
A horizontal line for a signature, ending with a small icon of a pen nib pointing upwards and to the right.

17

W2L9

Drugs used in immune diseases – Acetylcholinesterase inhibitors

Nicola Moore
n.moore1@uea.ac.uk

Learning objectives

By the end of this screencast, you should be able to:

- Describe some of the key **pharmaceutical care issues** associated with the treatment of myasthenia gravis
- Describe the **therapeutics of the acetylcholinesterase inhibitors** used in the symptomatic treatment of myasthenia gravis

Myasthenia Gravis (MG) chronic but treatable disease
and patients can achieve sustained remission and full functional capacity

Management:

- Avoid disease triggers known to exacerbate the disease
- Symptomatic treatment to produce - minimal symptoms + minimal drug side effects ↑ AChE inhibitors : increase amount of ACh at the NMJ
- Immunosuppressant drugs → which treat the underlying immune dysfunction
- Immunomodulatory treatments
 - ↳ plasma exchange & use of immunoglobulin
 - ↳ plasmapheresis

1)

Myasthenia Gravis (MG) - triggers

- This can be anything that **exacerbates muscle weakness**:

- Infection → patients w/ generalized or pulmonary effects of MG should have the annual flu & the pneumococcal vaccine to reduce the risk of infection
- Stress or trauma
- Thyroid dysfunction → affects on a patient's physical function
- Withdrawal of **acetyl**cholinesterase inhibitors
- Rapid introduction or increase of corticosteroids
- Anaemia
- Electrolyte imbalances → which can affect muscles
- Medicines

* community and secondary – reducing a patient's risk of these triggers

* pharmacists should always be checking co-prescribed medicines for their risk of deteriorating a patient's MG.

patients should be avoiding these medicines
Myasthenia Gravis (MG) – triggers - medicines

1) Interferes with neuromuscular transmission	2) Increase muscle weakness
Phenytoin, carbamazepine	Magnesium causing hypermagnesaemia
Aminoglycosides, colistimethate, clindamycin, fluoroquinolone, macrolides, telithromycin	Benzodiazepines
Antimuscarinic agents (unless s/e Tx)	Beta-blockers
Procainamide and lidocaine	Diuretics (secondary to electrolyte disturbances)
Lithium, chlorpromazine	Verapamil
Hydroxychloroquine	Statins

**This list is not exhaustive
As a pharmacist you should **ALWAYS** evaluate all prescriptions for a patient with MG for their risk of deteriorating MG symptoms

*not always available ∵ when treatment is specifically indicated,
patients should start and titrated very cautiously
with continual monitoring
for signs of deterioration of the disease.

*MG patients : all meds should be used w/ caution

2)

Myasthenia Gravis (MG) – symptomatic treatment

- Oral **acetyl**cholinesterase inhibitor → these inhibit ACh degradation at the NMJ and therefore prolong its effect
 - Pyridostigmine (neostigmine used less due to shorter duration of action)
- Provide a variable improvement in strength → muscle (but varies between patients)
- Dosing – starting 15mg QDS with food long tablets are split with food, yes it's safe to eat
 - Assess cholinergic s/e long tablets are split or melted to make appropriate dose
 - Typical maintenance 60mg four to six times a day
- Adverse effects – **dose dependent and predictable** (**nicotinic and muscarinic effects**):
 - Nicotinic effects – **muscle and abdominal cramps**
 - Muscarinic – **gut hypermotility** (cramps and diarrhoea), **increased sweat/salivations/lacrimation**, **hypotension**, **bradycardia**, **miosis**, **urinary incontinence**, **increased bronchial secretions** and **tachypnoea**

