevalence of heart failure in the general adult population, with reported rates of 1% to 4%.<sup>12,13</sup> Reports based mostly on retrospective data in hospitalised patients<sup>14,15</sup> suggest that around 50% of patients with heart failure have a normal ejection fraction and 50% have reduced ejection fraction, with a time trend towards an increase in heart failure with normal ejection fraction.

Population prevalence data among adults  $\geq 65$  years old living in the community with heart failure found that around 75% had a normal ejection fraction and 25% had a reduced ejection fraction.<sup>16</sup>

#### What is the aetiology?

There is general consensus that longstanding hypertension is the commonest precursor to heart failure with normal ejection fraction; as the main arteries stiffen, they reflect the systolic pressure wave instead of absorbing it, contributing to left ventricular pressure overload.<sup>3</sup> However, there is debate about whether other comorbidities are the cause of heart failure with normal ejection fraction or its consequence.<sup>3,17</sup> Heart failure with normal ejection fraction might develop over many years in response to obesity, hyperlipidaemia, type 2 diabetes, COPD, and chronic kidney disease.<sup>3</sup> These conditions are associated with low grade

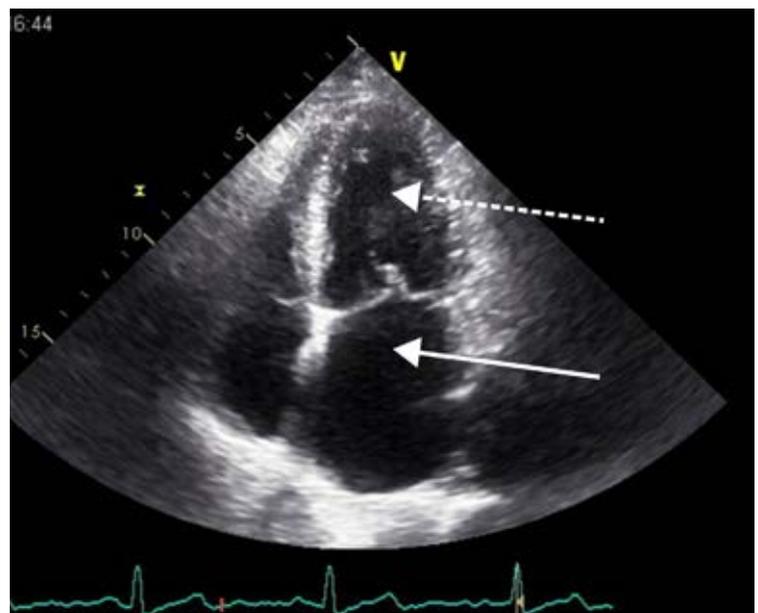


Fig 2 | Echocardiogram of an elderly man with breathlessness. Diagnosis of heart failure with normal ejection fraction was made based on the combination of symptoms, a raised concentration of N-terminal B-type natriuretic peptide, and a dilated left atrium (white arrow). Note that the left atrium is a similar size to the left ventricle (broken arrow). Left ventricular ejection fraction was 62%

## RECOMMENDATIONS FOR FURTHER RESEARCH

- To define the normal ranges of echocardiographic variables at different ages in a large, representative sample of community dwelling older people
- To develop robust diagnostic criteria for defining heart failure with normal ejection fraction
- To apply the diagnostic criteria to community dwelling adults to define the true prevalence and prognosis of heart failure with normal ejection fraction
- To apply the diagnostic criteria to participants in clinical trials evaluating drug therapy in heart failure with normal ejection fraction
- To determine the mechanisms underlying the development of heart failure with normal ejection fraction. Uncovering the pathobiology may reveal treatment pathways
- To design randomised controlled trials for patients with heart failure with normal ejection fraction with robust inclusion criteria: to investigate appropriate drugs, to compare interventions with usual care and placebo, and to evaluate the outcomes of mortality and hospitalisations

## IS ONGOING RESEARCH LIKELY TO PROVIDE RELEVANT EVIDENCE?

We searched <http://clinicaltrials.gov> databases and found several ongoing trials evaluating different drugs targeting different potential mechanisms in heart failure with normal ejection fraction:

- Inhibiting myocardial fibrosis
- Blocking interleukin-1
- Vasodilation
- Blocking the renin-angiotensin system together with inhibition of neprilysin with sacubitril valsartan

We also found trials evaluating:

- Exercise training
- Renal denervation
- Optimal management of comorbidities.

