

NEWSLETTER

Supporting the Derbyshire Health Community

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/clinical-guidelines-and-referral-guidelines.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Fentanyl nasal spray / tablet / lozenge	November 2009	BROWN
Saxagliptin	November 2009	BROWN
Mercaptamine	November 2009	RED
Trientine	November 2009	RED
Voriconazole	November 2009	RED
Ulipristal acetate (ellaOne)	November 2009	GREEN (between 72 and 120 hours)
Full Marks solution spray	October 2009	BROWN
Tredaptive (nicotinic acid + laropiprant)	October 2009	BROWN

Management of community acquired pneumonia

The British Thoracic Society has published updated guidance on the management of community acquired pneumonia (CAP) in adults¹. This updates the 2004 guidance (see www.npci.org.uk/blog/?=674).

Key messages for community-based health professionals

- Clinical judgement, supported by the CRB65 score (see below), should be used to decide whether to treat patients at home or in hospital. When deciding on home treatment, the patient's social circumstances and wishes must be taken into account in all instances.
- Patients in the community should be reviewed after 48 hours, or earlier if clinically indicated.
- Patients with suspected CAP should be advised to rest, drink plenty of fluids and not to smoke.
- Pleuritic pain should be managed with simple analgesia such as paracetamol.

- Pulse oximetry, should be considered, and should be available in the out-of-hours setting and in all locations where emergency oxygen is used.
- Amoxicillin 500mg three times daily is the preferred antibiotic, with doxycycline or clarithromycin as alternatives, for example in those patients hypersensitive to penicillins.
- Microbiological investigations are not recommended routinely but may be appropriate in certain circumstances. For example, examination of sputum should be considered for patients who do not respond to empirical antibiotic therapy.
- In patients with suspected severe, life-threatening CAP referred to hospital, GPs should administer antibiotics in the community: either benzylpenicillin 1.2g intravenously or amoxicillin 1g orally.

Assess the CRB-65 score for all people diagnosed with pneumonia:

One point is awarded for each of the following features:

- **C**onfusion – recent.
- **R**espiratory rate 30 breaths/min or greater.
- **B**lood pressure – systolic of 90 mmHg or less or a diastolic of 60 mmHg or less.
- **65** years of age or older.

Severity assessment of CAP in patients seen in the community

- For all patients, clinical judgement supported by the CRB65 score should be applied when deciding whether to treat at home or refer to hospital.
- Patients who have a CRB65 score of 0 are at low risk of death and do not normally require hospitalisation for clinical reasons.
- Patients who have a CRB65 score of 1 or 2 are at increased risk of death, particularly with a score of 2, and hospital referral and assessment should be considered.
- Patients who have a CRB65 score of 3 or more are at high risk of death and require urgent hospital admission.
- When deciding on home treatment, the patient's social circumstances and wishes must be taken into account in all instances.

1. Thorax 2009; 64 (Suppl III): iii1-iii55

More on aspirin for primary prevention

The MHRA have pointed out that aspirin is not licensed for primary prevention, only for secondary prevention¹. In 'Drug Safety Update', they also highlight a relevant randomised controlled trial recently presented at a meeting in Spain:

"The Aspirin for Asymptomatic Atherosclerosis trialists at the University of Edinburgh recently reported the outcome of their randomised study at the European Society of Cardiology Congress in Barcelona, Spain.

Between 1998 and 2001, 3350 people in Scotland were recruited who were asymptomatic but at high risk of vascular disease. Participants were randomly assigned aspirin (100 mg/day) or matching placebo, with a mean follow-up of 8.2 years. The primary endpoint was a composite of initial coronary event or stroke or revascularisation (non-fatal or fatal).

For the primary endpoint, no significant difference was found between those allocated aspirin or placebo (181 events vs 176 events; hazard ratio 1.03 [95% CI 0.84-1.27]). An initial event of major haemorrhage requiring hospital admission occurred in 34 (2%) patients in the aspirin group and in 20 (1.2%) in the placebo group (hazard ratio 1.71 [0.99-2.97]). This study therefore found no benefit of aspirin use and an increased risk of serious bleeding in asymptomatic individuals."