→ based on the pharmacology of the medication – that we use

↑ pupil contractions

Myasthenia Gravis (MG) – symptomatic treatment

- if too high = overdose:*
- Cholinergic crisis is the result of excessive **acetylcholinesterase inhibitor** treatment *in muscles*
 - This causes **weakness** and is **hard to distinguish** from worsening MG
 - With the described doses this is **rarely** if ever seen
- Management of side effects:
 - Taking with food can mitigate GI s/e
 - Co-prescribing **oral anti-cholinergic drugs** (that have little or no effect on nicotinic receptors (i.e. **do not produce muscle weakness**) *but can reduce some of the other side effects*
 - Glycopyrrolate
 - Propantheline
 - Diarrhoea can be controlled using **loperamide**

Sharing this information available for patients & prescribing doctors can be useful in patients outcome

*For medication
how this would help?*

*anti-cholinergics drugs block the action of acetylcholine ACh neurotransmitter
by co-prescribing this we can prevent excess acetylcholine in the synaptic cleft causing muscle weakness*

Summary:

Myasthenia Gravis (MG) – Pharmaceutical care

- Considerations:
 - any co-prescribed drugs - (review the drugs)
 - is there another appropriate drug to use?
- Drugs exacerbating MG
- Monitoring *symptoms and management*
- Ability to **swallow** or use **oral medication** (especially in generalized MG or myasthenic crisis) *what other formulation is available?*
- Treatment **step-up**
 - therapy to escalate? may be necessary*
 - drugs are outside the scope of the screenshot*

23

W3L23

Arthritis

Arthritis

OSTEOARTHRITIS
KYLIE FENWICK

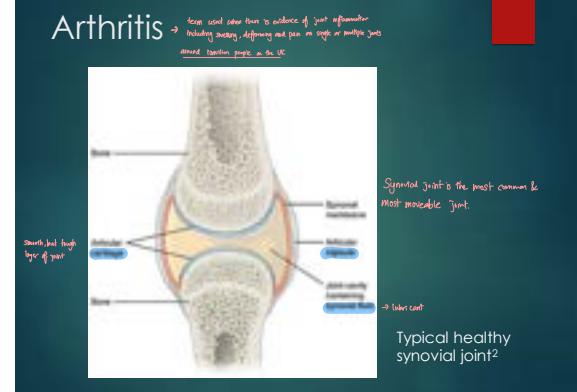
Learning Outcomes

- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Learning Outcomes

- ▶ **Define Arthritis**
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Arthritis



Learning Outcomes

- ▶ Define Arthritis
- ▶ **Define Osteoarthritis**
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Osteoarthritis

- not an autoimmune disease
- wear and tear arthritis
- ▶ Most common form of Arthritis
- ▶ NICE: "a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life"³
- ▶ Disorder of the joints
 - ▶ Articular cartilage loss
 - ▶ Accompanying periarticular bone response
- ▶ Can affect any joint
- ▶ Weight bearing and non-weight bearing joints

Learning Outcomes

- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ **Describe the impact of osteoarthritis on the population**
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Epidemiology

- ▶ ~8.75million people in the UK⁴ aged 45yr+
- ▶ Prevalence increases with age
- ▶ More common in women than men⁵
- ▶ Knee is most common site

18.2% of people aged over 45 years in England have osteoarthritis⁶ of the knee. That's 4.11 million people, 1.4 million of whom have severe knee osteoarthritis.

10.9% of people aged over 45 years in England have osteoarthritis⁶ of the hip. That's 2.46 million people, 726,000 of whom have severe hip osteoarthritis.

Impact?

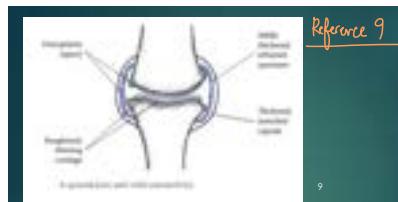
- Co-morbidities
- ▶ Women & men over 65 that have osteoarthritis have 17% & 15% increased risk of hospitalisation due to CVD
 - ▶ Cardiovascular disease
 - ▶ Depression 20% of patients
- Quality of Life
- ▶ Pain 1/3 1/6 being unbearable
 - ▶ Work 1/3 retire early

