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Blood Transfusion in Obstetrics

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Blood Transfusion in Obstetrics

This is the second edition of this guideline, which was previously published under the same title in 2007.

Executive summary of recommendations

How can the risk of transfusion be reduced?

Optimisation of haemoglobin in the antenatal period

Diagnosis

Anaemia in pregnancy is defined as first trimester haemoglobin (Hb) less than 110 g/l, second/third trimester Hb less than 105 g/l, and postpartum Hb less than 100 g/l, in line with British Committee for Standards in Haematology (BCSH) guidance. `B`

For normocytic or microcytic anaemia, a trial of oral iron should be considered as the first step and further tests should be undertaken if there is no demonstrable rise in Hb at 2 weeks and compliance has been checked. `✓`

Pregnant women should be offered screening for anaemia at booking and at 28 weeks. Women with multiple pregnancies should have an additional full blood count done at 20–24 weeks. `✓`

Treatment and management

Oral iron should be the preferred first-line treatment for iron deficiency. `A`

Parenteral iron is indicated when oral iron is not tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient time for oral supplementation to be effective. `C`

Women should receive information on improvement of dietary iron intake and factors affecting absorption of dietary iron. `C`

The role of recombinant human erythropoietin (rHuEPO) for non-end-stage renal anaemia is still to be established and it should only be used in the context of a controlled clinical trial or on the expert advice of the haematologist. `B`

Active management of the third stage of labour is recommended to minimise blood loss. `A`

Women at high risk of haemorrhage should be advised to deliver in hospital. `D`

General principles of blood transfusion

Consent for blood transfusion

Valid consent should be obtained where possible prior to administering a blood transfusion. `D`

In an emergency, where it is not feasible to get consent, information on blood transfusion should be provided retrospectively. `D`

The reason for transfusion and a note of the consent discussion should be documented in the patient's case notes. `D`

Requirements for group and screen samples and cross-matching

All women should have their blood group and antibody status checked at booking and at 28 weeks of gestation. `D`

Group and screen samples used for provision of blood in pregnancy should be less than 3 days old. `D`

In a woman at high risk of emergency transfusion, e.g. placenta praevia, and with no clinically significant alloantibodies, group and screen samples should be sent once a week to exclude or identify any new antibody formation and to keep blood available if necessary. Close liaison with the hospital transfusion laboratory is essential. `D`

Women should have a group and screen sample taken in line with clear locally agreed protocols for provision of blood. `✓`

Blood product specification in pregnancy and the puerperium

ABO-, rhesus D- (RhD-) and K- (Kell-) compatible red cell units should be transfused. `C`

If clinically significant red cell antibodies are present, then blood negative for the relevant antigen should be cross-matched before transfusion; close liaison with the transfusion laboratory is essential to avoid delay in transfusion in life-threatening haemorrhage. `D`

Cytomegalovirus- (CMV-) seronegative red cell and platelet components should be provided for elective transfusions during pregnancy. `D`

What are the strategies to minimise the use of banked blood?

Is there a role for preoperative/predelivery autologous blood deposit?

Predelivery autologous blood deposit is not recommended. `B`

Is there a role for intraoperative cell salvage (IOCS)?

Cell salvage is recommended for patients where the anticipated blood loss is great enough to induce anaemia or expected to exceed 20% of estimated blood volume. `C`

Consent should be obtained for IOCS where possible and its use in obstetric patients should be subject to audit and monitoring. `✓`

Cell salvage should only be performed by multidisciplinary teams who develop regular experience of IOCS. `✓`

Where IOCS is used during caesarean section in RhD-negative, previously nonsensitised women and where cord blood group is confirmed as RhD positive (or unknown), a minimum dose of 1500 iu anti-D immunoglobulin should be administered following the reinfusion of salvaged red cells. `C`

A maternal blood sample should be taken for estimation of fetomaternal haemorrhage 30–40 minutes after reinfusion in case more anti-D is indicated. `C`

Management of obstetric haemorrhage with blood components

There should be a clear local protocol on how to manage major obstetric haemorrhage. `D`

The protocol should be updated annually and practised in 'skills drills' to inform and train relevant personnel. ✓

Are there mechanical strategies that can be employed?

Clinicians should familiarise themselves with mechanical strategies that can be employed to reduce postpartum blood loss. ✓

What blood components can be used for obstetric haemorrhage?

When should red cells be used?

There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be made on clinical and haematological grounds. D

In an extreme situation and when the blood group is unknown, group O RhD-negative red cells should be given (although they may be incompatible for patients with irregular antibodies). D

Staff working in obstetric units should be aware of the location of the satellite blood fridge (where available) and should ensure that access is possible for blood collection. D

In what circumstances should fresh frozen plasma (FFP) and cryoprecipitate be used?

FFP at a dose of 12–15 ml/kg should be administered for every 6 units of red cells during major obstetric haemorrhage. Subsequent FFP transfusion should be guided by the results of clotting tests if they are available in a timely manner, aiming to maintain prothrombin time (PT) and activated partial thromboplastin time (APTT) ratios at less than 1.5 x normal. D

It is essential that regular full blood counts and coagulation screens (PT, APTT and fibrinogen) are performed during the bleeding episode. D

Cryoprecipitate at a standard dose of two 5-unit pools should be administered early in major obstetric haemorrhage. Subsequent cryoprecipitate transfusion should be guided by fibrinogen results, aiming to keep levels above 1.5 g/l. ✓

The FFP and cryoprecipitate should ideally be of the same group as the recipient. If unavailable, FFP of a different ABO group is acceptable providing that it does not have a high titre of anti-A or anti-B activity. D

No anti-D prophylaxis is required if a RhD-negative woman receives RhD-positive FFP or cryoprecipitate. D

When should platelets be used?

Aim to maintain the platelet count above 50 x 10^9/l in the acutely bleeding patient. D

A platelet transfusion trigger of 75 x 10^9/l is recommended to provide a margin of safety. ✓

The platelets should ideally be group compatible. RhD-negative women should also receive RhD-negative platelets. D

Is there a role for near patient testing of coagulation?

