

Malaria diagnosis and treatment guideline

The Hospital for Tropical Diseases

Trustwide guideline

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Owner / Sponsor	Hospital for Tropical Diseases (HTD)
Review By Date	1st November 2019
Responsible Director	Dr V Gant - Divisional Clinical Director, Infection
Monitoring Committee	Hospital for Tropical Diseases Consultants' Forum
Target Audience	All medical staff at all levels, involved in the care of patients with malaria
Related Trust Documents / Policies	Documents listed here must be referred to within the guideline
Number of Pages and Appendices	14 pages
Equalities Impact Assessment	Low

Document control information:

To be completed by Clinical Guidelines Facilitator or local governance lead in the case of local documents

Version number	2.0
Approved By	Antimicrobial Usage Committee
Date Approved	7 th November 2016
Publication Date	29 th November 2016
Document Control Number	AUC091/02
Title and document control number of document this replaces	Malaria diagnosis and treatment guideline, version 1.0
Summary of significant changes	<p><u>Update (7th Nov 2016)</u></p> <ul style="list-style-type: none"> • Errors in version 1.0 corrected in pregnancy section relating to chloroquine and proguanil • G6PD deficiency management statement clarified • Quinine dosing clarified • Chloroquine dosing clarified • Content now reflects new WHO guidance • Clarity statement regarding management of HIV infected individuals

Contents

Section	Page number
1.0 Summary	2
2.0 Introduction	2
3.0 Objectives	2
4.0 Scope	2
5.0 Duties & Responsibilities	2
6.0 Development & Evidence base	3
7.0 Consultation	3
8.0 Recognition	3
9.0 Diagnosis	4
10.0 Assessment of severity	
10.1 Classification of severity	5
10.2 Severe falciparum malaria: complications	5
11.0 Treatment	6
12.0 Pregnancy	8
13.0 Continuing care	8
14.0 HIV	8
15.0 Uncomplicated falciparum malaria	9
16.0 Non-falciparum malaria	10
16.1 Initial treatment	10
16.2 Relapse prevention	10
16.3 Patient with G6PD deficiency	11
16.4 Pregnancy	11
17.0 Guidance implementation	11
18.0 Review, Monitoring & Compliance	11
19.0 References	11

1.0 Summary

- 1.1 These guidelines are for doctors treating patients with malaria. Advice for healthcare workers on malaria prophylaxis is available via the National Travel Health Network and Centre website: www.nathnac.org.
- 1.2 Key Points
 - Test for malaria in all travellers returning from the tropics with a fever
 - Confirm a positive malaria dipstick rapid diagnostic test with a blood film
 - If you are not certain of the infecting species then treat as falciparum malaria
 - Admit patients with falciparum malaria for a minimum 24 hours observation
 - Assess severity based on a parasitaemia >2% and / or complicating clinical features:
 - Conscious level, acidosis, pulmonary oedema, renal failure, anaemia, hypoglycaemia
 - In severe malaria start IV Quinine with loading until IV Artesunate is available
 - Patients with severe falciparum malaria can deteriorate rapidly so involve ICU early
 - Discuss all cases of severe malaria with HTD
 - Read the more detailed notes below

2.0 Introduction

Imported malaria is responsible for approximately 11 000 cases per year in the European Union, of which up to 2000 a year are seen in the UK¹. It is one of the commonest diagnoses in Infectious Diseases units throughout the UK with around 2000 cases a year², and is the principal imported tropical infection causing avoidable deaths every year. Most cases are caused by Plasmodium falciparum with a case fatality rate of 1.2% in the UK³. In many non-tropical settings malaria is the commonest identified cause of fever in returned travellers^{4,5}. Over the past two decades, travel to malaria-endemic countries has been rising steadily, and health care providers are increasingly faced with returned travellers.

3.0 Objectives

To provide good practice and consistency in the diagnosis and management of patients with malaria

4.0 Scope

This document applies to all adult patients (18 years and above) who require diagnosis and / or treatment for malaria.

5.0 Duties & Responsibilities

The Hospital for Tropical Diseases at University College Hospital in London provides a 24 hour service to doctors for malaria-related advice. Contact the UCLH switchboard on 020 3456 7890 and ask to speak to the Tropical Medicine Registrar. Alternatively ring the on call mobile: 07908 250924. We may offer to transfer your patient to our intensive care unit, which has extensive experience at managing severe malaria, or provide an out of hours supply of Artesunate after discussion of the case.

