Executive summary of recommendations

Prepregnancy counselling

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Referral to a fetal medicine specialist for consideration of invasive treatment should take place if the MCA PSV rises above the 1.5 multiples of the median (MoM) threshold or if there are other signs of fetal anaemia.

Fetal monitoring is required (as above) once anti-K is detected.

Red cell preparations for IUT should be group O (low titre haemolysin) or ABO identical with the fetus

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If a woman is at risk of requiring significant amounts of transfused blood either antenatally, intrapartum or postnatally, consideration should be given to transferring her care to a centre capable of processing cross-match samples and providing appropriate compatible blood rapidly.

As these are 'high-risk' pregnancies, continuous electronic fetal heart monitoring is advised during labour.

Cord blood investigations

If a woman has clinically significant antibodies (Appendix 1) then cord samples should be taken for a direct antiglobulin test (DAT), haemoglobin and bilirubin levels.

Management

This depends on the risk of haemolysis or anaemia conferred by the relevant red cell antibody. The neonate should have regular clinical assessment of its neurobehavioural state and be observed for the development of jaundice and/or anaemia.

Regular assessment of bilirubin and haemoglobin levels should be made and early discharge is not advisable.

The mother should be encouraged to feed the baby regularly to guard against dehydration, since dehydration can increase the severity of jaundice.

Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required.

Pregnancies complicated by red cell alloimmunisation with a minimal or no risk of fetal or neonatal anaemia require no specific treatment.

Future Risks

A woman with a history of a pregnancy or infant affected by HDFN should be referred for early assessment to a fetal medicine specialist in all further pregnancies.

Long-term consequences of red cell antibodies to women and their offspring

Women can be advised that there are no long-term adverse health consequences associated with the presence of red cell antibodies.

Clinicians should be aware that some infants may experience anaemia persisting for a few weeks following birth.

Clinicians should be aware that some infants may develop late anaemia which is usually due to hyporegenerative anaemia.

1. Purpose and scope

The purpose of this guideline is to provide an evidence-based approach to the prevention of perinatal morbidity and mortality due to alloimmune fetal anaemia and thrombocytopenia. It is not intended to prescribe the management of pregnancies complicated by other causes of fetal anaemia or thrombocytopenia.

2. Introduction and background epidemiology

The presence of maternal red cell alloantibodies is usually detected during routine antenatal screening. Women who have been transfused or who have had a previous pregnancy affected by HDFN are at risk of developing red cell alloantibodies. Population studies suggest that the incidence of red cell alloimmunisation in pregnancy is around 1 in 100 pregnancies (see Appendix 1).

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Anti-D is the most common antibody encountered in pregnancy. Because routine antenatal anti-D prophylaxis has reduced the incidence of anti-D alloimmunisation, the proportion of cases of severe HDFN caused by other red cell antibodies has increased. Although the clinical management of pregnancies affected by anti-D, anti-c, anti-K and ABO incompatibility is similar, the management of pregnancies affected by other red cell antibodies may require specialist advice. Information about the prevalence of clinically significant red cell antibodies in the UK population is limited (see Appendix 1).

3. Identification and assessment of evidence

This guideline was developed in accordance with RCOG Green-top Guideline No. 8, Good Research Practice. A systematic review of the evidence was undertaken using the following databases: the Cochrane Library, Medline, Embase and CINAHL. Where appropriate, the findings of these searches were combined using standard methods of meta-analysis. The quality of the evidence was assessed using the SIGN 50 methodology checklists (see Appendix 2). The evidence was graded using the SIGN 50 system (see Appendix 3). Where no evidence was found, the recommendations were based on good practice points agreed by the Guideline Development Group. Further information about the development of this guideline is available from the Clinical Effectiveness Unit at the RCOG (see Appendix 4).

4. Prepregnancy counselling

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5. Assisted reproductive techniques (ART)

Invasive testing solely for the purpose of determining the need for further surveillance is not justified because the result rarely alters management. However, invasive testing is justified in order to provide information on the fetal blood group and to exclude fetal anaemia.