Centres that are using thromboelastography (TEG®, Haemonetics, Braintree, Massachusetts, USA) or rotation thromboelastometry (ROTEM®, Tem, Munich, Germany) for guiding blood transfusion during major obstetric haemorrhage must ensure that their transfusion algorithm protocol has been validated and that quality assurance measures are followed. D

Pharmacological strategies for management of major obstetric haemorrhage

Is there a role for recombinant factor VIIa (rFVIIa) therapy?

The use of rFVIIa may be considered as a treatment for life-threatening postpartum haemorrhage (PPH), but should not delay or be considered a substitute for a live-saving procedure such as embolisation or surgery, or transfer to a referral centre.

D

Is there a role for fibrinogen concentrate therapy?

Fibrinogen concentrate is not licensed in the UK for the management of acquired bleeding disorders. Thus, its use in PPH should be considered only in the context of clinical trials.

D

Is there a role for antifibrinolytics?

For those centres not participating in clinical trials, consideration should be given to using tranexamic acid during major obstetric haemorrhage.

D

How should intrapartum anaemia be managed?

In addition to major haemorrhage guidelines, obstetric units should have guidelines on criteria for red cell transfusion in anaemic women who are not actively bleeding. If the Hb is less than 70 g/l in labour or in the immediate postpartum period, the decision to transfuse should be made according to the individual's medical history and symptoms.

✓

How should women with postpartum anaemia be managed in the postnatal period?

If the Hb is less than 70 g/l in the postnatal period, where there is no ongoing or threat of bleeding, the decision to transfuse should be made on an informed individual basis.

✓

How should women who decline blood products be managed?

Hb should be optimised prior to delivery to prevent avoidable anaemia.

D

Consent/refusal of blood and components or other transfusion-sparing techniques should be discussed and documented during the antenatal period.

✓

Use of pharmacological, mechanical and surgical procedures to avert the use of banked blood and blood components should be considered early.

✓

IOCS has a role in the management of patients who refuse allogeneic blood transfusion.

C

1. Purpose and scope

Obstetric conditions associated with the need for blood transfusion may lead to morbidity and mortality if not managed correctly. The increasingly important issues in blood transfusion are adverse events associated with transfusion, including potential infection and potential transmission of prions, rising costs and the possible future problems of availability.

The aim of this guideline is to update the previous guidance about the appropriate use of blood products that neither compromises the affected woman nor exposes her to unnecessary risk. Strategies to maximise the haemoglobin (Hb) level at delivery as well as to minimise blood loss are also discussed.

2.   Introduction and background epidemiology

Obstetric haemorrhage remains a major cause of maternal mortality in the UK and is now the third leading cause of direct maternal deaths, accounting for approximately 10% of direct deaths. This does not represent a significant increase in mortality as deaths have decreased overall. Substandard management continues to be a significant contributor to mortality from haemorrhage.[1] It is estimated that there are more than 4000 cases of severe haemorrhage each year in the UK. The majority of these women will need blood transfusion.

Retrospective analyses of the clinical scenarios often criticise the employment of blood transfusion as 'too little, too late'. Women at high risk of losing greater than 1000 ml should be strongly advised to deliver in a setting where blood transfusion and intensive care facilities are available.[2]

Blood transfusion may be a life-saving procedure but it is not without risk. Recipients may rarely develop transfusion-transmitted infections or suffer immunological sequelae such as red cell alloimmunisation. The major risk, however, of blood transfusion is of a patient receiving an 'incorrect blood component'.[3] Strict adherence to correct sampling, cross-match and administration procedures is therefore of paramount importance, even in an emergency.

3.   Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects [DARE]), EMBASE, Trip, MEDLINE and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published between 2003 and March 2013. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings, and this was combined with a keyword search. A top-up search was performed in December 2014.

Terms and keyword search words included 'obstetrics and blood transfusion', 'tranexamic acid', 'factor VIIa', 'cell salvage', 'antifibrinolytics', 'fibrinogen concentrate', 'haematinics', 'autologous transfusion', 'transfusion triggers' and 'platelet'. The search was limited to humans and the English language. The National Library for Health and the National Guideline Clearinghouse were also searched for relevant guidelines and reviews. Guidelines and recommendations produced by organisations such as the British Committee for Standards in Haematology (BCSH) and various national bodies were considered. Where possible, recommendations are based on available evidence and the areas where evidence is lacking are annotated as 'good practice points'.

4.   How can the risk of transfusion be reduced?

4.1   Optimisation of haemoglobin in the antenatal period

4.1.1 Diagnosis

Anaemia in pregnancy is defined as first trimester haemoglobin (Hb) less than 110 g/l, second/third trimester Hb less than 105 g/l, and postpartum Hb less than 100 g/l, in line with BCSH guidance. `B`

For normocytic or microcytic anaemia, a trial of oral iron should be considered as the first step and further tests should be undertaken if there is no demonstrable rise in Hb at 2 weeks and compliance has been checked. `✓`

Pregnant women should be offered screening for anaemia at booking and at 28 weeks. Women with multiple pregnancies should have an additional full blood count done at 20–24 weeks. `✓`

The BCSH has defined what it considers to be adequate Hb levels at different stages of pregnancy.[4] The intrapartum and postpartum thresholds for Hb are derived from the World Health Organization with a modification suggested by the US Centers for Disease Control and Prevention because of the plasma expansion seen in the second trimester.[5-7]

<div style="text-align: right;">Evidence level 2+</div>

If the Hb is less than 110 g/l in the first trimester or less than 105 g/l in the second or third trimester, consider haematinic deficiency once haemoglobinopathies have been excluded.

Iron deficiency can be difficult to diagnose. The signs and symptoms are generally nonspecific. Serum ferritin is the most useful test for diagnosing iron deficiency but it is an acute phase reactant.[4] Other laboratory parameters also have their limitations.[8]

<div style="text-align: right;">Evidence level 2++</div>

Anaemia not due to haematinic deficiency (for example, haemoglobinopathies and bone marrow failure syndromes) should be managed by blood transfusion where appropriate in close conjunction with a haematologist.

