Guidance on Management of Malaria in Children

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Signature of ratifying Group Chair	John Pappachan Chair of Children's Hospital Policy Review Group
Author(s) and title	Dr Sanjay Patel, Consultant Paediatric Infectious Disease
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Other stakeholders consulted e.g. other clinical networks, departments	Paediatric Infectious Diseases network Kazeem Olelekan (Pharmacist, UHS)
Summary of most recent changes (if updated guideline):	n/a
Relevant national or international Guidance e.g. NICE, SIGN, BTS, BSPED	WORLD HEALTH ORGANIZATION 2016. Guidelines for the treatment of malaria. Third Edition. World Health Organization, Geneva. LALLOO, D. G., SHINGADIA, D., BELL, D. J., BEECHING, N. J., WHITTY, C. J., CHIODINI, P. L. & PHE Advisory Committee on Malaria Prevention in UK Travellers.. UK malaria treatment guidelines 2016. J Infect, 72, 635-49.
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Is this document to be published in any other format?	No
Does this document replace or revise an existing document?	No

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Contents

Flowchart 1: **An overview of diagnosis and management of suspected malaria in children.**

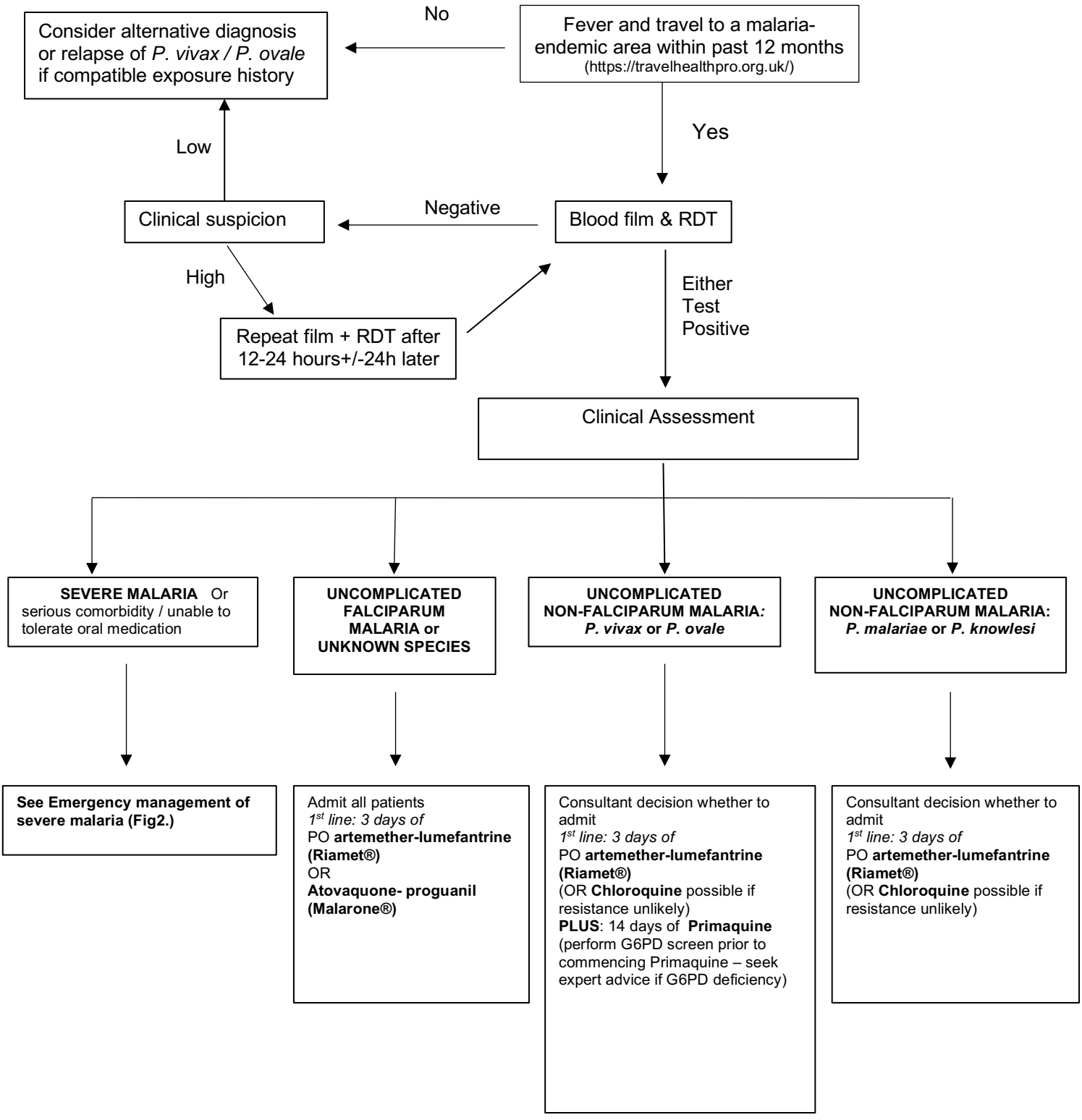
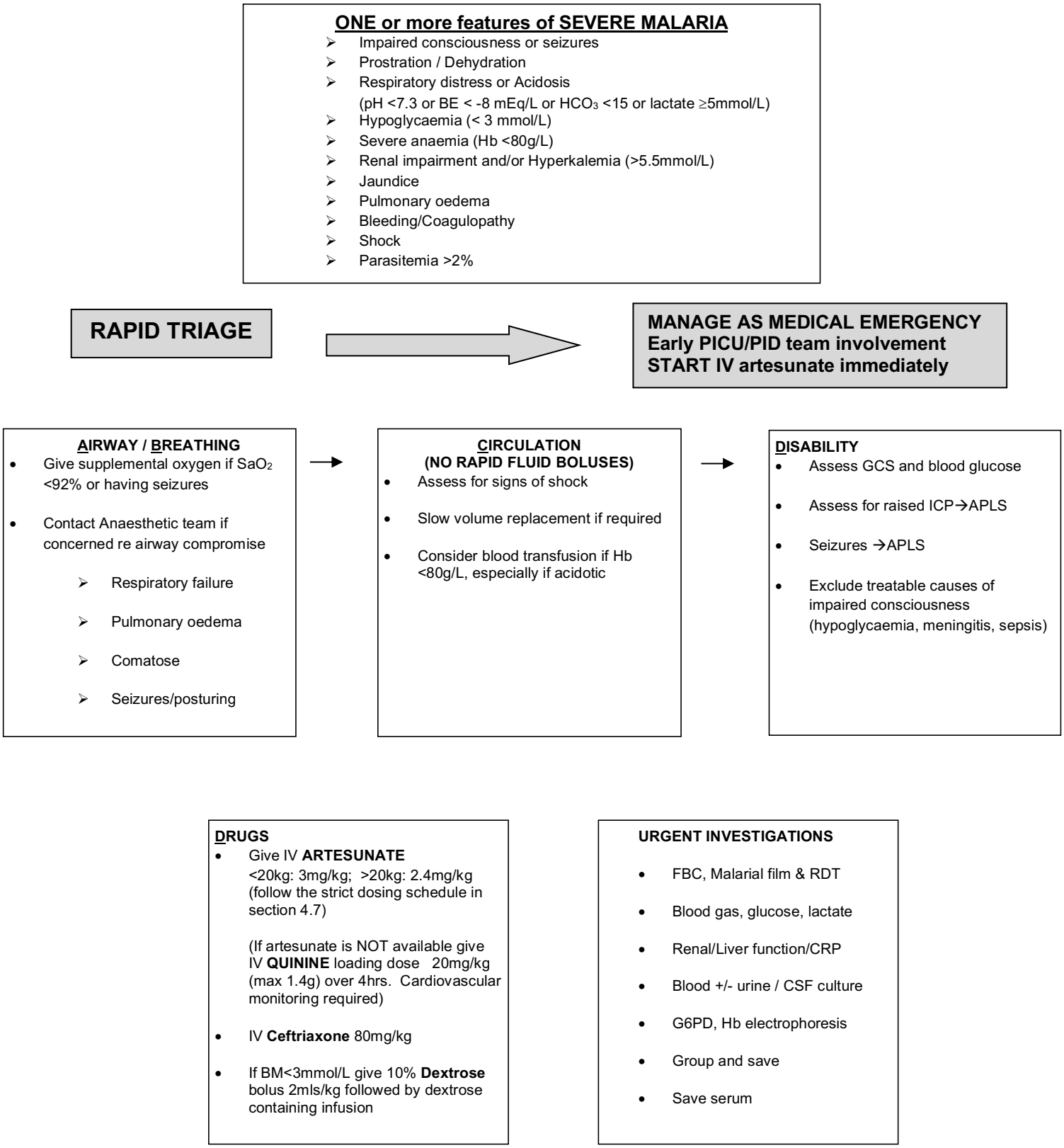


Fig 2. Emergency management of severe malaria



1) SUMMARY

- Call paediatric ID team (Southampton) if any concerns on 07824417993

- Malaria is an imported parasitic infection transmitted to humans by the bite of female Anopheles mosquitoes and is caused by five species of *Plasmodium - falciparum, vivax, ovale, malariae or knowlesi*.

