

β -Thalassaemia and Malaria 4.04

History of Presenting Illness (HPI)

! Thalassaemia symptoms NOT USUALLY SEEN until 6 months of age- UNLESS VERY SEVERE

Thalassaemia Major: clinical picture

- Increasing pallor
- Failure to thrive
- Irritability
- **Hepatosplenomegaly**
- Enlargement of facial bones to accommodate ectopic hematopoietic tissue

Thalassaemia Minor will present occasionally with anaemia, but most often it is picked up on a routine blood film (looks like an iron deficiency anaemia, but with an increased RBC count)

Malaria

- Jaundice
- **Fever** (either irregular swings, or regular periodic fever)
- Fever spikes, chills and rigor occurring at regular intervals suggest infection with *P. ovale* or *P. vivax*.
- Night sweats
- **Malaise**
- **Headache** (although this may be severe in malaria, there is **no neck stiffness or photophobia** resembling that in meningitis)
- **Fatigue**
- **Abdominal discomfort**
- Muscle aches followed by fever are all similar to symptoms of a minor viral infection

Generalised seizures are specifically associated with falciparum malaria and may herald the onset of cerebral disease

Differential Diagnoses (DDx) of malaria

- Viral or bacterial infection

thalassaemia

- hemoglobinopathy
- anaemia
- leucaemia
- developmental disability

Pertinent Findings on History (Hx)

TRAVEL HISTORY is very important, as is **HISTORY OF MALARIAL PROPHYLAXIS**

- how long before, how often during, how long after were the antimalarial drugs taken?

FAMILY HISTORY and **ETHNIC BACKGROUND** will give a clue as to the likelihood of thalassaemia

! NEED TO KNOW IMMUNISATION HISTORY !

- medications taken within the previous month,
- exposure to domestic pets and other animals,
- history of animal or arthropod bites,
- existence of cardiac abnormalities,
- presence of prosthetic material,
- recent exposure to ill individuals,
- exposure to sexually transmitted diseases.

Findings on Examination (Ex)

- **Pallor**
- **Jaundice**
- **Hepatosplenomegaly**
- **Petechiae / splinter haemorrhages**
- **Osler or Janeway lesions (suggestive of an infection other than malaria)**

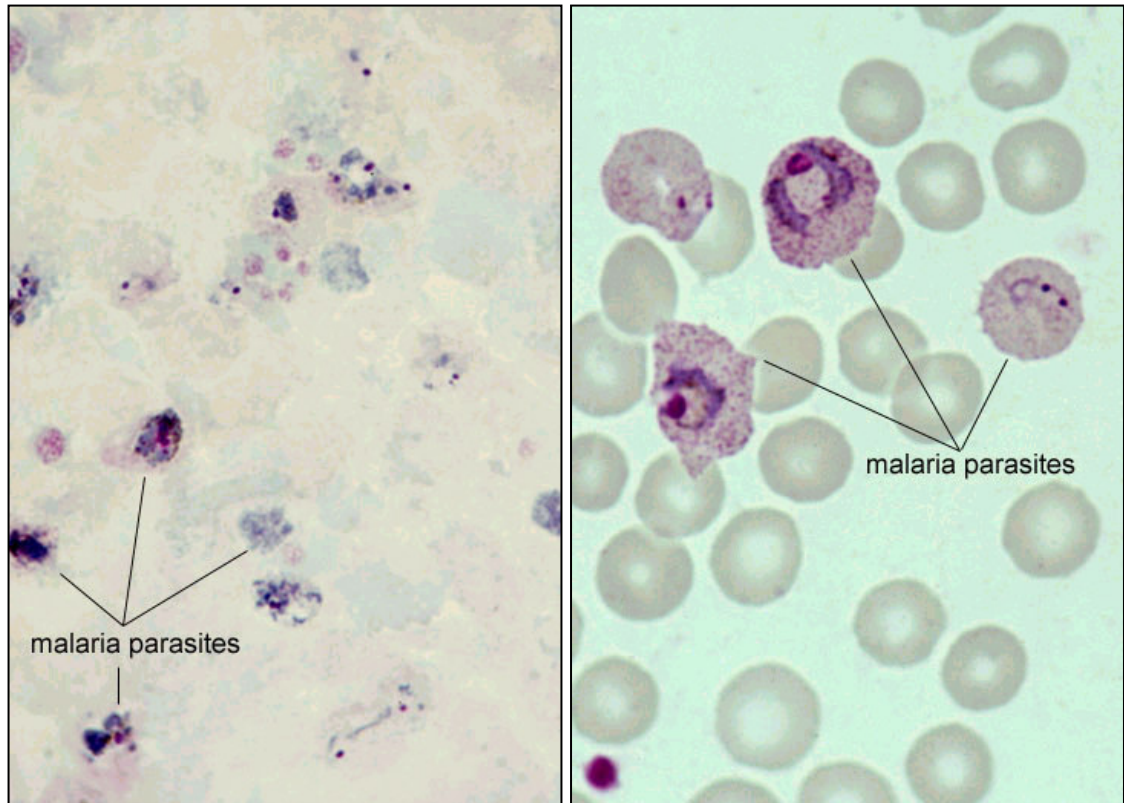
The case-fatality rate of **falciparum malaria** in the United States is 4%; however, **in only one-third of patients who die is the diagnosis of malaria considered before death.**

Tests and Investigations: MALARIA

FBC: will see a drop in haemoglobin

Blood film: Thick and Thin

Looking for malaria parasites - NO ERYTHROCYTE CHANGES IN MALARIA



Above: thick film.

Above: thin film.

Thick film- used to identify RBC infected with malarial parasite

Thin film- used to identify specific malarial parasite. Eg. *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*.

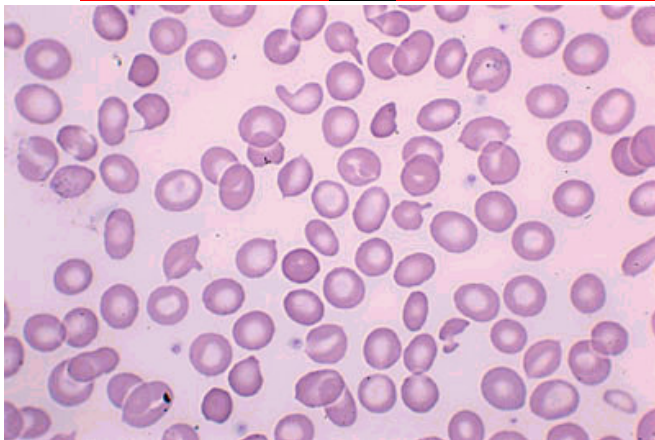
Serum Biochem looking for **bilirubin and LDH** consistent with RBC lysis