A Swedish record linkage study suggests that aspirin increases mortality when given to people with diabetes for primary prevention². All diabetic patients (n=58,465) in the Västra Götaland region from 1/7/05 to 30/6/06 were followed up with respect to bleeding until 31/10/06, and mortality until 31/12/06. When 19 confounding factors (diseases and interventions) were assessed, aspirin significantly increased the risk of death in diabetic patients without cardiovascular disease by 17% at 50 years of age and increased successively to 29% at the age of 85. In

contrast aspirin tended to decrease mortality among elderly diabetic patients with cardiovascular disease. Theoretical calculations indicated that aspirin caused 107 excess deaths among diabetic patients without CV disease and prevented 164 deaths among diabetic patients with CV disease. Aspirin also increased the risk of serious bleeding by 46% in diabetic patients without CV disease.

The authors state “we recommend that all diabetic patients should avoid aspirin, unless a clear indication is present (i.e. clinical cardiovascular disease)”.

These studies add to the growing evidence base that aspirin should not be used for primary prevention. **JAPC recommends that aspirin should only be recommended/prescribed for those people with existing symptomatic vascular disease.** However, as mentioned in the July 2009 issue, JAPC does support the ASCEND trial, which is currently recruiting patients.

1. [Drug Safety Update](#) Volume 3, Issue 3, October 2009
2. Pharmacoeconomics and Drug Safety 2009; DOI:10.1002/pds.1828

Smoking and clinically significant interactions

In a ‘Hot topic’ article, the MHRA highlights how a patient’s smoking status may affect prescribing decisions due to clinically significant interactions with medicines¹.

Pharmacokinetic interactions

Polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke are potent inducers of the hepatic cytochrome P450 (CYP) isoforms 1A1, 1A2, and possibly 2E1. Of these, 1A2 is the most important. Enzyme induction results in increased metabolism of substrates. Thus larger doses of CYP1A2 substrates may be required to ensure efficacy in people who smoke, and a reduction in dose may be needed during smoking cessation to prevent side effects.

Many commonly used medicines are substrates for CYP1A2: theophylline; fluvoxamine; caffeine; coumarins, including warfarin; and the antipsychotics clozapine and olanzapine. However, not all possible drug-smoking interactions are clinically significant. Important factors that determine the clinical significance of an interaction in smokers are:

- The extent to which the medicine is metabolised by CYP1A2 – ie, the fractional clearance. The interaction will be most significant when CYP1A2 is the main elimination pathway.
- The therapeutic index of the medicine metabolised for CYP1A2. For example, for a narrow therapeutic index drug such as theophylline, small changes in drug concentration may have significant clinical effects.

It is also important to remember that it takes about 1 week for the effect of the induction of CYP1A2 to wear off after smoking cessation, and thus dose adjustment is not usually necessary in situations where there is temporary smoking cessation (eg, during acute hospital stay).

Pharmacodynamic interactions

Pharmacodynamic interactions between medicines and smoking or smoking cessation are attributable to the effects of tobacco smoke, including nicotine. The most clinically significant pharmacodynamic interactions with smoking include: hormonal contraceptives (increased risk of cardiovascular disease); inhaled corticosteroids (efficacy may be reduced in smokers with asthma); and beta-blockers (nicotine activation of sympathetic nervous system may counteract effect).

Furthermore, stopping smoking, with or without the aid of drug treatment, may be associated with psychiatric symptoms, and stopping smoking may also exacerbate an underlying psychiatric condition.

Advice for healthcare professionals:

Clear guidelines for clinical practice are not available. We (the MHRA) would thus suggest the following general approach should be taken:

- On starting CYP1A2 substrates:
 - Obtain smoking status
 - Determine clinical significance of any potential interaction

- Monitor efficacy and side effects
 - Adjust dose if necessary
 - Monitor smoking status and advise patients to seek advice from doctor if smoking status is to change
- During smoking cessation:
 - Find out what medicines the patient is taking
 - Determine clinical significance of any potential interaction
 - Monitor for side effects
 - Adjust dose if necessary

The most important medicines to consider in those who smoke, or who are trying to quit, include theophylline, olanzapine, clozapine, caffeine, and warfarin.

1. [Drug Safety Update](#) Volume 3, Issue 3, October 2009

Bisphosphonates and osteonecrosis of the jaw

The EMEA has completed a review on the risk of osteonecrosis (death of bone tissue) of the jaw associated with the use of bisphosphonates¹. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there is an increased risk of osteonecrosis of the jaw but further studies should be carried out to better identify the factors that increase the risk and the measures needed to minimise it.

What are the conclusions of the CHMP?

