The first will address antimicrobial stewardship from a health and social care perspective.¹

Increasing antimicrobial resistance and the lack of new agents has been noted as a major risk to health in the future. In addition, the wide variation between GP practices in the prescribing rate of antibiotics for common clinical conditions, and the limited impact of prescribing guidelines aimed at reducing antibiotic use in UK primary care have been highlighted.²

With this in mind, the scope of the new guidance will address:
- supporting antimicrobial use by health and social care practitioners where their use is indicated;
- reducing the use of antimicrobials without increasing harm through changing behaviour of practitioners and patients;
- reducing emergence of antimicrobial resistance through effective antimicrobial stewardship.

The guideline will not cover use of specific named medicines or treatment of specific conditions. Review questions that will inform the development of the guidance will focus on which interventions, systems and processes are effective in changing practitioners’ decision-making to ensure appropriate antimicrobial stewardship; overcoming the barriers to decision-making by practitioners when ensuring appropriate antimicrobial stewardship; and reducing the emergence of antimicrobial resistance without increasing harm to patients.

The second guideline will provide public health guidance, which will focus on changing people’s knowledge, attitudes and behaviours in relation to the use of antimicrobials.³

Comment: Although the guidance will not be published until 2015, NICE has identified areas of antibiotic prescribing that healthcare professionals can tackle. These include increasing the use of 3-day courses of trimethoprim for uncomplicated urinary-tract infections in women; ensuring that prescribing of quinolones and cephalosporins is in line with national guidance; and reviewing the use of minocycline because of potential adverse effects.⁴,⁵


NICE to develop guidance to tackle antibiotic resistance

The National Institute for Health and Care Excellence (NICE) is developing two new guidelines to help encourage effective use of antimicrobials and reduce antibiotic resistance.
Reduction in diabetes risk after bariatric surgery?

Bariatric surgery has been shown to result in substantial weight loss, decreased morbidity and improvements in quality of life. Guidance from the National Institute for Health and Care Excellence (NICE) advises that bariatric surgery is a treatment option for people with obesity if all of the following criteria are fulfilled:1

- They have a body mass index (BMI) of 40kg/m² or more, or between 35 and 40kg/m² and other significant disease (e.g. type 2 diabetes or high blood pressure) that could be improved if they lost weight.
- All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically significant weight loss.
- The person has been receiving or will receive intensive management in a tier 3 service.
- The person is generally fit for anaesthesia and surgery.
- The person commits to the need for long-term follow-up.

A recently published cohort study using the UK’s Clinical Practice Research Datalink database has highlighted potential benefits of bariatric surgery in reducing the risk of diabetes; however, a linked commentary says some questions remain unanswered.2

In the study, researchers matched 2,167 obese adults without diabetes who had undergone bariatric surgery with 2,167 controls without diabetes who had a comparable BMI, age, sex, index year and glycated haemoglobin (HbA₁c). The primary outcome, extracted from electronic health records, was development of clinical diabetes. Patients were assessed as having a diagnosis of clinical diabetes if a medical code for diabetes was recorded, if insulin or oral hypoglycaemic drugs were prescribed, or if an HbA₁c value of 6.5% or higher was recorded.

During follow-up (maximum 7 years; median 2.8 years), 177 controls were diagnosed with type 2 diabetes compared with 38 people who had undergone surgery. Incidence of diagnoses per 1,000 person-years was 28.2 (95% CI 24.4 to 32.7) for controls and 5.7 (95% CI 4.2 to 7.8) for surgery patients, giving an adjusted hazard ratio of 0.20 (95% CI 0.13 to 0.30).

However, an associated article that commented on the results highlighted that many of the control patients had missing values for blood pressure or cholesterol levels, which suggested that they may not have been monitored and treated for their obesity as well as the patients who had bariatric surgery.1 That might indicate that sub-optimal care contributed to their diabetes, rather than lack of surgical intervention alone. In addition, the short follow-up for most of the people studied meant the researchers could not show whether people who had undergone bariatric surgery regained weight and, if so, whether they subsequently developed diabetes.

Comment: The results of the study raise some interesting questions. However, limitations associated with the observational data and the issues raised by the commentary highlight the need for caution. The complex relationship between bariatric surgery, weight loss and the development of diabetes is not yet clear.

