



Differential Diagnosis

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Differential Diagnosis Of General Symptoms



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PRESENTATION: PYREXIA (PUO)

DIFFERENTIAL DIAGNOSIS

Infective causes

Bacterial:

- ★ Abscesses (e.g. subphrenic, pelvic, hepatic, renal)
- Subacute bacterial endocarditis
- ★ Tuberculosis
- Typhoid
- Q fever
- Brucellosis
- Leptospirosis
- Cat scratch disease

Viral:

- Influenza
- ★ Glandular fever (infectious mononucleosis)
- Human immunodeficiency virus infection
- Cytomegalovirus infection

Fungal:

- Candidiasis
- Aspergillosis
- Pneumocystis jirovecii infection

Protozoal:

- ★ Malaria (common in endemic areas)
- Amoebiasis
- Toxoplasmosis

Neoplastic, Inflammatory & Other causes

Neoplastic causes:

- ★ Lymphoma
- Acute leukaemia
- Hypernephroma
- Metastatic malignancy
- Hypernephroma
- Hepatoma
- Sarcoma

Inflammatory / connective tissue disorders:

- ★ Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyarteritis nodosa and other vasculitides
- ★ Temporal (giant-cell) arteritis
- Polymyositis
- Sarcoidosis
- Dermatomyositis
- Crohn's disease

Other causes:

- Myocardial infarction
- Pulmonary embolism
- Drug-induced pyrexia
- Post-immunisation pyrexia
- Familial Mediterranean fever
- Factitious pyrexia (Munchausen's disease)

IMPORTANT CLINICAL WARNINGS

- **Prolonged pyrexia (>3 weeks) with no clear source** → Infection, malignancy, inflammatory disease
- **Pyrexia with weight loss, night sweats or lymphadenopathy** → Lymphoma, tuberculosis
- **Swinging or intermittent fever with rigors** → Abscess, bacteraemia, malaria
- **Pyrexia with cardiac murmur, anaemia or haematuria** → Subacute bacterial endocarditis
- **Pyrexia with jaundice and recurrent rigors** → Suppurative cholangitis
- **Persistent pyrexia in patients receiving multiple drugs** → Drug-induced pyrexia
- **Inconsistent or unexplained temperature readings** → Factitious pyrexia
- **Empirical treatment is not recommended, except in:**
 - Culture-negative endocarditis
 - Suspected disseminated tuberculosis
 - Suspected disseminated tuberculosis
 - Suspected temporal arteritis

INITIAL INVESTIGATIONS

- **Blood cultures** → Bacteraemia, infective endocarditis
- **Viral serology / antibodies** → Hepatitis B, hepatitis C, infectious mononucleosis, HIV, cytomegalovirus
- **Sputum culture** → Tuberculosis
- **Urine microscopy and culture** → Endocarditis-related haematuria, renal disease, infection
- **Stool microscopy and culture** → Enteric infection, parasites
- **Chest X-ray** → Tuberculosis, atypical pneumonia, malignancy, sarcoidosis
- **Rheumatoid factor** → Rheumatoid arthritis
- **Autoantibodies** → Connective tissue disease
- **Mantoux test** → Tuberculosis
- **Bone marrow aspirate** → Leukaemia, myeloma
- **Lumbar puncture** → Meningitis, subarachnoid haemorrhage
- **Ultrasound abdomen** → Intra-abdominal abscess
- **Gallium scan / labelled white cell scan** → Localised infection or abscess
- **Liver biopsy** → Hepatitis, infiltrative disease
- **Renal biopsy** → Glomerular disease, malignancy
- **Muscle biopsy** → Myositis
- **Computed tomography** → Occult infection or malignancy
- **Exploratory laparotomy** → Suspected intra-abdominal sepsis

REFERENCE: French's & Churchill's



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PRESENTATION: WEIGHT LOSS

DIFFERENTIAL DIAGNOSIS

Systemic, Endocrine, Infective & Psychiatric

Systemic disease:

- ★ Malignancy
- ★ Cardiac failure
- ★ Chronic respiratory disease
- Renal failure
- Liver failure
- ★ Malabsorption
- Connective tissue disease (e.g. systemic lupus erythematosus, rheumatoid arthritis)

Endocrine:

- ★ Diabetes mellitus
- ★ Hyperthyroidism
- Addison's disease

Infective:

- ★ Tuberculosis
- ★ Human immunodeficiency virus infection
- ★ Helminth (worm) infection
- Chronic infections (e.g. pulmonary tuberculosis)

Psychiatric:

- ★ Depression
- Anorexia nervosa
- Psychoses

Gastrointestinal, Malignant & Other Causes

Gastrointestinal:

