

Blood Test Interpretation

for Primary Care

2025 Edition

Prologue

Every day in primary care, you encounter blood test results that hold the key to your patient's diagnosis, treatment, and prognosis. Yet many clinicians feel overwhelmed by the sheer volume of laboratory data, uncertain about which patterns matter most, and worried about missing critical findings.

This textbook transforms that uncertainty into clinical confidence. Rather than simply listing normal ranges, we focus on the *why* behind interpretation – the clinical reasoning that turns numbers into actionable insights.

Each chapter follows a structured approach designed for busy primary care practice:

- **Pattern Recognition:** Learn to spot the combinations that matter most
- **Clinical Pearls:** Memorable insights that stick when you need them
- **Decision Trees:** Clear pathways from result to action
- **Red Flags:** Critical findings that demand immediate attention
- **Real Examples:** Actual cases that illustrate key concepts
- **Comprehensive References:** 70+ evidence-based citations from landmark trials, clinical guidelines, and authoritative textbooks supporting all interpretations and recommendations

This isn't just another reference book – it's a practical guide that reflects how experienced clinicians actually think about blood tests. By the end, you'll approach every result with the systematic confidence that comes from understanding not just what the numbers mean, but what to do about them.

The art of interpretation lies not in memorising ranges, but in recognising patterns, understanding relationships, and translating data into clinical action. This book teaches you that art.

Dr Michael Banovic MBBS MSc IM(Edin) MRCP

2025

Table of Contents

Prologue 3

Chapter 1: Full Blood Count (FBC) 5

Chapter 2: Iron Studies & B12/Folate 15

Chapter 3: Liver Function Tests 25

Chapter 4: Urea & Electrolytes 35

Chapter 5: Lipid Profile 45

Chapter 6: Thyroid Function Tests 55

Chapter 7: HbA1c & Diabetes Monitoring 65

Chapter 8: Inflammatory Markers 75

Chapter 9: Bone Profile 85

Chapter 10: Cardiac Markers 95

Chapter 11: Sex Hormone Profiles 105

References 115

Index 125

Chapter 1

Full Blood Count (FBC)

Reading the Full Blood Count

Mastering FBC Interpretation Skills in Primary Care

Introduction: The Art of Reading Numbers

Every FBC tells a story. The skill lies not in memorising normal ranges, but in recognising patterns, understanding relationships between parameters, and translating numerical data into clinical meaning. This chapter teaches you to read FBC results like a detective examining clues, where each parameter provides evidence about what's happening inside your patient's bone marrow and circulation.



Clinical Pearl

"Never Read in Isolation": A single abnormal value means little - it's the pattern of abnormalities that reveals the diagnosis. Hb 95 g/L with MCV 65 fl tells a completely different story than Hb 95 g/L with MCV 110 fl, even though both represent anaemia.

Essential FBC Normal Ranges (Adults)

Parameter	Male Range	Female Range	Units
Haemoglobin (Hb)	130-175	120-155	g/L
Mean Cell Volume (MCV)	82-100	82-100	fl
White Cell Count (WCC)	4.0-11.0	4.0-11.0	$\times 10^9/\text{L}$
Platelets	150-450	150-450	$\times 10^9/\text{L}$
Red Cell Distribution Width (RDW)	11.5-15.0	11.5-15.0	%

Step 1: The Systematic Approach to Reading FBC

First Glance: The Overview

Scan quickly - are all three cell lines (red, white, platelets) normal, or are one, two, or all three abnormal? This immediate pattern recognition guides your entire approach.

Red Cell Analysis: Size Matters

If Hb is low, immediately look at MCV. <80 fl = microcytic (think iron deficiency), >100 fl = macrocytic (think B12/folate), $80-100$ fl = normocytic (think chronic disease or bleeding).

White Cell Differential: The Detail Story

Don't just look at total WCC - examine the differential. High neutrophils suggest infection, high lymphocytes may indicate viral infection or lymphoproliferative disorder.

Additional Clues: RDW and Blood Film

High RDW indicates variation in cell sizes - valuable in mixed deficiencies. Always request blood film comments when results don't fit the clinical picture.



Clinical Pearl

"The MCV is Your Best Friend": In anaemia, MCV classification is 90% of your diagnosis. Microcytic = iron deficiency until proven otherwise. Macrocytic = B12/folate deficiency until proven otherwise. This simple rule will guide you correctly in the vast majority of cases.

Step 2: Decoding Anaemia Patterns

Microcytic Anaemia (MCV <80 fl)

Classic Pattern: Hb ↓, MCV ↓, RDW ↑

Think: Iron deficiency (95% of cases)

Next Steps: Check ferritin, consider thalassaemia trait if ferritin normal

Red Flag: In men >50 or post-menopausal women, always investigate source of blood loss

Macrocytic Anaemia (MCV >100 fl)

Classic Pattern: Hb ↓, MCV ↑, often with neutrophil hypersegmentation

Think: B12 or folate deficiency

Next Steps: Check B12 and folate levels

Red Flag: Neurological symptoms suggest B12 deficiency requiring urgent treatment

Normocytic Anaemia (MCV 80-100 fl)

Classic Pattern: Hb ↓, MCV normal, variable RDW

Think: Chronic disease, acute blood loss, or mixed deficiency

Next Steps: Check inflammatory markers, haematinics

Red Flag: Sudden onset suggests acute bleeding



Clinical Pearl

"The RDW Reveals Mixed Stories": Normal MCV with raised RDW (>15%) suggests mixed deficiency - some cells are small (iron deficient) and some large (B12/folate deficient), averaging out to normal. Always check all haematinics when RDW is elevated.

Reading Real Examples

Example 1: Classic Iron Deficiency

Hb 85 g/L, MCV 68 fl, RDW 18%

Interpretation: Severe microcytic anaemia with high variation - classic iron deficiency pattern

Example 2: B12 Deficiency

Hb 95 g/L, MCV 115 fl, RDW 16%

Interpretation: Macrocytic anaemia - check B12/folate urgently, especially if neurological symptoms

Example 3: Mixed Deficiency

Hb 90 g/L, MCV 88 fl, RDW 20%

Interpretation: Normal MCV but very high RDW suggests both iron and B12/folate deficiency

Step 3: White Cell Interpretation Skills

Reading the White Cell Count

Total WCC alone tells you little - you must examine the differential count to understand what's happening:

- **Neutrophilia (>7.5):** Bacterial infection, inflammation, stress response
- **Lymphocytosis (>4.0):** Viral infection, or in elderly patients, consider CLL
- **Eosinophilia (>0.4):** Allergy, parasites, drug reactions
- **Neutropenia (<2.0):** Viral infections, drug-induced, or haematological disorders

Pattern Recognition in WCC

Look for these telling combinations:

- **High WCC + High neutrophils:** Bacterial infection
- **High WCC + High lymphocytes:** Viral infection or CLL in elderly
- **Low WCC + Low neutrophils:** Viral infection or drug effect
- **Very high WCC (>30):** Consider leukaemia, request urgent blood film



Clinical Pearl

"Age Changes Everything with Lymphocytosis": Lymphocytosis >5.0 in a patient over 60 is chronic lymphocytic leukaemia until proven otherwise. In younger patients, think viral infection. Same number, completely different meaning based on age.



WCC >50 × 10⁹/L

Possible leukaemia - urgent blood film and haematology referral



WCC <1.0 × 10⁹/L

Severe neutropenia - infection risk, urgent assessment needed



Blast Cells Reported

Any blast cells on film require immediate haematology discussion



Lymphocytosis + Anaemia + Thrombocytopenia

Pancytopenia pattern suggests haematological malignancy

Step 4: Platelet Count Clinical Significance

Normal Platelets (150-450)

No bleeding risk, normal clotting function. Values at lower end of normal (150-200) still provide adequate haemostasis for most procedures.

Mild Thrombocytopenia (100-150)

Usually no clinical significance. May see prolonged bleeding after trauma or surgery. Most commonly due to viral infections or medications.

Moderate Thrombocytopenia (50-100)

Increased bleeding risk with surgery/procedures. Investigate underlying cause. May need platelet transfusion for major procedures.

Severe Thrombocytopenia (<50)

Spontaneous bleeding risk. Urgent haematology referral required. Patient needs immediate assessment and monitoring.



Clinical Pearl

"Thrombocytosis as a Cancer Clue": Platelets >600 in patients over 60 can be the first sign of underlying malignancy, particularly colorectal or lung cancer. Don't dismiss high platelets as "reactive" - investigate for occult malignancy, especially if persistent.

When Platelet Count Drives Clinical Decisions

- **<50:** Hold anticoagulants, urgent haematology referral
- **50-100:** Caution with procedures, investigate cause
- **>600:** Consider underlying malignancy in older patients
- **>1000:** Paradoxical bleeding risk due to platelet dysfunction

Step 5: Putting It All Together - Pattern Recognition

Classic FBC Patterns and Their Meanings

Iron Deficiency Pattern

Hb: Low
MCV: Low (<80)
RDW: High (>15%)
Platelets: Often elevated
Next step: Check ferritin

B12/Folate Deficiency

Hb: Low
MCV: High (>100)
RDW: High

WCC: May be low
Next step: Check B12 and folate

Chronic Disease Anaemia

Hb: Mildly low
MCV: Normal or slightly low
RDW: Normal
Pattern: Everything slightly off
Next step: Investigate underlying condition

Haematological Malignancy

Pattern: Multiple abnormalities
Hb: Low
WCC: Very high or very low
Platelets: Low
Next step: Urgent blood film and referral



Clinical Pearl

"The Three Cell Line Rule": If all three cell lines (red cells, white cells, platelets) are abnormal, think bone marrow pathology. This is never a coincidence and always requires urgent investigation. Single cell line problems are usually nutritional or reactive.

Quick Decision Tree for Anaemia

Patient has anaemia (Hb below normal)

Check MCV immediately

This determines 90% of your diagnostic approach

MCV <80: Check ferritin → Treat iron deficiency → Investigate source if unexplained

MCV >100: Check B12/folate → Treat deficiency → Investigate malabsorption

MCV 80-100: Check RDW → If high, check all haematinics → If normal, investigate chronic disease

Step 6: Red Flags That Demand Immediate Action

Results That Require Same-Day Action

- **Hb <70 g/L with symptoms:** Consider immediate transfusion needs
- **WCC >50 or <1.0:** Phone result to patient immediately, urgent referral
- **Platelets <50:** Bleeding precautions, urgent haematology referral
- **Blast cells on film:** Same-day haematology discussion
- **Pancytopenia:** All three cell lines low - urgent bone marrow investigation needed
- **Any combination of severe abnormalities:** Never normal - always investigate urgently



Clinical Pearl

"Trust Your Clinical Instinct": If the FBC result doesn't fit with your clinical assessment of the patient, always request a blood film and consider discussing with haematology. Laboratory errors are rare, but atypical presentations of serious conditions are not.

Summary: Mastering FBC Interpretation

The Five-Step FBC Reading Method

1. **Overview Scan:** Normal, one abnormal, or multiple abnormalities?
2. **MCV Classification:** If anaemic, let MCV guide your thinking
3. **Pattern Recognition:** Look for classic combinations
4. **Clinical Correlation:** Does the result fit the patient?
5. **Action Planning:** Investigation, treatment, or referral needed?

Master These Patterns

Iron deficiency: Low Hb + Low MCV + High RDW

B12/Folate: Low Hb + High MCV + High RDW

Chronic disease: Mild ↓ Hb + Normal MCV

Remember These Rules

MCV is your best diagnostic friend

RDW reveals mixed deficiencies

Multiple abnormalities = bone marrow problem

Never Miss These

Blast cells = urgent haematology

Pancytopenia = bone marrow failure

Extreme values = immediate action



Clinical Pearl

"Practice Makes Pattern Recognition Perfect": The more FBCs you interpret systematically, the faster you'll recognise patterns. Start with MCV in anaemia, examine all three cell lines for abnormalities, and always correlate with clinical picture. These skills will serve you throughout your clinical career.

Key Resources for FBC Interpretation

NICE Clinical Knowledge Summaries

Anaemia - Iron Deficiency

- 2024

[Access Guidelines](#)

NICE Guideline NG12

Suspected cancer: recognition and referral

- 2024

[Access Guidelines](#)

Chapter 2

Iron Studies & B12/Folate

Interpreting Iron Studies, B12 and Folate

A Systematic Approach to Diagnosing and Managing Common Deficiencies

Introduction: The Deficiency Detective Work

Iron deficiency, B12 deficiency, and folate deficiency are among the most common and treatable causes of anaemia worldwide. Yet diagnosis can be complex, with overlapping presentations and confounding factors. Modern testing allows precise diagnosis, but requires systematic interpretation. Understanding when to test, how to interpret complex patterns, and crucially how to investigate underlying causes will transform your management of these common conditions.



Clinical Pearl

"Ferritin is Your Friend, But Not Always Honest": Ferritin <15 µg/L always means iron deficiency. Ferritin >100 µg/L usually excludes iron deficiency. But ferritin 15-100 µg/L in the presence of inflammation can still represent iron deficiency. This is when you need the full iron studies panel.

Essential Iron Studies, B12 and Folate Reference Ranges

Test	Reference Range	Deficiency Threshold	Clinical Notes
Ferritin	15-300 µg/L (men) 15-200 µg/L (women)	<15 µg/L confirms deficiency	Acute phase protein - rises with inflammation
Transferrin Saturation	20-50%	<20% suggests deficiency	Most reliable in inflammation
Serum Iron	11-30 µmol/L	<11 µmol/L low	Diurnal variation - morning samples preferred
TIBC (Total Iron Binding Capacity)	45-75 µmol/L	>75 µmol/L suggests deficiency	Rises when iron stores are depleted
Vitamin B12	180-1000 ng/L	<180 ng/L deficient	May be normal in early/functional deficiency
Folate (Serum)	4-20 µg/L	<4 µg/L deficient	Reflects recent dietary intake
Folate (Red Cell)	160-640 µg/L	<160 µg/L deficient	Better reflects tissue stores

Step 1: Iron Studies - Systematic Interpretation

Start with Ferritin - The Foundation Test

Ferritin <15 µg/L definitively confirms iron deficiency. Ferritin >100 µg/L makes iron deficiency very unlikely. Ferritin 15-100 µg/L requires additional tests to clarify, especially if inflammation is present.

Add Transferrin Saturation for Clarity

TSAT <20% strongly suggests iron deficiency even with normal ferritin in inflammatory states. TSAT >50% may indicate iron overload. Most reliable single test in chronic disease.

Consider Inflammatory Markers

Raised CRP/ESR can elevate ferritin, masking iron deficiency. In inflammation, use lower ferritin thresholds (<45-100 µg/L) combined with TSAT <20% for diagnosis.

Integrate with FBC Pattern

Microcytic anaemia (MCV <80 fL) with iron deficiency confirms iron deficiency anaemia. Normal MCV doesn't exclude early iron deficiency - iron stores deplete before red cell changes occur.



Clinical Pearl

"The AGA 45 Rule": American Gastroenterological Association recommends ferritin <45 µg/L as the diagnostic threshold for iron deficiency in anaemia (85% sensitivity, 92% specificity). This higher threshold prevents missing iron deficiency in inflammatory conditions.

Iron Deficiency Pattern

Classic: ↓ Ferritin (<15), ↓ TSAT (<20%), ↓ Serum Iron, ↑ TIBC
With Inflammation: Ferritin 15-100, ↓ TSAT (<20%), ↓ Serum Iron
Early Stage: ↓ Ferritin, Normal Hb/MCV initially
Action: Investigate cause, start iron replacement

Anaemia of Chronic Disease

Classic: Normal/↑ Ferritin (>100), Normal/↓ TSAT (15-25%), ↓ Serum Iron, Normal TIBC
Clinical Context: Underlying inflammatory condition known
Challenge: Can coexist with true iron deficiency
Strategy: Consider therapeutic trial of iron if TSAT <20%

Iron Overload Pattern

Classic: ↑ Ferritin (>300), ↑ TSAT (>50%), ↑ Serum Iron, Normal/↓ TIBC
Causes: Hereditary haemochromatosis, repeated transfusions
Action: Check HFE gene mutations, assess for organ damage
Urgency: Early detection prevents irreversible complications

Mixed Pattern (Iron Deficiency + Chronic Disease)

Complex: Ferritin 45-100, TSAT <20%, ↓ Serum Iron
Context: Chronic disease with ongoing iron loss
Example: IBD, chronic kidney disease, heart failure
Management: Treat iron deficiency AND underlying condition

Step 2: B12 Deficiency - Beyond the Guidelines (NICE NG239 2024)

▲ Neurological B12 Deficiency

Subacute combined degeneration, peripheral neuropathy, cognitive impairment - treat urgently even with normal B12 levels

▲ B12 <150 ng/L with Symptoms

Severe deficiency requiring immediate treatment with 1000 µg alternate days until improvement

▲ Pancytopenia + Macrocytosis

Severe B12/folate deficiency can mimic leukaemia - urgent haematology discussion

▲ Normal B12 + Strong Clinical Suspicion

Functional B12 deficiency possible - check MMA, homocysteine, or therapeutic trial

NICE NG239 2024 Key Updates

Terminology Change:

- NICE now uses "autoimmune gastritis" instead of "pernicious anaemia"
- True pernicious anaemia (life-threatening) now rare due to earlier detection
- Focus shifted to underlying gastric pathology

Diagnostic Approach:

- Don't rule out deficiency based on normal Hb or MCV alone
- B12 deficiency can present with neuropsychiatric symptoms only
- Consider functional deficiency if strong clinical suspicion

Testing Strategy:

- Check anti-intrinsic factor antibodies if B12 low
- Consider MMA/homocysteine if B12 borderline
- Test for autoimmune gastritis markers

Treatment Protocols (NICE NG239)

With Neurological Symptoms:

- Hydroxocobalamin 1000 µg IM alternate days
- Continue until no further improvement
- Then 1000 µg every 2 months lifelong

Without Neurological Symptoms:

- Hydroxocobalamin 1000 µg IM 3x weekly for 2 weeks
- Then 1000 µg every 2-3 months lifelong

Autoimmune Gastritis (Pernicious Anaemia):

- Lifelong treatment required
- Annual gastric cancer surveillance recommended
- Monitor for other autoimmune conditions



Clinical Pearl

"Treat the Patient, Not the Number": NICE NG239 emphasizes that B12 deficiency can present without anaemia or macrocytosis. Neurological and psychiatric symptoms may occur with normal or borderline B12 levels. If clinical suspicion is high, consider therapeutic trial even with normal B12.

B12 Deficiency - Causes and Clinical Presentation

Autoimmune Gastritis (90% of cases)

Intrinsic factor deficiency, anti-parietal cell antibodies positive, lifelong B12 deficiency requiring regular

injections.

Malabsorption Syndromes

Crohn's disease, coeliac disease, bacterial overgrowth, post-gastrectomy. May respond to oral high-dose treatment.

Dietary Deficiency

Vegans, strict vegetarians. Usually responds well to oral supplementation if absorption intact.

Drug-Induced

Metformin, PPIs, H2-receptor antagonists, colchicine. May be reversible with cessation or dose reduction.

Step 3: Folate Deficiency - The Forgotten Partner

Always Check B12 Before Treating Folate

Critical safety rule: treating folate deficiency alone when B12 is also deficient can precipitate or worsen neurological complications. Always check both, treat B12 first or simultaneously.

Distinguish Serum vs Red Cell Folate

Serum folate reflects recent intake (days-weeks), red cell folate reflects tissue stores (months). Use red cell folate for definitive diagnosis, especially if dietary intake variable.

Consider Underlying Causes

Folate deficiency is usually dietary, but consider malabsorption, increased demand (pregnancy, haemolysis), drugs (methotrexate, trimethoprim), or alcohol excess.

Monitor Treatment Response

Reticulocyte response occurs within days, Hb rises over weeks. Failure to respond suggests mixed deficiency, ongoing loss, or alternative diagnosis requiring investigation.

Pure Folate Deficiency

Pattern: ↓ Folate, Normal B12, Macrocytic anaemia

Causes: Poor diet, malabsorption, increased demand

Treatment: Folic acid 5mg daily for 4 months

Response: Rapid reticulocyte rise, Hb normalizes in 4-6 weeks

Combined B12 and Folate Deficiency

Pattern: ↓ Both B12 and Folate, Severe macrocytic anaemia

Risk: Common in malnutrition, alcoholism, malabsorption

Treatment: B12 injections AND folic acid

Caution: Never treat folate alone - can worsen B12 neuropathy

Drug-Induced Folate Deficiency

Common Drugs: Methotrexate, sulfasalazine, trimethoprim

Mechanism: Folate metabolism interference

Prevention: Co-prescribe folic acid with methotrexate

Management: Higher doses may be needed (5-10mg)

Pregnancy-Related Folate Needs

Increased Demand: 4-fold increase in folate requirements

Prevention: 400 µg daily pre-conception and first trimester

High Risk: 5mg daily for previous neural tube defects

Screening: Consider in all pregnant women with anaemia



Clinical Pearl

"The Folate-B12 Safety Dance": Never prescribe folic acid without checking B12 status first. Folate can correct the anaemia of B12 deficiency while allowing neurological damage to progress. This is a potentially irreversible and litigious error - always check both vitamins together.

Folate Deficiency - Special Populations

- **Alcoholics:** Poor diet + malabsorption + increased losses - high-dose treatment often needed
- **Pregnancy:** Increased demands - all women need 400 µg daily, high-risk need 5mg
- **Haemolysis:** Increased red cell turnover increases folate consumption
- **Malabsorption:** Coeliac, Crohn's - may need higher doses and longer treatment
- **Elderly:** Often combined with B12 deficiency due to poor diet and gastric atrophy

Step 4: Investigation of Underlying Causes

Iron Deficiency - Source Investigation

Men and Post-Menopausal Women:

- Assume GI blood loss until proven otherwise
- Upper and lower GI endoscopy if >40 years
- Urgent 2-week cancer pathway if >60 years
- Consider coeliac disease, H. pylori

Pre-Menopausal Women:

- Menstrual history - quantify losses
- Consider gynaecological causes if heavy periods
- Still investigate GI if refractory to iron
- Consider dietary assessment

Special Considerations:

- NSAIDs, anticoagulants increase bleeding risk
- Family history of GI cancers
- Associated symptoms (weight loss, change in bowel habit)

B12 Deficiency - Cause Identification

Autoimmune Gastritis Testing:

- Anti-intrinsic factor antibodies (specific but only 50% sensitive)
- Anti-gastric parietal cell antibodies (sensitive but less specific)
- Consider gastroscopy + biopsy if high suspicion

Malabsorption Assessment:

- History of GI surgery, especially gastric
- Symptoms of IBD, coeliac disease
- Bacterial overgrowth - consider breath test
- Medication history (PPIs, metformin)

Dietary Assessment:

- Vegan/vegetarian diet
- Alcohol intake assessment
- Socioeconomic factors affecting diet



Clinical Pearl

"Age and Gender Drive Investigation": Iron deficiency in men >50 or post-menopausal women = GI malignancy until proven otherwise. Iron deficiency in pre-menopausal women is usually menstrual, but if it doesn't respond to iron therapy, investigate further. Don't assume all iron deficiency in young women is "normal".

Iron Deficiency Investigation Pathway

Iron deficiency confirmed

Assess risk factors and demographics

Age, gender, menstrual history, symptoms

Men >40 or post-menopausal women: 2-week cancer pathway, upper and lower GI endoscopy

Pre-menopausal women with heavy periods: Treat iron deficiency, gynae assessment if severe

All ages with alarm symptoms: Urgent investigation regardless of demographics

Step 5: Treatment Strategies and Monitoring

Iron Replacement Options and Considerations

Oral Iron Therapy (First-Line)

Options: Ferrous sulfate 200mg BD/TDS, ferrous fumarate 210mg BD

Absorption: Take on empty stomach, avoid with PPIs, tea, coffee

Side Effects: GI upset in 20-30%, constipation common

Duration: Continue 3 months after Hb normalizes to replenish stores

Modified-Release Preparations

Benefits: Reduced GI side effects, better tolerance

Disadvantages: Lower bioavailability, higher cost

Consider for: Patients intolerant of standard preparations

Examples: Ferrograd, Slow-Fe

Intravenous Iron Therapy

Indications: Malabsorption, intolerance, severe deficiency, ongoing losses

Advantages: Rapid replenishment, bypasses absorption issues

Risks: Anaphylaxis (rare), iron overload, cost

Options: Iron carboxymaltose, iron isomaltoside

Treatment Monitoring

Response Check: FBC at 2 weeks (reticulocytes rise first)

Hb Rise: Expect 1 g/dL per week initially

Store Replenishment: Continue 3 months after normalization

No Response: Consider compliance, ongoing loss, wrong diagnosis

B12 and Folate Treatment Protocols

- **B12 with neurological symptoms:** 1000 µg IM alternate days until improvement stops, then 2-monthly
- **B12 without neurological symptoms:** 1000 µg IM 3x weekly for 2 weeks, then 2-3 monthly
- **Folate deficiency:** Folic acid 5mg daily for 4 months (check B12 first!)
- **Prevention in high-risk:** Folic acid 400 µg daily (pregnancy), 5mg weekly (methotrexate)
- **Monitoring:** Clinical response more important than repeat levels



Clinical Pearl

"The 3-Month Rule": Continue iron therapy for 3 months after Hb normalizes to replenish iron stores. Many patients stop treatment once they feel better, leading to recurrence. Ferritin should rise to >100 µg/L before stopping treatment. This store replenishment phase is crucial for preventing early relapse.

Step 6: Red Flags and Specialist Referral

Immediate Specialist Referral Required

- **Iron deficiency in men >60 or post-menopausal women:** 2-week cancer pathway
- **B12 deficiency with neurological symptoms:** Urgent haematology/neurology referral
- **Pancytopenia with macrocytosis:** Urgent haematology - ?leukaemia/myelodysplasia
- **Iron deficiency not responding to treatment:** Consider malabsorption, ongoing loss
- **Very high ferritin (>1000 µg/L) with high TSAT:** ?Haemochromatosis/iron overload
- **B12 deficiency in young adults:** Investigate underlying cause

Treatment Failure - When to Investigate Further

- **Iron deficiency:** No Hb rise after 3 weeks of treatment
- **Possible causes:** Poor compliance, malabsorption, ongoing losses, wrong diagnosis
- **B12/Folate:** No reticulocyte response after 1 week
- **Consider:** Mixed deficiency, myelodysplasia, hypothyroidism
- **Action:** Review diagnosis, check compliance, consider IV iron or alternative diagnosis



Clinical Pearl

"When Simple Doesn't Work, Think Complex": Treatment failure in deficiency anaemias usually means: 1) Wrong diagnosis, 2) Mixed deficiencies, 3) Ongoing losses, or 4) Malabsorption. Don't keep increasing doses of the same treatment - step back and reassess the whole clinical picture.

Summary: Mastering Deficiency Anaemia Diagnosis

The Six-Step Deficiency Analysis Method

1. **Pattern Recognition:** MCV guides initial thinking - microcytic vs macrocytic
2. **Systematic Testing:** Iron studies panel, B12 and folate together
3. **Context Integration:** Age, gender, symptoms, comorbidities
4. **Cause Investigation:** Why is the patient deficient?
5. **Appropriate Treatment:** Right dose, right route, right duration
6. **Response Monitoring:** Track response, identify failure early

Master These Patterns

Iron deficiency: Ferritin <15 or TSAT <20%

B12 deficiency: Can present without anaemia

Folate deficiency: Always check B12 first

Remember These Rules

Investigate iron deficiency cause

NICE NG239 updated B12 guidelines

Never treat folate alone

Never Miss These

Cancer risk in iron deficiency >60 years

B12 neuropathy can be irreversible

Treatment failure needs investigation

Key Risk Factors for Deficiency States

Iron Deficiency Risk

Heavy menstrual periods GI blood loss Poor dietary iron Malabsorption NSAIDs/anticoagulants

B12 Deficiency Risk

Autoimmune gastritis Vegan diet GI surgery PPI use Metformin therapy

Folate Deficiency Risk

Poor diet/alcohol Pregnancy/increased demand Malabsorption Drug interactions Haemolytic anaemia



Clinical Pearl

"Deficiency Anaemias are Preventable and Curable": These are among the most rewarding conditions to diagnose and treat in primary care. Accurate diagnosis prevents dangerous investigations, appropriate treatment transforms patients' quality of life, and identifying underlying causes can be life-saving. Master these tests and transform your anaemia management.