- *P. falciparum* is the most common cause of severe malaria in humans but *P. knowlesi,* and more rarely *P. vivax* can also cause severe illness.

- Severe malaria is a medical emergency. Children with malaria can deteriorate extremely quickly, especially those with comorbidities. The diagnosis must be confirmed urgently and treatment started as soon as possible.

- Malaria should be ruled out in any child with fever (current or recent history) returning from a malaria endemic area within the last year, even if anti-malarial chemoprophylaxis was taken. Symptoms may be non-specific and "flu-like" including malaise, headache, rigors, cough, abdominal pain, myalgia, vomiting or diarrhoea.

    - Incubation period of malaria between 7 days and 3 months

- Up-to-date information on malaria endemicity, drug resistance patterns and chemoprophylaxis recommendations is available at:

  http://www.cdc.gov/malaria/travelers/country_table/a.html

  http://travelhealthpro.org.uk/country-information/

- All cases of malaria should be confirmed by parasitological tests (microscopy or Illumigene (LAMP technology) for malarial parasites and Rapid Diagnostic Test (RDT). Malaria cannot be clinically distinguished from other causes of fever.

- Intravenous (IV) artesunate is the treatment of choice for all children with severe malaria. If there is an anticipated delay in administering artesunate, IV quinine should be used until artesunate is available (NOTE: there is currently a long standing supply issue with IV quinine meaning that it may be challenging to obtain.) Broad spectrum antibiotics (e.g. IV ceftriaxone) should be administered to children presenting with severe malaria to cover for sepsis after appropriate septic screen (see full guideline below).
- Contact pharmacist to obtain IV artesunate. They should know where to obtain IV artesunate urgently out of hours:
    - Southampton – stored in emergency drug cupboard (key from security)
    - Chichester - kept in pharmacy. Out of hours need to call the on-call pharmacist to come in to access.
    - Dorchester – available in Yeovil and Bournemouth; agreement for artesunate to be urgently sent by taxi.
- Specialist Paediatric Infectious Diseases advice should be obtained as early as possible and cases of severe malaria should ideally be managed in a tertiary centre with paediatric intensive care facilities.

2) DEFINITIONS / ABBREVIATIONS

a. *Severe Malaria* – It is defined as the presence of one or more of impaired consciousness or seizure, prostration, acidosis, hypoglycaemia, severe anaemia, renal impairment, jaundice, pulmonary oedema, bleeding sites, shock, parasitaemia >2% (See section 4.4 for more details).

b. Uncomplicated malaria – Malaria with no severe features.

c. Artemisinin-based combination Therapy (ACT) – Combination of an artemisinin derivative and another class of antimalarial drug. Unless otherwise specified, this refers to artemether-lumefantrine (Riamet®) which is the preferred ACT for the purpose of this guideline.

d. Asymptomatic parasitaemia – presence of asexual parasites in the blood without symptoms. This may be seen in children who live in malaria endemic areas and have a degree of acquired immunity.

e. Cerebral malaria – Encephalopathy caused by severe *P. falciparum* malaria presenting as impaired conscious level, seizures, posturing and altered respiratory pattern. It is associated with a high mortality rate.

f. Asexual stages – The asexual stages of the parasite (rings, trophozoites, and schizonts) are the only stages which cause symptoms. These are the parasites which are counted when determining the percentage parasitaemia.

g. Gametocytes – Sexual stages of the parasite which do not cause symptoms. They may circulate in blood for some time after treatment of malaria. They indicate recent infection, but do not indicate treatment failure if they persist after clearance of asexual stages.

h. Hypnozoites – Liver stages exclusively of *P. vivax* and *P. ovale* that remain dormant and may result in relapse of malaria months after initial infection. Not detectable by blood test.

i. Rapid diagnostic test (RDT) – Rapid test for *Plasmodium* antigens, usually performed **in conjunction** with blood films.

