

# Selected abstracts from the 48th St Andrew's Day Festival symposium: updates on acute medicine

## ACCELERATED HYPERTENSION: NOT JUST THE NUMBERS

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Accelerated hypertension is categorically different from the 'benign' hypertension from which it arises. The rate and severity of increased pressure causes the pathological change of fibrinoid necrosis of the resistance arteries. This in turn causes loss of autoregulation of blood flow in the two organs – brain and kidney – where flow is normally independent of pressure. The clinical consequences are twofold: One is the diagnostic, sight-threatening neuroretinal oedema. The other is the risk of cerebral hypoperfusion on treatment of hypertension.

For clinicians, the essential task is to differentiate accelerated hypertension from hypertensive emergencies and urgencies in which the prompt and aggressive reduction of blood pressure is indicated. In accelerated hypertension, reduction must be gradual, and the only reason to use parenteral therapy would be to protect against unpredictable excessive falls.

Most hypertension lies on a spectrum between pure vasoconstriction and pure volume overload. Accelerated hypertension causes, and is caused by, almost pure vasoconstriction, and many patients illustrate the phenomenon of pressure natriuresis. The consequent hypovolaemia renders the hypertension initially very sensitive to blood pressure reduction. Once blood pressure falls, and autoregulation is restored, patients progress to a more common-or-garden mixture of vasoconstrictor and volume-dependent hypertension and require additional treatment.

Because renin is high in the accelerated phase, most blockers of the renin system are avoided as too risky. Low-dose  $\beta$ -blockade, which reduces renin secretion, is safer in most patients. Sodium nitroprusside infusion is titratable against blood pressure reduction, allowing a daily maximum fall of 20/10 mmHg. Diuretics and short-acting calcium blockers – particularly sub-lingual nifedipine – are contraindicated.

Prognosis is no longer malignant, but patients are at a higher risk of complications than in benign hypertension. Accelerated hypertension is most safely considered 'not an emergency', and understanding this encourages rational treatment both of the condition itself and of other patients with less extreme forms of hypertension.

## Further reading

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**Declaration of interest** Prof. Brown consults for Novartis and receives research funding from Menarini.

## RECENT ADVANCES IN THE DIAGNOSIS AND STAGING OF LUNG CANCER

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One million new cases of lung cancer and 900,000 deaths caused by the disease are registered each year worldwide. Only 22% of lung cancer patients will be offered curative treatment. There is no effective screening modality reducing lung cancer mortality. Overall, the five years relative survival rate is approximately 15%.

There are various invasive and non-invasive techniques to diagnose and stage lung cancer. Accurate evaluation of the mediastinal lymph-nodes (LN) determines staging and thus prognosis and treatment plans in patients with lung cancer. Standard staging methods include mediastinoscopy and positron-emission tomography (PET-CT). Mediastinoscopy allows access to LN in the anterior-superior mediastinum and has a sensitivity of 70–95%. PET-CT has a moderate positive but high negative predictive value in assessment of LN metastases (75% vs 96% respectively).

New diagnostic and staging methods in lung cancer include endobronchial and endoscopic ultrasound techniques (EBUS and EUS). Both procedures are minimally invasive and are performed under conscious sedation in out-patients. Combined, they provide access to the majority of mediastinal and hilar LN stations. EBUS has high positive and negative predictive values for LN metastases.<sup>1,2</sup>

We have performed more than 550 EBUS procedures to date and audited data on the first 250 cases. The diagnosis and staging was achieved in a single procedure in 87% of cases. There were no complications. Our sensitivity was 95% with negative predictive value 93%. EBUS  $\pm$  EUS in conjunction with PET-CT should be considered as a safe and effective alternative for mediastinoscopy in the diagnostic and staging algorithm in lung cancer.