In line with the National Institute for Health and Care Excellence (NICE),[9,10] screening for anaemia should be offered at booking and at 28 weeks, with an additional full blood count at 20–24 weeks for women with multiple pregnancies.

<div style="text-align: right;">Evidence level 4</div>

4.1.2 Treatment and management

Oral iron should be the preferred first-line treatment for iron deficiency.

<div style="text-align: right;">**A**</div>

Parenteral iron is indicated when oral iron is not tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient time for oral supplementation to be effective.

<div style="text-align: right;">**C**</div>

Women should receive information on improvement of dietary iron intake and factors affecting absorption of dietary iron.

<div style="text-align: right;">**C**</div>

The role of recombinant human erythropoietin (rHuEPO) for non-end-stage renal anaemia is still to be established and it should only be used in the context of a controlled clinical trial or on the expert advice of the haematologist.

<div style="text-align: right;">**B**</div>

Active management of the third stage of labour is recommended to minimise blood loss.

<div style="text-align: right;">**A**</div>

Women at high risk of haemorrhage should be advised to deliver in hospital.

<div style="text-align: right;">**D**</div>

A meta-analysis of randomised trials on the antenatal use of iron, with or without folic acid, showed a 50% reduction in the risk of anaemia in the third trimester or at delivery.[11]

<div style="text-align: right;">Evidence level 1++</div>

A Cochrane review of studies comparing iron supplementation with no iron or placebo found that iron supplementation decreased the incidence of low birthweight babies and prevented maternal anaemia and iron deficiency anaemia.[12] A second Cochrane review comparing intermittent versus daily iron supplementation showed that intermittent supplementation produced a similar risk of anaemia at term, prematurity and low birthweight babies, but was associated with fewer side effects.[13]

<div style="text-align: right;">Evidence level 1+</div>

Parenteral therapy offers a shorter duration of treatment and a quicker response than oral therapy.[14] It is, however, more invasive and expensive to administer. Severe allergic reactions are possible with all iron preparations. Intravenous iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions, as well as resuscitation facilities, are immediately available.

<div style="text-align: right;">Evidence level 2+</div>

Rich sources of dietary iron are red meat, fish and poultry. These provide haem iron that is more easily absorbed than non-haem iron but the latter forms the vast majority of iron taken through the diet.[15] Vitamin C enhances the absorption of non-haem iron whereas tea and coffee inhibit iron absorption from food.[15]

Evidence level 2+

rHuEPO is mostly used in the anaemia of end-stage renal disease. rHuEPO has been used both antenatally and postpartum in patients without end-stage renal disease without any maternal, fetal or neonatal adverse effects.[16,17] Its use in clinical practice for non-end-stage renal anaemia is still to be established and should only be used in the context of a controlled clinical trial and/or under haematological advice.

Evidence level 1–

Clear evidence from randomised trials supports the active management of the third stage of labour as a method of decreasing postpartum blood loss.[18–20]

Evidence level 1+

Maternal deaths from haemorrhage in the UK have fallen over the years and one contributor is considered to be the hospitalisation for delivery of women at higher risk of haemorrhage (older women, grand multiparae and those with pre-eclampsia). Analysis of such deaths has led to a recommendation that women at high risk of haemorrhage should not be delivered in units without immediate access to consultant-led care, blood products and intensive care.[2]

Evidence level 3

5. General principles of blood transfusion

5.1 Consent for blood transfusion

Valid consent should be obtained where possible prior to administering a blood transfusion.

D

In an emergency, where it is not feasible to get consent, information on blood transfusion should be provided retrospectively.

D

The reason for transfusion and a note of the consent discussion should be documented in the patient's case notes.

D

The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), following a consultation exercise looking at consent for blood transfusion, recommended that valid consent for blood transfusion should be obtained wherever possible before administering a transfusion. While this does not entail specific written consent, valid consent does require the provision of information to patients on risks and benefits together with alternatives available with clear documentation in the clinical records.[21]

Evidence level 4

Where transfusion of all or specific blood components is refused, or an advance directive exists, this should be documented in the patient's clinical records and communicated to all relevant healthcare professionals (see section 11).

Patients who require an emergency blood transfusion may not be able to give valid consent prior to the transfusion. Transfusion should not be delayed, but attempts should be made to provide information retrospectively.[21] Patient information leaflets on blood transfusion are available from the UK blood transfusion services (see section 14).

Evidence level 4

The decision process leading to transfusion including indication for transfusion and obtaining valid consent should be documented in the patient's clinical record.[22,23] There is some limited evidence[24] that when the decision or reason for transfusion is documented there is a lower rate of inappropriate transfusion.

5.2 Requirements for group and screen samples and cross-matching

All women should have their blood group and antibody status checked at booking and at 28 weeks of gestation. **D**

Group and screen samples used for provision of blood in pregnancy should be less than 3 days old. **D**

In a woman at high risk of emergency transfusion, e.g. placenta praevia, and with no clinically significant alloantibodies, group and screen samples should be sent once a week to exclude or identify any new antibody formation and to keep blood available if necessary. Close liaison with the hospital transfusion laboratory is essential. **D**

Women should have a group and screen sample taken in line with clear locally agreed protocols for provision of blood. ✓

Maternal red cell antibodies are relatively common.[25] These can cause haemolytic disease of the fetus and newborn (HDFN) and will also have implications for the selection of blood for transfusion in the mother to avoid the risk of haemolytic transfusion reactions. Accordingly, the blood group and antibody status of the mother should be tested at booking and at 28 weeks of gestation.[26,27]

Evidence level 3

When red cell antibodies are detected in the booking sample, further testing of maternal blood should be undertaken to determine the specificity and the level of antibody or antibodies and to assess the likelihood of HDFN,[25] with early referral to a specialist fetal medicine unit depending on the nature of the antibody, level and previous history. Further details on the assessment and management of women with red cell antibodies during pregnancy are covered in the RCOG Green-top Guideline.[25]