During the working day urgent blood films for review should be sent to the Parasitology Department, Hospital for Tropical Diseases, Mortimer Market Centre, Capper Street, London, WC1E 6JB: telephone 020 3456 7890 ext 75414. To review films out of hours and at weekends you should discuss the patient with the Tropical Medicine Registrar and then courier samples to the Nurse in Charge, Ward T8, University College Hospital, 235 Euston Road, London NW1 2PG. S/he will contact the Parasitologist on call when the sample arrives.

6.0 Development & Evidence Base

Locally, there is a need for guidelines that aid clinicians with the diagnosis and management of malaria. These guidelines have been amended from the previous version based on international guidance^{6,7}.

7.0 Consultation

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8.0 Recognition

Five species of malaria parasite cause clinical disease in humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and, in specific parts of SE Asia, *P. knowlesi*. Falciparum malaria has the potential to cause severe disease and this section concentrates on identifying and treating these patients. *P. knowlesi* and occasional *P. vivax* can also produce severe and complicated malaria, especially in older patients.

All travellers returning from the tropics with a fever or recent history of fever should have a blood film for malaria. This should be done as an emergency and the result followed-up on the same day. Delay in requesting a blood film is an avoidable reason for poor outcome.

Patients with falciparum malaria generally present within a month of returning from the tropics but 10% of cases present up to 3 months after travel. Patients infected with other species of malaria can present many months later and therefore **we recommend that malaria is considered in the differential diagnosis up to one year after returning from the tropics.** Occasionally it can present after a year (mainly vivax). Anti-malarial prophylaxis is at best 95% effective but often patients miss doses and a history of prophylaxis should not lower your index of suspicion for malaria.

For more detailed guidelines see the UK malaria treatment guidelines (on HTD website) which have a fuller referencing of the evidence base.

9.0 Diagnosis

A thick and thin blood film examined by an experienced microscopist and correlated with a clinical history **is the gold standard for diagnosis**. Once the blood arrives in the lab it takes about 45 minutes to prepare the film and a further 15 – 20 minutes to examine and report the slide. The report should include (1) the species (2) the parasite density or 'parasitaemia' and (3) the parasite stage: trophozoites, (pre)schizonts and gametocytes.

The presence of schizonts may mean the peripheral parasitaemia is under representative of true parasitaemia due to sequestration and that a further replication cycle is imminent (so parasite counts will go up).

Antigen dip stick tests are simple and reliable alternatives for hospitals where malaria is uncommon and lab technicians may have less experience in microscopy. The tests have three main problems: (1) they are less sensitive than good thick film microscopy, (2) they rely on detecting parasite antigen rather than live parasites and may therefore be positive in patients who have been recently treated (up to 2 weeks), (3) it is not possible to determine the parasitaemia or stage of parasite. PCR is the most sensitive test but is not widely used in routine clinical practice. It is available at HTD and LSHTM for complex cases after discussion with the HTD Parasitology team.

We therefore recommend that all positive antigen tests are followed up with microscopy and where there is uncertainty that the film is urgently sent for review to either the Parasitology Laboratory at the Hospital for Tropical Diseases or the Malaria Reference Laboratory at the London School of Hygiene & Tropical Medicine. For rapid clinical advice use the HTD. The HTD provides a 24 hour referral service for clinical advice and emergency review of blood films.

Empirical treatment for malaria is usually not indicated, nor is there a rule for the number of negative blood films that exclude malaria as a diagnosis. In the HTD lab it is rare that malaria is not seen on the first film. If in doubt discuss the case with the tropical medicine registrar on call at HTD.

Patients with falciparum malaria can deteriorate rapidly, even with correct treatment. **We therefore recommend you consider admitting all patients with falciparum malaria for initial treatment. If there is doubt about the species, or there is co-infection on the film, then treat as falciparum malaria until it is clear.**

10.0 Assessment of severity

A good clinical assessment of severity can be made in the emergency department using simple signs. The main syndromes that lead to deaths in adults are cerebral malaria (reduced level of consciousness in practice), acute lung injury and renal failure. Note the following: conscious level, blood pressure, respiratory rate, evidence of prostration (including GCS), presence of jaundice, blood glucose, lactate and urine output. All patients should have a blood film with parasitaemia plus standard laboratory tests for creatinine and haemoglobin. All pregnant women should be treated as potentially severe and senior advice sought

A chest radiograph is recommended in breathless patients.