Based on the evaluation of the data and the scientific discussion within the Pharmacovigilance Working Party and the Committee, the CHMP concluded on the definition of osteonecrosis of the jaw related to bisphosphonates. This is defined as an area of exposed or dead bone in the jaw that has lasted for more than eight weeks, in a patient who has been exposed to a bisphosphonate and has not had radiation therapy on the jaw.

Regarding the mechanisms through which bisphosphonates may cause osteonecrosis of the jaw, the Committee noted that several mechanisms have been suggested in published literature. However, further studies are required and a suitable experimental model should be developed.

When looking at all cases of osteonecrosis of the jaw, the Committee noted that:

- the risk of osteonecrosis of the jaw is greater in cancer patients receiving intravenous bisphosphonates than in patients being treated for non-cancer indications, such as osteoporosis;
- the risk appears to be low in patients taking bisphosphonates by mouth.

Although the most important risk factors seem to be the potency of the bisphosphonate used, the dose and how it is given, the CHMP concluded that further research on risk factors is needed and that a European registry collecting information on cases of osteonecrosis of the jaw could be helpful.

Finally, the Committee concluded that further data are needed to determine the precise measures that could minimise the risk of osteonecrosis of the jaw, including looking at how intravenous bisphosphonates should be given (such as their dose, how often they are given and for how long), and looking into the risk of osteonecrosis of the jaw in patients taking bisphosphonates by mouth for long periods. The CHMP noted that other possible risk factors for developing osteonecrosis of the jaw should be considered, such as gender, genetic factors, smoking and other treatments or diseases that the patient has, as well as the type of cancer a patient has and how long they have had it. Finally, the Committee concluded that information on the known and potential risks of osteonecrosis of the jaw with bisphosphonates should be clearly communicated to healthcare professionals and to patients.

What are the recommendations for patients, dentists and prescribers?

- Before taking any decisions concerning treatment with bisphosphonates, prescribers should take the risks and benefits for each individual patient into account.
- Prescribers should ensure that patients with cancer go to their dentist for a check-up and find out if they need any dental treatment before they start taking a bisphosphonate. They should also ensure that patients who do not have cancer go to their dentist for a check-up if their dental health is poor.

- During treatment with bisphosphonates, patients should maintain good oral hygiene, go for routine dental check-ups and report any symptoms in the mouth such as loose teeth, pain or swelling.
- Dentists should be aware of the risks in patients taking bisphosphonates and should keep dental treatment as conservative and preservative as possible.
- It is essential that prescribers, dentists and patients work together to manage the risk of osteonecrosis of the jaw.
- Patients who have any questions or concerns should speak to their doctor or dentist.

1. www.emea.europa.eu/pdfs/human/opinion/Q&A_Bisphosphonates_29247509en.pdf

Inhaled corticosteroids in COPD and the risk of pneumonia

The RCTs TORCH¹ and INSPIRE², two meta-analyses^{3,4}, and a case-control study⁵ all show increased risk of pneumonia with the use of inhaled corticosteroids (ICS) in COPD. The ICS predominantly used in these studies was fluticasone. A recent meta-analysis suggests that budesonide does not increase pneumonia risk in COPD patients⁶.

The meta-analysis pooled patient data from seven clinical trials of inhaled budesonide (320-1280 mcg/day). A total of 7042 patients were included, of whom 3801 were on inhaled budesonide and 3241 were on control treatment. They found no significant difference between treatment groups for the occurrence of pneumonia as an adverse event or for time to pneumonia over 12 months.

On the basis of this study, budesonide could be considered a safer option than fluticasone with respect to the risk of pneumonia. However, the NPC recommends that this study should not change practice⁷. They advise that when considering adding an ICS to treatment regimes for people with COPD, prescribers should still consider, and discuss with patients, the potential increased risk of pneumonia, as well as osteoporosis and other side effects.

The bigger question is perhaps not which ICS, but whether an ICS should be used at all in COPD management?

1. N Engl J Med 2007; 356:775-89
2. Am J Respir Crit Care Med 2008; 117:19-26
3. JAMA 2008; 300:2407-16
4. Arch Intern Med 2009; 169:219-29
5. Am J Respir Crit Care Med 2007; 176:162-6
6. Lancet 2009; 374:712-19
7. www.npci.org.uk/blog/?p=659

Seretide/Symbicort in COPD

The evidence that a combination of long-acting beta-agonist (LABA) with inhaled corticosteroid (ICS) is superior to LABA monotherapy in the management of COPD has been inconclusive. A recently published systematic review was specifically undertaken to assess the safety and effectiveness of the use of LABA/ICS in COPD patients compared with LABA monotherapy¹. Two specific questions were identified: (1) what are the risks of adding an ICS to a LABA compared with LABA monotherapy and (2) does therapy with LABA/ICS provide significant clinical benefits compared with LABA monotherapy?