In addition to providing information on fetal blood group and fetal anaemia, invasive procedures carry a risk of miscarriage, fetal loss and other complications. Discussion of these risks should be undertaken before proceeding to invasive testing.

6.6 If the fetus is at risk of anaemia, when should referral to a fetal medicine specialist take place?

Referral to a fetal medicine specialist should occur when there are rising antibody levels/titres, a level/titre above a specific threshold (see section 6.7) or ultrasound features suggestive of fetal anaemia.

Referral should take place if there is a history of unexplained severe neonatal jaundice, neonatal anaemia requiring transfusion or exchange transfusion, in order to exclude HDFN as the cause.

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[illegible]

[illegible]

[illegible]

6.8 Once detected how often should antibody levels be monitored during pregnancy?

Anti-D and anti-c levels should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery.

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6.14 Should RhD-negative women who have anti-D or non-anti-D antibodies receive routine antenatal or postnatal prophylaxis?

Anti-D immunoglobulin should be given to RhD-negative women with non-anti-D antibodies for routine antenatal prophylaxis, for potential antenatal sensitising events and postnatal prophylaxis.

If immune anti-D is detected, prophylaxis is no longer necessary.

Discussion and liaison with the transfusion laboratory are essential in determining whether anti-D antibodies are immune or passive in women who have previously received anti-D prophylaxis.

Ant D I I uno, o, u n prop , s s , y n to pr y nt. D n , t y d , n or n, nt D

t u n nt n st tus For nt o s t r t n nt D C E n oo ost n to o t n rd t r on oo tr ns us on ntr so t on tr nsport t r qu r For nt o s r d p t oo s r r n t on s r or d p t oo r qu r I nsu nt oo s v oo n to o t n rd t t on Fro n B oo B n n v rpoo or r r oo onors up to on t t n n ro n oo nt s o ppro t ours or un ts to t u t p s n pro ss to r ov ro t un t ours or t on un ts p us t on tr nsport t on t

s o ro n un ts on t s t ours n t nnot r ro n C n up r r onors to on t r qu r s v n not t on r poss r t on s us o n ss r v ro o t st n n o t r pro ss n t up to or n t n o o t n n ppropr t onor oo s ou t ount o n t d n s ost t on t t oo

7.1.2 Blood for intrauterine transfusion (IUT)

Clinicians should be aware that blood for IUT has the same requirements as blood for neonatal exchange (see 7.1.3), except that plasma is removed by the blood centre to increase the haematocrit to 0.70–0.85 and it is always irradiated.

D

B oo or I s pro ss to or r s t on s ours t r pro ss n n not r qu r s n u o or n s not un ss n r n [11] As t n on t n oo t rn nt o s o t r t n nt D C E or r pr s nt v n rn n s ou v n r poss to nsur t t su t oo n t v or r v nt nt ns s v

Ev n V

7.1.3 Blood for neonatal exchange

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative, negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample.

D

Blood should be less than 5 days old (to ensure low supernatant potassium levels), CMV negative and irradiated unless the risk to the baby of delaying exchange transfusion while obtaining irradiated blood outweighs this. It should be plasma reduced (rather than in saline-adenine-glucose-mannitol [SAGM] additive solution), with a haematocrit of 0.50–0.60.

D

I t rn nt o s o t r t n nt D C E or r pr s nt un ts n t v or t os nt ns r qu r s r o o t r ntr s I nv o t s z st s ou s uss su s s t t oo tr ns us on or tor n v n o r v r to nsur t t ppropr t oo s v n rr t n oo s s z o ours [11]

B oo s ou G n t v to n s t r s o G n t on n t n on t n rr t to pr v nt tr ns us on sso t r t v rsus ost s s u to t r vo u o oo tr ns us to n on t P s r u oo spr r s oo susp n n AG ont ns u os n r su t n r oun po n nn to t pot nt ur t n ntr r r pr ssur ts r d n to r t o s or su nt orr t on o n t r n ut t out n un pt to r t t ts sso t r s s to t n on t [11]