Bacterial co-infection is uncommon in adult travellers but should be considered when a malaria patient presents with shock or with focal signs such as pulmonary consolidation.

10.1 Classification of severity

UNCOMPLICATED Parasitaemia <2% and no schizonts and no clinical complications

POTENTIALLY SEVERE

Requires parenteral (iv) treatment Parasitaemia >2%
 or Parasitaemia <2% with schizonts reported on blood film
 or Parasitaemia <2% with complications

The above criteria are based on evidence to provide the safe management of people with severe malaria in a non-endemic setting. In exceptional circumstances, where no blood film is available, consider using intravenous treatment after discussion with HTD. The Hospital for Tropical Diseases provides a 24 hour service for emergency review of blood films (details above).

Even patients with low parasitaemias can develop complications.

NB: in malaria-endemic countries the World Health Organisation recommends a parasitaemia of 5% as the cut off for severe disease. This is in part because frequently infected patients develop partial immunity. However this immunity wanes rapidly when patients stop being infected regularly and we recommend that all patients presenting to UK hospitals are considered 'non-immune'.

There are 200 to 300 cases of severe malaria a year in the UK with a significant mortality rate. Older age (>60) is an independent predictor of poor outcome. ([Checkley et al 2012](#))⁸

10.2 Severe falciparum malaria in adults: complications

Note that children and especially young children have a different spectrum of severe disease.

The priority in severe malaria is to get an effective antimalarial at high doses into patients as soon as possible. All other management is secondary.

1 Cerebral involvement

- May manifest as drowsiness, confusion, stupor, fits or coma - even mild drowsiness or confusion should be regarded as showing possible cerebral involvement
- Exclude hypoglycaemia, especially in pregnant women
- Maintain airway, consider ventilation if unconscious
- Convulsions should be controlled with diazepam
- Status epilepticus should be managed with anti-convulsants, but beware of potential interactions with quinine

2 Renal Failure

Defined as a urine output <0.5 ml/kg body weight/hour, failing to improve after re-hydration and serum creatinine >265 mol/l. It may come on several days into treatment.

- Rising plasma urea and creatinine, oliguria, and finally anuria. (Hyponatraemia is common in malaria and does not usually require correction)
- Consider a 500ml fluid challenge to exclude pre-renal failure.
- Consider early haemofiltration or dialysis especially if potassium is rising.
- Almost all patients eventually regain renal function

3 Pulmonary Oedema

- Correction of hypovolaemia should be carried out with caution
- Earliest sign is a rise in the respiratory rate
- An **acute lung injury** (ALI/ARDS) may develop as a late complication as the peripheral parasitaemia is resolving. The management is to optimise oxygenation generally by ventilation.

4 Hypoglycaemia

- In adults, particularly common in pregnancy. It is exacerbated by quinine stimulating insulin release
- In children hypoglycaemia is more common and may contribute to impaired consciousness
- Give 1 ml/kg 50% dextrose by IV bolus followed by an infusion of dextrose

5 Anaemia

- Severe anaemia is uncommon in travellers and non-pregnant adults but common in children and some pregnant women.
- Correct Hb <8g/dl with packed cells and monitor fluid balance, taking care not to overload. Otherwise only transfuse if there is evidence anaemia is causing medical compromise (e.g. angina).

6 Metabolic and lactic acidosis

- is common and predictive of severity and sometimes a poor prognosis

7 Hypovolaemia / Shock

- Dehydration requires careful clinical assessment
- Monitor for signs of pulmonary oedema during rehydration – patients can easily be over-hydrated; non-cardiogenic pulmonary oedema is much more common in severe malaria than bacterial sepsis
- Children with malaria in Africa are particularly prone to bacterial co-infection. This is less common in previously healthy adult travellers.
- Shock is not common in malaria and often indicates bacterial co-infection. If an adult patient presents with malaria and shock send blood cultures and consider adding in empirical broad spectrum antibiotics covering Gram negative organisms

8 Bleeding / DIC

- Thrombocytopenia is almost invariable and is not necessarily an indication of severity.
- Platelet transfusions are only indicated if there is evidence of bleeding and a very low count (<50); hypersplenism in malaria means platelets if transfused are consumed very quickly.
- Beware early DIC and check clotting, fibrinogen and D-dimers in severe malaria. There is no specific evidence-based treatment.