Eighteen randomised controlled trials fulfilled the inclusion criteria, five of which were unpublished. Seretide was compared with salmeterol in 14 trials and Symbicort with formoterol in 4. The mean age of patients was 64 years and they had moderate-to-very severe COPD exacerbations, with an average baseline FEV₁ of 40% of predicted normal values.

Compared with LABA monotherapy, LABA/ICS combination did not significantly decrease the risk of severe COPD exacerbations (requiring hospitalisation or withdrawal) and was not associated with a significant decrease in overall mortality, respiratory deaths, or cardiovascular mortality. There was a small reduction in the risk of a moderate exacerbation (requiring systemic corticosteroids or antibiotic use) with an NNT of 31 (95% CI 20 to 93). The authors comment that the 16% relative decrease seen in the rate of moderate exacerbations was smaller than the suggested threshold value of 22% for clinical significance. LABA/ICS showed a statistically significantly greater reduction in the SGRQ total score (WMD of -1.88) but this did not reach the clinically important minimum difference of a 4-point decrement.

The use of LABA/ICS was associated with significantly increased rates of pneumonia with a NNH of 40 [CI 26 to 72] (63% increase in relative risk), viral respiratory infections (22% increase in RR), and oropharyngeal candidiasis (59% increase in RR) compared with use of LABA alone. In the discussion, the authors speculate that ICS may increase the risk of pneumonia due to their immunosuppressive effects. They point out that inhaled fluticasone at doses of 1,000mcg/day exerts effects on serum cortisol levels that are equivalent to 10mg/day of oral prednisolone, a dose that may double the risk of pneumonia in patients with arthritis.

The authors highlight that this is the largest systematic review designed to evaluate the safety and efficacy of the regular use of LABA/ICS compared to LABA alone in moderate-to-very severe COPD. They conclude that combination therapy with LABA/ICS presents a borderline statistical and limited clinical significance compared with LABA monotherapy. Moreover, combination therapy offers no significant additional survival benefit and increased the risk of serious adverse effects. There is widespread prescribing of LABA/ICS in COPD – do these patients now need reviewing?

Other evidence shows us that tiotropium is the preferred long-acting bronchodilator in COPD patients as it has a greater effect on reducing moderate and severe exacerbations than LABAs. The onus is on prescribers to follow the JAPC algorithm for drug use in COPD, in order to maximise health gain in the most cost-effective manner. Only add ICS to a long-acting bronchodilator if the criteria are met (see page 8).

1. Chest 2009; 136:1029-38

Hypertension in the elderly

A Cochrane review has quantified the antihypertensive drug effect on mortality and morbidity and adverse effects in people aged 60 years and older with mild to moderate systolic or diastolic hypertension¹.

Main results

Fifteen trials (24,055 subjects \geq 60 years) with moderate to severe hypertension were identified. These trials mostly evaluated first-line thiazide diuretic therapy for a mean duration of treatment of 4.5 years. Treatment reduced total mortality, RR 0.90 (0.84, 0.97); event rates per 1000 participants reduced from 116 to 104. Treatment also reduced total cardiovascular morbidity and mortality, RR 0.72 (0.68, 0.77); event rates per 1000 participants reduced from 149 to 106. In the three trials restricted to persons with isolated systolic hypertension the benefit was similar. In very elderly patients \geq 80 years the reduction in total cardiovascular mortality and morbidity was similar RR 0.75 [0.65, 0.87] however, there was no reduction in total mortality, RR 1.01 [0.90, 1.13]. Withdrawals due to adverse effects were increased with treatment, RR 1.71 [1.45, 2.00].

Authors' conclusions

Treating healthy persons (60 years or older) with moderate to severe systolic and/or diastolic hypertension reduces all cause mortality and cardiovascular morbidity and mortality. The decrease in all cause mortality was limited to persons 60 to 80 years of age.