Ev n V

B oo or n tr ns us on s not o t n rd r on oo ntr routn sto s roups n t v n pos t v n t v n n t v n un ts on t s B oo tr nsport t n t or ross t s ou so t n nto ount

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7.1.4 Blood for neonatal small volume ('top-up') transfusion

Blood should be ABO compatible with the neonate and mother (to avoid ABO HDFN from the woman's anti-A or -B antibodies present), RhD negative (or RhD identical with neonate), K negative and negative for the corresponding antigen to which the woman has an antibody and cross-match compatible with the woman's blood sample.

Blood should be CMV negative but does not need to be irradiated unless the neonate has had a previous IUT and blood can be stored in SAGM (rather than plasma reduced) and be up to 35 days old (as a top-up transfusion is a much smaller volume than an exchange transfusion).

Clinicians considering transfusion in a neonate must check if the baby has had an IUT, as if so, blood must be irradiated to prevent transfusion-associated graft-versus-host disease.

[illegible]

[illegible]

Clinicians should be aware that if bilirubin levels rise rapidly or above the interventional threshold, phototherapy and/or exchange transfusion may be required.

C

Pregnancies complicated by red cell alloimmunisation with a minimal or no risk of fetal or neonatal anaemia require no specific treatment.

✓

Gu n rd ICE su l r s s t ppro to t n nt o-n on t un n u n ru n n o o n l on tor n n t ons or p otc t r p ntr v nous l uno o u n us n n tr ns-us on E n tr ns-us on l us to n s v r n l t t n to tr t s v r p r ru n l u tr ns-us on s un rt n t t l so-r l ov n, o t t nt o o t r s n t ss ru n

Ev n v

11. Future risks

11.1 What is the risk of recurrence in a future pregnancy?

A woman with a history of a pregnancy or infant affected by HDFN should be referred for early assessment to a fetal medicine specialist in all further pregnancies.

✓

r s o-r urr n o-HDF p n son t p o- nt o t p t rn not p s s t s v r t n st t on ons to- t n l

12. Long-term consequences of red cell antibodies to women and their offspring

12.1 What are the long-term health consequences for the woman?

Women can be advised that there are no long-term adverse health consequences associated with the presence of red cell antibodies.

✓

r r no on t k t ons qu n s-or d n ut n nt o r s ou rr- n s tr ns-us on s r qu r-

Ev n v

12.2 What are the long-term health concerns for the children of women with red cell antibodies during pregnancy?

Clinicians should be aware that some infants may experience anaemia persisting for a few weeks following birth.

C

Clinicians should be aware that some infants may develop late anaemia which is usually due to hyporegenerative anaemia.

C

An p rs st n, or s- s t r t s usu t r su t o-p ss y qu r- l t rn nt o s us n, ont nu- l o ss

t n l v op u to tr ns nt suppr ss on o-n on t r t ropo s s ts s- u to tr ns-us on B s o v r qu r- s y r l s r t p rt u r r s

Ev n v

A- t- n-nt s v suppr ss on o- r t ropo s s t o nu rs o-r t u o t s- sp t o p vo u n no r t ropo t n v u s op up tr ns-us ons r r qu r- on t n-nt s s l pt t r s ss v n t t n- n r qu n o- top up tr ns-us ons r s- r d n nt r t ropo t n s us

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13. Recommendations for future research

