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Every month, *DTB* scans sources of information on treatments, disease management and other healthcare topics for key items to bring to our readers' attention and help them keep up to date. To do this, we produce succinct, contextualised summaries of the information concerned. We also include comments on, for example, the strengths of the information, whether it contains anomalies, ambiguities, apparent error or omissions, or whether or how it affects current practice.

Bleeding risk with dabigatran compared with warfarin

An analysis of data from US Medicare patients found that the bleeding risk associated with dabigatran was higher than that with warfarin and also much higher than was reported in trials prior to the drug's approval by the US Food and Drug Administration (FDA). However, the risk of intracranial bleeding was higher among patients taking warfarin.[1]

The retrospective cohort study analysed pharmacy and medical data records from 2010 and 2011 based on a random 5% sample of Medicare beneficiaries. Among people newly diagnosed with atrial fibrillation, the researchers identified 1,302 patients taking dabigatran and 8,102 taking warfarin. A propensity score weighting mechanism was used along with Cox proportional hazards regression models to balance patient characteristics between the groups and to assess bleeding risk. The mean follow-up period was 177 days for dabigatran users and 228 days for warfarin users.

Compared with warfarin, dabigatran was associated with a significantly higher risk of any bleeding event (32.7% vs. 26.5%; hazard ratio [HR] 1.30, 95% CI 1.20 to 1.41), major bleeding (9.0% vs. 5.9%; HR 1.58, 95% CI 1.36 to 1.83) and gastrointestinal bleeding (17.4% vs. 10.0%; HR 1.85, 95% CI 1.64 to 2.07). Only the risk of intracranial haemorrhage was lower in the dabigatran group (0.6% vs. 1.8%; HR 0.32, 95% CI 0.20 to 0.50).

In its guidance on the use of dabigatran, the National Institute for Health and Care Excellence (NICE) concluded that treatment with dabigatran resulted in more gastrointestinal bleeding than warfarin, but also recognised the particular importance of the effects of dabigatran on reducing the risk of haemorrhagic stroke and intracranial haemorrhage for people with atrial fibrillation when compared with warfarin.[2]

Comment: *The relative risks and benefits associated with dabigatran and warfarin in the prevention of stroke in patients with atrial fibrillation are still subject to debate. Ongoing monitoring of dabigatran's safety profile will be important to help guide clinicians in its appropriate place in therapy. Patients should be informed of the benefits, risks and uncertainties associated with the use of both drugs.*

1. Hernandez I et al. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med* [Epub ahead of print] 3 November 2014; DOI:10.1001/jamainternmed.2014.5398.
2. National Institute for Health and Care Excellence, 2014. *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (TA249)* [online]. Available: https://www.nice.org.uk/guidance/ta249 [Accessed 17 December 2014].

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.

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]

1. National Institute for Health and Care Excellence, 2014. *Draft scope—antimicrobial stewardship: systems and processes for effective antimicrobial medicine use* [online]. Available: https://www.nice.org.uk/guidance/gid-antimicrobialstewardship/documents/antimicrobial-stewardship-scope-consultation3 [Accessed 17 December 2014].
2. Hawker JI et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother* 2014; 69: 3423-30.
3. National Institute for Health and Care Excellence, 2014. *Scope—antimicrobial resistance: changing risk-related behaviours in the general population* [online]. Available: http://www.nice.org.uk/guidance/gid-phg89/documents/antimicrobial-resistance-changing-riskrelated-behaviours-in-the-general-population-final-scope2 [Accessed 17 December 2014].
4. National Institute for Health and Care Excellence, 2014. *Advice list* [online]. Available: http://www.nice.org.uk/advice?type=ktt [Accessed 17 December 2014].
5. Minocycline for acne—an update. *DTB* 2009; 47: 7-8.

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/m^2 or more, or between 35 and 40kg/m^2 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 beneficial 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 (HbA_{1c}). 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 HbA_{1c} 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.[3] 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.*

1. National Institute for Health and Care Excellence, 2014. *Obesity: identification, assessment and management of overweight and obesity in children, young people and adults (CG189)* [online]. Available: http://www.nice.org.uk/guidance/cg189/ [Accessed 17 December 2014].
2. Booth H et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *Lancet Diabetes Endocrinol* 2014; 2: 963-8.
3. Himpens JM. Can we safely state that bariatric surgery helps prevent type 2 diabetes? *Lancet Diabetes Endocrinol* 2014; 2: 929-30.

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 Trialists' 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.[1]

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/m^2), 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/m^2 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.*

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: a meta-analysis of randomised trials. *Lancet* [Epub ahead of print] 4 November 2014; DOI:10.1016/S0140-6736(14)61171-5.
2. Franklin SS, Weber MA. Optimum antihypertensive therapy: does adiposity matter? *Lancet* [Epub ahead of print] 4 November 2014; DOI:10.1016/S0140-6736(14)61336-2.

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.*

1. Medicines and Healthcare products Regulatory Agency. Interferon-beta: risk of thrombotic microangiopathy and risk of nephrotic syndrome. *Drug Safety Update* 2014; 8 (3): A1 [online]. Available: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON462300 [Accessed 17 December 2014].