Transfusion or pregnancy may stimulate the production of unexpected antibodies against red cell antigens through either a primary or secondary immune response.[28] To ensure that the specimen used for compatibility testing is representative of a patient's current immune status, serological studies should be performed using blood collected no more than 3 days in advance of the actual transfusion when the patient has been transfused or pregnant within the preceding 3 months.[28]

A formal deviation to the 3-day rule may be used in pregnant women with no clinically significant alloantibodies who require blood standing by for potential obstetric emergencies, e.g. placenta praevia,[28] with samples sent once a week to the transfusion laboratory for testing. Fetomaternal haemorrhage constitutes a smaller stimulus than transfusion because the number of foreign antigens is limited and in many pregnancies the volume of red cells transferred from fetus to mother is too small to stimulate a primary response.[29]

Evidence level 4

The majority of laboratories in the UK now use automated testing for blood grouping and antibody testing with advanced information technology systems for documentation and reporting of results. The hospital transfusion laboratory can readily provide red cells that are ABO and rhesus D (RhD) compatible using electronic issue with no cross-matching needed, provided that the patient does not have any antibodies and there are robust automated systems in place for antibody testing and identification of the patient.[28] In this setting, since blood can be readily issued, there is no need to reserve units for individual cases. Where electronic issue is not available, a locally agreed maximum surgical blood ordering schedule should be used to decide how many red cell units should be reserved and available for particular cases, based on the obstetric diagnosis. In patients with red cell antibodies, cross-match between the patient's blood and the red cell units to be transfused is essential to ensure compatibility.

It should be borne in mind that many hospitals send antenatal serology off-site for economies of scale. If hospitals send antenatal serology samples for testing off-site, it is advised that the results of the grouping and antibody screen should be made readily available for the local unit. If laboratory provision is off-site, there should be robust systems in place for local arrangements for the provision of blood, and components if required, taking into account transport times and whether or not the woman has red cell antibodies.

Unless secure electronic patient identification systems are in place, a second sample should be requested for confirmation of the ABO group of a first-time patient prior to transfusion, where this does not impede the delivery of urgent red cells or other components.[28]

Evidence level 4

5.3 Blood product specification in pregnancy and the puerperium

ABO-, RhD- and K- (Kell-) compatible red cell units should be transfused.

C

If clinically significant red cell antibodies are present, then blood negative for the relevant antigen should be cross-matched before transfusion; close liaison with the transfusion laboratory is essential to avoid delay in transfusion in life-threatening haemorrhage.

D

Cytomegalovirus- (CMV-) seronegative red cell and platelet components should be provided for elective transfusions during pregnancy.

D

Pregnant women (and women of childbearing age) who are RhD negative must only receive RhD-negative blood to avoid the risk of RhD alloimmunisation.[28] Previous blood transfusion is an important cause for alloimmunisation with antibodies other than anti-D, in particular anti-K, which can cause severe HDFN.[25] Accordingly, unless a woman is known to be K positive, only K-negative blood should be used for transfusion in women of childbearing age.[28]

Evidence level 2+

Major obstetric haemorrhage protocols must include the provision of emergency blood with immediate issue of group O, RhD-negative and K-negative units, with a switch to group-specific blood as soon as feasible.

The aim of antibody screening is to determine the presence of atypical red cell antibodies of likely clinical significance. When the antibody screen is positive, further testing is required to identify the relevant antibody or antibodies and the laboratory should select red cell units negative for the relevant antigen for cross-matching.[28] However, in a major obstetric haemorrhage there should be no delay in the provision of blood with the initial use of group O-negative units if needed, with subsequent transfusion of cross-matched antigen-negative units when available.[30] Close liaison with the transfusion laboratory is essential, with input if needed from the clinical haematology team and specialist advice from the national blood service.

Evidence level 4

In 2012, SaBTO stated that CMV-seronegative red cells and platelets should be provided, where possible, for pregnant women.[31] The UK policy of universal leucocyte depletion substantially reduces the risk of CMV transmission.[32] In an emergency, such as major haemorrhage, standard leucocyte-depleted components should be given to avoid delay and CMV-negative blood or platelets are not needed for transfusion during delivery or in the postpartum period.[31]

6. What are the strategies to minimise the use of banked blood?

6.1 Is there a role for preoperative/predelivery autologous blood deposit?

Predelivery autologous blood deposit is not recommended.

B

A Cochrane review on preoperative autologous donations[33] considered randomised controlled trials and concluded that the studies were of poor quality, with insufficient numbers of

Evidence level 1–

patients and high transfusion rates. None of the studies were conducted on pregnant women. Preoperative/predelivery deposit of autologous blood is not a service that is available routinely in the UK.

<div style="text-align: right;">Evidence level 1–</div>

6.2 Is there a role for intraoperative cell salvage (IOCS)?

Cell salvage is recommended for patients where the anticipated blood loss is great enough to induce anaemia or expected to exceed 20% of estimated blood volume.

C

Consent should be obtained for IOCS where possible and its use in obstetric patients should be subject to audit and monitoring.

✓

Cell salvage should only be performed by multidisciplinary teams who develop regular experience of IOCS.

✓

Where IOCS is used during caesarean section in RhD-negative, previously nonsensitised women and where cord blood group is confirmed as RhD positive (or unknown), a minimum dose of 1500 iu anti-D immunoglobulin should be administered following the reinfusion of salvaged red cells.

C

A maternal blood sample should be taken for estimation of fetomaternal haemorrhage 30–40 minutes after reinfusion in case more anti-D is indicated.

C

In general, intraoperative cell salvage (IOCS) has been recommended for nonobstetric patients undergoing elective or emergency surgical procedures where the anticipated blood loss is great enough to induce anaemia or expected to exceed 20% of estimated blood volume.[34-36] Therefore, IOCS would not be required for most caesarean sections if a similar threshold were to be adopted.