j. APLS – Advanced Paediatric Life Support

k. G6PD – Glucose 6 phosphate dehydrogenase

l. PfHRP2 – *Plasmodium falciparum* histidine rich protein 2

m. pLDH – parasite lactate dehydrogenase

n. Parasitaemia – The presence of parasites in the blood, quantified as the percentage red blood cells infected by parasites

o. RDT- Rapid Diagnostic Test

3) SCOPE

This guideline is to be used by staff working within Acute Children's Services across Wessex. It should be used in conjunction with advice from a consultant in Paediatric Infectious Diseases (contactable via 07824417993).

4) **FULL GUIDELINE**

Malaria is notifiable and Public Health England should be informed once diagnosis is confirmed (https://www.gov.uk/health-protection-team).

4.1 Diagnosis

A full travel history must be taken, including: dates of all travel, detailed itinerary, vaccinations, chemoprophylaxis, bite avoidance measures, and any treatment received while abroad. This history will aid the interpretation of diagnostic tests for malaria and inform the differential diagnosis.

Identification of *Plasmodium* parasites on blood film is the gold standard for diagnosis (thick and thin films). These allow speciation, staging and quantification of parasitaemia.

- Gametocytes (the sexual stage of Plasmodium) may be detected in the blood of individuals who live in a malaria endemic country – they do not cause illness unless there are also asexual stage parasites and should NOT be assumed to be the cause of illness.

- Results should be available within 2 hours. Ensure the lab has been informed to expect the sample and its delivery to the lab is expedited.

- If the initial test is negative, and index of suspicion high (e.g. ongoing fever) repeat blood film (in conjunction with an RDT) after 12-24 hours and again after another 24 hours. This may be especially relevant in cases where some chemoprophylaxis was given. Repeat testing is not required if there is a low clinical threshold for malaria, fever has resolved spontaneously and initial blood film **and** RDT are negative.

- Rapid diagnostic tests (RDT) have a high sensitivity (except for *P. knowlesi*) and specificity and are performed on all blood samples being tested for malaria parasites. These are particularly useful in providing a rapid result, where malarial blood film examination is likely to be delayed. RDTs can remain positive for several weeks after recovery, therefore they are not useful for monitoring response to treatment.
  - The results from the malaria RDTs are reported as either 'Negative' or 'Positive'
  - RDTs should always be interpreted in conjunction with blood film results

- In travellers from Indonesia, Malaysia and surrounding countries in South East Asia, a suspicion of *P. knowlesi* malaria should be maintained until negative blood films exclude parasitaemia. As *P. knowlesi* and *P. malariae* have a similar appearance on microscopy, children returning from these areas should be treated as for *P. knowlesi* if either of these parasites is reported on the blood film (based on clinical features i.e. severe or uncomplicated.)

4.2 Differential Diagnosis

It is important to remember that fever in a returning traveller can be caused by the same organisms as we see causing severe illness in any child (see list below). Co-infections are common especially in severe malaria and should always be considered in overseas visitors and returning travellers. Specifically, *P. falciparum* malaria increases the risk of enteric Gram-negative bacteraemia. Thus the detection of *Plasmodium* parasites does not mean that malaria is the only cause of the illness and a high index of suspicion of co-infection should be maintained, particularly in a seriously ill child.

Whilst any parasitaemia should be treated, alternative diagnoses should be considered and excluded including:

- Typhoid and other bacterial infections
- Common viral infections e.g. Influenza
- Rarer tropical infections e.g. viral haemorrhagic fevers, dengue, Japanese B encephalitis (depending upon travel history)

4.3 Investigations

- FBC, Blood film for malarial parasites and malaria rapid diagnostic test
  - Note that thrombocytopenia is a typical feature in malaria
  - Category 4/query viral haemorrhagic fever samples will still be processed urgently and this **should not delay testing**; discuss with the on-call microbiologist who can risk assess to decide whether samples need to be processed in safety cabinet
- Blood gas (including lactate)
- Blood glucose
- Renal function, liver function, CRP

- **Additional investigations based on clinical features and differentials**
  - G6PD level (expedite result if *P. vivax* or P. *ovale* confirmed and before giving primaquine)
  - Sickle screen (increased risk of severe malaria in children with functional asplenia)
  - Clotting (all severe cases)
  - Group and save (all severe cases)
  - Save serum (serology and virology)
  - Blood culture (all severe cases)
  - Chest x-ray
  - Cultures – Urine, CSF, Throat
  - Viral panel – CSF, Throat