BMI and antihypertensive therapy regimens

Should obese people with hypertension be prescribed different blood pressure-lowering regimes than people of normal weight with hypertension? There is a hypothesis that the pathogenesis of hypertension is different for lean and obese individuals and that different therapeutic approaches may be best suited for reduction of their cardiovascular risk. Post-hoc analyses of large scale trials of antihypertensives have had conflicting results. The Blood Pressure Lowering Treatment Trials’ Collaboration (BPLTTC) has used individual patient data from 22 trials (135,715 participants) to compare the effects of different classes of drugs at different body mass index (BMI) categories and as a continuous variable.3

The trialists used the primary outcome of major cardiovascular events (defined as stroke, coronary heart disease, heart failure and cardiovascular death). When assessing interactions between treatment group and categories of BMI (<25, 25 to <30 and ≥30kg/m²), they found no evidence of a difference of effect. When they analysed the results with BMI as a continuous variable, they found that ACE inhibitors provided slightly higher protection for each additional 5kg/m² of BMI compared with calcium-channel blockers or diuretics (hazard ratio for both comparisons 0.93, 95% CI 0.89 to 0.98). The study did not find any difference in efficacy of calcium-channel blockers compared with diuretics that was related to BMI.

This was in contrast to a previous report that suggested that diuretics were less effective than calcium-channel blockers for normal-weight patients, while the two drugs were of equivalent efficacy for obese patients. The trialists concluded that there was ‘little evidence’ that selecting different combinations of drug classes based on BMI would have a substantial impact on the outcomes for patients.

In a linked commentary, two US cardiologists question the trialists’ conclusion that the calcium-channel blockers result in one previous study could have been a chance finding.2 They point to an earlier trial that also found that diuretics were less effective in lean patients. In addition, they suggest that randomised controlled trials are needed to directly test the hypothesis that aldosterone inhibitors provide better cardiovascular protection in overweight or obese hypertensive patients.

Comment: The trial and commentary demonstrate the difficulty in extrapolating data to support hypotheses from trials that were not designed with this purpose in mind, even when individual patient data are available.


MHRA update on interferon beta safety

Healthcare professionals should be vigilant for early signs and symptoms of thrombotic microangiopathy and nephrotic syndrome in people undergoing treatment with interferon beta, the Medicines and Healthcare products Regulatory Agency (MHRA) advises.1 To date, the MHRA has received 13 Yellow Card reports of thrombotic microangiopathy, haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura linked to interferon beta treatment, and five reports of nephrotic syndrome linked to interferon beta treatment. A European review is investigating the link between interferon beta treatment and incidents of thrombotic microangiopathy and nephrotic syndrome. In addition, the European review is examining a potentially increased risk of thrombotic microangiopathy associated with a change in formulation of interferon beta.
Clinical features of thrombotic microangiopathy include:

- thrombocytopenia
- new-onset hypertension
- fever
- central nervous system symptoms (e.g. confusion and paresis)
- impaired renal function.

Clinical features of nephrotic syndrome include:

- oedema
- proteinuria
- impaired renal function, especially in patients at high risk of renal disease.

Thrombotic microangiopathy and nephrotic syndrome can occur weeks to years after starting treatment with interferon beta.

If clinical features of thrombotic microangiopathy are seen, clinicians are advised to test blood platelet levels, serum lactate dehydrogenase levels and renal function. Also advised is testing for red blood cell fragments on a blood film. If thrombotic microangiopathy is diagnosed, it should be treated promptly and interferon beta treatment should be stopped immediately. Thrombotic microangiopathy is a potentially fatal complication.

If clinical features of nephrotic syndrome are seen, this should be treated promptly and interferon beta treatment should be re-assessed and stopped if necessary.

Comment: Prescribing and supply of interferon beta may not be the responsibility of primary care healthcare professionals. However, it is important that use of interferon beta and any monitoring requirements are recorded in the patient’s primary care medical record.


Limited evidence that allopurinol prevents gout attacks

Allopurinol acts by inhibiting the enzyme xanthine oxidase, which catalyses the end stage of the metabolism of purines to uric acid, and has been used as prophylaxis in chronic gout for many years. However, questions remain as to whether the reduction in urate translates to fewer acute attacks of gout, less pain or other clinically important outcomes.

A recent Cochrane review (11 randomised controlled trials; 4,521 participants) has concluded that moderate-quality evidence suggests that there was a similar incidence of acute attacks of gout when allopurinol was compared with placebo and other urate-lowering drugs. In one short-term randomised controlled trial (57 participants), there were two acute attacks of gout among 26 people (7.7%) taking 300mg allopurinol daily, and three acute attacks among 25 people (12%) taking placebo (risk ratio [RR] 0.64, 95% CI 0.12 to 3.52; p=0.61) over a 30-day period. The study confirmed that allopurinol increased the number of participants achieving a target serum urate over 30 days (25/26 with allopurinol vs. 0/25, number-needed-to-treat [NNT]=1). It found no difference between allopurinol and placebo for pain reduction or tophus regression. Three trials (1,136 participants) provided low-quality evidence that allopurinol up to 300mg daily and febuxostat 80mg daily showed no significant difference in the incidence of acute gout attacks. In four trials with 2,618 participants, more people achieved target serum urate level with febuxostat (70%, compared with 38% with allopurinol, RR 0.56, 95% CI 0.48 to 0.65). The NNT for febuxostat for one additional person reaching target serum urate level was 4. The studies of febuxostat found no differences in regression of tophi and did not report on pain reduction or function.

