Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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THE MANAGEMENT OF SEVERE PRE-ECLAMPSIA/ECLAMPSIA

This is the first combined guideline for the management of severe pre-eclampsia and eclampsia. It replaces the previous guideline entitled *Management of Eclampsia*, published in November 1996 and reviewed in July 1999. Mild pre-eclampsia is not considered.

1. Purpose and scope

Severe pre-eclampsia and eclampsia are relatively rare but serious complications of pregnancy, with around 5/1000 maternities in the UK suffering severe pre-eclampsia[1] and 5/10 000 maternities suffering eclampsia.[2] In eclampsia, the case fatality rate has been reported as 1.8% and a further 35% of women experience a major complication.[2] The Confidential Enquiries into Maternal Deaths persistently show substandard care in a significant percentage of the deaths.[3] The aim of this guideline is to standardise the approach to the management of severe pre-eclampsia and eclampsia in the immediate pre- and post- delivery interval in order to improve the outcome for the mother and child. It is envisaged that the guideline will be adapted for use at a local or regional level.

2. Introduction and background

Eclampsia is defined as the occurrence of one or more convulsions superimposed on pre-eclampsia.[4] Pre-eclampsia is pregnancy-induced hypertension in association with proteinuria (> 0.3 g in 24 hours) ± oedema and virtually any organ system may be affected.[5] Severe pre-eclampsia is variously defined.[1,4] There is consensus that severe hypertension is confirmed with a diastolic blood pressure ≥ 110 mmHg on two occasions or systolic blood pressure ≥ 170 mmHg on two occasions and that, together with significant proteinuria (at least 1 g/litre), this constitutes severe pre-eclampsia. There is less agreement about the degree of moderate hypertension, which together with other symptoms or signs constitutes severe pre-eclampsia. A diastolic blood pressure ≥ 100 mmHg on two occasions and significant proteinuria with at least two signs or symptoms of imminent eclampsia will include many women with severe pre-eclampsia, although it is to be remembered that some women who present with eclampsia have no prodromal signs.[2,4] An important variant of severe pre-eclampsia is the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count). Ultimately, as many clinical criteria are subjective, women should be managed according to a careful clinical assessment rather than relying on overly precise criteria. Each unit or region may wish to produce a locally adapted approach to implementation of the guideline addressing blood pressure monitoring, including the use of mean arterial pressure, thresholds for the use of magnesium sulphate and preferred first- and second-line anti-hypertensive agents.

Clinical features of severe pre-eclampsia (in addition to hypertension and proteinuria) are:

- symptoms of severe headache
- visual disturbance
- epigastric pain and/or vomiting
- signs of clonus
- papilloedema
- liver tenderness
- platelet count falling to below 100 x 10^6/l
- abnormal liver enzymes (ALT or AST rising to above 70 iu/l)
- HELLP syndrome.

The Confidential Enquiries reveal that deaths from pre-eclampsia/eclampsia have been reduced from 11.9/million maternities in 1985–1987 to 7.0/million maternities in 2000–2002, when there were 14 deaths.[3] Nine women died from cerebral causes, with substandard care in 50% of cases. Therefore, there is yet room for improvement. In particular, the control of hypertension and the management of fluid balance were highlighted.[3] The Yorkshire series[1] had no deaths in over 1000 cases of severe pre-eclampsia and eclampsia and supports the view that a standardised care package for pre-eclampsia over delivery, with proven interventions, may reduce the rate of eclampsia.

3. Identification and assessment of evidence

The Cochrane Library and the Cochrane Register of Controlled Trials were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. Recent consensus documents were also studied, including an RCOG Study Group proceedings.[6] A search of MEDLINE and PUBMED (electronic databases) from 1966 to 2005 was also carried out. Search words included: 'pregnancy', 'hypertension', 'pre-eclampsia', 'eclampsia' and 'toxaemia'.

4. Assessment and diagnosis

4.1 Assessment of the woman

How should women be assessed at initial presentation?