## References

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## RECOGNISING AND MANAGING PARKINSON'S DISEASE

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Nigrostriatal dopamine levels are reduced by 80% before Parkinson's disease (PD) is clinically apparent. Thus the disease has been present for sometime before it is recognised. The diagnosis remains clinical, dependent on the finding of at least two of the cardinal motor features: hypokinesia, rigidity, rest tremor and postural instability. Non-motor features such as impaired sense of smell, sleep fragmentation, depression and constipation may precede the onset of motor features. Hypokinesia is not a single phenomenon but includes delayed initiation, slowness, poverty and imprecision of movement, not all of which may be evident at presentation. Rigidity is often most easily detected axially and there may be action or postural components to the tremor. If these signs are symmetrical or accompanied by the early occurrence of falls, severe autonomic dysfunction or cognitive decline or by the presence of gaze palsy, cerebellar or pyramidal signs alternative diagnoses should be considered.

Central to the effective management of PD is the education and involvement of the patient in the process. Advice on health maintenance with diet, exercise and social activities has a major role. Drug therapy is symptomatic rather than curative, and the current verdict on neuroprotective agents is 'not proven'. The decision on when to start treatment should be made with an informed patient taking account of the impact of the symptoms on their daily life. Levodopa, in use for about 40 years, remains the mainstay of effective drug therapy, with dopamine agonists and dopamine breakdown enzyme inhibitors useful additions to our armamentarium.

## PROBLEMS IN THE MANAGEMENT OF PARKINSON'S DISEASE

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While most motor symptoms of Parkinson's disease respond well (at least initially) to dopamine replacement therapy, it is now increasingly recognised that a number

of non-motor complications develop over time (mental health problems, sleep disorders, autonomic problems), which are either unresponsive to dopamine replacement or exacerbated by it. These complications have an enormous impact on the quality of life of patients but are difficult to treat.

Mental health issues are common in Parkinson's disease. After 15 years, about 50% of patients have dementia, hallucinations and depression and these are the most important predictors of poor quality of life and institutionalisation. About 10% of patients on treatment have an impulse control disorder. Autonomic complications are also common, with 30–40% of people having postural hypotension and urinary incontinence at 15 years. The management of dementia and psychosis includes simplifying the dopaminergic treatment and multidisciplinary input. There is some evidence for the use of atypical antipsychotics and cholinesterase inhibitors.

Postural hypotension can be treated by minimising hypotensive medication, non-pharmacological strategies (positional changes, hydration, bed tilt) and additional medication (fludrocortisone, domperidone, pyridostigmine, adrenergic drugs).

Gait freezing is a disabling motor complication that frequently predisposes to falls and becomes more common over the course of the disease. If associated with motor 'off' periods it may respond to increasing dopaminergic treatment, but otherwise it is best managed by using external cues.

Non-motor complications have a major impact on patients' and carers' quality of life in Parkinson's disease, but these complications often respond poorly to present management strategies.

## Further reading

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## ACUTE PANCREATITIS FOR THE PHYSICIAN

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Acute pancreatitis can run a variable clinical course ranging from a mild self-limiting illness to a severe condition resulting in the development of local and systemic complications, such as infected pancreatic

necrosis or multiorgan failure, with a significant risk of mortality. Early identification of patients with severe disease allows selection of patients who should be monitored and managed in a critical care facility and may require management in a specialist centre.

Numerous scoring systems permit severity stratification, but novel methods such as artificial neural networks are also being developed. Several studies have highlighted the importance of deteriorating organ function and a persistent systemic inflammatory response syndrome response in predicting a poor prognosis.

Following early assessment, specific intervention can be considered such as endoscopic retrograde cholangio-pancreatography, antibiotics and enteral nutrition. The evidence base for these is often conflicting; however, the contemporary views on early specific therapies will be presented. It is now widely accepted that any surgical intervention for the management of infected necrosis should be delayed if possible. Conventional open necrosectomy may still have a role, but minimally invasive techniques are now widely practised.

The British Society of Gastroenterology has produced guidelines and audit standards for the management of patients with acute pancreatitis.

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## HOW I MANAGE ABNORMAL LIVER FUNCTION TESTS

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Liver function tests are a core part of the investigative pathway for patients presenting with a wide range of symptoms. There is clear evidence that medical interventions such as statin prescribing are increasing the frequency with which liver enzyme levels are requested. Despite this, there is widespread misunderstanding of the implications of abnormal results, particularly where the patient has no symptoms or signs suggesting overt liver disease and where tests of liver synthetic function are normal.