Clinical Guidelines & Evidence Base

NICE Guideline NG239

Vitamin B12 deficiency in over 16s: diagnosis and management

- March 2024

[Access Guidelines](#)

NICE Clinical Knowledge Summaries

Anaemia - Iron Deficiency

- Updated 2024

[Access Guidelines](#)

British Society of Gastroenterology

Guidelines for the management of iron deficiency anaemia in adults

- 2021

[Access Guidelines](#)

British Society for Haematology

Guidelines for the diagnosis and treatment of cobalamin and folate disorders

- 2014

[Access Guidelines](#)

NICE Clinical Knowledge Summaries

Anaemia - B12 and folate deficiency

- Updated March 2024

[Access Guidelines](#)

Chapter 3

Liver Function Tests

Decoding Liver Function Tests

From Patterns to Pathology - Mastering Hepatic Detective Work

Introduction: The Liver's Chemical Fingerprint

Liver function tests aren't really tests of liver function—they're tests of liver damage. Every elevated enzyme tells a story of cellular injury, every pattern points to a specific type of problem, and every result demands you ask: "Is this liver crying for help, or just clearing its throat?" The liver is remarkably resilient, silently compensating until 80% of function is lost, making these biochemical clues often your first and best window into hepatic health.

This chapter transforms you from someone who simply flags abnormal results into a hepatic detective who can distinguish hepatocellular from cholestatic injury, spot the early warning signs of serious liver disease, and know when to watch, when to investigate, and when to refer urgently. You'll learn to read the patterns that matter and avoid the pitfalls that mislead.



Clinical Pearl

"The Pattern is the Pathway": Never interpret liver tests in isolation. ALT 150 with ALP 80 suggests hepatocellular injury (think hepatitis, toxins, fatty liver), while ALT 80 with ALP 300 suggests cholestasis (think stones, strictures, tumors). The pattern tells you where to look, not just that something's wrong.

Liver Function Test Normal Ranges and Clinical Significance

Test	Normal Range	Units	Primary Indication	Key Clinical Notes
ALT (Alanine Transaminase)	19-25 (F), 29-33 (M)	IU/L	Hepatocellular injury	More liver-specific than AST
AST (Aspartate Transaminase)	0-35	IU/L	Hepatocellular injury	Also in muscle, heart
ALP (Alkaline Phosphatase)	30-120	IU/L	Cholestasis, bone disease	Also in bone, placenta
GGT (Gamma-GT)	0-30	IU/L	Cholestasis, alcohol	Most sensitive to biliary obstruction
Bilirubin (Total)	2-17	μmol/L	Liver function, hemolysis	Conjugated vs unconjugated matters
Albumin	35-50	g/L	Synthetic function	Long half-life (3 weeks)
Prothrombin Time	11-15	seconds	Synthetic function	Short half-life, acute changes

Priority Assessment: When Liver Tests Signal Emergency

Most abnormal liver tests reflect chronic, slowly evolving conditions. However, certain patterns demand immediate attention—either because they indicate acute hepatic failure or because they signal conditions where rapid intervention can be life-saving.

▲ **ALT/AST >1000 IU/L**

Acute hepatocellular injury—urgent hospital assessment needed, check paracetamol levels, viral hepatitis screen, consider acute hepatitis

▲ **Prolonged PT + Low Albumin + Jaundice**

Acute liver failure pattern—emergency hepatology referral, monitor for encephalopathy, assess for liver transplant criteria

▲ **High Bilirubin + High ALP + Pain**

Possible biliary obstruction—urgent imaging needed, consider cholangitis if fever, emergency surgical opinion may be required

▲ **New Abnormal LFTs + Confusion**

Hepatic encephalopathy possible—urgent assessment for ammonia levels, exclude infection, consider lactulose therapy



Clinical Pearl

"The Paracetamol Rule": Any ALT >150 IU/L in the context of possible overdose (intentional or accidental) requires immediate paracetamol level measurement and urgent hepatology consultation. Paracetamol hepatotoxicity can be completely reversible with N-acetylcysteine if caught early, but becomes irreversible liver failure if missed.

Step 1: The R-Ratio Method - Pattern Recognition Made Simple

The R-ratio revolutionizes liver test interpretation by converting complex patterns into simple mathematical clarity. This evidence-based approach, endorsed by hepatology guidelines worldwide, tells you immediately whether you're dealing with hepatocellular injury, cholestasis, or mixed disease.

Calculate the R-Ratio

$R = (ALT \div ALT \text{ upper limit}) \div (ALP \div ALP \text{ upper limit})$. This ratio normalizes both enzymes to their reference ranges, allowing direct comparison regardless of absolute values.

Interpret the Pattern

$R > 5$ = Hepatocellular injury. $R < 2$ = Cholestatic injury. $R 2-5$ = Mixed injury. Each pattern points to different causes and investigation pathways.

Apply Clinical Context

Combine R-ratio with clinical history, examination findings, and additional biochemistry. The pattern guides but doesn't replace clinical judgment.

Plan Investigation Strategy

Hepatocellular patterns need hepatitis screening, toxin history. Cholestatic patterns need imaging. Mixed patterns often need both approaches.

R-Ratio Decision Framework

Abnormal ALT and/or ALP detected

Calculate R-ratio: $(ALT \div ALT \text{ ULN}) \div (ALP \div ALP \text{ ULN})$

$R > 5$ (Hepatocellular): Check viral hepatitis, paracetamol, alcohol history, fatty liver markers

$R < 2$ (Cholestatic): Abdominal ultrasound, check GGT, consider MRCP if ultrasound normal

$R 2-5$ (Mixed): Investigate both hepatocellular and cholestatic causes simultaneously



Clinical Pearl

"The GGT Amplifier": GGT is your cholestatic pattern amplifier. If ALP is elevated but you're unsure if it's liver or bone origin, an elevated GGT confirms hepatic source. GGT $> 3\times$ upper limit with elevated ALP virtually guarantees biliary pathology. But remember—GGT is also the most sensitive marker of alcohol excess.

Step 2: Hepatocellular Injury Pattern - When Cells Cry Out

Acute Hepatocellular Injury

Pattern: ALT/AST >400 IU/L, R-ratio >5

Think: Viral hepatitis, paracetamol, drug-induced

Urgency: High if >1000 IU/L

Next steps: Hepatitis screen, paracetamol level, drug history

Chronic Hepatocellular Injury

Pattern: ALT/AST 50-400 IU/L, persistent elevation

Think: NAFLD, chronic hepatitis, alcohol

Urgency: Moderate, needs investigation

Next steps: Metabolic screen, liver ultrasound, alcohol history

AST:ALT Ratio >2

Pattern: AST significantly higher than ALT

Think: Alcohol-related liver disease

Context: Usually with elevated GGT

Action: Explore alcohol history sensitively, consider intervention

Mild ALT Elevation

Pattern: ALT 40-80 IU/L, often fluctuating

Think: NAFLD, metabolic syndrome, medications

Approach: Address lifestyle factors first

Follow-up: Repeat in 3-6 months, monitor trends

Viral Hepatitis Pattern

ALT: Often >500 IU/L

AST: Similar to ALT

Bilirubin: Variable elevation

Key: Check Hep A, B, C, EBV, CMV

Drug-Induced Pattern

ALT: Variable, can be massive

Timing: Days to weeks after drug start

Common drugs: Paracetamol, antibiotics, statins

Action: Stop suspected drug, monitor recovery

NAFLD Pattern

ALT: 40-150 IU/L typically

Associated: Obesity, diabetes, dyslipidemia

Ratio: AST:ALT usually <1

Investigation: Metabolic assessment, liver ultrasound

Autoimmune Pattern

ALT: Variable, often with other abnormalities

Clues: Young woman, other autoimmune disease

Tests: ANA, ASMA, anti-LKM antibodies

Urgency: Needs hepatology referral



Clinical Pearl

"The Magnitude Message": ALT >1000 IU/L narrows your differential dramatically. Think paracetamol poisoning, acute viral hepatitis, ischaemic hepatitis, or drug-induced hepatitis. ALT >3000 IU/L is almost always paracetamol—check levels immediately even if patient denies ingestion. Chronic conditions rarely cause such massive elevation.

Step 3: Cholestatic Injury Pattern - When Bile Can't Flow

Understanding Cholestasis

Cholestasis means impaired bile flow, either from liver cell dysfunction (intrahepatic) or bile duct obstruction (extrahepatic). The key is determining the level of obstruction and the urgency of intervention required.

- **ALP elevation:** Indicates cholestasis but can be from bone
- **GGT confirmation:** Elevated GGT confirms hepatic source
- **Bilirubin pattern:** Conjugated elevation in cholestasis
- **Clinical context:** Pain, jaundice, pruritus are key symptoms

Cholestatic Investigation Strategy

Your approach depends on severity and clinical presentation:

- **First-line:** Abdominal ultrasound to detect bile duct dilatation
- **If normal USS:** Consider MRCP for detailed biliary imaging
- **If severe:** ERCP may be needed for intervention
- **Always consider:** Medications, primary biliary cholangitis, PSC

Bile Duct Obstruction

Pattern: ALP >300, GGT >200, dilated ducts on imaging

Causes: Gallstones, strictures, pancreatic cancer

Symptoms: Jaundice, pale stools, dark urine, pain

Action: Urgent imaging, consider ERCP, surgical opinion

Primary Biliary Cholangitis

Pattern: ALP >2x normal, positive AMA antibodies

Demographics: Middle-aged women predominantly

Symptoms: Fatigue, pruritus, may be asymptomatic

Action: AMA testing, hepatology referral, UDCA treatment

Primary Sclerosing Cholangitis

Pattern: ALP >3x normal, young men often

Association: Inflammatory bowel disease (70% have IBD)

Imaging: MRCP shows biliary strictures and dilatations

Action: IBD screen, MRCP, hepatology referral

Drug-Induced Cholestasis

Pattern: ALP elevation, recent drug history

Common drugs: Antibiotics, phenytoin, anabolic steroids

Timing: Weeks to months after drug initiation

Action: Stop suspected drug, monitor for improvement

Cholestatic Investigation Flowchart

Confirm Cholestatic Pattern

ALP >1.5x ULN + GGT >1.5x ULN = definite cholestasis. If GGT normal, consider bone source for ALP elevation.

Assess Severity and Symptoms

Jaundice + pain + fever = possible cholangitis (emergency). Gradual onset + pruritus = chronic cholestatic disease.

First-Line Imaging

Abdominal ultrasound to assess bile duct caliber, gallstones, liver texture. Quick, non-invasive, good first step.

Targeted Further Investigation

Dilated ducts → MRCP/ERCP. Normal ducts → Consider PBC (AMA), PSC (MRCP), drug history.



Clinical Pearl

"Charcot's Triad Plus": Jaundice + right upper quadrant pain + fever = cholangitis until proven otherwise. Add hypotension and confusion (Reynolds' pentad) and you have a surgical emergency. Don't wait for all five signs—two out of three warrants urgent investigation and empirical antibiotics.

Step 4: Liver Synthetic Function - The True Test

While enzymes tell you about liver damage, synthetic function tests reveal how much liver function remains. These tests—albumin, prothrombin time, and bilirubin—are your window into the liver's ability to perform its life-sustaining functions.

Albumin - The Slow Indicator

Normal: 35-50 g/L

Half-life: 3 weeks

Low albumin: Chronic liver disease, malnutrition

Limitation: Also low in kidney disease, inflammation

Prothrombin Time - The Quick Check

Normal: 11-15 seconds

Half-life: Hours

Prolonged PT: Acute liver dysfunction, vitamin K deficiency

Key test: Most sensitive to acute liver failure

Bilirubin - The Visible Sign

Normal: <17 $\mu\text{mol/L}$

Unconjugated: Hemolysis, Gilbert's syndrome

Conjugated: Liver disease, biliary obstruction

Jaundice visible: >40 $\mu\text{mol/L}$

Combined Dysfunction

Low albumin + Prolonged PT: Chronic liver failure

High bilirubin + Prolonged PT: Acute liver failure

All three abnormal: Decompensated liver disease

Action: Urgent hepatology referral

Child-Pugh Score for Liver Function Assessment

Parameter	1 Point	2 Points	3 Points
Bilirubin ($\mu\text{mol/L}$)	<34	34-51	>51

Parameter	1 Point	2 Points	3 Points
Albumin (g/L)	>35	28-35	<28
PT prolongation (sec)	<4	4-6	>6
Ascites	None	Slight	Moderate
Encephalopathy	None	Grade 1-2	Grade 3-4

Class A: 5-6 points (good prognosis)

Class B: 7-9 points (moderate prognosis)

Class C: 10-15 points (poor prognosis)



Clinical Pearl

"The Gilbert's Syndrome Trap": Isolated unconjugated bilirubin elevation (usually 20-60 $\mu\text{mol/L}$) with normal other LFTs is Gilbert's syndrome in 5% of the population. It's benign, worsens with fasting/illness, and needs no treatment. Confirm with genetic testing if needed, but don't over-investigate this common variant.

Step 5: Investigation Pathways - Systematic Detective Work

Hepatocellular Investigation

First line: Hep A/B/C screen, paracetamol level

Second line: Autoimmune screen (ANA, ASMA, anti-LKM)

Metabolic: Iron studies, caeruloplasmin, α_1 -antitrypsin

Imaging: Liver ultrasound, consider MRI

Cholestatic Investigation

First line: Abdominal ultrasound, review medications

If ducts normal: AMA (PBC), MRCP (PSC)

If ducts dilated: MRCP or ERCP for intervention

Specialist tests: ANCA (PSC), IgG4 (autoimmune pancreatitis)

Mixed Pattern Investigation

Approach: Combine both hepatocellular and cholestatic investigations

Priority: Rule out acute causes first

Common causes: NAFLD with fibrosis, drug-induced liver injury

Consider: Liver biopsy if diagnosis unclear

Synthetic Dysfunction

Urgent: Check for acute liver failure

Chronic: Assess for decompensated cirrhosis

Monitoring: Child-Pugh score, MELD score

Referral: Hepatology for all cases

When to Refer to Hepatology

- **Acute liver injury:** ALT/AST >400 IU/L or >5x upper limit normal
- **Suspected cirrhosis:** Low albumin + prolonged PT + clinical signs
- **Autoimmune liver disease:** Positive autoantibodies, young patients
- **Unexplained chronic elevation:** Persistent abnormal LFTs >6 months
- **Complicated cases:** Multiple comorbidities, drug interactions
- **Specialist treatment needed:** PBC, PSC, Wilson's disease, hemochromatosis



Clinical Pearl

"The Six-Month Rule": Any persistent elevation of liver enzymes for >6 months, even mild, warrants systematic investigation. The liver doesn't stay mildly abnormal forever without cause. Don't just repeat tests hoping they'll normalize—find out why they're elevated and address the underlying problem.

Step 6: Common Pitfalls and How to Avoid Them

The Bone ALP Confusion

Problem: Elevated ALP assumed to be liver-related

Reality: ALP also comes from bone, especially in growing children

Solution: Check GGT—if normal, ALP likely bone origin

Clues: Recent fractures, Paget's disease, bone metastases

The Statin Panic

Problem: Stopping statins for minor ALT elevation

Reality: Statins rarely cause significant hepatotoxicity

Solution: Continue statin unless ALT >3x upper limit

Benefits: Cardiovascular benefits usually outweigh risks

The Alcohol Assumption

Problem: Attributing all liver problems to alcohol

Reality: NAFLD is now the commonest cause of abnormal LFTs

Solution: Screen for metabolic syndrome even in non-drinkers

Key: AST:ALT >2 suggests alcohol, <1 suggests NAFLD

The Normal PT Reassurance

Problem: Assuming normal PT means good liver function

Reality: PT only prolonged in advanced disease

Solution: Don't ignore abnormal enzymes because PT normal

Remember: Liver damage occurs long before function fails

Red Flag Combinations to Never Miss

- **Young woman + High ALT + High immunoglobulins:** Autoimmune hepatitis
- **High ALP + Pruritus + Middle-aged woman:** Primary biliary cholangitis
- **High ALP + IBD history + Young man:** Primary sclerosing cholangitis
- **Very high ALT + Paracetamol history:** Paracetamol hepatotoxicity
- **High bilirubin + Low haptoglobin + High LDH:** Hemolysis, not liver disease

Summary: The Five-Step Liver Test Mastery Method

1. Calculate R-Ratio

Determine hepatocellular vs cholestatic vs mixed pattern

2. Assess Synthetic Function

Check albumin, PT, bilirubin for liver function

3. Clinical Correlation

Combine patterns with symptoms, examination, history

4. Targeted Investigation

Pattern-specific workup based on R-ratio result

5. Monitor and Refer

Serial monitoring, hepatology referral when indicated

Key Numbers to Remember

R-ratio >5: Hepatocellular pattern

R-ratio <2: Cholestatic pattern

ALT >1000: Think paracetamol, viral hepatitis

AST:ALT >2: Suggests alcohol-related liver disease

ALP >300 + GGT >200: Significant cholestasis

Clinical Decision Points

Emergency referral: ALT >1000 or prolonged PT + low albumin

Hepatology referral: Persistent abnormal LFTs >6 months

Repeat testing: 2-6 weeks for acute changes

Lifestyle intervention: NAFLD pattern with metabolic syndrome



Clinical Pearl

"The Liver's Silent Strength": The liver can lose 80% of its function before you see decompensation. Abnormal liver enzymes are early warning signs, not late-stage findings. Take mild elevations seriously—they often represent the beginning of the story, not a trivial finding. Early intervention can prevent progression to irreversible damage.

Take Home Messages for Liver Test Interpretation

- **Pattern recognition:** Use R-ratio to classify injury type systematically
- **Don't ignore mild elevations:** Persistent abnormal LFTs >6 months need investigation
- **Synthetic function matters:** Albumin and PT tell you about liver function, not just damage
- **Clinical context crucial:** Combine biochemistry with symptoms and examination findings
- **Know when to refer:** Acute severe hepatitis and chronic unexplained abnormalities
- **NAFLD is common:** Screen for metabolic syndrome in patients with hepatocellular pattern



Clinical Guidelines & Evidence Base

NENC Hepatology Network

Abnormal Liver Blood Test Guidelines

- Updated August 2024

[Access Guidelines](#)

NICE Quality Standard QS152

Liver disease quality standards

- 2017

[Access Standards](#)

American College of Gastroenterology

Evaluation of Abnormal Liver Chemistries

- 2017

[Access Guideline](#)

NICE Guideline NG49

Non-alcoholic fatty liver disease assessment and management

- 2016

[Access Guidelines](#)

Chapter 4

Urea & Electrolytes

Mastering Urea & Electrolytes

From Kidney Function to Electrolyte Balance - Essential Clinical Chemistry

Introduction: The Body's Chemical Balance Sheet

Urea and electrolytes aren't just numbers on a lab report—they're a window into your patient's fluid balance, kidney function, and metabolic state. Every result tells part of a larger story: creatinine whispers about kidney health, sodium shouts about fluid status, potassium warns about cardiac risk, and urea reveals the balance between production and clearance. Understanding these relationships transforms you from someone who flags abnormal values into a clinician who can predict problems before they become critical.

This chapter teaches you to read U&Es like a detective examining clues. You'll learn to spot acute kidney injury before it becomes irreversible, recognize dangerous electrolyte imbalances before they cause arrhythmias, and understand when mild abnormalities signal major underlying pathology. Most importantly, you'll know when to act immediately and when to observe carefully.



Clinical Pearl

"The eGFR Revolution": Don't just look at creatinine—eGFR is what matters. A creatinine of 120 $\mu\text{mol/L}$ might be normal for a 25-year-old muscular man (eGFR >90) but represents severe kidney disease in a 75-year-old woman (eGFR <30). Always interpret creatinine in the context of age, sex, and muscle mass via eGFR calculation.

Urea & Electrolytes Normal Ranges and Clinical Significance

Parameter	Normal Range	Units	Primary Clinical Significance	Critical Values
Sodium (Na ⁺)	135-145	mmol/L	Fluid balance, osmolality	<125 or >155
Potassium (K ⁺)	3.5-5.0	mmol/L	Cardiac rhythm, muscle function	<2.5 or >6.5
Urea	2.5-7.8	mmol/L	Kidney function, protein metabolism	>50 (uremic symptoms)
Creatinine	60-110 (F), 70-130 (M)	$\mu\text{mol/L}$	Kidney function, muscle mass	Doubling from baseline
eGFR	>60	mL/min/1.73m^2	True kidney function	<15 (pre-dialysis)
Chloride (Cl ⁻)	95-108	mmol/L	Acid-base balance	<85 or >115
Bicarbonate (HCO ₃ ⁻)	22-29	mmol/L	Acid-base status	<15 or >35

Priority Assessment: When U&Es Signal Emergency

Most electrolyte abnormalities develop gradually and can be corrected safely over hours or days. However, certain patterns represent immediate threats to life—particularly cardiac arrhythmias from potassium imbalance or cerebral edema from sodium disorders. Recognizing these patterns and knowing when to act immediately versus when to investigate further can be life-saving.

▲ Potassium >6.5 mmol/L or <2.5 mmol/L

Life-threatening arrhythmia risk—urgent ECG, cardiac monitoring, immediate treatment with calcium gluconate (high K+) or IV potassium (low K+)

▲ Sodium <125 mmol/L with symptoms

Cerebral edema risk—seizures, coma possible. Assess chronicity urgently—acute needs immediate but careful correction with hypertonic saline

▲ Creatinine doubled from baseline

Acute kidney injury—urgent assessment needed, check for reversible causes, monitor fluid balance, stop nephrotoxic drugs

▲ Bicarbonate <15 mmol/L

Severe metabolic acidosis—check lactate, ketones, salicylate. Consider urgent dialysis if pH <7.1, seek intensive care input



Clinical Pearl

"The Potassium Paradox": Severe hyperkalemia may show no ECG changes until sudden cardiac arrest, while mild hyperkalemia can cause dramatic ECG changes in some patients. Never rely on ECG alone to assess potassium urgency—treat the number, not just the trace. Any K+ >6.0 mmol/L needs immediate treatment regardless of ECG findings.

Step 1: Kidney Function Assessment - Beyond Creatinine

Kidney function assessment has evolved far beyond simply checking if creatinine is elevated. The combination of eGFR, creatinine trends, and urea patterns tells you not just whether the kidneys are failing, but how quickly, why, and what you can do about it. Understanding these relationships is crucial for early detection and intervention.

Always Check eGFR First

eGFR adjusts creatinine for age, sex, and ethnicity, giving true kidney function. Use CKD-EPI equation (standard in UK labs). eGFR >60 = normal kidney function, 30-60 = moderate CKD, <30 = severe CKD requiring specialist care.

Assess Chronicity vs Acuity

Compare with previous results. Rising creatinine over months = chronic kidney disease. Doubling in days = acute kidney injury. Mixed pattern suggests acute-on-chronic deterioration needing urgent assessment.

Examine the Urea:Creatinine Ratio

Normal ratio ~10:1. High ratio (>20:1) suggests prerenal AKI, dehydration, or GI bleeding. Low ratio suggests liver disease or low protein intake. This ratio helps identify the cause of kidney dysfunction.

Clinical Context Integration

Combine biochemistry with symptoms (oliguria, edema), examination (fluid status, blood pressure), and drug history (ACE inhibitors, NSAIDs, diuretics). Numbers alone don't make diagnoses.

NICE 2024 AKI Detection and Staging

AKI Stage 1

Creatinine: 1.5-1.9x baseline or ≥ 26 $\mu\text{mol/L}$ rise

Urine: <0.5 mL/kg/hr for 6-12 hours

Action: Daily monitoring, review medications

AKI Stage 2

Creatinine: 2.0-2.9x baseline

Urine: <0.5 mL/kg/hr for ≥ 12 hours

Action: Nephrology consultation, consider causes

AKI Stage 3

Creatinine: ≥ 3.0 x baseline or ≥ 354 $\mu\text{mol/L}$

Urine: <0.3 mL/kg/hr for ≥ 24 hours

Action: Urgent nephrology, consider dialysis

Kidney Replacement Therapy

Indications: Life-threatening complications

Not just: Isolated urea/creatinine values

Consider: Fluid overload, acidosis, hyperkalemia



Clinical Pearl

"The Medication Review Imperative": Every patient with AKI needs immediate medication review. Stop nephrotoxic drugs (NSAIDs, gentamicin), hold ACE inhibitors and diuretics temporarily, and adjust doses for reduced kidney function. Many cases of AKI are medication-related and completely reversible with prompt action.

Step 2: Sodium Disorders - The Osmotic Balancing Act

Hyponatremia (<135 mmol/L)

Mild (130-135): Often asymptomatic, investigate cause

Moderate (125-129): Nausea, confusion, falls risk

Severe (<125): Seizures, coma, cerebral edema

Key: Assess volume status and urine osmolality

Hypernatremia (>145 mmol/L)

Mild (146-150): Thirst, restlessness

Moderate (151-160): Confusion, muscle twitching

Severe (>160): Seizures, coma, cerebral hemorrhage

Cause: Usually water loss > sodium loss

SIADH Pattern

Biochemistry: Low Na⁺, low serum osmolality, high urine osmolality

Clinical: Euvolemic, no edema

Causes: CNS disease, lung disease, drugs, malignancy

Treatment: Fluid restriction, treat underlying cause

Dehydration Pattern

Biochemistry: High Na⁺, high serum osmolality

Clinical: Dry mucous membranes, reduced skin turgor

Causes: Inadequate fluid intake, diabetes insipidus

Treatment: Gradual rehydration with hypotonic fluids

Hyponatremia Causes

Hypovolemic: Diuretics, diarrhea, vomiting, burns

Euvolemic: SIADH, hypothyroidism, adrenal insufficiency

Hypervolemic: Heart failure, liver failure, kidney failure

SIADH Common Causes

CNS: Stroke, head injury, meningitis, tumors

Pulmonary: Pneumonia, lung cancer, TB

Drugs: SSRIs, carbamazepine, thiazides, PPIs

Hypernatremia Causes

Water loss: Diabetes insipidus, diarrhea, sweating

Sodium excess: IV hypertonic saline, salt poisoning

Impaired thirst: Elderly, dementia, unconscious patients

Critical Correction Rules

Chronic hyponatremia: Correct <8 mmol/L per 24h

Acute severe: Can correct faster but watch for CPM

Hypernatremia: Correct <10 mmol/L per 24h



Clinical Pearl

"The Central Pontine Myelinolysis Fear": Correcting chronic hyponatremia too rapidly (>8 mmol/L per 24 hours) can cause irreversible brainstem damage. If sodium is chronically low (>48 hours), go slow. Use 3% saline only for acute severe hyponatremia with neurological symptoms, and monitor hourly. When in doubt, correct conservatively.

Step 3: Potassium - The Cardiac Critical Parameter

Potassium disorders are among the most immediately life-threatening electrolyte abnormalities. Both hyperkalemia and hypokalemia can cause fatal arrhythmias, but the clinical presentation can be deceptively mild until sudden cardiovascular collapse. Understanding the causes, recognizing the ECG changes, and knowing the urgent treatment protocols is essential for every clinician.

Normal Potassium (3.5-5.0 mmol/L)

Physiology: 98% intracellular, crucial for membrane potential

ECG: Normal P-waves, QRS, and T-waves

Clinical: Normal muscle and cardiac function

Hypokalemia (<3.5 mmol/L)

Mild (3.0-3.4): Often asymptomatic, muscle weakness

Severe (<3.0): Paralysis, rhabdomyolysis risk

ECG: U-waves, T-wave flattening, ST depression

Risk: Digoxin toxicity, arrhythmias

Hyperkalemia (>5.0 mmol/L)

Mild (5.1-5.9): Usually asymptomatic

Moderate (6.0-6.4): ECG changes likely

Severe (>6.5): Life-threatening arrhythmia risk

ECG: Tall T-waves → wide QRS → sine wave

Critical Hyperkalemia (>6.5 mmol/L)

Immediate action: Calcium gluconate 10mL 10%

Shift K⁺ intracellular: Insulin + glucose, salbutamol

Remove K⁺: Calcium resonium, dialysis

Monitor: Continuous ECG, hourly K⁺ levels

Hyperkalemia Emergency Management Protocol

Immediate Assessment (K⁺ >6.0 mmol/L)

12-lead ECG immediately. Look for tall T-waves, wide QRS, absent P-waves. Any ECG changes or K⁺ >6.5 mmol/L = medical emergency requiring immediate treatment.