Although the classification of severity is primarily based on the level of blood pressure and the presence of proteinuria, clinicians should be aware of the potential involvement of other organs when assessing maternal risk, including placental disease with fetal manifestations. C

Senior obstetric and anaesthetic staff and experienced midwives should be involved in the assessment and management of women with severe pre-eclampsia and eclampsia. ✓

Some women will present with convulsions, abdominal pain or general malaise. In these cases, pre-eclampsia should always be considered and the blood pressure taken and the urine analysed. Clinical symptoms are important components of worsening disease, particularly headache and abdominal pain.[1] However, increasing oedema is not in itself a sign that should determine management. Maternal tendon reflexes, although useful to assess magnesium toxicity, are not of value in assessing the risk of convulsion, although the presence of clonus may be. Continuous oxygen saturation monitoring with a pulse oximeter is valuable, as it will often give early signs of pulmonary oedema.

Evidence level IV

How should the blood pressure be taken?

When taking blood pressure, the woman should be rested and sitting at a 45-degree angle. The blood pressure cuff should be of the appropriate size and should be placed at the level of the heart. Multiple readings should be used to confirm the diagnosis. Korotkoff phase 5 is the appropriate measurement of diastolic blood pressure. The method used should be consistent and documented. A

Automated methods need to be used with caution, as they may give inaccurate blood pressure readings in pre-eclampsia. B

It is important to standardise methods of blood pressure assessment with the woman appropriately positioned. The cuff should be of an appropriate size and should be placed at the level of the heart. Multiple readings are required to accurately assess blood pressure because of natural variation. Korotkoff phase 5 is the appropriate method for diastolic blood pressure.[7] Concerns have been raised about the use of automated methods. Automated methods can systematically underestimate

Evidence level Ib and level IIb

particularly the systolic blood pressure.[3] It has been suggested that mercury sphygmomanometers should be used to establish baseline blood pressure as a reference unless the automated machine has been validated in pregnancy.[8,9] However, many units no longer have mercury sphygmomanometers and so a baseline check with another validated device would be an alternative.

Evidence level Ib and level IIb

How should proteinuria be measured?

The usual screening test is visual dipstick assessment. A two plus dipstick measurement can be taken as evidence of proteinuria but ideally a more accurate test (either a spot protein creatinine ratio or ideally a 24-hour urine collection) is required to confirm this.

C

While it has to be acknowledged that there is poor predictive value from urine dipstick testing,[10] approximate equivalence is 1+ = 0.3 g/l, 2+ = 1 g/l and 3+ = 3 g/l. False negative as well as false positive rates are recorded with the use of visual dipstick assessment.[10–12] Problems can be reduced by training. An automatic dipstick reader can overcome some of the observer error found with urinary dipsticks but these are not routinely available. Newer techniques such as protein/creatinine ratios have not been fully evaluated but may be a valid alternative. A level of 0.03 g/mmol appears to be equivalent to 0.3 g/24 hours.[6] In view of the high false positive rates with dipsticks, laboratory testing, usually by 24-hour urine collection, is recommended to confirm significant proteinuria, unless the clinical urgency dictates immediate delivery.[6]

Evidence level IV

How should the woman be monitored?

The blood pressure should be checked each 15 minutes until the woman is stabilised and then every 30 minutes in the initial phase of assessment. The blood pressure should be checked 4-hourly if a conservative management plan is in place and the woman is stable and asymptomatic.

✓

Assessment of the woman requires a full blood count, liver function and renal function tests. These should be repeated at least daily when the results are normal but more often if the clinical condition changes or if there are abnormalities.

✓

Clotting studies are not required if the platelet count is over 100 x 10^6/l.

✓

Close fluid balance with charting of input and output is essential. A catheter with an hourly urometer is advisable in the acute situation, especially in the immediate postpartum period.

✓

In pre-eclampsia, there can be a rise in uric acid that correlates with poorer outcome for both mother and baby.[13,14] This rise confirms the diagnosis of pre-eclampsia and confers an increased risk to the mother and baby but the levels, in themselves, should not be used for clinical decision-making. Renal function is generally maintained in pre-eclampsia until the late stage unless HELLP syndrome develops.[15,16] If creatinine is found to be elevated early in the disease process, underlying renal disease should be suspected. In severe disease, serum creatinine can be seen to rise and is associated with a worsening outcome[16] but renal failure is now uncommon in pre-eclampsia in the developed world[3] and when it does occur it is usually associated with haemorrhage, HELLP syndrome or sepsis.