1. Musini VM et al. *Cochrane Database of Systematic Reviews* 2009, Issue 4

Statins in people with renal impairment

Dyslipidaemia is a common complication of chronic kidney disease (CKD) and it contributes to the high cardiovascular morbidity and mortality in CKD patients. What is the evidence base for lipid lowering in CKD patients? A UKMi Q&A has considered the evidence base for statins in people with renal impairment (RI)¹.

Summary

- Dyslipidaemia is a common complication of CKD and contributes to high CV morbidity and mortality of CKD patients. The results of studies of low density lipoprotein-cholesterol (LDL-C) reduction in patients with CKD have been conflicting. Some observational studies in dialysis patients have shown a clear, linear relation between LDL-C and CV end points, whereas others have not.
- RCTs of simvastatin, pravastatin, fluvastatin and atorvastatin have included patients with varying degrees of RI (CKD stages 2-5 or CrCl 30-90 mL/min). There is evidence of beneficial effects on cardiovascular outcomes and renal function. There is also some evidence for some statins of increased risk of adverse effects. Prospective RCTs evaluating the efficacy and long-term safety of statins in reducing CV events and death in patients with established CKD are in progress.

- NICE guidance on CKD advises the use of statins for the primary prevention of CV disease in the same way as in people without CKD. NICE also advises that statins should be offered for the secondary prevention of CV disease irrespective of baseline lipid values in patients with CKD.
- There is insufficient evidence to support the routine use of statins to prevent or ameliorate progression of CKD.
- All UK licensed statins can be used in people with CKD stages 1-4. Individual statins have been shown to be effective at lower levels of renal function, but there are no comparative studies of statins in CKD.
- Advice on dosing is available in standard sources although there is some inconsistency in their recommendations. It would be reasonable to dose conservatively at lower levels of renal function with close monitoring of desired effect on lipid levels and of adverse effects.

Limitations

The use of statins in transplant patients and clinically important drug interactions with statins in patients with RI, are not discussed here. A detailed discussion of the use of statins in renal replacement therapy is outside the scope of this review. Whilst some of the trials reported adverse effects, this has not been reviewed in detail.

An 'uncertainties page' article in the BMJ² makes the following points:

- Whether the association between CKD and CV disease is causal remains unknown.
- The benefits of lowering lipid levels in the general population cannot be extrapolated to patients with CKD.
- The LDL-cholesterol level is a poor surrogate for CV risk among patients with CKD.
- Patients with CKD who also have established CV disease should be prescribed statins.
- The uncertainties should be discussed with patients before prescriptions for statins are issued for primary prevention.

1. [UKMi Q&A 125.2](#)

2. BMJ 2009; 339: 803-4

Heart failure with atrial fibrillation

Previous studies have consistently shown no benefit for rhythm control over rate control in patients with atrial fibrillation (AF), provided they were anticoagulated. A new study investigated an important subset of patients with AF and who also have left ventricular dysfunction¹.

This was a multicentre, randomised trial comparing the maintenance of sinus rhythm (rhythm control) with control of the ventricular rate (rate control) in patients with a left ventricular ejection fraction of 35% or less, symptoms of congestive heart failure, and a history of AF. The primary outcome was the time to death from cardiovascular causes.

A total of 1376 patients were enrolled and 27% in the rhythm-control group died from CV causes, as compared with 25% in the rate-control group (HR 1.06 [95% CI 0.86 to 1.30];p=0.59). Secondary outcomes were similar in the two groups, including death from any cause, stroke and worsening heart failure. There were also no significant differences favouring either strategy in any pre-defined sub-group. The authors conclude that in patients with AF and congestive heart failure, a routine strategy of rhythm control does not reduce the risk of death from CV causes, as compared with a rate-control strategy.

The authors of the accompanying editorial² state "it is difficult to support a primary approach of rhythm control that relies on anti-arrhythmic drugs in any patient with atrial fibrillation, including those with heart failure. Even for symptomatic patients, it seems prudent first to attempt to eliminate symptoms with drugs that control the ventricular rate and then to consider therapy with anti-arrhythmic drugs only if symptoms persist. Anticoagulation should be prescribed to all appropriate patients on the basis of the CHADS₂ score".

A review of AF and heart failure³ recommends that beta-blockers should be the first choice for rate control in patients with heart failure and AF as they may both control the ventricular response to AF and improve survival in patients with heart failure. Digoxin may be useful as an adjunct therapy to beta-blockers in these patients.