Tests and Investigations: THALASSAEMIA

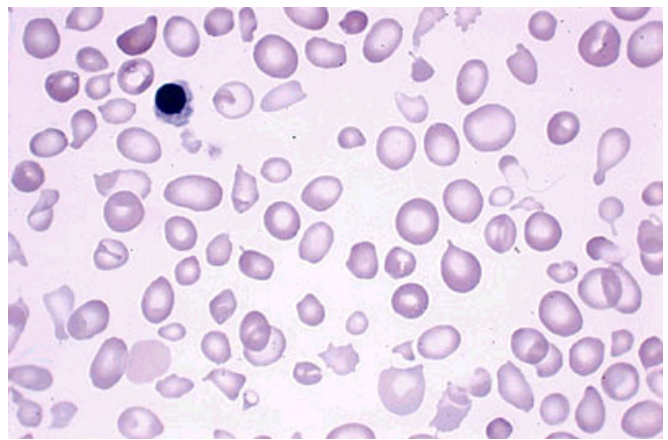
Blood Film: ← Must also investigate the family

Microscopy will reveal **ANISOPOIKILOCYTOSIS** and **HYPOCHROMIC MICROCYTOSIS**

With **TARGET CELLS** and **ELLIPTOCYTES;**



Above: T. minor



Above: T. major

HEMOGLOBIN ELECTROPHORESIS: demonstrates the concentration of HbA

The diagnosis of beta-thalassaemia can be confirmed by the finding of a compensatory rise in the level of haemoglobin A2 to about 4-7%, which is the most useful screening test. HbA2 is composed of two alpha- and two delta-globin chains.

Haemoglobin F (two alpha- and two gamma-globin chains) is usually also raised.

The diagnosis of alpha-thalassaemia can be confirmed by the finding of haemoglobin H inclusions in a methylene blue stain of the peripheral blood.

X-RAY: to look for “crew-cut”

bony nodules appearing @ skull → ectopic haematopoietic tissue

How is this diagnosis made ?

Malaria: thick+thin film is pathognomic, combined with history of travel and poor compliance with chemoprophylaxis

Thalassaemia: hemoglobin electrophoresis confirms blood film suspicion

Management

Malaria:

- Test family for infection
- **3 days of chloroquine** (remains the drug of choice for treatment and prophylaxis against drug-sensitive forms of malaria)
- **14 days of primaquine**
- **monitor hemoglobin**

In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature; however, cooling blankets should not be used without oral antipyretics. In hyperpyretic patients with central nervous system disease or trauma, reducing core temperature mitigates the ill effects of high temperature on the brain.

THUS: attempt to reduce fever if it goes above 40 degrees. Paracetamol and NSAIDS

Thalassaemia: DEPENDS ON SEVERITY.

Thalassaemia trait: no treatment is necessary,

as these people have only the very slightest glimmer of anaemia

OTHERWISE:

6-8 cc/kg of Packed RBC's every 2-3 weeks

yearly requirement of <200 cc/kg/year of PRBC's

each transfusion takes 4-6 hrs

Monitoring for Iron Overload:

- **Cardiac baseline** at age 10, then every 2 years for a few years, then every year;
EKG, echo, treadmill

- **Endocrine evaluation**

- monitor growth and puberty
- IV glucose tolerance test -- same schedule as cardiac
- yearly TFTs
- serum Ca, Mg, P, alk phos, vit D, PTH
- yearly bone age, knee films if delayed growth

If unable to counter iron load with chelation therapy, consider **erythrocytapheresis**.

COMBAT IRON OVERLOAD WITH DESFERAL (desferrioxamine)

which can break down and remove excess iron from body:

- **it is injected under the skin from a small pump**
- **it picks up excess iron and carries it out in the urine**
- **It runs for 6 to 7 hours, overnight**
- **7 days/wk optimal; 6 nights/wk practical**

MONITOR for desferal toxicity = Annual hearing and ophthalmologist exams

Prognosis of Malaria:

Severe falciparum malaria:

- If treated properly, uncomplicated falciparum malaria is associated with a mortality rate <0.1%.
 - However, once vital organ dysfunction occurs, or the level of parasitaemia increases beyond 3%, mortality rises steeply.
 - Most of the 1-3 million people who die of falciparum malaria each year are young African children.
- **Cerebral malaria:**
 - Coma is a characteristic feature of falciparum malaria and is associated with mortality rates of approximately 20% despite treatment
 - Manifested as a **diffuse symmetric encephalopathy**, with focal neurologic signs being unusual.
- **Hypoglycaemia:**
 - A common complication of malaria, hypoglycaemia is associated with a poor prognosis and is particularly problematic in children and pregnant women
 - In malaria, hypoglycaemia results from a failure of hepatic gluconeogenesis in combination with an increased consumption of glucose by both the host and parasite.
 - In addition, the quinine and quinidine drugs used to treat chloroquine-resistant malaria are both potent stimulants of pancreatic insulin secretion.
- **Lactic acidosis:**
 - Lactic acidosis commonly co-exists with hypoglycaemia.
 - In adults, renal impairment compounds the acidosis.
 - Acidotic breathing is a sign of poor prognosis.
 - It is caused by a combination of anaerobic glycolysis in tissue where sequestered parasites interfere with microcirculatory flow, lactate production by the parasites and a failure of hepatic and renal clearance of lactate.
- **Renal impairment:**
 - Common among adults but rare among children with severe falciparum malaria.
 - Most likely related to RBC sequestration interfering with renal microcirculatory flow and metabolism.
 - Manifested as acute tubular necrosis.
- **Haematologic abnormalities:**
 - Anaemia results from accelerated RBC destruction and removal by the spleen in conjunction with ineffective erythropoiesis.
 - Slight coagulation abnormalities are common in falciparum malaria and mild thrombocytopenia is usual.
- **Liver dysfunction:**
 - Mild haemolytic jaundice is common in malaria
 - Severe jaundice is associated with falciparum infection.
 - It is more common among adults and is a result of haemolysis, hepatocyte injury and cholestasis.
- **Non-cardiogenic pulmonary oedema:**
 - The pathogenesis of this syndrome is unclear
 - The mortality rates in these cases is >80%.
- **Chronic complications of malaria:**
 - Tropical splenomegaly or hyperreactive malarial splenomegaly
 - Burkitt's lymphoma and EBV infection:
 - It is possible that malaria-related immunosuppression provokes infection with lymphoma viruses
 - The prevalence of this childhood tumour is highest in malarious areas of Africa.

Prognosis of Thalassaemia

Thalassaemia minor is relatively mild and does not impact significantly on life chances

Classically in thalassaemia major, **the treatment is the cause of death.**

The children are maintained by transfusions until about age ten years, at which time they start to show symptoms of excess iron loading. This happens because the transfusion bypasses the body's normal gastrointestinal mechanism of iron intake and excretion.

The iron is poured into the bloodstream directly; the body cannot excrete it fast enough.

First iron (as hemosiderin) fills the cytoplasm of the RES phagocytes and then starts to be deposited in the parenchymal cells of just about every organ of the body.

The pancreas, liver, myocardium, adrenals, and gonads are among the organs most sensitive to iron toxicity.

The clinical result is **diabetes mellitus, hepatic cirrhosis, congestive heart failure, adrenal insufficiency, and failure to undergo puberty.**

Death used to occur in the second or third decade of life, the most common immediate cause being complications of heart failure.

