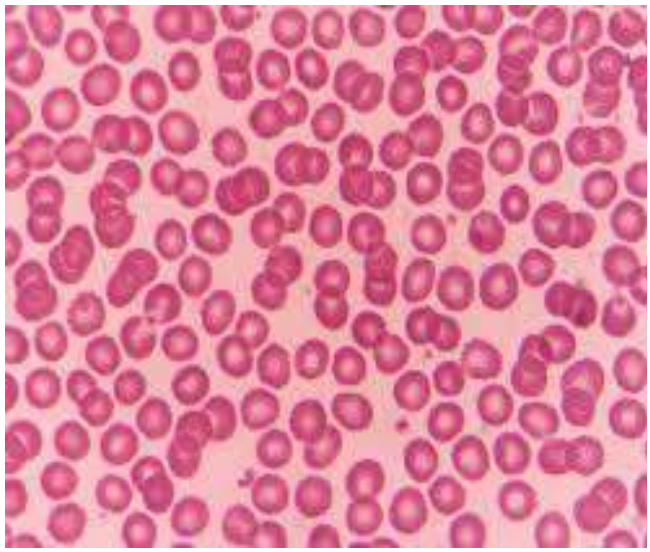
Coursebook
Autumn 2020



Demystifying blood tests in musculoskeletal practice

Dr Giles Hazan

Welcome! What follows is designed to complement the course on understanding the relevance and use of the most common blood tests within musculoskeletal medicine. To do this it helps to have the some of the background pathophysiology behind what we see in practice and the aim of this workbook is to do just that along with providing some cases to work through.

I have written it as a GP on the front line of community MSK practice and therefore is a pragmatic guide rather than a definitive textbook, but I hope it might help untangle some of the mysteries of blood tests and how they can help your practice.

Bibliography

I currently work as a GP with an Extended Role (GPwER) in Musculoskeletal Medicine alongside being a salaried GP in Sussex. I trained as a doctor at University College London Medical School before completing several years as a hospital doctor and ultimately qualifying as a GP in Brighton before then developing an interest in Musculoskeletal Medicine.

I have a keen interest in medical education and, having qualified as a GP trainer, I now work with Versus Arthritis as a trainer on their popular Core Skills courses and for Red Whale as a tutor for their MSK & Chronic Pain Update as well as delivering courses and conferences nationally to support MSK education and professional development.

I was previously Vice-President of the British Institute of Musculoskeletal Medicine and now sit on the education board of the British Association of Sports and Exercise Medicine (BASEM) as well as acting as a representative for the Royal College of General Practitioners (RCGP).

Contents

Cases

Case 1: Robert the Builder, 45year-old with acutely, swollen knee

- Recent trauma to right knee – slipped and grazed knee whilst on holiday
- 1/12 later presents with acutely painful, swollen knee
- Had bout of 'traveler's tummy' on return, still feels run down
- Borderline hypertension and raised lipids on recent well-man check

What is your differential diagnosis?

What tests might you consider & Why?

How would this change if…

- He was systemically unwell?
- He reported that this has happened before?
- He also complained of some urethral discharge (I know……nice)?

Case 2: Miss Mel N. Colly, 27year-old with polyarthralgia

- 12 months of gradually worsening pain in multiple joints with stiffness in the morning
- RTA 18months ago
- History of depression and worsening fatigue
- Co-morbid diarrhoea and abdominal pains

What is your differential diagnosis?

What tests might you consider & Why?

How would this change if;

- There is a family history of psoriasis?

- She has a very raised BMI and difficulty staying awake during the day?

Case 3: Ivy Stand, 80year-old with back pain

- Intermittent lower back pain over 30 years
- Worsened of late, increased severity and now more persistent
- Fatigue, disturbed sleep
- No lower limb, bladder or bowel dysfunction
- History of rhinitis and more recent nosebleeds
- Previous history of breast cancer fully treated 10 years ago

What is your differential diagnosis?

What tests might you consider & Why?

How would this change if;

1. It was an 80year-old ***male***?

2. She had a history of an osteoporotic fracture?

3. She had more significant proximal thigh and shoulder pain (bilateral) than back pain?

Case 4: Mr Lee Vitoff, 53year-old with 'tingling toes'

- Hypertension, BMI of 37
- Associated with numbness up to ankles
- Recent fall and ankle sprain (sent home from A&E with air-cast boot)
- Tired and run down

What is your differential diagnosis?

What tests might you consider & Why?

What lifestyle factors may be most relevant to ask about?

How might your approach change if he describes a recent illness and worsening breathlessness?

Reflective template – Demystifying bloods course

Golden Nuggets (key learning points)

What will you do differently as a result of this course?

What more do you need to know about (further reading/courses/skills development)?

Feedback Form

Please rate the following on a scale of 0-10

1. Speaker……..
2. Presentation……..
3. Course workbook……

Was there anything you would like to see changed?

Were there any topics not included that you would have liked to see?

Any other comments?

Fundamentals of Investigations

"Tests do not make a diagnosis, Clinicians do"[1]

Blood

The average adult has around 5.5L of blood in their body, constantly circulated by the heart that acts as a pump. It has a number of functions including the transport of oxygen to tissues (and waste products and gases away from them), temperature regulation, transport of cells that fight infection and maintaining the chemical balance of the body.

It is comprised of fluid and cells that can be separated out by spinning the sample in a centrifuge where the heaviest cells (red cells) fall to the bottom and can be measured as a percentage of the total (called the haematocrit, normally around 45% of the sample), next come the white cells and platelets at around 1% of the total then lastly a pale liquid called plasma which is 92% water but has lots of proteins, nutrients, hormones and chemical dissolved within.

Types of blood test & Sampling

Blood tests are described in reporting as being 'serum' or 'plasma' samples – the main difference is a serum sample is one where the blood has been allowed to clot as opposed to a plasma sample is where anticoagulants have been added to prevent this from happening and is more representative of circulating blood.

Serum
Advantages: can measure constituents normally destroyed by anticoagulant chemicals
Disadvantages: the blood is already clotted, and the clotting process, being an active metabolic process, can change results e.g. Potassium

Plasma
Advantages: quicker and higher yield and avoids the changes mentioned above
Disadvantages: the anticoagulants can affect other constituents in the blood

Different tubes are used for a range of samples with slightly different additives to optimise sampling (this can vary by country/area of the country so always check);

- PURPLE (EDTA): FBC, ESR, Hba1c, Blood film
- BLUE (Citrate): Clotting screen, Thrombophilia and Lupus screen
- GREEN (Heparin): Homocysteine, white cell enzymes
- RED (No additives-serum sample) Serology; Viral, Bacterial, Parasite, Fungal
- GREY (Oxalate): Glucose
- PINK (EDTA) for crossmatched blood samples

How was it taken?

[1] Cooper, N. and Frain, J. eds., 2016. *ABC of clinical reasoning*. John Wiley & Sons. Chapter 3: Using and Interpreting Diagnostic Tests.

The seemingly simple act of taking a blood test can have a marked effect on the result, normally a tourniquet is used, this stops venous return but allows arterial supply to dilate the veins and make it easier to take the sample, but taking a sample can often be challenging in elderly or young patients or those who have had blood taken numerous times. This can lead to it taking much longer to take the sample and the blood clotting, which changes the nature of the sample.

The sample itself can be damaged during taking, transferring to the bottles or in transit to the laboratory and the red cells break open (lyse) spilling a range of elements (potassium, magnesium, phosphate) into the sample, rendering it inaccurate. This can sometimes be managed by some sampling techniques but otherwise is reported as a 'haemolysed sample' and needs repeating.

Reference ranges

These may vary over time as different assays and techniques are used and will often vary between countries and what units are used may also vary, so double check.

Blood tests are quoted with reference ranges which are based on a huge number of factors including: Age, Ethnic background, Sex, Exercise , Pregnancy (e.g. dilutional effects of increased blood volume by 1.25L, increased ALP), Diet, Time of day/Circadian rhythms

The ranges quoted normally have a 95% confidence, in other words 95% of people will have results within this range, therefore some *healthy* people will have results **outside** of a 'normal range' and some people *with a disease* will have results **inside** this 'normal' range. Where you draw the line is called the cut off value and accepts a small percentage of people will fall either side of this. The ability of the test to detect true positives (someone with the disease/condition) is called the test **Sensitivity**, and the ability to detect a true negative (someone without the condition/disease) is called **Specificity**,

	Patient Status		
Test result		**Diseased**	**Healthy**
	Diseased	True Positive (TP)	False Positive (FP)
	Healthy	False Negative (FN)	True Negative (TN)

Predictive values:

Almost every test has less than 100% sensitivity and specificity therefore there are always true and false positives and negatives. This means the results need to be considered in the context of the prevalence of a certain condition with any given population expressed in terms of predictive value.

A positive predictive value (PPV) is probability that a subject with a positive (abnormal) test actually has the disease whereas a negative predictive value (NPV) is the post-test probability that the subject has no disease given a negative test result
Even well known 'red flags' have poor PPV, e.g. weight loss has a PPV of 0 – 3.3% for underlying malignancy, rectal bleeding has a PPV of 2.2- 15.8%. Blood tests are no different e.g. cancer markers when applied to low risk patients in primary care have low PPV and high false positive rates so need to be used with caution as a screening tool (see PSA section/cancer markers).

Disease/condition	Screening test	Diagnostic test
Bowel Cancer	FIT test	Colonoscopy & Biopsy
UTI	Urine dipstick	Urine culture
Ischaemic heart disease	Exercise ECG	Coronary Angiography

The test results always needs to be considered in the context of the patient story e.g. an elderly osteoporotic lady presenting with hip pain following a fall with a shortened, externally rotated leg has a *high pre-test probability* of a fracture, so if she then had an X-Ray that is reported as 'normal' it may need to be reconsidered as you would still have a high index of suspicion there is a fracture whereas a 23 year old rugby player with a normal hip on exam complaining of groin pain and would have a very *low pre-test probability* of a fracture and a 'normal' x-ray in this case would be seen to reliably exclude a fracture.

The D-Dimer test is a good example of this in terms of blood tests, it has a very high *sensitivity* to detect blood clots at 98% but it is also raised in other conditions such as pregnancy, infection, trauma, renal disease and other coagulopathies which means its *specificity* is nearer 40% and should not be used in isolation.

In the case of detecting DVTs, the use of additional clinical criteria (The Well's Criteria) to identify a high pre-test probability enables a more refined approach. This gives a guide as to whether the d-dimer should be ordered at all and helps identify those more at risk. So for example, whilst technically you could say the differential for calf pain in a 20 year-old, otherwise well, runner includes a DVT it would be inappropriate to order a d-dimer on them if there are no risk factors for a DVT evident.

The Wells Score: The *sensitivity* of the Wells criteria for detecting DVT is between 77–98% while the *specificity* is 38–58%

Factor	Points
Active cancer (treatment within last six months or palliative)	1
Calf swelling ≥3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity)	1
Collateral superficial veins (non-varicose)	1
Pitting oedema (confined to symptomatic leg)	1
Swelling of entire leg	1
Localised tenderness along distribution of deep venous system	1
Paralysis, paresis, or recent cast immobilisation of lower extremities	1
Recently bedridden ≥3 days, or major surgery requiring regional or general anaesthetic in the previous 12 weeks	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as DVT	-2

DVT "likely" - 2 points or more
DVT is "unlikely" - 1 point or less

Summary

Blood tests provide an additional source of information to add to your subjective and objective assessment of the patient BUT it is rare for any single test to be conclusive evidence for, or against, any pathology, they must always be viewed in the context of the patient and one should be careful to avoid false reassurance or misplaced concern.

Questions to ask before ordering a blood test

WHAT…..

- is the differential diagnosis?
- blood tests are going to help me distinguish between these different diagnoses?
- is the context?
- are the factors relevant to the individual that might affect the test result?

WHY…..

- am I doing this test?
- What will it tell me, and do I need to do it at all?
  (Is it; Diagnostic, Screening, Monitoring, to identify comorbidities?)

HOW….

- would I expect the test to change with the pathology I am considering?
- is this going to change my management?
- will I deal with an abnormal result?

A final word – there is no definitive answer as to what tests to order, and when; it requires use of clinical acumen as well as an understanding of local protocols and pathways, so it's always worth checking what they are before you start the process of investigating.

Avoid blanket testing/fishing expeditions, consider what the essential tests are, and avoid the temptation to go click/tick-happy on the template/forms!

Full blood Count: Part 1: How it's made and what the cells do

Making blood

We are born with only a few thousand embryonic blood forming (haematopoeitic) stem cells (HSCs) but these have an amazing capacity for self-renewal, differentiation and amplification so they can produce blood for a lifetime. Each time a stem cells divides it creates a copy of itself as well as another cell that becomes differentiated (hence self-regulating in a 'one for me one for you' approach).

These stem cells have diverse potentials depending on transcription factors and the local microenvironment and, along with other stromal (connective tissue) stem cells, have the capacity to also produce cells associated with other tissues including bone, liver, lung and muscles which is why this is an exciting area of research.

The location for haematopoiesis and formation of blood is the bone marrow, in an adult 70% of this is in the pelvis, vertebrae and sternum (hence is the location for most bone marrow biopsies).
The structure of marrow includes collections of blood forming cells clustered together with cells of varying maturity surrounded by fat spaces and networks of blood vessels into which the mature cells are released and enter the blood stream.

Control of haematopoiesis is mediated by regulatory molecules (growth factors) and transcription factors that regulate (turn on and off) genes in order to make sure that they are expressed in the right cell at the right time and in the right amount throughout the life of the cell and they direct cell division, growth and death throughout life

Blood cells

The Full blood count (or FBC) is the name used to describe the range of cells, and their characteristics, that are found in the blood and that are affected by a wide range of pathological and non-pathological factors.

1. Red Cells

We need to produce two million new red cells every second to replace those lost due to normal wear and tear. They lose their nuclei as they leave the bone marrow so form their shape as a biconcave disc (useful as this means they are lower in weight and more flexible)

Their role is to transport respiratory gases, Oxygen and Carbon Dioxide, and they function for around 120 days (and will go on a journey of around 300 miles during this time)

The principle red cell growth factor is erythropoietin (EPO) that is produced in kidneys in response to hypoxia and binds to receptors on primitive red cells in marrow and induces maturation

Gas transport is dependent on a specialised protein called haemoglobin, normal adult haemoglobin molecule (HbA) contains 4 globin chains (2 alpha and 2 beta) and each chain is combined with a 'haem' molecule made of iron and protoporphyrin, the iron combines reversibly with oxygen and becomes the

carrier and offload the oxygen at lower oxygen saturations by having a high affinity for oxygen in the lungs and low affinity in the tissues where it is exchanged for CO2.

Increased red cells (polycythemia) and reduced red cells (anaemia) are discussed in the next chapter.

2. White cells (aka leucocytes)

Are the nucleated cells of blood & are further subdivided into; Neutrophils, Lymphocytes, Monocytes, Eosinophils & Basophils.

They defend us against infection and destroy foreign material and damaged cells. Neutrophils, monocytes, eosinophils and basophils are phagocytes (they engulf and destroy their target). Each has a characteristic appearance in the blood film (or 'peripheral blood smear', a thin layer of blood smeared on a glass microscope slide and then stained to allow the various blood cells to be examined under a microscope)

a. Neutrophils

Have a limited lifespan of 5-6 days and are the most abundant (60-70%) of leucocytes, they have a multilobed nucleus on microscopy and their job is to enter tissues and combat infection by travelling via the blood stream to site of infection (this is called 'chemotaxis' mediated via chemotactic factors generated by bacteria and leucocytes already on site, a bit like following the smell of fresh bread to a bakery!) then using adhesion molecules on the cell surface and actin-myosin assembly that allows locomotion & destruction of the foreign material (phagocytosis). They Identify foreign material by cell surface receptors recognising a foreign antigen or particle.

- Increased neutrophils are seen in;
    - Physiological changes in pregnancy
    - Bacterial infections
    - Inflammatory disease
    - Trauma/surgery
    - Malignancy
    - Acute haemorrhage
    - Metabolic disorders e.g. Diabetic Ketoacidosis
    - Myeloproliferative disorders e.g. chronic myeloid leukaemia & myelofibrosis
    - Iatrogenic (treatment with steroids or growth factors)

- Decreased neutrophils in
    - Drugs (cancer chemotherapy, penicillin, cotrimoxazole, carbimazole)
    - Benign/idiopathic/constitutional
    - Autoimmune (Connective Tissue Disease)
    - Infections (viral/typhoid/Tuberculosis)

b. Eosinophils

Make up around 1-3 % of leucocytes and have a characteristic 2 lobed nucleus and red/orange staining granules. They have significant proinflammatory role and cytotoxic activity with significance in allergies (asthma/eczema/hayfever), parasitic infection and cancers. IL-5 is a key mediator in differentiation and activation.

Raised eosinophils (eosinophil count is greater than 0.44 x 10^9/l) may be a feature of the following conditions:

- Asthma and allergic disorders - asthma, hypersensitivity, drugs, angioneurotic oedema
- Parasitic infections e.g. schistosomiasis
- Addison's disease (adrenal glands produce too little cortisol)
- skin disease - pemphigus, urticaria, eczema, dermatitis herpetiformis, erythema multiforme
- Malignancy:
    - Hodgkin's disease
    - Carcinoma
    - haematological malignancies e.g. leukaemia
- scarlet fever
- irradiation
- post-splenectomy
- drugs - penicillins, streptomycin

c. Basophils

Are by contrast, the smallest group of leucocyctes (0.5-1% of White cells) with an abundance of dark-purple cytoplasmic granules that contain mediators of acute inflammation including heparin and histamine. Basophils and their tissue equivalent mast cells have receptors for IgE and play a significant role in immediate hypersensitivity reactions including anaphylaxis.

Increased basophils (> 0.1 x 10^9/l) seen in:

- viral infections
- urticaria
- post-splenectomy
- ulcerative colitis
- malignancy
- myeloproliferative disorders e.g. chronic myeloid leukaemia & myelofibrosis
- haemolysis

d. Monocytes

Represent only 2-10% of white cells but have multiple roles in adaptive immune system as well as replenishing stores of macrophages. They mobilise within 8-12 hours of infection and travel (by chemotaxis) to site of infection where they can enter tissues becoming macrophages (or dendritic cells)

Increase in response to chronic bacterial infections such as TB but also seen in a wide range of infectious, malignant and inflammatory disorders as well as becoming raised in steroid treatment

e. Lymphocytes (aka B-Cells/T-Cells)

Found in large numbers in the blood, lymph and lymphoid tissues (thymus/lymph nodes and spleen) making up 20-40% of leucocytes. Primary lymphoid organs like the bone marrow and thymus are where the cells are made and the secondary organs like the spleen and lymph nodes are where mature lymphocytes meet antigens and the immune response is triggered. They are essential for immunity and their roles include; Making antibodies, Providing assistance in generating antibodies, Detecting and destroying cells infected with a virus (think of them as members of a sports team all wearing the same shirts but some assist, some score the goal and others defend or support the attack).

There are two types;

- **B-Lymphocytes** (aka 'B-Cells' or 'Plasma Cells') produce antibodies against a specific antigen (humeral immunity), with or without help of other 'helper' T-lymphocytes.
- **T-Lymphocytes** (aka T-Cells) are cells of the cell mediated response (see section on immunity/infection)

3. Platelets

Are an essential component of the blood, contributing to the formation of clots with a normal range: 150-450 $x10^9$/L, of note whilst their levels are considered low if below 150 but can be life threatening below 20 (requiring referral/discussion with haematology same day).

Low platelets (Thrombocytopaenia) is seen in…

- Acute infection – generally seen to be temporary in viral infections but recovers rapidly
- Drugs – Aspirin, Heparin but also with antibiotics (penicillin), frusemide, phenytoin and more
- Alcohol & liver disease
- ITP- Idiopathic Thrombocytopaenia Purpura
- Leukaemia
- Bone Marrow Infiltration – metastatic malignancy, myeloma
- Pregnancy
- Other rare causes – hypersplenism, SLE, B12/Folate deficiency

High platelets (Thrombocytosis) is seen in…

- Blood loss
- Surgery/trauma
- Infection
- Inflammatory disorders
- Malignancy – an important cause of persistent thrombocytosis
- Myeloproliferative disorders e.g. chronic myeloid leukaemia & myelofibrosis
- Essential thrombocythaemias

The Full Blood Count: Part 2: Anaemia and Polycythaemia

Anaemia

This refers to a *reduction* in circulating red blood cells (below 13.5g/dl in men and 11.5g/dl in women) and is a symptom of disease rather than a disease itself the type of anaemia can be classified by the characteristic change in size of the red cells found.

Symptoms of anaemia include pallor, tiredness, breathlessness on exertion, palpitations, reduced appetite, bowel disturbance, headache, peripheral neuropathy (see separate section), glossitis, cognitive deficit, depression. Signs include flattened or concave nails (koilonychia), pale conjunctiva and increased pulse rate.

When a sample shows low numbers of red cells it can then be examined under a microscope (a blood film) and their size or 'mean cell volume' (MCV) and appearance used to categorise the cells as either normal size (normocytic), smaller than usual cells (microcytic,) or larger than usual (macrocytic). These changes are characteristic of certain causes and helpful to clarify the possible diagnosis using flow charts such as the one in the reference section at the back.

Microcytic anaemia (<75fL)

Aetiology

- Iron deficiency anaemia – by far the most common cause, normally due to;
    - Loss of blood either in Gi tract (men or post-menopausal women)
        - NSAIDs
        - **Malignancy**
        - Gastric duodenal ulcers
    - Menstrual loss
    - Failure to absorb iron – drugs (PPI/antacids/tetracyclines), coeliac disease, post-gastrectomy
    - Increased requirement – pregnancy, exfoliative skin conditions
- Anaemia of chronic disease (see also under normocytic anaemia)
- Rare causes
    - Thallasaemia – (alpha/beta) genetically inherited blood disorder
    - Sideroblastic anaemia – inherited or acquired abnormal condition whereby red cells cannot incorporate iron into haemoglobin
    - Hyperthyroidism – bone marrow suppression, reduced erythropoietin, comorbid disease or reduction in B12/Folate

Normocytic anaemia (76-96fL)

The commonest caused for this is anaemia associated with other chronic diseases however be aware that if there are reduced numbers of other cells such as white cells & platelets this may imply failure of the bone marrow (discuss with haematology as may need bone marrow biopsy).