<div style="text-align: right;">Evidence level 2+</div>

IOCS has been used during caesarean section in a number of case reports and case series without any reported complications related to receiving salvaged blood.[37] Although current evidence supports the use of IOCS in obstetrics,[38,39] evidence from large randomised controlled trials are needed to support the routine practice of IOCS in obstetrics.

Preoperative discussions on blood transfusion should be undertaken according to SaBTO guidance,[21] as outlined in the section above. These discussions should include oral and written information on cell salvage, if it is available in the facility where the woman is to give birth. More information for staff and patients is available from the UK Cell Salvage Action Group website (see section 14 for link details).

<div style="text-align: right;">Evidence level 4</div>

The NICE guideline on IOCS in obstetrics states that this procedure should only be performed by multidisciplinary teams who have regular experience of IOCS.[37] UK centres with high levels of experience of IOCS in obstetrics have developed this experience by training staff to use cell salvage during elective routine low-risk caesarean sections.

Using disposables for low-risk cases to ensure that theatre staff are trained requires financial resource. If a hospital trust/maternity service provider cannot afford to purchase disposables to train staff in the elective, low-risk setting, then they cannot provide cell salvage in an emergency setting.

IOCS, together with the use of modern leucocyte depletion filters, has been shown to be effective at removing the common markers of amniotic fluid contamination.[40] However, it will not remove fetal blood cells and therefore adequate anti-D immunisation (as determined by Kleihauer test 30–40 minutes after the procedure) will be required to prevent rhesus immunisation in RhD-negative women.[41]

<div style="text-align: right;">Evidence level 2+</div>

7. Management of obstetric haemorrhage with blood components

There should be a clear local protocol on how to manage major obstetric haemorrhage.   `D`

The protocol should be updated annually and practised in 'skills drills' to inform and train relevant personnel.   ✓

In October 2010, the National Patient Safety Agency (NPSA) reported 94 incidents (23 obstetric cases) where there was a delay in accessing blood components for life-threatening bleeding patients, resulting in unacceptable morbidity and mortality.[42] The report highlighted the need for local protocols that allow provision of emergency blood (including out of hours) in patients with major haemorrhage. These protocols should waive restrictions on special blood components, such as irradiated blood components or CMV, in order to avoid unnecessary delays of red blood cell (RBC) provision and to allow for rapid delivery of uncross-matched blood (i.e. group O RhD and K negative).[42]

Evidence level 3

A randomised controlled trial found that practical, multidisciplinary, obstetric emergency training increased midwives' and doctors' knowledge of obstetric emergency management, including postpartum haemorrhage (PPH);[43] thus, the major haemorrhage protocol should be practised in 'skills drills' and updated annually so as to inform and train relevant personnel.

Evidence level 1+

7.1 Are there mechanical strategies that can be employed?

Clinicians should familiarise themselves with mechanical strategies that can be employed to reduce postpartum blood loss.   ✓

The mechanical strategies that can be employed to minimise blood loss during PPH are outlined in RCOG Green-top Guideline No. 53, *Prevention and Management of Postpartum Haemorrhage.*[30]

7.2 What blood components can be used for obstetric haemorrhage?

7.2.1 When should red cells be used?

There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be made on clinical and haematological grounds.   `D`

In an extreme situation and when the blood group is unknown, group O RhD-negative red cells should be given (although they may be incompatible for patients with irregular antibodies).   `D`

Staff working in obstetric units should be aware of the location of the satellite blood fridge (where available) and should ensure that access is possible for blood collection.   `D`

There are no firm criteria for initiating red cell transfusion.[44] The decision to perform blood transfusion should be made on both clinical and haematological grounds. Blood transfusion is almost always required when the Hb is less than 60 g/l and it is rarely required when the Hb is greater than 100 g/l.[44] It should also be remembered that patients with acute haemorrhage can have normal Hb; hence the clinical evaluation of the patient in this situation is extremely important.

Evidence level 4

Between October 2006 and September 2010, the Rapid Response Report from the NPSA reported 11 deaths and 83 incidents where the patient suffered harm as a result of delays in the provision of blood. One of the reasons for the delay in blood transfusion during life-threatening bleeding episodes was a lack of understanding concerning the term 'cross-matched', whereby clinicians frequently request 'cross-matched blood' without realising that this could take some time, which

is not optimal in an emergency.[42] Thus, in the event of life-threatening haemorrhage, even if a woman has RBC alloantibodies, the transfusion of group O RhD-negative red cells, or group-specific red cells, must not be delayed.

In order to facilitate the immediate provision of uncross-matched group O red cell units for patients who suffer massive haemorrhage, some National Health Service (NHS) organisations have introduced satellite blood fridges in different clinical areas. Medical staff working in these organisations and who are involved in the management of major bleeding should be aware of the fridge location and should ensure that access is possible for blood collection.[42]

7.2.2 In what circumstances should fresh frozen plasma (FFP) and cryoprecipitate be used?

FFP at a dose of 12–15 ml/kg should be administered for every 6 units of red cells during major obstetric haemorrhage. Subsequent FFP transfusion should be guided by the results of clotting tests if they are available in a timely manner, aiming to maintain prothrombin time (PT) and activated partial thromboplastin time (APTT) ratios at less than 1.5 x normal.

D

It is essential that regular full blood counts and coagulation screens (PT, APTT and fibrinogen) are performed during the bleeding episode.

D

Cryoprecipitate at a standard dose of two 5-unit pools should be administered early in major obstetric haemorrhage. Subsequent cryoprecipitate transfusion should be guided by fibrinogen results, aiming to keep levels above 1.5 g/l.

✓

The FFP and cryoprecipitate should ideally be of the same group as the recipient. If unavailable, FFP of a different ABO group is acceptable providing that it does not have a high titre of anti-A or anti-B activity.

D

No anti-D prophylaxis is required if a RhD-negative woman receives RhD-positive FFP or cryoprecipitate.