Nowadays, that major patients live longer because of advances in chelation therapy. To achieve such longevity, they must submit to daily subcutaneous injections of the parenteral chelating agent, deferoxamine. These injections are given by pump, usually overnight, and last 9 to 12 hours each.

Epidemiology: MALARIA

- Malaria occurs throughout most of the tropical regions of the world:
 - *P. falciparum* predominates in Africa, PNG and Haiti
 - *P. vivax* is more common in Central America and the Indian subcontinent.
 - *P. malariae* is found in most endemic regions
- P. ovale* is relatively uncommon outside of Africa and, where it is found, comprises <1% of isolates.

Epidemiology: Thalassaemia

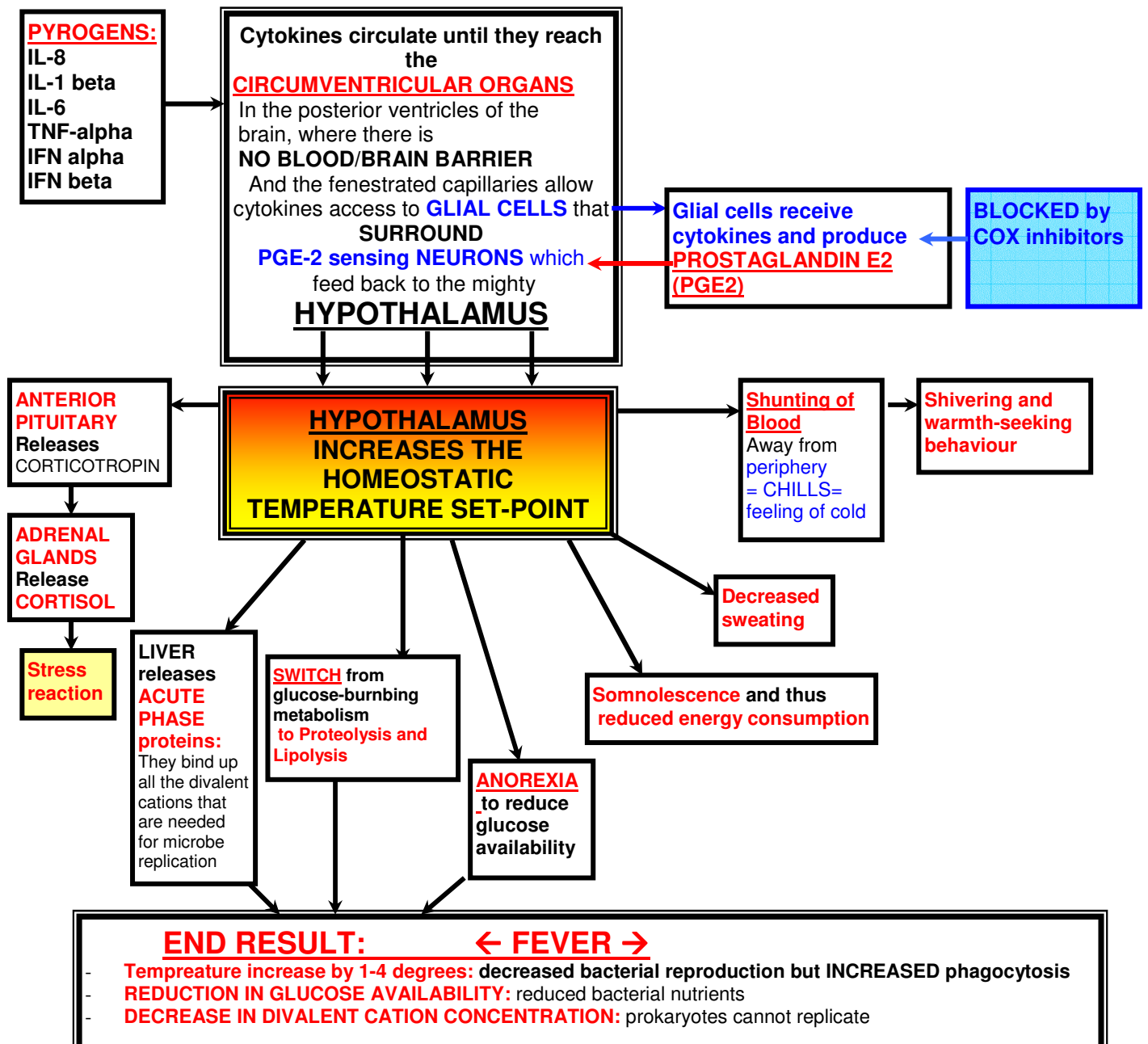
age of onset:

- 2-4 years (Thal. Intermedia); 1st year of life (Thal. Major)

risk factors:

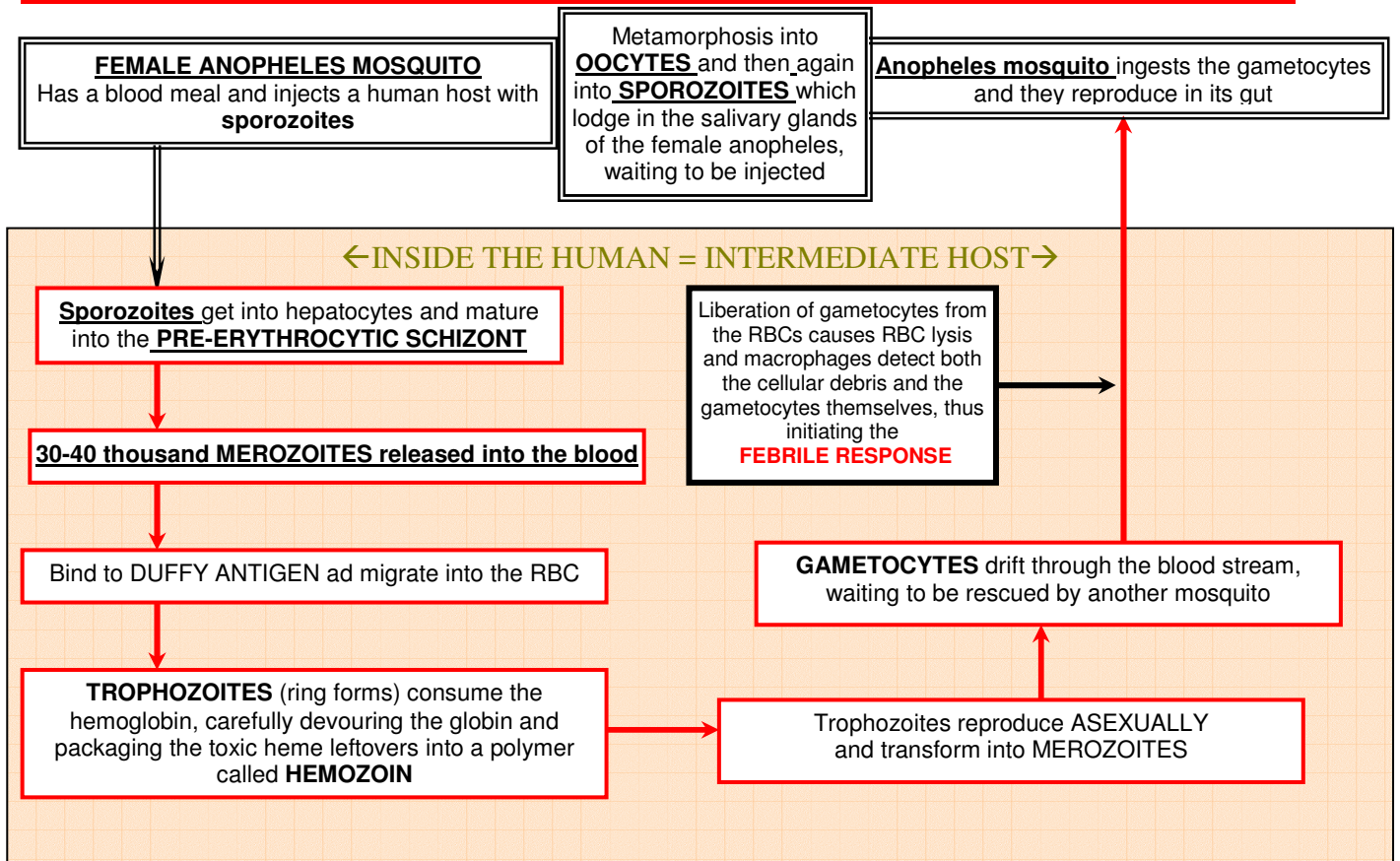
- **familial - autosomal recessive**
 - chrom.#: 11p15.5
 - gene: beta-globin chain
- **certain ethnic groups:**
 - Mediterranean, Near and Middle Eastern, Southeast Asia
- type of mutation is usually specific to a given ethnic group