There are two large studies investigating the clinical significance of abnormal liver enzymes in different patient populations in both primary and secondary care. These studies suggest that unexplained abnormal liver biochemistry has a significant yield.

In a primary care setting, an audit of 873 abnormal liver enzyme results in a single laboratory over a six-month period; on review 157 (18%) of the case records required further investigation. Of these, no further tests had been

requested in 91 cases (58%) and in seven a diagnostic follow-up test had been carried out but a significant positive result not acted on. Overall, 97 (62%) patients had a diagnosis made when appropriate follow-up was undertaken (alcoholic liver disease n=42, non-alcoholic fatty liver disease n=26, autoimmune liver disease n=7, haemochromatosis n=4, viral hepatitis n=8, other n=10). Retesting after an interval showed that 25% of abnormal transaminases normalise and can probably be ignored. In those with persistent abnormality, screening with ultrasound scan, hepatitis B and C serology, auto-antibodies, immunoglobulins and coeliac serology plus screening for alpha-1-antitrypsin deficiency and Wilson's disease in selected patients will often yield a diagnosis.

In secondary care, the situation is different, with most patients referred for outpatient investigation having an appropriate set of serological investigations if abnormal liver enzymes are noted. In this setting of abnormal liver enzymes in the absence of diagnostic serology, the yield of significant pathology on liver biopsy in a study of 354 patients was high, with 26% having fibrotic liver disease and 6% cirrhosis. The most common finding in this group of patients was one of the fatty liver variants, approximately 66% having either pure fatty liver or non-alcoholic steatohepatitis. Other potentially treatable liver disorders were found in this patient group and management was altered directly by the liver histology findings in 18%. Serum fibrosis markers and fibroscan may alter the management algorithm in the future, but, for now, if weight loss and exercise do not normalise liver function tests, biopsy should be considered.

Routine measurement of liver enzymes is a good screening tool for the detection of many forms of liver disease, both in primary and secondary care. Appropriate further investigation of asymptomatic liver enzyme abnormalities in primary care yields a significant diagnosis in more than 60% of patients. In secondary care non-alcoholic fatty liver disease accounts for the majority of cases.

### Further reading

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## IMPROVING THE MANAGEMENT OF POISONING

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Acute overdose remains a common hospital presentation. The National Poisons Information Service (NPIS) was

formed 45 years ago, and its internet database TOXBASE is now 25 years old.

Over this period the epidemiology of poisoning has changed, both with respect to incidence and available agents. Approaches to the management of poisoning are becoming more evidence-based, but for rare poisons clinical trials are always going to be problematic. The NPIS has developed consensus statements to support its advice, and a range of treatment advice statements for common clinical scenarios. This process assists in identification of areas of uncertainty but will also highlight new developments by use of regular literature scanning.

Key issues in current practice include the management of paracetamol, antidepressants, cardiovascular agents and drugs of abuse. Recently introduced new therapies for toxic alcohols and cyanide will be discussed, and developing areas highlighted.

This presentation will give a brief outline on the work of the NPIS and illustrate how evidence is brought forward and presented within the largest point of care clinical support system in Europe. New treatment modalities and approaches will be outlined.

#### Further reading

- NPIS. *Annual report 2007/2008*. Available from: [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1221379221266](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1221379221266)
- TOXBASE: <http://www.toxbase.org>

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### APPROACHES TO THE PREVENTION OF DIABETES

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The most serious potential public health impact of the worsening epidemic of type 2 diabetes is the cardiovascular consequences of hyperglycaemia. Three critical factors affect the choice of prevention strategy: the shape of the distribution of glucose levels in the population, the magnitude and shape of the risk curve relating glucose levels to cardiovascular risk and the degree to which that risk can be reduced by glucose-lowering therapy. Overall glucose levels are normally distributed and the relationship between glucose and cardiovascular risk is linear, but more importantly shallow.<sup>1</sup> The majority of the cardiovascular disease risk attributable to higher than desirable glucose levels lies with the large number of people within the population with moderately elevated levels. These characteristics have important implications for the balance between individual and societal approaches to prevention.