Bo n [illegible] o [illegible] nn n FA H n G nt o ou
[illegible] t rn oo roup o un t on *Obstet Gynecol*
r G D t r C rp nt r n F Z n
os r t Co or t y Group or Dopp r Ass ss nt
o t Boo t o t n An F tus s on nv s y nos s
Dopp r u tr sono r p o t n u to t rn
r o un t on *N Engl J Med*
B A A r G B r o G Br n C C D
H rn n An r E t I G pr t u n s us o
Dopp r u tr sono r p n o st tr s *Ultrasound Obstet Gynecol*
Br ts Co tt or t n r s n H to o r ns us on
s For r ns us on u n s or n on t s n o r
r n *Br J Haematol*
r ns us on s For A n nts n orr t ons to
r ns us on Gu n s or n on t s n o r r n
BC H n to Gu n s or us o r s
ro n p s r opr p t t n r osup rn t nt BC H
Br J Haematol
Br ts Co tt or t n r s n H to o Gu n s or
pr tr ns us on p t t pro ur s n oo tr ns us on
or tor s on on BC H
s u n s o u nts Co p t Gu n or
su ss on to F p
A v sor Co tt ont t o Boo ssu s n r ns
B C to ov rus t st oo o pon nts pos t on
st t nt on on D p rt nt o H
ovu n t ons n st t st s t ons
t ons An Gu n DH
n H o on s sA out n nt n t nt D
prop s or D n t y n s st t r v n
ond v u t on *Health Technol Assess*
oo o BE r A s H o t tr ns us on
r t on su ss u tt nu t on t pr n so on n
os uno o u n *Clin Lab Haematol*
n t H B r Gr A H s ss E or o D t
BC H B oo r ns us on s For Gu n on t
nv st t on n n nt o ut tr ns us on r t ons

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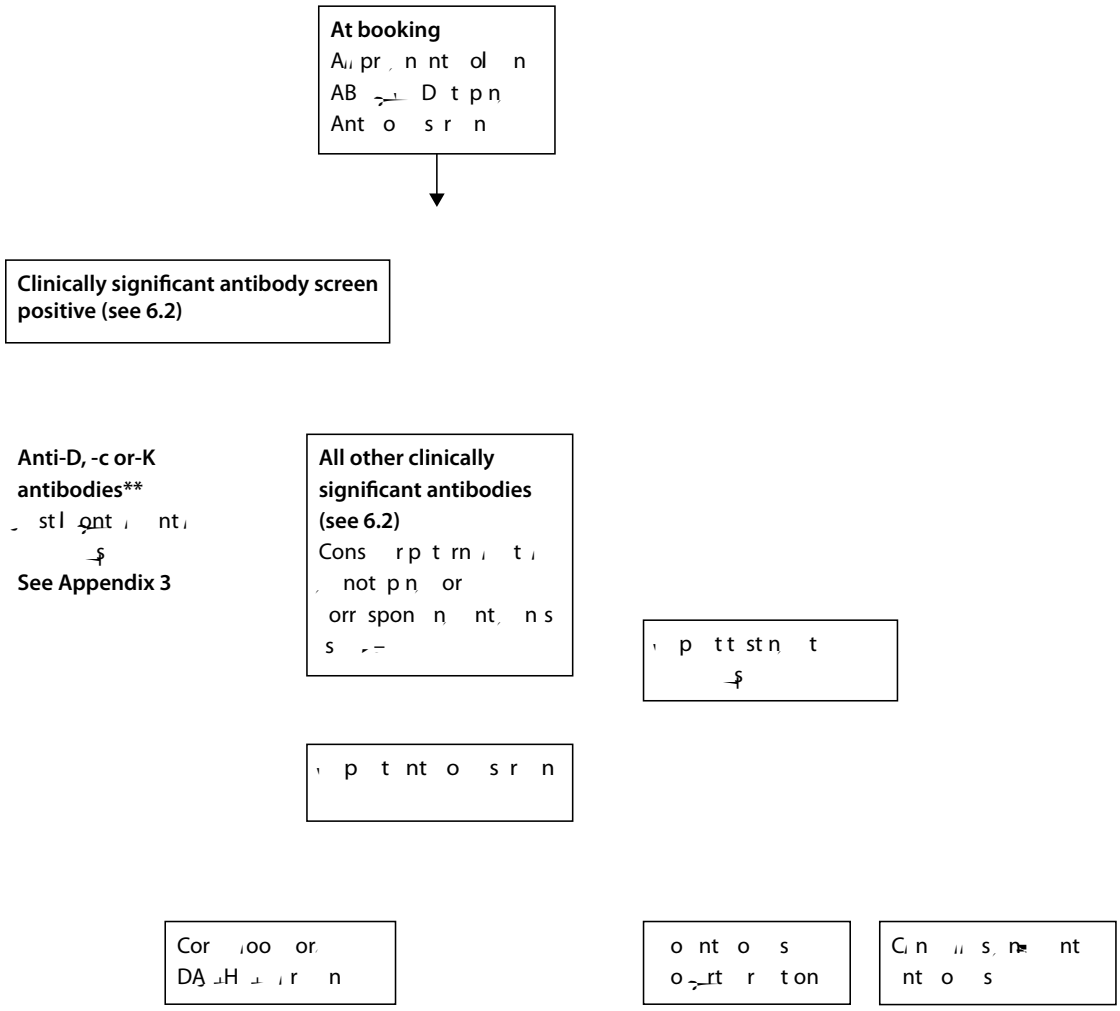
Appendix I: Red cell antibodies showing published clinical significance