MECHANISM OF FEVER

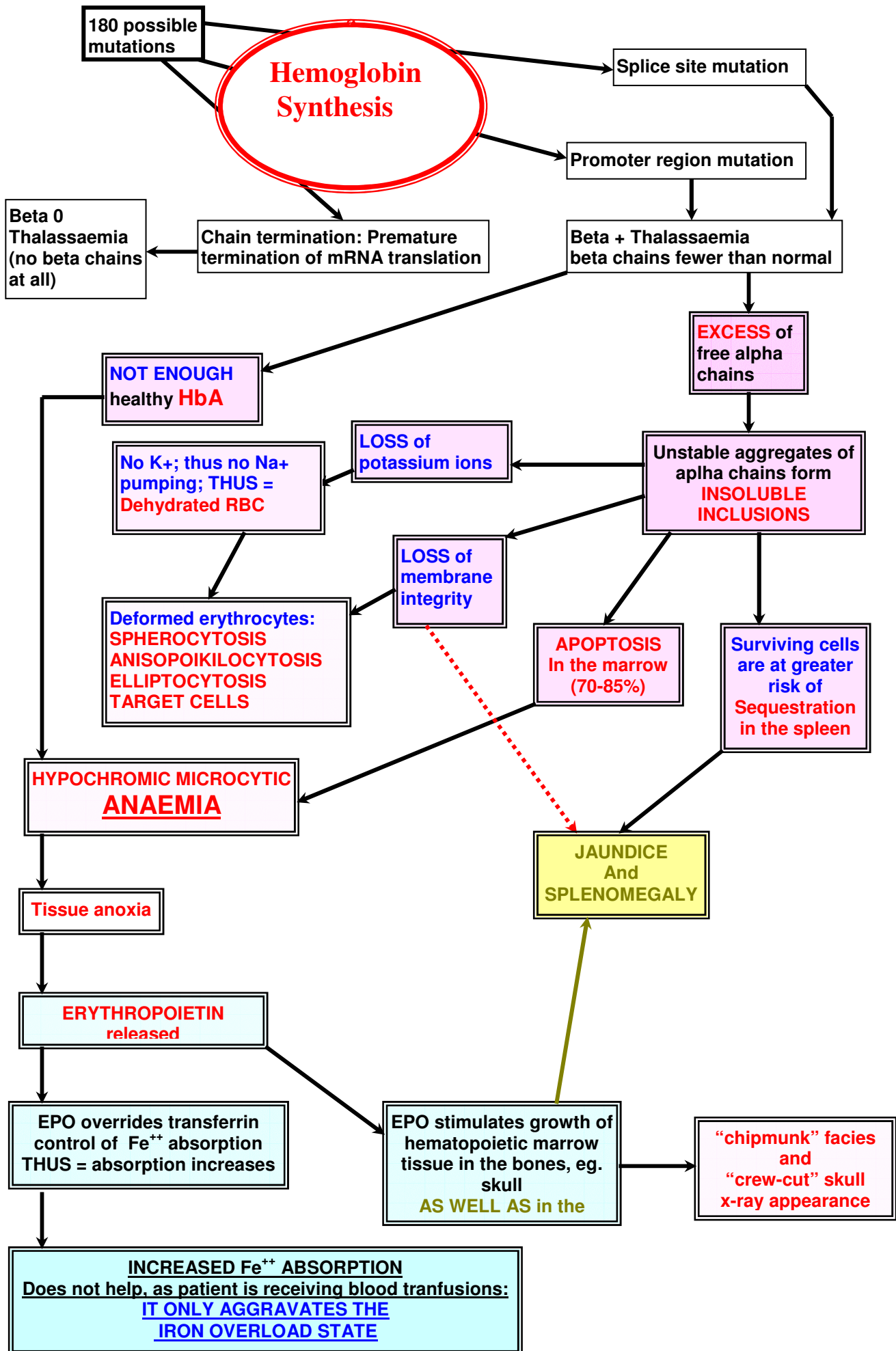


Aetiology:

LIFE CYCLE of the MALARIA PARASITE



MECHANISM OF THALASSAEMIA



Relevant anatomy: the SPLEEN

The spleen is an oval shaped organ that is 13 x 18cm long and weighs about 180 - 250 g found in the left upper quadrant (hypochondriac) behind the stomach and close to the diaphragm.

The spleen has an **outer capsule** composed of collagen fibres which enter the parenchyma of the spleen as short trabeculae and internally reticular fibres provide support.

The spleen has a hilus where the splenic artery, vein and efferent lymph vessels pass into the spleen.

Dense connective tissue surrounds the spleen (capsule) and trabeculae extend inward from the capsule and are covered by a serous membrane (visceral peritoneum).

The stroma is composed of the capsule, trabeculae, reticular fibres and fibroblasts while the parenchyma consists of red and white pulp.

White pulp is the lymphoid tissue containing lymphocytes and macrophages around branches of the splenic artery (central arteries) forming the periarteriolar lymphoid sheaths (PALS) which contain T and B cell regions. The T cells are around the central arteriole while the B cells may be in primary (unstimulated) follicles (virgin B cells) or secondary (stimulated) follicles that have a germinal centre with memory cells. The germinal centres contain follicular dendritic cells and phagocytic macrophages. In the marginal zone (the region overlying the mantle of the secondary follicles) are found specialised macrophages and a subset of B cells that resp polysaccharides). Macrophages and follicular dendritic cells present a and other lymphocytes are free to leave and enter the PALS by the ca the marginal zone. Some lymphocytes (especially maturing plasmabl into the red pulp.