A falling platelet count is associated with worsening disease and is itself a risk to the mother.[17] However, it is not until the count is less than 100 x 10^6/l that there may be an associated coagulation abnormality.[18] Other parameters, such as platelet volume, may be of benefit but are as yet unproven.[19–21] A platelet count of less than 100 should be a consideration for delivery. An AST level of above 75 iu/l is seen as significant and a level above 150 iu/l is associated with increased morbidity to the mother.[22] A diagnosis of HELLP syndrome needs confirmation of haemolysis, either by LDH levels, as commonly assessed in the USA, or by blood film to look for fragmented red cells. An AST or ALT level of above 70 iu/l is seen as significant and a level above 150 iu/l is associated with increased morbidity to the mother.[13] The platelet count would have to be below 100 x 10^6 to support the diagnosis.

4.2 How should the fetus be assessed?

In the acute setting, an initial assessment with cardiotocography should be undertaken. This gives information about fetal wellbeing at that time but does not give any predictive information. **B**

Women in labour with severe pre-eclampsia should have continuous electronic fetal monitoring. **B**

If conservative management is planned then further assessment of the fetus with ultrasound measurements of fetal size, umbilical artery Doppler and liquor volume should be undertaken. Serial assessment will allow timing of delivery to be optimised. **A**

The value of Doppler in other fetal vessels has yet to be clarified. **C**

Cardiotocography (non-stress test) is the mainstay of fetal monitoring in most units. It can be repeated regularly and easily without need of expensive equipment or highly skilled personnel. It gives information concerning fetal wellbeing at that time but has little predictive value. If the woman is in labour then continuous electronic fetal monitoring is appropriate.[23]

Evidence level III

The main pathology affecting the fetus, apart from prematurity, is placental insufficiency leading to intrauterine growth restriction (IUGR). IUGR occurs in around 30% of pre-eclamptic pregnancies. Ultrasound assessment of fetal size, at the time of the initial presentation with hypertension, is a valuable one-off measurement to assess fetal growth. Growth restriction is usually asymmetrical so measurement of the abdominal circumference is the best method of assessment.[24] Reduced liquor volume is also associated with placental insufficiency and fetal growth restriction. Serial estimations of liquor volume can detect fetal compromise. Randomised trials have shown that investigation with umbilical artery Doppler assessment, using absent or reversed-end diastolic flow, improves neonatal outcome[25] and serial investigations of this and other fetal vessels can be used to follow pregnancies under treatment and optimise delivery.[24]

Evidence level Ia

5. Management of severe pre-eclampsia

The management of severe pre-eclampsia is based on careful assessment, stabilisation, continued monitoring and delivery at the optimal time for the mother and her baby. This means controlling blood pressure and if necessary convulsions. Senior obstetric and anaesthetic staff and experienced midwives should be involved.

5.1 How should we control the blood pressure?

Antihypertensive treatment should be started in women with a systolic blood pressure over 160 mmHg or a diastolic blood pressure over 110 mmHg. In women with other markers of potentially severe disease, treatment can be considered at lower degrees of hypertension. **C**

Labetalol, given orally or intravenously, nifedipine given orally or intravenous hydralazine can be used for the acute management of severe hypertension. **A**

In moderate hypertension, treatment may assist prolongation of the pregnancy. Clinicians should use agents with which they are familiar. **C**

Atenolol, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor-blocking drugs (ARB) and diuretics should be avoided. **B**