Antibody	HDFN	Haemolytic transfusion reaction
D	evere in fetus and neonate	evere
c	evere in fetus and neonate	evere
K	evere in fetus and neonate	evere
c, E	evere in fetus and neonate	evere
E	Yes in neonate	Yes
C	Yes in neonate	Yes
e	Yes in neonate	Yes
Ce	Yes in neonate	Yes
Fy[a]	Yes in neonate	Yes
Fy[b]	Yes in neonate	Yes
Fy	No	Yes
J[a]	Yes in neonate	Yes
J[b]	No	Yes
	Yes in neonate	Yes
s	Yes in neonate	Yes
	Yes in neonate	Yes
M	Yes occasiona y	Yes if active at C
N	Mi d case	Yes
H Bo bay	Yes in neonate	Yes
G	Yes in neonate	Yes
	Yes in neonate	Yes
Kp[a]	Yes in neonate occasiona y	No
C[w]	Yes in neonate occasiona y	No
e	No	Yes

Anti D c and K are the three ain antibodies that have been reported to cause severe anae ia aundice or death in the fetus or neonate. Many other antibodies can cause anae ia or aundice predo inant y in the neonata period but there have a so been occasiona case reports of the **fetus** being e ret fecc et fecc et gw of i te oc g her aundice p is ana e hatatic