Red pulp contains venous sinuses filled with blood and cords of sple cords consist of red blood cells, macrophages, platelets, plasma cells and granulocytes. Aged and damaged red blood cells and platelets are destroyed by the spleen in the red pulp by haemocatheresis. Central arteries surrounded by PALS end with arterial capillaries which open freely into the red pulp cords so circulating cells reach the cords and are trapped. The aged and damaged cells are recognised and phagocytosed by macrophages. Cells not ingested and destroyed re-enter the circulation by squeezing through the holes in the discontinuous endothelial wall of venous sinuses where the plasma can freely flow.

Schematic organization of lymphoid tissue in the spleen

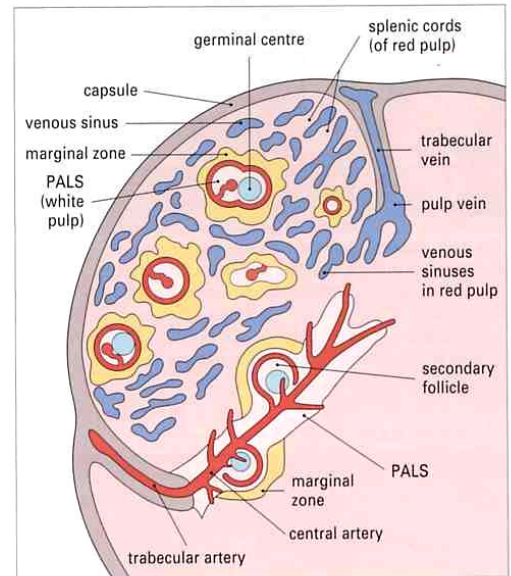


Fig. 2.46 The white pulp is composed of periarteriolar lymphoid sheaths (PALS), frequently containing lymphoid follicles. The white pulp is surrounded by the marginal zone which contains numerous macrophages, APCs, slowly recirculating B cells and NK cells. The red pulp contains venous sinuses separated by splenic cords. Blood enters the tissue via the trabecular arteries which give rise to the many-branched central arteries. Some end in the white pulp, supplying the germinal centres and mantle zones of the follicle, but most empty into or near the marginal zones. Some arterial branches run directly into the red pulp, mainly terminating in the cords. The venous sinuses drain blood into the pulp veins, trabecular veins and then the splenic vein.

The white pulp of the spleen functions as a dating agency for lymphocytes and antigen presenting cells. The activation of B cells enables them to 'turn on' their antibody production.

The red pulp removes aged and damaged RBCs and platelets – a process called haemocatheresis. The identified cells are recognized and phagocytosed by macrophages.

CONSEQUENCES OF SPLENECTOMY:

Splenectomy is performed mainly for trauma, autoimmune thrombocytopenic purpura, haemolytic anaemias and hypersplenism.

Problems include:

- Increased platelet count immediately after surgery ($600-1000 \times 10^9$) for 2-3 weeks
- Thrombocytosis persists in about 30%
- The WBC count is usually normal but there might be a mild lymphocytosis and monocytosis

Abnormalities in red cell morphology are the most prominent changes and include **Howell-Jolly bodies**, pappenheimer bodies, target cells and irregular contracted red cells. Pitted red cells can be counted.

Causes of Splenomegaly by severity:

Massive: (extends below the umbilicus)

- CML
- Myelofibrosis
- Malaria
- Kala Azar
- Primary lymphoma of the spleen

Moderate:

- Above causes
- Portal hypertension
- Lymphoma
- Leukaemia
- Thalassaemia
- Storage diseases such as Gaucher's disease

Small:

- The above causes
- Other myeloproliferative disorders such as polycythaemia rubra vera
- Haemolytic anaemia
- Megaloblastic anaemia
- Infection – viral (hepatitis), bacterial (infective endocarditis), protozoal (malaria)
- Connective tissue disease such as RA

Splenomegaly may be found in 3-12% of the population

Genetics of Thalassaemia

There are over 100 β Thalassaemia mutations known but each ethnic group has a subset of mutations and so 5 different mutations may account for more than 90% of affected people in a population. Most of the mutations in β Thalassaemia are point mutations affecting the coding sequence, splice sites or promoter of the β globin gene.

Methods used to detect these are ARMS (amplification refractory mutation system) or reverse dot blot analysis. Larger deletions can be identified directly from the size of the amplification product and if the mutation is not known then it can be identified by sequence analysis

The loss of one gene

- diminishes the production of the alpha protein only slightly.
- This condition is so close to normal that it can be detected only by specialized laboratory techniques that, until recently, were confined to research laboratories.
- A person with this condition is called a "silent carrier" because of the difficulty in detection.

The loss of two genes

- (two-gene deletion alpha thalassaemia) produces a condition with small red blood cells, and at most a mild anemia.
- People with this condition look and feel normal.
- The condition can be detected by routine blood testing, however.

The loss of three alpha genes

- produces a serious hematological problem (three-gene deletion alpha thalassaemia).
- Patients with this condition have a severe anemia, and often require blood transfusions to survive.
- The severe imbalance between the alpha chain production (now powered by one gene, instead of four) and beta chain production (which is normal) causes an accumulation of beta chains inside the red blood cells.
- Normally, beta chains pair only with alpha chains.
- With three-gene deletion alpha thalassaemia, however, beta chains begin to associate in groups of four, producing an abnormal hemoglobin, called "hemoglobin H". The condition is called "hemoglobin H disease".
- Hemoglobin H has two problems:
- First it does not carry oxygen properly, making it functionally useless to the cell.
- Second, hemoglobin H protein damages the membrane that surrounds the red cell, accelerating cell destruction.
- The combination of the very low production of alpha chains and destruction of red cells in hemoglobin H disease produces a severe, life-threatening anemia.
- Untreated, most patients die in childhood or early adolescence.

The loss of all four alpha genes

- produces a condition that **is incompatible with life**.
- The gamma chains produced during fetal life associate in groups of four to form an abnormal hemoglobin called "hemoglobin Barts".
- Most people with four-gene deletion alpha thalassaemia die *in utero* or shortly after birth.
- Rarely, four gene deletion alpha thalassaemia has been detected *in utero*,
- usually in a family where the disorder occurred in an earlier child.
- *In utero* blood transfusions have saved some of these children.
- These patients require life-long transfusions and other medical support.

Recent population genetic studies of the distribution of alpha+ thalassaemia in Melanesia using DNA analysis have provided strong support for the hypothesis that high frequencies of this genetic disorder are the result of **natural selection by malaria**

SCREENING: Blood from 18-20wk old fetus can be examined for β chain and α chain production.

Pathology of THALASSAEMIA

thalassaemia = reduced production of one type of globin chain
THUS = reduced production of functional haemoglobin tetramers
= *imbalance* in synthesis of individual alpha and beta subunits.

As a result, **there is a problem with haemoglobin switching from Hb F ($\alpha_2\gamma_2$) to Hb A ($\alpha_2\beta_2$).**

**beta thalassaemia = excess alpha chains accumulate.
alpha thalassaemia = excess beta chains accumulate.**

In β -thalassaemia, there can be reduced (β^+) or no β chains (β^0) and an over production of α -chains. Over 200 molecular defects lead to β -thalassaemia. It has variable penetration and results from carrier through to thalassaemia major.