- Gastric ulcer
- ★ Gastrointestinal
- Chronic colitis
- Hepatobiliary disease
- Chronic pancreatitis
- Gluten enteropathy
- Whipple's disease
- Carcinoid
- Dysphagia (e.g. scleroderma)
- Short-circuit operations / post-gastrectomy / post-colectomy states

Other causes:

- ★ Chronic lung disease (e.g. obstructive airways disease)

Malignant conditions:

- ★ Carcinoma
- ★ Lymphoma
- Leukaemia
- Sarcoma

Other causes:

- ★ Chronic lung disease (e.g. obstructive)
- ★ Heart failure-related cachexia
- ★ Alcohol abuse
- Chronic intoxications (addictive drugs, heavy smoking, lead)
- Substance abuse (laxatives, amphetamines, opiates)
- ★ Poor nutrition
- Any terminal illness
- Food intolerance

IMPORTANT CLINICAL WARNINGS

- **Significant or rapid unintentional weight loss** → Malignancy until proven otherwise
- **Weight loss with night sweats and lymphadenopathy** → Tuberculosis, lymphoma, human immunodeficiency virus infection
- **Weight loss despite normal or increased appetite** → Hyperthyroidism, diabetes mellitus
- **Weight loss with diarrhoea or steatorrhoea** → Malabsorption, chronic pancreatitis, Whipple's disease
- **Weight loss with dyspnoea, orthopnoea or peripheral oedema** → Cardiac failure
- **Weight loss with pigmentation and postural hypotension** → Addison's disease
- **Weight loss with psychiatric symptoms or distorted body image** → Depression, anorexia nervosa
- **Weight loss in patients from endemic or developing regions** → Tuberculosis, human immunodeficiency virus infection, helminth infection
- **Dramatic weight loss over a short period** → Urgent investigation mandatory

INITIAL INVESTIGATIONS

- **Chest X-ray** → Malignancy, tuberculosis, heart failure, lymphadenopathy
- **Urine dipstick** → Glucose (diabetes mellitus), protein/blood (renal disease)
- **Full blood count**
- **Erythrocyte sedimentation rate / C-reactive protein** → Malignancy, connective tissue disease
- **Urea and electrolytes** → Renal failure, electrolyte disturbance in Addison's disease
- **Liver function tests**
- **Thyroid-stimulating hormone and free thyroxine** → Hyperthyroidism
- **Blood glucose** → Diabetes mellitus
- **Faecal fat estimation** → Fat malabsorption
- **Faecal occult blood** → Colorectal carcinoma
- **Short synacthen test** → Addison's disease
- **Colonoscopy / gastroscopy** → Gastrointestinal malignancy, inflammatory bowel disease
- **Ultrasound abdomen** → Malignancy, chronic renal disease, liver disease
- **Echocardiography** → Cardiac failure
- **Human immunodeficiency virus antibodies** → Human immunodeficiency virus infection
- **Stool microscopy and culture** → Helminth infection

REFERENCE: French's & Churchill's



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PRESENTATION: FATIGUE

DIFFERENTIAL DIAGNOSIS

Emotional & Psychological, Malignant, Infection & HIV

Emotional and psychological causes:

- ★ Anxiety
- ★ Depression
- ★ Stress, overwork
- ★ Lack of sleep
- Emotional unhappiness, boredom
- Neurasthenia

Malignant disease:

- ★ Any malignancy

Chronic infection:

- ★ Tuberculosis
- Brucellosis
- Infective endocarditis
- Toxoplasmosis

Human immunodeficiency virus infection:

- ★ Human immunodeficiency virus disease

Post-viral, Hypoxia, Connective Tissue, Endocrine, Malnutrition, Pain, Weakness & Drugs

Post-viral fatigue:

- ★ Post-viral fatigue syndrome
- Infectious mononucleosis
- Myalgic encephalomyelitis / chronic fatigue syndrome

Tissue hypoxia:

- ★ Anaemia
- ★ Cardiac failure
- Severe pulmonary hypertension
- Valvular heart disease
- Addison's disease
- Excessive diuretic therapy

Connective tissue diseases:

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Polymyalgia rheumatica
- Giant-cell arteritis
- Polymyositis

Malnutrition:

- ★ Poor dietary intake
- Coeliac disease
- Ulcerative colitis
- Crohn's disease

Chronic pain:

- ★ Osteoarthritis
- Paget's disease
- Metastatic bone disease

Endocrine and metabolic disorders:

- ★ Hypothyroidism
- Diabetes mellitus
- Addison's disease
- Renal failure
- Hepatic failure
- Mast cell disorders

Malnutrition:

- ★ Poor dietary intake
- Coeliac disease
- Ulcerative colitis
- Crohn's disease

Muscular weakness:

- ★ Myasthenia gravis
- Motor neurone disease
- Multiple sclerosis
- Myopathies

Drug-related causes:

- ★ Beta-adrenergic blockers
- Alcohol abuse
- Benzodiazepines

Drug withdrawal:

- Opiates
- Corticosteroids
- Benzodiazepines
- Alcohol
- Antidepressants

IMPORTANT CLINICAL WARNINGS

- **Fatigue as an early symptom** → May precede weight loss in malignancy
- **Fatigue on waking in the morning** → More commonly psychological in origin
- **Fatigue with exertion and recovery with rest** → Consider myasthenia gravis
- **Persistent fatigue with fever or weight loss** → Chronic infection, malignancy, connective tissue disease
- **Fatigue in patients with HIV infection** → Often multifactorial and potentially severe
- **Fatigue with anaemia, dyspnoea or palpitations** → Tissue hypoxia or cardiac disease

INITIAL INVESTIGATIONS

- **Full blood count** → Anaemia, infection, malignancy
- **Erythrocyte sedimentation rate / C-reactive protein** → Inflammatory, infective or malignant disease
- **Thyroid function tests** → Hypothyroidism
- **Renal and liver function tests** → Metabolic causes
- **Blood glucose** → Diabetes mellitus
- **Human immunodeficiency virus testing** → Unexplained or persistent fatigue
- **Autoimmune screen** → Connective tissue disease
- **Creatine kinase** → Myopathy

REFERENCE: French's



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PRESENTATION: HEADACHE

DIFFERENTIAL DIAGNOSIS

Primary & Vascular Causes & Infection

- **Primary headache disorders:** ★ Migraine
- ★ Tension-type headache, ★ Cluster headache
- Trigeminal autonomic cephalgias
- Medication overuse headache
- **Vascular causes:**
- Subarachnoid haemorrhage, Intracranial haemorrhage, Cerebral infarction
- Cerebral venous sinus thrombosis
- Cervical artery dissection
- Reversible cerebral vasoconstriction syndrome
- ★ Severe hypertension, Temporal arteritis
- **Intracranial space-occupying lesions:**
- ★ Brain tumour, Cerebral abscess
- Hydrocephalus
- Benign intracranial hypertension
- Raised intracranial pressure
- **Infection:** ★ Meningitis, Encephalitis
- ★ Systemic infection

Other Causes & Systemic Issues

- **Cranial and extracranial causes:**
- Acute angle-closure glaucoma
- Eye disorders, Ear disorders
- Sinus disease, Dental disease
- Temporomandibular joint disorders
- Cranial neuralgias
- **Trauma:**
- Head injury, Post-traumatic headache
- **Drug and substance-related causes:**
- Drugs (e.g. glyceryl trinitrate, nifedipine)
- ★ Substance withdrawal (especially alcohol)
- Alcohol, Carbon monoxide poisoning
- **Musculoskeletal causes:**
- Cervical spondylosis
- **Psychiatric causes:** ★ Anxiety
- ★ Depression
- **Metabolic and systemic causes:**
- Paget's disease of bone, Pre-eclampsia

IMPORTANT CLINICAL WARNINGS

- ★ **Sudden severe headache ("thunderclap headache")** → Subarachnoid haemorrhage
- **Headache with fever and neck stiffness** → Meningitis
- **Progressive worsening headache** → Intracranial tumour
- **Headache with focal neurological deficit** → Tumour, haemorrhage, stroke
- **Headache worse in the morning, coughing, or straining** → Raised intracranial pressure
- **Headache with visual loss and temporal artery tenderness** → Temporal arteritis
- **Headache with altered consciousness** → Serious intracranial pathology

INVESTIGATIONS

General investigations:

- **Full blood count (FBC)** → Infection, meningitis, cerebral abscess
- **Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)** → Temporal arteritis, infection, inflammation
- **Urea and electrolytes (U&Es)** → Renal disease causing hypertension
- **Alkaline phosphatase** → Paget's disease of bone
- **Blood pressure measurement** → Hypertensive headache
- **Fundoscopy** → Papilloedema indicating raised intracranial pressure
- **X-rays (cervical spine, skull)** → Cervical spondylosis, Paget's disease

Specific investigations:

- **Blood cultures** → Meningitis, systemic infection
- **CT brain** → Haemorrhage, tumour, hydrocephalus
- **MRI brain** → Tumour, infection, structural lesions
- **Lumbar puncture** → Meningitis, subarachnoid haemorrhage, intracranial pressure disorders
- **CT / MR angiography** → Vascular causes (aneurysm, thrombosis, dissection)
- **Temporal artery biopsy** → Temporal arteritis
- **Tonometry (intraocular pressure measurement)** → Glaucoma

