Treatment of Fever and Infection in Children with Transfusion Dependent Thalassaemia

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Background

Acute infection remains a major cause of death in thalassaemia patients. A vigilant approach to recognising and treating serious infection will help prevent unnecessary mortality. Patients should be educated on management of fever and acute symptoms, with advanced understanding of who to call and where to seek care. Children who are at particular increased risk of serious infection are those who are splenectomised, those who have iron overload, those being chelated with desferrioxamine, and those with central venous access devices (Portacath, Hickman line). Gram-negative organisms are the major cause of bacteraemia in thalassemia patients. Patients on deferiprone have an increased risk of neutropenia due to agranulocytosis.

This guideline is aimed at staff caring for all children with significant thalassaemia who present with possible sepsis or a temperature >38.5^{0}C. The guideline applies to patients who are currently under the care of the paediatric haemoglobinopathy team. It is mainly aimed at being a tool for the medical team managing these patients, but any member of the multidisciplinary team may find it useful.

Contents of guideline:

Indications

This guideline applies to patients who have transfusion-dependent thalassaemia, who may have indwelling central venous devices, who may be iron overloaded, and/or chelated with desferrioxamine, deferiprone or deferasirox (Exjade FCT).

Children should be assessed as for any child with possible infection or fever. History and examination should be focused on identifying possible sources of infection and likely organisms. The child should be admitted to hospital if the temperature >38.5^{0}C, or if systemically unwell, and the following investigations performed. The paediatric haemoglobinopathy team should be informed of the patient's admission.
If a patient on Deferiprone is neutropenic (neutrophils <1.5) and unwell the Deferiprone must be stopped immediately. G-CSF can be considered in neutropenia or agranulocytosis (neutrophils <0.5 x 10^9/L).

Initial Assessment of the Febrile Thalassaemia Patient

- History and Examination
  - History to include details of iron chelation, central lines, diarrhoea, recent foreign travel and previous splenectomy.
  - Full clinical examination looking for any site of sepsis, including ears, throat and possible mucositis, and examination of any central venous access device for exit-site or tunnel infection. Abdominal examination for tenderness, PEWS score.
  - Check for previous positive microbiology results and sensitivities
- Bloods
  - FBC with differential, urea and electrolytes, liver function tests and ALT, blood glucose CRP and lactate.
  - Blood group and antibody screen – consider delayed haemolytic transfusion reaction
  - If indicated, serum for viral serology
  - Malaria screen (depending on travel history).
  - Consider Parvovirus B19 serology IgG & IgM if significant unexplained anaemia, particularly if associated with reticulocytopenia.
  - Blood cultures from each lumen of the central venous line if present, using the initial 3-5ml discard for culture, or peripheral cultures if no central line.
  - Consider Malaria in a child with a relevant travel history and send urgent malaria screen.
- Cultures
  - Urine microscopy and culture.
  - Swabs from sites of clinical infection
  - Respiratory virus swab if respiratory tract signs and Coronavirus RNA swab.
  - Stool culture and sensitivities, specifically requesting culture for detection of *Yersinia enterocolitica* infection if diarrhoea, fever, abdominal pain or vomiting.
- Clinical Investigations to consider
  - ECG
  - CXR
  - Abdominal ultrasound if abdominal pain and/or jaundice.

Infections in children with Thalassemia

Children with Thalassemia are at increased risk of infections due to:

- Splenic dysfunction/splenectomy

- Iron overload
- Iron chelation
- Transfusion transmitted infections (low risk within the UK)
- Central venous line-associated infection

Empiric Antibiotic Treatment of Fever and Sepsis in Children with Thalassaemia:

- Treatment should start urgently and within 1 hour of the child presenting with fever:

Please consult BNFc dose recommendations and modifications for renal impairment.

- First line antibiotics as per local guidance - if no local guidance in place then the protocol below can be followed:
  - Co-amoxiclav (Augmentin) - if not neutropenic and /or septic/unstable (see below)
  - Gentamicin IV – add if not neutropenic, but septic
  - Piperacillin-Tazobactam (Tazocin) and gentamicin if neutropenic and septic /unstable and continue until cultures are reported
  - Add Vancomycin or teicoplanin if the child has pain/inflammation around Port or Hickman site or tunnel infection.

- If meningitis suspected use ceftriaxone IV, If non-severe penicillin allergy e.g. rash – meropenem IV. If more severe penicillin allergy discuss with microbiology.

- Second line/penicillin allergy:
  - Ciprofloxacin & gentamicin: if line sepsis suspected add vancomycin or teicoplanin
    Refer to BNFc for dosing

  - The empirical regimen is the same irrespective of previous antibiotic courses unless there are known antibiotic resistance patterns guiding recommendations for an individual patient.