D

Observational studies in military combat casualties have suggested that early administration of FFP in high ratios improves clinical outcomes of trauma bleeding patients.[45-47] However, due to the lack of randomised controlled trials, the optimum FFP-to-RBC ratio for management of major bleeding remains unknown.[48-51] Further, no studies have evaluated the optimum dose of FFP during major bleeding. Until further evidence becomes available, we recommend that FFP at a dose of 12–15 ml/kg should be administered for every 6 units of red cells during a major obstetric bleed.[30]

Subsequent FFP transfusion should be guided by the results of clotting tests (if they are available in a timely manner), aiming to maintain PT and APTT ratios at less than 1.5 x normal.[52]

Once the FFP has been ordered, it takes at least 30 minutes to thaw and issue.[52] During this time, resuscitation should be continued with volume expanding fluids or red cells as appropriate.

It should be borne in mind that, at present in the UK, most units of FFP (as is the case with red cells, platelets and cryoprecipitate) are not virally inactivated and that transfusion with these products offers a small risk of transfusion-transmitted infection.[52]

Full blood counts play an important role in guiding red cell and platelet transfusion during major haemorrhage, while PT/APTT and fibrinogen results should be used to guide FFP and cryoprecipitate transfusion respectively.[53]

Observational studies have indicated that a fibrinogen level of less than 2.9 g/l is associated with increased risk of PPH.[54] One study showed that the decrease in fibrinogen levels was an early predictor of PPH and that the risk for severe PPH was 2.63-fold higher for each 1 g/l decrease in fibrinogen, with the positive predictive value being 100% if the fibrinogen level was 2 g/l or less.[55] It is important to recognise that during pregnancy fibrinogen levels increase above normal ranges (varying between 3.5 and 6.5 g/l) and the above studies have indicated that during PPH a fibrinogen level of 2.0 g/l or less is abnormally low.

Evidence level 3

Although the above studies have indicated that fibrinogen levels reduce significantly during PPH, no clinical studies have looked into the timing of when to introduce fibrinogen replacement therapy during PPH and what the minimum fibrinogen level should be when managing PPH. Cryoprecipitate at a standard dose of two 5-unit pools should be administered early in major obstetric haemorrhage and subsequent cryoprecipitate transfusion should be guided by fibrinogen results, aiming to keep a fibrinogen level of more than 1.5 g/l.

In order to avoid the low risk of ABO-associated haemolysis, FFP and cryoprecipitate should ideally be of the same blood group as the recipient. If this is not possible, FFP of a different group may be acceptable if it does not possess high-titre anti-A or anti-B activity.[52]

Evidence level 3

Sensitisation following the administration of RhD-positive FFP or cryoprecipitate to RhD-negative patients is most unlikely; hence no anti-D prophylaxis is required if a RhD-negative woman receives RhD-positive FFP or cryoprecipitate.[52]

Evidence level 2–

7.2.3 When should platelets be used?

Aim to maintain the platelet count above 50 x 10⁹/l in the acutely bleeding patient.

D

A platelet transfusion trigger of 75 x 10⁹/l is recommended to provide a margin of safety.

✓

The platelets should ideally be group compatible. RhD-negative women should also receive RhD-negative platelets.

D

The platelet count should not be allowed to fall below 50 x 10⁹/l in the acutely bleeding patient as this represents the critical level for haemostasis. Such a low platelet count may be anticipated when approximately two blood volumes have been replaced by fluid or blood components.[56] A platelet transfusion trigger of 75 x 10⁹/l is recommended in a patient with ongoing bleeding, so as to provide a margin of safety.[57]

Evidence level 4

Platelets may not be on-site in many units; therefore their need should be anticipated and good communication with the transfusion laboratory maintained.

Platelet concentrates should ideally be of the same ABO group as the recipient. ABO-nonidentical platelet transfusions have been associated with poorer platelet count increments in some studies, but this is not usually clinically significant in terms of the haemostatic effectiveness of the platelet transfusion.[58] Administration of ABO-nonidentical platelets is an acceptable transfusion practice, in particular, when platelet concentrates are in short supply or when human leucocyte antigen (HLA)-matched platelets are required and the best match is not ABO compatible.[58]

Evidence level 3

In order to avoid the development of anti-D antibodies, RhD-negative platelet concentrates should be given where possible to RhD-negative women of childbearing potential.[58]

If RhD-positive platelets are transfused to a RhD-negative woman of childbearing potential, anti-D immunoglobulin should be administered. A dose of 250 iu anti-D immunoglobulin is sufficient to

cover five adult therapeutic doses of platelets given within a 6-week period. This may be given subcutaneously to minimise bruising and haematomas in thrombocytopenic women.[58]

<div style="text-align:right">Evidence level 3</div>

Platelets may be given via an unused blood giving set, although a platelet giving set reduces wastage because it has less dead space. Transfusion of platelets through a giving set previously used for red cells is not recommended.[59]

<div style="text-align:right">Evidence level 4</div>

7.2.4 Is there a role for near patient testing of coagulation?

Centres that are using thromboelastography (TEG®, Haemonetics, Braintree, Massachusetts, USA) or rotation thromboelastometry (ROTEM®, Tem, Munich, Germany) for guiding blood transfusion during major obstetric haemorrhage must ensure that their transfusion algorithm protocol has been validated and that quality assurance measures are followed.

D

TEG® and ROTEM® are viscoelastic whole-blood assays that provide information on the coagulation process through the graphic display of clot initiation, propagation and lysis. Experiences in cardiac and liver surgery have suggested that TEG® or ROTEM® can be used to guide transfusion of blood components, although currently there is no validated transfusion algorithm for TEG®/ROTEM®. NHS Quality Improvement Scotland (now known as Healthcare Improvement Scotland) has reviewed the evidence on the clinical and cost effectiveness of TEG®/ROTEM® in liver and cardiac surgery; the report concluded that this intervention is cost-effective (assuming a usage of 200 tests annually) since it reduces inappropriate transfusions, thus improving transfusion management and patients' clinical outcome.[60]

<div style="text-align:right">Evidence level 1–</div>

There are no randomised controlled trials on the use of TEG® or ROTEM® in major obstetric haemorrhage. At the current time, unless a centre has special expertise in the use of TEG®/ROTEM®, conventional testing should be performed regularly during major obstetric haemorrhage to guide transfusion of blood components.