4.4 Management of ***SEVERE MALARIA*** **(see Flowchart 2. for management, see Table 2. drug doses)**

- Manage as a MEDICAL EMERGENCY. ONE or more of the following features
  - Impaired consciousness or seizures
  - Prostration
  - Clinical dehydration
  - Respiratory distress or Acidosis (pH <7.3 or BE < -8 mEq/L or HCO_3 <15 or lactate ≥5mmol/L)

- Hypoglycaemia (< 3 mmol/L)
- Severe anaemia (Hb <80g/L)
- Renal impairment and/or Hyperkalaemia (>5.5mmol/l)
- Jaundice (>50 μmol/L)
- Pulmonary oedema – SaO_2 < 92% or suggestive x-ray associated with clinical signs
- Significant bleeding – e.g. nose, gums, venepuncture sites, haematemesis, malaena
- Shock: CRT ≥ 3, temperature gradient on legs, cool peripheries. May have compensated (normal BP) or decompensated shock (BP < 70 systolic).
- Parasitaemia >2% (parasitaemia is a very poor predictor of outcome and the relevance of the parasite counts depends upon prior immunity/exposure).

- Provide supportive care in line with the APLS guidelines 2015, EXCEPT FOR FLUID RESUSCITATION (SEE BELOW), and manage in a high dependency or paediatric intensive care unit.

- Seek early expert advice from a paediatric infectious diseases consultant who is experienced in the management of severe malaria.

- Provide oxygen to maintain saturations ≥92%

- RAPID FLUID BOLUS IS CONTRAINDICATED. Judicious and slow fluid resuscitation is recommended in children presenting with shock and should be evaluated on an individual basis in conjunction with paediatric intensive care and infectious diseases consultants.

    - Do not base decision about fluid resuscitation on lactate levels – lactate is usually raised in malaria due to obstructed blood vessels, not shock.

- Blood transfusion should be performed if severe anaemia is present (especially if there is also metabolic acidosis). Thrombocytopenia is common, and platelet transfusion is not indicated unless there is active bleeding. Severe coagulopathy or spontaneous bleeding are rare, and should be managed in conjunction with expert haematology advice. Exchange transfusion is not recommended.

- Watch for signs of raised ICP and institute neuroprotective measures accordingly

- **IV artesunate** is the antimalarial drug of choice for severe malaria. It should be given as soon as the diagnosis is confirmed in children with severe features.

- **Where can I find artesunate?**
    - Usually found in Emergency drug cupboard or in adult ED

    Once prescribed, request supplies from pharmacy to enable a second dose 12 hours later.

- If IV artesunate is likely to be delayed/not available, IV quinine should be administered as soon as possible as a second line antimalarial drug (note risk of hypoglycaemia with IV quinine). This should be switched to IV artesunate as soon as it is available.

- All children with severe malaria should be commenced on broad spectrum antibiotics (IV ceftriaxone is a reasonable empirical choice)

- IV artesunate / quinine can be switched to oral artemether-lumefantrine (Riamet®) or atovaquone-proguanil (Malarone®) after at least 24 hours and when child is able to tolerate orally. A 3 day course of Riamet® (or Malarone®) should be completed.

4.5 Management of ***uncomplicated malaria –*** Divided into *P. falciparum* and non-Falciparum and defined as absence of features of severe malaria.

- **Uncomplicated *P. falciparum* malaria**

  - Good practice is? to admit all children with uncomplicated *P. falciparum* malaria.
  - Treat with IV artesunate if not tolerating/vomiting oral medication.
  - Artemether-lumefantrine (Riamet®) should be used as first line treatment for a total of 3 days to complete a full course. If not available or contraindicated due to hypersensitivity, atovaquone-proguanil (Malarone®) may be used instead.
  - Screen for co-existing infections.