It can be helpful to further separate out causes of normocytic anaemia by checking the reticulocyte count (these are immature blood cells that are only normally seen in this form for around a day in

circulation before maturing). Normal or reduced reticulocyte count – includes anaemia of chronic disease therefore suits screen other bloods for;

- Chronic inflammation e.g. TB, RA, SLE, Malignancy
- Endocrine disease e.g. Hypothyroidism, Addison's disease
- Chronic kidney disease (U&Es)
- Malnutrition
- Liver disease (LFTs)
- Haemochromatosis (raised ferritin)

Raised reticulocyte count

- Haemolytic anaemia (causes include inborn errors of red cell manufacture, autoimmune haemolysis, infection (e.g. malaria) and some drugs and toxins)
- Anaemia that follows a significant bleed/haemorrhage (e.g. GI bleed)

Macrocytic anaemia (Macrocytosis)

Can be further sub-characterised by the changes in the red cells seen in the bone marrow where some have immature nuclei and are called megaloblasts - megaloblastic anaemia, or not (non-megaloblastic anaemia). Of note, macrocytosis can be seen with faulty sampling (incorrect storage), paraproteins in myeloma, hypercalcaemia or leucocytosis.

Aetiology

Megaloblastic:

- B12 Deficiency – Pernicious anaemia* (Autoimmune Addisonian 80%), after bowel surgery, dietary deficiency (strict vegans)
- Folate Deficiency – dietary deficiency, malabsorption, increased demand (haemolysis, leukaemia), increased excretion (heart failure, hepatitis, dialysis), medication (alcohol, sulfasalazine, methotrexate, anticonvulsants, trimethoprim- only with prolonged courses)

*an autoimmune disease-causing atrophy of lining of stomach/gut and loss of parietal cells (and others)B12/Folate are important B vitamins involved in nerve function, red cell production and a number of DNA pathways.

Non-megaloblastic

- Alcohol abuse
- Liver disease
- Severe hypothyroidism
- Reticulocytosis
- Drugs e.g. azathioprine

Polycythaemia

This describes an *increase* in haemoglobin concentration above the reference range for age/sex.
The approach to diagnosis is to distinguish between polycythaemias due to

1. An increased red cell mass (primary and secondary polycythaemias)
2. Due to a reduced plasma volume (relative polycythaemias).

Polycythaemia rubra vera (primary polycythaemia)

A rare myeloproliferative (essentially a blood cancer) disorder generally seen in middle or older age in which red cells, and often white cells and platelets, are increased. Can cause itching, enlarged spleen, blood clots/bleeding and neurological symptoms from the increased red cell size and increased plasma volume (dizziness, headache, lethargy, visual disturbances).

Treatment aims to reduce the risk of clots and complications with a variety of medications.

Laboratory features

Blood test	**Result**
Haemoglobin	Increased
Mean Cell Volume	Increased (often >36ml/kg in males)
White Blood Cells	Increased neutrophils
Platelets	Raised (400-800x10^9 potentially over 1000x10^9)

Secondary polycythaemia

Increase in the red cell mass due to tissue hypoxia caused by:

- Chronic respiratory disease
- Congenital heart disease
- High altitude.

Secondary polycythaemia also occurs in some renal disorders, especially tumours, where there is increased production of erythropoietin.

Relative or “stress” polycythaemia

The commonest form of polycythaemia, the increased haemoglobin is secondary to a reduction in the plasma volume, the Mean Cell Volume (MCV) is therefore normal.

Clinical associations are:

- Smoking
- Alcohol
- Stress
- Dehydration
- Diuretics.

Inflammation and Infection

Tissue damage

Whether by infection, heat, chemical or mechanical trauma, the effect on our bodies is tissue damage and cell death. This causes a release of substances from the damaged cells that trigger the body's natural healing response by way of an acute inflammatory response. This serves a number of functions.

1. It fills the area with a liquid called an inflammatory exudate which is a chemical soup packed full of proteins/fluids and cells to help mediate local defences.
2. It destroys any infective agents
3. It removes damaged material from the site.

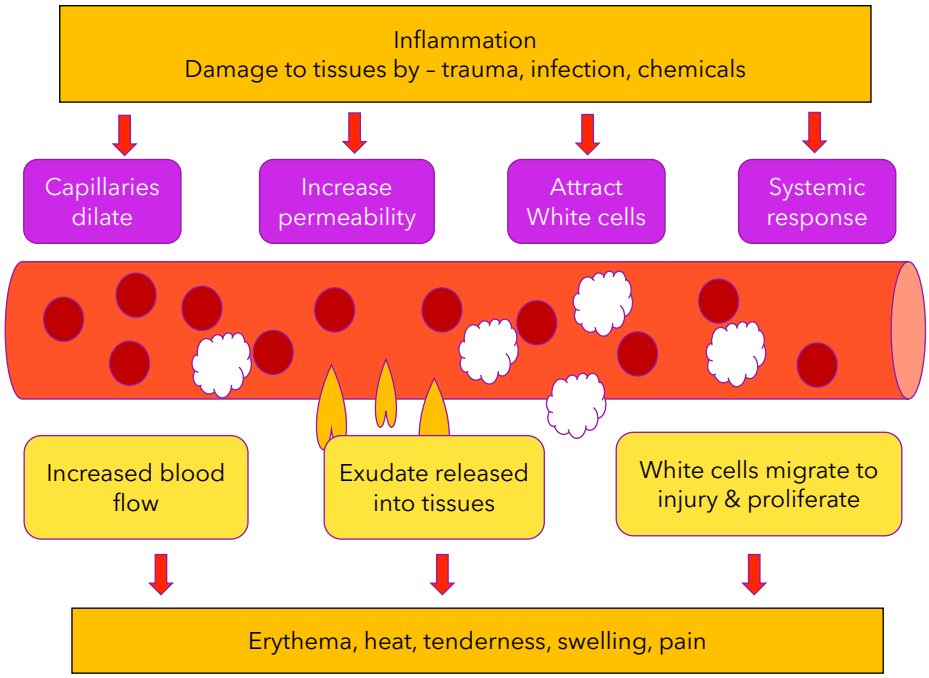
The outcome of the acute inflammatory process can either be to lead to reorganisation and replacement of the original tissues, replacement of the original cells with scar tissue or, if the damaging agent remains present, ongoing tissue damage and an immune response.

Inflammation & Infection

One of the key components of the initial inflammatory response is the inflammatory exudate contains a range of cells and products including;

- Fluid containing salts and immunoglobulins (antibodies)
- Fibrin- formed from an aggregation of smaller plasma proteins (called Fibrinogen) that pass out of the blood and forms longer strands by activation of the coagulation cascade - this is thought to produce a scaffold to prevent spread of bacteria and allow migration of neutrophils
- Neutrophils – these are the first, and main, cells to join the battle these kill micro-organisms and break down tissue and are triggered into action by mediators and more are generated from bone marrow, if required, stimulated by growth factors produced by the inflammatory process. They are short lived and
- Macrophages – small numbers present initially (come later compared to neutrophils) and are phagocytic cells (that destroy bacteria) that last longer than neutrophils they also produce more cytokines and growth factors.
- Lymphocytes (aka plasma cells) – in small numbers – role in synthesising/secreting antibodies
- Monocytes – phagocytes also involved in engulfing bacteria

These cells migrate out of the circulating blood and into tissues by the vessels increasing in size, permeability and blood flow directed by chemical messengers attracting them to the site where they are required. This process is mediated by a range of messengers produced by the local damaged cells and from within the blood itself.



The change in the nature of the blood vessels and the increased production and presence of this array of clinical messengers both locally and systemically causes the classic clinical features we recognise within acute inflammation;

- **Fever** – driven by endogenous (cytokines) or exogenous (micro-organisms) acting on the hypothalamus producing prostaglandins that act to 're-set' the thermostat.
- **Pain** – localised to site of tissue damage/infection, sensitisation of neurons by PG/Bradykinin
- **General malaise** – central nervous system effects of prostaglandins
- **Rapid pulse rate**
- **Pus** – seen as a feature when neutrophils dominate and material is liquified = 'purulent exudate' (worth noting that if the liquid is more fluid based it is a 'serous' exudate or can be 'fibrinous' when more containing fibrin on surface of tissues) – when large amounts of localised tissue necrosis and pus form this creates a collection called an abscess

For initial investigation (screen), the following tests can be done:

Blood test	**Result**
FBC	Raised white cells (neutrophilia commonly with bacterial infection)
CRP	Raised (>150 in bacterial infections)
ESR	Raised

Inflammatory markers (aka Acute Phase Reactants)

As well as local cellular changes and those related to the circulating blood there are changes in products produced by the liver in response to inflammation that act as important biomarkers to help detect and monitor inflammation, these are the acute phase reactants. The most commonly noted are Fibrinogen and its impact on the Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP).

Whilst they are used widely in our assessment of infection and inflammation, they are known to lack specificity (and sensitivity) so need to be seen as adjuncts to good clinical history and examination.

Erythrocyte Sedimentation Rate (ESR)

This is a measurement of how far red blood cells (erythrocytes) will fall in sample of anticoagulated blood in a vertical tube in an hour and is measured in millimetres/hour.

Normally the red cells are negatively charged so tend to repel each other but when the blood is filled with more fibrinogen as part of the inflammatory response, as a large, positively charged protein, it causes the red cells to clump together and create heavier clusters that fall quicker down a vertical tube and hence the ESR will increase.

Erythrocytes aggregation is also triggered by high levels of immunoglobulins (antibodies) so is also raised in *non-infective* auto-immune disease. Both immunoglobulins and fibrinogen take a few days to increase to significant levels but have long half-lives so the ESR tends to take longer to rise but stay raised for longer compared to CRP.

ESR – Confusingly there are different formulae used to calculate the upper limit of normal but perhaps most usefully is one based on a calculation allowing for age and sex;

Men: ESR = age ÷ 2 e.g. a 70year-old male would expect an ESR <35
Women: ESR = (age +10) ÷ 2 e.g. a 70year-old female would expect an ESR <40

Raised ESR is seen in;

- Infection
- Renal Failure
- Inflammation
- Diabetes mellitus
- Malignancy
- Physiological: Female gender, Pregnancy (hyperfibrinogenaemia), Old age
- Anaemia
- Red blood cell abnormalities
- Technical factors (Dilutional problem, Increased temperature of specimen, tilted ESR tube)
- Elevated fibrinogen level

C-Reactive Protein (CRP)

Is made in the liver and produced by the action of cytokines (IL-1/6 and TNF-alpha). This (and other acute phase proteins e.g. haptoglobin) have a role in marking and trapping of micro-organisms and their products, modulating aspects of the immune response and neutralizing enzymes.

It increases within 4-6 hours of the onset of inflammation, doubling every 8 hours but has a short half-life (4-7hrs) so go up early and decrease rapidly once the inflammation has eased (within 3-7 days).

As a general rule, bacterial infections will cause a greater rise in CRP (150-350mg/L) compared to a viral infection and this has been used as a bedside test to differentiate between the two types of infections and indicate which patients may suit antibiotic therapy

A word on fever – why do we experience this? Well it is postulated that when the body is battling an infection a fever (i.e. a rise of the body temperature to above the 37.5 degree Celsius) serves to reduce the rate at which bacteria propagate (this is at an optimum below 37 degrees), enhances the body's immune response as well as increasing efficacy of antibiotics. This holds true until the temperature gets above 40 degrees when it is a more destructive influence on the body.

<u>Inflammatory markers in practice</u>

ESR/CRP (Plasma Viscosity can also be used but is less common) are used frequently in practice for a range of reasons including;

- Diagnosing inflammatory conditions, infections, autoimmune conditions and cancers
- Monitoring disease progression or treatment
- Testing for conditions such as Myeloma, Polymyalgia and Pneumonia

They can often be used as a form of reassurance as a 'rule out' in cases of patients with non-specific tiredness, malaise, memory problems and so on but can often lead to a cascade of subsequent tests when raised. A large cohort study showed that when used to investigate a wide range of symptoms they found Infection in 6.3% cases, Autoimmune conditions in 5.6% & Cancers in only 3.7%. Although the higher the level was the increased likelihood there was of disease it amounted to a relatively low sensitivity at 50% and it tended to cause a raft of subsequent tests, often unnecessarily

Another cohort study compared the accuracy of use both CRP & ESR together to pick up infection, cancer and autoimmune disease and found that doing multiple inflammatory markers together does not improve the ability to rule out disease but CRP was slightly better at detecting infections and they were the same at picking up autoimmune conditions and cancers

A notable exception to this rule is when testing for Polymyalgia Rheumatica or Giant Cell Arteritis where current guidance suggests test both.

Immunity & Autoimmunity

There are three levels of immunity:

- *Physical barriers* including skin & mucous membranes of lung (skin=2sq m vs lungs 400sqm)
- *The Innate immune system* - a swift, non-specific response – includes inflammatory response
- *The Adaptive immune system* - a slower, measured response that can adapt and 'learn' to help improve the defences of the host

Innate Immune system

This includes systems shared across all animals with some features that have been around for more than 500million years.

This includes the inflammatory response mentioned above, within the inflammatory exudate are the destroyers cells called macrophages ('macro'-large, 'phage' from Greek word 'to eat' i.e. 'large eater'!) that use the receptors on their surface to recognize abnormal components (antigens) on the cells surface of foreign cells called Lipopolysaccharides that are not found on any cells of the human body. Macrophages come from monocytes that migrate from the blood and spread throughout the body in readiness to fight infection especially in areas like the gut, lungs and mucous membranes where they are more likely to encounter foreign cells.

Macrophages are called 'phagocytes' as they engulf bacteria and are also joined by neutrophiles and monocytes that similarly engulf bacteria. Macrophages give off proteins called cytokines (hormone-like messengers) that help communication between cells. These alert monocytes and other immune cells that the battle is on.

Other cells of the innate immune system are from the Complement protein family (that function by punching holes in bacteria) and Natural Killer Cells (NK) that are able to destroy some bacteria, parasites, viruses and some cancer cells.

Adaptive Immune system

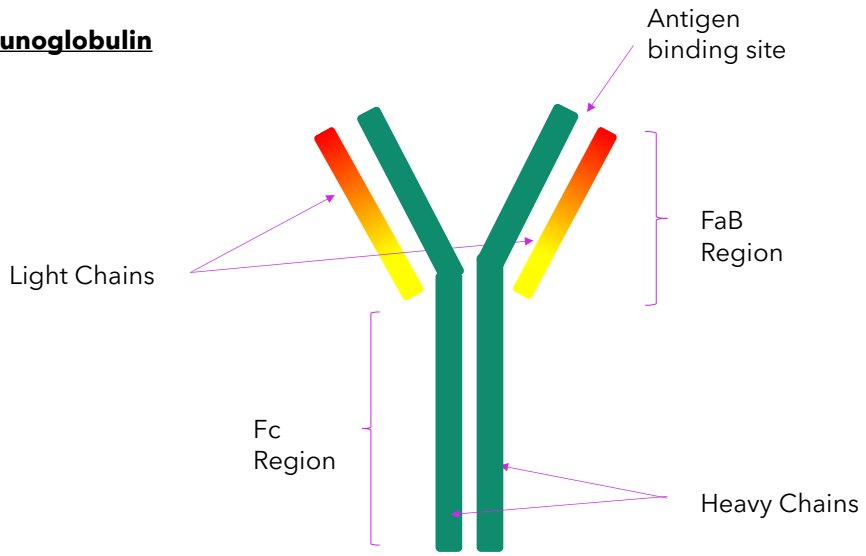
This enables us to adapt against almost any invader based on presence of specialist proteins that circulate in the blood called antibodies

Each type of antibody is produced by B-Cells that form in bone marrow that mature into antibody factories called plasma B-Cells

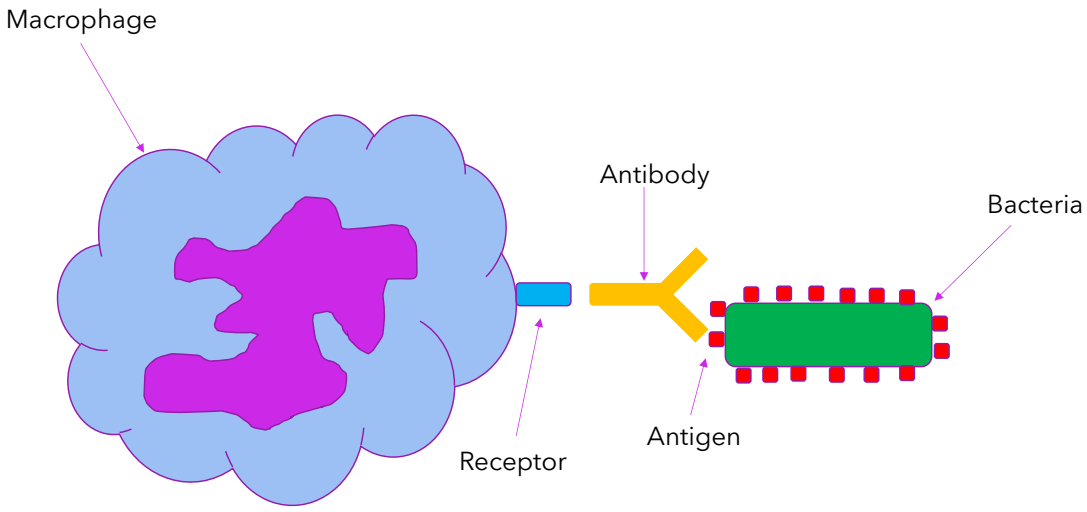
The antibody has two areas that can connect to other cells

- an antigen binding region (Fab)
- a constant region (Fc) which can bind to receptors (Fc receptors) on the surface of other cells including macrophages – the special structure of the Fc region determines the antibodies class (e.g. IgG or IgA)

Immunoglobulin



Their role is to 'tag' the invader for destruction (also called 'Opsonization' = 'to prepare for eating'). They bind to the invader with their Fab region leaving their Fc tails available to bind to the Fc receptors on macrophages – forming a bridge between invader and phagocyte



We need around 100 million different types of antibodies to face all of the different invaders but cannot have them all available in enough quantities all the time (only 3 billion available in the blood stream) so we need them to be made on demand (like a shop ordering more stock from the warehouse)

The ability to manufacture this many different antibodies comes from varying the combination of a multitude of gene segments that code for both the heavy and light chains rather than just using our, more limited, original gene code (like a mix and match of gene segments)

The B-cells then produce a range of ‘tester’ antibodies called B-cell receptors that are expressed on the surface of the B-cells and then circulate, ‘fishing’ for their specific antigen. Once it binds to the antigen the B-cells double in size and proliferate by dividing into two and two again etc until multiple copies are made and they produce multiple copies of the antibody that are no longer anchored to the surface of the B Cell but are transported out of the B-Cell and into the blood stream (one B-Cell can produce about 200 antibody molecules per second at full capacity).

This avoids having to carry multiple copies of the B-cells around in the blood stream all the time.

After leaving the bone marrow, the B cell acts as an antigen-presenting cell (APC) and internalizes offending antigens (endocytosis). Pieces of the antigen are loaded onto MHC II molecules, and then presented on its extracellular surface to CD4+ T cells (sometimes called *T helper cells*). These T cells bind to the MHC II-antigen molecule and cause activation of the B cell.

This is a type of safeguard to the system, almost like a two-factor authentication method. First, the B cells have to encounter a foreign antigen, and are then required to be activated by T helper cells before they differentiate to specific cells.

After stimulation by a T cell, which usually occurs in secondary lymphoid organs like the spleen and lymph nodes, the activated B cell begins to differentiate into more specialized cells.

These new B cells may differentiate into memory B cells or plasma cells. Most of these B cells will become plasmablasts (or "immature plasma cells"), and eventually plasma cells, and begin producing large volumes of antibodies.

<u>Viral attack</u>

Viruses use the receptors on cells to enter and use the cells machinery to make multiple copies of itself – some antibodies can bind to a virus when it’s still outside a cell and stop it entering or from reproducing (these are called neutralising antibodies)

<u>Autoimmunity</u>

Fundamentally our immune system is designed to distinguish between the cells and tissues of our own bodies ‘self’ and those belonging to another organism that may be potentially damaging ‘non-self’. When this system breaks down the immune system can start to damage its own cells and organs and lead to severe and enduring health problems.

This can be through problems with both the adaptive immune system with the production of antibodies (autoantibodies) directed against its own cells/tissues, more often than not against components *within* cells, and the innate immune system with a cell-mediated response more likely to damage cells themselves.

These can affect specific organs or more widespread, non-specific autoimmune diseases including the following;

Organ specific

Organ	Condition	Autoantibody	Features
Skeletal Muscle	Myasthenia Gravis	Acetylcholine receptor autoantibody	Muscle fatigue
Thyroid	Grave's Disease	Thyroid stimulating antibodies Thyroid growth stimulating antibodies	Hypothyroidism
	Hashimoto's Disease	Anti-thyroid specific antibodies	Hyperthyroidism
Skin	Vitiligo		Hypopigmentation
Adrenal Cortex	Addison's Disease	Anti-adrenal antibodies	Hypoadrenocorticalism
Pancreas	Type I Diabetes mellitus	Anti-islet β-cell (insulin) antibody	Diabetes
Stomach		Anti-intrinsic factor and parietal cell antibodies	Pernicious anaemia

Non-organ specific

Condition	Autoantibody	Features
Systemic Lupus Erythematosus	ANA	Skin, kidney, joint, heart and lung features
Systemic Sclerosis	ENA – Anti La & Scl	Skin, gut, lung
Polymyositis& Dermatomyositis	ENA – Anti Ro, Jo & Mi2	Skeletal muscle and skin
Rheumatoid Arthritis	Rheumatoid factor (Anti-IgG)	Joint, lung, vessels

The precise mechanisms behind autoimmunity are not fully understood but there are likely to be multifactorial including genetic predisposition, environmental factors and disordered regulation of the immune system.
Patterns of inheritance in families and ethnicities that suggest a genetic component likely to be changes in the genetic code causing abnormal regulation and control of the immune cells. The most well know associations are with the HLA alleles but cytokine and cytokine receptor genetic polymorphisms have also been implicated amongst others and whilst precise mechanisms may be uncertain these cells all have a role in the immune system.