The review also reported on the comparison of allopurinol with benzbromarone (not licensed in the UK). One trial of 65 participants found no significant difference in the numbers of acute attacks of gout, and two trials (102 participants) found no significant difference in the numbers reaching target serum urate levels.

Overall, the studies found similar withdrawals due to adverse effects for allopurinol, placebo, benzbromarone and febuxostat.
10 years of EU herbal standards

The European Medicines Agency (EMA) is marking a decade of collaboration across member states to standardise the assessment and authorisation of herbal medicines. Since the introduction of EU legislation on herbal treatments in 2004, more than 1,300 traditionally used herbal medicines have been registered and more than 600 herbal medicines have received a marketing authorisation. These medicines are now accompanied with standardised product information, with the goal of helping individuals and healthcare professionals make informed choices when considering herbal treatments.

For the assessment of herbal substances, the EMA’s Committee on Herbal Medicinal Products (HMPC) publishes monographs, which contain information on recommended therapeutic uses, contraindications, interactions with other medicines and possible adverse effects. These are based on a review of all available scientific data on safety, efficacy and quality, as well as information on the historic use of the herbal ingredients. In addition, the HMPC has developed more than 20 scientific guidelines to provide common standards for the registration and authorisation of herbal medicines by member states. These guidelines also provide a reference for applicants when drafting national applications.

The HMPC is expanding its scope to include herbal medicines that contain a combination of herbal ingredients, as well as non-European traditional herbal treatments, such as Chinese medicines. The EU Directive on traditional herbal medicinal products came fully into force in the UK in April 2011. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for regulating herbal medicines in the UK. Details of registered traditional herbal medicines are available on the MHRA website.

Comment: The introduction of traditional herbal registration and the statutory regulation of practitioners supplying unlicensed herbal medicines have acted as safeguards for the public and are to be welcomed. In particular, having clear and reliable information on herbal medicines—including their contraindications and interactions—is of considerable value to patients and healthcare professionals.


Prophylactic antibiotic therapy for prelabour membrane rupture

A recent Cochrane review assessed the balance of risks and benefits to the mother and infant of prophylactic use of antibiotics for prelabour membrane rupture at or near term. The authors found that the risks outweigh the benefits and advise that antibiotic therapy is only indicated for women with clinical evidence of infection.

The updated review investigated the effects of prophylactic antibiotic therapy in women with prelabour membrane rupture at 36 weeks’ gestation or beyond. Maternal, fetal and neonatal outcomes were assessed. The review included four randomised trials of 2,639 women with term prelabour rupture of membranes, comparing antibiotics with placebo or no antibiotics. Overall, the evidence was considered to be weak.

The meta-analysis showed no difference between the group that received antibiotics and the control group (placebo or no antibiotic) in terms of probable early-onset neonatal sepsis, definite early onset neonatal sepsis, maternal infectious morbidity (chorioamnionitis and/or endometritis), stillbirth and perinatal mortality. There were no cases of neonatal mortality or serious maternal outcome (defined as death, cardiac arrest, respiratory arrest, anaphylaxis or admission to intensive care). The review found that caesarean section was increased with the use of antibiotics (risk ratio 1.33, 95% CI 1.09 to 1.61). However, an absence of data meant that the authors were unable to assess the short-term and long-term harms associated with the use of antibiotics.

Subgroup analyses by timing of induction of labour showed no difference in probable or definite early-onset neonatal sepsis in either early or late induction. For maternal infectious morbidity, no difference was found in either subgroup. No differences were shown in stillbirth or perinatal mortality in the subgroup analysis.

Comment: In 2011 DTB reviewed the role of antibacterials in women at risk of pre-term birth, and noted that clinical distinction between those who have rupture of membranes and those who have intact membranes is not always clear. The UK Royal College of Obstetricians and Gynaecologists recommends the use of erythromycin for 10 days for pre-term prelabour rupture of membranes. This latest Cochrane review suggests that for women with prelabour membrane rupture at or near term there may be little benefit from using antibiotics unless there is clinical evidence of infection or other risk factors.