Prescribing in Penicillin Allergic Patients

THE SYMPTOMS OF THE PENICILLIN ALLERGY MUST BE DEFINED AND DOCUMENTED.

Severe penicillin allergy includes anaphylaxis, collapse, hypotension, difficulty in breathing, bronchospasm, wheeze, lip swelling, angio-oedema, tracheal or laryngeal swelling, immediate rash & urticaria. Note: these symptoms can occur up to 5 days (occasionally longer) after receiving the antibiotic.

- These patients **must not** be given any beta-lactam agents (penicillins, cephalosporins, carbapenems and aztreonam) – see table below.
- Patients with a history of drug reactions after beta lactams including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), Acute Generalised Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) should not be given them.

Less severe penicillin allergy includes a minor, non-confluent rash >72 hours after the antibiotic dose.

- These patients may be given cephalosporins or carbapenems if there is no satisfactory alternative and the benefits outweigh the risks of cross reactivity.

Treatment if there is fever and diarrhoea or vomiting

Thalassemia patients are at increased risk of *Yersinia enterocolitica* and *Klebsiella spp*. if they are iron overloaded or chelated with desferrioxamine, and may present with fever, abdominal pain, and diarrhoea. Stool and blood cultures should be sent; contact the lab about specific cultures for Yersinia, since this organism requires particular lab conditions for culture. However, antibiotics should be started empirically, before results are available. In general, all chelation therapy should be stopped until the child has fully recovered.

- Ciprofloxacin is the antibiotic of choice, given intravenously until gastrointestinal symptoms have resolved. Gentamicin and Metronidazole can be added if signs of systemic sepsis.

- Co-trimoaxazole (Septrin®) or doxycycline (>12 years) can be used as an alternative or if the patient has a known allergy to ciprofloxacin.

Transfusion-Transmitted Infections

Patients with transfusion-dependent thalassaemia are at increased risk of transfusion-transmitted infections, including hepatitis B, C and HIV. This is particularly true if the patient has received blood transfusions abroad, in countries without established safe blood supplies. This should be considered when assessing patients with acute febrile illness.

All regularly transfused patients should have been vaccinated against hepatitis A and B

- Hepatitis serology should requested on all patients presenting with an ALT>100 IU/l. If viral hepatitis is confirmed the paediatric hepatology team should be contacted.

- If suspected sepsis occurs following a blood transfusion, the possibility of bacterial or malarial contamination of the transfused blood should be considered; in addition to taking blood cultures and treating the patient, the relevant blood unit(s) should be returned to the Blood Transfusion Laboratory for investigation and the Trust Investigation of Suspected Transfusion Reaction form should be completed.

Splenectomised patients

- These patients are at increased risk of overwhelming bacterial sepsis, particularly encapsulated organisms: pneumococcus, *Haemophilus influenzae* and *Neisseria meningitidis*, as well as Gram negative organisms, (and other infections including malaria). Adherence to Penicillin V prophylaxis,
- or Erythromycin if penicillin allergic, and Pneumovax immunization help to reduce the risk, but these infections should still be considered.
- Send paired blood cultures (line and peripheral), urine for pneumococcal antigen and discuss specific Yersinia cultures with microbiology if known iron overload.
- Splenctomised children who present post-dog bite should have assessment for sepsis and commence antibiotics which cover *Capnocytophaga* spp. Please contact the microbiology team urgently to discuss these cases.

Contact details:

KCH Paed sickle CNS: 02032994752
KCH Paed sickle consultants: david.rees2@nhs.net subarna.chakravorty@nhs.net, j.brewin@nhs.net, sue.height@nhs.net.
GSTT Paed sickle CNS: 0207 188 9432
GST Paed sickle consultants: samah.babiker@gstt.nhs.uk, nick.fordham@gstt.nhs.uk
QE Paed sickle sickle CNS: 07741233556
QE Paed sickle consultants: julie.lord@nhs.net aruj.qayum@nhs.net
UHL Paed sickle CNS: 07741233556
UHL/QE Paeds sickle consultants: s.wilkinson6@nhs.net julie.lord@nhs.net
CUH Paeds sickle CNS: 0208 2517229
CUH Paeds sickle consultants: nazmachowdhury@nhs.net

Additional contacts can be found on the STSTN website (www.ststn.co.uk)

References

Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK 3rd Edition (2016)

Related guidelines

Clinical Guidelines on the Use of Iron Chelation in Children Receiving regular Blood Transfusion
Investigation of Suspected Transfusion Reaction

Guidelines written by the STSTN paediatric writing group:

Dr Sue Height
Dr Sarah Wilkinson
Dr Rachel Kesse-Adu
Professor Baba Inusa
Dr Samah Babiker
Dr John Brewing
Dr Helen Oram