- **Uncomplicated non-falciparum malaria**

  - Caused by *Plasmodium* species other than *P. falciparum*
  - Consultant decision whether to admit based on clinical condition. Need to ensure appropriate safety netting and compliance with full course of treatment
  - ACT (Riamet®) is the most universally effective treatment and is given for 3 days.
  - Chloroquine may be used in travellers from areas where there is no/very low chloroquine resistance. The treatment duration is 3 days as for ACT.
  - Patients with *P. vivax* and *P. ovale* malaria require treatment with primaquine for radical cure, in order to prevent relapse through hypnozoites in the liver. This should be started as soon as G6PD status has been confirmed (ideally concomitantly with ACT/chloroquine) to minimise the risk of relapse.
  - Primaquine is contraindicated in patients with severe G6PD deficiency. Test all patients with these infections for G6PD enzyme activity. Expert advice should be sought if there is evidence of G6PD deficiency

4.6 Monitoring of parasitaemia and laboratory tests

- Perform daily parasite counts for in-patients
  - **Note that parasitaemia may increase over the first 24-36 hours (especially in severe malaria) and does not indicate treatment failure or resistance**

  - Continue monitoring until asexual blood stage parasites are no longer seen on the blood film
  - Note that gametocytes (sexual stages) may persist or appear during or after treatment – these do not indicate treatment failure
- Perform additional monitoring of blood parameters as indicated by initial values
- Check FBC 2 weeks after presentation if treated with iv artesunate, as there is often a delayed fall in haemoglobin which may be clinically significant

4.7 ANTIMALARIALS

<table>
<tr><th>TYPE</th><th>DRUGS*</th><th>COMMENTS</th></tr>
<tr><td rowspan="3">Severe/Complicated Malaria</td><td>1st Choice

IV artesunate

3mg/kg <20kg or
2.4mg/kg >20kg
(round doses to nearest 5mg)

at 0, 12, 24 hours then DAILY until changed to oral regimen (IV up to 5 days in total)

<table><tr><td>Hours</td><td>Day 1</td><td>Day 2</td><td>Day 3</td></tr><tr><td>0</td><td>✓</td><td>✓</td><td>✓</td></tr><tr><td>12</td><td>✓</td><td></td><td></td></tr></table>
If IV access is unavailable, Artesunate can be given via the intramuscular (IM) route</td><td>Add the ampoule (1ml) of 5% sodium bicarbonate provided to 60mg of Artesunate powder and shake for 2-3 minutes until dissolved (see Appendix A for reconstitution information). The solution will be cloudy initially but should clear in 2 about 2 minutes. Do not use if cloudy. Use within 1 hour of reconstitution

• IV injection: Then add 5ml of 0.9% sodium chloride or 5% glucose to the vial to give 10mg/ml solution. Use immediately and discard any remaining solution.

Give by slow IV injection at a rate of 3-4ml/min

• IM injection: Then add 2ml of 0.9% sodium chloride or 5% glucose to the vial to give a 20mg/ml solution. Use immediately and discard any remaining solution.

In travellers from areas with documented evidence of Artemisinin resistance (Cambodia, Laos, Myanmar, Thailand, Vietnam) it may be recommended to add IV Quinine to IV artesunate treatment: discuss with expert in malaria treatment</td></tr>
<tr><td colspan="2">• Prescribe full 3-day course of Artemether-lumefantrine (Riamet®) once oral medication is tolerated. (see doses for uncomplicated falciparum malaria below)
• This should be prescribed between 8 and 12 hours after last injection of artesunate</td></tr>
<tr><td><u>2nd Choice</u>
<u>(if artesunate not available)</u>

IV quinine (NOTE: long standing supply issue with IV quinine means that it may be challenging to obtain).

20mg/kg (maximum 1.4g) loading dose of Quinine (as hydrochloride, dihydrochloride or sulfate NOT bisulfate) in 5% glucose or 0.9% sodium chloride over 4hrs
Then 8 hours after start of first dose:, 10mg/kg (maximum 700mg) THREE times a day for first 48hrs
Then:
5-7mg/kg (maximum 700mg) THREE times a day after first 48hrs
(for 5-7 days or until change to oral regimen)</td><td>• Usual concentration is 2mg/ml but can be increased to max of 30mg/ml if child is fluid restricted. Infuse at up to 5mg/kg/h

• IV quinine is associated with hypoglycaemia, arrhythmias and hypotension - monitor blood glucose 4 hourly and provide continuous cardiac monitoring during administration

• Try to source artesunate as soon as feasible</td></tr>
</table>

<table>
<tr>
<td>Uncomplicated Falciparum malaria</td>
<td>
1st Choice artemether-lumefantrine (Riamet®)

At 0,8,24,36,48,60hrs
5-14 kg 1 tablet
15-24 kg 2 tablets
25-35 kg 3 tablets
>35 kg 4 tablets