Other research will explore:

- The process of normal ageing of the healthy heart, and the differentiation of heart failure with normal ejection fraction from normal ageing
- Refined diagnostic criteria for heart failure with normal ejection fraction

systemic inflammation and may cause coronary microvascular endothelial dysfunction, thus triggering myocardial hypertrophy and stiffening as well as interstitial fibrosis.<sup>3</sup>

The uncertainty matters to patients: if these (or other) comorbidities cause heart failure with normal ejection fraction, then they should be intensively managed before the condition develops.

### What is the prognosis?

The prognosis of patients with heart failure with normal ejection fraction depends on the severity of the disease. Around one in 10 will have died five years after diagnosis, rising to around one in three for cases first detected during hospitalisation.<sup>18,19</sup> As a comparison, the five year mortality of colon cancer is around one in three.

A long term, hospital based, observational study found a lower cardiovascular mortality in patients with heart failure with normal ejection fraction compared with heart failure with reduced ejection fraction (adjusted hazard ratio 0.79 (95% confidence interval 0.67 to 0.95). There was no difference in non-cardiovascular mortality.<sup>15</sup> An individual patient data analysis of 31 studies (both hospital based observational studies and randomised controlled trials) found an adjusted hazard ratio for all-cause mortality of 0.68 (0.64 to 0.71) for

heart failure with normal ejection fraction compared with heart failure with reduced ejection fraction.<sup>18</sup> Among patients over 60 years old with type 2 diabetes and living in the community who were screened for heart failure, all-cause mortality in newly detected cases of heart failure with normal ejection fraction was also lower than that for heart failure with reduced ejection fraction (1.51 v 3.31 per 100 person years).<sup>19</sup>

### How should it be managed?

No therapy significantly improves survival or prevents hospitalisations in patients with heart failure with normal ejection fraction.<sup>1,2</sup> Four large randomised controlled trials of drugs counteracting the renin-angiotensin system (RAS) showed no clear impact on survival.<sup>20-23</sup> However, the trial inclusion criteria meant that healthy people might have been included because no clear criteria for echocardiographic diastolic dysfunction were applied, and natriuretic peptides were not used as an inclusion criterion.<sup>20-23</sup>

The quality of life of patients with heart failure with normal ejection fraction may be improved by exercise training, according to a recent meta-analysis of six randomised controlled trials (276 patients combined), but its validity is questionable given the small sample size.<sup>24</sup>

### What should we do in the light of the uncertainty?

#### Assessment

In older people with shortness of breath, consider heart failure with normal ejection fraction as a potential cause. Offer the following diagnostic work-up (based on expert consensus and the available evidence).<sup>1,2</sup>

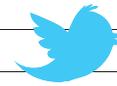
- History and clinical examination. In patients with suspected heart failure and previous myocardial infarction, NICE recommends echocardiography with specialist assessment within two weeks.<sup>2</sup>
- Measurement of serum natriuretic peptide levels in patients with no previous myocardial infarction. If BNP level is >400 ng/L or NTproBNP >2000 ng/L, NICE recommends echocardiography and specialist assessment within two weeks; if BNP level is 100-400 ng/L or NTproBNP is 400-2000 ng/L, assessment should be within six weeks.<sup>2</sup>
- Echocardiography in both of the above situations is to confirm or exclude heart failure, to differentiate normal and reduced ejection fraction, and to assess valvular heart disease.
- Consider alternative diagnoses and therefore additional tests where relevant—such as electrocardiography, chest radiography, lung function tests, urine analysis, full blood count and film, renal and liver function tests, thyroid stimulating hormone level, and plasma glucose and serum lipid levels.<sup>2</sup>

#### Management

Offer people with a confirmed diagnosis of heart failure with normal ejection fraction diuretics titrated to symptoms (treatment based on consensus opinion). Hypertension and other comorbidities should be adequately managed. Consider encouraging exercise after reassuring patients it is safe.

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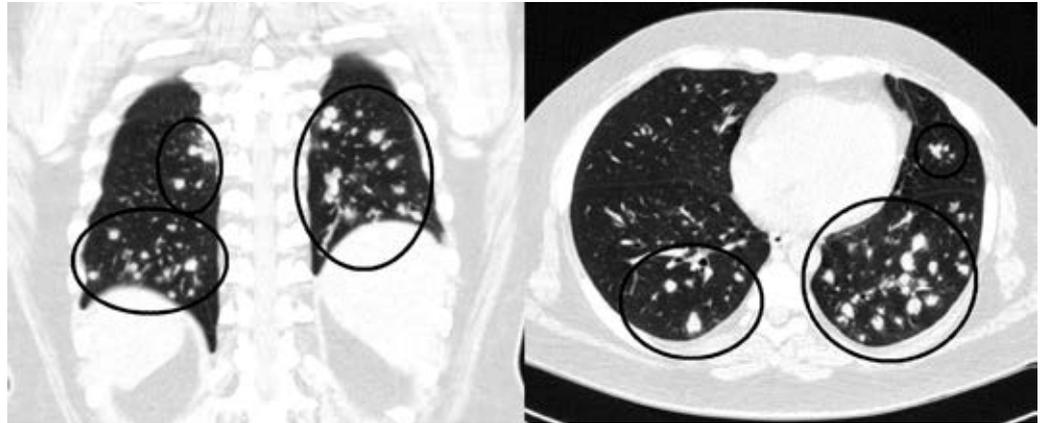
Find this at: <http://dx.doi.org/10.1136/bmj.i1706>