If hospitals are using TEG® or ROTEM® for guiding blood transfusion during major obstetric haemorrhage, it is important that the transfusion algorithm protocol has been validated and that quality assurance measures are followed.[61]

<div style="text-align:right">Evidence level 2–</div>

8.   Pharmacological strategies for management of major obstetric haemorrhage

8.1   Is there a role for recombinant factor VIIa (rFVIIa) therapy?

The use of rFVIIa may be considered as a treatment for life-threatening PPH, but should not delay or be considered a substitute for a live-saving procedure such as embolisation or surgery, or transfer to a referral centre.

D

Factor VIIa has a pivotal role in initiating the process of blood coagulation. Recombinant factor VIIa (rFVIIa) is licensed for treatment of inherited bleeding disorders. Outside of these settings, a review of 35 randomised controlled trials that used rFVIIa on an off-licence basis demonstrated that rFVIIa significantly increased the risk of arterial thrombosis.[62]

<div style="text-align:right">Evidence level 1+</div>

There have been no randomised controlled trials to assess the efficacy of rFVIIa in PPH. A number of case series and national registries have indicated that administration of rFVIIa during PPH might reduce bleeding and transfusion requirements. However, none of these reports were powered to assess the safety of rFVIIa. Moreover, these studies vary significantly with respect to the timing and dosing of rFVIIa administration.[63–65] The incidence of thrombotic complications in a review of 272 women with PPH who had received rFVIIa was reported to be 2.5%.[66]

<div style="text-align:right">Evidence level 3</div>

There is no evidence to support the prophylactic use of rFVIIa to reduce blood loss for caesarean sections.

In order to ensure the maximum effect of rFVIIa on clot formation, attempts should be made to correct thrombocytopenia, acidosis and hypofibrinogenaemia.[67]

Evidence level 4

In the event of intractable obstetric haemorrhage, the administration of rFVIIa may be an option to be discussed with the haematologists. It is important that each unit or hospital prepares local guidance on indications for rFVIIa in managing intractable obstetric haemorrhage. A protocol should be available for how to procure it urgently.

8.2   Is there a role for fibrinogen concentrate therapy?

Fibrinogen concentrate is not licensed in the UK for the management of acquired bleeding disorders. Thus, its use in PPH should be considered only in the context of clinical trials.

D

The main advantages of fibrinogen concentrate compared with cryoprecipitate are faster reconstitution, ease of use and not requiring thawing or ABO compatibility. No randomised controlled trials or prospective clinical studies have assessed the efficacy of fibrinogen concentrate in obstetric haemorrhage. One retrospective study compared the clinical outcomes of 20 and 14 women with PPH who had received fibrinogen concentrate and cryoprecipitate respectively.[68] There were no significant differences between the two groups with regard to estimated blood loss, RBC transfusion, FFP transfusion and high dependency unit or intensive therapy unit stay.

Evidence level 2–

8.3   Is there a role for antifibrinolytics?

For those centres not participating in clinical trials, consideration should be given to using tranexamic acid during major obstetric haemorrhage.

D

The main antifibrinolytic agent used in the UK is tranexamic acid. Tranexamic acid is a synthetic derivative of the amino acid lysine that reversibly binds to the lysine-binding sites of the plasminogen molecule. In doing so, it prevents activation of plasminogen to plasmin, leading to inhibition of fibrinolysis. The CRASH-2 study showed that tranexamic acid reduces mortality in bleeding trauma patients without an increase in the rate of venous thromboembolism.[69]

Evidence level 1–

In obstetric settings, several small randomised trials have compared the use of tranexamic acid with placebo[70–72] or no treatment.[73–76] Apart from one study,[75] all others were performed in women undergoing caesarean section. The overall conclusion was that tranexamic acid significantly reduces blood loss.[77] However, none of these trials were statistically powered to assess mortality rates and the safety of tranexamic acid. Further, they were heterogenous in their definition of PPH, the dosing of tranexamic acid and the timing when blood loss was measured.

Evidence level 2–

9.   How should intrapartum anaemia be managed?

In addition to major haemorrhage guidelines, obstetric units should have guidelines on criteria for red cell transfusion in anaemic women who are not actively bleeding. If the Hb is less than 70 g/l in labour or in the immediate postpartum period, the decision to transfuse should be made according to the individual's medical history and symptoms.

☑

Concerns about the safety and availability of donor blood have promoted greater scrutiny of blood transfusion practice with a focus on restrictive transfusion triggers and avoidance strategies where available. Outside the context of major haemorrhage, there is little evidence of the benefit of blood transfusion in fit, healthy, asymptomatic patients. The decision to transfuse must be based on careful clinical assessment in conjunction with the Hb level.

Evidence level 4

Transfusion will be indicated in women with continued bleeding or at risk of further bleeding, imminent cardiac compromise or significant symptoms requiring urgent correction.[4]

<div style="text-align:right">Evidence level 4</div>

10.   How should women with postpartum anaemia be managed in the postnatal period?

If the Hb is less than 70 g/l in the postnatal period, where there is no ongoing or threat of bleeding, the decision to transfuse should be made on an informed individual basis.

<div style="text-align:right">✓</div>

Audits indicate that a high proportion of blood transfusions administered in the postpartum period may be inappropriate, with underutilisation of iron supplements.[78,79] Prompt recognition of iron deficiency in the antenatal period followed by iron therapy may reduce the subsequent need for blood transfusion.[4] If, after careful consideration, elective transfusion is required, women should be fully counselled about the potential risks. Written information should be provided and valid informed consent should be obtained before the transfusion is administered.

<div style="text-align:right">Evidence level 4</div>

11.   How should women who decline blood products be managed?

Hb should be optimised prior to delivery to prevent avoidable anaemia.

<div style="text-align:right">D</div>

Consent/refusal of blood and components or other transfusion-sparing techniques should be discussed and documented during the antenatal period.