<table>
<tr><th>Hours</th><th>Day 1</th><th>Day 2</th><th>Day 3</th></tr>
<tr><td>0</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>8</td><td>✓</td><td></td><td></td></tr>
<tr><td>12</td><td></td><td>✓</td><td>✓</td></tr>
</table>

OR

Atovoquone-proguanil (Malarone® or Malarone® paediatrics) DAILY for 3 days

5-8 kg 2 Malarone® paediatrics tablets

9-10 kg 3 Malarone® paediatrics tablets

11-20 kg 1 Malarone® tablet

21-30 kg 2 Malarone® tablets

31-40 kg 3 Malarone® tablets

>40 kg 4 Malarone® tablets
</td>
<td>
Artemether-lumefantrine (Riamet®)
• should be used as 1st choice
• Absorption is enhanced by fat therefore recommended with milk/similar.
• Can be crushed and mixed with food or milk
• Refer to BNFc for list of interactions

Atovaquone-proguanil (Malarone® and Malarone® paediatrics)
• Tablets can be crushed and mixed with food or milk.
• Atovaquone-proguanil tablets (Malarone®) contain 250mg Atovaquone and 100mg proguanil
• Atovaquone-proquanil paediatric tablets (Malarone® paediatrics) contain 62.5mg Atovaquone and 25mg proguanil
• Refer to BNFc for list of interactions
</td>
</tr>
<tr>
<td>Uncomplicated Non falciparum malaria</td>
<td>
1st Choice (artemether/lumefantrine) (Riamet®)

At 0,8,24,36,48,60hrs (as charted above):

<15kg 1 tablet
15-24 kg 2 tablets
25-35 kg 3 tablets
>35 kg 4 tablets

2nd Choice

chloroquine (if resistance unlikely)

10mg/kg base (max 620mg), then 5mg/kg after 6-8 hours (maximum 310mg) then 5mg/kg (max 310mg) on days 2 and 3.

PLUS Primaquine DAILY 14 days (P ovale – 0.25mg/kg (max 15mg / P vivax – 0.5mg/kg (max 30mg)
</td>
<td>
Chloroquine
• Ensure correct dose prescribed as chloroquine base.
• Avloclor tablets contain 250 mg chloroquine phosphate, which is equivalent to 155 mg chloroquine base. The liquids are no longer available in the UK, discuss with a pharmacist as required.
Primaquine
• start as soon as possible after confirming G6PD status (ideally concomittently with ACT/chloroquine)
• For radical cure in mild-moderate G6PD deficiency modified dosing of Primaquine 0.75mg/kg (maximum 45mg per week) is given once a week for 8 weeks (discuss with expert)
• Primaquine is contraindicated in severe G6PD deficiency
• Primaquine can cause gastrointestinal upset and should be given after food.
</td>
</tr>
</table>

*If a child appears significantly overweight consider using a dose based on ideal body weight. Discuss with pharmacy if in doubt.

5) IMPLEMENTATION

Training required for staff	Case based training of medical staff as part of Wessex & Thames Valley annual infection course
If yes, who will provide training:	*Sanjay Patel (Paeds ID Cons, Southampton) and Stephane Paulus (Paeds ID cons, Oxford)*
When will training be provided?	
Date for implementation of guideline:	

6) MONITORING / AUDIT

When will this guideline be audited?	After 2 years (due to small number of cases)
Who will be responsible for auditing this guideline?	Sanjay Patel
Are there any other specific recommendations for audit?	No

7) REVIEW

Frequency of review	**Please indicate frequency of review: 2 years** **Person and post responsible for the review:** Sanjay Patel, Consultant in Paediatric Infectious Diseases, Southampton Children's Hospital

8) References

1. DYER, E., WATERFIELD, T. & EISENHUT, M. 2016. How to interpret malaria tests. Arch Dis Child Educ Pract Ed, 101, 96-101.

2. KIANG, K. M., BRYANT, P. A., SHINGADIA, D., LADHANI, S., STEER, A. C. & BURGNER, D. 2013. The treatment of imported malaria in children: an update. Arch Dis Child Educ Pract Ed, 98, 7-15.