9 Jaundice

- Jaundice is common and defined on clinical grounds or bilirubin > 50 mol/l
- Jaundice alone is not an indication for parenteral treatment. It generally indicates red cell destruction rather than liver disease.
- Usually pre-hepatic due to RBC destruction causing unconjugated hyperbilirubinaemia

11.0 Drug treatment of Severe Falciparum Malaria

This is a medical emergency; early treatment is life-saving. Start effective anti-malarial drug therapy immediately – with artesunate if available. Quinine is the alternative if artesunate is not available but artesunate is associated with lower mortality. If parenteral treatment is not immediately available (e.g. pharmacy out of hours) start oral treatment whilst waiting for it to arrive. Oral quinine is available on almost all wards.

N.B All requests for artesunate from peripheral hospitals (i.e. non-UCLH hospitals) to HTD must be supplied via pharmacy, including out-of-hours. Receiving pharmacy will arrange the courier.

Artesunate is the drug of choice for all patients with severe malaria: it has a rapid effect on parasite clearance and has been shown to reduce mortality compared to quinine in clinical trials in patients of all ages (SEAQUAMAT Lancet 2005; AQUAMAT Lancet 2010). However Artesunate is not yet licensed in the UK and some hospitals do not keep a supply. .

The HTD may be able to facilitate a supply to you after discussion with the Tropical Medicine registrar on call; this will however need to be a pharmacist to pharmacist discussion. **In the meantime do not delay giving IV Quinine whilst waiting for Artesunate to arrive** as this may take 6 – 12 hours.

If the patient has features of severe malaria consider managing in a specialist infection unit or High Dependency Unit with frequent medical review and accurate fluid balance. It is not uncommon for patients to develop an acute lung injury (especially if over hydrated) or to develop renal failure several days after admission.

Artesunate

The dose of Artesunate is 2.4mg/kg (ABW) given as an IV bolus at 0 hours, 12 hours, 24 hours and once daily thereafter. Artesunate has few side effects and there is no need to adjust for renal impairment or to monitor for cardiac toxicity. It does not promote hypoglycaemia.

- Switch to an oral antimalarial drug once the patient is improving, parasitaemia is falling and the patient can reliably swallow and complete a course of oral treatment. Many options are acceptable and it does not need to be an artemisinin-based compound, although **Riamet (Artemether 20mg/Lumefantrine 120mg)** is licensed and available in the UK at an adult dose (>35kg weight) of 4 tablets initially then a further 4 tablets at 8 hours, 24h, 36h, 48h and 60 hours.
- Dihydroartemisinin/Piperaquine is an acceptable alternative ACT to Riamet and is now licensed in the UK (NB – dihydroartemisinin/piperaquine is not formulary at UCLH).
- If the patient has already received IV artesunate then this can be prescribed as 4 tablets PO BD (12 hourly) for 3 days.

It is good practice to examine daily blood films until the parasitaemia clears, or the patient is discharged; it is important to do so in severe cases. In most cases 48 hours of IV Artesunate followed by three days of oral ACT is sufficient treatment for cure. Occasionally, and particularly in patients with reduced ability to clear parasites (e.g. hyposplenism), a longer course of treatment may be required. If in doubt discuss with the HTD consultant on call.

Other oral switch options include (adult doses):

- Doxycycline 200mg once daily for 7 days
- Atovaquone-proguanil (Atovaquone 250mg/Proguanil 100mg) 4 tablets once daily for 3 days
- Clindamycin 450mg 3 times daily for total 7 days (safe in pregnancy)

The full duration (including of artemisin combination treatment) of the second line drug should be prescribed irrespective of if the patient has already received IV quinine or artesunate.