Finding people at risk of diabetes is relatively straightforward,<sup>2</sup> and the effectiveness of lifestyle interventions in reducing progression to diabetes is a clear demonstration that risk is reversible by behaviour change.<sup>3</sup> This risk reduction is sizeable and sustained. The major challenge is how to effect sustained changes in behaviour in populations.<sup>4</sup> This requires a move from research on individual-level determinants of behaviour to consideration of the wider societal determinants of those behaviours and on the effectiveness of true population intervention strategies.<sup>5</sup> Although this is a difficult task, it is the only strategy that has the potential to impact on this global public health problem.

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### SPONTANEOUS HYPOGLYCAEMIA IN NON-DIABETIC INDIVIDUALS

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Acute hypoglycaemia occurs most commonly in individuals with diabetes treated with insulin and/or sulphonylureas. In non-diabetic individuals, acute, symptomatic hypoglycaemia occurs rarely. Presentation is incredibly variable and reflects the very large number of potential causes of acute hypoglycaemia and the wide spectrum of symptoms and signs it can provoke.

The symptoms of hypoglycaemia can be divided into autonomic and neuroglycopenic groups. Autonomic symptoms include sweating, tremor and palpitations and are a consequence of activation of the autonomic nervous system. Neuroglycopenic symptoms, a consequence of cerebral neuron glucose deficiency, include blurred vision, irritability and confusion. As hypoglycaemia deepens, seizures and coma can result and ultimately permanent neurological damage and death will occur.

In the acute receiving unit, the most common cause of acute hypoglycaemia is alcohol excess. Alcohol acutely

impairs hepatic gluconeogenesis, and this can cause significant hypoglycaemia on a background of depleted glycogen reserves seen in cirrhosis and/or chronic alcohol excess. Acute hypoglycaemia may also be a consequence of a critical illness, such as acute liver failure or sepsis. In older adults, acute hypoglycaemia can cause focal neurological deficits, such as hemiparesis, and so blood glucose should always be measured in people presenting with acute neurological signs or symptoms. Factitious or felonious administration of insulin (or sulphonylureas) is rare.

In the non-acute setting, hypoglycaemia is more challenging to confirm and diagnose. There is no absolute cut-off for what represents an episode of hypoglycaemia, and it is important to recognise that apparently 'low' venous blood glucose concentrations can occur in healthy individuals. The key to diagnosing a hypoglycaemic disorder is to meet all the criteria of Whipple's triad:

- There are symptoms of hypoglycaemia;
- There is a low blood glucose concentration;
- The symptoms disappear on correction of the low blood glucose concentration.

Many people are referred to endocrine clinics with apparent symptoms of hypoglycaemia while others are referred with a random low blood glucose concentration, but very few ever turn out to have a hypoglycaemic disorder. The concept of 'reactive hypoglycaemia', that is hypoglycaemia occurring a few hours after food, is largely discredited. The key diagnostic test in a non-acute setting is a 72-hour fast – if symptomatic hypoglycaemia does not occur after such a fast, then a hypoglycaemic disorder is excluded. If hypoglycaemia is confirmed, then measuring contemporaneous insulin and C-peptide will help clarify the aetiology.

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## NEW TECHNIQUES IN CARDIAC IMAGING

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With significant advances in magnetic resonance imaging (MRI) and computerised tomography (CT) technology, the field of cardiac imaging is expanding rapidly in terms of applications in relation to cardiological practice.

Specifically, cardiac CT and cardiac CT angiography allow non-invasive coronary arterial imaging and cardiac function as well as thoracic assessment of respiratory and thoracic aortic pathologies. These are becoming established techniques on all new CT scanners, and the challenges of how best to integrate these into cardiac imaging practice and patient pathways are now being addressed.