There are links to environmental triggers such as infection e.g. rheumatic fever – whereby after a β-Haemolytic streptococcal infection (throat infection) the antibodies that develop to fight the infection also bind to antigenic components of heart muscle causing inflammation and damage.

Certain medications have been implicated such as α-methyldopa (a drug previously used to treat high blood pressure) which was linked to haemolytic anaemia as it has been suggested the drug may cause some change on the surface of the blood cells to render them recognised as 'non-self'.

There is also a growing evidence base for the role of the microbiome in the development of disease including local and systemic inflammatory disorders. Changes in the trillions of bacteria in our guts can affect the absorption of cellular components such as lipo-polysaccherides that then create an inflammatory response as well as local changes implicated in the development of inflammatory bowel disease.

Importantly we know autoantibodies exist in a 'normal' population implying there are mechanisms to hold back and restrain aberrant B-Cell immune responses, likely through the action of T-Suppressor Cells. It is plausible that a reduction in these cells can lead to unrestrained auto-reactive B Cell activity and damage and example of this is the identification of low levels of T Suppressor cells seen in some autoimmune conditions such as Multiple Sclerosis.

Autoantibodies

Antinuclear antibodies (ANA)

The ANA is a screening blood test looking for antibodies in the blood to attack proteins in the nucleus of its own cells and estimating the severity of any autoimmune disease. It is not diagnostic of any single condition; in other words, it identifies the likelihood of having an autoimmune condition but not which one.

ANA is found in up to 5% of the healthy population and this is commoner in women and increases with age (seen in up to 30% in women 80 years or older) but is also dependant on ethnicity and the type of test used.

It is predominantly done to screen for Systemic Lupus Erythematosus (SLE) where it is positive in 95+% of cases – this means a negative result suggests SLE is unlikely, but a positive result would warrant further investigations.

It is also seen to be positive in other autoimmune disorders including;

- Diffuse scleroderma 80%
- Mixed connective tissue disorder (MCTD) 80%
- Sjogren's syndrome 60%
- Limited Scleroderma (CREST syndrome) 50%
- Rheumatoid Arthritis 30%
- Polymyositis 30%
- Autoimmune Liver disease <10%

ANA testing is normally reported using two key parameters;

- The Titre
- The Pattern

The Titre

This identifies the amount of anti-nuclear antibodies in a sample of blood. It is done by separating a sample of serum and diluting it with another liquid (called a diluent), a bit like making a glass of orange squash – the squash is the serum and the water the diluent, before testing for the presence of autoantibodies in the diluted sample.

There are serial dilutions where, initially, 1 part of serum is diluted with 40 parts of diluent (a "1:40 titre") – this is then tested and if the sample is positive for ANA antibodies then a further dilution is made to half the strength (1:80) and tested again and, if positive for autoantibodies, its diluted again to 1:160 and onwards (1:320, 1:640, right up to 1:2560).

In other words, if autoantibodies are found in very dilute samples then it is likely that there were very high numbers of autoantibodies to start with and the chance of having an autoimmune condition is greater.

<1:40	Negative
1:40 or 1:80	Borderline
>1:160	Consistent with autoimmune disease

The Pattern

This is tested by adding a sample of the patient's serum to a layer of cells on a slide then adding a fluorescent detection system and if any ANA is present it shows up as a fluorescing pattern, lighting up the areas of the nucleus where they are present and active.

The *patterns* are not necessarily specific to any type of disease however some associations are seen hence they tend to be reported on and they include;

- Homogenous (aka peripheral or diffuse) – entire nucleus stained with ANA (most common pattern) seen in any autoimmune disease including SLE
- Nucleolar pattern – staining around nucleoles inside the nucleus – seen in Diffuse Scleroderma/Systemic sclerosis
- Centromere – staining across the chromosomes associated with limited Scleroderma/CREST
- Speckled – fine and coarse staining throughout the nucleus seen more with antibodies to extractable nuclear antigens (ENA) MCTD, Sjogren's, Polymyositis, RA

Of note – certain drugs can cause an SLE like reaction with a positive ANA including; Procainamide (anti-arrythmic), anticonvulsants, isoniazid, hydralazine, chlorpromazine, methyldopa

Having established a positive, relevant ANA it is then a matter of further tests to identify which proteins are being attacked by the antibodies using anti-DNA and ENA tests.

<u>Anti-dsDNA antibodies</u>

Anti- double stranded DNA test specifically assess for autoantibodies to double stranded DNA.

This is relevant as Anti-dsDNA antibodies are only found in Systemic Lupus Erythmatosus so a positive result means an individual likely has SLE although 30-50% of people with SLE will have a negative anti-dsDNA antibody test so a negative result does not exclude SLE.

< 1:20 or <1:40	Equivocal
>1:80	Consistent with SLE

Of note anti-single stranded DNA is found in many connective tissue disorders so of little diagnostic use

Extractable Nuclear Antigens (ENA)

As another follow up to the ANA it is possible to extract some of the nuclear antigens and test the patient's serum to see if they have antibodies against these – this can add information to aid the diagnosis but, as before, is not on its own, diagnostic.

Described as a ENA 'panel' it checks for antibodies against a range of protein

Antigen	Association
Anti-Ro	Sjogrens (90%) SLE (40%) Polymyositis (5%) Rheumatoid Arthritis (5%)
Anti-La	Sjogrens (80% - usually seen with Ro) SLE (10%) Diffuse scleroderma
Anti-Sm	SLE (20-30%) MCTD ('most patients')
Anti-RNP	SLE (20%)
Anti-Scl 70	Diffuse scleroderma (50%0 CREST (10%)
Anti-Jo 1	Polymyositis (30% but is 95% specific when found)
Anti-centromere	Limited Scleroderma & CREST

Rheumatoid Arthritis

Is a chronic, disabling disease, the most common inflammatory arthritis affecting around 1% of the population. Characterised by auto-antibodies including Rheumatoid Factor (usually IgM) that attack a variety of tissues in the body and anti-cyclic citrullinated peptide (anti-CCP). CCP is a protein not normally found in the body so the immune system attacks it – this is an issue in RA as the proteins are found in joints – hence causing joint destruction.

Aetiology

It is more common in men than women (3:1) and found in higher incidence in certain populations (e.g. Native Americans) and although the cause is unknown there is a clear genetic component (with an association with the HLA-DR4 marker) alongside hormonal and environmental factors. Lifestyle factors such as smoking, being overweight and having a diet high in red meat and low in vitamin C have been implicated in increasing the risk of RA.
It is characterised by inflammation with a persistent immune response (the key cytokines being TNF-α and IL-1) mounted against the synovium of joints causing hypertrophy and subsequent destruction.

Signs and Symptoms

Classically it is described as starting earlier in life (30's) but, as it is a diagnosis that can be missed, or the presentation delayed, it is an important diagnosis to consider irrespective of age. There are multiple, widespread effects on most systems in the body including generalised features of weight loss and fatigue.

System	Signs& Symptoms
Joints	Synovitis (tender joints, boggy swelling, +ve squeeze test) usually in a symmetrical pattern affecting the small joints of the hands and feet (>3 joints has specificity of 73%) with morning stiffness (>30min has sensitivity 75%, specificity 50%) & waking with pain in the early hours of the morning. Can be in an acute mono-arthropathy or palindromic (flares of joint pain that return to normal between episodes). Can include cervical spine (atlanto-axial+/-subluxation) but not normally thoracolumbar spine
Skin	Rheumatoid nodules, peripheral vasculitis, and leg ulcers
Neurological	Carpal Tunnel syndrome (and other entrapment neuropathies), mononeuritis, peripheral neuropathies – secondary to synovial hypertrophy and joint subluxation
Renal	Amyloidosis – watch for leg oedema, renal function changes and protein in urine
Haematological	Anaemia (with low platelets & white cells)
Respiratory	Serositis – causing pleural effusions (SOB, pleural rub), interstitial lung disease
Cardiac	Pericardial effusion/Pericarditis - chest pains, pericardial rub
Eye symptoms	Scleritis – eye pain, increased tear production, inflammation

Investigations

Of note it is a *clinical* diagnosis with no single test or investigation making a definitive distinction, N.B. up to 1/3 of people with RA will have normal blood tests.

Blood test	**Result**
Full Blood Count	Normochromic, normocytic anaemia (chronic inflammation can reduce production Red cells)
ESR	Raised
CRP	Raised
LFT	Low albumin
TFT	Normal (but could be abnormal in Thyroid disease)
Creatinine Kinase	Normal (helpful to distinguish between RA and myositis)
Bone profile	Should be normal (abnormal in bone pathologies e.g. Osteomalacia with raised ALP/PTH, reduced Ca/phosphate/Vit D)
Rheumatoid Factor	Positive (70% sensitive and 85% specific)
Anti-CCP	Positive (60-70%% sensitivity but is more specific at 95%) – consider if negative Rh Factor – usually 2ndary care
Urate	To rule out gout in mono-arthropathies

Other investigations include;

- Joint fluid aspiration – rule out gout/infection
- Imaging
    - X-rays (hands/feet can be done as part of initial work up) may show periarticular erosions, joint space narrowing, disease monitoring
    - Ultrasound – identifying synovitis
    - MRI – can identify early synovitis

Differential diagnosis

Depends on the pattern at presentation but could include;

- Other joint diseases
    - Osteoarthritis
    - Spondyloarthropathy
- Systemic disease
    - Fibromyalgia/chronic pain syndromes
    - Thyroid disease
    - Osteomalacia -
    - Hypermobility/EDS
    - Connective tissue disease
    - Malignancy – including leukaemia/lymphoma
    - Hepatitis/HIV

Referral

Of great import is the fact that when diagnosed and treated within the first 3 months or so of symptoms emerging the course and progression of the disease can be radically altered and virtually halted in its tracks. Initiating DMARDs within 3 months can lead to; Improved function, Reduction in disability, Reduction in long term joint damage. So have a low threshold for referral ans DO NOT WAIT FOR BLOOD TESTS

Referral from primary care (from NICE guideline [NG100] Published date: 11 July 2018)

Refer for specialist opinion any adult with suspected persistent synovitis of undetermined cause. Refer urgently (even with a normal acute-phase response, negative anti-cyclic citrullinated peptide [CCP] antibodies or rheumatoid factor) if any of the following apply:

- the small joints of the hands or feet are affected
- more than one joint is affected
- there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

Treatment

As with any long-term condition a multidisciplinary approach considering the variety of biopsychosocial factors is vital, there is a 40% prevalence of depression in RA, 30% give up work within 12m of diagnosis and this is 20% prevalence of anxiety. It also has a strong association with chronic pain disorders such as Fibromyalgia (25% prevalence in RA).

- Medical
    - Disease Modifying Drugs (DMARDs)
        - Biologics
            - Anti-TNF drugs – e.g. Etanercept
            - Others e.g. Rituximab
        - Non-biologics – e.g. methotrexate, leflonumide, hydroxychloroquine
    - Analgesics – NSAIDs
    - Steroids
- Lifestyle changes – Exercise, Diet, Weight management, smoking cessation
- Surgical management – Joint replacement, arthrodesis, osteotomy, tendon surgery

Spondyloarthropathies

This is a group of arthropathies including;

- Ankylosing Spondylitis
- Psoriatic arthritis
- Reactive arthritis including Reiter's Syndrome
- Enteropathic arthritis (i.e. associated with UC/Crohns)

They share the following characteristics;

- *Sero-negativity*: main distinguishing characteristic to rheumatoid arthritis as they tend to be negative to rheumatoid factor, autoantibodies and anti-CCP
- Association with *Human Leukocyte Antigen (HLA) B27*
- *Asymmetrical large joint arthritis* - often lower limb oligoarthritis (<5joints)
- *Axial involvement* – including SIJ involvement
- *Enthesitis* – plantar fasciitis, achilles tendinitis (+ bursitis)
- *Dactylitis* - inflammation of a digit (either finger or toe)
- *Extra-articular features* – uveitis (iritis=anterior uveitis is seen in up to 40% of AS patients), oral ulcers, aortic valve incompetence, Inflammatory bowel disease

Ankylosing Spondylitis
(ankylosis=stiffening and immobility of a joint, spondylitis=vertebral inflammatory changes,)

- Is an aseptic arthritis affecting joints and entheses of the spine
- Accounts for 5% of patients presenting with back pain
- Affects 0.2% of gen pop, 2% of HLA B27 +ve population, 20% of +ve pop with affected family member
- Males>Females (2.5-5:1)
- Typical onset young adulthood – but found both earlier (and often later as delayed diagnosis)
- Symptoms – back/buttock pain – inflammatory pattern (am stiffness, eases with movement, wakes early hours am), progressive loss spinal movement (Schobers test +ve), enthesitis, costochondritis, reduced chest expansion and fatigue.
- Diagnosis – radiographic sacroiliitis (late sign), spine-squaring of vertebrae and 'shiney' corners pf vertebrae, syndesmophytes and facet joint fusion late signs.

Based on a combination of clinical symptoms/signs and blood tests – as always, the predictive value of symptoms is variable but worth noting that out of the following 4 characteristics (in patients <50years old;

- Morning stiffness>30mins
- Improvement of back pain with exercise but not with rest
- Waking in the second part of the night only
- Alternating buttock pain

Number of characteristics seen	Post-test probability of AS
0	1.3%
1	2.6%
2	10.8%
3+	39.4% (sensitivity 33.6%, specificity 97.3%)

Psoriatic Arthritis

This type of inflammatory arthritis seen in 10-40% of patients with psoriasis (and inflammatory skin condition characterised by scaly plaques on the skin). It can be seen to overlap with other types of spondyloarthropathy.

Pattern of presentation can be before the development of skin features and includes;

- Asymmetrical and oligoarticular arthritis (in some textbooks it states can be symmetrical polyarthritis and mistaken for RA so be aware!)
- DIPJs (characteristic of PsA but not that common)
- Dactylitis
- Low back pain and sacroiliitis (in 20% of patients)
- Conjunctivitis and anterior uveitis (but less often than in AS)

Reactive Arthritis

Reactive arthritis is an aseptic arthritis that develops after an infection elsewhere in the body, usually the gastrointestinal or genitourinary tract.

- Post–gastrointestinal illness e.g. Campylobacter, Salmonella, Yersinia
- Post–sexually transmitted disease e.g. Chlamydia
- Viral: e.g. Arbovirus

Symptoms normally develop 1-3/52 after infection and in epidemics of Salmonella/Yersinia reactive arthritis is found in up to 7% of individuals (this rises to 20% in HLA B27+ve people).

The pattern of symptoms usually of;

- Asymmetrical oligoarthritis (up to 4 joints in 6/12)
- Enthesitis
- Dactylitis
- Reiter's disease is the pattern that describes arthritis alongside eye symptoms that includes;
    - Conjunctivitis (normally bilateral and painful)
    - Anterior uveitis (unilateral often with conjunctivitis so hard to differentiate)
    - Urethritis (dysuria and urethral discharge)
    - Skin changes that include circinate balanitis and keratoderma blennorrhagicum (painless papular eruption on palms of hands or soles of feet)

60–90% of affected patients are positive for HLA-B27 antigen & the main differential diagnosis is septic arthritis so a joint aspirate/culture is recommended where possible.

Most cases last 2-3 months with the presence of HLAB27 increasing chances of axial involvement and chronicity

Enteropathic Arthritis

Is an inflammatory arthritis associated with Inflammatory Bowel Disease, normally Ulcerative Colitis or Crohn's disease.

Tends to follow two patterns;

- Type 1
  - 5% of patients with IBD
  - Peripheral arthritis – oligoarticular, generally the knees
  - Is normally self-limiting and doesn't lead to joint deformity
  - Joint symptoms can start before bowel symptoms
  - Enthesitis (achilles), plantar fasciitis and dactylitis can occur
- Type 2
  - 3% of patients with IBD
  - Polyarticular arthritis can include: MCPJs, knees, ankles, elbows, shoulders, wrists, PIPJs & MTPJs (can move from joint to joint)

Sacroiliitis and spondylitis is seen in around 20% of patients with IBD.

Investigations

Blood test	**Result**
ESR/CRP	Raised (prognosis worse if ESR>30)
HLA B27	Positive (see below)
FBC	Normocytic anaemia
RhF	Negative
Infectious serology	Identify relevant infective source
Autoantibodies/ Anti-CCP	Negative

<u>HLA-B27</u>
The principal members of the group with the % positivity for HLA B27 are:

- Ankylosing spondylitis 95-98%
- Reactive arthritis 60-85%
- Psoriatic arthritis 60-70%
- Acute anterior uveitis 50-60%
- Enteropathic arthritis 50-60%

I

WARNING!

Do not be falsely reassured by

- Negative HLA B27
- Normal Inflammatory Markers
- Absence of radiographic sacroiliitis on X-Ray

If the symptoms fit, then refer

Referral

To rheumatologist if

- New onset suspected inflammatory arthritis
- Dactylitis
- Enthesitis with no mechanical cause especially if multisite and persistent
- Inflammatory back pain
- Non-mechanical back pain with personal or family history of psoriasis, uveitis, IBD, GU/GI infection.

Same day ophthalmology assessment

- Suspected acute anterior uveitis
    - Painful eye
    - Redness
    - Sensitive to light
    - Altered (blurred) vision

Management

- Physiotherapy & Exercise
- NSAIDs
- Oral and IM Steroids
- TNFα Blockers (e.g. etanercept, adalimumab) is a third line treatment and shown to reduce spinal pain and stiffness
- Surgery

Gout

Incidence/Prevalence

- The most common inflammatory arthritis
- Affecting 3-4% of the population
- Men>Women
- 35-50's
- Frequently associated with metabolic comorbidities and indicate early intervention required

Aetiology

Gout is caused by the build-up of uric acid in the blood leading to deposition of urate crystals in joints – these then trigger an immune inflammatory response. Uric acid is the end product of protein metabolism (either through a breakdown product of cell nuclei releasing purines that then get converted to uric acid *or* by consumption of purines in the diet) and is excreted by the kidneys.

Uric acid tends to build up in the blood if the kidneys fail to excrete this due to the normal age-related decline in renal function or by anything that increases the amount of purines compared to how much is excreted by the kidneys.

- High purine diet (meat, shellfish)
- Alcohol – beer more so (high amounts of guanosine (a purine))
- Fructose containing sugary drinks (2/day doubles risk)
- Renal insufficiency
- Genetic inherited
- Drugs – diuretics, chemotherapy, salicylates
- Metabolic syndrome
- Pregnancy
- Hypothyroidism
- Malignancies (leukaemia/lymphoma especially)

Signs/Symptoms

- Acute attacks of joint pain
    - Gt toe
    - Knee
    - Other joints including ankle, wrist, elbows, fingers (rarely)
- Swelling
- Erythema
- Tophi – hardened deposits of uric acid in tissues (generally seen after prolonged raised/untreated gout) – seen on elbows, achilles tendon, ears – can rupture and cause infections.

Investigations

Blood test	Result
ESR/CRP	Raised
HbA1c & Lipids	Screen for metabolic comorbidities like DM/Hypertriglyceridaemia common
LFT	May be abnormal in heavy alcohol use (consider checking GGT)
TFT	Hypothyroidism seen in up to 15% cases of gout
U&E	To identify renal disease (relevant also for treatment (e.g. allopurinol)
Urate	Raised but may be normal in acute attack (best tested 4-6/52 after flare) *Men* 210-480 μmol/L *Women* 150-390μmol/L
FBC	Exclude myelo/lymphoproliferative disorders, polycythaemia, haemoglobinopathies WCC may be raised in gout but consider septic arthritis (especially if very high)

Joint aspirate and examination for presence of crystals (described as 'negatively bi-refringent' under polarised light as opposed to pseudogout (calcium pyrophosphate crystal deposition (CPPPD) which is positively birefringent) **NB** time to lab is important here – long delays can affect samples and give false negatives.

Management

Treat symptoms – acute flare management

- NSAIDs
- Colchicine
- Steroids
    - Oral
    - Intra-articular

Treat Cause – medium to longer term therapy

- Urate Lowering therapy – target urate below 360umol/L, can take 6-12/12 to lower tissue as well as blood levels
    - Allopurinol
    - Feboxustat (2nd line)
- Manage co-morbidities
    - Hypertension
    - Diabetes
    - Abnormal lipids
- Dietary advice
    - Reduce purine rich foods (meat/seafood)
    - Limit sugary drinks
    - Reduce alcohol (beer especially)

Polymyalgia Rheumatica and Giant Cell Arteritis

Both Polymyalgia Rheumatica (PMR) and Giant Cell Arteritis (GCA) are forms of arteritis with overlapping features and tend to affect the same population so worth considering both pathologies as 20% of patients with PMR have GCA symptoms and 50% of GCA patients show symptoms of PMR.

They symptoms can be widespread and vague and as a clinician you need to consider the broader differential to screen for serious pathologies. They respond well to rapid use of steroids but can be significantly disabling if left undiagnosed and managed.

Aetiology

Tends to affect an older population with peak onset between 70-80 and is very rarely seen in people under the age of 50. Women more than men in a 2:1 ratio and higher rates in northern European population.

Is uncertain, but likely to be multifactorial with a combination of genetic and environmental triggers involved including;

- Infection (Mycoplasma, Chlamydia, Parvovirus, Herpes and others implicated)
- Genetic – familial patterns and racial differences in prevalence seen with links to HLA-DR4
- Immune – increased levels of circulating cytokines have been seen

Signs & Symptoms

PMR	GCA
Rapid (sub-acute) onset over days to weeks	Age >50
Age >50, normally >65	New onset headache (normally around side of head) *but this is absent in 25% cases*
Pain and stiffness – proximal muscles of shoulder and pelvic girdle, worse at night and first thing in the morning (difficulty raising arms above head (reaching high shelves, getting out of a chair, walking up stairs)	Tenderness of scalp (on brushing hair, putting on glasses) and jaw claudication (pain in jaw on chewing)
Fatigue	Fatigue
Low grade fever	Visual disturbances – in around 10% (sudden onset blindness most serious potential consequence)
Weight loss	Tenderness on palpation of scalp/temporal artery region (with palpable 'nodular' change in late stage) – visibly dilated temporal artery with a bounding pulse

Depressed mood	Different BP reading between both arms (GCA affecting aorta and its branches-with aneurysms and stenosis as late stage feature)
Polyarthritis and Synovitis can be present (this is a self-limiting, non-erosive form of arthritis)	

Of note;

- Weakness is **NOT** normally seen and should raise suspicion of myositis
- Tenderness of muscles can be seen but may be suggestive of Fibromyalgia

Differential diagnosis

- Rheumatoid Arthritis
- Fibromyalgia
- Cancer (including Multiple Myeloma)
- Infection
- Osteoarthritis
- Frozen Shoulder
- TMJ Dysfucntion (GCA)
- Cervical spondylosis
- Connective Tissue Diseases (SLE, Polymyositis)
- Hypothyroidism
- Pagets' Disease/Osteomalacia

Investigations

Blood test	**Result**
Full Blood Count	Normochromic, normocytic anaemia can be seen
ESR	Raised (in over 95% patients), generally >40 in PMR and >50 in GCA and has better sensitivity and specificity than CRP
CRP	Raised (in over 95% patients)
LFT	ALP raised in 30%
Creatinine Kinase	Normal (helpful to distinguish between PMR and myositis)
Bone profile	Should be normal (abnormal in bone pathologies)
Rheumatoid Factor	Normal (but may be normal in RA too!)
TFT	Normal (abnormal in thyroid disorders)

Of note this means that in up to 5% of patients the inflammatory markers will be normal!