CASE REVIEW

**Pulmonary nodules in a man with a history of bone marrow transplantation**

Our patient was diagnosed as having Philadelphia chromosome positive pre-B acute lymphoblastic leukaemia with lymphoid blast crisis (blast crisis of chronic myeloid leukaemia) in 2011. Treatment with two cycles of hyper-CVAD (alternating cyclophosphamide+vincristine+doxorubicin+dexamethasone with methotrexate+cytarabine) plus dasatinib resulted in a negative bone marrow biopsy (remission). He had an allogeneic peripheral blood stem cell transplant from a 10/10 HLA matched unrelated donor in 2013. Conditioning was with cyclophosphamide and 1200 cGy total body irradiation. Graft versus host disease prophylaxis was with tacrolimus and methotrexate. Dasatinib was continued after his transplant. In late 2013 he developed relapsed acute lymphoblastic leukaemia. He was treated with fludarabine, cytarabine, and granulocyte colony stimulating factor. Bone marrow biopsy after chemotherapy showed persistent acute lymphoblastic leukaemia, even after he was switched to ponatinib and dexamethasone. Daunorubicin and vincristine were added for one cycle but were discontinued when he was admitted to hospital for cellulitis. Bone marrow biopsy was negative but one three months later showed



Coronal and axial plane reconstructions showing numerous nodules (circled) throughout both lungs with peribronchovascular predominance

recurrent acute B lymphoblastic leukaemia. Remission occurred after re-induction with clofarabine in the autumn of 2014; this was followed by 6-mercaptopurine, methotrexate, vincristine, and prednisone maintenance therapy.

He had no history of graft versus host disease and was not taking additional immunosuppressants. After his transplant, both *Aspergillus versicolor* and *A fumigatus* were isolated from his sputum, but he had no other evidence of invasive fungal infection. *Pneumocystis jirovecii* nucleic acid was isolated from his sputum but was thought to represent colonisation rather than infection. He had no evidence of tuberculosis at any time. His prophylactic antimicrobial regimen

did not include an antifungal drug (voriconazole was discontinued in 2015 owing to raised liver transaminases) but did include dapsone and aciclovir. About three weeks before admission, pus was noted around his peripherally inserted central catheter (PICC). There was no cellulitis and his PICC was removed. He then developed night sweats and cough productive of green sputum but did not report fever. He was prescribed levofloxacin at the oncology clinic about one week after these symptoms began. His symptoms persisted and worsened and he was admitted to hospital on day +792 after transplantation. He was clinically stable and without fever at the time of admission. Unenhanced

computed tomography of the chest showed about 50 predominantly peribronchovascular nodules (some with possible cavitation) within both lungs (figure).

- 1 What is the differential diagnosis of pulmonary nodules after allogeneic bone marrow transplantation?
- 2 What laboratory studies are available to evaluate these pulmonary nodules?
- 3 What invasive diagnostic techniques are available to establish a diagnosis?

Submitted by Neil Mendoza and Paritosh Prasad

Patient consent obtained.

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We welcome contributions that would help doctors with postgraduate examinations.

We also welcome submissions relevant to primary care.

See [thebmj.com/endgames](http://thebmj.com/endgames)

- Pulmonary nodules in a man with a history of bone marrow transplantation**
- 1 The most likely cause is infection, followed by lung cancer, post-transplant lymphoproliferative disorder, pulmonary cytolytic thrombi, or vasculitides.
  - 2 Sputum and blood cultures, serum markers of fungal infection, urinary antigen testing for pathogens, multiplex molecular assay for selected respiratory pathogens from a nasopharyngeal swab, and Epstein-Barr virus polymerase chain reaction testing of whole blood.
  - 3 Bronchoscopy with bronchoalveolar lavage, transbronchial biopsy or needle aspiration, trans thoracic needle aspiration, and surgical resection by video assisted thoracoscopic surgery or open thoracotomy.