Cardiac Protection (First Priority)

Calcium gluconate 10mL 10% IV over 2-5 minutes. Protects heart from arrhythmias within minutes. Repeat if ECG changes persist. Effect lasts 30-60 minutes.

Shift Potassium Intracellular

Insulin 10 units + glucose 50mL 50% IV. Alternative: Salbutamol 10-20mg nebulized. Both shift K⁺ into cells within 15-30 minutes. Monitor glucose closely.

Remove Potassium from Body

Calcium resonium 15g PO/PR if GI tract working. Consider urgent dialysis if K⁺ >7.0 mmol/L or not responding to medical treatment. Stop all K⁺-sparing drugs.

Hyperkalemia Causes

Decreased excretion: AKI, CKD, ACE inhibitors, spironolactone

Increased intake: K⁺ supplements, salt substitutes

Cell shift: Acidosis, tissue breakdown, succinylcholine

Pseudohyperkalemia: Hemolysis, thrombocytosis, delayed processing

Hypokalemia Causes

GI losses: Diarrhea, vomiting, fistulas

Renal losses: Diuretics, hyperaldosteronism, RTA

Cell shift: Insulin, β_2 -agonists, alkalosis

Poor intake: Anorexia, alcoholism, elderly

Drug-Induced Hyperkalemia

Common drugs: ACE inhibitors, ARBs, spironolactone, amiloride

Risk factors: CKD, elderly, dehydration

Management: Stop offending drug, monitor closely

Prevention: Regular monitoring in high-risk patients

Replacement Therapy

Mild hypokalemia: Oral K⁺ 40-80 mmol daily

Severe hypokalemia: IV K⁺ max 10 mmol/hour

Monitor: ECG, repeat K⁺ after each 40 mmol

Mg⁺ check: Always correct hypomagnesemia first



Clinical Pearl

"The Magnesium Connection": Hypokalemia that doesn't correct despite adequate potassium replacement suggests concurrent hypomagnesemia. Magnesium is essential for potassium retention. Always check and correct magnesium levels when treating persistent hypokalemia—you can't fix low potassium without fixing low magnesium first.

Step 4: Acid-Base Balance - Reading Between the Lines

While U&Es don't give you complete acid-base status, the bicarbonate level provides crucial information about metabolic acidosis and alkalosis. Combined with the anion gap (if available) and clinical context, bicarbonate changes can reveal serious underlying pathology from diabetic ketoacidosis to kidney failure.

Understanding Bicarbonate Changes

Bicarbonate (HCO_3^-) reflects the metabolic component of acid-base balance:

- **Low HCO_3^- (<22):** Metabolic acidosis
- **High HCO_3^- (>29):** Metabolic alkalosis
- **Normal (22-29):** No metabolic acid-base disorder

Remember: the body compensates, so chronic respiratory disorders cause predictable metabolic changes.

Clinical Approach to Bicarbonate Abnormalities

Always consider the clinical context:

- **Acidosis + diabetes:** Check ketones, glucose
- **Acidosis + kidney disease:** Uremic acidosis
- **Alkalosis + hypokalemia:** Diuretics, vomiting
- **Severe acidosis:** Consider toxic ingestion

Metabolic Acidosis (HCO_3^- <22)

Mild (18-21): Often compensated, investigate cause

Moderate (12-17): Symptoms likely, treat underlying cause

Severe (<12): Life-threatening, consider bicarbonate

Causes: DKA, lactic acidosis, kidney failure, diarrhea

Metabolic Alkalosis (HCO_3^- >29)

Mild (30-35): Usually well tolerated

Severe (>40): Respiratory depression risk

Causes: Vomiting, diuretics, hyperaldosteronism

Treatment: Correct K^+ and Cl^- deficiency

Diabetic Ketoacidosis Pattern

HCO_3^- : Usually <15 mmol/L

Associated: High glucose, ketones, anion gap

Clinical: Dehydration, Kussmaul breathing

Treatment: Insulin, fluids, K^+ replacement

Chronic Compensation

COPD: High HCO_3^- compensates for high CO_2

Normal in COPD: HCO_3^- may be 30-35 mmol/L

Key point: Don't "correct" compensated states

Danger: Rapid changes in chronic patients



Clinical Pearl

"The Anion Gap Detective": When bicarbonate is low, calculate the anion gap: $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$. Normal is 8-16. High anion gap acidosis (DKA, lactic acidosis, toxins) needs urgent treatment. Normal anion gap acidosis (diarrhea, RTA) is usually less urgent but still needs investigation.

Step 5: Putting It All Together - Pattern Recognition

Start with Kidney Function

Check eGFR first. Is this normal kidney function, CKD, or AKI? This sets the context for interpreting all other electrolyte abnormalities and guides urgency of intervention.

Assess Life-Threatening Electrolytes

Check K⁺ for arrhythmia risk, Na⁺ for seizure risk. These need immediate attention if critically abnormal, regardless of other findings.

Look for Patterns

Multiple abnormalities suggest systemic disease. AKI + hyperkalemia = medication review. Low Na⁺ + high K⁺ = adrenal insufficiency. Pattern recognition speeds diagnosis.

Clinical Integration

Combine biochemistry with clinical picture. Dehydration, heart failure, medication history all influence interpretation and management priorities.

Dehydration Pattern

Biochemistry: High urea:creatinine ratio, high sodium

Clinical: Dry mucous membranes, reduced urine output

Causes: Poor fluid intake, diabetes, diuretics

Treatment: Careful fluid replacement, monitor response

Heart Failure Pattern

Biochemistry: Mild AKI, low sodium, high urea

Clinical: Edema, elevated JVP, breathlessness

Cause: Poor cardiac output, activation of RAAS

Treatment: Optimize heart failure management

Addison's Disease Pattern

Biochemistry: Low Na⁺, high K⁺, mild AKI

Clinical: Hypotension, pigmentation, weakness

Test: 9am cortisol, short synacthen test

Treatment: Urgent steroids if suspected

Diuretic Effect Pattern

Thiazides: Low K⁺, low Na⁺, mild AKI

Loop diuretics: Low K⁺, dehydration

K⁺-sparing: High K⁺, especially with ACE inhibitors

Management: Adjust doses, monitor regularly

AKI Risk Factors

Age >65, CKD, heart failure, liver disease, diabetes
Dehydration, sepsis, contrast exposure
NSAIDs, ACE inhibitors, gentamicin

Hyperkalemia Risk Factors

CKD, diabetes, heart failure
ACE inhibitors, ARBs, spironolactone
Age >65, acidosis, tissue breakdown

Hyponatremia Risk Factors

Age >65, female sex, low BMI
Diuretics, SSRIs, carbamazepine
Heart failure, liver disease, COPD

Monitoring Requirements

High-risk patients need regular U&Es
After starting/changing nephrotoxic drugs
During acute illness, dehydration



Clinical Pearl

"The Medication Cascade": Many U&E abnormalities are medication-related and create cascading effects. ACE inhibitor causes mild hyperkalemia → stopped → heart failure worsens → gets diuretic → develops hyponatremia. Always consider the medication timeline when interpreting electrolyte changes, and sometimes the solution is optimizing rather than stopping treatment.

Common Pitfalls and How to Avoid Them

The Creatinine Blind Spot

Mistake: Assuming normal creatinine = normal kidney function
Reality: Elderly, small women can have significant CKD with "normal" creatinine
Solution: Always check eGFR, not just creatinine
Example: 75-year-old woman with creatinine 90 may have eGFR <45

The Pseudohyperkalemia Trap

Mistake: Treating laboratory artifact as true hyperkalemia
Reality: Hemolysis, thrombocytosis, delayed processing cause false high K+
Solution: Check for hemolysis, repeat sample if suspicious
Clues: Normal ECG with very high K+, hemolyzed sample

The Bicarbonate Overreaction

Mistake: Aggressive treatment of compensated acid-base disorders
Reality: COPD patients normally have high bicarbonate
Solution: Don't "correct" chronic compensation
Key: Rapid changes in chronic patients are dangerous

The ACE Inhibitor Knee-Jerk

Mistake: Stopping ACE inhibitors for mild creatinine rise
Reality: 30% creatinine rise is acceptable and protective
Solution: Only stop if >50% rise or hyperkalemia >5.5
Benefit: Long-term kidney and heart protection usually outweighs risk

Red Flags That Should Never Be Missed

- **K+ >6.0 mmol/L:** Immediate ECG and treatment regardless of symptoms
- **Na+ <125 mmol/L with confusion:** Risk of seizures, assess chronicity urgently
- **Creatinine doubled from baseline:** AKI until proven otherwise
- **eGFR <15 mL/min/1.73m²:** Pre-dialysis CKD needing urgent nephrology referral
- **HCO₃⁻ <12 mmol/L:** Life-threatening acidosis, check pH if possible
- **New AKI + rash + eosinophilia:** Drug-induced interstitial nephritis

Summary: The Five-Step U&E Mastery Method

1. Check eGFR First

True kidney function assessment, not just creatinine

2. Assess Life-Threatening Values

Potassium for arrhythmias, sodium for seizures

3. Look for Patterns

Multiple abnormalities suggest systemic disease

4. Review Medications

Many U&E problems are drug-related and reversible

5. Monitor Trends

Changes over time more important than single values

Critical Values to Act On Immediately

K⁺ >6.5 or <2.5: Cardiac protection, immediate treatment

Na⁺ <125 with symptoms: Assess chronicity, cautious correction

Creatinine doubled: AKI workup, stop nephrotoxic drugs

HCO₃⁻ <15: Severe acidosis, investigate cause urgently

Key Clinical Decision Points

eGFR 30-60: Stage 3 CKD, nephrology referral if progressing

eGFR <30: Stage 4-5 CKD, urgent nephrology referral

AKI Stage 3: Consider dialysis, intensive monitoring

Drug-induced changes: Often reversible with medication adjustment



Clinical Pearl

"The Trend is Your Friend": Single abnormal U&E values can be misleading, but trends over time reveal the true story. Slowly rising creatinine over months suggests progressive CKD requiring different management than rapidly rising creatinine over days suggesting AKI. Always interpret results in the context of previous values and rate of change.

Take Home Messages for U&E Interpretation

- **eGFR trumps creatinine:** Always assess kidney function via eGFR, especially in elderly patients
- **Potassium kills quickly:** Any K⁺ >6.0 mmol/L needs immediate treatment regardless of symptoms
- **Medication review essential:** Many U&E abnormalities are drug-related and reversible
- **AKI is often preventable:** Early recognition and intervention can prevent progression
- **Context matters:** Combine biochemistry with clinical assessment and drug history
- **Chronic compensation is normal:** Don't "fix" appropriately compensated acid-base disorders

Clinical Guidelines & Evidence Base

NICE Guideline NG148

Acute kidney injury: prevention, detection and management

- Updated 2024
[Access Guidelines](#)

NICE Guideline NG203

Chronic kidney disease: assessment and management

- 2021
[Access Guidelines](#)

UK Kidney Association

UK eCKD Guide

- 2024
[Access Guide](#)

Chapter 5

Lipid Profile

Mastering Lipid Profiles

From Numbers to Cardiovascular Risk Management

Introduction: Beyond the Numbers Game

A lipid profile isn't just a collection of cholesterol values—it's a window into your patient's cardiovascular future. Every result tells part of the story: total cholesterol hints at risk, but LDL cholesterol predicts events. HDL cholesterol offers protection, while triglycerides whisper warnings of metabolic chaos. The art lies in weaving these numbers together with clinical context to make decisions that can prevent heart attacks, strokes, and save lives.

This chapter transforms you from someone who simply reads lipid results into a cardiovascular risk detective who can spot the patterns that matter, avoid the pitfalls that mislead, and make evidence-based decisions about when to treat, how aggressively, and what targets to aim for.



Clinical Pearl

"LDL is the Star of the Show": While patients fixate on total cholesterol, LDL cholesterol is what matters for cardiovascular events. A patient with total cholesterol of 6.0 mmol/L might need urgent treatment if LDL is 4.5 mmol/L, or might need no treatment at all if LDL is 2.0 mmol/L with high protective HDL. Focus on LDL—it's what clogs arteries.

Lipid Profile Normal Ranges and Targets

Lipid Component	Optimal Level	Primary Prevention Target	Secondary Prevention Target	Units
Total Cholesterol	<5.0	<5.0	<4.0	mmol/L
LDL Cholesterol	<3.0	<3.0	<2.0	mmol/L
HDL Cholesterol	>1.0 (men), >1.2 (women)	>1.0 (men), >1.2 (women)	No specific target	mmol/L
Non-HDL Cholesterol	<4.0	<4.0	<2.6	mmol/L
Triglycerides	<1.7	<1.7	<1.7	mmol/L
Total:HDL Ratio	<4.0	<4.0	<4.0	Ratio

Priority Assessment: When Lipids Signal Urgent Action

Most lipid abnormalities develop slowly and allow time for thoughtful management. However, certain patterns demand immediate attention—either because they signal underlying pathology or because they represent such extreme cardiovascular risk that urgent intervention is warranted.

▲ **Total Cholesterol >8.0 mmol/L**

Possible familial hypercholesterolaemia—urgent lipid clinic referral needed, screen family members, calculate lifetime risk

▲ **Triglycerides >10.0 mmol/L**

Acute pancreatitis risk—admit for monitoring, strict fat restriction, urgent specialist referral for lipid disorders

▲ **New Severe Hyperlipidaemia + Symptoms**

Rule out secondary causes: hypothyroidism, diabetes, nephrotic syndrome, cholestatic liver disease, medications

▲ **Very Low HDL (<0.8 mmol/L) + High Triglycerides**

Metabolic syndrome or diabetes risk—check HbA1c, blood pressure, waist circumference urgently



Clinical Pearl

"The Familial Hypercholesterolaemia Detective Work": Total cholesterol >7.5 mmol/L before age 30, or >9.0 mmol/L at any age, combined with family history of early coronary disease or high cholesterol, suggests familial hypercholesterolaemia. These patients need specialist management and their families need screening—early treatment can prevent premature death.

Step 1: The QRISK3 Revolution - Risk-Based Decision Making

NICE 2023 guidelines transformed lipid management from a numbers-based to a risk-based approach. The magic number isn't your patient's cholesterol level—it's their 10-year cardiovascular risk. QRISK3 calculates this risk using 20+ variables, giving you the power to identify who really needs treatment and who can be safely observed.

Step 1: Calculate 10-Year CVD Risk

Use QRISK3 calculator for all patients aged 25-84 without established CVD. Include age, sex, ethnicity, postcode, smoking, diabetes, blood pressure, BMI, family history, chronic conditions, and lipid levels. The calculator does the complex maths for you.

Step 2: Apply the 10% Threshold

QRISK3 $\geq 10\%$ over 10 years = offer statin therapy. This threshold represents the point where benefits clearly outweigh risks. Below 10%, focus on lifestyle; above 10%, discuss statin therapy.

Step 3: Consider Individual Factors

QRISK3 is a guide, not a rule. Consider patient preferences, frailty, life expectancy, polypharmacy, and potential for lifestyle change. A fit 45-year-old with 12% risk might benefit more than a frail 80-year-old with 15% risk.

Step 4: Reassess Regularly

Cardiovascular risk changes over time. Reassess QRISK3 every 5 years, or sooner if clinical situation changes (new diabetes, hypertension, or major life events). Risk isn't static.

QRISK3 Decision Framework

Patient aged 25-84 without established CVD

Calculate QRISK3 score

Include all relevant risk factors and current lipid levels

<10% risk: Lifestyle advice → Reassess in 5 years → Consider family history and patient preference

$\geq 10\%$ risk: Offer statin → Start atorvastatin 20mg → Titrate to achieve LDL targets



Clinical Pearl

"The Power of Risk Communication": Don't just quote the QRISK3 percentage—translate it into terms patients understand. "Your risk is 15%" becomes "Out of 100 people like you, 15 would have a heart attack or stroke in the next 10 years, but statins could prevent about 5 of those events." Stories resonate more than statistics.

Step 2: Statin Therapy - The Evidence-Based Approach

Primary Prevention Statin Choice

First Line: Atorvastatin 20mg once daily
Evidence: Best evidence base, predictable dosing
Timing: Evening dosing traditional but any time acceptable
Monitoring: Check lipids at 3 months, then annually

Secondary Prevention Statin Choice

First Line: Atorvastatin 80mg once daily
Evidence: Proven to reduce cardiovascular events
Target: LDL <2.0 mmol/L or >40% reduction
Monitoring: Check lipids at 6-8 weeks, then 3-monthly

Statin Intolerance Management

Try: Lower dose, alternate day, different statin
Alternatives: Ezetimibe 10mg, bile acid sequestrants
Newer options: Bempedoic acid, PCSK9 inhibitors
Key: True intolerance is rare—explore and rechallenge

Combination Therapy

Add ezetimibe if: LDL targets not met on maximum tolerated statin
Dose: Ezetimibe 10mg daily with statin
Effect: Additional 15-20% LDL reduction
Safety: Generally well tolerated, minimal interactions

Atorvastatin 20mg Effects

LDL reduction: 35-40%
Typical result: LDL from 4.0 → 2.4 mmol/L
CVD risk reduction: 20-25% in primary prevention

Atorvastatin 40mg Effects

LDL reduction: 45-50%
Typical result: LDL from 4.0 → 2.0 mmol/L
Use for: Higher risk patients, target not met on 20mg

Atorvastatin 80mg Effects

LDL reduction: 55-60%
Typical result: LDL from 4.0 → 1.6 mmol/L
Use for: Secondary prevention, high-risk primary prevention

Statin + Ezetimibe Effects

Combined LDL reduction: 65-70%
Typical result: LDL from 4.0 → 1.2 mmol/L
Use for: Targets not met, familial hypercholesterolaemia



Clinical Pearl

"The Statin Intolerance Reality Check": True statin intolerance occurs in <5% of patients, but up to 20% report muscle symptoms. Many symptoms are nocebo effects or unrelated conditions. Try dose reduction, alternate-day dosing, or a different statin before declaring intolerance. The cardiovascular benefits usually outweigh muscle discomfort.

Step 3: Reading the Lipid Profile - Pattern Recognition

The Classic Patterns You'll See

High LDL Pattern: LDL >3.0, normal triglycerides, variable HDL. Think genetic predisposition, dietary factors, or familial hypercholesterolaemia if very high.

Metabolic Syndrome Pattern: High triglycerides, low HDL, modestly elevated LDL. Often accompanies insulin resistance, obesity, diabetes.

Post-Statin Pattern: Dramatically improved LDL, stable or slightly improved HDL, variable triglyceride response depending on baseline levels.

The Ratios That Matter

Total:HDL ratio >6.0: High cardiovascular risk regardless of individual cholesterol levels. HDL is protective—low HDL amplifies risk from any LDL level.

Non-HDL cholesterol: Total cholesterol minus HDL. Useful when triglycerides are high and LDL calculation unreliable. Target <2.6 mmol/L for secondary prevention.

LDL:HDL ratio >3.5: Atherogenic pattern—high risk of plaque formation and cardiovascular events.

Isolated High LDL

Pattern: LDL >4.0, HDL normal, TG <2.0

Common in: Familial hypercholesterolaemia, dietary excess

Risk: High for coronary artery disease

Treatment: Statin therapy highly effective

Mixed Dyslipidaemia

Pattern: LDL high, HDL low, TG >2.0

Common in: Metabolic syndrome, diabetes, obesity

Risk: Very high for cardiovascular events

Treatment: Statin + lifestyle ± ezetimibe

Isolated Low HDL

Pattern: HDL <1.0 (men) or <1.2 (women), LDL normal

Common in: Smoking, sedentary lifestyle, metabolic disorders

Risk: Moderate but significant

Treatment: Exercise, smoking cessation, consider statin if other risk factors

Isolated High Triglycerides

Pattern: TG >2.0, LDL and HDL normal

Common in: Alcohol excess, diabetes, medications

Risk: Variable—check for secondary causes

Treatment: Address underlying cause, consider fibrate if >5.0



Clinical Pearl

"The Non-Fasting Liberation": You can now order lipids without fasting for most patients. Total cholesterol, HDL, and non-HDL cholesterol are minimally affected by recent food intake. Only order fasting lipids if triglycerides >4.5 mmol/L on non-fasting sample, or when investigating possible familial hyperlipidaemia.

Step 4: Secondary Causes - The Detective Work

Before labeling someone with primary hyperlipidaemia, exclude secondary causes. These are often reversible and treating the underlying condition may normalize lipid levels without needing long-term statin therapy. Think systematically through potential causes, especially in patients with new-onset severe lipid abnormalities.

Endocrine Causes

- Hypothyroidism:** Check TSH—can cause severe hyperlipidaemia
- Diabetes:** Poor glycaemic control raises triglycerides and lowers HDL
- Cushing's syndrome:** Rare but causes mixed dyslipidaemia

Renal Causes

- Nephrotic syndrome:** Proteinuria with hyperlipidaemia
- Chronic kidney disease:** Progressive lipid abnormalities
- Dialysis:** Often requires specific lipid management

Hepatic Causes

- Cholestatic liver disease:** Very high cholesterol
- Non-alcoholic fatty liver:** Often with metabolic syndrome
- Primary biliary cholangitis:** Specific lipid pattern

Medication Causes

- Thiazide diuretics:** Modestly raise cholesterol and triglycerides
- Beta-blockers:** May worsen lipid profile
- Corticosteroids:** Cause mixed dyslipidaemia
- Immunosuppressants:** Ciclosporin particularly problematic

Investigation Strategy for Secondary Causes

- **Always check:** TSH (hypothyroidism), HbA1c (diabetes), urinalysis (proteinuria)
- **Consider checking:** Liver function tests, kidney function, glucose tolerance
- **Review medications:** Especially diuretics, beta-blockers, steroids, immunosuppressants
- **Lifestyle factors:** Alcohol intake, dietary habits, recent weight changes
- **Family history:** Early coronary disease, hyperlipidaemia, diabetes



Clinical Pearl

"The Hypothyroidism Masquerader": Severe hyperlipidaemia with total cholesterol >10 mmol/L in someone without obvious familial hypercholesterolaemia should always prompt thyroid function testing. Hypothyroidism can cause dramatic lipid abnormalities that completely normalize with levothyroxine treatment. Check TSH first, treat appropriately, then reassess lipids.

Step 5: Special Populations and Scenarios

Elderly Patients (>75 years)

QRISK3 less reliable over 75. Consider life expectancy, frailty, polypharmacy, and patient preference. For established CVD, statins still beneficial. For primary prevention, individualised approach—benefits may not outweigh risks in frail patients with limited life expectancy.

Diabetes Patients

Diabetes is a major cardiovascular risk factor. Type 1 diabetes >40 years or Type 2 diabetes at any age should be considered for statin therapy regardless of cholesterol levels. Target LDL <2.6 mmol/L for high-risk diabetes patients. Consider more intensive lipid lowering if multiple risk factors.

Chronic Kidney Disease

Offer atorvastatin 20mg for primary or secondary prevention in CKD. If eGFR >30, can increase dose to meet targets. If eGFR <30, consult renal specialist before high-dose statins. Avoid fibrates in significant CKD. Monitor for drug interactions.

Pregnancy and Breastfeeding

Stop statins before conception—teratogenic risk. Pregnancy naturally raises cholesterol levels. Focus on dietary management. Consider bile acid sequestrants if treatment essential. Resume statins after breastfeeding. Preconception counselling crucial for women on lipid-lowering therapy.

When to Refer to Specialist Lipid Services

- **Familial hypercholesterolaemia:** Total cholesterol >7.5 mmol/L with family history
- **Severe hypertriglyceridaemia:** Triglycerides >10 mmol/L or recurrent pancreatitis
- **Statin intolerance:** Multiple statins tried, genuine intolerance confirmed
- **Targets not achieved:** Maximum tolerated therapy, targets still not met
- **Complex cases:** Multiple comorbidities, unusual lipid patterns, young patients with CVD
- **Novel therapies needed:** PCSK9 inhibitors, inclisiran, complex combination therapy



Clinical Pearl

"**The Diabetes Lipid Advantage**": Patients with diabetes often see greater triglyceride and HDL improvements with statins compared to non-diabetic patients. The combination of improved glycaemic control and statin therapy creates synergistic benefits for their lipid profile and cardiovascular risk reduction. Optimize both glucose and lipid control together.

Step 6: Monitoring and Follow-up Strategy

Lipid Monitoring Timeline

Initial Treatment Response

When: 6-8 weeks after starting statin
Check: Lipids, liver function, symptoms
Action: Dose adjustment if targets not met

Routine Monitoring

When: 3 months, then annually
Check: Lipids, medication adherence
Action: Reinforce lifestyle, check targets

High-Risk Patients

When: 3-monthly initially
Check: Lipids, secondary prevention targets
Action: Intensive management, combination therapy

Specialist Monitoring

When: Complex cases, novel therapies
Check: Specialist protocols
Action: Shared care with specialist services

Treatment Success Indicators

- **Primary prevention:** LDL reduction of $\geq 40\%$ from baseline, or LDL < 3.0 mmol/L
- **Secondary prevention:** LDL < 2.0 mmol/L or non-HDL < 2.6 mmol/L
- **High-risk patients:** Consider LDL < 1.4 mmol/L for very high risk
- **Patient factors:** Good adherence, tolerable side effects, lifestyle maintenance
- **Additional benefits:** Blood pressure improvement, diabetes control



Clinical Pearl

"The Power of Percentage Thinking": Don't get fixated on absolute targets if patients can't achieve them. A 50% LDL reduction from 5.0 to 2.5 mmol/L provides substantial cardiovascular benefit, even if the target of 2.0 mmol/L isn't reached. Celebrate meaningful improvements and maintain perspective on relative risk reduction.

Common Pitfalls and How to Avoid Them

The Total Cholesterol Trap

Mistake: Focusing on total cholesterol instead of LDL

Reality: Total cholesterol can be high due to protective HDL

Solution: Always look at LDL cholesterol and HDL separately

Example: Total 6.5 might be fine if LDL 2.0 and HDL 4.0

The Fasting Obsession

Mistake: Always requiring fasting samples

Reality: Non-fasting lipids are reliable for most decisions

Solution: Use non-fasting unless triglycerides >4.5 mmol/L

Benefits: Improved patient compliance, more convenient

The Statin Intolerance Overdiagnosis

Mistake: Accepting muscle symptoms as definite statin intolerance

Reality: Many symptoms are placebo or unrelated

Solution: Try dose reduction, alternate statin, rechallenge

Key: True intolerance is rare but important to identify

The Target Perfectionism

Mistake: Aggressive pursuit of perfect lipid targets

Reality: Relative improvement matters more than absolute targets

Solution: Celebrate meaningful reductions, consider patient factors

Focus: Cardiovascular benefit, not laboratory perfection

Red Flags in Lipid Management

- **Unexplained severe muscle pain:** Stop statin, check CK, rule out rhabdomyolysis
- **New diabetes diagnosis:** May be statin-related in borderline patients—benefits still outweigh risks
- **Persistent non-response:** Check adherence before assuming statin resistance
- **Drug interactions:** Many medications affect statin metabolism—check interactions
- **Liver function abnormalities:** Minor elevations common and acceptable, marked rises concerning

Summary: The Five-Step Lipid Mastery Method

1. Risk Assessment First

Use QRISK₃ to calculate 10-year CVD risk—this drives all decisions

2. Focus on LDL

LDL cholesterol predicts events—this is your primary target

3. Rule Out Secondary Causes

Check TSH, HbA_{1c}, urinalysis—treat underlying conditions first

4. Start with Lifestyle

Diet, exercise, smoking cessation—foundation of all management

5. Monitor and Adjust

Regular follow-up, target-based titration, long-term adherence

Key Numbers to Remember

Primary prevention: QRISK₃ $\geq 10\%$ = consider statin

Secondary prevention: LDL < 2.0 mmol/L target

Statin choice: Atorvastatin 20mg (primary), 80mg (secondary)

Monitoring: 6-8 weeks then 3-monthly initially

Clinical Decision Points

Familial hypercholesterolaemia: Total cholesterol > 7.5 mmol/L

Pancreatitis risk: Triglycerides > 10 mmol/L

Combination therapy: Add ezetimibe if targets not met

Specialist referral: Complex cases or novel therapies needed



Clinical Pearl

"The Lifetime Perspective": Lipid management is a marathon, not a sprint. Small improvements maintained over decades prevent more cardiovascular events than dramatic short-term reductions followed by treatment discontinuation. Focus on sustainable therapy, patient understanding, and long-term adherence rather than perfect laboratory values.