Temporal Artery Biopsy

- 1cm portion of TA taken and examined for histopathological evidence of arteritis
- Can be negative due to 'skip' lesions (patchy/segmental distribution of change in artery wall)
- Useful if just before treatment started or within 24hrs, chance of seeing a positive result drops to 10% at 1 week after starting steroids but can remain positive up to a year.
- Ultrasound can now often be used as a pre-biopsy screen (oedema seen)

Management

GCA

Is an urgent condition to treat due to risk of visual impairment – treatment should not be delayed by waiting for diagnostics and **patients with visual disturbance need same day specialist assessment** (rheumatology or ophthalmology normally, depending on local pathways (do you know yours?))

Early intervention with high dose steroids and discussion with rheumatology in cases without visual disturbance is sensible

PMR

Is similarly treated with steroids (normally a trial of 15mg should produce a marked reduction in symptoms and a useful diagnostic as well as therapeutic feature) with a subsequent slow taper.

Given the long-term use of steroids treatment normally also includes bone protection (Bisphosphonates/Calcium/VitD), Aspirin has been used to reduce risk strokes (but increased risk of gastric bleeds) & PPI.

Monitoring for diabetes 2ndary to steroid treatment is advised as well as a CXR every 2 years (for life) to screen for thoracic aortic aneurysms.

Referral to outpatient Rheumatologist for review is advised if;

- Age <60
- Chronic pattern of onset
- Lack of shoulder involvement
- Lack of stiffness (inflammatory pattern)
- Presence of red flags
- Suspicion of other rheumatological diagnosis
- Normal or very high acute phase proteins

Connective tissue diseases (CTDs)

These are a cluster of autoimmune diseases that includes; SLE, Sjogren's syndrome, dermatomyositis, polymyositis and antiphospholipid antibody syndrome that can exist in isolation or overlap with each other.

As with other autoimmune conditions the body has failed to recognise part of itself and the immune system mounts a response against its own tissues and cells.

In CTDs the tissues involved are the connective tissues within joints, muscles, blood vessels and skin so they tend to have widespread impact and presentation. This can include generalised joint pain/swelling, more non-specific features and Raynaud's phenomenon (vasospasm of the small arteries supplying fingers causing temporary loss of blood flow shown as changing colour (white→blue then red with reperfusion) associated with pain.

Of note, Raynaud's can be a benign, primary condition seen more in younger women or *secondary*, seen in conjunction with connective tissue diseases or with medication such as b-blockers.

They can present in a non-specific way that can sounds a lot like Fibromyalgia so careful consideration of CTDs as part of a differential for chronic pain conditions is important.

Systemic Lupus Erythmatosus (SLE)

Is a multisystem autoimmune disease more common in women and those of non-white ethnicity (Afro-Caribbean/Asians) with genetic and environmental risk factors (sunlight, smoking, drugs and infection). It is relatively rare and complex and can present in a non-specific pattern that can be mistaken for other conditions.

Signs/symptoms

System	Symptoms
Skin	Acute or chronic lupus • Malar rash (butterfly) - face • Discoid rash (chronic) • Non-scarring alopecia
Joints	Synovitis – normally 2+ joints with morning stiffness
Renal	Nephropathy
Neurological	Seizures, psychosis, mononeuritis, myelitis, neuropathy, confusion
Haematological	Anaemia (with low platelets & white cells)
Respiratory	Serositis – causing pleural effusions (SOB, pleural rub)
Cardiac	Pericardial effusion (chest pains)
Non-specific	Malaise, fatigue, oral ulcers, photosensitive rash, Raynaud's phenomenon

NB It can also present in teenage years with growing pains, migraine and glandular fever in the context of a family history that may include thyroid disease, fatigue, ME. In women there may be recurrent miscarriages.

Sjogren's Syndrome

The second most common autoimmune condition affecting up to 0.5% of the population and can be primary or secondary in individuals with SLE or other conditions including RA, Primary Biliary Cirrhosis & Systemic sclerosis.

It has a peak onset is around the age of 50, more so with women (9:1, F:M)

Signs and symptoms

Classically a cluster of 'sicca' symptoms (derived from Latin, 'siccus' meaning dry) caused by failure of the mucosal and salivary glands described as;

- Sicca symptoms
  - Keratoconjunctivitis (dry eyes)
  - Xerostomia (dry mouth)
- Synovitis
- Fatigue

The triad of these three symptoms are seen in up to 80% of cases with other symptoms including rashes, myositis, lung disease, renal disease and peripheral neuropathies much more rarely seen.

Other tests for Sjogren's include Schirmer test (paper strips in eye to measure tear production (!)) and salivary gland biopsy.

Systemic Sclerosis (Scleroderma)

Scleroderma means 'hard skin'. There are a number of subtypes of systemic sclerosis including diffuse and limited; the distinction being the involvement of the trunk in diffuse compared to limited affecting only the limbs.

It is a rare condition (affecting 1/100,000 people) and generally women in their 40-50's. It is seen, in around 20%, to co-exist with SLE, Myositis or Inflammatory arthritis.

Systemic sclerosis has a widespread impact on the body with a significant increase in mortality of up to 60%, generally with cardiorespiratory complications.

Signs and symptoms

- Raynaud's phenomenon can manifest before the development of other symptoms by a number of years
- Generalised symptoms such as fatigue, weight loss, arthralgia

- Depression – seen in up to 50% of patients
- Skin - tightening and thickening of the skin due to an accumulation of scar tissue giving it a characteristic shiny appearance – most often seen in the fingers with ulceration of tips of fingers/toes. This can contribute to loss of movement and muscle atrophy.
- Respiratory symptoms – breathlessness (on exertion) and a chronic cough caused by pulmonary fibrosis and pulmonary hypertension
- Cardiac complications – congestive cardiac failure (late stage symptom)
- Renal failure – seen associated with rapidly increasing hypertension
- Gastrointestinal – oesophageal stricture/immobility, small bowel malabsorption

The designation **'CREST** Syndrome' has been used to describe a subtype of patients with;

- Calcinosis – deposits of calcium in skin (associated with digital ulcers)
- Raynaud's phenomenon
- Esophageal hypomotility
- Sclerodactyly (thickening/swelling of fingers/toes)
- Telangiectasia (non-blanching red spots on skin)

Polymyositis/Myositis

Again, these are rare conditions characterised by the slow onset of symptoms caused by autoimmune-mediated muscle and skin damage including;

- Progressive symmetrical muscle weakness and inflammation (myositis) – affecting shoulder and pelvic girdle muscles
- Arthralgia/myalgia
- Difficulty swallowing and speaking (Dysphagia/Dysphonia) caused by muscle weakness
- Respiratory difficulties – respiratory muscle weakness & lung fibrosis
- Skin – in Dermatomyositis there is a purplish rash (mostly hands and face), redness of nails, red papules over the knuckles (Gottron's papules)
    - Dermatomyositis carries an increased risk of cancer by about 30% (particularly ovarian, lung) and iatrogenic cancers related to immunosuppressants (e.g. cyclophosphamide with bladder cancer, azathioprine with Non-Hodgkins Lymphoma)

Investigations

The differential diagnosis most obvious includes Polymyalgia Rheumatica and the cardinal differences between the two are;

1. PMR does not characteristically cause weakness of muscles (Polymyositis/Myositis does)
2. PMR would not normally cause a rise in Creatinine Kinase (Polymyositis/Myositis does)

Also seen to have

- Positive ANA
- Positive Anti-Jo1 & Anti-Mi2 (ENA)
- EMG shows fibrillation potentials

Anti-phopsholipid Antibody Syndrome

Is associated with the presence of antiphospholipid antibodies

- Anticardiolipin antibodies
- Lupus Anticoagulant -confusingly most people with lupus anticoagulant do not go on to have SLE (around 20-30%)

Features include;

- Thrombosis - arterial (CVBA/TIA) and venous (DVT/PE)
- Recurrent miscarriages-2nd/3rd trimester
- Thrombocytopaenia (low platelets) – in up to 50% patients
- Livido reticularis – pink/blue mottling of skin (seen in cold weather but also vasculitis)

Investigations for Connective Tissue Diseases

Blood test	Result
Full Blood Count	Anaemia (may be haemolytic in SLE), leucopaenia, thrombocytopaenia
ESR/Plasma Viscosity	May be raised (significantly in Sjogrens)
CRP	Often *normal* in SLE/Sjogrens
U&E	Abnormal – nephritis seen in 50% SLE patients Urinalysis may show haematuria/proteinuria
Rheumatoid Factor	Positive in most CTDs (38% of cases with Sjogren's)
ANA	Usually positive – main screening blood tests for CTDs
Anti-DNA	Positive in 60-80% SLE
ENA	Positive (see autoantibodies section)
Creatinine Kinase (CK)	Raised in polymyositis

Myeloma

This is a cancer of the plasma cells in the blood (of note, 'plasma cells' are just another name for Lymphocytes) you might remember that these cells produce antibodies (also known as immunoglobulins) but in myeloma the cells produced are abnormal and therefore produce abnormal immunoglobulins/antibodies as called 'paraproteins'.

Incidence

- More commonly seen in older people (mean age in UK around 70)
- Around 5 new cases/100,000 people diagnosed per year.
- 15% patients are 60 or younger at diagnosis

Aetiology

Remains a bit of a mystery but likely a combination of genetic and environmental factors. Risk factors include; increasing age, male sex, Afro-Caribbean origin, obesity, a diet low in fish and green vegetables and a positive family history.

Signs/Symptoms

Symptoms may include **CRAB**s…..

Hyper**C**alcaemia
Renal impairment
Anaemia
Bony lesion

Consider in an older patient, signs of immunocompromise (recurrent infections), bleeding, persistent back pain, night pain, structural deformity

As the malignant cells proliferate, they infiltrate the bone marrow filling it with abnormal cells types in solid tumour form mostly seen where most bone marrow is (pelvis, sternum and vertebrae – as well as long bones and the skull), they secrete osteoclasts that cause localised bony erosions called 'lytic lesions' (that can be seen on X-Rays).

These lytic lesions (seen in 80% cases) cause *bone pain* with back pain being seen in up to 60% of presentations. More advanced cases may present with a fragility fracture as a result.

Destruction of bone can cause **hypercalcaemia** (in up to 40% of cases) that can cause *confusion, polydipsia (excessive thirst), polyuria (excessive urination), constipation, anorexia (reduced appetite), if excessive then it can cause seizures, coma, cardiac arrythmia and death*. (N.B. you should always check albumin and Parathyroid Hormone (it should be suppressed in Myeloma – see section on Bone Profile).

As the bone marrow is filled with tumour (plasmacytoma) it prevents production of the normal cell lines resulting in **anaemia, low white cells (leucopenia) and low platelets (thrombocytopaenia)** causing *lethargy/fatigue, breathlessness, increased risk of infections and nosebleeds***.**

As the abnormal cells proliferate, they spill into the blood stream causing an increasing the plasma viscosity as well as causing end organ damage as plasma cells infiltrate the liver and parts of the paraproteins clog up the filters in the kidneys causing renal impairment. This is seen in 20-40% of those newly diagnosed with myeloma, although normally asymptomatic it can cause low urine output (oliguria) or high levels or urea in the blood (uraemia). Smaller sections (light chains) can be filtered out of the blood stream and are detectable in the urine (Bence-Jones Proteins).

The symptoms alone are not good at identifying those with multiple myeloma, the combination of bone pain, fatigue, breathlessness and weight loss was shown to only have a positive predictive value (PPV) of around 1% as they are non-specific and frequently encountered symptoms in primary care ***but*** when used in combination with blood tests it can push the PPV up above 10% (still pretty poor).

Investigations

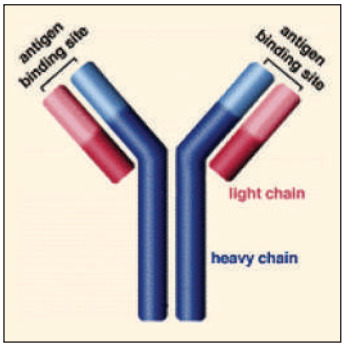
Blood test	**Result**
Full Blood Count	Anaemia (Hb typically 9-10g/dL), leucopaenia, thrombocytopaenia
ESR/Plasma Viscosity	Increased (often >100)
CRP	Should be *normal* in myeloma – if raised consider other causes
Calcium	Raised
U&E/LFT/LDH	Abnormal – end organ damage
PSA	Should be normal but worth considering ordering in men as differential includes prostate Ca
Serum Protein Electrophoresis	Monoclonal (paraprotein) band
Serum Free Light Chain analysis	Abnmormal ratio
Urinary Electrophoresis	Looking for light chains (Bence Jones proteins)

In multiple myeloma one type of Plasma cell (B-Cell) is produced a huge number of times causing a build-up of only one type of immunoglobulin (antibody) called a monoclonal protein (i.e. from a single original clone) or M-protein, of note the other 'normal' production of antibodies is reduced.

Immunoglobulins

Normal immunoglobulins are formed of a combination of heavy and light chains.

- There are 5 types of heavy chains abbreviated as IgG, IgA, IgM, IgD and IgE.
- There are two types of light chains – kappa and lambda



These are assembled within the plasma cell to form a whole – more light chains are produced than heavy chains and the excess is released into the blood stream as *free light chains* the *amount* of light chains is linked to plasma cell activity or myeloma.

Assessment of the immunoglobulins and light chains is done by looking at the blood once all of the other blood cells have been removed (leaving just the serum) as well as looking at the urine, where they get filtered out of the blood and excreted, and identifying abnormally raised monoclonal proteins (M-protein) and free light chains there as well (the so-called 'Bence Jones Proteins' which are either kappa or lamda proteins first described by an English doctor Henry Bence Jones in the 19th century).

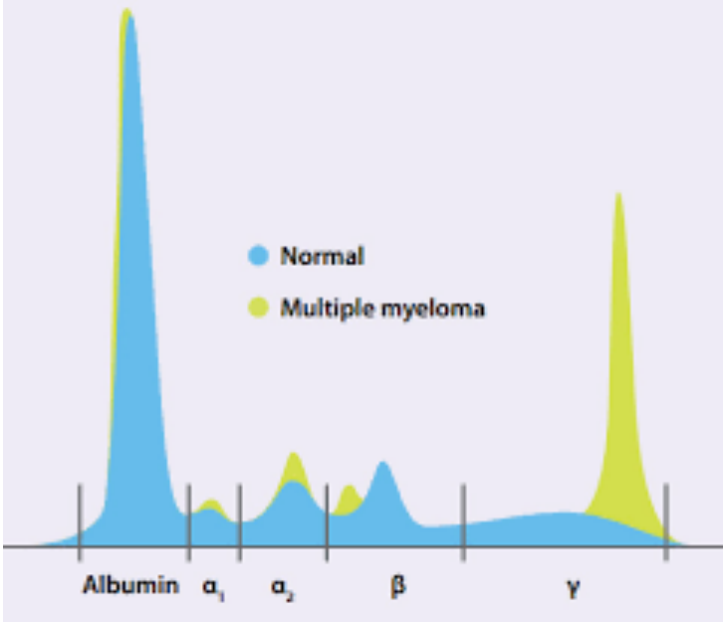
Immunoglobulin levels

Measures amounts of the different immunoglobulins

- Myeloma protein will be an IgG or IgA, or less commonly IgD or IgE
- Levels will help monitor the course of the disease
- Important to be aware of the levels of the normal (non-myeloma) immunoglobulins
- IgG Gammopathy – the most common (60% of patients) occurs +/- urinary light chains (Bence-Jones proteins)
- IgA Gammopathy (16% patients)
- Bence Jones Gammopathy (aka light chain disease. – 9-15% of patients)
- IgE and IgD gammopathy is very rare

Myeloma is more commonly IgG & IgA, (and more rarely IgE & IgD) and BJP gammopathies
IgM gammopathy is seen more with Macroglobulinaema and rarely (0.5% cases) with Myeloma

Serum protein electrophoresis can identify a 'spike' in monoclonal proteins but doesn't tell you which type whereas **immunofixation electrophoresis** can go on to tell you the sub-type of M-protein.



Albumin is the most abundant protein in blood (hence the biggest spike) but the changes in multiple myeloma are normal seen in the Gamma band

Serum free light chain assay can detect normal levels of free light chains in the blood and is more sensitive at detecting free light chains than electrophoresis – done on serum as urine has lower levels of proteins in (i.e. not all gets filtered out of the blood stream).

In myeloma only one type of light chain is produced to excess meaning the total number of either kappa or lambda light chains will increase, and the ratio will be outside of the normal range. These results can be used both for diagnosis and for monitoring myeloma.

Normal levels of serum free light chains are;

- Kappa: 3.3-19.4 mg/L
- Lambda: 5.71-26.3 mg/L
- Kappa/lambda ratio: 0.26-1.65

O**ther tests** in primary care might include skeletal survey (whole body X-Rays) but the irradiation implications mean these are not usual done in primary care. Secondary care investigations may also include bone marrow aspirates, viral serology and MRI (STIR Sequences)

Interpreting results:

Having established that there is the presence of an M-Protein band and possible presence of urine or serum light chains they can be categorised by type as below;

The next step is to consider the significance and categorise into benign or malignant, the groups are classified as follows;

Benign

- Monoclonal gammopathy of uncertain significance (MGUS)

Malignant

- Myeloma
- Waldenstroms macroglobulinaemia
- Heavy Chain Disease

Waldenstroms macroglobulinaema is a proliferation of B-Lymphocytes producing IgM but is associated with a different prognosis and treatment approach – it tends to be seen with lymphadenopathy, hepatosplenomegaly, hyperviscosity and rarely causes renal dysfunction.

There are different types of myelomas and it's important to note that around 15% only secrete light chains in excess, therefore the presence of **either** M-proteins **or** serum free light chains above normal levels should trigger a referral to haematology (under 2WW).

Making a diagnosis is based on a combination of clinical features including these tests as well as bone biopsy and screening for end-organ damage

Diagnostic Criteria are based on the International Myeloma Working group guidelines and break down Myeloma into the following categories;

Monoclonal Gammopathy of Uncertain Significance	Smouldering (asymptomatic) myeloma	Multiple Myeloma
Serum monoclonal protein <30g/L	Serum monoclonal protein >/= 30g/L	Monoclonal protein in serum (M-Band/paraprotein band) and/or urine (BJP)
Bone marrow clonal plasma cells <10%	Bone Marrow plasma cells >/= 10%	Bone marrow clonal plasma cells or biopsy proven plasmacytoma
No evidence of other lymphoproliferative disorders	No myeloma related organ or tissue impairment	Myeloma related organ or tissue impairment
No myeloma-related organ or tissue impairment		

A case-controlled study of nearly 15,000 patients in primary care tested 5 years before a diagnosis myeloma showed;

- plasma viscosity and ESR are better at ruling in and out the disease compared to CRP (93% sensitivity- only increases to 94% when including calcium and creatinine)
- A combination of a normal ESR/PV and a normal haemoglobin is a simple rule out test

Referral

- **Same day review** if evidence of
  - renal failure
  - spinal cord compression
  - hypercalcaemia (risk of cardiac sequelae)

- **Urgent haematology (2 week wait)**
  - Paraprotein band
  - Symptomatic and concerns

- **Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence-Jones protein assessment) *alone* to exclude a diagnosis of myeloma**

Peripheral Neuropathy

Peripheral neuropathy refers to damage to the nerves outside of the brain and spinal cord and includes, sensory, motor and autonomic nerves (controlling automatic functions e.g. bladder and bowels)
The nerves affected have different structures and symptoms vary according to function;

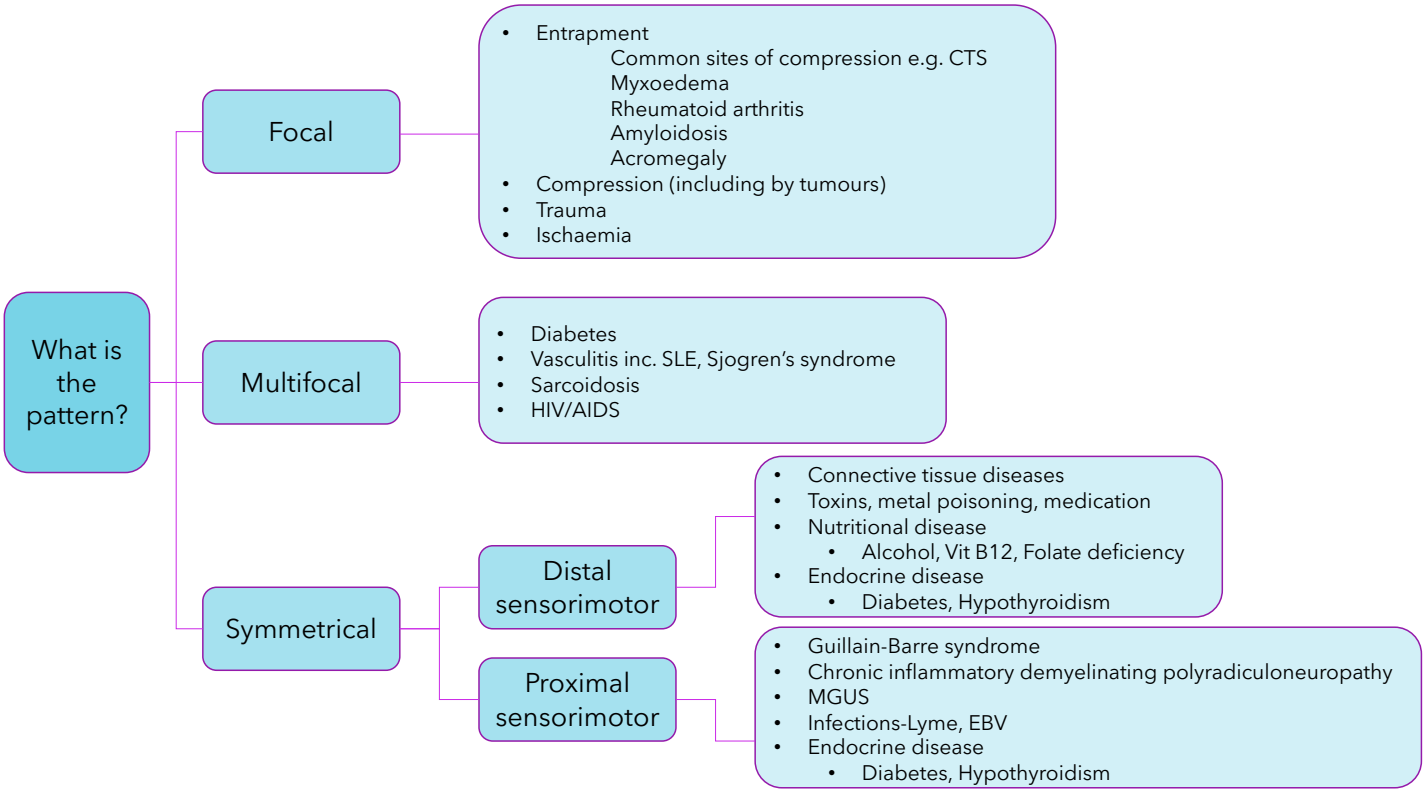
- large, myelinated axons including motor and sensory axons for vibration, proprioception and light touch)
- small, myelinated axons composed of autonomic fibres and sensory axons for light touch, pain and temperature
- small, unmyelinated axons for pain and temperature

Incidence

It is seen to affect around 2.4% of the European population going up to around 8% with increasing age, although mostly seen in connection with diabetes and alcoholism in the UK.