CASE REVIEW

answers

### Abdominal discomfort with an alarming scan

A 74 year old woman presented after two weeks of rigors and abdominal discomfort. She had raised inflammatory markers and cholestatic liver function tests. After an unhelpful ultrasound and magnetic resonance cholangiopancreatography, a computed tomography showed hepatic portal venous gas (HPVG) and an abscess over the left psoas. Rapid clinical deterioration necessitated emergency surgery. A diverticular abscess, with rupture into the inferior mesenteric vein was found. After bowel resection and end colostomy

she recovered well. HPVG is usually associated with intestinal ischaemia (~75% mortality) but can occur with severe abdominal infections. Cholestatic presentations can be secondary to intestinal causes and still be survivable.

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Patient consent obtained.

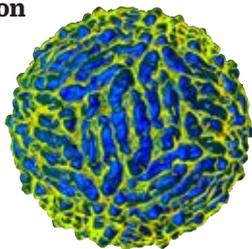
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### Dengue: the billion dollar question

The global cost of dengue is \$3.7bn-19.7bn, concludes a study on its economic burden across 141 countries and territories (*Lancet Infect Dis* doi:10.1016/S1473-3099(16)00146-8). The study was funded by Sanofi Pasteur, which has marketed the first dengue vaccine, Dengvaxia. It is currently available in the Philippines at about £270 a course. Given that half the world's population is at risk, mostly in low-to-middle income countries, there seems to be a mismatch.



### Disease orphanage (shut until further notice)

From 2005 to 2007 the Italian Medicines Agency (AIFA) ran a programme of independent research on drugs for rare diseases, spending €13.7m on 64 projects. Such drugs are rarely profitable for industry, so were they sufficiently worth while to justify this expenditure? The AIFA decided not and suspended the programme, but a study of its outputs finds that 10% may represent breakthroughs in their field and more than 30% provided definite clinical answers (*Orphanet J Rare Dis* doi:10.1186/s13023-016-0420-4). The publication rate was high (77%). The case for reopening this orphanage seems strong.

### Palliative gap for Parkinson's

Parkinson's disease can shorten life, have a high symptom burden, and require structured support, but patients seldom receive palliative care. A qualitative study (*Neuro Clin Pract* doi:10.1212/CPJ.000000000000233) shows that most patients are highly receptive to palliative care to help them cope with psychosocial problems, adjustment to illness, non-motor symptom control, and advance care planning.

### Dippers, surgers, and heart failure

Ambulatory blood pressure monitoring (ABPM) can tell us a lot about individual patterns of variation. Raised blood pressure is known to play a part in the development of heart failure, both with reduced systolic ejection fraction (HFREF) and preserved ejection fraction (HFPEF). Lifelong ABPM studies are needed for fuller understanding. In the meantime, a cross sectional study of 1191 elderly treated patients with hypertension provides new insights, such as an association between a morning surge in blood pressure and HFREF, and between a lack of nocturnal dipping and HFPEF (*Am J Hypertens* doi:10.1093/ajh/hpw015).

### Be a stimulating sham

Some people who work in medicine can stimulate for a few minutes and then turn out to be sham. A new device has managed to reduce this to 40 s while remaining convincing. A study recruited 75 subjects with chronic pain and tested a new device that delivers interferential current (IFC), but cuts out after 40 s, against another placebo device or active IFC (*Pain Med* doi:10.1093/pm/pnw039). For IFC, the new placebo method fooled the investigator in all cases and 60% of patients stimulated, whereas for inactive placebo, the figures were 0% and 34%.

### Potassium: not the good electrolyte?

Potassium intake does not affect cardiovascular outcomes, according to a cohort study of 7795 people followed for 10.5 years (*Am J Clin Nutr* doi:10.3945/ajcn.115.106773). Potassium excretion over 24 hours, which might be a more objective measure than food diaries, was measured at the start and middle of the study. After adjustment for multiple risk factors, potassium excretion was not associated with total cardiovascular disease, ischaemic heart disease, stroke, or new onset heart failure.

### Stemming myasthenia gravis

Custom demands that the words "stem cell" should be followed by "breakthrough." The latest is the use of autologous haematopoietic stem cell transplantation for treatment resistant myasthenia gravis. This approach did break through the disease in seven severely affected patients in a Canadian pilot trial (*JAMA Neurol* doi:10.1001/jamaneurol.2016.0113), with sustained benefit at a median of 40 months.

### Testing for amoxicillin allergy

Lots of febrile children who are given amoxicillin develop a rash. Most of them then have "allergic to amoxicillin" stamped on their notes for ever. But in Montreal Children's Hospital they have developed a graded provocation test with excellent predictive characteristics, as tested by later full treatment with amoxicillin (*JAMA Pediatr* doi:10.1001/jamapediatrics.2016.0033).

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