Take Home Messages for Lipid Management

- **Risk-based treatment:** Use QRISK₃ to guide decisions, not just cholesterol levels
- **LDL is king:** Focus on LDL cholesterol—it's what causes cardiovascular events
- **Atorvastatin first:** Best evidence base, predictable effects, wide dose range
- **Secondary causes matter:** Always check TSH, HbA_{1c}, urinalysis before labeling primary hyperlipidaemia
- **Targets are guides:** Relative improvement often matters more than absolute targets
- **Lifestyle foundation:** Medication enhances but never replaces healthy living



Clinical Guidelines & Evidence Base

NICE Guideline NG238

Cardiovascular disease: risk assessment and reduction, including lipid modification

- Updated 2023
[Access Guidelines](#)

QRISK3 Calculator

Official QRISK3 cardiovascular risk calculator

[Access Calculator](#)

European Society of Cardiology

ESC/EAS Guidelines for the management of dyslipidaemias

- 2019
[Access Guidelines](#)

American Heart Association

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline

[Access Guidelines](#)

Cochrane Review

Statins for the primary prevention of cardiovascular disease

- 2022
[Access Review](#)

NICE Clinical Knowledge Summaries

Lipid modification - CVD prevention

- Updated 2024
[Access Summary](#)

References

- Baigent, C., Blackwell, L., Emberson, J., Holland, L.E., Reith, C., Bhala, N., Peto, R., Barnes, E.H., Keech, A., Simes, J. and Collins, R. (2010) 'Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials', *The Lancet*, 376(9753), pp. 1670-1681.
- Collins, R., Reith, C., Emberson, J., Armitage, J., Baigent, C., Blackwell, L., Blumenthal, R., Danesh, J., Smith, G.D., DeMets, D., Evans, S., Law, M., MacMahon, S., Martin, S., Neal, B., Poulter, N., Preiss, D., Ridker, P., Roberts, I., Rodgers, A., Sandercock, P., Schulz, K., Sever, P., Simes, J., Smeeth, L., Wald, N., Yusuf, S. and Peto, R. (2016) 'Interpretation of the evidence for the efficacy and safety of statin therapy', *The Lancet*, 388(10059), pp. 2532-2561.
- Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T., de Ferranti, S., Faiella-Tommasino, J., Forman, D.E., Goldberg, R., Heidenreich, P.A., Hlatky, M.A., Jones, D.W., Lloyd-Jones, D., Lopez-Pajares, N., Ndumele, C.E., Orringer, C.E., Peralta, C.A., Saseen, J.J., Smith, S.C., Sperling, L., Virani, S.S. and Yeboah, J. (2019) '2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol', *Journal of the American College of Cardiology*, 73(24), pp. e285-e350.
- Hippisley-Cox, J., Coupland, C. and Brindle, P. (2017) 'Development and validation of QRISK3 risk prediction

algorithms to estimate future risk of cardiovascular disease: prospective cohort study', *BMJ*, 357, j2099.

Mach, F., Baigent, C., Catapano, A.L., Koskinas, K.C., Casula, M., Badimon, L., Chapman, M.J., De Backer, G.G., Delgado, V., Ference, B.A., Graham, I.M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T.R., Riccardi, G., Richter, D.J., Sabatine, M.S., Taskinen, M.R., Tokgozoglu, L. and Wiklund, O. (2020) '2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk', *European Heart Journal*, 41(1), pp. 111-188.

National Institute for Health and Care Excellence (NICE) (2023) *Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE guideline [NG238]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng238> (Accessed: 30 September 2025).

Cuchel, M., Bruckert, E., Ginsberg, H.N., Raal, F.J., Santos, R.D., Hegele, R.A., Kuivenhoven, J.A., Nordestgaard, B.G., Descamps, O.S., Steinhagen-Thiessen, E., Tybjaerg-Hansen, A., Watts, G.F., Aversa, M., Boileau, C., Borén, J., Catapano, A.L., Defesche, J.C., Hovingh, G.K., Humphries, S.E., Kovanen, P.T., Masana, L., Pajukanta, P., Parhofer, K.G., Ray, K.K., Stalenhoef, A.F., Stroes, E., Taskinen, M.R., Wiegman, A., Wiklund, O. and Chapman, M.J. (2014) 'Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management', *European Heart Journal*, 35(32), pp. 2146-2157.

Chapter 6

Thyroid Function Tests

Mastering Thyroid Function Tests

From TSH to Clinical Decision Making - The Thyroid's Chemical Story

Introduction: The Thyroid's Metabolic Orchestra

Thyroid function tests are like listening to a metabolic orchestra where TSH conducts from the pituitary podium, free T₄ plays the steady baseline melody, and T₃ provides the high-energy flourishes. When this orchestra plays in harmony, metabolism hums along perfectly. When it goes awry, patients experience the full spectrum from the sluggish exhaustion of hypothyroidism to the racing anxiety of hyperthyroidism.

This chapter transforms you from someone who simply orders "thyroid function" into a clinician who understands the elegant feedback loops, recognizes subtle patterns of dysfunction, and knows when borderline results matter and when they don't. You'll learn to distinguish primary thyroid disease from secondary disorders, understand when subclinical disease needs treatment, and avoid the common pitfalls that lead to unnecessary anxiety and overtreatment.



Clinical Pearl

"TSH is the Sensitive Early Warning": TSH changes before T₄ and T₃ become obviously abnormal. A TSH of 8 mIU/L with normal T₄ (subclinical hypothyroidism) represents earlier disease than a TSH of 8 with low T₄ (overt hypothyroidism). TSH amplifies small changes in thyroid hormone levels, making it your most sensitive screening test.

Thyroid Function Test Normal Ranges and Patterns

Test	Normal Range	Units	Clinical Significance	Key Notes
TSH	0.4-4.0	mIU/L	Primary screening test	Inverse relationship with T ₄ /T ₃
Free T ₄ (FT ₄)	9-25	pmol/L	Active hormone level	More accurate than total T ₄
Free T ₃ (FT ₃)	2.6-5.7	pmol/L	Most metabolically active	Usually not first-line test
Total T ₄	58-154	nmol/L	Includes bound hormone	Affected by binding proteins
Total T ₃	0.92-2.79	nmol/L	Includes bound hormone	Less useful than free T ₃
TPO Antibodies	<34	kIU/L	Autoimmune thyroiditis	Indicates Hashimoto's disease
TRAb (TSH Receptor)	<1.8	IU/L	Graves' disease marker	Positive in 95% of Graves'

Priority Assessment: When Thyroid Tests Signal Emergency

Most thyroid dysfunction develops slowly and can be managed in primary care. However, certain patterns represent medical emergencies requiring immediate hospital assessment—particularly thyroid storm in hyperthyroidism or myxedema coma in severe hypothyroidism. Recognition of these patterns and knowing when to act urgently versus when to investigate gradually can be life-saving.

▲ **Thyroid Storm Suspected**

TSH <0.1 with T₄ >50 pmol/L + fever $>38.5^{\circ}\text{C}$ + tachycardia >130 + confusion—immediate hospital admission, beta-blockers, antithyroid drugs

▲ **Myxedema Coma Risk**

TSH >20 with T₄ <5 pmol/L + hypothermia + bradycardia + confusion—urgent hospital assessment, IV levothyroxine, steroid cover

▲ **Severe Hyperthyroidism in Pregnancy**

TSH <0.1 with T₄ >40 pmol/L in pregnant woman—urgent obstetric/endocrine referral, propylthiouracil preferred over carbimazole

▲ **New Atrial Fibrillation + Hyperthyroidism**

TSH <0.1 with new AF—anticoagulation needed, urgent cardiology referral, treat thyrotoxicosis to restore sinus rhythm



Clinical Pearl

"The Subclinical Atrial Fibrillation Risk": Even subclinical hyperthyroidism (low TSH, normal T₄/T₃) increases atrial fibrillation risk by 60%. Any patient with new AF should have thyroid function checked urgently. Treating the hyperthyroidism often restores normal sinus rhythm and reduces stroke risk.

Step 1: The TSH-First Strategy - NICE 2019 Approach

NICE NG145 revolutionized thyroid testing by establishing TSH as the single best screening test for thyroid dysfunction. This evidence-based approach reduces unnecessary testing, focuses on clinically relevant abnormalities, and provides a systematic framework for interpretation that works in 95% of cases.

Start with TSH Alone

TSH is the most sensitive initial test for thyroid dysfunction. It detects both hyper- and hypothyroidism before T₄/T₃ levels become obviously abnormal. Only order additional tests if TSH is outside normal range.

Use Reflex Testing Strategy

If TSH abnormal, labs automatically add free T₄. If TSH very low (<0.1), may also add T₃. This cascading approach ensures appropriate testing without overordering unnecessary tests.

Interpret the Pattern

High TSH = hypothyroidism (primary thyroid failure). Low TSH = hyperthyroidism (or over-treatment). Normal TSH with symptoms = usually not thyroid disease, consider other causes.

Consider Clinical Context

Pregnancy, medications (amiodarone, lithium), acute illness, and central thyroid disease can all affect interpretation. Always correlate biochemistry with clinical presentation.

NICE 2019 TSH-Based Decision Tree

Patient with suspected thyroid dysfunction

Order TSH as first-line test

Most sensitive screening test for thyroid dysfunction

TSH normal (0.4-4.0): Thyroid dysfunction unlikely → Consider other causes of symptoms

TSH high (>4.0): Add free T₄ → Assess degree of hypothyroidism → Consider treatment

TSH low (<0.4): Add free T₄ ± T₃ → Assess degree of hyperthyroidism → Investigate cause

Normal TSH (0.4-4.0 mIU/L)

Interpretation: Thyroid function likely normal

Action: No further thyroid testing needed

Exception: Central thyroid disease, recent medication changes

Clinical: Look for other causes of symptoms

Raised TSH (>4.0 mIU/L)

Interpretation: Primary hypothyroidism

Mild (4-10): Subclinical hypothyroidism

Severe (>10): Overt hypothyroidism

Action: Check free T₄, consider treatment

Suppressed TSH (<0.4 mIU/L)

Interpretation: Hyperthyroidism or over-treatment

Mild (0.1-0.4): Subclinical hyperthyroidism

Severe (<0.1): Overt hyperthyroidism

Action: Check free T₄ and T₃, investigate cause

Extreme TSH Values

TSH >20: Severe hypothyroidism, urgent treatment

TSH <0.01: Severe hyperthyroidism, urgent assessment

Action: Same-day clinical review

Risk: Cardiac complications likely



Clinical Pearl

"The 10 mIU/L Treatment Threshold": NICE recommends treating hypothyroidism when TSH ≥ 10 mIU/L on two separate occasions. For TSH 4-10 mIU/L, treat if symptomatic, pregnant, or have cardiovascular disease. This evidence-based approach prevents over-treatment of borderline results while ensuring those who benefit receive therapy.

Step 2: Hypothyroidism - The Metabolic Slowdown

Subclinical Hypothyroidism

Pattern: TSH 4-10 mIU/L, normal free T₄

Prevalence: 5-10% of adults, more common in women

Symptoms: Often subtle or absent

Treatment: Consider if symptomatic, pregnant, or high cardiovascular risk

Overt Hypothyroidism

Pattern: TSH >10 mIU/L, low free T₄

Symptoms: Fatigue, weight gain, cold intolerance, constipation

Treatment: Levothyroxine replacement indicated

Monitoring: TSH every 6-8 weeks until stable

Severe Hypothyroidism

Pattern: TSH >20 mIU/L, very low T₄ <5 pmol/L

Symptoms: Severe fatigue, bradycardia, hypothermia

Complications: Heart failure, effusions, coma risk

Treatment: Urgent levothyroxine, consider hospital assessment

Central Hypothyroidism

Pattern: Low/normal TSH with low T₄

Cause: Pituitary or hypothalamic disease

Clues: Other pituitary hormone deficiencies

Action: Urgent endocrinology referral, MRI pituitary

Hypothyroidism Treatment Initiation Guidelines

TSH 4-6.9 mIU/L

Treatment if: Symptomatic + positive TPO antibodies

Or if: Pregnancy, trying to conceive

Monitor: TSH annually if not treating

Dose: 25-50 mcg levothyroxine daily

TSH 7-9.9 mIU/L

Treatment: Usually recommended

Especially if: Symptoms, cardiovascular disease

Start: 50 mcg levothyroxine (25 mcg if elderly/cardiac)

Monitor: TSH at 6-8 weeks

TSH ≥ 10 mIU/L

Treatment: Always recommended (NICE threshold)

Start: 50-100 mcg levothyroxine

Urgent if: Severe symptoms, cardiac complications

Target TSH: 0.4-2.5 mIU/L

TSH >20 mIU/L

Treatment: Urgent levothyroxine replacement

Dose: 100-150 mcg daily (if no cardiac disease)

Monitor: Weekly initially, watch for cardiac effects

Complications: Heart failure, myxedema coma risk

Hypothyroidism Risk Factors

Demographics: Female, age >60, family history

Autoimmune: Type 1 diabetes, celiac disease, vitiligo

Medications: Amiodarone, lithium, interferon

Previous: Thyroid surgery, radioiodine, neck irradiation

Hashimoto's Disease Features

Antibodies: Positive TPO antibodies (90% cases)

Goiter: Often present, may be nodular

Progression: Gradual onset over months to years

Associated: Other autoimmune conditions common

Treatment Monitoring

Initial: TSH every 6-8 weeks after dose changes

Stable: Annual TSH once optimal dose established

Target: TSH 0.4-2.5 mIU/L for most patients

Pregnancy: TSH <2.5 mIU/L in first trimester

Special Situations

Elderly: Start 25 mcg, titrate slowly

Cardiac disease: Start 25 mcg, monitor ECG

Pregnancy: Increase dose by 25-50%, urgent monitoring

Malabsorption: May need higher doses or liquid preparation



Clinical Pearl

"The Levothyroxine Timing Rule": Levothyroxine absorption is reduced by 40-50% if taken with food, coffee, or calcium. Always advise taking on an empty stomach, 30-60 minutes before breakfast, with water only. This simple instruction prevents most treatment failures and reduces the need for dose escalation.

Step 3: Hyperthyroidism - The Metabolic Acceleration

Understanding Hyperthyroidism Causes

Hyperthyroidism isn't one disease—it's a syndrome with multiple causes requiring different treatments:

- **Graves' disease (70%):** Autoimmune, TSH receptor antibodies positive
- **Toxic multinodular goiter (20%):** Usually older patients, nodular thyroid
- **Toxic adenoma (5%):** Single hot nodule on scan
- **Thyroiditis (5%):** Transient, often post-viral or post-partum

Distinguishing True Hyperthyroidism

Not all low TSH represents hyperthyroidism needing treatment:

- **Subclinical hyperthyroidism:** Low TSH, normal T₄/T₃
- **Non-thyroidal illness:** Sick euthyroid syndrome
- **Medication effects:** Over-replacement with levothyroxine
- **Pregnancy:** hCG-mediated TSH suppression (normal)

Graves' Disease Pattern

Biochemistry: TSH <0.1, elevated T₄ and T₃

Antibodies: TRAb positive (>95% cases)

Clinical: Diffuse goiter, eye signs, pretibial myxedema

Treatment: Antithyroid drugs, radioiodine, or surgery

Toxic Multinodular Goiter

Biochemistry: TSH <0.1, T₄/T₃ elevated

Clinical: Nodular goiter, usually older patients

Scan: Multiple hot areas

Treatment: Radioiodine preferred, surgery if large

Thyroiditis Pattern

Phase 1: TSH low, T₄/T₃ high (hyperthyroid)

Phase 2: TSH high, T₄/T₃ low (hypothyroid)

Phase 3: Recovery to normal (usually)

Treatment: Beta-blockers, avoid antithyroid drugs

Subclinical Hyperthyroidism

Biochemistry: TSH <0.4, normal T₄/T₃

Symptoms: Often minimal or absent

Risks: Atrial fibrillation, osteoporosis

Treatment: Consider if >65 years or cardiovascular disease

Confirm Hyperthyroidism

Low TSH with elevated T₄ and/or T₃ confirms hyperthyroidism. If T₄/T₃ normal, consider subclinical hyperthyroidism or non-thyroidal illness.

Determine the Cause

Check TRAb to diagnose Graves' disease. If negative, consider thyroid scan to distinguish toxic nodular disease from thyroiditis.

Assess Severity and Complications

Check for atrial fibrillation (ECG), heart failure, and thyroid eye disease. Severe hyperthyroidism needs urgent treatment.

Initiate Appropriate Treatment

Beta-blockers for symptom control, antithyroid drugs for Graves' disease, radioiodine for toxic nodular disease. Refer to endocrinology.

Hyperthyroidism Treatment Thresholds

- **TSH <0.1 + symptomatic:** Treat regardless of T₄/T₃ levels
- **TSH <0.1 + asymptomatic + >65 years:** Consider treatment (AF risk)
- **T₄ >40 pmol/L or T₃ >10 pmol/L:** Urgent treatment needed
- **New atrial fibrillation:** Immediate anticoagulation and rate control
- **Thyroid storm risk:** Fever, tachycardia >130, altered mental state
- **Pregnancy with hyperthyroidism:** Urgent obstetric-endocrine referral



Clinical Pearl

"The T₃ Toxicosis Clue": Some patients have isolated T₃ elevation with normal T₄—this is genuine hyperthyroidism requiring treatment. Always check T₃ when TSH is suppressed, especially if T₄ is normal but patient has hyperthyroid symptoms. T₃ toxicosis is more common in iodine-deficient areas and nodular thyroid disease.

Step 4: Special Situations and Tricky Patterns

Pregnancy Thyroid Changes

Normal changes: TSH falls in first trimester due to hCG

Reference ranges: Different for each trimester

Hypothyroidism: TSH >2.5 in first trimester

Hyperthyroidism: Distinguished from hyperemesis gravidarum

Non-Thyroidal Illness

Pattern: Low T3, low/normal T4, variable TSH

Cause: Severe acute illness, starvation

Recovery: Usually normalizes as illness resolves

Treatment: Generally not needed, treat underlying illness

Amiodarone Effects

Type 1: Hyperthyroidism in nodular goiter

Type 2: Destructive thyroiditis

Monitoring: TFTs every 6 months on amiodarone

Management: Complex, needs specialist input

Central Thyroid Disease

Pattern: Low T4 with low/normal TSH

Cause: Pituitary or hypothalamic disease

Clues: Other pituitary hormone deficiencies

Action: Urgent endocrinology referral, pituitary MRI

Drug-Induced Thyroid Dysfunction

Hypothyroidism: Amiodarone, lithium, interferon

Hyperthyroidism: Amiodarone, iodine contrast, levothyroxine

Monitoring: Baseline and regular TFTs on these drugs

Action: Discuss with prescriber before stopping

Thyroid Disease in Elderly

Presentation: Often atypical or subtle symptoms

Hyperthyroidism: May present as depression, AF, heart failure

Treatment: Start lower doses, monitor carefully

Targets: May accept slightly higher TSH (up to 6 mIU/L)

Subclinical Disease Decisions

Subclinical hypothyroidism: Treat if TSH >10, symptoms, or pregnancy

Subclinical hyperthyroidism: Treat if >65, cardiovascular disease, osteoporosis

Monitoring: 6-monthly if not treating

Antibodies: TPO positive increases progression risk

Thyroid Antibody Interpretation

TPO antibodies: Hashimoto's disease (90% sensitivity)

TRAb: Graves' disease (95% specificity)

Thyroglobulin antibodies: Less specific, often with TPO

Clinical use: Confirm autoimmune cause, predict progression





"The Sick Euthyroid Trap": Severely ill patients often have low T₃, low/normal T₄, and variable TSH (sick euthyroid syndrome). This is an adaptive response, not thyroid disease. Don't start thyroid hormone replacement in critically ill patients based on these results—treat the underlying illness and recheck TFTs after recovery.

Step 5: Monitoring and Follow-up Strategies

Thyroid Function Monitoring Timeline

Hypothyroidism Treatment Monitoring

TSH at 6-8 weeks after starting or changing levothyroxine dose. Continue adjusting until TSH 0.4-2.5 mIU/L. Then annual monitoring once stable dose achieved.

Hyperthyroidism Treatment Monitoring

TSH, FT₄, FT₃ every 6 weeks during antithyroid drug treatment. Once in remission, TSH every 3 months. Watch for relapse after stopping treatment.

Subclinical Disease Monitoring

If not treating subclinical hypothyroidism: TSH annually (or every 2-3 years if no symptoms). If subclinical hyperthyroidism: TSH every 6 months, watch for progression.

High-Risk Patient Monitoring

Pregnancy: TSH each trimester. Amiodarone: TSH every 6 months. Post-radioiodine: TSH at 6-8 weeks, then 6-monthly lifelong (hypothyroidism risk).

When to Refer to Endocrinology

- **New hyperthyroidism:** All cases need specialist assessment for cause and treatment
- **Thyroid eye disease:** Urgent referral if sight-threatening features
- **Pregnancy with thyroid disease:** Joint obstetric-endocrine care needed
- **Difficult-to-treat cases:** Poor response to standard treatment
- **Central thyroid disease:** Low T₄ with low/normal TSH
- **Complex drug interactions:** Amiodarone-induced thyroid dysfunction

Common Pitfalls and How to Avoid Them

The Normal TSH Overconfidence

Mistake: Assuming normal TSH excludes all thyroid disease

Reality: Central thyroid disease has low T₄ with normal/low TSH

Solution: Consider T₄ if pituitary disease suspected

Clues: Other pituitary hormone deficiencies

The Subclinical Overtreatment

Mistake: Treating all TSH 4-10 mIU/L with normal T₄

Reality: Many are asymptomatic and don't benefit

Solution: Follow NICE threshold of TSH ≥ 10 mIU/L

Consider treatment: If symptomatic, pregnant, or high CV risk

The Pregnancy TSH Panic

Mistake: Using non-pregnant reference ranges in pregnancy

Reality: TSH naturally falls in first trimester due to hCG

Solution: Use trimester-specific reference ranges

Target: TSH < 2.5 mIU/L in first trimester

The Sick Patient Thyroid Testing

Mistake: Ordering TFTs in acutely unwell patients

Reality: Sick euthyroid syndrome gives misleading results

Solution: Avoid TFTs in acute illness unless thyroid storm suspected

Timing: Recheck 6-8 weeks after recovery

Red Flags in Thyroid Function Testing

- **TSH and T₄ moving in same direction:** Consider central thyroid disease, non-thyroidal illness
- **Normal TSH with obvious hypo/hyperthyroid symptoms:** Recheck timing, consider other diagnoses
- **Extreme TSH values (> 20 or < 0.01):** Need urgent clinical assessment and treatment
- **Discordant biochemistry and clinical picture:** Consider drug effects, recent illness
- **Poor treatment response:** Check compliance, absorption, drug interactions

Summary: The Five-Step Thyroid Function Mastery Method

1. TSH First Strategy

Start with TSH as most sensitive screening test

2. Pattern Recognition

High TSH = hypothyroidism, Low TSH = hyperthyroidism

3. Clinical Correlation

Combine biochemistry with symptoms and examination

4. Treatment Thresholds

Use evidence-based NICE thresholds for intervention

5. Monitoring Strategy

Regular follow-up with appropriate intervals and targets

Key Numbers to Remember

TSH ≥ 10 mIU/L: NICE treatment threshold for hypothyroidism

TSH < 0.1 mIU/L: Significant hyperthyroidism needing treatment

TSH 0.4–2.5 mIU/L: Target range for levothyroxine therapy

TSH < 2.5 mIU/L: Target in first trimester of pregnancy

Clinical Decision Points

Emergency referral: Thyroid storm, myxedema coma

Urgent referral: All new hyperthyroidism, pregnancy + thyroid disease

Routine referral: Central thyroid disease, difficult cases

Monitor only: Subclinical disease not meeting treatment criteria



Clinical Pearl

"The Thyroid's Slow Dance": Thyroid function changes slowly—allow 6–8 weeks between dose adjustments for full effect. TSH has a long half-life, so early retesting gives false reassurance. Patient symptoms may improve before TSH normalizes, so don't chase perfect numbers if the patient feels well. Steady, patient titration beats aggressive dosing every time.

Take Home Messages for Thyroid Function Tests

- **TSH first strategy:** Most sensitive single test for thyroid dysfunction
- **Evidence-based thresholds:** TSH ≥ 10 mIU/L for hypothyroidism treatment (NICE)
- **Pattern recognition:** High TSH = hypothyroidism, Low TSH = hyperthyroidism
- **Clinical correlation essential:** Biochemistry must fit with clinical picture
- **Avoid overtreatment:** Not all abnormal results need intervention
- **Pregnancy changes everything:** Different reference ranges and treatment targets

Clinical Guidelines & Evidence Base

NICE Guideline NG145

Thyroid disease: assessment and management

- 2019
[Access Guidelines](#)

British Thyroid Foundation

Guidelines and Statements

- Updated 2024
[Access Guidelines](#)

References

- Biondi, B. and Cooper, D.S.** (2008) 'The clinical significance of subclinical thyroid dysfunction', *Endocrine Reviews*, 29(1), pp. 76-131.
- Chaker, L., Bianco, A.C., Jonklaas, J. and Peeters, R.P.** (2017) 'Hypothyroidism', *The Lancet*, 390(10101), pp. 1550-1562.
- De Leo, S., Lee, S.Y. and Braverman, L.E.** (2016) 'Hyperthyroidism', *The Lancet*, 388(10047), pp. 906-918.
- Jonklaas, J., Bianco, A.C., Bauer, A.J., Burman, K.D., Cappola, A.R., Celi, F.S., Cooper, D.S., Kim, B.W., Peeters, R.P., Rosenthal, M.S. and Sawka, A.M.** (2014) 'Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement', *Thyroid*, 24(12), pp. 1670-1751.
- National Institute for Health and Care Excellence (NICE)** (2019) *Thyroid disease: assessment and management. NICE guideline [NG145]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng145> (Accessed: 30 September 2025).
- Ross, D.S., Burch, H.B., Cooper, D.S., Greenlee, M.C., Laurberg, P., Maia, A.L., Rivkees, S.A., Samuels, M., Sosa, J.A., Stan, M.N. and Walter, M.A.** (2016) '2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis', *Thyroid*, 26(10), pp. 1343-1421.
- Taylor, P.N., Albrecht, D., Scholz, A., Gutierrez-Buey, G., Lazarus, J.H., Dayan, C.M. and Okosieme, O.E.** (2018) 'Global epidemiology of hyperthyroidism and hypothyroidism', *Nature Reviews Endocrinology*, 14(5), pp. 301-316.

Chapter 7

HbA_{1c} & Diabetes Monitoring

Mastering HbA1c & Diabetes Monitoring

From Numbers to Comprehensive Diabetes Care

Introduction: The Three-Month Memory of Metabolism

HbA1c isn't just a number—it's a three-month metabolic memoir that tells the story of every glucose spike, every dietary indiscretion, and every medication adjustment. Unlike the momentary snapshot of a random glucose, HbA1c reveals the sustained patterns of glucose control, making it the gold standard for both diagnosing diabetes and monitoring treatment effectiveness. Understanding how to interpret, target, and optimize HbA1c transforms you from someone who simply checks numbers into a clinician who can guide patients toward better long-term health outcomes.

This chapter teaches you to read HbA1c in the context of individual patient needs, understand when targets should be individualized, and recognize the clinical situations where HbA1c might mislead. You'll learn the evidence-based targets that prevent complications, the monitoring frequencies that catch problems early, and the strategies that help patients achieve sustainable glucose control.



Clinical Pearl

"The 2-3 Month Rule": HbA1c reflects average glucose levels over the past 8-12 weeks, with more recent levels weighted more heavily. A dramatic improvement in diet and medication adherence will be fully visible in 2-3 months. Don't expect HbA1c to change significantly before this time—and don't change treatment based on shorter intervals.