Aetiology

Can be distinguished by the characteristic patterns of presentation



Pathophysiology

Whilst there are lots of causes of nerve damage, the ways in which a nerve responds to the injury are limited and broadly speaking fit into three categories;

Segmental demyelination

- Involves degeneration of the myelin sheath not the axon
- Present in mononeuropathies, sensorimotor and motor neuropathies
- Often caused by inflammation or immune mediated e.g. Charcot Marie-Tooth or MGUS

Wallerian degeneration

- A consequence of chemical, mechanical (compression/contusion/trauma) or ischaemic damage to the nerve axon
- Degeneration of the axon itself after occurs in the part of the nerve downstream from the lesion then wastes away

Axonal degeneration ('dying-back' phenomenon)

- Symmetrical polyneuropathy (as in Diabetic neuropathy, Guillain-Barre, Charcot Marie Tooth) with a pattern that starts distally and progresses proximally
- Due to distally being furthest from cell body so most prone to damage (loss of metabolic support), with Diabetic peripheral neuropathy likely mixture of microvascular disease and metabolic factors (hyperglycaemia damaging nerve cells)

Medication is an important possible cause of neuropathy of various types and relevant to lithium, phenytoin, amiodarone to name just a few. Diabetes can cause a number of different patterns including distal symmetrical polyneuropathy (the more common type), autonomic neuropathy (bladder/bowel dysfunction/gastroparesis), proximal neuropathy (diabetic amyotrophy) weakness in proximal muscles (thighs/hips/buttocks), pain (inc. abdo pains), mononeuropathies

The pattern of symptom presentation in the context of a good history is vital. Screening past medical history and lifestyle factors for presence of thyroid disease (polyneuropathy and entrapment neuropathy), diabetes, HIV/AIDs, Inflammatory or connective tissue disease alongside considering drug and alcohol misuse, nutritional status and exposure to toxins in work. Be aware of features of malignancy and a family history of heritable muscular or neurological conditions and presence of gait abnormalities is of value.

Symptoms, Signs & Stages

Time course can indicate possible pathologies;

Acute onset neuropathies

- Ischaemic neuropathy
- Nerve compression (direct compression, haemorrhage, swelling)
- Trauma, penetrating wounds, iatrogenic (e.g. injection), thermal injury

Subacute onset over days/weeks

- Rheumatoid arthritis

- Toxic & metabolic neuropathies

Chronic course over months to years

- Hereditory neuropathy
- Chronic inflammatory demyelinating neuropathies (CIDP)

Relapsing remitting

- Guillain-Barre Syndrome

The symptoms and signs can be indicative of the type of pathology,

Ischaemic neuropathy – usually pain is the predominant features
Small fibre neuropathy – sharp, shooting pain with associated tingling/paraesthesia with either numbness or increased sensation (hypesthesia) and allodynia to light touch.
'Dying back' or axonal degeneration is characterised by starting at the tips of the toes (or fingers) and slowly progressing proximally in a stocking (and/or glove) distribution.

The progression is also classified into stages as follows;

Stage		Symptoms/Signs
0/1	No clinical neuropathy	No symptoms or signs
2	Acute painful	• Less common • Hyperaesthesia • Minor sensory signs or normal examination
	Chronic Painful	• Burning, shooting, stabbing pains, worse at night with pins and needles • Absent sensation (in more than one modality e.g. fine touch/pin prick/vibration etc)
	Painless with complete or partial sensory loss	• No symptoms or numbness, reduced thermal sensitivity, painless injury • Reduced or absent sensation with absent reflexes
3	Late complications of clinical neuropathy	• Ulcers • Neuropathic deformity • Non-traumatic amputation

Investigations

Test	Result
Urine dipstick	For glucose/protein
FBC	Macrocytic anaemia seen in B12/Folate deficiency and alcoholism
ESR	Inflammatory conditions
Vitamin B12/Folate	Low in nutritional deficiencies/Pernicious anaemia
Fasting blood sugar (or HbA1C)	For diabetes
U&E & LFT (including GGT)	Organ damage (renal failure/uraemia) and metabolic problems (GGT often seen raised in alcoholic liver disease)
TFTs	Low in hypothyroidism

Additional investigations might include;

- Serum protein electrophoresis - myeloma
- Autoantibodies – Sjogren's/SLE etc
- Chest X-Ray - malignancy
- Nerve conduction studies/EMG
- Serology for Lyme disease/HIV
- Heavy Metal toxin screen

Treatment

Pharmacological

Neuropathic pain in adults: pharmacological management in non-specialist settings
Clinical guideline [CG173] Published date: 20 November 2013 Last updated: 22 September 2020

- Amitriptyline, duloxetine, gabapentin or pregabalin
- Topical capsaicin
- PRN Tramadol

Non-pharmacological

- Holistic assessment and management including specialist pain services with MDT input

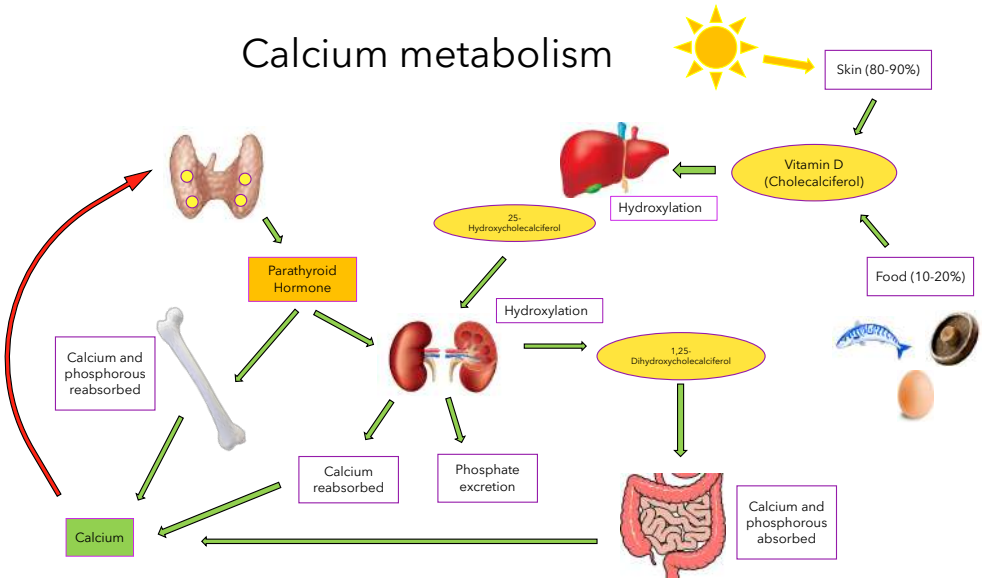
Bone metabolism

Calcium is an essential mineral used in formation of bone and teeth, muscle contraction, enzyme & nerve function, tissue repair and normal heart rhythm. 99% of it is stored in bone and levels in the blood are carefully controlled by a process of storage (via osteoblasts) and release (via osteoclasts) in bone.

The balance of calcium (homeostasis) relies on parathyroid glands (4 small endocrine glands on the thyroid) using calcium sensing receptors that then reduce or increase Parathyroid Hormone (PTH). An increase in PTH has the following effects

- Increasing release of calcium from the bone
- Reducing amount of calcium excreted by the kidneys
- Stimulates activation of Vitamin D
- Increases phosphate loss from kidneys

Vitamin D plays a vital role in calcium homeostasis, predominantly produced by the action of sunlight on the skin (UV light acting on 7-dehydrocholesterol to produce cholecalciferol) as well as being sourced from our diet it is metabolized first by the liver to 25 hydroxycholesterol, then by the kidneys to 1,25 dihydroxycholecalciferol which is the active form of vitamin D (technically making it more of a hormone in its actions than a vitamin). Its main action is to encourage the gut to absorb calcium.



Metabolic bone disease

A range of problems can occur with bone metabolism causing a range of problems including;

- Reduced **quantity** of bone (mass) - Osteoporosis
- Reduced **quality** of bone (low mineral content) - Osteomalacia & Rickets
- Increased **bone turnover & remodeling** – Paget's Disease

Osteoporosis & Osteoporotic fractures

Is a progressive condition characterised by reduced bone mass. Historically, following a fragility fracture, patients have often not been investigated for underlying causes including osteoporosis and anyone presenting to an MSK clinic with a new fragility fracture should be investigated (or re-investigated if osteoporotic and on treatment).

Incidence & Impact

Incidence of osteoporosis runs at around 18% in women >50 and 6% of men >50 (the bony trabeculae in men remain stable in men compared to women even though they lose bone mass).

Fragility fractures have a significant personal and economic cost with 20% of patients dying within a month of sustaining a hip fracture and 50% remaining permanently disabled with a combined mortality and morbidity of fractures costing around £1.8 billion in the UK alone.

Prevalence varies but they are seen in up to a quarter of women over the age of 50.

Aetiology

Peak bone mass is achieved in your 20s, then it steadily decreases, in women this is accelerated in the 5-10 years post-menopause when the balance of osteoclast activity (resorbing bone) increases compared to osteoblast activity (bone build up).

It can be primary (age-related) or secondary (caused by other medical conditions or drugs) and risk fractures for those more likely to sustain fragility fractures are remembered by the mnemonic '**SHATTERED**'.

Steroid use of >5mg for >3 months
Hyperthyroidism
Alcohol use
Thin (BMI<18.5)
Testosterone reduced (e.g. with anti-androgen therapy in prostate cancer)
Early menopause
Renal or liver failure
Erosive or inflammatory bone disease (Myeloma/rheumatoid arthritis)
Dietary calcium reduced - malabsorption

Signs & symptoms

Vertebral fractures are the most common but often asymptomatic and undiagnosed in up to 1/3 of patients and 20% go on to have another fracture within a year. The principle complaint is of pain & tenderness potentially associated with a restricted range of movement, loss of height and a change in the contour of the spine or none of these (!). Hip fractures are the second most common fragility fracture

Investigations

Blood tests form part of the screen of investigations, they are helpful in identifying secondary causes of osteoporosis more so than age-related osteoporosis. Although it should be noted that in a study of 107 patients in primary care with a new diagnosis of osteoporosis the tests only yielded a return in 3 of them (identifying a secondary cause of osteoporosis)

Blood test	**Result**
Full Blood Count	May be abnormal in myeloma
ESR	If raised, consider other causes, including Myeloma
Bone profile/Calcium	$Ca^{2+,}$ PO_4^{3-} and ALP usually normal
U&E	Abnormal in renal failure
LFTs	May be abnormal (liver disease, alcohol)
GGT	May be raised in etoh use
PSA	Should be normal but worth considering ordering in men as differential includes prostate Ca
TFTs	Exclude hyperthyroidism
Serum Protein Electrophoresis	Looking for Monoclonal (paraprotein) band (Myeloma)
Serum Free Light Chain analysis	Looking for an abnormal ratio (myeloma)

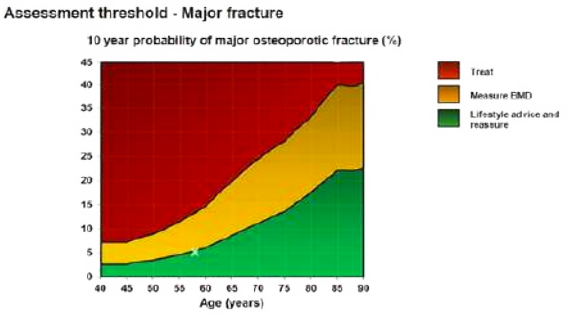
Diagnosis

<u>FRAX Score</u>

This is a tool with an online calculator designed to help evaluate the risk of fracture in patients. It is sued by clinicians to guide when to undertake DEXA scans as well as when to start treatment for post-menopausal women and men over 50 (including those on steroids).

It is based on a combination of clinical risk factors with age and BMI, with or without a score for the Bone Mineral Density and gives a score quantified as a percentage risk of a major osteoporotic fracture or a hip fracture in the next 10 years.

This score is then plotted on a graph which outlines advice on whether a BMD is needed (if not already available), treatment with lifestyle changes is suited or to start treatment.



DEXA Scan

Stands for dual energy X-ray absorptiometry. – low dose x-rays are passed through selected regions of bone (usually spine and hip) to assess how much radiation passes through as a measure of bone density. This amounts to small amounts of radiation, less than equivalent of 2 days normal background radiation (CXR = 3 days). Results are expressed as the difference (number of standard deviations (SD)) between the individual and;

1. A healthy young adult = T Score
2. Someone of the same age = Z Score

The higher the standard difference, the lower the bone mineral density and hence significance of the osteoporosis.

- above -1 SD is normal
- between -1 and -2.5 SD is defined as mildly reduced bone mineral density (BMD) compared with peak bone mass (PBM)
- at or below -2.5 SD (T Score) is diagnostic of osteoporosis

The T score is needed for diagnosis according to WHO whereas the Z score is used more to give a clinician an idea of risk compared to an age-matched population.

Management points

Whilst the vogue for interventional treatments for osteoporotic wedge fractures is reducing, getting patients on the right treatment for osteoporosis can save reduce fracture rates by 30-50% in high risk patients over three years.

Treatments include;

Lifestyle changes

- Smoking cessation and alcohol reduction
- Weight bearing exercise
- Balance exercises/falls prevention strategies
- Calcium and Vitamin D rich diet

Medication

- Calcium & Vitamin D (adverse cardiac events seen with calcium used in isolation) supplements used if deficient but limited effect if used in isolation.
- Bisphosphonates – e.g. alendronate, risedronate – work by decreasing osteoclast activity – but of note prolonged therapy associated with abnormal calcium deposition causing subtrochanteric fractures.
- Teriparatide – increases osteoblastic activity significantly and reduces the relative fracture risk of vertebral and non-vertebral fractures by 50-65%. Its expensive so tends to be used if bisphosphonates ineffective or not tolerated
- Denosumab – given as an injection (subcutaneously)twice yearly – reduces bone resorption

- Strontium ranelate – osteoblastic and osteoclastic activity but generally well tolerated oral therapy.

Notes

Hyperthyroidism and Osteoporosis

Thyroid hormones play an important role in the development of the skeleton and are needed to achieve peak bone mass.

Thyroid hormone receptors are found in osteoblasts and osteoclasts and overt hyperthyroidism causes an acceleration of bone turnover and loss of mineral density in 10-20% (mainly cortical bone) and an increased risk of fractures.

Lifestyle factors and Osteoporosis

Alcohol appears to have an effect on the bone forming cells (osteoblasts) slowing bone turnover, although the mechanism is unclear.

Smoking is associated with lower bone mass and a range of mechanisms have been suggested including increased breakdown of oestrogen in women (and hence increased bone loss) as well as other potential mechanisms including direct effects on bone cells, lower body weight, associated decreased physical activity and increased alcohol use, decreased absorption of calcium and resistance to the hormone calcitonin.

Exercise – weight bearing exercise acts as a stimulus for bone formation and improves bone density and reduces risk of falls.

Medication and osteoporosis

Steroids (glucocorticoids) are the most common medication related cause of osteoporosis and have an effect via reduction in bone formation caused by the effect on decreasing osteoblast formation and differentiation. Fractures have been seen in low dose steroid use, but the risk increases 5 fold above doses of 7.5mg, this incidence increases dramatically (17x) when using steroids above 10mg/day for more than 3 months.

Other drugs relevant include thyroxine (see above), aromatase inhibitors (e.g. letrozole/anastrozole: used for treating oestrogen receptor sensitive breast cancer) increase bone turnover, decrease BMD and increase relative risk of vertebral fractures. Similarly, drugs that reduce testosterone (androgen reducing therapy) e.g. goserelin/leuprolide used in the treatment of Prostate cancer also increase bone turnover and bone loss. Anticonvulsants such as carbamazepine have been seen to also induce osteoporosis affecting vitamin d metabolism and potentially by inhibiting osteoblast activity.

Others drug classes that affect bone include SSRI's, PPI's, loop diuretics and anticoagulants (including heparin)

Osteomalacia & Rickets

This is all about the *quality* not q*uantity* of bone with abnormal mineralisation of bone, if this happens during childhood (during period of bone growth) this is called Rickets, if it occurs after the fusion of the epiphyses then it is classified as Osteomalacia

Signs & symptoms

*Rickets***:** characterised by bony deformities including bowed legs, knock-kneed, short stature, loss of muscle tone, malaise.
Osteomalacia: may be asymptomatic (early) before causing bone pain, proximal muscle weakness and fragility fractures.

Aetiology

- Vitamin D Deficiency – is generally the most common cause in the UK caused by;
    - Dietary deficiency
    - Lack of exposure to sunlight – housebound, institutionalised, full body covering
    - Malabsorption – e.g. untreated coeliac disease
    - Pregnancy (or prolonged breastfeeding)
    - Liver disease – failure of liver to hydroxylate cholecalciferol & malabsorption of Vit D
    - Renal Osteodystrophy – failure of kidney to hydroxylate 25-hydroxycholecalciferol
- Drug induced
    - Anticonvulsants (induce liver enzymes and breakdown 25 hydroxycholecalciferol)

Investigations

Blood test	**Result**
Vitamin D	May be low
Bone profile/Calcium	Reduced Ca^{2+} and PO^{4+}
LFTs	Increased ALP

Diagnosis

The differential includes stress fractures and rarer conditions including Fibrogenesis imperfecta ossium (defective collagen) or chronic overdose of drugs (fluoride/etidronate/aluminium).

Management

Treat the cause e.g. Vitamin D replacement

Paget's Disease of Bone

This has also been called osteitis deformans and relates to the increased turnover and remodelling of bone causing an overgrowth of bone and affects the integrity of the bone itself.

Incidence & Impact

Is surprisingly common rated at affecting around 1-2% of the adult population in the UK where it has the highest prevalence in the world, it is more common with age but asymptomatic in the majority. Useful to be aware of as can be mistaken for osteoarthritis (think older patient presenting with bony pain)

Aetiology

Likely a genetic component as a family history increases risk of developing but suspected epigenetic factors too (several environmental factors suspected but unconfirmed)

Signs & symptoms

Given many are asymptomatic it could be found as incidental findings on screen of bloods (raised ALP) or seeing characteristic X-ray findings. When symptomatic it is due to the pain of the lesions or the impact of bony overgrowth/deformities.

System	Symptoms
Bone	Deep bone pain – may affect hips, pelvis, lumbar spine, skull, femur and tibia. Bony deformity (bowed 'sabre' tibia) & enlargement Pathological fractures
Joints	Osteoarthritis
Cardiac	Cardiac Failure
Neurological	Nerve compression caused by bone overgrowth

Investigations

Blood test	**Result**
Full Blood Count	Consider alternative diagnosis if anaemic
ESR	If raised, consider other causes including malignancy
Bone profile/Calcium	$Ca^{2+,}$ PO_4^{3-} usually normal
U&E	Abnormal in renal failure
LFTs	Raised ALP (can be up to 10x) but with normal LFTs - if abnormal look for another cause - see 'Raised ALP' Flowchart.
GGT	May be raised in Liver disease
TFTs	Exclude hyperthyroidism

Vitamin D	Screen for Vit D Deficiency as cause asymptomatic raised ALP

X-rays: Localised bone enlargement, cortical thickening and deformity.

Management

These would always require referral to secondary care and treatment may include alendronic acid and analgesia.

Primary Bone Cancer

Malignancies affecting bone can be divided into primary and secondary tumours, whilst rare, primary bone cancers are important to consider as part of a broad differential diagnosis in MSK pathologies.

They are caused by abnormal growth and division of any of the cells that are found in bone. There are three main types of primary bone cancer that make up 84% of all cases;

- Osteosarcoma – most common form in young people from abnormal osteoblast cells
- Ewing's Sarcoma – second most common
- Chondrosarcoma – most common in adults (from cartilage cells)

Additional rarer forms include; Chordoma, Adamantinoma, Angiosarcoma of the bone, Giant cell tumour of the bone and Spindle cell sarcoma of the bone.

Incidence

These are rare, representing only 0.2% of all cancers. It is an unusual type of cancer in that it can affect a broad range of age groups including young people compared to most other cancers.