EMA advises on PML fatality linked to dimethyl fumarate

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has warned that a patient with relapsing-remitting multiple sclerosis (MS) who was being treated with dimethyl fumarate (Tecfidera) has died after developing progressive multifocal leukoencephalopathy (PML), a rare viral infection.[1]

This is the first case of PML to be associated with dimethyl fumarate, which is licensed in the UK as a treatment for adults with relapsing-remitting MS.[2] PML is a rare viral brain infection with symptoms that can resemble those of an MS attack. The patient who died had been receiving long-term treatment with dimethyl fumarate and had already developed severe long-lasting lymphopenia. Dimethyl fumarate may decrease lymphocyte counts, with average reductions of 30% seen in placebo-controlled studies, and the Summary of Product Characteristics lists lymphopenia as a common (≥1 in 100 to <1 in 10) adverse effect.[2]

PML has previously been reported in patients taking Fumaderm, a product used in Germany for treating psoriasis. Dimethyl fumarate is the principal fumaric acid ester in Fumaderm. The EMA's Committee for Medicinal Products for Human Use (CHMP) has previously advised that serious and opportunistic infection should be considered an important potential risk for dimethyl fumarate and this will be monitored as part of the risk management plan for dimethyl fumarate.[3]

Comment: *In September 2014,* DTB *reviewed the evidence for dimethyl fumarate in relapsing-remitting MS and highlighted the lack of data on the long-term safety of the drug.[4] Until more is known about the safety of this treatment, we recommend that it should be reserved for patients unable to tolerate first-line treatment with interferon beta or glatiramer. It should also only be prescribed under the direct supervision of clinicians experienced in the management of MS. Use of dimethyl fumarate and any monitoring requirements should be recorded in the patient's primary care medical record, even if the drug is not prescribed or dispensed in primary care.*

1. European Medicines Agency, 2014. *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3–6 November 2014* [online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/11/news_detail_002206.jsp&mid=WC0b01ac058004d5c1 [Accessed 17 December 2014].
2. *Tecfidera 120mg gastro-resistant hard capsules*. Summary of product characteristics, EU. Biogen Idec Ltd, July 2014.
3. European Medicines Agency, 2013. *Assessment report: Tecfidera* [online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002601/WC500162070.pdf [Accessed 17 December 2014].
4. ▼Dimethyl fumarate for relapsing-remitting multiple sclerosis. *DTB* 2014; 52: 105-8.

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.[1] However, questions remain as to whether the reduction in urate translates to fewer acute attacks of gout, less pain or other clinically important outcomes.[2]

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.[3] 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.[4] 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.

Current guidance from the British Society of Rheumatology suggests that initial long-term treatment of recurrent uncomplicated gout should normally be with allopurinol, starting with a dose of 50–100mg/day and increasing by 50–100mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (serum uric acid <300µmol/L) is reached.[5] A European guideline suggests that the goal of urate lowering therapy is achieved by maintaining serum uric acid below 360µmol/L.[6]

Comment: *Although several treatments have been shown to reduce serum urate levels, evidence supporting treatments to reduce the incidence of attacks of gout is limited. The dose of allopurinol should be titrated to achieve the target serum urate level. However, the absolute benefit in reducing attacks of gout remains uncertain.*

1. Allopurinol for chronic gout. *DTB* 1966; 4: 41-2.
2. Underwood M, 2011. *Gout—prevention of recurrence: xanthin oxidase inhibitors* [online]. Available: http://clinicalevidence.bmj.com/x/systematic-review/1120/intervention/sr-1120-i4.html#key-points [Accessed 17 December 2014].
3. Seth R et al. Allopurinol for chronic gout. *Cochrane database Syst Rev* 2014; 10: CD006077. DOI:10.1002/14651858.CD006077.pub3 [Last assessed as up-to-date 14 January 2014].
4. Taylor TH et al. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med* 2012; 125: 1126-34.e7.
5. Jordan KM et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2007; 46: 1372-4.
6. Zhang W et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; 65: 1312-24.

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.[1]

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.[2] 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.[3]

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.*

1. European Medicines Agency, 2014. *Herbal medicines 2004—2014: EMA celebrates ten years of harmonised standards across EU* [online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/11/news_detail_002211.jsp&mid=WC0b01ac058004d5c1 [Accessed 17 December 2014].
2. Herbal medicine—all change. *DTB* 2011; 49: 37.
3. Medicines and Healthcare products Regulatory Agency, 2014. *Herbal medicines regulation: Registered traditional herbal medicines* [online]. Available: http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalmedicinesregulation/RegisteredTraditionalHerbalMedicines/index.htm [Accessed 17 December 2014].

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.[1] 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.[2] The UK Royal College of Obstetricians and Gynaecologists recommends the use of erythromycin for 10 days for pre-term prelabour rupture of membranes.[3] 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.*

1. Wojcieszek AM et al. Antibiotics for prelabour rupture of membranes at or near term. *Cochrane Database Syst Rev* 2014; 10: CD001807. DOI:10.1002/14651858.CD001807.pub2 [Last assessed as up-to-date 31 July 2014].
2. The role of antibacterials in women at risk of preterm birth. *DTB* 2011; 49: 105-8.
3. Royal College of Obstetricians and Gynaecologists, 2010. *Preterm prelabour rupture of membranes. Green-top guideline No. 44* [online]. Available: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg44pprom28022011.pdf [Accessed 17 December 2014].

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