<div style="text-align:right">✓</div>

Use of pharmacological, mechanical and surgical procedures to avert the use of banked blood and blood components should be considered early.

<div style="text-align:right">✓</div>

IOCS has a role in the management of patients who refuse allogeneic blood transfusion.

<div style="text-align:right">C</div>

There are additional challenges in the management of pregnancy in mothers refusing blood transfusion, including for religious reasons, i.e. Jehovah's Witnesses (JW), with a higher risk of morbidity and mortality.[80-82] Accordingly, all women declining blood transfusion require careful multidisciplinary planning with senior clinician input during pregnancy to minimise anaemia and to manage blood loss. Early use of iron replacement is indicated with, if needed, use of intravenous iron.[83,84]

<div style="text-align:right">Evidence level 2–</div>

Antenatal planning is essential and haematinic deficiencies should be corrected if the Hb is less than 105 g/l for all women before delivery.

The treating clinician will need to establish which blood components or blood-sparing techniques (e.g. clotting factor products) are acceptable. An example of a suggested care plan for managing women refusing blood transfusion is available at: http://www.transfusionguidelines.org.uk/transfusion-handbook/12-management-of-patients-who-do-not-accept-transfusion/12-2-jehovah-s-witnesses-and-blood-transfusion.

The woman should have an opportunity to discuss consent alone (witnessed) with an experienced clinician. Treating clinicians should ensure that the woman is fully informed of the risks of refusing transfusion and of maternal mortality data for JW compared with non-JW women.[80] This needs to be handled sensitively to avoid any possibility of coercion.

An advance directive should be completed and carried in the hand-held notes, although a woman should always be given the opportunity to change her mind about the use of blood products.

The woman may wish to wear a 'no blood' wristband to make it clear to all members of the treating team that blood transfusion is not to be used.

The use of a Patient Blood Management (PBM) programme is recommended by AABB (formerly the American Association of Blood Banks), the Australian National Blood Authority and the National Blood Transfusion Committee, which covers England and North Wales (see section 14). PBM involves an all-encompassing approach to avoid unnecessary transfusion by optimising preoperative/predelivery Hb, avoiding overtransfusion, using cell salvage where appropriate, accepting evidence-based lower transfusion triggers and using intravenous or oral iron supplements in women who are not actively bleeding and are cardiovascularly stable.[85]

Evidence level 4

The *Code of Practice for the Surgical Management of Jehovah's Witnesses* by the Royal College of Surgeons of England and *Management of Anaesthesia for Jehovah's Witnesses* by the Association of Anaesthetists of Great Britain and Ireland provide useful information.[86,87]

Evidence from orthopaedic and cardiac surgery supports the premise that use of autologous blood from IOCS decreases the requirement for allogeneic transfusion. In one study with 68 patients included in the review by NICE, the mean postoperative Hb level was significantly greater in the group that had blood cell salvage compared with the control group (104 [SD 15] versus 81 [SD 14] g/l). Also, 2.9% (1/34) of patients who received cell salvage required an allogeneic blood transfusion compared with 23.5% (8/34) of the control group.[88] Current evidence supports the use of IOCS in obstetrics, which has been endorsed by several bodies and is likely to become increasingly commonplace.[37]

Evidence level 2+

12. Recommendations for future research

- Define the coagulation abnormalities during major obstetric haemorrhage and investigate the role of point of care testing (i.e. TEG® or ROTEM®) in the diagnosis and management of obstetric haemorrhage.
- Determine the optimal dose and timing of cryoprecipitate and FFP transfusion during major obstetric haemorrhage.
- Randomised controlled trials are needed to determine the role of fibrinogen concentrate during major haemorrhage. The WOMAN study (Clinicaltrials.gov ID: NCT00872469), a large, international, randomised, double-blind, placebo-controlled trial, will be addressing the role of tranexamic acid in women with a clinical diagnosis of PPH and data collection is due to finish in 2016.

13. Auditable topics

Standards for audit of documentation:

- Provision of local protocols for the management of massive obstetric haemorrhage in all obstetric hospitals (100%).
- 100% of the staff members, including clinicians, midwives, biomedical scientists and porters, are familiar with this local protocol.
- Provision of local guidelines for red cell transfusion in anaemic women who are not actively bleeding (100%).
- Provision of local guidelines for the treatment of antenatal and postnatal anaemia (100%).
- Documentation of the reasons for transfusion in all patients receiving blood products (100%).

Standards for audit of practice:

- Proportion of cases of major obstetric haemorrhage that were incident reported (100%).
- All cases of major obstetric haemorrhage to be reviewed to ensure that the communication chain worked and that there was no delay in the provision of blood products (100%).
- Provision of written information on the risks of blood transfusion to women who are transfused (100%).
- All women who have had a blood transfusion should have their post-transfusion Hb checked (100%).

14. Useful links and support groups

- NHS Blood and Transplant. *Patient Information Leaflets* [http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets/].
- NHS Choices. *Blood transfusion* [http://www.nhs.uk/Conditions/Blood-transfusion/Pages/Introduction.aspx].
- Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. *UK Cell Salvage Action Group* [http://www.transfusionguidelines.org.uk/transfusion-practice/uk-cell-salvage-action-group].
- Patient Blood Management
  - AABB. *Patient Blood Management* [http://www.aabb.org/pbm/Pages/default.aspx].
  - National Blood Authority Australia. *Patient Blood Management Guidelines* [http://www.blood.gov.au/pbm-guidelines].
  - Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. *Patient Blood Management* [http://www.transfusionguidelines.org.uk/uk-transfusion-committees/national-blood-transfusion-committee/patient-blood-management].
- The Royal College of Surgeons of England. *Code of Practice for the Surgical Management of Jehovah's Witnesses.* London: The Royal College of Surgeons of England; 2002 [http://www.rcseng.ac.uk/publications/docs/jehovahs_witness.html].

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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 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). 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

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g. case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

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

The review process will commence in 2018, unless otherwise indicated.