1. N Engl J Med 2008; 358:2667-77

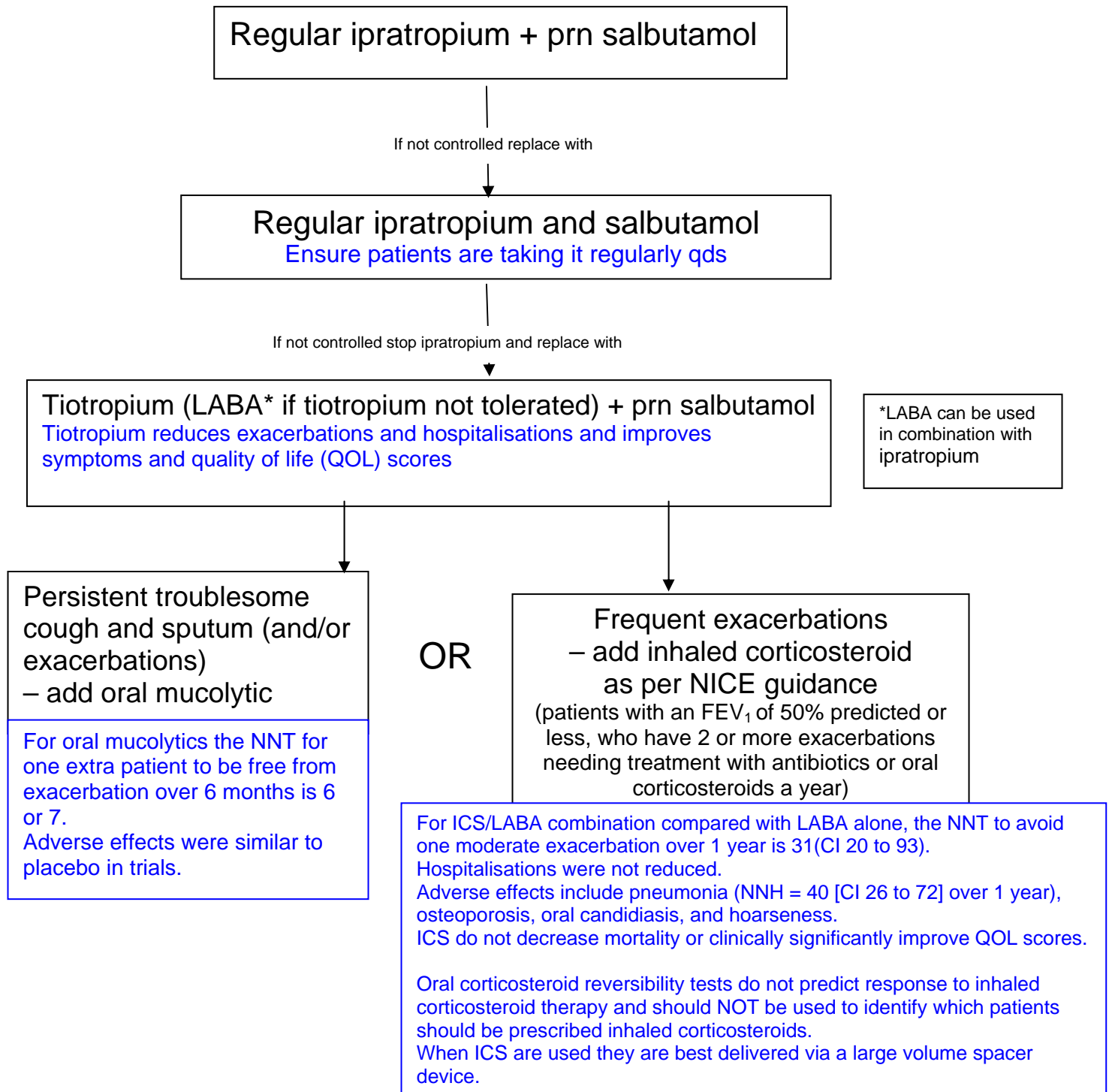
2. N Engl J Med 2008; 358:2725-7

3. Circulation 2009; 119:2516-25

Algorithm for drug use in COPD

Airflow obstruction must be present before using bronchodilators

When prn salbutamol is insufficient -



NNT is the number-needed-to-treat i.e. how many patients have to be treated for how long for one of them to benefit. NNH is the number-needed-to-harm i.e. how many patients have to be treated for how long for one of them to have an adverse event.

Which option would you choose – oral mucolytic or inhaled corticosteroid?