Most cases of beta thalassaemia are due to point mutations

In α -thalassaemia, there are reduced or no α chains.

Where there are no chains, the infant is incompatible with life. It is often caused by genetic deletions rather than mutations.

β -thalassaemia

Mechanisms of anaemia:

- Erythropoiesis is increased up to ten fold
- 95% of erythropoiesis is ineffective
- Excess α chains
- Intramedullary cell death in G phase
- Apoptosis of late erythroblasts
- RBC membrane damage
- Excess RBC membrane bound iron

Clinical consequences of anaemia:

- Erythroid marrow expansion up to 3 times normal
- Increased plasma volume, due to marrow shunting and splenomegaly
- Extramedullary haemopoiesis
- Skull deformities, osteopenia, microfractures, bone pain
- Increased iron absorption and TISSUE DAMAGE

Foetal HB production:

- Compensatory increase in HbF – specific β alleles produce erythroid expansion that increases gamma chain production.
- Effect of regulators on chromosome 6 and X

Pharmacology

- *primaquine*: Has effect on gametocytes and hypnozoites. Contraindicated in G6PD deficiency- causes severe haemolytic anaemia. Weekly administration.
- *mefloquine*: Usually effective against multi-drug resistant falciparum. Acts on erythrocytic stage of development. Weekly administration.
- *doxycycline*: Daily administration. Acts on pre-erythrocytic stage of development
- *chloroquine*: Drug of choice for prevention of infection with drug sensitive falciparum. Acts on erythrocyte stage of parasitic development. Few areas left with chloroquine-sensitive falciparum
- *dihydrofolate reductase inhibitors*: pyrimethamine and proguanil resistant strains of falciparum and vivax limit their use. Inhibits pre-erythrocytic growth in the liver and development in the mosquito

The MAJOR Anti-malarial agents

Chloroquine	
Mechanism of Action	4-aminoquinoline . Mainly used to treat malaria but also has some DMARD effect via an unknown mechanism. Inhibits digestion of Haemoglobin, thus restricting nutrient supply for malarial parasites.
Dosage	300 mg once weekly
Other Uses	Malaria treatment and prophylaxis; Amoebic hepatitis; Rheumatoid arthritis, related collagen diseases; Lupus;
Contraindication	High doses, prolonged use; Hepatic or renal impairment; Porphyruria; Psoriasis; Alcoholism; Pregnancy;
Side Effects	Nausea, vomiting; Dizziness, blurring of vision; Headache; Retinopathy (v. rare); Hypotension; Dysrhythmias;
Risk in Pregnancy	D

Primaquine	
Mechanism of Action	8-aminoquinoline . Mechanism of action is unknown. Affects hypnozoites in liver and the only curative antimalarial for <i>P. vivax</i> and <i>P. ovale</i> species. Prevents transmission by affecting gametocytes.
Dosage	15 mg daily for 14 days up to 30 mg daily
Other Uses	Prevention of relapses (radical cure) for <i>P. vivax</i> , <i>P. ovale</i> ; Adjunctive therapy for malaria caused by other organisms; Prevention of transmission of malaria;
Contraindication	Severe G-6-PD deficiency; NADH reductase deficiency; RA, SLE, other causes of granulocytopenia predisposition; Bone marrow depression; Concurrent haemolytics; Lactose intolerance; Pregnancy, lactation;
Side Effects	GIT upset; Haemolysis; Methaemoglobinaemia; Headache; Dizziness;
Risk in Pregnancy	D

Parasitology a'la Amanda + Masumi

Organism: *Toxoplasma gondii*

Causes: Toxoplasmosis

Characteristics: an intracellular sporozoan parasite of humans and animals where the rapidly multiplying trophozoites are found in the red and white blood cells, the slowly replicating bradyzoites are found in tissue cysts and oocysts are found in feline faeces (natural host is the cat). Worldwide distribution.

Pathogenesis: The cysts ingested transform to trophozoites in the small intestine and then invade the gut wall reaching the blood and lymphatics where they multiply in the red and white blood cells. The trophozoites reach the internal organs (skeletal or heart muscle, brain or eye etc) and encyst. An immune response occurs in 4-6 weeks which controls the infection but does not remove the tissue cysts and so reactivation can occur during immunosuppression. A primary infection of a pregnant woman during the first trimester can infect the fetus causing congenital defects ('part of the TORCH' syndrome which includes chorioretinitis, hydrocephalus and brain damage). In the immunosuppressed a severe reactivation or primar occurs.

Epidemiology: A zoonotic infection that affects many species (humans, sheep, cattle, pigs as intermediate hosts) and felines which are definitive hosts. The rates vary in the different countries, seropositive adults in Australia are ~23% while in France over 90% adults are seropositive. The rates of infection may be influenced by dietary preferences (raw/ uncooked meat) and hygiene standards

Transmission: consumption of raw or undercooked meat with cysts or food contaminated by oocytes and transplacental.

Clinical signs: mild flu like symptoms in adults where lymph nodes may be enlarged however in the immunocompromised the symptoms are more severe and congenital infections can have brain and eye damage and can be fatal.

Investigations: Serology for haemagglutination, ELISA or immunofluorescence to detect IgM especially in pregnant women and neonates with possible congenital infections. Blood or tissue biopsies can be examined for cysts and

sporozoites and culture can be done in mice or cell cultures but is difficult

Management: Pyrimethamine and sulphadoxine or clindamycin however in pregnant women use spiramycin as it is less toxic

Prevention: Do not handle cat faeces, remove kitty litter after a day and wear gloves when changing the tray (hygiene) and eat well cooked meat.

Organism: *Giardia duodenalis* (*Giardia lamblia*)

Characteristics: a flagellated protozoa that lives on the mucosa of the small bowel and produces cysts that are excreted in faeces.

Causes: Giardiasis with worldwide distribution

Pathogenesis: There are two life cycle forms the motile binucleate trophozoite (flagellate) with a characteristic 'face' formed by the nuclei and chromatid bodies and the binucleate cysts.

The cysts transform to trophozoites in the small intestine and attach to the epithelium of duodenum and jejunum via a central sucking disc. They do not have a cytotoxic effect but large numbers of parasites contribute to mechanical malabsorption. The host inflammatory response leads to a loss of intestinal villi and increased malabsorption and severe diarrhoea. The IgA antibodies are mainly responsible for recovery and immunity.

Epidemiology: worldwide and found in animals and humans as cysts are resistant to chlorination so can survive in the water supplies. This is the most common cause of water-borne diarrhoeal illness in some regions especially in young children and homosexual males.

Transmission: ingestion of cysts via the oral-faecal route of contaminated food and water. There can be person to person spread by poor hygiene and oral-anal sexual transmission. Animal reservoirs of infection.

Clinical signs: mild but persistent (up to 6 mths) diarrhoea, flatulence, malabsorption of fats producing greasy, foul smelling stools (floaters), anorexia and weight loss.