Appendix II: Timing and frequency of antibody screening in pregnancy



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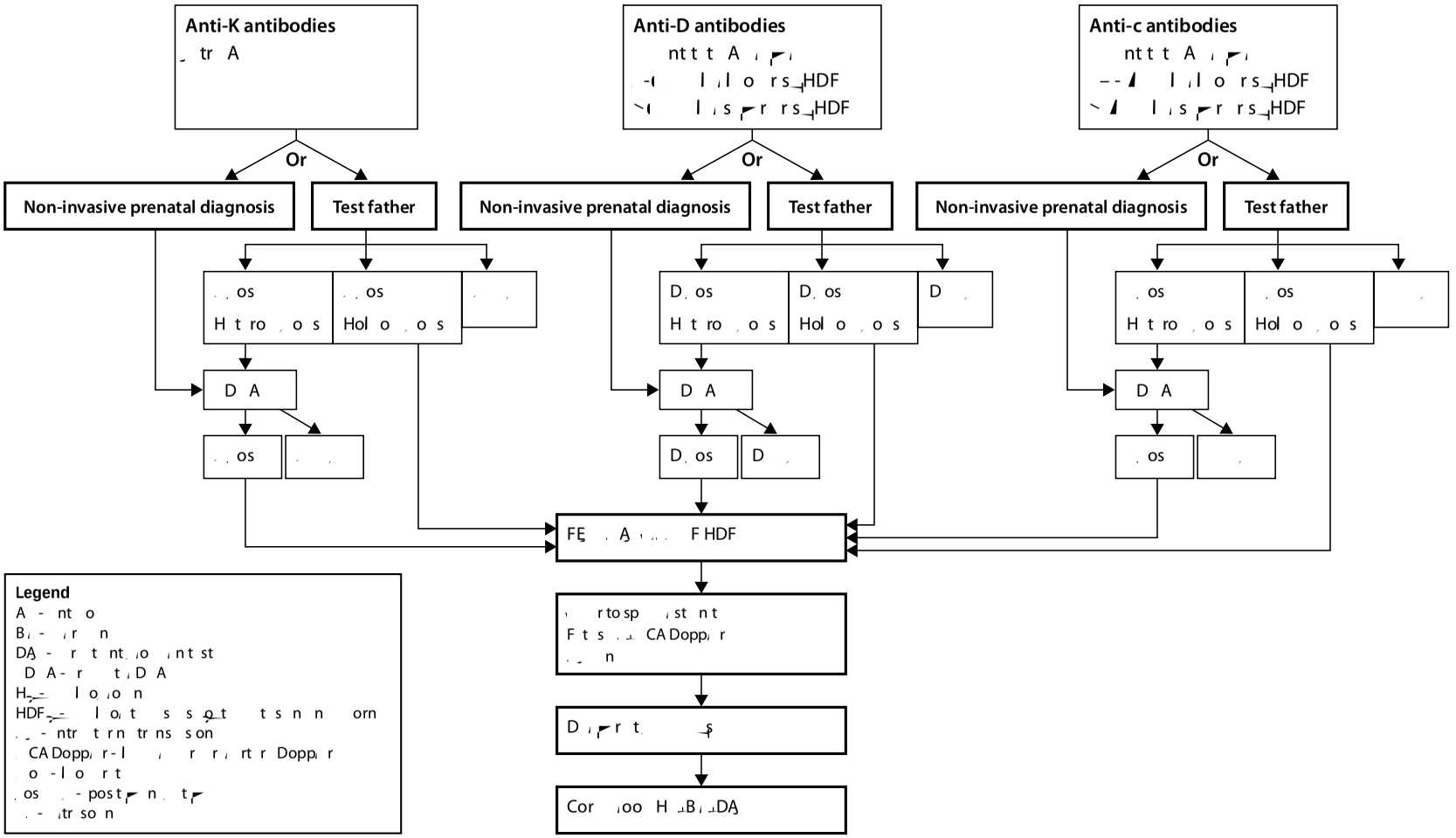
Appendix III: Management algorithm for pregnancies complicated with anti-D, anti-K or anti-c alloimmunisation



Appendix IV: List of abbreviations

A	ss st r pro u t v t n qu s
BC H	Br t s Co l tt or t n r s n H l to o
C	td ov rus
C D	tr t p osp t tros
DA	r t nt o u n t st
FB	t oo s l p n
D A	r t D A
HDF	l o t s s o t tus n n orn
H	l o t tr ns us on r t on
IA	n r t nt o u n t st
I G	l uno o u n G
I	ntr ut r n tr ns us on
CA	l r r rt r p s sto v o t s
o	l u t p s o t l n
ICE	t on Inst tut or H t n C r E n
	p vo u
AAD	rout n nt n t nt D prop s
D	sus D
AG	s n n n u os l nn to

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Appendix V: Explanation of guidelines and evidence levels

C n , u , n s r s st\ t , , v op st t\ , nts ● ● ss st , n ns n p t, nts n \ n, , s ons , out ppropr t tr t , nt ›or sp , ›› , on t ons E ● , u , n s s st\ t , , v op us n, st n r s \ , t o o o, E t , t s o-t s pro , ss n , , ›oun n C n , Gov rn n , A v , o , *Development of RCOG Green-top Guidelines*' v , , , ont , ‹ C G , s t , t