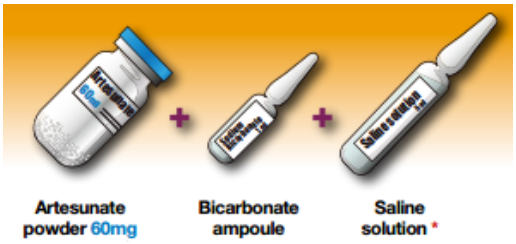
3. LALLOO, D. G., SHINGADIA, D., BELL, D. J., BEECHING, N. J., WHITTY, C. J., CHIODINI, P. L. & PHE Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines 2016. J Infect, 72, 635-49.

4. MAITLAND, K., KIGULI, S., OPOKA, R. O., ENGORU, C., OLUPOT-OLUPOT, P., AKECH, S. O., NYEKO, R., MTOVE, G., REYBURN, H., LANG, T., BRENT, B., EVANS, J. A., TIBENDERANA, J. K., CRAWLEY, J., RUSSELL, E. C., LEVIN, M., BABIKER, A. G., GIBB, D. M. & GROUP, F. T. 2011. Mortality after fluid bolus in African children with severe infection. N Engl J Med, 364, 2483-95.

5. WORLD HEALTH ORGANIZATION 2016. Guidelines for the treatment of malaria. Third Edition. World Health Organization, Geneva.

9) Appendix A – Preparation of artesunate

Preparation
Each artesunate vial comes as 60mg powder for reconstitution, supplied with 1ml of 5% sodium bicarbonate solution. It must be further diluted with 5% glucose or 0.9% saline.



Dosing
Each dose = 3mg/kg if <20kg, or 2.4mg/kg if > 20kg (rounded to the nearest 5mg)
(If a child appears significantly overweight consider using a dose based on ideal body weight. Discuss with pharmacy if in doubt.)

Reconstitution & IV administration (Artesunate injection must NOT be given subcutaneously)

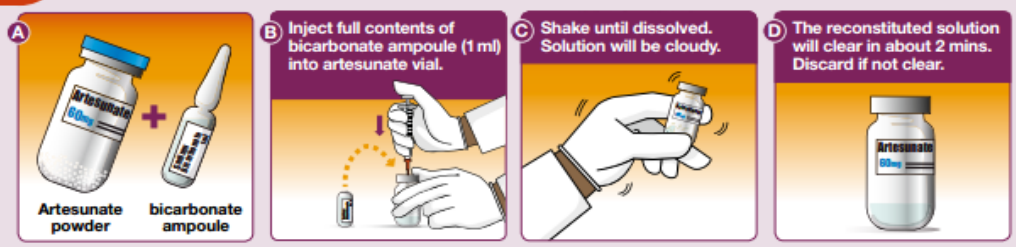
1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE

- Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)

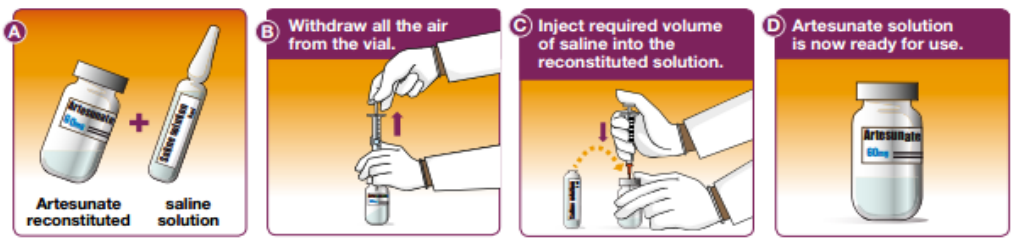


4 DILUTE

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

	IV
Bicarbonate solution volume	1 ml
Saline solution volume	5 ml
Total volume	**6 ml**
Artesunate 60 mg solution concentration	10 mg/ml

IMPORTANT
Water for injection is not an appropriate dilutant



- Give by slow IV injection at a rate of 3-4ml per minute.

Appendix B - Documentation of regional consultation

Trust	Name of person consulted* (print)	Designation	Signature
Dorchester	Will Verling		
Hampshire Hospitals Foundation Trust	Katie Yallop		
Poole	Steve Wadams		
Portsmouth	Amanda Freeman		
Salisbury	Seb Gray		
Southampton	Sanjay Patel		
IOW	Arun Gulati		

*this person agrees they have read the guidelines, consulted with relevant colleagues and members of MDT, managers and patients, young people & their families as appropriate. Any queries raised during consultation and review process should be documented with responses and any changes made to the guideline.