Nifedipine should be given orally not sublingually. ✓

Labetalol should be avoided in women with known asthma. ✓

There has been a general consensus that blood pressure greater than 170/110 mmHg requires treatment in the maternal interest, although this is not supported by randomised trials.[13] There is, however, a clear rationale supported by the desire to prevent the known risk of vascular damage due to uncontrolled hypertension. The Confidential Enquiries into Maternal Deaths have suggested a lower threshold of 160 mmHg systolic.[3] The preferred therapeutic agents are labetalol, nifedipine or hydralazine. Labetalol has the advantage that it can be given initially by mouth in severe hypertension and then, if needed, intravenously. A review has suggested that hydralazine may be less preferable, although the evidence is not strong enough to preclude its use.[26] There is also a consensus that, if the blood pressure is below 160/100 mmHg, there is no immediate need for antihypertensive therapy. An exception may be if there are markers of potentially more severe disease, such as heavy proteinuria or disordered liver or haematological test results. Since, in this situation, alarming rises in blood pressure may be anticipated, anti-hypertensive treatment at lower blood pressure levels may be justified.[3]

Evidence level Ia *(but small trials of mixed quality)*

There is continuing debate concerning women with a blood pressure between 100 mmHg and 110 mmHg diastolic. Maternal treatment is associated with a reduction of severe hypertensive crises and a reduction in the need for further antihypertensive therapy; however, there appears to be a small reduction in infant birth weight.[5] With treatment a prolongation of pregnancy of an average of 15 days is possible as long as there is no other reason to deliver.[5]

Methyldopa and labetalol were the most commonly used therapies in the UK.[27] Methyldopa has been proven safe in long term follow-up of the delivered babies,[28] while some studies have suggested some benefits of labetalol.[29] Doctors should use the drug with which they are familiar. Atenolol is associated with an increase in fetal growth restriction. ACE inhibitors and ARBs would appear to be contraindicated because of unacceptable fetal adverse effects. Diuretics are relatively contraindicated for hypertension and should be reserved for pulmonary oedema.

Evidence level III

5.2 How should seizures be prevented?

Magnesium sulphate should be considered for women with pre-eclampsia for whom there is concern about the risk of eclampsia. This is usually in the context of severe pre-eclampsia once a delivery decision has been made and in the immediate postpartum period. In women with less severe disease the decision is less clear and will depend on individual case assessment. **A**

The MAGPIE study has demonstrated that administration of magnesium sulphate to women with pre-eclampsia reduces the risk of an eclamptic seizure.[30] Women allocated magnesium sulphate had a 58% lower risk of an eclamptic seizure, (95% CI 40–71%). The relative risk reduction was similar regardless of the severity of pre-eclampsia. More women need to be treated when pre-eclampsia is not severe (109) to prevent one seizure when compared with severe pre-eclampsia (63). When conservative management of a woman with severe hypertension and a premature fetus is made it would be reasonable not to treat until the decision to deliver has been made. If magnesium sulphate is given, it should be continued for 24 hours following delivery or 24 hours after the last seizure, whichever is the later, unless there is a clinical reason to continue. When magnesium sulphate is given, regular assessment of the urine output, maternal reflexes, respiratory rate and oxygen saturation is important.

Evidence level Ia

5.3 How should seizures be controlled?

The principles of management should follow the basic principles of airway, breathing and circulation. **C**

Magnesium sulphate is the therapy of choice to control seizures. A loading dose of 4 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure. **A**

Recurrent seizures should be treated with either a further bolus of 2 g magnesium sulphate or an increase in the infusion rate to 1.5 g or 2.0 g/hour. **A**

Do not leave the woman alone but call for help, including appropriate personnel such as the anaesthetist and senior obstetrician. Ensure that it is safe to approach the woman and aim to prevent maternal injury during the convulsion. Place the woman in the left lateral position and administer oxygen. Assess the airway and breathing and check pulse and blood pressure. Pulse oximetry is helpful.[1,31] Once stabilised, plans should be made to deliver the woman but there is no particular hurry and a delay of several hours to make sure the correct care is in hand is acceptable, assuming that there is no acute fetal concern such as a fetal bradycardia. The woman's condition will always take priority over the fetal condition.