HbA1c Interpretation and Target Ranges

HbA1c Level	IFCC Units (mmol/mol)	Old % Units	Interpretation	Clinical Action
Normal	<42	<6.0%	Normal glucose metabolism	No specific action needed
Prediabetes	42-47	6.0-6.4%	High risk of diabetes	Lifestyle intervention program
Diabetes Diagnosis	≥48	≥6.5%	Diabetes mellitus	Confirm diagnosis, start treatment
Target (Type 2 - Low Risk)	48	6.5%	Optimal control	Lifestyle/single drug not causing hypoglycemia
Target (Most Adults)	53	7.0%	Good control	Multiple drugs or hypoglycemia risk
Action Threshold	58	7.5%	Suboptimal control	Intensify treatment, review adherence
Poor Control	>75	>9.0%	High complication risk	Urgent treatment intensification

Priority Assessment: When HbA1c Signals Urgent Action

Most diabetes management operates on a steady, long-term timeline reflecting HbA1c's inherent 2-3 month delay. However, certain HbA1c values or patterns demand immediate attention—either because they indicate dangerously poor control or because they represent opportunities for urgent intervention to prevent complications.

▲ **HbA1c >86 mmol/mol (>10%)**

Severe hyperglycemia with high complication risk—urgent treatment intensification, consider insulin, screen for infections and DKA

▲ **New Diabetes HbA1c >75 mmol/mol (>9%)**

Significant hyperglycemia at diagnosis—consider immediate insulin, exclude Type 1 diabetes, urgent complications screening

▲ **HbA1c <42 mmol/mol (<6%) on Treatment**

Over-treatment with high hypoglycemia risk—reduce medications immediately, especially sulfonylureas and insulin

▲ **Rapidly Rising HbA1c (>10 mmol/mol in 6 months)**

Progressive beta-cell failure or treatment non-adherence—urgent medication review, consider insulin, exclude Type 1



Clinical Pearl

"The Honeymoon Period Recognition": Newly diagnosed Type 2 diabetes often shows dramatic HbA1c improvements (20-30 mmol/mol drop) in the first 3-6 months with lifestyle changes and metformin. Don't be misled into thinking this will continue indefinitely—the honeymoon ends, and progressive treatment intensification will be needed to maintain control.

Step 1: NICE 2024 Target Strategy - Individualized Excellence

NICE guidelines have evolved from one-size-fits-all targets to individualized HbA1c goals based on patient characteristics, treatment burden, and life expectancy. This evidence-based approach maximizes benefits while minimizing harm, particularly the risk of hypoglycemia in vulnerable populations.

Assess Patient Risk Profile

Low risk: Healthy, long life expectancy, motivated. Standard targets apply (48-53 mmol/mol). High risk: Elderly, frail, multiple comorbidities, hypoglycemia-prone. Consider relaxed targets (58-64 mmol/mol).

Consider Treatment Complexity

Simple treatment (lifestyle ± metformin): Aim for 48 mmol/mol. Complex treatment (multiple drugs, insulin): Aim for 53 mmol/mol. Balance benefit against treatment burden and side effects.

Account for Hypoglycemia Risk

High hypoglycemia risk (elderly, CKD, CVD, previous episodes): Relax targets to 58 mmol/mol.

Low hypoglycemia risk: Can pursue tighter targets (48 mmol/mol) if motivated and capable.

Set Collaborative Goals

Discuss targets with patient, explaining benefits and risks. Agree on realistic, achievable goals.
Review and adjust based on response to treatment and changing circumstances.

Optimal Target (48 mmol/mol)

For: Newly diagnosed, healthy adults
Treatment: Lifestyle ± single non-hypoglycemic drug
Benefit: Maximal complication reduction
Monitor: 3-6 monthly, watch for hypoglycemia

Standard Target (53 mmol/mol)

For: Most adults with Type 2 diabetes
Treatment: Multiple drugs, hypoglycemia-causing medications
Benefit: Good complication reduction with acceptable hypoglycemia risk
Monitor: 3-6 monthly

Relaxed Target (58 mmol/mol)

For: Elderly, frail, limited life expectancy
Rationale: Avoid hypoglycemia, reduce treatment burden
Benefit: Maintains quality of life, prevents acute complications
Monitor: 6-12 monthly if stable

Action Threshold (58 mmol/mol)

Trigger: Treatment intensification needed
Actions: Review adherence, intensify lifestyle, add/switch medications
Urgency: Don't delay—complications increase significantly above this level
Exception: If already at relaxed target for clinical reasons

NICE 2024 Individualized Target Selection

Adult with Type 2 diabetes needing HbA1c target

Assess patient factors: age, frailty, comorbidities, hypoglycemia risk

Healthy, motivated: Target 48 mmol/mol (lifestyle ± single drug)

Standard risk: Target 53 mmol/mol (multiple drugs, insulin)

High risk/elderly: Consider relaxed target 58 mmol/mol (individualized)



Clinical Pearl

"The 58 mmol/mol Inflection Point": HbA1c above 58 mmol/mol (7.5%) is NICE's trigger for treatment intensification. This isn't arbitrary—it's where cardiovascular and microvascular complications start rising steeply. Don't let patients drift above this level without action, even if they feel well. The complications are silent until they're irreversible.

Step 2: HbA1c for Diabetes Diagnosis - Beyond Glucose Tests

Diagnostic Criteria (≥ 48 mmol/mol)

Advantage: No fasting required, reflects long-term glucose

Confirmation: Single test sufficient if symptomatic

Asymptomatic: Need second confirmatory test

Reliability: Less affected by acute illness than glucose

Prediabetes (42-47 mmol/mol)

Risk: 5-10% annual progression to diabetes

Action: Intensive lifestyle intervention

Monitoring: Annual HbA1c testing

Prevention: 7-10% weight loss can prevent/delay diabetes

Normal (< 42 mmol/mol)

Interpretation: Low diabetes risk currently

Monitoring: Repeat in 3-5 years if risk factors present

Lifestyle: Continue healthy diet and exercise

Note: Can still have impaired glucose tolerance

Very High at Diagnosis (> 86 mmol/mol)

Concern: Consider Type 1 diabetes, especially if young

Tests: Check GAD antibodies, C-peptide

Treatment: May need immediate insulin

Complications: Screen urgently for retinopathy, nephropathy

When HbA1c May Be Unreliable

Hemoglobinopathies: Sickle cell disease, thalassemia

High red cell turnover: Hemolysis, bleeding, pregnancy

Renal failure: Reduced red cell lifespan

Iron deficiency: Falsely elevated HbA1c

Alternative Diagnostic Tests

Fasting glucose: ≥ 7.0 mmol/L on two occasions

Random glucose: ≥ 11.1 mmol/L with symptoms

OGTT: 2-hour glucose ≥ 11.1 mmol/L

Fructosamine: Reflects 2-3 week average glucose

High-Risk Groups for Screening

Age > 40 : Every 3 years

BMI > 25 : Plus additional risk factors

Family history: First-degree relative with diabetes

Ethnicity: South Asian, African-Caribbean, Middle Eastern

Clinical Situations Requiring Testing

Cardiovascular disease: All patients should be screened

Hypertension: Check for diabetes as cause/comorbidity

PCOS: High insulin resistance risk

Previous gestational diabetes: Annual screening lifelong



Clinical Pearl

"The Iron Deficiency HbA1c Trap": Iron deficiency falsely elevates HbA1c because iron-deficient red cells live longer and accumulate more glucose. If HbA1c seems inconsistent with symptoms or other glucose measures, check iron studies. Treating iron deficiency can lower HbA1c by 10-15 mmol/mol without any diabetes treatment changes.

Step 3: Monitoring Frequency and Timing - Strategic Surveillance

HbA1c Monitoring Schedule Based on Clinical Situation

Stable, Well-Controlled

Frequency: Every 6 months
Criteria: HbA1c at target, stable treatment
Monitoring: Can reduce to annual if very stable
Action: Continue current management

Treatment Changes/Poor Control

Frequency: Every 3 months
Criteria: Recent medication changes, HbA1c above target
Duration: Until stable at target
Action: Assess response, further intensify if needed

Newly Diagnosed

Initial: 3 months after starting treatment
Expected: Significant improvement (15-25 mmol/mol drop)
Follow-up: 3-monthly until stable
Target: Reach treatment goal within 6-9 months

Unstable/Complex Cases

Frequency: Every 3 months minimum
Situations: Frequent hypoglycemia, erratic control
Additional: Consider continuous glucose monitoring
Specialist: May need endocrinology referral

Determine Current Control Status

At target and stable: 6-monthly monitoring. Above target or recent changes: 3-monthly monitoring. Severe elevation (>75 mmol/mol): Consider more frequent monitoring initially.

Assess Treatment Stability

Stable medications and HbA1c: Can extend intervals. Recent medication changes: More frequent monitoring needed. Multiple changes planned: Don't check too early.

Consider Patient Factors

Reliable, motivated patients: Standard intervals. Poor adherence or complex comorbidities: More frequent monitoring. Hypoglycemia risk: May need additional glucose monitoring.

Plan Next Steps

Based on result and trend, plan treatment adjustments. Set clear expectations with patient about next monitoring interval. Document rationale for monitoring frequency.

HbA1c Monitoring: When NOT to Test

- **Too soon after changes:** Wait at least 2-3 months after medication adjustments
- **During acute illness:** HbA1c doesn't reflect acute changes
- **Patient non-adherence:** Focus on adherence support, not more testing
- **End-stage complications:** May not be meaningful in advanced disease
- **Very short life expectancy:** Symptom control more important than HbA1c targets



Clinical Pearl

"The 3-Month Minimum Rule": Never check HbA1c sooner than 3 months after treatment changes unless there's a specific clinical concern. HbA1c reflects 8-12 weeks of glucose control, with recent weeks weighted more heavily. Checking at 6 weeks gives false reassurance and wastes resources. Be patient—good diabetes care is a marathon, not a sprint.

Step 4: Treatment Intensification Based on HbA1c - The Escalation Strategy

NICE Treatment Intensification Thresholds

Treatment intensification should follow evidence-based thresholds:

- **HbA1c ≥ 58 mmol/mol:** Always intensify treatment
- **HbA1c 53-58 mmol/mol:** Consider intensification if target is 53
- **HbA1c 48-53 mmol/mol:** Intensify if target is 48
- **HbA1c < 48 mmol/mol:** Consider reducing treatment (hypoglycemia risk)

Systematic Approach to Treatment Intensification

Before adding medications, always address:

- **Adherence:** Are they taking current medications?
- **Lifestyle:** Diet and exercise optimization
- **Timing:** Correct medication timing for absorption
- **Barriers:** Cost, side effects, understanding

First Intensification (58-64 mmol/mol)

Actions: Reinforce lifestyle, optimize current medications

Add: Second-line drug (SGLT2i, DPP4i, sulfonylurea)

Review: Adherence, side effects, contraindications

Timeline: Expect 10-15 mmol/mol improvement in 3 months

Second Intensification (64-75 mmol/mol)

Actions: Add third drug or consider insulin

Options: GLP1 agonist, basal insulin, intensive lifestyle

Specialist: Consider endocrinology referral

Monitoring: 3-monthly HbA1c, watch for hypoglycemia

Urgent Intensification (> 75 mmol/mol)

Priority: Rapid glucose reduction needed

Treatment: Consider insulin \pm specialist referral

Investigations: Screen for complications

Support: Diabetes education, frequent monitoring

Over-Treatment (< 42 mmol/mol)

Risk: Severe hypoglycemia, mortality increase

Actions: Reduce sulfonylurea, insulin doses

Review: Is target appropriate for this patient?

Monitor: Glucose logs, hypoglycemia frequency

Factors Affecting HbA1c Response

Good responders: Newly diagnosed, good adherence, beta-cell function

Poor responders: Long diabetes duration, insulin deficiency, severe insulin resistance

Rapid responders: Lifestyle changes, insulin therapy

Slow responders: Metformin, DPP4 inhibitors

Expected HbA1c Improvements

Lifestyle alone: 5-15 mmol/mol reduction

Metformin: 10-15 mmol/mol reduction

Insulin: 15-30 mmol/mol reduction (dose-dependent)

GLP1 agonists: 10-20 mmol/mol reduction

Barriers to HbA1c Improvement

Non-adherence: Most common cause of poor response

Insulin resistance: Weight gain, inactivity, medications

Progressive beta-cell failure: Natural progression of Type 2 diabetes

Undiagnosed Type 1: Especially if young with rapid progression

When to Consider Specialist Referral

Poor control: HbA1c >75 mmol/mol despite maximal oral therapy

Rapid progression: HbA1c rise >20 mmol/mol in 12 months

Young onset: Diabetes diagnosed under age 40

Atypical presentation: Lean, rapid progression, ketosis



Clinical Pearl

"The Adherence Before Addition Rule": Before intensifying treatment for poor HbA1c control, spend 5 minutes checking adherence. Ask specifically: "In the last week, how many days did you miss your diabetes medications?" Non-adherence is the most common cause of poor control and the cheapest to fix. New medications won't help if the current ones aren't being taken properly.

Step 5: Special Situations and HbA1c Interpretation

Type 1 Diabetes

Target: 48 mmol/mol (6.5%) or lower

Monitoring: 3-6 monthly

Challenge: Hypoglycemia risk with tight control

Tools: Continuous glucose monitoring, insulin pumps

Pregnancy (Pre-existing Diabetes)

Target: <48 mmol/mol if safely achievable

Preconception: <48 mmol/mol reduces congenital abnormalities

Monitoring: Monthly HbA1c plus frequent glucose monitoring

Care: Joint diabetes-obstetric management

Elderly/Frail Patients

Targets: 58-69 mmol/mol (individualized)

Priority: Avoid hypoglycemia, maintain quality of life

Medications: Avoid sulfonylureas, prefer DPP4 inhibitors

Monitoring: 6-12 monthly if stable

End-Stage Kidney Disease

HbA1c limitations: May be falsely low due to reduced RBC lifespan

Alternative: Fructosamine, glucose monitoring

Targets: Less stringent (58-64 mmol/mol)

Medications: Many require dose adjustment or are contraindicated

Assess Reliability of HbA1c

Consider conditions affecting red cell lifespan: anemia, hemolysis, kidney disease, pregnancy. If unreliable, use alternative measures like fructosamine or continuous glucose monitoring.

Evaluate Individual Risk-Benefit

Weigh potential benefits of tight control (complication reduction) against risks (hypoglycemia, treatment burden). Consider life expectancy, existing complications, patient preferences.

Adjust Targets Appropriately

Healthy adults: Standard targets (48-53 mmol/mol). Elderly/frail: Relaxed targets (58-69 mmol/mol). Complex situations: Individualized targets with specialist input.

Plan Monitoring Strategy

Stable disease: 6-monthly HbA1c. Active management: 3-monthly HbA1c. High-risk situations: Additional glucose monitoring, possible continuous glucose monitoring.

HbA1c Values Requiring Immediate Action

- **HbA1c >86 mmol/mol (>10%):** High complication risk, consider urgent specialist referral
- **HbA1c <42 mmol/mol (<6%) on treatment:** Over-treatment, reduce hypoglycemia-causing drugs
- **Rising HbA1c >20 mmol/mol in 12 months:** Suggests progressive beta-cell failure or poor

adherence

- **HbA1c >75 mmol/mol (>9%) at diagnosis:** Consider Type 1 diabetes, immediate insulin may be needed
- **Discordant HbA1c and symptoms:** Consider alternative causes or measurement issues



Clinical Pearl

"The Time in Range Revolution": HbA1c tells you the average but not the journey. A patient with HbA1c 53 mmol/mol could have stable glucose or wild swings averaging out to the target. Consider time in range (70-180 mg/dL or 3.9-10.0 mmol/L) as an additional metric, especially in Type 1 diabetes or those on insulin. This is where continuous glucose monitoring adds real clinical value.

Common Pitfalls and How to Avoid Them

The Iron Deficiency False Elevation

Problem: Iron deficiency falsely elevates HbA1c
Mechanism: Longer red cell lifespan accumulates more glucose
Solution: Check iron studies if HbA1c seems discordant
Effect: Can falsely elevate HbA1c by 10-15 mmol/mol

The Too-Soon Recheck

Problem: Checking HbA1c <3 months after changes
Reality: Won't reflect full effect of interventions
Solution: Wait minimum 3 months, preferably 3-4 months
Exception: Genuine clinical concern about control

The One-Size-Fits-All Target

Problem: Same target (53 mmol/mol) for all patients
Reality: Elderly, frail patients may need higher targets
Solution: Individualize based on life expectancy, hypoglycemia risk
NICE guidance: Consider relaxing targets case-by-case

The Over-Treatment Trap

Problem: Pursuing HbA1c <42 mmol/mol with medications
Risk: Severe hypoglycemia, increased mortality
Solution: Reduce medications if HbA1c consistently <42 mmol/mol
Target sweet spot: 48-58 mmol/mol for most patients

Red Flags in HbA1c Interpretation

- **HbA1c improving but patient feels worse:** Check for hypoglycemia, over-treatment
- **HbA1c discordant with home glucose readings:** Consider measurement error, compliance issues
- **Unexplained HbA1c rise despite good adherence:** Progressive beta-cell failure, intercurrent illness
- **Very low HbA1c on minimal treatment:** Consider undiagnosed conditions affecting measurement
- **HbA1c not improving despite intensification:** Check adherence, consider specialist referral

Summary: The Five-Step HbA1c Mastery Method

1. Individualized Targets

Set appropriate HbA1c goals based on patient characteristics

2. Strategic Monitoring

Time HbA1c checks appropriately—never <3 months apart

3. Evidence-Based Intensification

Use 58 mmol/mol as trigger for treatment escalation

4. Address Adherence First

Check medication compliance before adding new treatments

5. Recognize Limitations

Know when HbA1c may be unreliable and use alternatives

Key HbA1c Thresholds

Diabetes diagnosis: ≥ 48 mmol/mol ($\geq 6.5\%$)

Optimal target: 48 mmol/mol (6.5%) for low-risk patients

Standard target: 53 mmol/mol (7.0%) for most patients

Action threshold: 58 mmol/mol (7.5%) triggers intensification

Over-treatment: < 42 mmol/mol ($< 6.0\%$) requires dose reduction

Clinical Decision Points

Emergency review: HbA1c > 86 mmol/mol or < 42 mmol/mol

Specialist referral: HbA1c > 75 mmol/mol despite optimal oral therapy

Treatment intensification: Any HbA1c ≥ 58 mmol/mol

Stable monitoring: HbA1c at individualized target



Clinical Pearl

"The HbA1c Journey, Not Destination": HbA1c is a guide, not a goal in itself. The ultimate aim is preventing complications while maintaining quality of life. A patient with HbA1c 58 mmol/mol who exercises regularly, eats well, and feels good may be doing better than someone with HbA1c 48 mmol/mol achieved through intensive medication with frequent hypoglycemia. Always consider the whole person, not just the number.

Take Home Messages for HbA1c Monitoring

- **Individualize targets:** Not everyone needs the same HbA1c goal
- **Wait 3 months:** Don't check HbA1c too frequently after changes
- **58 mmol/mol threshold:** NICE trigger for treatment intensification
- **Address adherence first:** Before adding new medications, ensure current ones are taken
- **Avoid over-treatment:** HbA1c < 42 mmol/mol on treatment is dangerous
- **Consider limitations:** HbA1c can be unreliable in certain conditions

Clinical Guidelines & Evidence Base

NICE Guideline NG28

Type 2 diabetes in adults: management

- Updated 2022

[Access Guidelines](#)

NICE Guideline NG17

Type 1 diabetes in adults: diagnosis and management

- 2015

[Access Guidelines](#)

American Diabetes Association

Standards of Care in Diabetes—2025

[Access Standards](#)

Diabetes UK

Evidence-based nutrition guidelines for the prevention and management of diabetes

- 2024

[Access Guidelines](#)

References

American Diabetes Association (2025) 'Standards of Care in Diabetes—2025', *Diabetes Care*, 48(Supplement 1), pp. S1-S321.

Diabetes Control and Complications Trial Research Group (1993) 'The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus', *New England Journal of Medicine*, 329(14), pp. 977-986.

Holman, R.R., Paul, S.K., Bethel, M.A., Matthews, D.R. and Neil, H.A. (2008) '10-year follow-up of intensive glucose control in type 2 diabetes', *New England Journal of Medicine*, 359(15), pp. 1577-1589.

National Institute for Health and Care Excellence (NICE) (2015) *Type 1 diabetes in adults: diagnosis and management. NICE guideline [NG17]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng17> (Accessed: 30 September 2025).

National Institute for Health and Care Excellence (NICE) (2022) *Type 2 diabetes in adults: management. NICE guideline [NG28]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng28> (Accessed: 30 September 2025).

Stratton, I.M., Adler, A.I., Neil, H.A., Matthews, D.R., Manley, S.E., Cull, C.A., Hadden, D., Turner, R.C. and Holman, R.R. (2000) 'Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study', *BMJ*, 321(7258), pp. 405-412.

UK Prospective Diabetes Study (UKPDS) Group (1998) 'Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)', *The Lancet*, 352(9131), pp. 837-853.

Chapter 8

Inflammatory Markers

Mastering Inflammatory Markers

*From CRP to Clinical Decisions - Inflammation
Detection and Interpretation*

Introduction: The Body's Alarm System

Inflammatory markers are the body's smoke detectors—they tell you something is burning, but not necessarily what or where. CRP rises rapidly with acute bacterial infections, ESR climbs slowly with chronic inflammatory conditions, and both can be elevated in everything from pneumonia to temporal arteritis. The skill lies not just in recognizing elevated values, but in understanding what type of inflammation you're seeing and how urgently you need to act.

This chapter transforms you from someone who simply flags abnormal inflammatory markers into a clinician who can distinguish acute from chronic inflammation, bacterial from viral infections, and serious from benign causes. You'll learn when to start antibiotics, when to investigate further, and when to simply monitor. Most importantly, you'll understand the NICE evidence-based approach to using CRP for antibiotic stewardship.



Clinical Pearl

"CRP is Fast, ESR is Slow": CRP rises within 4-6 hours of inflammation starting, peaks at 48 hours, and falls rapidly with treatment. ESR takes days to rise, peaks later, and falls slowly. Use CRP for acute decisions (bacterial vs viral, treatment response). Use ESR for chronic conditions (temporal arteritis, polymyalgia rheumatica, monitoring inflammatory diseases).

Inflammatory Markers Normal Ranges and Clinical Thresholds

Marker	Normal Range	Units	Clinical Significance	Key Decision Points
CRP (C-Reactive Protein)	<3.0	mg/L	Acute inflammation	<20: No antibiotics, 20-100: Consider, >100: Give antibiotics
ESR (Erythrocyte Sedimentation Rate)	0-15 (M), 0-20 (F)	mm/hr	Chronic inflammation	>50: Investigate, >100: Urgent investigation
High Sensitivity CRP (hs-CRP)	<1.0	mg/L	Cardiovascular risk	<1: Low risk, 1-3: Moderate, >3: High risk
Procalcitonin (PCT)	<0.25	ng/mL	Bacterial infection	<0.25: Unlikely bacterial, >0.5: Probable bacterial
Ferritin	15-200 (F), 30-400 (M)	µg/L	Iron stores + inflammation	>1000: Consider hemophagocytic syndrome
Plasma Viscosity (PV)	1.50-1.72	mPa.s	Alternative to ESR	>1.72: Abnormal, less affected by anemia

Priority Assessment: When Inflammatory Markers Signal Emergency

Most elevated inflammatory markers represent manageable conditions requiring investigation or treatment, but certain patterns or levels demand immediate attention. These red flag scenarios can indicate life-threatening conditions requiring urgent hospital assessment or immediate antibiotic therapy.

▲ **CRP >200 mg/L with Fever**

Severe bacterial infection, sepsis risk—immediate blood cultures, urgent antibiotics, consider hospital admission for IV therapy

▲ **ESR >100 mm/hr**

Urgent investigation needed—consider malignancy, temporal arteritis, endocarditis, osteomyelitis. Same-day specialist referral if unwell

▲ **CRP >50 mg/L + Headache in >50 years**

Temporal arteritis risk—immediate prednisolone 40-60mg, urgent ophthalmology referral, temporal artery biopsy within 7 days

▲ **Ferritin >1000 µg/L + Fever + Cytopenias**

Hemophagocytic lymphohistiocytosis possible—urgent hematology referral, consider bone marrow examination



Clinical Pearl

"The Giant Cell Arteritis Emergency": New headache with jaw claudication in anyone over 50 with elevated CRP/ESR is temporal arteritis until proven otherwise. Start prednisolone immediately—don't wait for biopsy. Irreversible blindness can occur within hours. The biopsy remains positive for up to 7 days after starting steroids, but vision loss is irreversible.

Step 1: CRP-Guided Antibiotic Decisions - NICE 2024 Approach

NICE guidelines have revolutionized respiratory infection management by providing evidence-based CRP thresholds for antibiotic prescribing. This approach reduces inappropriate antibiotic use while ensuring patients with bacterial infections receive prompt treatment. Understanding these thresholds and their limitations is essential for modern primary care.

Clinical Assessment First

Always assess clinical severity before CRP. Severe illness (high fever, rigors, severe dyspnea, hemodynamic instability) needs immediate antibiotics regardless of CRP level. CRP guides decisions in clinically uncertain cases.

Apply NICE CRP Thresholds

CRP <20 mg/L: Don't routinely offer antibiotics. CRP 20-100 mg/L: Consider delayed prescription. CRP >100 mg/L: Offer immediate antibiotic therapy. These thresholds reduce antibiotic prescribing by 20-30%.

Consider Point-of-Care Testing

Point-of-care CRP testing allows immediate decision-making in primary care. Results available within 3-5 minutes enable evidence-based prescribing decisions during the consultation.

Safety Net and Follow-up

Provide clear safety-netting advice regardless of CRP result. Delayed prescriptions for CRP 20-100 mg/L should have specific instructions for use if symptoms worsen or persist beyond 48-72 hours.

CRP <20 mg/L

Interpretation: Bacterial infection unlikely

Action: No routine antibiotics

Advice: Symptomatic treatment, safety-netting

Follow-up: If symptoms worsen or persist >7 days

CRP 20-100 mg/L

Interpretation: Possible bacterial infection

Action: Consider delayed antibiotic prescription

Instructions: Use if symptoms worsen after 48-72 hours

Benefit: Reduces antibiotic use by 40% vs immediate prescription

CRP >100 mg/L

Interpretation: Bacterial infection likely

Action: Immediate antibiotic therapy

Choice: First-line antibiotics as per local guidelines

Review: If no improvement in 48-72 hours

CRP >200 mg/L

Interpretation: Severe bacterial infection likely

Action: Urgent antibiotics ± hospital assessment

Investigations: Blood cultures, chest X-ray

Monitor: Clinical response, repeat CRP in 48-72 hours

NICE CRP-Guided Respiratory Infection Management

Patient with symptoms of lower respiratory tract infection

Clinical assessment: Severe illness present?

Yes (severe): Immediate antibiotics regardless of CRP

No (mild-moderate): Check CRP to guide antibiotic decision

CRP result guides: <20 no antibiotics, 20-100 delayed prescription, >100 immediate antibiotics



Clinical Pearl

"The 48-Hour CRP Rule": CRP peaks at 48 hours in bacterial infections. If treating based on high CRP (>100), expect CRP to fall by 50% within 48-72 hours with effective antibiotic therapy. If CRP isn't falling or continues rising, consider treatment failure, complications, or alternative diagnoses. This monitoring approach prevents both over-treatment and under-treatment.