Investigations: Fresh faecal examination for four nucleate cysts or motile binucleate trophozoites. ELISA or immunofluorescent tests for *Giardia* antigens.

Management: Metronidazole, tinidazole

Prevention: Improve sanitation, water treatment and hygiene

Organism: *Entamoeba histolytica*

Characteristics: an amoebic protozoa that lives in the intestine as a trophozoite and produces resistant cysts passed in the faeces

Causes: Amoebic dysentery common in tropical and subtropical regions but distributed worldwide

Pathogenesis: Trophozoites invade the large intestinal epithelium via galactose receptors on mucosal surfaces and in carriers anti-amoebic Ig A inhibits the invasion of the gut wall. Cytotoxic changes occur in infected cells via insertion of pore forming proteins into the cell membranes. Colitis with ulcer formation and inflammation develops which can lead to severe ulceration that can perforate the intestinal wall (peritonitis). Trophozoites can enter the portal venous system and result in a liver infection with large hepatic abscesses and may secondarily infect other organs

Epidemiology: A disease of humans and is common in tropical and subtropical regions (where prevalence can exceed 50%), with 5 - 10 % of the world infected however in Australia it is found only in tourists returning from endemic areas. There are many strains (zymodemes) that differ in pathogenicity and can be differentiated by isoenzyme patterns.

Transmission: ingestion of cysts via the faecal – oral route mainly but can be spread by anal sex. Carriers can be asymptomatic and excrete large numbers of infective cysts that can survive for weeks outside of the body. The cysts germinate (excystate) into motile trophozoites in the small intestine.

Clinical signs: symptoms include diarrhoea with pus, mucus (+ blood), fever, abdominal cramps, nausea and vomiting however carriers may be asymptomatic. Patients with invasive disease with liver abscess involvement or peritonitis may die.

Investigations: Fresh faecal specimens are examined for motile trophozoites and four-nucleate cysts. Antibodies to *E.histolytica* are found in 90% with active intestinal disease and in 96-100% with hepatic involvement. Colonoscopy/sigmoidoscopy and aspiration of abscesses in liver and colon.

Management: Antiprotozoal drugs: for luminal trophozoites – paromycin, dioxanide and for invasive disease use metronidazole or tinidazole.

Prevention: Hygiene prevents faecal contamination of water supplies and routine boiling of water in endemic areas.

Organism: *Cryptosporidium parvum*

Characteristics: intestinal sporozoan that invades and reproduces in epithelial cells of the small intestine with the oocytes being passed in the faeces.

Causes: Cryptosporidiosis

Pathogenesis: Ingestion of about 100 of the resistant oocytes in faecally contaminated matter (usually water contaminated by humans or animals) results in the transmission of the parasite. In the small intestine the cyst releases infective sporozoites that invade the epithelial cells but remain associated with the apical plasma membrane where they form schizonts that divide into merozoites which reinvade further epithelial cells. Eventually a sexual stage occurs and oocytes are released. Infection results in watery diarrhoea which can be profuse in the immunocompromised and if irreversible can be life threatening. The parasite has a complex lifecycle that involves asexual and sexual stages in the same host.

Epidemiology: Worldwide distribution.

Transmission: faecal –oral transmission by swallowing infective oocytes in contaminated water. There are animal reservoirs of infection

Clinical signs: symptoms range from a moderate to severe diarrhoea that is self limiting in the immunocompetent (can last 20 days) but can be chronic in the immunosuppressed and so it is prevalent in AIDS patients.

Investigations: concentration of faeces is required to find oocytes (5 µm) by flotation techniques and modified acid fast staining

Management: No treatment routinely but spiramycin (a macrolide) is used in the immunocompromised with limited success

Prevention: improve sanitation but *Cryptosporidium* is resistant to chlorination.

Organism: *Enterobius vermicularis*

Characteristics: a small (1cm) round worm (nematode) in the bowel that emerges at night from the anus to lay eggs

Causes: Enterobiasis or pinworm

Pathogenesis: The eggs are ingested and they hatch in the small intestine and the larvae mature in the ileum and large intestine. The female of the species lives in the large bowel and releases infective eggs onto the perianal skin after migration nocturnally to the perianal region. This causes an itching and pruritis around the anus and perianal skin. Human – human transmission only

Epidemiology: the most common intestinal nematode in developed countries and is the least pathogenic. There is a world wide distribution and it is more common in children.

Transmission: faecal –oral transmission by swallowing eggs that can be carried on fingers (after itching the anal area) and in the dust. The eggs are infective when laid and so direct reinfection is common. Only human – human transmission

Clinical signs: a minor disease with itching of anal area and seeing worms emerge from the anus at night to lay their eggs. The diagnosis is often made clinically

Investigations: the small thin shelled eggs are recovered from the perianal skin by tape (sticky tape test) and by finding adult worms in faeces. The perianal area can be viewed by a torch at night and the tiny mobile worms are visible

Management: Mebendazole, piperazine, pyrantel. There are over the counter preparations for anti-helminthics that contain pyrantel or mebendazole that can come in a syrup, chocolate flavoured square or tablet form.

Prevention: good hygiene and in cases of infection it is good to wash the sheets and underwear in hot water with detergent to remove the infective eggs.

Organism: *Echinococcus granulosus*

Characteristics: large fluid filled (hydatid) cysts in the abdomen, liver, lungs and CNS from a small tapeworm (few mm in length). The tapeworm has a head, neck and tail (strobila) with a chain of connected segments (proglottids) and the most mature (lower ones) contain large numbers of eggs.

Causes: hydatidosis, hydatid disease

Pathogenesis: the eggs from adult worms in canid intestines are passed out in faeces which contaminate the environment and are ingested by other animals including man. The intermediate hosts such as ruminants do not transmit the infection unless they are consumed raw or undercooked as the cysts of internal organs are infective. The eggs hatch to 'oncospheres' that invade the gut wall and reach internal organs where they encyst. Over time the cysts enlarge and exert a pressure on internal organs and the release of the cyst fluid can cause anaphylaxis and the formation of many 'daughter cysts'.

Epidemiology: World wide distribution but more common in sheep rearing countries. The definitive hosts are carnivores that develop an asymptomatic intestinal infestation with adult tapeworms. The intermediate hosts are humans and

herbivores (sheep, cattle) that develop extra-intestinal disease with large cysts in organs (liver, lung, brain)

Transmission: swallowing eggs released from adult tapeworms in dogs. The natural cycle is adult dog and larval cysts in sheep

Clinical signs: various as it depends where the cysts form

Investigations: Scans (x-ray, CT etc), serology for antibodies to *Echinococcus granulosus* however false negatives are not uncommon

Management: mebendazole or albendazole, surgical cyst removal which can cause daughter cysts occurring if leakage occurs

Prevention: prevent dogs eating infected viscera from the sheep, worming dogs with anti-cestodals especially in rural areas, meat inspection and hygiene after dog handling

Organism: *Trichomonas vaginalis*

Characteristics: flagellate protozoan that lives in the urogenital system of females and occasionally males. There is a trophozoite form only with no cyst

Causes: Trichomoniasis

Pathogenesis: the disease is mild in males (often asymptomatic) and involves the urethra and sometimes prostate. In females it causes vaginitis with a discharge

Epidemiology: worldwide distribution

Transmission: sexual

Clinical signs: a heavy infection causes vaginitis with a characteristic copious foul smelling discharge with an associated increase in vaginal pH.