- Osteosarcoma and Ewing sarcoma affect a younger age group – normally 10-25 year olds
- Chondrosarcoma and chordomas tend to affect those above the aged of 40

Males are affected more commonly than females, with a ratio of approximately 2:1.
Osteosarcomas are more common in certain sites :

- lower end of femur - about 40%
- upper end of humerus - about 10%
- pelvic bones - about 10%

It is estimated that in the UK and Ireland 12 patients are diagnosed with a primary bone tumour every week.

Aetiology

There are a range of mechanisms identified dependant on the type of cancer these include;

- *Radiotherapy* for cancer can damage the DNA in bone cells and cause the cells to become cancerous.
- *Genetic predisposition*: damaged genes can be inherited from a person's parents, making it more likely that a person will develop cancer.
- Underlying *bone abnormalities* – people with conditions such as Paget's Disease of the Bone are more likely to develop cancer.
- *Gene translocation* (seen in Ewing's Sarcoma) – this is when sections of genes are broken apart and joined together (translocation) in an abnormal combination that produces a 'fusion gene' that produces translocation factors that act as switches in cells and can cause uncontrolled growth of cells. N.B. These changes occur in cells that are not passed on (sperm and egg cells) so this type of cancer is not inheritable.

Symptoms & Signs

WARNING! The symptoms can be very generalised and mimic sports injuries or MSK pathologies and include….

- Bone pain
  - this can be constant but BEWARE can also be intermittent and appear to be resolving (recall story of SR pain easing as stopped going to the gym ?less weight bearing)
  - pain may not respond to analgesia or usual therapies and can be worse at night
- Tenderness
  - Focal bony tenderness on palpation
- Lump or mass
  - May be palpable but not always if tumour within confines of bone
- Limp
- Reduced mobility
- Bruising easily
- Systemic features
  - Malaise
  - Weight loss
  - Muscle atrophy
  - Loss of muscle tone
- Pathological fracture
  - Is a late stage sign

Investigations

Blood test	Result
Full Blood Count	Anaemia, leucopaenia, thrombocytopaenia
ESR/Plasma Viscosity	Increased
Calcium	Raised
U&E/LFT/LDH	Abnormal – end organ damage

- Plain X-Ray – this doesn't exclude bone cancer if normal but is a useful first line investigation (NB in long bones e.g. Femur don't just image hip/knee but need whole length of bone)
- CT/MRI/PET scan/Bone scan
- **Bone Biopsy is the diagnostic investigation of choice**

Treatment

- Chemotherapy
- Radiotherapy
- Surgery
- Rehabilitation – including physiotherapy, dietician support, occupational therapists, prosthetics, orthotists

5 year survival rates

Osteosarcoma:	40%
Chondrosarcoma:	70%
Ewings Sarcoma:	50%
Chordoma:	60%

Secondary/Metastatic Bone cancer

This relates to the distinction between cancers of the bone and cancers in the bone. These cancers represent the spread of cancerous cells from other 'primary' cancers to the bone marrow where they grow and proliferate creating 'secondary' tumours that disrupt the bony structure.

Aetiology

Can easily be remembered by the **rule of 'b's –** cancers that most commonly spread to bone include;

- **B**reast
- **B**rostate (Prostate)
- **B**ronchus (Lung)
- **B**ryroid (Thyroid)
- **B**idney (Kidney)
- **B**owel (rare)

Of these Breast and Prostate represent two thirds (66%) of all metastatic secondaries.

Incidence and prevalence is harder to quantify but in one study[2] the cumulative incidence of bone metastases in 569,000 patients in the US with solid tumours (>18y.o.)
was 2.9% 30 days rising to 8.4% at ten years. Incidence varied according to which type with prostate>breast/lung/colorectal

Signs & Symptoms

Can produce bone pain, usually localised to the site of metastasis, if there is significant destruction of the bone then a pathological fracture (and in the spine this may be accompanied by metastatic spinal cord compression).

There can be extensive replacement of the bone marrow causing anaemia and as the calcium is released from the destruction of bone via a destructive osteolytic process, symptoms of hypercalcaemia may be present. This is the most common metabolic abnormality in cancer patients seen in 10-20% of patients with cancer causing *confusion, polydipsia (excessive thirst), polyuria (excessive urination), constipation, anorexia (reduced appetite), if excessive then it can cause seizures, coma, cardiac arrythmia and death*. (N.B. you should always check albumin and Parathyroid Hormone (it should be suppressed in Myeloma – see section on Bone Profile).

This is prognostically poor as it indicates extensive disease with a mortality of 75% within 3 months.

Investigations

Non-specific

Blood test	Result
Full Blood Count	Anaemia, leucopaenia, thrombocytopaenia
ESR/Plasma Viscosity	May be increased
CRP	If raised, consider other causes
Calcium	May be raised
U&E/LFT/LDH	Abnormal – end organ damage

Specific

Blood test	Result
PSA	May be raised in prostate Ca
Serum Protein Electrophoresis	Monoclonal (paraprotein) band in myeloma
Serum Free Light Chain analysis	Abnormal ratio in myeloma
Urinary Electrophoresis	Looking for light chains (Bence Jones proteins) in Myeloma

Hypercalcaemia

Symptoms

- Skeletal
  - Bone pain, skeletal deformities.
  - Osteoporosis & Fractures

- Neuromuscular and neuropsychiatric
  - Drowsiness, delirium, coma, fatigue, lethargy, muscle weakness, insomnia
  - Impaired concentration and memory, confusion
  - Depression, anxiety, irritability, psychosis
  - Neurological signs (e.g. UMN signs, hypotonia, hyporeflexia, and ataxia).
- Gastrointestinal
  - Nausea, vomiting, anorexia, weight loss.
  - Constipation, abdominal pain
  - Peptic ulcer, pancreatitis (both rare)
- Renal
  - Renal colic due to renal stones (nephrolithiasis).
  - Thirst, polyuria, polydipsia, nocturia, and dehydration
  - Renal impairment (due to nephrocalcinosis and/or obstructive uropathy).
- Cardiovascular
  - Hypertension
  - Shortened QT interval; prolonged PR interval on electrocardiogram (ECG).
  - Cardiac arrhythmias such as ventricular fibrillation (rare).
- Other
  - Flushing, itching, band keratopathy (rare)

Causes

Common:

1. Primary Hyperparathyroidism
2. Malignancy
3. Chronic Renal failure

Uncommon

1. Familial benign hypercalcaemia
2. Sarcoidosis
3. Thyrotoxicosis
4. Milk alkali syndrome
5. Vitamin D treatment

Blood test	Purpose
FBC	Diagnose or exclude anaemia of chronic disease or haematologic malignancy.
ESR/CRP	May be increased in malignancy or other inflammatory conditions.
U&E	to assess hydration status, for acute kidney injury (AKI) and chronic kidney disease (CKD).
LFTs	to exclude liver metastases or chronic liver failure; ALP may be increased in primary hyperparathyroidism, Paget's disease with immobilization, myeloma, or bone metastases.
PTH	typically raised in primary (and tertiary) hyperparathyroidism and suppressed or undetectable in malignancy-related hypercalcaemia ornon PTH-dependent causes.
TFTs	to exclude thyrotoxicosis
Serum & urine protein electrophoresis	Screen for Myeloma

Hyperparathyroidism

This is one of the more common endocrine disorders affecting women more than men (2>1) with a peak incidence at age 50-60. Characterised by an increase in the release of Parathyroid Hormone causing a subsequent raised calcium

Symptoms

Whilst normally asymptomatic it can cause joint pain, kidney stones, abdominal pain and mood disturbance ("bones, stones, groans and abdominal moans"), fragility fractures, polyuria/polydipsia…can be fatal

Causes

- Primary
  - Parathyroid Adenoma (85% cases)
  - Multiglandular Hyperplasia
  - Parathyroid Carcinoma
  - Medication
    - Thiazide Diuretics
    - Lithium
    - Anticonvulsants
    - Steroids
    - Isoniazid
    - Rifampicin

- Secondary
  - Chronic Renal Failure
    - failure of the kidney to excrete phosphate and resorption of calcium
    - failure of endocrine function of kidney
  - Malabsorption & Vitamin D Deficiency

Phosphate

Is involved in lots of critical processes including energy metabolism, bone formation, nerve and cell function and muscle contraction – it is predominantly (85%) stored in bones and levels are controlled by the kidneys so an important marker of renal disease as well as bone metabolism. As levels of calcium in the blood stream rise, levels of phosphate fall.

It is absorbed from the small intestine and is reabsorbed via the kidneys. Its excretion via the kidneys is increased by PTH so increased levels of this in hyperparathyroidism are an important cause of hypophosphataemia.

Causes of Hypophosphataemia

- Hypercalcaemia
    - Associated with hyperparathyroidism or malignancy
- Aluminium antacid therapy
- Hyperalimentation
- Nutritional recovery
- Alkalaemia
- Treated diabetic acidosis
- Alcoholism
- Hypomagnesaemia.

Causes of Hyperphosphataemia

- Renal failure – kidney is unable to excrete phosphate
- Hypoparathyroidism
- PTH resistance
- Artefactual (Haemolysis) - delayed separation of plasma from RBC
- Infancy and childhood (hence higher reference ranges)
- Increased intake
- Vitamin D excess

Raised ALP

The two main sources of ALP are from liver or bone. However, other sources include intestinal and placental ALP.
May be caused by:

1. Physiological: Pregnancy, Growing child (puberty)
2. Bone disease
    a. Paget's Disease
    b. Osteomalacia
        i. Vitamin D Deficiency
    c. Renal osteodystrophy – check for abnormal U&E's
    d. Bone metastases – check ESR/CRP
    e. Primary bone tumour e.g. sarcoma
    f. Recent fracture
3. Non-bony malignancies – including those that secrete ALP-like genome e.g. Seminomas (testicular cancer)

If ALP < 1.5x upper limit of normal corelate with symptoms and consider if it may be physiological (is the patient young <20 or pregnant?) then recheck 1-3months, if >1.5 times then further ix indicated.
Can be distinguished by looking for other markers of hepatic causes by imaging (USS Liver) and other blood tests including;

- LFTs – see below
- GGT - a marker of cholestasis and biliary disease – useful to distinguish between liver and bone origins
- vitamin D - vitamin D deficiency can be a cause
- U+Es - renal osteodystrophy
- TFTs – raised ALP can be seen with raised ALT in hyperthyroidism
- FBC, ESR, CRP – anaemia and raised inflammatory markers might suggest malignancy or metastatic disease

In some areas ALP Isoenzymes can be requested to identify type of ALP

- Placental
    - Includes possible malignancy (lung/ovary/pancreas)
- Liver
    - Cholestatic liver disease
- THI (Transient hypophosphataemia of infancy) in young child
- Bone
    - Paget's disease
    - Malignancy
    - Fractures (healing)
    - Renal Osteodystrophy
    - Osteomalacia
    - Hyperparathyroidism
    - Hyperthyroidism

Thyroid Function Tests

The thyroid hormones have a number of roles in the body and changes in their levels link to the relevant symptoms;

- Temperature regulation & basal metabolic rate (BMR)
  - Hypo – Low BMR, sensitivity to cold, decreased food appetite
  - Hyper – High BMR, sensitivity to heat, increased food appetite & catabolism
- Normal Growth
  - Hypo – growth retardation in children
- Nervous system maturation in foetus
  - Hypo – mental retardation
- Sympathetic nervous system function (stimulate receptors for adrenaline/noradrenaline)
  - Hyper – sympathetic system activation – e.g. inc heart rate, sweating

Tests used for assessing thyroid function include: Thyroid stimulation hormone (TSH) &Free T3 and free T4 (occasionally some labs measure total T3 and total T4 but an estimate of the concentration of thyroid binding protein concentrations would be needed before interpreting).

Some typical reference ranges in adults are:

- TSH: 0.4 – 4.5 mU/L
- Free T4: 9.0 – 25 pmol/L
- Free T3 3.5 – 7.8 nmol/L

TSH test costs £1.67 and nationally 10 million TFTs are ordered every year costing over £30 million. Studies show widespread, indiscriminate use with a study showing of 2267 patients tested only 2.1% had hypothyroidism.

Hypothyroidism

Prevalence 2%, incidence of 4/1000 women (0.8/1000 men),10x more common in women
Caries an increased risk of cardiovascular disease, osteoporosis, cognitive dysfunction and lipid disorders.

There is a widespread location of receptors with affinity for T_3 found in muscle, fat, brain, liver and kidney, hence a wide range of symptoms caused by abnormalities in their levels.

Symptoms – can be a slow, insidious development and goes missed by patient and clinician alike. Causes tiredness, depressed mood, cold intolerance, dry/thin skin and hair, cold hands, reduced memory/cognitive function, menstrual changes (heavy periods and infertility) weight gain, myalgia, cramps and weakness.

Signs include goitre (in Hashimoto's), slow relaxing reflexes, ataxic, dry skin/hair, round/puffy face/obesity, ileus, cardiac failure.

Associations: often seen alongside other autoimmune disorders e.g. diabetes as well as in genetic disorders such as Down's and Turner's syndromes.

Causes mostly caused by primary autoimmune hypothyroidism (Hashimoto's thyroiditis) with the next most frequent cause being post-treatment of the thyroid gland (surgically/radio-iodine therapy). Secondary hypothyroidism caused by hypo-pituitarism leading to reduced production of TSH is very rare.

Investigations
As a general rule the diagnosis is made with an assessment of TSH (low or normal) and a raised T_4, T_3 is not routinely used for diagnosis and the monitoring of treatment is based on the TSH primarily.

Blood test	Result
TSH	Increased (treatment advised if TSH >10mU/L)
T_4	Reduced
FBC	May see a normochromic anaemia
Lipids	Raised cholesterol and triglycerides may be seen
Autoantibodies	Thyroid peroxidase (TPO) antibodies (positive in 95% of those with hypothyroidism)

Treatment
Use of the drug Levothyroxine is the principle approach and it can take months for the symptoms to resolve following initiation of treatment.

There is some debate and controversy surrounds its use in 'subclinical' hypothyroidism and cases with symptoms, but a TSH below 10mU/L, factors taken into account include; pregnancy, presence of thyroid autoantibodies, presence of goitre, <65 with associated abnormal lipids or cardiovascular risk factors.

Hyperthyroidism (thyrotoxicosis)

Much rarer prevalence of 0.4% (women 0.77/1000, men 0.14/10000)
Symptoms – diarrhoea, sweating, weight loss, heat intolerance, palpitations, tremor, menstrual changes (irregular/infrequent periods) – more rarely psychosis, panic, itch.
Signs- fast, irregular pulse (Atrial fibrillation/ventricular tachycardia), tremor, sweats, thin hair, 'staring' appearance to eyes, goitre (might be seen)

Pathogenesis
Grave's disease accounts for 2/3 of cases – women>men, 40-60year old average age of onset with production of IgG autoantibodies that drive the thyroid gland to enlarge and overproduce thyroid hormone production (and have an effect on orbital autoantigens – hence eye symptoms/signs).

Other drivers include a multinodular goitre (more in elderly patients), toxic nodules in the thyroid gland (adenomas), thyroid cancer and rarer causes such as excessive iodine (contrast media/contamination), iatrogenic (lithium/nsaids, amiodarone) and post viral.

Investigations

Standard test is blood Thyroid Stimulating Hormone

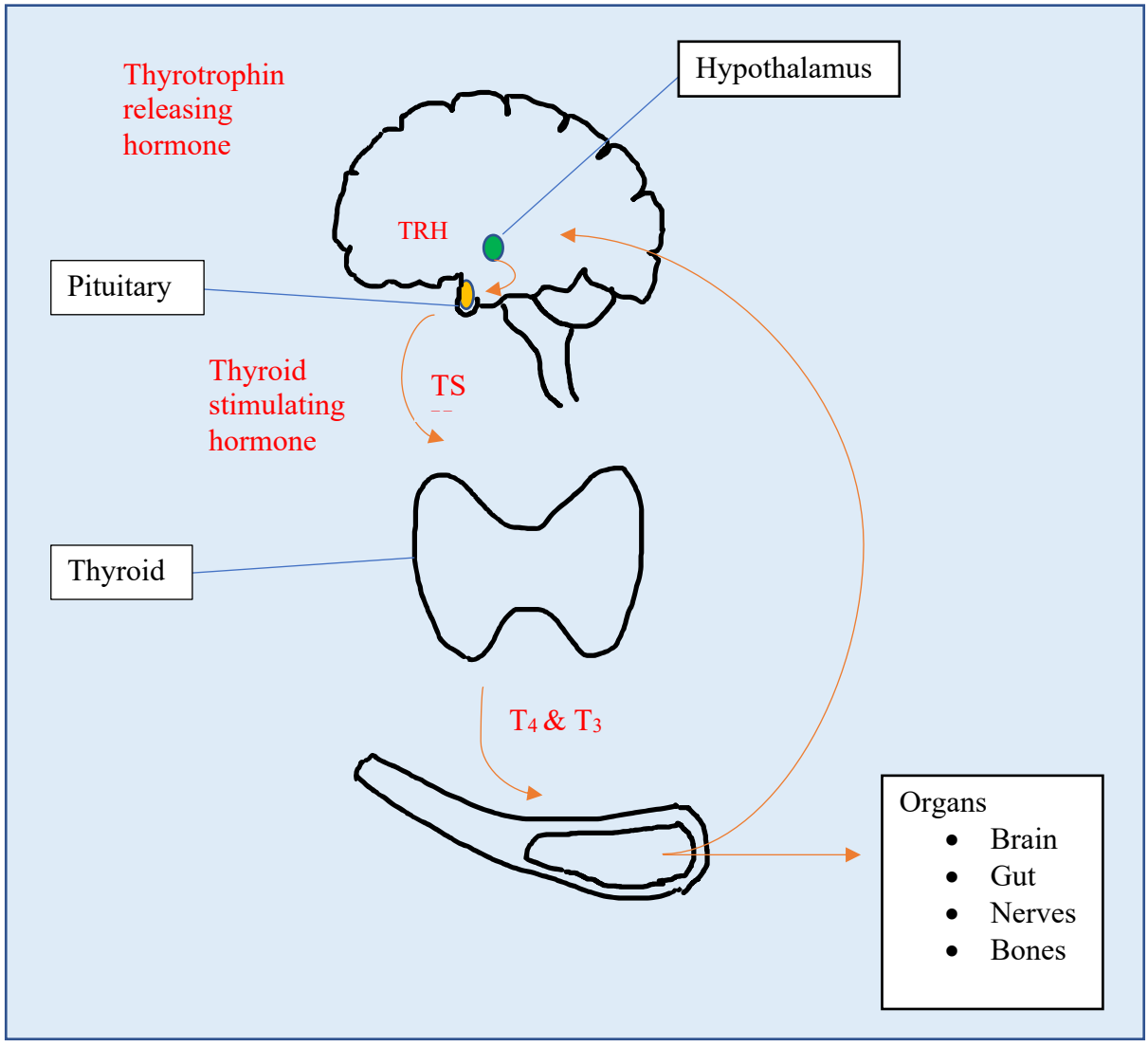
British Thyroid Association guideline (2006) suggests a normal TSH effectively rules out thyrotoxicosis but suggests using clinical judgement more in hypothyroidism.

Blood test	Result
TSH	Reduced
T_4 & T_3	Increased
FBC	Mild normocytic anaemia
ESR	Raised
Calcium	Raised
LFTs	Abnormal
Thyroid autoantibodies	

Treatments are dependent on cause but can include;

- Surgery, Radio-iodine treatment (Often causes post-treatment hypothyroidism), Medication (Anti-thyroid drugs e.g. carbimazole)

Hypothalamic-Pituitary-Thyroid Hormone Axis



Fibromyalgia & chronic pain syndromes

Fibromyalgia is part of a group of conditions sharing similar clinical features including fatigue, muscle and joint pain, depression and widespread tenderness that include;

- Chronic Fatigue Syndrome
- Myalgic Encephalitis (ME)

Whilst much controversy remains about grouping these together or considering them individually there are commonalities in presentation and treatment that justify considering them as a family of conditions in terms of assessment and treatment.

Prevalence has been suggested to be up to 5% of the population in European countries with up to 2.9 million adults affected in the UK (roughly 1 in 20 people).

Aetiology

Many mechanisms have been suggested for Fibromyalgia including;

- Neuroendocrine disturbance – associated with thyroid disorders
- Psychosomatic – including relating to PTSD
- Genetic predisposition to pain sensitivity– 1st degree relatives have up to 8x risk, 50% risk in twin studies
- Trauma – physical/sexual/emotional
- Abnormal pain processing – with increased Substance P, Glutamate & decreased noradrenaline/serotonin (central sensitisation)
- Autonomic nervous system dysfunction
- Sleep abnormalities (lack of stage 4 sleep)
- Allergy, infection (EBV/Lyme), drugs, toxicity and nutritional deficiencies

Risk factors

Each patient needs to be assessed as an individual with unique circumstances. There can be a degree of chronicity to the symptoms often with a high degree of functioning until a certain trigger event occurs. The risk factors for the development and deterioration of chronic pain syndromes can best be thought of within a 3P's model;

Predisposing	Adverse childhood events - sexual, physical, emotional abuse & neglect
	Mental health problems including anxiety/depression/stress
	Gender – women>men
	Comorbidities – significant increase associated with chronic back pain and inflammatory conditions (found in 25% of patients with rheumatoid

	arthritis/spondyloarthritis) as well as association with Thyroid disorders
Precipitating	Trauma (e.g. RTA – where individual is victim or catastrophic events (manmade more so than natural disasters)
	Significant Illness, Infection (EBV/Lyme) or Operation
	Emotional trigger– bereavement, loss of work
	Childhood history of Physical/Sexual abuse/Neglect
	High levels of Stress
	Medication/vaccines/chemical exposure
Perpetuating	Abnormal health beliefs – 'pain and activity are harmful'
	Social withdrawal/isolation
	Work related problems – bullying/dissatisfaction/compensation claims
	Low levels of patient activation (i.e. low participation in treatment)
	Overprotective family/spouse or lack of support

Signs and symptoms

A formal diagnosis should comprise of a full history, examination and relevant tests to ensure there is no other likely and potentially significant diagnosis given the wide differential diagnosis for the symptoms involved.