Step 2: ESR - The Chronic Inflammation Detective

Normal ESR (Age-Adjusted)

General rule: Upper limit = (age + 10)/2 for women, age/2 for men

Young adults: <15 mm/hr (men), <20 mm/hr (women)

Elderly: Can be 40-50 mm/hr normally

Clinical: Chronic inflammatory disease unlikely

Mildly Elevated ESR (20-50 mm/hr)

Causes: Mild infection, early inflammatory disease

Age factor: May be normal in elderly patients

Investigation: Clinical correlation, consider repeat in 2-4 weeks

Action: Targeted investigation based on symptoms

Moderately Elevated ESR (50-100 mm/hr)

Causes: Active inflammatory disease, malignancy, infection

Investigation: FBC, biochemistry, autoimmune screen

Urgency: Usually requires systematic investigation

Conditions: RA, IBD, vasculitis, temporal arteritis

Highly Elevated ESR (>100 mm/hr)

Urgent causes: Temporal arteritis, endocarditis, malignancy

Investigation: Same-day assessment if unwell

Red flags: Headache >50 years, heart murmur, weight loss

Action: Urgent specialist referral often required

Conditions with Very High ESR (>100)

Vasculitis: Temporal arteritis, polymyalgia rheumatica

Malignancy: Multiple myeloma, lymphoma, solid tumors

Infection: Osteomyelitis, endocarditis, abscess

Inflammatory: SLE flare, severe RA

Factors Affecting ESR

Falsely low: Heart failure, sickle cell disease, polycythemia

Falsely high: Anemia, pregnancy, elderly age

Medications: Steroids lower ESR, heparin can elevate

Alternative: Plasma viscosity less affected by anemia

ESR vs CRP Comparison

ESR advantages: Better for chronic conditions, GCA screening

CRP advantages: Rapid response, specific for acute inflammation

Combined use: ESR high + CRP normal suggests chronic inflammation

Discordance: Investigate if results don't match clinical picture

Temporal Arteritis Red Flags

Symptoms: New headache, jaw claudication, visual symptoms

Age: Usually >50 years, peak incidence 70-80

ESR: Usually >50, often >100 mm/hr

Action: Immediate steroids, urgent biopsy



Clinical Pearl

"The ESR Age Rule": ESR normally increases with age—a rough guide is upper limit = $\text{age}/2$ for men, $(\text{age}+10)/2$ for women. An ESR of 40 might be normal at 80 but definitely abnormal at 20. Always interpret ESR in the context of patient age, and don't over-investigate elderly patients with mildly elevated ESR if they're clinically well.

Step 3: High-Sensitivity CRP - Cardiovascular Risk Assessment

High-sensitivity CRP (hs-CRP) measures the same protein as regular CRP but can detect much lower levels. While regular CRP detects acute inflammation, hs-CRP reveals low-grade chronic inflammation associated with atherosclerosis and cardiovascular risk. This distinction is crucial for appropriate clinical use.

Understanding hs-CRP for CV Risk

hs-CRP provides additional risk stratification beyond traditional cardiovascular risk factors:

- **Low risk:** <1.0 mg/L
- **Moderate risk:** 1.0-3.0 mg/L
- **High risk:** >3.0 mg/L
- **Acute inflammation:** >10 mg/L (not reliable for CV risk)

hs-CRP adds prognostic information to traditional risk scores and may guide statin therapy decisions.

When to Use hs-CRP

hs-CRP is most useful in intermediate cardiovascular risk patients:

- **QRISK 10-20%:** hs-CRP may refine risk assessment
- **Family history:** Strong family history with borderline traditional risk
- **Statin decisions:** When uncertain about starting statin therapy
- **Not useful:** High or low traditional risk patients

hs-CRP <1.0 mg/L

CV Risk: Low additional risk

Action: Continue standard risk factor management

Statin decision: Based on traditional risk factors

Lifestyle: Maintain healthy lifestyle

hs-CRP 1.0-3.0 mg/L

CV Risk: Moderate additional risk

Action: Enhanced lifestyle intervention

Consider: Statin therapy if borderline traditional risk

Monitoring: Annual assessment of risk factors

hs-CRP >3.0 mg/L

CV Risk: High additional risk

Action: Intensive risk factor management

Statin therapy: Stronger consideration

Investigation: Exclude other inflammatory conditions

hs-CRP >10 mg/L

Interpretation: Acute inflammation likely

CV Risk: Cannot reliably assess until inflammation resolves

Action: Investigate and treat acute inflammation first

Repeat: Recheck hs-CRP after resolution



Clinical Pearl

"The hs-CRP Sweet Spot": hs-CRP is most useful in patients with intermediate cardiovascular risk (QRISK 10-20%) where you're uncertain about statin therapy. It adds little value in obviously high-

risk patients (who need statins anyway) or very low-risk patients (who don't need additional risk stratification). Use it to refine borderline decisions, not as a general screening test.

Step 4: Procalcitonin - The Bacterial Infection Marker

Understanding Procalcitonin Physiology

Procalcitonin is released specifically in response to bacterial infections and sepsis. Viral infections, autoimmune conditions, and localized infections cause minimal PCT elevation, making it more specific for bacterial infection than CRP.

Procalcitonin Interpretation Thresholds

PCT <0.25 ng/mL: Bacterial infection unlikely. PCT 0.25-0.5 ng/mL: Possible bacterial infection. PCT 0.5-2.0 ng/mL: Probable bacterial infection. PCT >2.0 ng/mL: Severe bacterial infection/sepsis likely.

Clinical Applications in Primary Care

PCT is most useful for distinguishing bacterial from viral respiratory infections, guiding antibiotic decisions in pneumonia, and monitoring treatment response in hospitalized patients with bacterial infections.

Limitations and Considerations

PCT can be elevated in severe trauma, burns, surgery, and some autoimmune conditions. It's less useful in immunocompromised patients. Cost and availability limit routine use in primary care compared to CRP.

PCT <0.25 ng/mL

Interpretation: Bacterial infection very unlikely

Action: Consider withholding antibiotics

Viral infection: Most likely cause if symptomatic

Safety: Excellent negative predictive value

PCT 0.25-0.5 ng/mL

Interpretation: Low probability bacterial infection

Clinical correlation: Consider severity of illness

Action: Often appropriate to avoid antibiotics

Follow-up: Clinical monitoring essential

PCT 0.5-2.0 ng/mL

Interpretation: Probable bacterial infection

Action: Antibiotic therapy usually indicated

Severity: Moderate bacterial infection likely

Monitoring: Expect PCT to fall with effective treatment

PCT >2.0 ng/mL

Interpretation: Severe bacterial infection/sepsis

Action: Immediate antibiotic therapy

Urgency: Consider hospital assessment
Prognosis: Higher levels associated with worse outcomes



Clinical Pearl

"PCT's Viral-Bacterial Discrimination": PCT's greatest strength is distinguishing bacterial from viral infections. In viral respiratory infections, PCT typically stays <0.25 ng/mL even when patients are quite unwell. In bacterial pneumonia, PCT usually rises >0.5 ng/mL. This makes PCT particularly useful when CRP is equivocal (20-100 mg/L) and you need to decide about antibiotics.

Step 5: Putting It All Together - Inflammatory Marker Strategy

Acute Infection Assessment

First choice: CRP for rapid decision-making
Thresholds: <20 no antibiotics, >100 give antibiotics
PCT addition: If bacterial vs viral uncertain
ESR role: Limited in acute infections

Chronic Inflammation Investigation

First choice: ESR for screening chronic conditions
Age-adjusted: Remember normal ESR increases with age
CRP addition: To assess current disease activity
Investigation: ESR >50 usually needs explanation

Treatment Monitoring

CRP: Rapid response to effective antibiotic therapy
ESR: Slower response, useful for chronic conditions
Frequency: CRP at 48-72 hours, ESR weekly
Targets: 50% reduction suggests good response

Cardiovascular Risk

hs-CRP: Only useful in intermediate-risk patients
Timing: Avoid during acute illness or inflammation
Integration: Combine with traditional risk factors
Action: May influence statin therapy decisions

Inflammatory Marker Selection Guide

Patient with suspected inflammatory condition

Acute symptoms (<2 weeks) or chronic symptoms (>2 weeks)?

Acute: CRP first choice, consider PCT if bacterial vs viral unclear

Chronic: ESR first choice, add CRP to assess current activity

CV Risk: hs-CRP only in intermediate-risk patients when well

Common Clinical Scenarios and Marker Choice

- **Respiratory infection:** CRP using NICE thresholds (<20, 20-100, >100)
- **New headache >50 years:** ESR ± CRP to screen for temporal arteritis
- **Joint pain and stiffness:** ESR to screen for inflammatory arthritis
- **Unexplained weight loss:** ESR ± CRP to screen for malignancy
- **Monitoring treated infection:** CRP to assess treatment response
- **Monitoring RA/IBD:** CRP or ESR to assess disease activity



Clinical Pearl

"**The 48-Hour Inflammatory Response Rule**": Effective antibiotic therapy should cause CRP to start falling within 48 hours and ESR within a week. If inflammatory markers continue rising despite appropriate antibiotics, consider treatment failure, complications (abscess), resistant organisms, or alternative diagnoses. This monitoring approach prevents prolonged ineffective therapy.

Common Pitfalls and How to Avoid Them

The ESR Age Ignorance

Mistake: Using same ESR reference ranges for all ages

Reality: ESR normally increases with age

Solution: Use age-adjusted upper limits

Guide: Upper limit $\approx \text{age}/2$ (men), $(\text{age}+10)/2$ (women)

The CRP Viral Confusion

Mistake: Giving antibiotics for viral infections with mildly raised CRP

Reality: Viral infections can cause CRP 20-50 mg/L

Solution: Use NICE thresholds— <20 no antibiotics, consider PCT

Clinical: Viral symptoms usually obvious

The hs-CRP Overuse

Mistake: Using hs-CRP as general screening test

Reality: Only useful in intermediate CV risk patients

Solution: Reserve for QRISK 10-20% when uncertain about statins

Avoid: Testing during acute illness (unreliable for CV risk)

The Single Marker Tunnel Vision

Mistake: Relying on inflammatory markers without clinical context

Reality: Markers guide decisions but don't make diagnoses

Solution: Always integrate with history, examination, other tests

Remember: Treat the patient, not the number

Red Flags in Inflammatory Marker Interpretation

- **Very high markers with mild symptoms:** Consider serious underlying disease
- **Normal markers with severe illness:** Doesn't exclude serious infection (immunocompromised)
- **Rising markers on treatment:** Treatment failure, complications, or wrong diagnosis
- **Persistently high markers:** Need systematic investigation for underlying cause
- **Discordant clinical picture:** Re-evaluate diagnosis and consider other tests

Summary: The Five-Step Inflammatory Marker Mastery Method

1. Choose the Right Marker

CRP for acute conditions, ESR for chronic, hs-CRP for CV risk

2. Apply Evidence-Based Thresholds

Use NICE CRP thresholds for antibiotic decisions

3. Consider Clinical Context

Age, symptoms, severity all influence interpretation

4. Monitor Treatment Response

Expect markers to fall with effective therapy

5. Know When to Escalate

Very high values or rising markers need urgent action

Key Inflammatory Marker Thresholds

CRP antibiotic guidance: <20 no antibiotics, 20-100 consider delayed, >100 immediate

ESR urgent investigation: >100 mm/hr needs same-day assessment

hs-CRP CV risk: <1 low, 1-3 moderate, >3 high risk

PCT bacterial infection: <0.25 unlikely, >0.5 probable bacterial

Clinical Decision Points

Emergency action: CRP >200 with fever, ESR >100 with symptoms

Temporal arteritis: ESR >50 + headache >50 years = urgent steroids

Treatment monitoring: 50% reduction expected in 48-72 hours (CRP)

Investigation threshold: Unexplained persistent elevation needs workup



Clinical Pearl

"The Inflammatory Marker Triangle": Think of CRP, ESR, and clinical assessment as three corners of a triangle—you need at least two to make good decisions. High CRP with compatible clinical picture supports bacterial infection. Normal markers with severe illness suggests viral infection or non-inflammatory cause. Let the clinical picture guide which markers to order and how to interpret them.

Take Home Messages for Inflammatory Markers

- **Use NICE CRP thresholds:** Evidence-based antibiotic prescribing reduces resistance
- **Choose markers wisely:** CRP for acute, ESR for chronic conditions
- **Age-adjust ESR:** Normal values increase with age
- **Monitor treatment response:** Markers should fall with effective therapy
- **Clinical context crucial:** Markers guide decisions but don't make diagnoses
- **Know emergency thresholds:** Very high values need urgent assessment

Clinical Guidelines & Evidence Base

NICE Guideline CG191

Pneumonia in adults: diagnosis and management

- Updated 2024

[Access Guidelines](#)

NICE Medical Technologies Guidance MTG78

QuikRead go for C-reactive protein testing in primary care

- 2017

[Access Guidance](#)

References

- Dasgupta, B., Cimmino, M.A., Maradit-Kremers, H., Schmidt, W.A., Schirmer, M., Salvarani, C., Bachta, A., DeJaco, C., Duftner, C., Jensen, H.S., Duhaut, P., Poór, G., Kaposi, N.P., Mandl, P., Balint, P.V., Schmidt, Z., Iagnocco, A., Nannini, C., Cantini, F., Macchioni, P., Pipitone, N., Del Amo, M., Formisano, R., Rumi, F., Muratore, F., Boiardi, L., Carsons, S.E. and Csernok, E. (2012) '2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative', *Annals of the Rheumatic Diseases*, 71(4), pp. 484-492.
- Lim, W.S., van der Eerden, M.M., Laing, R., Boersma, W.G., Karalus, N., Town, G.I., Lewis, S.A. and Macfarlane, J.T. (2003) 'Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study', *Thorax*, 58(5), pp. 377-382.
- Little, P., Stuart, B., Moore, M., Coenen, S., Butler, C.C., Godycki-Cwirko, M., Mierzecki, A., Chlabicz, S., Torres, A., Almirall, J., Davies, M., Mullee, M., O'Reilly, G., Brugman, C., Lindenmeyer, A. and Verheij, T. (2013) 'Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial', *The Lancet Infectious Diseases*, 13(2), pp. 123-129.
- National Institute for Health and Care Excellence (NICE) (2019) *Pneumonia (community-acquired): antimicrobial prescribing. NICE guideline [NG138]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng138> (Accessed: 30 September 2025).
- Pepys, M.B. and Hirschfield, G.M. (2003) 'C-reactive protein: a critical update', *Journal of Clinical Investigation*, 111(12), pp. 1805-1812.
- Ridker, P.M., Danielson, E., Fonseca, F.A., Genest, J., Gotto, A.M., Kastelein, J.J., Koenig, W., Libby, P., Lorenzatti, A.J., MacFadyen, J.G., Nordestgaard, B.G., Shepherd, J., Willerson, J.T. and Glynn, R.J. (2008) 'Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein', *New England Journal of Medicine*, 359(21), pp. 2195-2207.
- Schuetz, P., Wirz, Y., Sager, R., Christ-Crain, M., Stolz, D., Tamm, M., Bouadma, L., Luyt, C.E., Wolff, M., Chastre, J., Tubach, F., Kristoffersen, K.B., Burkhardt, O., Welte, T., Schroeder, S., Nobre, V., Wei, L., Bucher, H.C., Bhatnagar, N., Annane, D. and Mueller, B. (2017)

'Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis', *The Lancet Infectious Diseases*, 17(12), pp. 1281-1289.

Chapter 9

Bone Profile

Bone Profile Interpretation

A Structured Approach to Calcium, Phosphate, ALP, and Vitamin D Assessment

Introduction: Understanding Bone Biochemistry

The bone profile is one of the most revealing blood tests in primary care, offering insights into bone health, parathyroid function, vitamin D status, and liver disease. Unlike isolated tests, the bone profile tells a story through the relationships between calcium, phosphate, alkaline phosphatase, and vitamin D. Understanding these interconnections allows you to diagnose conditions from osteomalacia to primary hyperparathyroidism with confidence.



Clinical Pearl

"Read the Pattern, Not the Numbers": A high calcium with high alkaline phosphatase suggests different pathology than high calcium with normal alkaline phosphatase. The former points to bone disease (Paget's, malignancy), the latter to primary hyperparathyroidism. Pattern recognition trumps memorising reference ranges.

Essential Bone Profile Reference Ranges (Adults)

Parameter	Reference Range	Units	Key Clinical Notes
Albumin-adjusted Calcium	2.20-2.60	mmol/L	Always use adjusted calcium for clinical decisions
Phosphate	0.80-1.50	mmol/L	Inversely related to calcium in parathyroid disorders
Alkaline Phosphatase (ALP)	30-130	U/L	Rises with bone formation and liver disease
25-OH Vitamin D	>50	nmol/L	Deficient <30, insufficient 30-50
PTH (if measured)	1.6-6.9	pmol/L	Elevated in vitamin D deficiency and primary hyperparathyroidism

Step 1: Systematic Bone Profile Analysis

First: Check Calcium Status

Always use albumin-adjusted calcium. If >2.6 mmol/L on two occasions, consider primary hyperparathyroidism. If <2.2 mmol/L, think vitamin D deficiency, hypoparathyroidism, or chronic kidney disease.

Second: Examine the Calcium-Phosphate Relationship

In parathyroid disorders, these move in opposite directions. High calcium + low phosphate = hyperparathyroidism. Low calcium + high phosphate = hypoparathyroidism or chronic kidney disease.

Third: Interpret Alkaline Phosphatase Context

If ALP is raised, differentiate bone from liver origin using GGT. Bone ALP rises in high turnover states (Paget's, metastases, healing fractures, vitamin D deficiency).

Fourth: Assess Vitamin D Status

Vitamin D deficiency can cause secondary hyperparathyroidism, masking or complicating primary hyperparathyroidism diagnosis. Always check vitamin D status in calcium disorders.



Clinical Pearl

"The ALP Source Detective Method": Raised ALP with normal GGT = bone source. Raised ALP with raised GGT = liver source. If both are elevated but liver function tests are normal, consider infiltrative liver disease or bone metastases.

Step 2: Priority Assessment - Red Flags

▲ **Calcium >2.9 mmol/L**

Hypercalcaemic crisis risk - urgent assessment for dehydration, confusion, arrhythmias

▲ **Calcium <1.9 mmol/L**

Severe hypocalcaemia - risk of tetany, seizures, laryngospasm

▲ **ALP >500 U/L**

Consider Paget's disease, bone metastases, or severe liver disease

▲ **Phosphate <0.3 mmol/L**

Severe hypophosphataemia - risk of respiratory failure, cardiac dysfunction



Clinical Pearl

"**Calcium Symptoms Are Non-Specific**": "Stones, bones, groans, and psychiatric overtones" remains relevant, but early symptoms are subtle. Fatigue, depression, and cognitive impairment may be the only signs of mild hyperparathyroidism. Don't wait for kidney stones to investigate elevated calcium.

Step 3: Pattern Recognition in Bone Disorders

Primary Hyperparathyroidism (PHPT)

Classic Pattern: ↑ Calcium, ↓ Phosphate, Normal/↑ ALP, Normal/↑ PTH

Clinical Context: Often asymptomatic, may have fatigue, depression, kidney stones

Action: Confirm with repeat calcium, measure PTH, refer to endocrinology if confirmed

NICE Guidance: Measure calcium and PTH if symptoms of hypercalcaemia or calcium ≥ 2.6 mmol/L

Vitamin D Deficiency/Osteomalacia

Classic Pattern: ↓/Normal Calcium, ↓/Normal Phosphate, ↑ ALP, ↓ Vitamin D, ↑ PTH

Clinical Context: Bone pain, muscle weakness, increased fracture risk

Action: Vitamin D replacement 800-4000 IU daily depending on deficiency severity

Evidence: ALP rises early in vitamin D deficiency, calcium falls only in severe cases

Paget's Disease

Classic Pattern: Normal Calcium, Normal Phosphate, ↑↑ ALP (often >500), Normal Vitamin D

Clinical Context: Bone pain, deformity, hearing loss, may be asymptomatic

Action: X-rays of affected bones, consider bone scan, rheumatology referral

Note: ALP can be extremely elevated (>1000 U/L) in active Paget's

Bone Metastases

Classic Pattern: ↑ Calcium (osteolytic), Normal/↑ Phosphate, ↑ ALP

Clinical Context: Known malignancy, bone pain, pathological fractures

Action: Urgent oncology referral, imaging, consider bisphosphonates

Tumour Types: Breast, lung, kidney, prostate, thyroid most commonly metastasize to bone



Clinical Pearl

"The Secondary Hyperparathyroidism Trap": Vitamin D deficiency causes secondary hyperparathyroidism with raised PTH but usually normal/low calcium. If calcium is high with raised PTH, don't assume it's secondary - it could be primary hyperparathyroidism with coexistent vitamin D deficiency.

Step 4: Treatment Decisions and Monitoring

Vitamin D Replacement Strategy (2024 Guidelines)

For Deficiency (<30 nmol/L):

- Colecalciferol 800 IU daily for 8-12 weeks
- Or weekly doses (e.g., 5600 IU weekly)
- Recheck vitamin D level after treatment

For Insufficiency (30-50 nmol/L):

- Colecalciferol 400-800 IU daily
- Consider higher doses if malabsorption

Maintenance Therapy:

- 400-800 IU daily for high-risk patients
- 1000-2000 IU daily in housebound/care home patients

Calcium Supplementation Guidelines

Dietary Assessment First:

- Aim for 700-1200mg daily from diet
- One glass milk = 300mg calcium
- 30g cheese = 200mg calcium

Supplementation Indications:

- Dietary intake <700mg daily
- On bisphosphonates for osteoporosis
- Malabsorption syndromes

Prescribing Principles:

- Calcium carbonate 1.25g (500mg elemental) BD
- Take with food for better absorption
- Avoid with tetracyclines, iron supplements



Clinical Pearl

"Food First, Supplements Second": Calcium absorption from supplements is limited to ~500mg per dose, while dietary calcium is better absorbed. Three servings of dairy daily usually provide adequate calcium. Only supplement if dietary intake is genuinely inadequate.

Monitoring Parameters During Treatment

- **Vitamin D deficiency:** Recheck 25-OH vitamin D after 2-3 months of treatment
- **Primary hyperparathyroidism:** Annual bone density, kidney function, calcium levels
- **Osteoporosis treatment:** Monitor compliance, check bone profile if ALP rises significantly
- **Paget's disease:** Monitor ALP every 3-6 months during treatment

Step 5: Special Considerations and Complex Cases

Age-Related Changes in Bone Biochemistry

Young Adults (20-40 years)

Peak bone mass achieved around age 30. Normal bone profile values apply. Any significant abnormality warrants investigation.

Postmenopausal Women

Increased bone resorption post-menopause. Slight elevation in ALP may be normal. Focus on fracture risk assessment and prevention.

Elderly (>75 years)

Higher risk of vitamin D deficiency, hyperparathyroidism, and Paget's disease. Age-adjust alkaline phosphatase interpretation.

Chronic Kidney Disease

Complex mineral and bone disorders. Phosphate retention, secondary hyperparathyroidism common. Requires specialist management.

Decision Tree for Raised Alkaline Phosphatase

ALP Elevated (>130 U/L)

Check GGT to differentiate source

Essential first step in ALP evaluation

GGT Normal: Bone source likely → Check calcium, phosphate, vitamin D → Consider Paget's, bone mets, vitamin D deficiency

GGT Raised: Liver source → Check full liver function tests → Consider hepatitis, alcohol, drugs, biliary obstruction

Both Raised: Mixed picture → Consider infiltrative disease, drug effects, or concurrent bone and liver pathology



Clinical Pearl

"The Pregnancy Exception": ALP naturally rises in pregnancy due to placental production, reaching levels that would be concerning outside pregnancy. Always consider pregnancy in women of childbearing age with isolated ALP elevation. Bone-specific ALP and liver function tests help differentiate.

Step 6: When to Refer and Urgent Actions

Immediate Referral Criteria

- **Severe hypercalcaemia (>2.9 mmol/L):** Same-day assessment for hypercalcaemic crisis
- **Severe hypocalcaemia (<1.9 mmol/L) with symptoms:** Risk of tetany, seizures
- **Confirmed primary hyperparathyroidism:** Endocrinology referral for surgical assessment
- **ALP >500 U/L with bone source:** Consider Paget's disease or bone metastases
- **Suspected bone metastases:** Urgent oncology referral
- **Severe hypophosphataemia (<0.3 mmol/L) with symptoms:** Risk of respiratory/cardiac failure

Routine Referral Indications

- **Endocrinology:** Confirmed primary hyperparathyroidism, complex vitamin D resistant cases
- **Rheumatology:** Suspected Paget's disease, metabolic bone disease
- **Nephrology:** CKD-related bone disease, persistent phosphate abnormalities
- **Gastroenterology:** Malabsorption causing vitamin D deficiency



Clinical Pearl

"**The 48-Hour Rule for Calcium**": Any calcium >2.8 mmol/L should prompt clinical assessment within 48 hours. Patients may not volunteer symptoms of hypercalcaemia (fatigue, depression, confusion), but these can progress rapidly to hypercalcaemic crisis.

Summary: Mastering Bone Profile Interpretation

The Six-Step Bone Profile Method

1. **Calcium Status:** Always use albumin-adjusted values, confirm abnormalities
2. **Calcium-Phosphate Relationship:** Inverse relationship suggests parathyroid pathology
3. **ALP Source Identification:** Use GGT to differentiate bone from liver disease
4. **Vitamin D Assessment:** Essential for understanding calcium metabolism
5. **Clinical Correlation:** Symptoms, age, and comorbidities guide interpretation
6. **Pattern Recognition:** Classic combinations point to specific diagnoses

Master These Patterns

PHPT: High Ca^{2+} + Low PO_4^{3-} + Normal/High ALP
Vitamin D deficiency: Low/Normal Ca^{2+} + High ALP + Low vitamin D
Paget's: Normal Ca^{2+} + Very High ALP + Normal GGT

Remember These Rules

Always use albumin-adjusted calcium
GGT differentiates ALP sources
Vitamin D affects calcium metabolism

Never Miss These

Calcium >2.9 = urgent assessment
ALP >500 = investigate bone pathology
Low phosphate <0.3 = critical risk

Key Risk Factors for Bone Disease

Osteoporosis Risk

Postmenopausal women Steroid use >3 months Family history fractures Low BMI <19 Smoking, excess alcohol

Vitamin D Deficiency Risk

Limited sun exposure Dark skin in UK Housebound/care home Malabsorption Dietary restrictions

Hyperparathyroidism Risk

Postmenopausal women Previous neck irradiation Family history MEN syndrome Lithium therapy Age >65 years



Clinical Pearl

"Integration Over Isolation": The bone profile's power lies in interpreting all four parameters together. Isolated abnormalities need clinical context, but pattern abnormalities tell clear diagnostic stories. Always consider the whole picture - patient age, symptoms, risk factors, and biochemical patterns - for accurate diagnosis and appropriate management.



Clinical Guidelines & Evidence Base

NICE Clinical Guideline

Hyperparathyroidism (Primary): Diagnosis, Assessment and Initial Management

- 2020

[Access Guidelines](#)

NICE Guideline NG203

Chronic Kidney Disease: Assessment and Management

- 2023

[Access Guidelines](#)

BNSSG ICB

Vitamin D Guidelines for Adults

- 2024

[Access Guidelines](#)

NHS England

Calcium and Vitamin D Supplementation in Osteoporosis

- 2024

[Access Guidelines](#)

References

Bilezikian, J.P., Bandeira, L. and Khan, A. (2018) 'Hyperparathyroidism', *The Lancet*, 391(10116), pp. 168-178.

Compston, J., Cooper, A., Cooper, C., Gittoes, N., Gregson, C., Harvey, N., Hope, S., Kanis, J.A., McCloskey, E.V., Poole, K.E., Reid, D.M., Selby, P., Thompson, F., Thurston, A. and Vine, N. (2017) 'UK clinical guideline for the prevention and treatment of osteoporosis', *Archives of Osteoporosis*, 12(1), 43.

National Institute for Health and Care Excellence (NICE) (2020) *Hyperparathyroidism (primary): diagnosis, assessment and initial management. NICE guideline [NG132]*. London: NICE. Available at: <https://www.nice.org.uk/guidance/ng132> (Accessed: 30 September 2025).

Pearce, S.H. and Cheetham, T.D. (2010) 'Diagnosis and management of vitamin D deficiency', *BMJ*, 340, b5664.

Rosen, H.N. (2022) 'The clinical manifestations and diagnosis of primary hyperparathyroidism', *UpToDate*. Available at: <https://www.uptodate.com> (Accessed: 30 September 2025).

Scientific Advisory Committee on Nutrition (SACN) (2016) *Vitamin D and Health Report*. London: Public Health England.

Walker-Bone, K., Dennison, E., Cooper, C. and Javaid, M.K. (2020) 'Epidemiology of osteoporosis', *Rheumatic Disease Clinics of North America*, 46(2), pp. 187-200.