In relation to MRI, the additional recent advances allow non-invasive imaging in the full range of cardiac conditions. In particular, these are the assessment of cardiac morphology, cardiomyopathies, pericardial and valvular disease as well as in ischaemic heart disease assessment of myocardial perfusion and viability.

*Declaration of interest* The author is a director of Tayside Flow Technologies Ltd.

## ADVANCES IN THE TREATMENT OF SEPSIS

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The systemic response to the ingress of pathogenic micro-organisms remains a leading cause of morbidity and mortality in both developed and developing nations.<sup>1</sup> In the UK, for example, it is estimated that the annual toll from sepsis is approximately 100,000 people, making it the second most common cause of death. Established management principles include the use of broad-spectrum empirical antibiotics chosen on the basis of the clinical presentation, resuscitation using intravenous fluids and vasopressors, organ support and source control.<sup>2</sup> A common, unifying and relatively undisputed theme across these principles appears to be the role of procrastination as a significant contributor to poor outcomes.<sup>3</sup>

Besides these 'known knowns', other potential therapies that constitute the advances in the treatment of sepsis fall into three categories. First, we have treatments or strategies that are currently used in the management of sepsis, but whose role remains to be clarified. This category would include activated protein C, steroids and glycaemic control, among others. Second, there are treatments that show significant potential but require further evaluation, and examples in this category would include statins. Finally, there are treatments that are either on, or even slightly over, the therapeutic horizon.

By reducing or eliminating delays in the identification and treatment of patients with sepsis, outcomes could be improved in the short term, even with therapies currently available. In the medium term, clarification of the role of currently available therapies or the introduction of agents under development is only likely to make a relatively modest impact.

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## MEDICAL MANAGEMENT OF PERIPHERAL VASCULAR DISEASE

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Peripheral arterial disease (PAD) and its most common manifestation, intermittent claudication (IC), are associated with considerable cardiovascular (CV) morbidity and mortality. Patients with PAD, even in the absence of myocardial infarction or ischaemic stroke, have approximately the same relative risk of death from CV causes as do patients with a history of coronary or cerebrovascular disease. Thus, for PAD patients, the focus must be on the CV complications of atherosclerosis, i.e. vascular risk factor management. However, PAD is also associated with significant pain and a poor quality of life, which can equate to that seen in cancer patients. A recent study in the USA assessed the 'wish lists' of patients with IC and their primary care physicians, and alleviation of symptoms was the top priority. As these patients have a similar mortality to patients with angina, management of ischaemic muscle pain in the leg should receive as much attention as the aetiologically similar pain of angina.

With its prevalence in Europe and North America estimated at approximately 27 million people, PAD is a critical public health issue. Furthermore its deleterious nature is compounded by its status as an underdiagnosed and undertreated disease. Many symptomatic patients are not diagnosed, and there are equal numbers of PAD patients who are asymptomatic but who have the same CV risk as their symptomatic counterparts.

However, several recent developments suggest that this may be an opportune time to re-examine traditional assumptions regarding the management of PAD.

### Further reading

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**Declaration of interest** The author is chairman of Sanofi/BMS advisory committee.

## TUBERCULOSIS: AN OLD FOE REVISITED

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Tuberculosis (TB) has witnessed some advances and setbacks over the past 30 years. The disease remains a major challenge in the UK as well as in the developing world.<sup>1</sup>

Diagnostic tests have improved. Liquid media culture now gives results in about 10 days compared to many weeks for conventional solid media. The method suits sensitivity testing. Host production of TB-specific gamma interferon can now be assayed by a blood test. This has a higher specificity and sensitivity than Mantoux testing.

Latent TB has become an important issue for immunocompromised patients, particularly those who take anti-TNF therapy for chronic inflammatory conditions.<sup>2</sup>

Tuberculosis is an alert to undiagnosed HIV infection, so all new TB cases should consider HIV testing as routine.<sup>3</sup>

The arrival of multi-drug resistant TB and extensively drug resistant TB have highlighted the importance of public health measures and hospital isolation facilities.<sup>4</sup>

### References

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