Evidence level IV

Magnesium sulphate is the therapy of choice and diazepam and phenytoin should no longer be used as first-line drugs.[32] The intravenous route is associated with fewer adverse effects. Although a trial in Bangladesh[33] has shown no significant reduction in recurrent seizures when using only a loading dose as opposed to the standard regimen, further studies would be needed before this practice could be recommended, as this finding may relate to body size. The seizure rates were 3.96% in loading versus 3.51% in standard regimen ($P > 0.05$). Magnesium toxicity is unlikely with these regimens and levels do not need to be routinely measured. Magnesium sulphate is mostly excreted in the urine. Urine output should be closely observed and if it becomes reduced below 20 ml/hour the magnesium infusion should be halted. Magnesium toxicity can be assessed by clinical assessment as it causes a loss of deep tendon reflexes and respiratory depression. If there is loss of deep tendon reflexes, the magnesium sulphate infusion should be halted. Calcium gluconate 1 g (10 ml) over 10 minutes can be given if there is concern over respiratory depression.

Evidence level Ia

In the collaborative eclampsia trial,[32] a further bolus of 2 g magnesium sulphate was administered for recurrent seizures. An alternative is to increase the rate of infusion of magnesium sulphate to 1.5 g or 2.0 g/hour. If there are repeated seizures then alternative agents such as diazepam or thiopentone may be used, but only as single doses, since prolonged use of diazepam is associated with an increase in maternal death.[32] If convulsions persist, intubation is likely to be necessary to protect the airway and maintain oxygenation. Transfer to intensive care facilities with intermittent positive pressure ventilation is appropriate in these circumstances.

Evidence level Ib

5.4 How should fluid balance be managed?

Fluid restriction is advisable to reduce the risk of fluid overload in the intrapartum and postpartum periods. In usual circumstances, total fluids should be limited to 80 ml/hour or 1 ml/kg/hour. **C**

Over the last 20 years, pulmonary oedema has been a significant cause of maternal death.[3] This has often been associated with inappropriate fluid management. There is no evidence of the benefit of fluid expansion[34] and a fluid restriction regimen is associated with good maternal outcome.[1] There is no evidence that maintenance of a specific urine output is important to prevent renal failure, which is rare. The regime of fluid restriction should be maintained until there is a postpartum diuresis, as oliguria is common with severe pre-eclampsia. If there is associated maternal haemorrhage, fluid balance is more difficult and fluid restriction is inappropriate.

5.5 Planning delivery

When and how should the baby be delivered?

The decision to deliver should be made once the woman is stable and with appropriate senior personnel present. C

If the fetus is less than 34 weeks of gestation and delivery can be deferred, corticosteroids should be given, although after 24 hours the benefits of conservative management should be reassessed. A

Conservative management at very early gestations may improve the perinatal outcome but must be carefully balanced with maternal wellbeing. A

The mode of delivery should be determined after considering the presentation of the fetus and the fetal condition, together with the likelihood of success of induction of labour after assessment of the cervix. C

The third stage should be managed with 5 units intramuscular Syntocinon® (Alliance) or 5 units intravenous Syntocinon given slowly. Ergometrine or Syntometrine® (Alliance) should not be given for prevention of haemorrhage, as this can further increase the blood pressure. ✓

The delivery should be well planned, done on the best day, performed in the best place, by the best route and with the best support team. A few hours' delay in delivery may be helpful if it allows the neonatal unit to be more organised or to transfer a mother to a place where a cot is available. This assumes the mother is stable before delivery and prior to transfer.

Evidence level IV

If the gestation is greater than 34 weeks, delivery after stabilisation is recommended. If less than 34 weeks and the pregnancy can be prolonged in excess of 24 hours, steroids help to reduce fetal respiratory mortality.[35] There is probable benefit from steroid therapy even if delivery is less than 24 hours after administration.[36,37]

Evidence level Ia

Prolonging the pregnancy at very early gestations may improve the outcome for the premature infant but can only be considered if the mother remains stable.[36–47] Two small randomised controlled trials have reported a reduction in neonatal complications with an expectant approach to management of severe early-onset pre-eclampsia.[46,47] Pregnancy was prolonged for a mean of 7 days and 15 days, respectively, at gestations of 28–34 weeks and 28–32 weeks, with no increase in maternal complications. Several case series have reported similar outcomes in different settings with gestations as early as 24 weeks.[36–45]

Evidence level Ib and level III

In all situations, a carefully planned delivery suiting all professionals is appropriate. Vaginal delivery is generally preferable but, if gestation is below 32 weeks, caesarean section is more likely as the success of induction is reduced. After 34 weeks with a cephalic presentation, vaginal delivery should be considered. The consultant obstetrician should discuss the mode of delivery with the mother. Vaginal prostaglandins will increase the chance of success. Anti-hypertensive treatment should be continued throughout assessment and labour.