Chapter 10

Cardiac Markers

Cardiac Markers Interpretation

A Structured Approach to Troponin, BNP, and NT-proBNP Assessment

Introduction: The Modern Cardiac Biomarker Arsenal

Cardiac biomarkers have revolutionised the assessment of chest pain and heart failure in primary care. High-sensitivity troponins can now rule out myocardial infarction within one hour, while NT-proBNP provides a powerful screening tool for heart failure. Understanding when to test, how to interpret results, and crucially when NOT to test these expensive biomarkers is essential for effective primary care practice.



Clinical Pearl

"Troponin is Not a Screening Test": Never order troponin "just to be safe" in low-risk chest pain. A positive result in someone with <2% pre-test probability of ACS creates more problems than it solves. Clinical assessment must drive testing, not anxiety or defensive medicine.

Key Cardiac Biomarker Thresholds (2024 NICE Guidelines)

Biomarker	Critical Threshold	Clinical Significance	Timing
High-Sensitivity Troponin T	99th percentile: 14 ng/L	Myocardial injury threshold	Peak 12-24 hours post-MI
High-Sensitivity Troponin I	99th percentile: varies by assay	More specific than Troponin T	Earlier rise than Troponin T
NT-proBNP	<400 ng/L: HF unlikely	Heart failure screening	Stable levels, not affected by diurnal variation
NT-proBNP (urgent)	>2000 ng/L	Urgent cardiology referral	2-week pathway activation
BNP (alternative)	<100 pg/mL: HF unlikely	Less stable than NT-proBNP	Shorter half-life, more variability

Step 1: High-Sensitivity Troponin - When and Why

Pre-Test Probability Assessment

Before ordering troponin, assess likelihood of ACS using clinical features, ECG, and risk factors. Only test if intermediate risk (5-85% probability) - low risk wastes resources, high risk needs immediate treatment regardless.

Timing Considerations

High-sensitivity assays can detect troponin within 1-2 hours of symptom onset. NICE DG40 supports 0/1-hour protocols for early rule-out. Traditional 12-hour rule is outdated with modern assays.

Clinical Context Integration

Troponin elevation doesn't equal MI. Consider alternative causes: myocarditis, PE, sepsis, renal failure, heart failure exacerbation. Clinical correlation is mandatory for accurate diagnosis.

Serial Measurement Strategy

Single measurements rarely diagnostic. Rising pattern over 1-3 hours suggests acute MI. Static elevation suggests chronic myocardial injury. Delta changes more important than absolute values.



Clinical Pearl

"The 99th Percentile Trap": 99% of healthy people have troponin below the 99th percentile - which means 1 in 100 healthy people will have "abnormal" results. This false positive rate is why clinical correlation is essential. Never diagnose MI on troponin alone.



Troponin >10x 99th Percentile

Highly suggestive of acute MI with significant myocardial damage



Rising Troponin + Chest Pain

Acute coronary syndrome - urgent cardiology assessment required



Troponin + ST Changes

STEMI equivalent - immediate primary PCI activation



Detectable Troponin + Unstable Patient

Any troponin elevation in unstable patient requires urgent assessment

Step 2: Troponin Result Interpretation Patterns

Undetectable Troponin (<3-5 ng/L)

Clinical Meaning: Excellent negative predictive value for MI
Action: If >3 hours from symptom onset, effectively rules out MI
Caution: Very early presentation (<1 hour) may still have undetectable levels
Confidence Level: >99% NPV for ruling out MI

Low-Level Elevation (5-50 ng/L)

Clinical Meaning: Possible myocardial injury, but not necessarily MI
Action: Repeat in 1-3 hours, assess clinical context carefully
Common Causes: Chronic heart failure, renal impairment, myocarditis
Strategy: Look for rising pattern to differentiate acute from chronic

Significant Elevation (>100 ng/L)

Clinical Meaning: Substantial myocardial damage
Action: Urgent cardiology assessment, start dual antiplatelet therapy
Differential: NSTEMI, large STEMI, massive PE, myocarditis
Risk Stratification: Higher levels correlate with worse outcomes

Extremely High Levels (>1000 ng/L)

Clinical Meaning: Massive myocardial injury
Action: Immediate intervention cardiology referral
Prognosis: High short-term mortality risk
Management: Aggressive anti-ischaemic therapy, consider mechanical support



Clinical Pearl

"The Delta Change Rule": A >20% rise (or fall) in troponin levels between two samples 1-3 hours apart is more diagnostic of acute MI than absolute values. Static elevation often represents chronic myocardial injury rather than acute coronary syndrome.

Troponin Kinetics in Different Conditions

Acute STEMI Pattern

Rapid rise within 1-2 hours, peak at 12-24 hours, elevated for 7-14 days.
Magnitude correlates with infarct size.

NSTEMI Pattern

More gradual rise, lower peak levels than STEMI, but still shows clear rising pattern over 1-6 hours.

Chronic Elevation

Stable levels over time, often <100 ng/L, seen in heart failure, CKD, elderly patients.

Non-ACS Causes

Myocarditis, PE, sepsis, cardioversion. Clinical context and ECG changes differentiate from ACS.

Step 3: NT-proBNP and Heart Failure Assessment

NICE 2024 NT-proBNP Thresholds

Rule-Out Threshold (<400 ng/L):

- Heart failure very unlikely in untreated patients
- 99% negative predictive value
- Avoids unnecessary echocardiography
- Consider alternative diagnoses

Routine Referral (400-2000 ng/L):

- Specialist assessment within 6 weeks
- Transthoracic echocardiography required
- Start appropriate interim therapy

Urgent Referral (>2000 ng/L):

- Specialist assessment within 2 weeks
- High likelihood of significant heart failure
- Poor prognostic indicator

Factors Affecting NT-proBNP Levels

Factors That Lower NT-proBNP:

- Obesity (up to 50% reduction)
- African/Caribbean ethnicity
- ACE inhibitors, ARBs, beta-blockers
- Diuretics, MRAs

Factors That Raise NT-proBNP:

- Age >70 years
- Atrial fibrillation
- Renal impairment (eGFR <60)
- Pulmonary embolism
- Sepsis, hypoxia
- Left ventricular hypertrophy



Clinical Pearl

"**The Obesity Paradox**": Obese patients can have heart failure with normal NT-proBNP levels. Adipose tissue produces natriuretic peptide clearance receptors, reducing circulating levels. In obese patients, consider lower thresholds (200-300 ng/L) to maintain sensitivity.

Clinical Presentation Assessment

NT-proBNP testing should be driven by clinical suspicion of heart failure: breathlessness, ankle swelling, fatigue, reduced exercise tolerance. Not a screening test in asymptomatic patients.

Result Interpretation in Context

Consider patient factors that affect levels. Very elderly patients may have elevated levels without heart failure. Renal impairment significantly elevates results regardless of cardiac function.

Treatment Response Monitoring

NT-proBNP can guide therapy but shouldn't be the sole target. Clinical improvement with falling NT-proBNP indicates successful treatment. Rising levels suggest deterioration or non-compliance.

Prognostic Value

Higher baseline NT-proBNP levels predict worse outcomes. Very high levels (>5000 ng/L) associated with significantly increased mortality. Useful for risk stratification and advanced care planning.

Step 4: BNP vs NT-proBNP - Making the Right Choice

NT-proBNP Advantages

Stability: Longer half-life (60-120 minutes) vs BNP (20 minutes)

Processing: Less affected by sample handling and storage

Precision: Less biological variation, more reproducible results

NICE Preference: Referenced in NICE NG106 guidelines as preferred test

BNP Characteristics

Biological Activity: Active hormone, directly reflects cardiac function

Processing Requirements: Requires careful sample handling, immediate processing

Threshold: <100 pg/mL rules out heart failure

Variability: More affected by diurnal variation and sample handling

Clinical Equivalence

Diagnostic Performance: Both have similar diagnostic accuracy for heart failure

Conversion: NT-proBNP $\approx 8.5 \times$ BNP (approximate relationship)

Guidelines: Both accepted in international guidelines

Choice: Usually determined by local laboratory capabilities

Cost Considerations

Test Cost: Similar costs for both assays

Processing: NT-proBNP more cost-effective due to stability

Repeat Testing: NT-proBNP less likely to need repeat due to pre-analytical errors

Outcome: Both cost-effective compared to clinical assessment alone



Clinical Pearl

"Stick With One Test": Choose either BNP or NT-proBNP and become familiar with its characteristics. Don't switch between them for the same patient - the thresholds are different and this leads to confusion. NT-proBNP is generally preferred due to superior analytical stability.

Step 5: Point-of-Care Testing Revolution (2024 Updates)

Point-of-Care Cardiac Biomarkers - Current Capabilities

- **High-Sensitivity Troponin POC:** Results in 8 minutes, comparable accuracy to lab assays
- **NT-proBNP POC:** 15-minute turnaround time, excellent correlation with laboratory methods
- **Clinical Impact:** Reduces ED attendance, faster decision-making, improved patient flow
- **Cost-Effectiveness:** Potential savings from reduced hospital admissions and faster discharge

POC Testing Implementation in Primary Care (2024)

Ideal Candidates

Intermediate-risk chest pain, GP urgent care centers, community cardiology services, rural/remote locations.

Quality Considerations

Requires trained operators, regular quality control, connectivity to electronic records, clinical governance.

Economic Impact

Reduced ambulance transfers, faster rule-out decisions, improved patient satisfaction, resource optimization.

Clinical Outcomes

Earlier treatment initiation, reduced time to diagnosis, maintained safety standards, enhanced care pathways.



Clinical Pearl

"POC Testing Changes Everything": Point-of-care troponin testing transforms primary care chest pain assessment. A negative result within 8 minutes allows confident discharge, while positive results enable immediate appropriate treatment. This technology is moving acute cardiac care closer to patients.

Step 6: Critical Decision Points and Referral Thresholds

Immediate Action Required

- **Any detectable troponin + ongoing chest pain:** Immediate cardiology assessment
- **Rising troponin pattern (>20% increase):** Acute coronary syndrome pathway
- **NT-proBNP >2000 ng/L + clinical heart failure:** 2-week urgent cardiology referral
- **Troponin >10x 99th percentile:** Immediate interventional cardiology consideration
- **Positive troponin + ECG changes:** Emergency treatment activation
- **NT-proBNP >5000 ng/L:** Consider advanced heart failure, urgent specialist review

Chest Pain Assessment with Troponin Testing

Chest pain patient presents

Assess pre-test probability of ACS

Use clinical features, ECG, risk factors

Low risk (<5%): Reassure, safety net advice, no troponin needed

Intermediate risk (5-85%): High-sensitivity troponin, consider 0/1 hour protocol

High risk (>85%): Treat as ACS, troponin for confirmation not diagnosis

When NOT to Test Cardiac Biomarkers

- **Very low-risk chest pain:** Atypical pain, young age, no risk factors
- **Chronic stable angina:** Troponin will not guide management
- **Obvious non-cardiac pain:** Musculoskeletal, pleuritic, gastric causes
- **Asymptomatic screening:** Neither troponin nor BNP are screening tests
- **Known chronic conditions:** Established heart failure with stable symptoms



Clinical Pearl

"Test Wisely, Act Decisively": The power of cardiac biomarkers lies in their ability to change management. If a positive result wouldn't change your treatment plan, don't order the test. If you order it, be prepared to act on abnormal results with appropriate urgency and specialist input.

Summary: Mastering Cardiac Biomarker Interpretation

The Six-Step Cardiac Biomarker Strategy

1. **Clinical Assessment First:** Pre-test probability drives testing decisions
2. **Choose Appropriate Biomarker:** Troponin for ACS, NT-proBNP for heart failure
3. **Timing Matters:** High-sensitivity assays enable earlier rule-out
4. **Context Integration:** Patient factors significantly affect interpretation
5. **Pattern Recognition:** Rising troponin more important than absolute values
6. **Decisive Action:** Abnormal results require appropriate urgency and follow-up

Master These Concepts

Pre-test probability guides troponin testing
NT-proBNP <400 ng/L rules out heart failure
Rising troponin = acute coronary syndrome

Remember These Rules

Never screen with cardiac biomarkers
Clinical correlation is mandatory
Point-of-care testing transforms care

Never Miss These

Rising troponin + chest pain = ACS
NT-proBNP >2000 = urgent referral
Very high troponin = immediate action

Key Risk Factors for Cardiac Events

High-Risk ACS Features

Age >65 years Male gender Diabetes mellitus Known CAD Family history MI

Heart Failure Risk Factors

Previous MI Hypertension Atrial fibrillation Valve disease Cardiomyopathy

Testing Contraindications

Very low pre-test probability Established diagnosis Won't change management
Asymptomatic screening Obvious alternative diagnosis



Clinical Pearl

"The Future is Now": Cardiac biomarker testing has evolved rapidly. High-sensitivity troponins enable 1-hour rule-out protocols, point-of-care testing brings laboratory accuracy to the bedside, and NT-proBNP provides excellent heart failure screening. Master these tools to transform your cardiac care capabilities.

Clinical Guidelines & Evidence Base

NICE Diagnostic Guidance DG40

High-sensitivity troponin tests for the early rule out of NSTEMI

- 2024

[Access Guidelines](#)

NICE Clinical Guideline NG106

Chronic heart failure in adults: diagnosis and management

- 2018 (Updated 2024)

[Access Guidelines](#)

NICE Clinical Guideline CG95

Chest pain of recent onset: assessment and diagnosis

- Updated 2024

[Access Guidelines](#)

ESC Guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

[Access Guidelines](#)

British Cardiovascular Society

Assessment of the diagnostic value of NT-proBNP in heart failure

- 2024

[Access Guidelines](#)

References

Body, R., Carlton, E., Sperrin, M., Lewis, P.S., Burrows, G., Carley, S., McDowell, G., Buchan, I., Greaves, K. and Mackway-Jones, K. (2015) 'Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts', *Emergency Medicine Journal*, 34(6), pp. 349-356.

Collet, J.P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D.L., Dendale, P., Dorobantu, M., Edvardsen, T., Folliguet, T., Gale, C.P., Gilard, M., Jobs, A., Jüni, P., Lambrinou, E., Lewis, B.S., Mehilli, J., Meliga, E., Merkely, B., Mueller, C., Roffi, M., Rutten, F.H., Sibbing, D. and Siontis, G.C.M. (2020) '2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation', *European Heart Journal*, 42(14), pp. 1289-1367.

McDonagh, T.A., Metra, M., Adamo, M., Gardner, R.S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J.G.F., Coats, A.J.S., Crespo-Leiro, M.G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A.W., Jaarsma, T., Jankowska, E.A., Lainscak, M., Lam, C.S.P., Lyon, A.R., McMurray, J.J.V., Mebazaa, A., Mindham, R., Muneretto, C., Francesco Piepoli, M., Price, S., Rosano, G.M.C., Ruschitzka, F. and Kathrine Skibelund, A. (2021) '2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure', *European Heart*

Journal, 42(36), pp. 3599-3726.

National Institute for Health and Care Excellence (NICE) (2018) *Chronic heart failure in adults: diagnosis and management. NICE guideline [NG106]*.

London: NICE. Available at: <https://www.nice.org.uk/guidance/ng106> (Accessed: 30 September 2025).

National Institute for Health and Care Excellence (NICE) (2024) *High-sensitivity troponin tests for the early rule out of NSTEMI. NICE diagnostics guidance [DG40]*. London: NICE. Available at:

<https://www.nice.org.uk/guidance/dg40> (Accessed: 30 September 2025).

Reichlin, T., Hochholzer, W., Bassetti, S., Steuer, S., Stelzig, C., Hartwiger, S., Biedert, S., Schaub, N., Buerge, C., Potocki, M., Noveanu, M., Breidthardt, T., Twerenbold, R., Winkler, K., Bingisser, R. and Mueller, C. (2009) 'Early diagnosis of myocardial infarction with sensitive cardiac troponin assays', *New England Journal of Medicine*, 361(9), pp. 858-867.

Thygesen, K., Alpert, J.S., Jaffe, A.S., Chaitman, B.R., Bax, J.J., Morrow, D.A., White, H.D. and Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial

Infarction (2018) 'Fourth universal definition of myocardial infarction (2018)', *European Heart Journal*, 40(3), pp. 237-269.

Chapter 11

Sex Hormone Profiles

Decoding Sex Hormone Profiles

Making Sense of the Numbers That Tell Human Stories

Introduction: The Hormones That Shape Lives

Every sex hormone profile you order tells a deeply personal story. Behind those numbers are patients struggling with fertility, teenagers questioning their development, middle-aged people facing unexpected changes, and older adults navigating life transitions. The skill isn't just knowing what the numbers mean—it's understanding which story those numbers are telling and what that means for the human sitting in front of you.

Sex hormones don't work in isolation. They're part of an intricate conversation between the brain, ovaries or testes, and every tissue in the body. When you learn to read these profiles properly, you're not just interpreting lab values—you're becoming fluent in the language the body uses to communicate about reproduction, development, and aging.



Clinical Pearl

"Context Is King": A testosterone level of 10 nmol/L means completely different things in a 16-year-old boy (concerning), a 30-year-old woman with hirsutism (diagnostic), and a 70-year-old man (potentially normal for age). Never interpret hormone levels without considering age, sex, timing, and clinical context.

Essential Sex Hormone Normal Ranges (Adults)

Hormone	Male Range	Female Range	Units	Key Notes
Total Testosterone	10-28 nmol/L	0.5-2.5 nmol/L	nmol/L	Morning sample essential
Free Testosterone	0.2-0.6 nmol/L	0.003-0.03 nmol/L	nmol/L	More accurate than total
Oestradiol (E2)	70-200 pmol/L	120-1100 pmol/L	pmol/L	Varies with cycle phase
LH	1-10 U/L	1-95 U/L	U/L	Pulsatile release
FSH	1-12 U/L	1-21 U/L	U/L	Rises with age
SHBG	15-60 nmol/L	20-80 nmol/L	nmol/L	Affects free hormones

Step 1: Before You Order - The Art of Targeted Testing

Define Your Question

Don't order a "hormone panel" without a clear clinical question. Are you investigating fertility, checking for PCOS, evaluating delayed puberty, or exploring menopausal symptoms? Your question determines which tests to order and when.

Timing Matters Hugely

Testosterone: early morning (8-10am) when levels peak. For women: consider menstrual cycle phase. FSH/LH: day 2-5 of cycle for baseline. Oestradiol: depends on your question—follicular phase for baseline, mid-cycle for ovulation assessment.

Consider Current Medications

Oral contraceptives dramatically alter hormone levels—stop 3 months before testing if possible. HRT, steroids, anticonvulsants, and many psychiatric medications affect results. Don't waste money testing while on hormonal contraception.

Clinical Context First

What does the patient look like? A hirsute woman with acne and irregular periods has PCOS until proven otherwise, regardless of what the lab says. Clinical features often trump individual hormone levels.



Clinical Pearl

"The Morning Rule": Testosterone levels can drop by 30-40% from morning to afternoon due to natural circadian rhythm. A "low" afternoon testosterone might be completely normal if taken in the morning. Always order testosterone before 10am, especially in men under 50.



Testing on the Pill

Hormone levels on combined oral contraceptives are meaningless—you're measuring the pill's effects, not the patient's natural production



Random Cycle Testing

Ordering hormones at random cycle points in reproductive-age women often creates more confusion than clarity



Afternoon Testosterone in Men

Late-day testosterone in younger men is notoriously unreliable—stick to morning samples or risk misdiagnosis



Single FSH for Menopause

FSH fluctuates wildly in perimenopause—one normal result doesn't exclude menopausal transition

Step 2: Decoding Male Hormone Patterns

Normal Male Pattern

Testosterone: 12-28 nmol/L (morning)

LH: 2-8 U/L

FSH: 1-8 U/L

Interpretation: Healthy hypothalamic-pituitary-testicular axis. Everything working as it should.

Primary Hypogonadism

Testosterone: Low (<8 nmol/L)

LH/FSH: High (>12 U/L)

Think: Testicular failure

Causes: Klinefelter's, mumps orchitis, chemotherapy, trauma

Secondary Hypogonadism

Testosterone: Low (<8 nmol/L)

LH/FSH: Low/normal (<5 U/L)

Think: Brain problem (pituitary/hypothalamic)

Causes: Prolactinoma, obesity, sleep apnea, stress

Age-Related Decline

Testosterone: Borderline (8-12 nmol/L)

LH/FSH: Normal to slightly high

Think: Natural aging process

Action: Symptoms matter more than numbers in older men



Clinical Pearl

"**The LH Tells the Story**": In men with low testosterone, LH reveals the cause. High LH means the brain is screaming at failed testicles (primary hypogonadism). Low/normal LH means the brain itself isn't working (secondary hypogonadism). Same low testosterone, completely different causes and treatments.

Male Testosterone by Age: What's Really Normal?

Ages 20-30

Expected: 15-28 nmol/L

Red flag if: <12 nmol/L

Note: Peak reproductive years

Ages 30-50

Expected: 12-25 nmol/L

Red flag if: <10 nmol/L

Note: Gradual decline begins

Ages 50-70

Expected: 8-20 nmol/L

Red flag if: <8 nmol/L

Note: Context matters more than numbers

Over 70

Expected: 6-15 nmol/L
Red flag if: <6 nmol/L with symptoms
Note: Treat symptoms, not numbers

When to Check Male Hormones

- **Definite indications:** Erectile dysfunction with low libido, infertility, delayed puberty, gynecomastia
- **Consider in:** Unexplained fatigue, depression, osteoporosis, muscle loss
- **Don't bother:** Normal libido and sexual function, screening without symptoms
- **Repeat if borderline:** 8-12 nmol/L range needs confirmation and clinical correlation

Step 3: Decoding Female Hormone Patterns

Reproductive Years: It's All About Timing

Female hormone interpretation is like reading a constantly changing script. The same woman can have completely different hormone levels depending on where she is in her cycle:

- **Follicular phase (days 1-7):** Low oestradiol, rising FSH
- **Mid-cycle (days 12-16):** Oestradiol surge, LH peak
- **Luteal phase (days 15-28):** High progesterone, falling oestradiol

This is why random hormone testing in women often creates more confusion than clarity. Know when you're sampling, or the results are meaningless.

The PCOS Pattern: Learning to Spot It

PCOS is the most common hormone disorder you'll see in women of reproductive age, affecting 10-13% of women. The pattern is distinctive:

- **Testosterone:** Elevated (>2.5 nmol/L)
 - **Free androgen index:** >5
 - **LH:FSH ratio:** Often >2:1 (but not diagnostic)
 - **SHBG:** Often low due to insulin resistance
- Remember: clinical signs (hirsutism, acne, irregular periods) plus elevated androgens equals PCOS in most cases.



Clinical Pearl

"The Free Androgen Index Trick": Can't get free testosterone measured? Calculate free androgen index: (total testosterone × 100) ÷ SHBG. Values >5 suggest PCOS. It's not perfect, but it's widely available and clinically useful for detecting hyperandrogenism.

PCOS Hyperandrogenism

Testosterone: 2.5-4.8 nmol/L

FAI: >5

SHBG: Often low

Clinical: Hirsutism, acne, male-pattern hair loss

Action: Check metabolic screen, consider metformin

Tumor-Level Androgens

Testosterone: >4.8 nmol/L

DHEAS: >800 µg/dL if elevated

Clinical: Rapid virilization

Think: Ovarian or adrenal tumor
Action: Urgent imaging and endocrine referral

Ovarian Insufficiency

FSH: >25 U/L (under age 40)
Oestradiol: <100 pmol/L
Clinical: Amenorrhea, hot flushes
Think: Premature ovarian insufficiency
Action: HRT discussion, fertility counseling

Perimenopause Pattern

FSH: Fluctuating (15-40 U/L)
Oestradiol: Variable
Clinical: Irregular periods, symptoms
Note: Normal FSH doesn't exclude perimenopause
Action: Clinical diagnosis, HRT if appropriate

Female Hormone Red Flags Demanding Action

- **Testosterone >4.8 nmol/L:** Think tumor—urgent imaging needed
- **FSH >40 U/L under age 40:** Premature ovarian insufficiency—immediate HRT consideration
- **Very low oestradiol with amenorrhea:** Functional hypothalamic amenorrhea vs. organic cause
- **Rapid virilization:** Deepening voice, clitoromegaly—urgent endocrine referral
- **Prepubertal child with adult hormone levels:** Precocious puberty—urgent pediatric referral

Step 4: The Menopause Maze - Navigating Transition

NICE 2024 Guidelines: Menopause Diagnosis Made Simple

Over 45 with typical symptoms: Don't test—diagnose clinically based on symptoms and menstrual changes. Save your lab budget for cases that matter.

Ages 40-45: Consider FSH if diagnosis unclear, but remember it fluctuates wildly in perimenopause.

Under 40: Always test if menopause suspected—premature ovarian insufficiency has serious health implications.

Understanding Menopausal Hormone Patterns

Premenopause

FSH: <10 U/L

Oestradiol: Cyclic variation

Periods: Regular

Perimenopause

FSH: 15-40 U/L (variable)

Oestradiol: Erratic levels

Periods: Irregular, changing

Postmenopause

FSH: >30 U/L consistently

Oestradiol: <100 pmol/L

Periods: Absent >12 months



Clinical Pearl

"The Perimenopause Paradox": A woman can have a normal FSH on Monday and menopausal levels on Friday. During perimenopause, hormones fluctuate wildly, making single hormone tests unreliable. Trust the clinical picture—irregular periods and vasomotor symptoms trump lab values.

Menopause Testing Decision Tree

Woman with menopausal symptoms

Age >45 with typical symptoms?

Yes: No testing needed → Clinical diagnosis → Discuss HRT if appropriate

Age 40-45: Consider FSH if unclear → But normal result doesn't exclude perimenopause

Age <40: Always test → High FSH suggests premature ovarian insufficiency → Urgent action needed

Step 5: Putting It All Together - Pattern Recognition

Start with the Clinical Picture

What does the patient look like? What are their symptoms? A 25-year-old woman with hirsutism and acne probably has PCOS regardless of the exact hormone numbers. Clinical features guide interpretation, not the other way around.

Look for the Primary Pattern

High hormones with low LH/FSH = tumor or external source. Low hormones with high LH/FSH = gland failure. Low hormones with low LH/FSH = brain problem. This fundamental pattern tells you where the problem is.

Consider the Context

Age, medications, timing, and clinical presentation all matter enormously. The same hormone levels can be normal, concerning, or diagnostic depending on context. Never interpret numbers in isolation.

Know When to Refer

Complex patterns, tumor-level hormones, discordant clinical and biochemical findings, or when you're unsure—these all warrant specialist input. Don't struggle alone with confusing results.

Always Recheck If:

- Borderline results
- Doesn't fit clinical picture
- Patient on medications
- Wrong timing suspected

Refer Urgently If:

- Tumor-level hormones
- Rapid virilization
- Prepubertal abnormalities
- Discordant findings

Don't Test If:

- On hormonal contraception
- Clear clinical diagnosis
- Wouldn't change management
- Menopause >45 with symptoms

Remember to Consider:

- Sample timing
- Patient age
- Current medications



Clinical Pearl

"The Most Important Test": Your clinical assessment matters more than any single hormone level. If the biochemistry doesn't fit the clinical picture, trust your clinical judgment and either retest or refer. Laboratories make mistakes, assays have limitations, and patients are complex.

Step 6: Common Pitfalls and How to Avoid Them

The Afternoon Testosterone Trap

Mistake: Ordering testosterone any time of day

Reality: Levels drop 30-40% by afternoon

Solution: Always before 10am, especially in younger men

Exception: Less critical in older men with lower amplitude variation

The Contraceptive Confusion

Mistake: Testing hormones on the pill

Reality: You're measuring pill effects, not natural production

Solution: Stop hormones 3 months before testing

Exception: Not always practical—discuss with patient first

The Single FSH Fallacy

Mistake: One normal FSH rules out menopause

Reality: FSH fluctuates wildly in perimenopause

Solution: Diagnose clinically over 45, repeat if under 45

Remember: Symptoms matter more than single values

The Reference Range Trap

Mistake: Normal range = normal for this patient

Reality: Ranges are population-based, not individualized

Solution: Consider age, sex, and clinical context always

Example: FSH 15 U/L is normal at 50, concerning at 25

The "Always Remember" List for Hormone Testing

- **Timing is everything:** Wrong timing can make normal look abnormal and vice versa
- **One abnormal result isn't a diagnosis:** Confirm unexpected findings with repeat testing
- **Medications matter:** Many drugs affect hormone levels—check current medications
- **Age changes everything:** The same level can be normal at one age, abnormal at another
- **Clinical correlation is key:** If it doesn't fit, don't force it—recheck or refer
- **Stress affects results:** Acute illness, psychological stress, and extreme exercise alter levels

Summary: Mastering Hormone Interpretation

The Five-Step Hormone Reading Method

1. Clinical Context

Age, symptoms, timing, medications - these shape interpretation more than numbers

2. Pattern Recognition

High/low hormones with high/low LH/FSH reveals the site of pathology

3. Physiological Sense

Does this result make biological sense given the patient's presentation?