Investigations: vaginal smear to detect motile trophozoites

Management: metronidazole, tinidazole

Prevention: use of condoms

Organism: *Leishmania* (*L.brasiliensis*, *L.donovani* and *L.tropica*)

Characteristics: a sporozoa living intracellularly in macrophages as amastigote stage and is transmitted by phlebotomine sandflies

Causes: Visceral (*donovani*), cutaneous (*tropica*) and mucocutaneous (*brasiliensis*) leishmaniasis the disease is also called kala-azar, Oriental sore, espundia

Pathogenesis: Visceral form- hepatosplenomegaly from the invasion of macrophages in the liver and spleen and there can be allergic reactions after treatment that causes dermal nodules.

Mucocutaneous form – progressive invasion of mucocutaneous tissues in the nose and mouth

Cutaneous form – localised ulcers which resolve

Epidemiology: commonest in tropical and subtropical countries

Transmission: by a sandfly bite

Clinical signs: Varied depending on the species involved

Investigations: amastigotes in biopsy material or in vitro tissue culture of specimens to obtain promastigotes

Management: antimonials, pentamidine

Prevention: avoid sandflies

Organism: *Plasmodium* (*P.falciparum*, *P.malariae*, *P.ovale*, *P.vivax*)

Characteristics: a sporozoa that lives intracellularly in the liver and primarily red blood cells

Causes: malaria

Pathogenesis: the bursting of the red cells causes the fevers. In *P.falciparum* the sequestration of infected cells in the brain capillaries can cause fatal cerebral malaria and it can be associated with intravascular haemolysis. *P.malariae* can lead to nephritis due to immune complex deposition

Epidemiology: common in tropical and subtropical regions

Transmission: bite of the female anopheles mosquito

Clinical signs: fever, myalgia, headache, malaise, nausea, tachycardia, tachypnoea, cough (esp in children) and vomiting

Investigations: blood smear detects parasites, chromatographic tests available for *P.falciparum*. In developed countries PCR can be used

Management: anti-malarials: for casual prophylaxis – proguanil, prymethamine, for longer term prophylaxis – mefloquine (Larium – causes psychotic effects), doxycycline, chloroquine or proguanil, for anti-relapse- primaquine, for treatment – quinine, chloroquine, mefloquine, artemether, tetracyclines, doxycycline

Prevention: avoid mosquitoes and mosquito control

Organism: *Trypanosoma* (*T.gambiense*, *T.rhodesiense* - African, *T.cruzi* - American)

Characteristics: flagellated protozoa living in blood and tissues, *T.cruzi* has intracellular phases

Causes: African sleeping sickness (trypanosomiasis), American trypanosomiasis (Chaga's disease)

Pathogenesis: African- the CNS is affected causing meningoencephalitis

South American- destruction of infected cells especially neurones, megaoesophagus and cardiac failure

Epidemiology: African sleeping sickness (trypanosomiasis) is found in subSaharan Africa, American trypanosomiasis (Chaga's disease) is found in South America

Transmission: bite of an insect vector : in Africa the Tsetse fly and in South America the reduviid bug

Clinical signs: African – after the bite a swollen chancre develops with widespread lymph node involvement esp in the back of the neck, fever, splenomegaly and often myocardial involvement. After weeks or months the CNS may be more involved with headache, psychologic changes, voracious appetite, weight loss, coma and death
South American - after the bite one or more swollen chancre develops with a transient febrile illness but may rarely lead to death by heart failure. The disease is chronic and slow with involvement of the heart and intestinal tract with the heart problems being the major cause of death

Investigations: detection of organisms in blood or CSF(African), or in blood, biopsy or culture (American). Serology is also possible

Management: arsenicals (tryparsamide or melarsoprol) but cured patient can have severe residual neurologic and mental disabilities

Prevention: avoid and control vectors

Organism: *Taenia* (*T.saginata*, *T.solium*)

Characteristics: large (metres) adult tapeworms in the intestine that have scolices with suckers (*saginata*) or suckers and hooks (*saginata* and *solium*). The proglottids (segments) are passed in the faeces and the small cysts (larval stages of the *solium*) can infect the muscles, CNS and eyes

Causes: Taeniasis (beef and pork tapeworms), Cysticercosis (*T.solium* only)

Pathogenesis: the adult worms are harmless but in cysticercosis the cysts in the brain can result in neurological symptoms

Epidemiology: worldwide distribution

Transmission: adult worms ingested by raw or undercooked meat *T.saginata* in beef and *T.solium* in pork. The *T.solium* eggs can hatch in humans allowing cysts to form

Clinical signs: varied depending on species

Investigations: detection of proglottids in the faeces, the species are identified by the number of branches to the uterus *T.saginata* -15-20 and *T.solium* –5-10

Management: niclosamide, praziquantel

Prevention: cook meat and prevent grazing on human faecal contaminated areas.

Organism: *Ascaris lumbricoides*

Characteristics: large (30 cm) intestinal round worm with migratory phase through the liver and lungs

Causes: Ascariasis

Pathogenesis: The eggs require incubating for several days at warm temperature and high humidity for the infective larvae to develop. After incubation the eggs are infective for months depending on the microenvironment. Once the eggs are swallowed they hatch in the intestine releasing larvae, the migrating larvae cause pneumonia like symptoms. The larvae penetrate the gut wall and move in the blood to the liver then to the lungs before being swallowed to reach the intestines again. The adults can obstruct the intestines, interfere with digestion and absorption of food and migrate in the bile duct.

Epidemiology: World wide common in tropical and subtropical

Transmission: swallowing infective eggs in contaminated food, soil or water

Clinical signs: pneumonia like symptoms, intestinal problems, allergies

Investigations: faecal check for thick shelled eggs or worms

Management: mebendazole, pyrantel, piperazine

Prevention: hygiene and sanitation

Organism: Hookworms (*Ancylostoma duodenale* and *Necator americanus*)

Characteristics: small (1cm) roundworm of the intestines with migratory stages that pass through the skin and lungs. The adult worms have expanded mouths for attachment to the intestinal mucosa

Causes: Hookworm disease

Pathogenesis: The larvae feed on bacteria until infective then migrate away from the faecal mass and then infect the unprotected skin (or are swallowed in *Ancylostoma*). They penetrate the skin and migrate to the lungs, climb the trachea and are swallowed. The adults attach by large mouths to the intestinal mucosa, ingest a plug of tissue, rupture blood capillaries and suck blood. The sucking worms can lead to anaemia and protein loss, there can be larval associated dermatitis

Epidemiology: widespread in tropical and subtropical regions

Transmission: infective larvae penetrate the skin or mucous membranes after ingestion in *Ancylostoma*

Clinical signs

Investigations: faecal tests for thin shelled eggs, culture can hatch the eggs and after 24 hrs the larvae are released

Management: mebendazole, pyrantel