In the years before diagnosis, people with fibromyalgia will often have been seen repeatedly by their GP for a wide range of symptoms, both painful and non-painful

Characteristic features described include *hyperalgesia,* an exaggerated response to a painful stimulus, and *allodynia,* a painful response to a non-painful stimulus. Symptoms include both pain and somatic features including;

Pain syndromes	Somatic features
Back pain	Fatigue (80%)
Headache	Depression (34%) & Anxiety (40%)
Regional pain syndromes	Dizziness
Chest pain	Irritable Bowel Syndrome/Dyspepsia (30-50%)
Myalgia	Rash/hypersensitivity
Arthralgia	Cognitive function (memory/concentration)

	Urinary dysfunction (12%)
	Stiffness
	Sleep dysfunction

Fibromyalgia is associated with regional pain syndromes such as back, neck or tempero-mandibular pain, as well as headache and chronic chest pain
Where these symptoms persist, people should be asked about other pain and somatic symptoms so a diagnosis of fibromyalgia can be made

Differential diagnosis

Rheumatological	Rheumatoid Arthritis Spondyloarthropathies Polymyalgia Rheumatica Polymyositis Vasculitis Hypermobility Syndrome Ehler-Dahlos Syndrome
Endocrine	Hypothyroidism Hyperthyroidism Osteomalacia
Neurological	Multiple sclerosis Neuropathies
Iatrogenic	Drugs e.g. Statins
Sleep disorders	Insomnia (difficulty initiating sleep), mid-sleep disruption and early morning waking

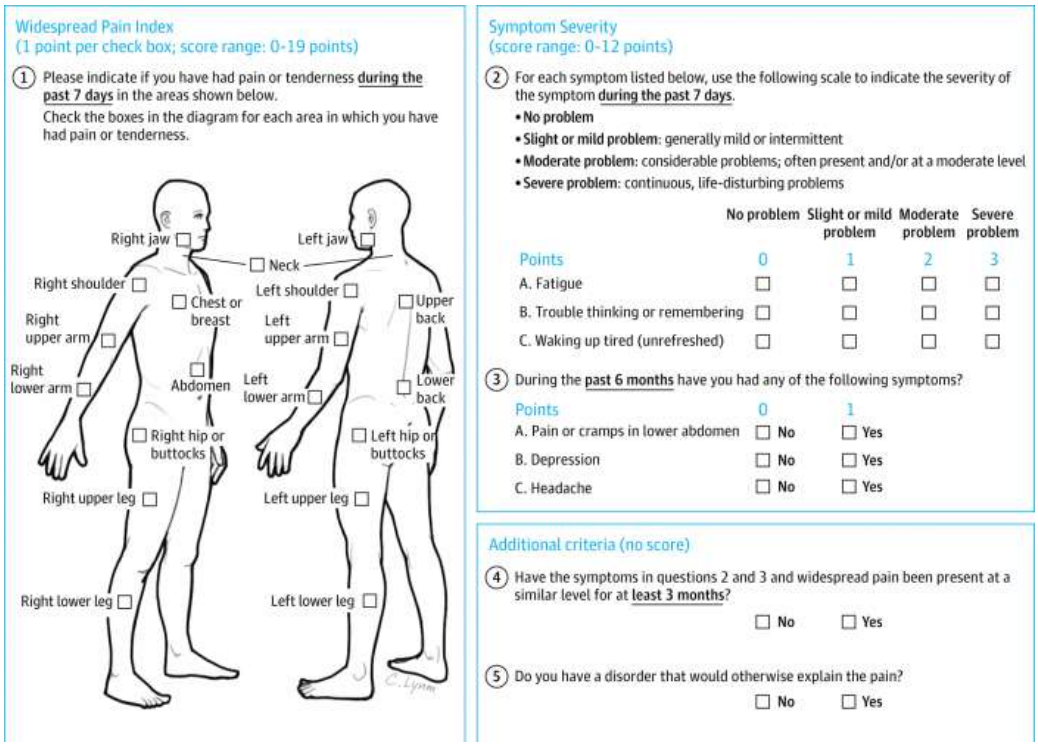
Investigations

There is some debate about what tests should be run and the general consensus would not be to go on an immunological fishing trip with multiple autoimmune screen however an ANA *would* be justified if there are symptoms/signs that suggest possible connective tissue disease

Blood test	**Result**
Full Blood Count	Screen for anaemia (consider ferritin in children/young adults)
ESR	Should be normal – may indicate inflammatory disease/PMR (when a CRP might be of additional value)
TFT	Exclude hypo/hyperthyroidism
U&E & LFT	Renal/liver dysfunction

Creatinine Kinase	Exclude myositis (if significant myalgia)
Bone profile	Bone metabolic problems
Hba1c	Diabetes screen
Urine dipstick	Screen for blood/protein

Diagnostic criteria (ACR 2016 Revised criteria)



Widespread Pain Index
(1 point per check box; score range: 0-19 points)

1. Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.

Right jaw ☐ Left jaw ☐
Neck ☐
Right shoulder ☐ Chest or breast ☐ Left shoulder ☐ Upper back ☐
Right upper arm ☐ Left upper arm ☐
Right lower arm ☐ Abdomen ☐ Left lower arm ☐ Lower back ☐
Right hip or buttocks ☐ Left hip or buttocks ☐
Right upper leg ☐ Left upper leg ☐
Right lower leg ☐ Left lower leg ☐

Symptom Severity
(score range: 0-12 points)

2. For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.
- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problems; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

3. During the **past 6 months** have you had any of the following symptoms?

	Points	0	1
A. Pain or cramps in lower abdomen		☐ No	☐ Yes
B. Depression		☐ No	☐ Yes
C. Headache		☐ No	☐ Yes

Additional criteria (no score)

4. Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at **least 3 months**?
☐ No ☐ Yes

5. Do you have a disorder that would otherwise explain the pain?
☐ No ☐ Yes

Scoring

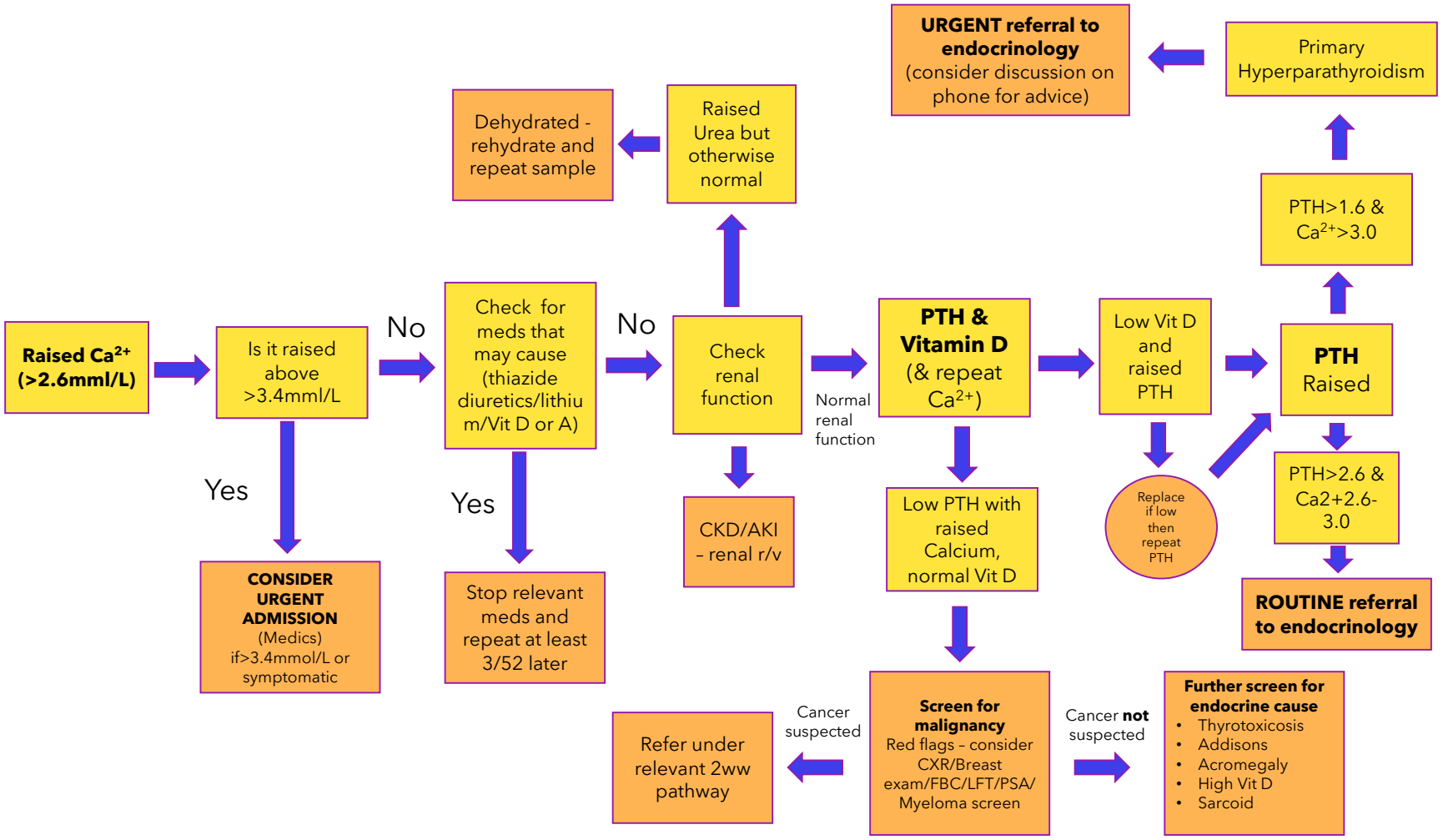
Widespread Pain Index of **7 or more** & Symptom Severity Score **5 or more**
OR
Widespread Pain Index of **4-6 or more** & Symptom Severity Score **9 or more**

Management

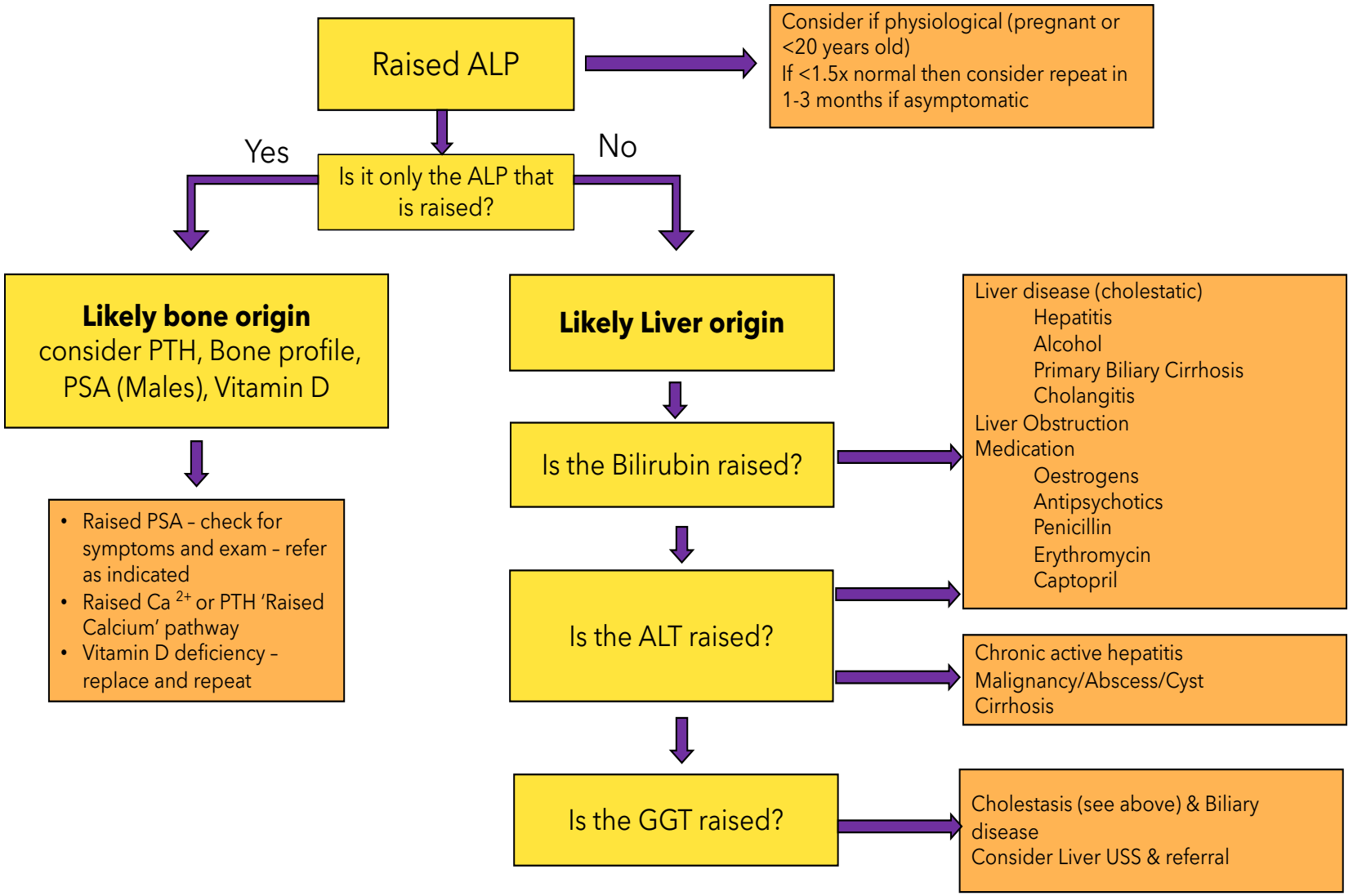
Based on ACR Criteria

- Patient education and Information (written/web based)
- Physical therapy with individualised graded physical exercise (may be combined with hydrotherapy/acupuncture)
- Psychological therapies
- Pharmacotherapy
    - Pain – Duloxetine, Pregabalin, Tramadol (prn not regularly) **NB** Not Opiates
    - Sleep disturbance – Low dose amitriptyline, pregabalin at night
- Multimodal rehabilitation programme (Pain Management Programme

Suggested management pathway for raised Calcium (derived from NICE CKS Summary (revised August 2019)



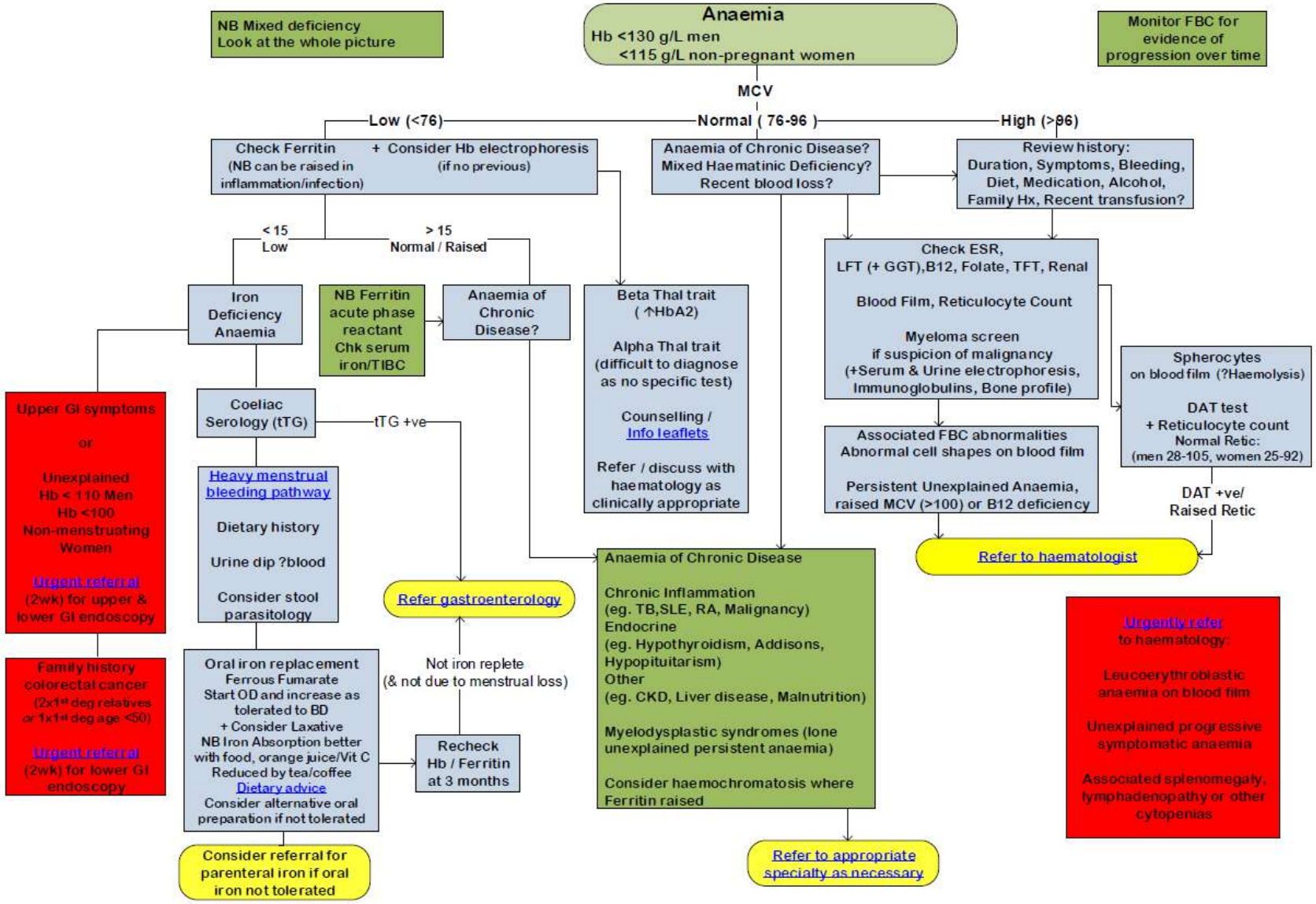
Suggested pathway for investigating raised ALP



Bone markers

	Calcium (Ca)	Alkaline Phosphatase (ALP)	Parathyroid Hormone (PTH)	Phosphate (PO4)	Vitamin D	Serum protein electrophoresis	ESR
Hyperparathyroidism (Primary)	↑	↑	↑ Raised in 90%	↓	-	-	-
Osteomalacia	↓	↑	↑	-	↓		
Paget's Disease	Normal or ↑	↑	-	-	-	-	
Myeloma	↑	Normal (unless healing fracture when ↑)	Normal		Normal	Serum - Monoclonal band Urine - Bence-Jones protein	↑
Vitamin D Deficiency	↓	Long term ↓ But ↑ in early stages	↑ can be raised	↓	↓	-	
Bone Metastases	↑	↑				-	↑
Renal Osteodystrophy* (Secondary Hyperparathyroidism)	↓		↑				

*abnormal renal function (U&Es) – high calcium and high PTH is seen in advanced renal failure (Tertiary hyperparathyroidism)



NHS Camden CCG. Abnormal FBC guidance - for adults (reproduced with permission)

Summary of blood tests

Test	Normal range	Purpose/Indication	Interpretation
Alanine aminotransferase (ALT)	5-35IU/L	Useful predominantly to identify and monitor liver disease as is found in cells of the liver but also in heart, kidney and skeletal muscle (anything causing damage to these organs will cause it to be released into the bloodstream).	*Increased:* Mildly; • Myositis • Pancreatitis • Myocardial infarction • Infectious mononucleosis (EBV) • Shock – injury to liver/heart/kidney/muscle Moderately; • Cirrhosis • Hepatic Tumour • Obstructive jaundice • Hepatotoxic drugs • Severe burns Significantly raised; • Hepatitis • Hepatic necrosis Hepatic ischaemia
Albumin (Alb)	35-50g/L	Main protein in the blood	*Increases:* in dehydration *Decreases:* • Acute/inflammatory illness • Urinary protein loss • Advanced liver disease • Gastrointestinal loss Severe malnutrition
Alkaline phosphatase (ALP)	30-130IU/L	Used to detect and monitor diseases of the liver and the bone.	*Increased:* • Liver disease – if so, expect a rise in GGT (as well as AST/ALT)

		It is seen in active osteoblasts so seen to increase in childhood, puberty and in healing fractures. It is also produced by the placenta and in the membranes of the bile ducts in the liver. It can also be raised after a recent meal.	• Bone & other diseases – including: Cancer (Primary/Secondary), Paget's disease, Hyperparathyroidism, Renal failure, thyrotoxicosis, Rheumatoid arthritis, Osteomalacia/rickets, Crohn's/Ulcerative Colitis • Puberty (up to 650U/L), • Pregnancy (up to 400U/L) • Transient hyperphosphatasaemia of childhood (up to 30000U/L for up to 3/12), • Familial Benign Hyperphosphatasaemia *Decreased:* • Malnutrition • Milk-alkali syndrome • Pernicious anaemia • Vitamin C deficiency (Scurvy)
Anti-nuclear antibodies (ANA)	Result is described as a titre	Screening for SLE (positive in 95% cases)	<1:40 = Negative 1:40 or 1:80 = Borderline >1:160 = consistent with autoimmune disease
Anti-Cyclic Citrullinated peptide (Anti-CCP)	Is a type of autoantibody that targets a protein (Citrullinated protein) that is found in some people's joints	Useful to help diagnose Rheumatoid Arthritis	+ve in 60-70% of people who get RA – needs interpretation in context but can indicate; • Risk of developing RA in a healthy person • Better than Rheumatoid Factor at predicting those in early stages of arthritis who will develop RA

			In those with RA +ve anti-CCP predicts increase chance of erosive disease
Anti-DNA antibodies	Result is described as a titre	Positive in 60-80% of SLE also present in low titres in RA, autoimmune hepatitis and other immune disorders.	<1:20 or 1:40 equivocal >1:80 supports diagnosis of SLE
Aspartate transaminase (AST)	5-35IU/L	Enzyme found in heart, liver, pancreas, skeletal muscle, kidney and red blood cells - damage to any of these organs causes a release of the enzyme into the bloodstream	*Increased:* • Liver disease • Myocardial Infarction (increases 6-12hrs post MI, peaking at 24-36hours) • Congestive cardiac failure • Trauma • Muscular dystrophy • Dermatomyositis • Haemolysis • Renal infarction • Acute pancreatitis • After surgery/IM injections • Hypothyroidism *Decreased:* Severe/end stage liver disease (no further enzyme to release)
Basophils	0.0-0.10 x10/L	Smallest group of white cells – circulate in blood stream and migrate into tissues becoming mast cells. Significant role in immediate hypersensitivity reactions (including anaphylaxis)	*Increased:* • viral infections • urticaria • post-splenectomy • myxoedema • ulcerative colitis • systemic mastocytosis • malignancy • myeloproliferative disorders:

			○ chronic myeloid leukaemia ○ myelofibrosis ○ polycythaemia rubra vera • haemolysis
Bilirubin	3-17μmol/L	Breakdown product of red cells – normally metabolised (conjugated) by the liver into a water soluble form and excreted via the kidneys.	*Increased:* Haemolysis, Gilberts disease (impaired conjugation), jaundice, Physiological (seen in first few days after birth as fetal red cells breakdown), Breast feeding, haemolytic disease of the newborn, (rhesus disease where mother and fetal rhesus blood types are different)
Ca 15-3		Tumour marker found in Breast cancer also raised in other benign and malignant conditions	
Ca 19-9		Tumour marker found in Pancreatic cancer (and other GI malignancies)	
Ca 125		Tumour marker found in Ovarian cancer - also lung, pancreas, colon, uterine (also seen to be raised in endometriosis, PID, cirrhosis and pregnancy)	NICE recommend Pelvic USS in women with symptoms (pelvic mass, abdominal pain/bloating and increased urinary frequency) and Ca125 >35kU/L
Calcium (corrected)	2.12-2.60mmol/L	Essential mineral used in formation of bone and teeth, Muscle contraction, Normal functioning of a number of enzymes, Blood clotting &Normal heart rhythm	Hypercalcaemia: More common causes: 1. Primary Hyperparathyroidism 2. Malignancy (Myeloma, Breast, Lung, Kidney, Thyroid, Prostate, Ovary or Colon) 3. Chronic Renal failure

Carcino Embryonic Antigen (CEA)		Tumour marker found in Colorectal cancer Pancreatic, breast, lung, small intestine, stomach, ovarian	
Cholesterol	<5mmol/L	Has a role in cell membranes and as a precursor of steroid hormones and bile salts – it is taken in the diet and synthesised in the liver and is associated with cardiovascular disease (and in gallstone production)	*Primary hyperlipidaemia* – predominantly genetically inherited *Secondary hyperlipidaemia* – has multiple causes including; hypothyroidism, obesity, steroids, diabetes, alcohol, biliary obstruction, drugs (b-blockers/thiazide diuretics)
Complement	C3 & C4 are the components most usually measured	Proteins within the complement cascade are involved in cell lysis, marking cells for destruction (opsonisation) and clearance of immune complexes.	*Increased* in bacterial infections, inflammatory conditions (RA, spondyloarthropathies) *Decreased* in SLE and in inherited syndromes (Hereditory hypocomplementemic syndrome)
C-Reactive Protein (CRP)	<10mg/L	Sensitive but non-specific marker of inflammation	
Creatinine (Cr)	70-100μmol/L	Breakdown product from muscle & protein metabolism and influenced by diet (meat) – excreted by the kidneys	Steadily increases with age as a measure of deteriorating glomerular filtration rate – anything that increases creatinine or reduces the kidneys ability to clear it will push it up – used to monitor renal disease/diabetic renal disease/transplants & monitoring nephrotoxic drugs (including NSAIDs)
Creatinine Kinase (CK)	<165U/L	CK is found mostly in heart muscle, skeletal muscle (and brain) and can be used as a marker of damage to cells in these structures.	*Increased;* • Myocardial Infarction • Myopathies including Myositis • Vigorous exercise • Cardioversion • Chronic alcoholism

<table>
<tr><td></td><td></td><td>The levels tend to rise at around 6 hours after injury and reach a peak at 18hours before returning to normal.</td><td>Surgery & repeated IM injections</td></tr>
<tr><td>Estimated Glomerular Filtration Rate (eGFR)</td><td>Stage 1: (Normal) >90
Stage 2: 60-89
Stage 3a: 45-59
Stage 3b: 30-44
Stage 4: 15-29
Stage 5: <15 (severe)</td><td>Uses the rate of glomerular filtration as a means to assess kidney function measured in millilitres per minute/1.73m^2</td><td>Decreases with age & renal disease
NB The rate of transition between stages is relevant as an indicator (common to find older patients with CKD2-3 with no change over years managed conservatively)</td></tr>
<tr><td>Eosinophils</td><td>0.004-0.4 x10^9/L</td><td>Pro-inflammatory cells with a significant role in allergies, parasitic infection and some cancers</td><td>Increased: seen in allergy, drug effects or parasitic infections in the gut as well as in infections such as TB and malignancies (Lymphoma, Hodgkin’s, Ovarian)</td></tr>
<tr><td>Erythrocyte Sedimentation Rate (ESR)</td><td>Increases with age
Men ESR = age ÷ 2
Women ESR = (age+10) ÷ 2</td><td>Non-specific measure of disease (including inflammation)</td><td>Increased: Inflammation (infection, rheumatoid arthritis, malignancy, myocardial infarction), anaemia and macrocytosis
Decreased: Polycythaemia, microcytosis, sickle-cell anaemia</td></tr>
<tr><td>Extractable Nuclear Antigens (ENA)</td><td></td><td>As a follow up to the ANA it is possible to extract some of the nuclear antigens and test the patient’s serum to see if they have antibodies against these – this can add information to aid the diagnosis but is not on its own, diagnostic.</td><td>
<table>
<tr><th>Antigen</th><th>Association</th></tr>
<tr><td>Ro</td><td>Sjogrens (90%)
SLE (40%)
Polymyositis (5%)
Rheumatoid Arthritis (5%)</td></tr>
<tr><td>La</td><td>Sjogrens (80% - usually seen with Ro)
SLE (10%)
Diffuse scleroderma</td></tr>
<tr><td>RNP</td><td>SLE (20%)</td></tr>
</table>
</td></tr>
</table>

			Scl 70 — Diffuse scleroderma (50%) CREST (10%) Jo 1 — Polymyositis (30% but is 95% specific when found) Mi2 — Polymyositis
Folate (aka Vitamin B9)	0.36-1.44μmol/l	A dietary vitamin (found in Liver & dark green leafy veg) – important in red cell synthesis and cause of anaemia when low	Levels can be low people with alcohol misuse, pregnancy & malabsorptive disorders.
Gamma-glutamyl transpeptidase (GGT)	*Men* 25-195u/L *Women* 7-33u/L	Liver enzyme - found in all liver cells – useful to differentiate between bone and liver causes of a raised ALP (raised GGT linked with liver disease)	*Increased:* Excessive alcohol use (but beware 30% heavy alcohol users have normal levels and can be normal in chronic alcoholism), cholestatic disorders, drugs (e.g. anticonvuslants)
Glucose (fasting)	3.5-5.5mmol/L	One of the body's fuel sources, a simple carbohydrate (aka monosaccharide – like fructose or ribose). Is the simple building block of carbohydrates found in bread, fruit, rice, vegetables	Has been used to diagnose diabetes (if fasting >7.0mmol/L or 2hrs post prandial is >11.1mmol/L) – should be repeated or used in conjunction with Hba1c as single result unreliable.
Glycosylated Haemoglobin (HbA1c)	4-6%	Is a measure of longer-term blood sugar control (over the previous 3 months) – it measures the glycosylation of haemoglobin that is affected by blood glucose concentration (and how long the red cells have been around).	6.1-7% good DM control 7.1-8.0% adequate 8.1-9.0% inadequate control
Haemoglobin (Hb)	*Men* 130-180g/L *Women.* 115-160g/L	Measure of the main component in red cells responsible for gas transfer – increased or decreased levels can indicate disease and guide treatment.	See section on Anaemia/Polycythaemia

High Density Lipoprotein (HDL)	>1.0mmol/L	Lipids (cholesterol, phospholipids and triglycerides) are insoluble in water so need to be linked with proteins in complexes (called lipoproteins) to enable transport around the body – these vary in size (smaller the size, increase in density from very low-density lipoprotein (VLDL) to high density (HDL))	HDL is anti-arthrogenic i.e. its concentration is *inversely* related to risk of cardiovascular disease (possibly because it has a role in transporting cholesterol from tissues to the liver). Decreased – • Smoking • Obesity (visceral fat especially) • Very low-fat diets • The presence of high triglycerides (that promote transfer of cholesterol from HDL to VLDL) • metabolic syndrome (as a risk factor) Genetic inherited e.g. Familial hypoalphalipoproteinaemia
HLA B-27 (Human Leucocyte Antigen)		Human Leucocyte antigens are proteins found on the surface of white blood cells, their role is to help identify differences between our own healthy tissues and foreign/dangerous substances – HLA B27 causes the white cells to attack our own healthy cells in error (termed 'autoimmune disease')	Found in 7-10% in general (healthy) population but seen in • Ankylosing spondylitis (95-98%) • Reiter's disease (90%) • Arthropathies related to Crohn's/UC (70%) • Juvenile Idiopathic Arthritis • Anterior uveitis
Human Chorionic Gonadotrophin (HCG)		Hormone produced by placental cells in pregnancy and tumours arising from uterine tissue	Relevant to assess progression of normal pregnancy as well as cancers including Choriocarcinoma, Hydatiform Mole & Trophoblastic disease
Lactate Dehydrogenase (LDH)	100-250U/L	Enzyme found in Liver, myocardium, skeletal muscle and red cells	*Increased:* Lymphoma, Myocardial infarction, tumours (germ cell), megaloblastic anaemia (low B12/Folate),

			liver disease (especially hepatitis), skeletal muscle damage,
Low Density Lipoprotein (LDL)	<2.5 mmol/L	As above – a lipid storage molecule – accounts for 2/3 -4/5 of serum cholesterol – mostly stores cholesterol (very little triglyceride) and main transport mechanism of cholesterol out of the liver	LDL interacts with HDL and passes cholesterol to HDL – these relatively 'empty' particles are atherogenic (increase lipid deposition in arteries) associated with vascular disease and are often raised alongside triglycerides even in normal total cholesterol
Lymphocytes	1.0-4.5 $x10^9$/L	Important Immune cells (T&B Cells), part of the adaptive immune response, involved in production of antibodies and identifying infected cells	*Increased:* Viral infections (EBV, Hepatitis, CMV), Chronic Lymphocytic Leukaemia (CLL) *Decreased:* Viral illness (!), Pancytopaenia, Hodgkin's, CCF, AIDs, Steroid therapy
Mean Cell Volume (MCV)	76-96fL	Indicator of red cell disease – helpful in identifying different causes of anaemia	*Macrocytosis* (Increased size >98fL) – B12/Folate deficiency, reticulocytosis, alcoholism, liver disease, myeloma, hypothyroidism, COPD, myelodysplasia, cytotoxic drugs (e.g. hydroxyurea) *Microcytosis* (microcytic anaemia) - Iron deficiency, thalassaemia trait
Monocytes	0.2-0.8$x10^9$/L	Multiple roles in adaptive immune system (replenishing macrophage stores) respond to infection, inflammation and cancers.	*Increased:* rarely in isolation but can be seen in chronic myeloid leukaemia, infections e.g. TB and polycythaemia rubra vera
Neutrophils	2.0-7.5$x10^9$/L	They are the most abundant cells of the immune response, designed to travel in the bloodstream to fight infection.	*Increased:* (Neutrophilia) – infection, injury, inflammation, malignancy, drugs (steroids, heparin, adrenaline), haemorrhage, metabolic disorders *Decreased:* (Neutropenia) considered mild when <$2x10^9$ but if below $0.5x10^9$ there is significant increased risk of spontaneous

			infection (much more so when below $0.2x10^9$) – causes – viral infection, typhoid, sepsis, B12/folate deficiency, aplastic anaemia, malignancy (haematological or bone marrow), immune mediated (e.g. post viral, SLE), hypertension, thyrotoxicosis, drugs – Cancer Chemotherapy (but also phenothiazines, carbamazepine, chlorpromazine, thiazides, sulphonamides, indomethacin)
Parathyroid Hormone (PTH)	1.0–6.0 pmol/L	Part of assessing bone metabolism	*Increased*: **with elevated calcium** seen in Primary hyperparathyroidism (adenoma (85%0 hyperplasia (15%), lithium therapy, familial benign hypocalciuric hypercalcaemia *Increased* **without raised calcium** seen in renal failure (2ndary hyperparathyroidism), vitamin d deficiency
Phosphate	Adults 0.80–1.50 mmol/L	Used in cases of hypercalcaemia and in renal failure to help identify cause	*Increased:* Sample error (haemolysed sample), renal failure, increased intake (IV therapy and vit d excess), hypoparathyroidism *Decreased:* in hypercalcaemia (associated with hyperparathyroidism/malignancy), alcoholism, antacids (aluminium containing – these are rarely used), nutritional recovery, post diabetic acidosis
Plasma Viscosity (PV)	1.50-1.72mPa/s	An alternative to ESR in many labs	*Increased:* Inflammation (infection, rheumatoid arthritis, malignancy, myocardial infarction), anaemia and macrocytosis

			Decreased: Polycythaemia, microcytosis, sickle-cell anaemia
Platelets (Plt)	150-400 x 10^9/L	Contribute to the formation of blood clots hence low platelets increases the risk of bleeding. 0-20 x10^9/L = severe & potentially life threatening and requires action (referral to haematology) Increased platelets are increasingly seen as a risk marker for cancer so important to think of this if noted on FBC.	*Increased (Thrombocytosis):* commonly seen up to 800x10^9/L – in blood loss, surgery, trauma, infection, inflammation, malignancy, myeloproliferative disorders, polycythaemia, thrombocythaemia *Decreased (Thrombocytopaenia)*: caused by Infection (often marked but transient), drugs: salicylates, sulphonamides, antibiotics (trimethoprim/penicillins/cephalosporins), furosemide, heparin, phenytoin & others, alcohol/liver disease, ITP, Leukaemia, Bone marrow infiltration (myeloma/malignancy), pregnancy and others
Potassium (K)	3.5-5.3IU/L	Is the most abundant cation (+vely charged ion) in the body and changes in this can affect cellular membrane excitability and impact on the function of nerves, muscles (cardiac muscle in particular).	*Increased:* Often raised due to haemolysis of sample. **NB** a level above 6 is important as potentially causes cardiac arrythmia/arrest – requires same day action to manage. Causes include: Renal failure, diabetic ketoacidosis, Addison's disease, mineralocorticoid deficiency (interstitial nephritis, amyloidosis, SLE, Diabetes, drugs: indomethacin/ibuprofen) *Decreased:* Drugs (diuretics, salbutamol, insulin, gentamicin), vomiting, diarrhoea, inadequate intake (alcoholism/anorexia)
Prostate specific antigen (PSA)	40–50 years < 2.6 µg/L 60 years < 3.6 µg/L 70 years < 4.6 µg/L	A screening test of prostate cancer	*Increases* in: prostate cancer, benign prostatic hypertrophy, urine infection, ejaculation, after rectal exam

	80 years < 6.6 µg/L		Should always assessed in context with symptoms and examination
Reticulocyte count	20–100x109/L	Immature blood cells used to identify conditions that affect red blood cells	*Increased* in chronic or acute blood loss (increased turn over), haemolytic anaemia, bone marrow infiltration and can be seen when treating iron/b12 or folate deficiency anaemia as a treatment response. *Decreased* in aplastic anaemia (autoimmune condition where body doesn't produce enough red cells).
Rheumatoid Factor (RhF)	Reported as +ve or -ve	RhF is an antibody present in autoimmune conditions	Present in normal population from 2-10% (rises with age) Also associated with autoimmune conditions primarily rheumatoid arthritis (80% of cases) but also; Sjogrens (90%), SLE (30%) and other Connective tissue disorders, infection and malignancy. **NB** Neither rules in or out rheumatoid arthritis
Sodium (Na)	135-145mmol/L	One of the essential minerals – effecting water distribution in the body and involved in nerve conduction. Originates in the diet and excreted via urine and sweat. Changes will often relate to diseases affecting the fluid/electrolyte balance in the body.	*Decreased* (Hyponatraemia) - needs to be assessed in the context of **plasma osmolality** (the measure of the balance between electrolytes (solutes) and water (solvent) this is either; • Raised osmolality – hyperglycaemia • Normal osmolality – hyperlipidaemia, hyperproteinaemia Decreased osmolality – hypovolaemia (diuretics, diarrhoea/vomiting, addisons

			disease) oedema – cirrhosis, cardiac failure, nephrotic syndrome or euvolaemia – increased water intake, drugs, hypothyroidism, renal insufficiency
Thyroid autoantibodies	Anti-TPO, anti-thyroglobulin antibodies & Thyroid Stimulating Antibody (aka TS antibody or TSH receptor antibody)		Anti-TPO & Anti-thyroglobulin antibodies present in; • Hashimoto's thyroiditis (their presence separates from non-toxic. Goitre) • Primary Hypothyroidism (seen in 90% of cases) • Autoimmune disease – these are found in presence of other autoimmune conditions such as diabetes and pernicious anaemia • Normal – (euthyroid) seen in 10% of population – may progress to thyroid disease Thyroid Stimulating Antibody Is seen in Grave's Disease (autoimmune thyrotoxicosis)
Thyroid Stimulating Hormone (TSH)	0.5-4.2mU/L	Main marker initially used to identify thyroid dysfunction	*Increased:* • Primary hypothyroidism, subclinical or clinical • Hashimoto's thyroiditis • Subacute thyroiditis, recovery phase • Ectopic TSH from tumours of e.g lung, breast • Drugs: lithium, metoclopramide, clomiphene,

			domperidone, amiodarone, contrast medium *Decreased:* • Hyperthyroidism – usually the TSH is < 0.03 in clinical thyrotoxicosis • Sub–clinical hyperthyroidism • Patients on excessive T4 or T3 therapy • Drugs: steroids, L–dopa, bromocriptine, heparin • Non–thyroidal illness.
Thyroxine (T_4)	70-140mmol/L	T^4 is effectively a 'pre-hormone' that gets converted into the active T^3 form in tissues	*Increased*: Hyperthyroidism, T^4 therapy, drugs: amiodorone, NSAIDs, steroids, iodine, heparin, Hashimoto's thyroiditis, subacute throiditis *Decreased:* Hypothyroidism, hypopituitarism, Hasimoto's thyroiditis, drugs: T^3, phenytoin, lithium, carbamazepine
Tri-iodothyronin (T_3)	1.2-3.0 nmol/L	T^3 is the active hormone 80% of which comes from T^3 and the rest is made directly in the thyroid gland	*Increased:* Hyperthyroidism, T^3 therapy, subacute thyroiditis, Hashimoto's Thyroiditis, *Decreased*: Hypothyroidism, T^4 therapy (although is generally normal), drugs (amiodorone, steroids, propranolol, lithium, iodine), hypopituitarism
Triglycerides (Fasting)	0.5-2.3mmol/L	One aspect of lipids with a significant link to morbidity – of note a triglyceride above 10.0mmol/L indicates a risk of acute pancreatitis and requires immediate treatment	*Increased:* Primary • Familial (either combined with other raised lipids or in isolation) Secondary

			• Obesity • Alcohol • Diabetes • Hypothyroidism • Liver disease • Nephrotic syndrome • Pancreatitis • Pregnancy • Drugs: Oestrogen, OCP, bblockers, steroids, thiazides
Urea (Ur)	2.5-6.7mmol/L	Another breakdown product of protein - used as a measure of renal function and is also made in the liver so affected by liver disease	*Increased:* • Renal impairment (but less reliable than creatinine) • High protein diet (can skew results) • Catabolic states such as acute illness – infection • Dehydration (increased reabsorption) • GI Bleeding (increased cell breakdown) • Prostatic Hypertrophy (outflow obstruction • Drugs – steroids, diuretics *Decreased:* • loss of albumin in dialysis • Liver disease • Malnutrition • In a normal pregnancy
Urate	*Men* 210-480 μmol/L	Used to identify Gout	*Increased:*

	Women 150-390μmol/L		• Gout • High purine diet (meat, shellfish) • Alcohol • Renal insufficiency • Drugs – diuretics, chemotherapy, salicylates • Metabolic syndrome • Pregnancy • Hypothyroidism Malignancies (leukaemia/lymphoma especially)
Vitamin B12	>170 pmol/L	Is a dietary vitamin (found in meat and animal proteins) relevant to manufacture of blood cells, it is absorbed from the diet via the gut requiring intrinsic factor (secretion of gastric. Mucosal (parietal) cells for transport across the gut wall.	*Increased:* • B12 Supplementation • Leukaemia, myeloproloferative disorders • Liver disease *Decreased:* • Vegetarian diet • Drugs: OCP, metformin, methotrexate, colchicine, anticonvulsants • Pregnancy • Pernicious anaemia • Malabsorption including past gastrectomy/ileectomy Folate deficiency
Vitamin D	<25nmol/L : Deficient 25-50 nmol/L: Insufficient >50 nmol/L : Sufficient	Regulates calcium and phosphate absorption – implicated in bone metabolic disorders (secondary hyperparathyroidism/rickets/osteomalacia) and as a potential cause for myalgia/fatigue	*Decreased:* Due to reduced intake of vitamin D • Lack of sunlight • Lack of dietary vitamin D • Fat malabsorption (Vit D is fat soluble) – e.g. coeliac disease

			Due to reduced liver production of 25 (OH) D3 • Deficiency of 1αhydroxylase (hereditary or in renal failure) • Drug effects – carbamazepine, phenytoin (increased degradation) • Nephrotic syndrome Due to reduced renal production of calcitriol • Deficiency of 1αhydroxylase • Suppression of 1αhydroxylase (PTH deficiency in hypoparathyroidism or end organ resistance seen in pseudohypoparathyroidism *Increased:* • Excessive intake – supplements or prescribed • Increased calcitriol production (hyperparathyroidism) Production by sarcoidosis, sarcomas & lymphomas

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Websites

- www.bjgp.org The British Journal of General Practice has access to full journal contents and quite a useful resource

- www.bcrt.org.uk the Bone Cancer Research Trust is a great wealth of information and leaflets with downloadable resources for patients and clinicians alike – well worth a look

- https://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf - for access to information on thyroid function tests use

- https://rheuminfo.com - a really great site on all things rheumatological

- www.paget.org.uk – useful resource and infographics around Paget's Disease

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