4. Confirmatory Testing

Unexpected results need confirmation - don't change management on single tests

5. Clinical Decision

What does this mean for the patient? How does it change management?

What to Remember About Each Hormone

Testosterone: Morning samples essential in men, context crucial in women. Free testosterone more accurate than total.

LH/FSH: The brain's messengers - high levels mean the brain is trying to stimulate failed gonads, low levels suggest brain problems.

Oestradiol: Fluctuates dramatically with menstrual cycle. Timing is everything for interpretation.

SHBG: The carrier protein that affects free hormone levels. High SHBG lowers free hormones, low SHBG raises them.

The Most Common Patterns You'll See

PCOS: High testosterone + clinical signs + irregular periods

Male hypogonadism: Low testosterone - check LH to find the cause

Menopause: Clinical diagnosis over 45, FSH confirmation under 40

Premature ovarian insufficiency: High FSH + low oestradiol under age 40



Clinical Pearl

"The Human Touch in Hormone Medicine": Behind every hormone profile is a person with hopes, fears, and concerns about their body and future. Whether they're struggling with fertility, worried about their development, or navigating life changes, remember that these numbers represent deeply personal experiences. Your skill in interpreting these results can provide answers, reassurance, and direction at crucial moments in their lives.

Take Home Messages for Hormone Interpretation

- **Context trumps numbers:** Clinical picture matters more than isolated lab values
- **Timing is critical:** Wrong timing can completely mislead interpretation
- **Patterns tell stories:** Look for the overall pattern, not individual values
- **Confirm unexpected findings:** One abnormal result doesn't make a diagnosis

- **Know when to refer:** Complex cases need specialist input
- **Remember the human:** These are deeply personal results affecting real lives

Evidence Base and Clinical Guidelines

NICE Guideline NG23

Menopause: identification and management

- Updated 2024

[Access Guidelines](#)

International PCOS Guidelines

Evidence-based Guideline for Assessment and Management of PCOS

- 2023

[Access Full Guideline](#)

American Urological Association

Testosterone Deficiency Guideline

- 2024

[Access Guidelines](#)

Clinical Practice Guidelines

Cases in primary care laboratory medicine: sex hormone testing

[Reference Article](#)

References

- Bhasin, S., Brito, J.P., Cunningham, G.R., Hayes, F.J., Hodis, H.N., Matsumoto, A.M., Snyder, P.J., Swerdloff, R.S., Wu, F.C. and Yialamas, M.A.** (2018) 'Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline', *Journal of Clinical Endocrinology & Metabolism*, 103(5), pp. 1715-1744.
- Balen, A.H., Morley, L.C., Misso, M., Franks, S., Legro, R.S., Wijeyaratne, C.N., Stener-Victorin, E., Fauser, B.C., Norman, R.J. and Teede, H.** (2016) 'The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance', *Human Reproduction Update*, 22(6), pp. 687-708.
- European Society of Human Reproduction and Embryology (ESHRE)** (2023) *Guideline on the management of women with premature ovarian insufficiency*. Available at: <https://www.eshre.eu/Guidelines-and-Legal/Guidelines> (Accessed: 30 September 2025).
- National Institute for Health and Care Excellence (NICE)** (2024) *Menopause: identification and management. NICE guideline [NG23]*. London:

NICE. Available at: <https://www.nice.org.uk/guidance/ng23> (Accessed: 30 September 2025).

Teede, H.J., Misso, M.L., Costello, M.F., Dokras, A., Laven, J., Moran, L., Piltonen, T., Norman, R.J. and International PCOS Network (2018) 'Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome', *Fertility and Sterility*, 110(3), pp. 364-379.

Webber, L., Davies, M., Anderson, R., Bartlett, J., Braat, D., Cartwright, B., Cifkova, R., de Muinck Keizer-Schrama, S., Hogervorst, E., Janse, F., Liao, L., Vlasisavljevic, V., Zillikens, C. and Vermeulen, N. (2016) 'ESHRE Guideline: management of women with premature ovarian insufficiency', *Human Reproduction*, 31(5), pp. 926-937.

Wu, F.C., Tajar, A., Beynon, J.M., Pye, S.R., Silman, A.J., Finn, J.D., O'Neill, T.W., Bartfai, G., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Kula, K., Lean, M.E., Pendleton, N., Punab, M., Boonen, S., Vanderschueren, D., Labrie, F. and Huhtaniemi, I.T. (2010) 'Identification of late-onset hypogonadism in middle-aged and elderly men', *New England Journal of Medicine*, 363(2), pp. 123-135.

References

This comprehensive references section provides evidence-based support for all clinical interpretations, reference ranges, and management recommendations presented throughout this textbook. References are organized by chapter and follow Harvard referencing style.

Chapter 1: Full Blood Count (FBC)

Bain, B.J., 2020. *Blood Cells: A Practical Guide*, 6th ed. Wiley-Blackwell, Oxford. doi: 10.1002/9781119641544

Cappellini, M.D. and Motta, I., 2015. Anemia in clinical practice—definition and classification: does hemoglobin change with aging? *Seminars in Hematology*, 52(4), pp.261-269. doi: 10.1053/j.seminhematol.2015.07.006

Hoffbrand, A.V. and Moss, P.A.H., 2022. *Hoffbrand's Essential Haematology*, 8th ed. Wiley-Blackwell, Oxford.

National Institute for Health and Care Excellence (NICE), 2021. *Anaemia - iron deficiency. Clinical Knowledge Summary*. Available at: <https://cks.nice.org.uk/topics/anaemia-iron-deficiency/> [Accessed 30 September 2025].

World Health Organization, 2011. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity*. WHO/NMH/NHD/MNM/11.1. Geneva: World Health Organization.

Bailey, D., Colantonio, D., Kyriakopoulou, L., Cohen, A.H., Chan, M.K., Armbruster, D. and Adeli, K., 2013. Marked biological variance in endocrine and biochemical markers in childhood: establishment of pediatric reference intervals using healthy community children from the CALIPER cohort. *Clinical Chemistry*, 59(9), pp.1393-1405. doi: 10.1373/clinchem.2013.204222

Chapter 2: Iron Studies, B12 & Folate

British Society for Haematology, 2020. UK guidelines on the management of iron deficiency in pregnancy. *British Journal of Haematology*, 188(6), pp.819-830. doi: 10.1111/bjh.16221

Devalia, V., Hamilton, M.S. and Molloy, A.M., 2014. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *British Journal of Haematology*, 166(4), pp.496-513. doi: 10.1111/bjh.12959

Goddard, A.F., James, M.W., McIntyre, A.S. and Scott, B.B., 2011. Guidelines for the

management of iron deficiency anaemia. *Gut*, 60(10), pp.1309-1316. doi: 10.1136/gut.2010.228874

Lopez, A., Cacoub, P., Macdougall, I.C. and Peyrin-Biroulet, L., 2016. Iron deficiency anaemia. *The Lancet*, 387(10021), pp.907-916. doi: 10.1016/S0140-6736(15)60865-0

Stabler, S.P., 2013. Clinical practice. Vitamin B12 deficiency. *New England Journal of Medicine*, 368(2), pp.149-160. doi: 10.1056/NEJMcpr1113996

World Health Organization, 2017. *Nutritional Anaemias: Tools for Effective Prevention and Control*. Geneva: World Health Organization.

Chapter 3: Liver Function Tests

European Association for the Study of the Liver (EASL), 2020. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *Journal of Hepatology*, 69(1), pp.154-181. doi: 10.1016/j.jhep.2018.03.018

National Institute for Health and Care Excellence (NICE), 2021. *Non-alcoholic fatty liver disease (NAFLD): assessment and management*. NICE guideline [NG49]. Available at: <https://www.nice.org.uk/guidance/ng49>

Newsome, P.N., Cramb, R., Davison, S.M., Dillon, J.F., Foulerton, M., Godfrey, E.M., Hall, R., Harrower, U., Hudson, M., Langford, A., Mackie, A., Mitchell-Thain, R., Sennett, K., Sheron, N.C., Verne, J., Walmsley, M. and Yeoman, A., 2018. Guidelines on the management of abnormal liver blood tests. *Gut*, 67(1), pp.6-19. doi: 10.1136/gutjnl-2017-314924

Pratt, D.S. and Kaplan, M.M., 2000. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *New England Journal of Medicine*, 342(17), pp.1266-1271. doi: 10.1056/NEJM200004273421707

Rinella, M.E., Lazarus, J.V., Ratziu, V., Francque, S.M., Sanyal, A.J., Kanwal, F., Romero, D., Abdelmalek, M.F., Anstee, Q.M., Arab, J.P., Arrese, M., Bataller, R., Beuers, U., Boursier, J., Bugianesi, E., Byrne, C.D., Castro Narro, G.E., Chowdhury, A., Cortez-Pinto, H., Cryer, D.R., Cusi, K., El-Kassas, M., Klein, S., Eskridge, W., Fan, J., Gawrieh, S., Guy, C.D., Harrison, S.A., Kim, S.U., Koot, B.G.P., Korenjak, M., Kowdley, K.V., Lacaille, F., Loomba, R., Mitchell-Thain, R., Morgan, T.R., Powell, E.E., Roden, M., Romero-Gómez, M., Silva, M., Singh, S.P., Sookoian, S.C., Spearman, C.W., Tiniakos, D., Valenti, L., Vos, M.B., Wong, V.W., Xanthakos, S.A., Yilmaz, Y., Younossi, Z., Hobbs, A., Villota-Rivas, M., Newsome, P.N. and NAFLD Nomenclature consensus group, 2023. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Journal of Hepatology*, 79(6), pp.1542-1556. doi: 10.1016/j.jhep.2023.06.003

Chapter 4: Urea & Electrolytes

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements*, 2(1), pp.1-138. doi: 10.1038/kisup.2012.1

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements*, 3(1), pp.1-150.

National Institute for Health and Care Excellence (NICE), 2021. *Acute kidney injury: prevention, detection and management*. NICE guideline [NG148]. Available at: <https://www.nice.org.uk/guidance/ng148>

National Institute for Health and Care Excellence (NICE), 2021. *Chronic kidney disease: assessment and management*. NICE guideline [NG203]. Available at: <https://www.nice.org.uk/guidance/ng203>

Levey, A.S., Stevens, L.A., Schmid, C.H., Zhang, Y.L., Castro, A.F., Feldman, H.I., Kusek, J.W., Eggers, P., Van Lente, F., Greene, T. and Coresh, J., 2009. A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, 150(9), pp.604-612. doi: 10.7326/0003-4819-150-9-200905050-00006

Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., Decaux, G., Fenske, W., Hoorn, E.J., Ichai, C., Joannidis, M., Soupart, A., Zietse, R., Haller, M., van der Veer, S., Van Biesen, W. and Nagler, E., 2014. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *European Journal of Endocrinology*, 170(3), pp.G1-47. doi: 10.1530/EJE-13-1020

Chapter 5: Lipid Profile

Cholesterol Treatment Trialists' (CTT) Collaboration, 2010. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *The Lancet*, 376(9753), pp.1670-1681. doi: 10.1016/S0140-6736(10)61350-5

European Society of Cardiology (ESC), 2019. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal*, 41(1), pp.111-188. doi: 10.1093/eurheartj/ehz455

Mach, F., Baigent, C., Catapano, A.L., Koskinas, K.C., Casula, M., Badimon, L., Chapman, M.J., De Backer, G.G., Delgado, V., Ference, B.A., Graham, I.M., Halliday, A., Landmesser, U., Mihaylova, B., Pedersen, T.R., Riccardi, G., Richter, D.J., Sabatine, M.S., Taskinen, M.R., Tokgozoglu, L., Wiklund, O. and ESC Scientific Document Group, 2020. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal*, 41(1), pp.111-188. doi: 10.1093/eurheartj/ehz455

National Institute for Health and Care Excellence (NICE), 2023. *Cardiovascular disease: risk assessment and reduction, including lipid modification*. NICE guideline [NG238]. Available at: <https://www.nice.org.uk/guidance/ng238>

Ridker, P.M., Danielson, E., Fonseca, F.A., Genest, J., Gotto, A.M., Kastelein, J.J., Koenig, W., Libby, P., Lorenzatti, A.J., MacFadyen, J.G., Nordestgaard, B.G., Shepherd, J., Willerson, J.T., Glynn, R.J. and JUPITER Study Group, 2008. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine*, 359(21), pp.2195-2207. doi: 10.1056/NEJMoA0807646

Scandinavian Simvastatin Survival Study Group, 1994. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *The Lancet*, 344(8934), pp.1383-1389. doi: 10.1016/s0140-6736(94)90566-5

Chapter 6: Thyroid Function Tests

Alexander, E.K., Pearce, E.N., Brent, G.A., Brown, R.S., Chen, H., Dosiou, C., Grobman, W.A., Laurberg, P., Lazarus, J.H., Mandel, S.J., Peeters, R.P. and Sullivan, S., 2017. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*, 27(3), pp.315-389. doi: 10.1089/thy.2016.0457

British Thyroid Association, 2016. UK guidelines for the use of thyroid function tests. Available at: <https://www.british-thyroid-association.org/>

Garber, J.R., Cobin, R.H., Gharib, H., Hennessey, J.V., Klein, I., Mechanick, J.I., Pessah-Pollack, R., Singer, P.A., Woeber, K.A. and American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults, 2012. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*, 22(12), pp.1200-1235. doi: 10.1089/thy.2012.0205

National Institute for Health and Care Excellence (NICE), 2019. *Thyroid disease: assessment and management*. NICE guideline [NG145]. Available at: <https://www.nice.org.uk/guidance/ng145>

Ross, D.S., Burch, H.B., Cooper, D.S., Greenlee, M.C., Laurberg, P., Maia, A.L., Rivkees, S.A., Samuels, M., Sosa, J.A., Stan, M.N. and Walter, M.A., 2016. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*, 26(10), pp.1343-1421. doi: 10.1089/thy.2016.0229

Chapter 7: HbA1c & Diabetes Monitoring

American Diabetes Association, 2024. Standards of Care in Diabetes—2024. *Diabetes Care*, 47(Supplement_1), pp.S1-S321. doi: 10.2337/dc24-Sint

Davies, M.J., Aroda, V.R., Collins, B.S., Gabbay, R.A., Green, J., Maruthur, N.M., Rosas, S.E., Del Prato, S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A. and Buse, J.B., 2022. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, 45(11), pp.2753-2786. doi: 10.2337/dci22-0034

The Diabetes Control and Complications Trial Research Group, 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*, 329(14), pp.977-986. doi: 10.1056/NEJM199309303291401

National Institute for Health and Care Excellence (NICE), 2022. *Type 2 diabetes in adults: management*. NICE guideline [NG28]. Available at: <https://www.nice.org.uk/guidance/ng28>

UK Prospective Diabetes Study (UKPDS) Group, 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*, 352(9131), pp.837-853. doi: 10.1016/S0140-6736(98)07019-6

World Health Organization, 2011. *Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation*. Geneva: World Health Organization.

Chapter 8: Inflammatory Markers (CRP & ESR)

Dasgupta, B., Cimmino, M.A., Kremers, H.M., Schmidt, W.A., Schirmer, M., Salvarani, C., Bachta, A., Dejaco, C., Duftner, C., Jensen, H.S., Duhaut, P., Poór, G., Kaposi, N.P., Mandl, P., Balint, P.V., Schmidt, Z., Iagnocco, A., Nannini, C., Cantini, F., Macchioni, P., Pipitone, N., Del Amo, M., Espígol-Frigolé, G., Cid, M.C., Martínez-Taboada, V.M., Nordborg, E., Direskeneli, H., Aydin, S.Z., Ahmed, K., Hazleman, B., Silverman, B., Pease, C., Wakefield, R.J., Luqmani, R., Abril, A., Michet, C.J., Marcus, R., Gonter, N.J., Maz, M., Pawlowski, C., Kolstad, K., Hutchings, A., Watts, R.A., Suppiah, R., Yacyshyn, E., Chew, S., Tomasson, G., Merkel, P.A., Matteson, E.L. and European League Against Rheumatism-American College of Rheumatology, 2012. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Annals of the Rheumatic Diseases*, 71(4), pp.484-492. doi: 10.1136/annrheumdis-2011-200329

Gabay, C. and Kushner, I., 1999. Acute-phase proteins and other systemic responses to inflammation. *New England Journal of Medicine*, 340(6), pp.448-454. doi: 10.1056/NEJM199902113400607

National Institute for Health and Care Excellence (NICE), 2020. *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. NICE guideline [NG188]. Available at: <https://www.nice.org.uk/guidance/ng188>

National Institute for Health and Care Excellence (NICE), 2023. *Pneumonia (community-acquired): antimicrobial prescribing*. NICE guideline [NG138]. Available at: <https://www.nice.org.uk/guidance/ng138>

Pepys, M.B. and Hirschfield, G.M., 2003. C-reactive protein: a critical update. *Journal of Clinical Investigation*, 111(12), pp.1805-1812. doi: 10.1172/JCI18921

Ridker, P.M., 2003. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*, 107(3), pp.363-369. doi: 10.1161/01.CIR.0000053730.47739.3C

Chapter 9: Bone Profile (Calcium, Phosphate, ALP, Vitamin D)

-
- Bilezikian, J.P., Brandi, M.L., Eastell, R., Silverberg, S.J., Udelsman, R., Marcocci, C. and Potts, J.T., 2014. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *Journal of Clinical Endocrinology & Metabolism*, 99(10), pp.3561-3569. doi: 10.1210/jc.2014-1413
- Bolland, M.J., Grey, A., Gamble, G.D. and Reid, I.R., 2014. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *The Lancet Diabetes & Endocrinology*, 2(4), pp.307-320. doi: 10.1016/S2213-8587(13)70212-2
- Eastell, R., Brandi, M.L., Costa, A.G., D'Amour, P., Shoback, D.M. and Thakker, R.V., 2014. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *Journal of Clinical Endocrinology & Metabolism*, 99(10), pp.3570-3579. doi: 10.1210/jc.2014-1414
- Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M. and Endocrine Society, 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 96(7), pp.1911-1930. doi: 10.1210/jc.2011-0385
- National Institute for Health and Care Excellence (NICE), 2020. *Vitamin D deficiency in adults - treatment and prevention*. Clinical Knowledge Summary. Available at: <https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults/>
- National Osteoporosis Guideline Group (NOGG), 2021. *UK clinical guideline for the prevention and treatment of osteoporosis*. Available at: <https://www.nogg.org.uk/>

Chapter 10: Cardiac Markers (Troponin, BNP/NT-proBNP)

- Amsterdam, E.A., Wenger, N.K., Brindis, R.G., Casey, D.E., Ganiats, T.G., Holmes, D.R., Jaffe, A.S., Jneid, H., Kelly, R.F., Kontos, M.C., Levine, G.N., Liebson, P.R., Mukherjee, D., Peterson, E.D., Sabatine, M.S., Smalling, R.W., Zieman, S.J. and ACC/AHA Task Force Members, 2014. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 130(25), pp.e344-426. doi: 10.1161/CIR.000000000000134
- Collet, J.P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D.L., Dendale, P., Dorobantu, M., Edvardsen, T., Folliguet, T., Gale, C.P., Gilard, M., Jobs, A., Jüni, P., Lambrinou, E., Lewis, B.S., Mehilli, J., Meliga, E., Merkely, B., Mueller, C., Roffi, M., Rutten, F.H., Sibbing, D., Siontis, G.C.M. and ESC Scientific Document Group, 2021. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*, 42(14), pp.1289-1367. doi: 10.1093/eurheartj/ehaa575
- McDonagh, T.A., Metra, M., Adamo, M., Gardner, R.S., Baumbach, A., Böhm, M.,

Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J.G.F., Coats, A.J.S., Crespo-Leiro, M.G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A.W., Jaarsma, T., Jankowska, E.A., Lainscak, M., Lam, C.S.P., Lyon, A.R., McMurray, J.J.V., Mebazaa, A., Mindham, R., Muneretto, C., Francesco Piepoli, M., Price, S., Rosano, G.M.C., Ruschitzka, F., Kathrine Skibelund, A. and ESC Scientific Document Group, 2021. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*, 42(36), pp.3599-3726. doi: 10.1093/eurheartj/ehab368

National Institute for Health and Care Excellence (NICE), 2020. *Acute coronary syndromes*. NICE guideline [NG185]. Available at: <https://www.nice.org.uk/guidance/ng185>

National Institute for Health and Care Excellence (NICE), 2023. *Chronic heart failure in adults: diagnosis and management*. NICE guideline [NG106]. Available at: <https://www.nice.org.uk/guidance/ng106>

Thygesen, K., Alpert, J.S., Jaffe, A.S., Chaitman, B.R., Bax, J.J., Morrow, D.A., White, H.D. and Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction, 2018. Fourth universal definition of myocardial infarction (2018). *European Heart Journal*, 40(3), pp.237-269. doi: 10.1093/eurheartj/ehy462

Chapter 11: Sex Hormone Profiles (FSH, LH, Testosterone, Oestradiol, Prolactin)

Bhasin, S., Brito, J.P., Cunningham, G.R., Hayes, F.J., Hodis, H.N., Matsumoto, A.M., Snyder, P.J., Swerdloff, R.S., Wu, F.C. and Yialamas, M.A., 2018. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 103(5), pp.1715-1744. doi: 10.1210/jc.2018-00229

Melmed, S., Casanueva, F.F., Hoffman, A.R., Kleinberg, D.L., Montori, V.M., Schlechte, J.A., Wass, J.A. and Endocrine Society, 2011. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 96(2), pp.273-288. doi: 10.1210/jc.2010-1692

National Institute for Health and Care Excellence (NICE), 2021. *Menopause: diagnosis and management*. NICE guideline [NG23]. Available at: <https://www.nice.org.uk/guidance/ng23>

Royal College of Obstetricians and Gynaecologists (RCOG), 2019. *Long-term Consequences of Polycystic Ovary Syndrome*. Green-top Guideline No. 33. London: RCOG.

Teede, H.J., Misso, M.L., Costello, M.F., Dokras, A., Laven, J., Moran, L., Piltonen, T., Norman, R.J. and International PCOS Network, 2018. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction*, 33(9), pp.1602-1618. doi: 10.1093/humrep/dey256

Wu, F.C., Tajar, A., Beynon, J.M., Pye, S.R., Silman, A.J., Finn, J.D., O'Neill, T.W., Bartfai, G., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Kula, K., Lean, M.E., Pendleton, N., Punab, M., Boonen, S., Vanderschueren, D., Labrie, F., Huhtaniemi, I.T. and EMAS Group, 2010. Identification of late-onset hypogonadism in middle-aged and elderly men. *New England Journal of Medicine*, 363(2), pp.123-135. doi: 10.1056/NEJMoa0911101

General Laboratory Medicine & Clinical Chemistry

Burtis, C.A., Bruns, D.E., Sawyer, B.G. and Tietz, N.W., 2023. *Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics*, 8th ed. Elsevier Health Sciences, St. Louis.

Collier, J., Longmore, M., Turmezei, T. and Mafi, A.R., 2020. *Oxford Handbook of Clinical Specialties*, 11th ed. Oxford University Press, Oxford.

Kumar, P. and Clark, M., 2021. *Kumar and Clark's Clinical Medicine*, 10th ed. Elsevier Health Sciences, Edinburgh.

Marshall, W.J., Lapsley, M., Day, A.P. and Ayling, R.M., 2021. *Clinical Biochemistry: Metabolic and Clinical Aspects*, 3rd ed. Elsevier Health Sciences, Edinburgh.

Rai, P., 2020. *Blood Sciences: A Guide to Blood Tests and Interpretation*. Springer Nature, Cham. doi: 10.1007/978-3-030-36665-4

Ralston, S.H., Penman, I.D., Strachan, M.W.J. and Hobson, R.P., 2023. *Davidson's Principles and Practice of Medicine*, 24th ed. Elsevier Health Sciences, Edinburgh.

Index

A

Acute Coronary Syndrome (ACS), 95-100
Acute Kidney Injury (AKI), 35-44
Albumin, 25-34
Alkaline Phosphatase (ALP), 25-34, 85-94
ALT (Alanine Aminotransferase), 25-34
Anaemia classification, 5-14
Anaemia, macrocytic, 5-14, 15-24
Anaemia, microcytic, 5-14, 15-24
Anaemia, normocytic, 5-14
AST (Aspartate Aminotransferase), 25-34
AST:ALT ratio, 25-34
Apolipoprotein B, 45-54

B

B12 deficiency, 15-24
Bilirubin, 25-34
Bone profile interpretation, 85-94
BNP (B-type Natriuretic Peptide), 95-100

C

Calcium, corrected, 85-94
Cardiac markers, 95-100
Cholestatic pattern, 25-34
Chronic Kidney Disease (CKD), 35-44
CRP (C-Reactive Protein), 75-84
Creatinine, 35-44
CURB-65 score, 75-84

D

Diabetes diagnosis, 65-74
Diabetes monitoring, 65-74

E

eGFR (estimated Glomerular Filtration Rate), 35-44
Electrolytes, 35-44
ESR (Erythrocyte Sedimentation Rate), 75-84

F

Familial hypercholesterolaemia, 45-54
Ferritin, 15-24
Folate deficiency, 15-24
Free T4 (FT4), 55-64
FSH (Follicle Stimulating Hormone), 105-114
Full Blood Count (FBC), 5-14

G

Giant Cell Arteritis, 75-84
Glycaemic control targets, 65-74

H

Haemoglobin (Hb), 5-14

- HbA1c interpretation, 65-74
- HDL cholesterol, 45-54
- Heart failure diagnosis, 95-100
- Hepatocellular pattern, 25-34
- Hypercalcaemia, 85-94
- Hyperkalaemia, 35-44
- Hyperparathyroidism, 85-94
- Hyperthyroidism, 55-64
- Hyponatraemia, 35-44
- Hypothyroidism, 55-64

I

- Inflammatory markers, 75-84
- Iron deficiency, 15-24
- Iron studies, 15-24

K

- KDIGO AKI criteria, 35-44

L

- LDL cholesterol, 45-54
- LH (Luteinizing Hormone), 105-114
- Lipid profile interpretation, 45-54
- Liver function tests (LFTs), 25-34

M

- Macrocytosis, 5-14, 15-24
- MCV (Mean Cell Volume), 5-14
- Menopause, 105-114
- Microcytosis, 5-14
- Myocardial infarction, 95-100

N

- Non-HDL cholesterol, 45-54
- NT-proBNP, 95-100

O

- Oestradiol, 105-114
- Osteoporosis, 85-94

P

- Parathyroid hormone (PTH), 85-94
- Pattern recognition, 3, 5-14, 25-34
- PCOS (Polycystic Ovary Syndrome), 105-114
- Phosphate, 85-94
- Platelets, 5-14
- Polymyalgia Rheumatica, 75-84
- Potassium, 35-44
- Prediabetes, 65-74
- Premature Ovarian Insufficiency, 105-114
- Progesterone, 105-114
- Prolactin, 105-114

Q

- QRISK score, 45-54

R

- RDW (Red Cell Distribution Width), 5-14
- Reference ranges, throughout
- Renal function, 35-44

S

Sex hormones, 105-114
SHBG (Sex Hormone Binding Globulin), 105-114
Sodium, 35-44
Statin therapy, 45-54
Subclinical hypothyroidism, 55-64

T

Testosterone, 105-114
Thyroid function tests, 55-64
Transferrin saturation, 15-24
Triglycerides, 45-54
Troponin, 95-100
TSH (Thyroid Stimulating Hormone), 55-64

U

Urea, 35-44
Urea:Creatinine ratio, 35-44

V

Vitamin D, 85-94

W

White Cell Count (WCC), 5-14