Quinine

Quinine is given as an IV infusion over 4 hours. The dose is 10mg/kg in 250ml of normal saline up to a maximum 700mg. **The first dose should be a loading dose of 20mg/kg (ABW)** unless the patient has received Mefloquine in the preceding day, when a normal dose of 10mg/kg should be

used. IV quinine is given 3 times daily. Tinnitus is expected, reversible and not an indication for stopping quinine.

Quinine is a class 1 anti-arrhythmic drug. It interacts with other class 1 agents to lengthen the QT interval, predisposing patients to Torsades de Pointes. Therefore check an ECG before starting IV quinine and in patients with underlying cardiac disease use cardiac monitoring and consider withholding regular anti-arrhythmic medication. IV quinine also induces endogenous secretion of insulin thereby promoting hypoglycaemia. Monitor a patient's BM every 2 – 4 hours whilst on IV quinine.

Give a follow on second line drug as above for artesunate (artemether-lumefantrive, or doxycycline, or clindamycin, or atovaquone-proguanil).

Patients do not need both IV quinine and IV artesunate. When the artesunate arrives you should discontinue the quinine once the patient has received the first dose of Artesunate.

When IV quinine alone is used then patients should receive a total of 7 days treatment (IV plus PO). Quinine therapy should be accompanied by a second drug such as Doxycycline or Clindamycin for seven days to be started when the patient can swallow (see details below). Otherwise the same principles for oral switching (above) apply to quinine as to artesunate.

Exchange transfusion is no longer recommended.

12.0 Continuing care

The decision to discharge a patient is based on a combination of clinical response, declining parasitaemia and home circumstances. Before leaving, offer patients advice on future anti-malarial prophylaxis.

There is increasing evidence of haemolytic anaemia following intravenous artesunate therapy. Anaemia tends to occur between 2-4 weeks after artesunate treatment. We recommend weekly full blood counts are done during this period in patients who have received intravenous artesunate, and for all patients who become symptomatic with shortness of breath or have other symptoms compatible with anaemia should have a full blood count.

13.0 Pregnancy

Falciparum malaria in pregnancy is likely to be more severe, and parasite counts may be higher than suggested by the peripheral blood film due to placental sequestration. Pregnancy complicates malaria treatment, and even when the mother makes an uncomplicated recovery there is an increased risk of stillbirth. **Involve HTD / infectious disease consultants early** in all cases.

Artesunate is the drug of choice for **severe** malaria in all stages of pregnancy; the risks of undertreating the malaria are serious to both mother and pregnancy. Quinine is an alternative where artesunate is not available in all stages of pregnancy and is used in standard doses (ABW) until artesunate becomes available. Note quinine and pregnancy both can lead to hypoglycaemia.

14.0 HIV

Malaria with HIV co-infection may be more severe, there is a higher likelihood of bacterial co-infection, and of antimalarial / antiretroviral interactions. Seek HTD consultant advice.

15.0 Uncomplicated Falciparum malaria treatment

Use oral treatment unless the patient is vomiting, in which case treat as severe falciparum malaria. Do not use a drug for treatment if the patient has been using it for prophylaxis (e.g. Malarone).

Oral Artemisinin Combination Therapy (ACT) is simple, effective and well tolerated. We recommend ACT as first line treatment although this may not be available in all UK hospitals. If there is a delay in sourcing ACT the priority is to start any effective anti-malarial drug; quinine is available everywhere.

First line:

Artemether-lumefantrine (Riamet)

4 tablets initially, followed by further doses of 4 tablets to be given at 8, 24, 36, 48 and 60 hours. Take with milk or fatty food as this aids absorption.

AL and other artemisinin (ACT) drugs should **not** be used for women with uncomplicated malaria in the first trimester of pregnancy without specialist advice; it is considered safe in the second two trimesters.

Second line

Alternative ACT: **Dihydroartemisinin/Piperaquine** (not formulary at UCLH, nor widely available). In patients 30-60 kg, 3 tablets daily for 3 days; in patients > 60k 4 tablets daily for 3 days.. It is currently recommended patients treated with DHA-Pip have a daily ECG.

Quinine plus Doxycycline

Quinine: 600mg PO every 8 hours (reduce to a 12 hourly regimen if patient develops severe cinchonism with tinnitus & deafness). Add to this Doxycycline 200mg once daily, both for a total of seven days unless infectious disease consultant suggests shorter quinine course. Do not give doxycycline in pregnancy or to children under 12 years.