Evidence level IV

5.6 How should the woman be managed following delivery?

Clinicians should be aware of the risk of late seizures and ensure that women have a careful review before discharge from hospital. C

Anti-hypertensive medication should be continued after delivery as dictated by the blood pressure. It may be necessary to maintain treatment for up to 3 months, although most women can have treatment stopped before this. C

Women with persisting hypertension and proteinuria at 6 weeks may have renal disease and should be considered for further investigation. C

Clinicians should be aware that up to 44% of eclampsia occurs postpartum, especially at term, so women with signs or symptoms compatible with pre-eclampsia should be carefully assessed. ✓

Severe pre-eclampsia or eclampsia can occur in the postpartum period. Up to 44% of eclampsia has been reported to occur postnatally, especially in women presenting at term.[2] Women who develop hypertension or symptoms of pre-eclampsia postnatally (headaches, visual disturbances, nausea and vomiting or epigastric pain) should be referred for a specialist opinion and investigation to exclude pre-eclampsia.[48] Women who deliver with severe pre-eclampsia (or eclampsia) should have continued close observation postnatally. As eclampsia has been reported up to 4 weeks postnatally, the optimum length of inpatient postnatal stay is unclear but the incidence of eclampsia and severe pre-eclampsia falls after the fourth postpartum day.[30] The decision about discharge from hospital needs to take account of the risk of late seizures. Most women with severe pre-eclampsia or eclampsia will need inpatient care for 4 days or more following delivery. Careful review to ensure improving clinical signs is needed before discharge.

Evidence level III

Anti-hypertensive therapy should be continued after delivery. Although, initially, blood pressure may fall, it usually rises again at around 24 hours postpartum. A reduction in anti-hypertensive therapy should be made in a stepwise fashion. There is no reason why the woman cannot go home on treatment, to be weaned off therapy as an outpatient. After pre-eclampsia, blood pressure can take up to 3 months to return to normal. During this time, blood pressure should not be allowed to exceed 160/110 mmHg. Currently, there is insufficient evidence to recommend any particular anti-hypertensive. However, it is good practice to avoid the use of alpha methyldopa in the postnatal period because of its adverse effect profile, particularly depression. In breastfeeding women, labetalol, atenolol, nifedipine and enalapril are currently in use, either singly or in combination.

Corticosteroids have been used in HELLP syndrome. The current evidence suggests they lead to a more rapid resolution of the biochemical and haematological abnormalities but there is no evidence that they reduce morbidity.[49]

6. Follow-up and final diagnosis

6.1 What should be offered following hospital discharge?

✓

An assessment of blood pressure and proteinuria by the general practitioner at the 6 weeks postnatal check is recommended. If hypertension or proteinuria persists then further investigation is recommended. ✓

Women whose pregnancies have been complicated by severe pre-eclampsia or eclampsia should be offered a formal postnatal review to discuss the events of the pregnancy. ✓

Preconceptional counselling should be offered where the events that occurred, any risk factors and any preventative therapies can be discussed.

Evidence suggests that up to 13% of women with pre-eclampsia will have underlying chronic or essential hypertension that was not suspected antenatally.[50–52]

7. Auditable standards

- Rate of documented involvement of consultant obstetrician and anaesthetist in acute management.
- Proportion of women with full complement of appropriate investigations.
- Proportion of women in whom fluid has been restricted appropriately to 80 ml/hour.
- Proportion of women receiving appropriate magnesium sulphate prophylaxis.
- Proportion of women with eclampsia treated with magnesium sulphate.
- Proportion of women attending for postnatal review and/or preconceptional counselling.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

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