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PRESENTATION: SWEATING ABNORMALITIES

DIFFERENTIAL DIAGNOSIS

Excessive sweating

Metabolic:

- ★ Hypoglycaemia
- Automnan

Infections:

- ★ Any systemic infection

Malignancy:

- Brain tumours
- ★ Hodgkin's lymphoma

Endocrine:

- Diabetic autonomic neuropathy
- ★ Menopause
- ★ Thyrotoxicosis
- Carcinoid syndrome
- Pheochromocytoma

Psychiatric / substance related:

- ★ Anxiety states
- ★ Substance dependency or withdrawal

Deficient sweating

- Heat stroke
- Miliaria
- Hypohidrotic ectodermal dysplasia
- Sympathetic tract lesions

IMPORTANT CLINICAL WARNINGS

- ★ **Drenching night sweats** → Lymphoma or chronic infection (especially tuberculosis); urgent investigation required
- **Episodic sweating with tremor, hunger and anxiety** → Hypoglycaemia
- **Paroxysmal sweating with hypertension, palpitations and headache** → Pheochromocytoma
- **Episodic sweating with flushing, diarrhoea and wheeze** → Carcinoid syndrome
- **Constant sweating with heat intolerance and weight loss** → Thyrotoxicosis
- **Absent sweating during heat exposure** → Heat stroke or congenital sweat gland disorders

INVESTIGATIONS

General investigations:

- **Blood glucose (BM stix)** → Detect hypoglycaemia or hyperglycaemia causing sweating
- **Full blood count** → Infection, anaemia, haematological malignancy
- **Erythrocyte sedimentation rate / C-reactive protein** → Infection, malignancy, lymphoma
- **Thyroid-stimulating hormone and free thyroxine** → Thyrotoxicosis
- **Chest X-ray** → Tuberculosis, chest infection, bronchial carcinoid, malignancy

Specific investigations:

- **Mantoux test / ELISpot assay** → Tuberculosis
- **Urinary 5-hydroxyindoleacetic acid** → Carcinoid syndrome
- **Urinary catecholamines and metanephrines** → Pheochromocytoma
- **Lymph node excision biopsy** → Hodgkin's lymphoma
- **Magnetic resonance imaging of the head** → Hypothalamic tumours

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PRESENTATION: APPETITE DISORDERS

DIFFERENTIAL DIAGNOSIS

Loss of appetite (Anorexia)

Gastrointestinal:

- Viral hepatitis (prodromal stage)
- Gastric carcinoma
- Gastric ulcer
- Coeliac disease

Chronic systemic disease:

- * Advanced malignant disease
- ★ Chronic alcoholism
- ★ Uraemia
- ★ Severe congestive cardiac failure
- ★ Chronic pulmonary disease
- ★ Cirrhosis of the liver

Endocrine:

- ★ Adrenal insufficiency

Psychiatric:

- ★ Anxiety
- ★ Depression
- Anorexia nervosa

Infective / parasitic:

- Roundworm infestation

Increased appetite

- ★ Recovery from illness
- ★ Strenuous exercise
- ★ Mania
- ★ Hyperthyroidism
- Hypoglycaemia (e.g. insulinoma – uncommon)
- Depression or mania with overeating
- ★ Bulimia nervosa

Drug-related:

- Megestrol acetate
- Dexamethasone
- Antidepressants (e.g. mirtazapine)

Perverted appetite (Pica)

- ★ Childhood
- Pregnancy
- ★ Iron-deficiency anaemia
- Autism
- Intellectual disability
- Schizophrenia

IMPORTANT CLINICAL WARNINGS

- **Loss of appetite without confirmed weight loss** → Usually non-specific; investigations are inappropriate
- **Loss of appetite with significant weight loss** → Indicates underlying organic or psychiatric disease
- **Profound weight loss disproportionate to calorie intake** → Advanced malignancy (cachexia; not reversible by feeding)
- **Weight loss with preserved or increased appetite** → Hyperthyroidism, diabetes mellitus
- **Apparent anorexia with obsessional interest in food** → Anorexia nervosa (misnomer)
- **Increased appetite with binge eating and compensatory behaviour** → Bulimia nervosa
- **Pica in adults** → Consider iron-deficiency anaemia or psychiatric illness

INITIAL INVESTIGATIONS

- **Weight measurement and body mass index** → Assess clinical significance of appetite loss
- **Assessment for weight loss** → Determines need for investigation
- **Screening for chronic disease** → Malignancy, liver, renal, cardiac or pulmonary disease
- **Endocrine evaluation** → Adrenal insufficiency, hyperthyroidism
- **Psychiatric assessment** → Anxiety, depression, eating disorders
- **Full blood count** → Anaemia (especially with pica)

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