Quinine plus Clindamycin

Quinine: 600mg PO every 8 hours (reduce to a 12 hourly regimen if patient develops severe cinchonism with tinnitus and deafness). Add to this Clindamycin 5mg/kg three times daily, both for a total of seven days unless infectious disease consultant suggests shorter quinine course. The combination is relatively safe and effective in pregnancy and is often recommended in the first trimester of pregnancy for uncomplicated pregnancy.

Atovaquone / Proguanil (Malarone)

4 tablets OD for 3 days. Take with milk or a fatty meal to increase absorption. Do not use if the patient took Malarone prophylaxis. Less evidence exists for the use of Atovaquone / Proguanil in treating malaria and there have been occasional reports of treatment failure in travellers, possibly linked to parasite resistance.

NB: Gametocytes, the sexual forms of the parasite, are relatively unaffected by most anti-malarial drugs and are of no clinical significance

Patients who have received halofantrine in the last 48 hours should not be given quinine without Consultant approval because of the potential risks of cardiac arrhythmias.

16.0 Non-falciparum malaria (*vivax*, *ovale*, *malariae*)

- Patients should be offered admission if unwell. Severe and occasionally fatal cases can occur, especially in the elderly⁹.
- If spleen enlarged, advise avoiding contact sports, strenuous activity.
- Generally patients with non-falciparum malaria can be managed as outpatients

16.1 Initial Treatment

First line: Artemether-lumefantrine (Riamet); if not available chloroquine

Artemether-lumefantrine (Riamet)

4 tablets initially, followed by further doses of 4 tablets to be given at 8, 24, 36, 48 and 60 hours. Take with milk or fatty food as this aids absorption. AL should **not** be used for women in the first trimester of pregnancy without specialist advice.

Chloroquine (as base) PO in divided doses (total dose) over 2 days.

Chloroquine phosphate 250mg tablets contain 155mg of chloroquine base. Therefore 310mg base is equivalent to 500mg chloroquine phosphate, which is two tablets

Standard adult dosing over 2 days, as in the table below

Time (hrs)	Dose (mg)	Tablets (No)
0	620	4
6	310	2
24	310	2
48	310	2

- Many patients of African origin report itching with chloroquine. This should not be considered as a contraindication to its use. It does not generally respond to anti-histamines and if troublesome an alternative such as quinine should be offered
- Patients with epilepsy should not be prescribed chloroquine without Consultant approval

16.2 Relapse prevention

No relapse prevention is completely effective, and patients should be warned to present to a doctor saying they had vivax if they have malaria symptoms in the 2 years following treatment.

***P. vivax*:**

The prevalence of both chloroquine and primaquine resistant *P. vivax* is increasing especially in Asia.

Primaquine 15mg bd for 14 days [Unlicensed drug] should be given to patients with *P. vivax*.

- **First** check G6PD level (heparin tube) - normal range 5.9 - 11.7 U/g Hb. If there is G6PD deficiency seek consultant advice before primaquine given; there is a real risk of haemolysis.

***P. ovale*:**

- *P. ovale* remains fully sensitive to chloroquine and primaquine. Therefore give a lower dose of **primaquine** 15 mg od x 14 days. Check G6PD (see above).

P. malariae has no hypnozoite stage and no second drug is required

16.3 Patient with G6PD deficiency

Discuss with HTD consultant. Where G6PD levels are mild or moderate consider once weekly primaquine 0.75mg/Kg for eight weeks .

16.4 Pregnancy

- Do not give primaquine in pregnancy or while breast-feeding.
- After treatment with chloroquine, relapse should be prevented by giving Chloroquine base 310mg (2 tablets) PO once a week
- After delivery & breast feeding primaquine can be given as normal

17.0 Guidance implementation

- The guidance will be available electronically on Insight and on the Hospital for Tropical Diseases website (www.thehtd.org)
- A paper copy of the guidance will be given to all medical staff working within Infection Division, during their Induction

18.0 Review, Monitoring & Compliance

Monitoring	Method	Lead	Frequency	Reporting	Acting on deficiencies/gaps
Adherent to treatment guideline	Audit	Prof D Lockwood, Clinical Audit Lead for Infection	2 yearly	HTD Audit Committee	HTD Audit Committee

19.0 References

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