Learning Outcomes

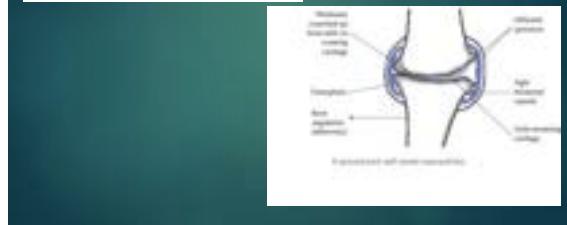
- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ **Detail the pathological changes in osteoarthritis**
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Pathophysiology

- ▶ Whole joint is involved → damage in cartilage
- ▶ Rate of damage exceeds rate of repair
- ▶ Joint fails to dissipate 'load' effectively
- ▶ Leads to cycle of degeneration
- ▶ Exposes bone to more load → attempt by the body to repair the joint cause cartilaginous growth at the edges of the joint which becomes calcified, causing osteophytes
- ▶ Further loss of cartilage and growth of osteophytes + bone spurs
- ▶ Narrowing of joint space
- ▶ Results in synovitis and effusion
 - ↳ painful and tender inflammation of the synovial lining of the joint
 - ↳ swelling of joint



Reference 9



Learning Outcomes

- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ **Describe the risk factors and causes of osteoarthritis**
- ▶ Describe how osteoarthritis is diagnosed
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Aetiology

- ▶ Primary – idiopathic – *exact cause is unknown*
- ▶ Secondary – specific cause
 - ▶ i.e. previous injury to joint, congenital abnormality or inflammatory arthritis
↳ joint or RA
- ▶ Risk factors:
 - ▶ Age (45+) reduction in growth hormone
 - ▶ Gender (female) drop in oestrogen levels during menopause
 - ▶ Obesity (BMI >25) 2.5-4.6% more likely
 - ▶ Occupation (physically demanding)
- ▶ Genetics
 - ▶ Estimated heritability of 40-65% depending on joint site
 - 60% hand, hip arthritis
 - 40% knee arthritis
 - ▶ no single genes to pin point

Learning Outcomes

- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ **Describe how osteoarthritis is diagnosed**
- ▶ Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis

Diagnosis

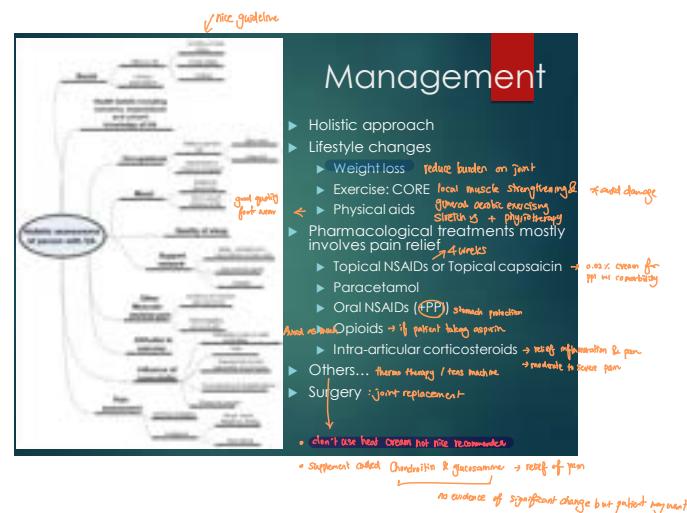
- ▶ Signs/Symptoms:
 - ▶ Activity related joint pain
 - ▶ Morning stiffness lasts no longer than 30 minutes
 - ▶ Muscle wasting due to not moving bc of pain
 - ▶ Hand/fingers often presents as 'nodes' ↗ visibly hard bony swelling at the distal interphalangeal joints
- ▶ Diagnosed clinically without investigations³
 - ▶ Activity related joint pain AND
 - ▶ Morning stiffness lasts no longer than 30 minutes (OR no morning stiffness) AND
 - ▶ Over 45 years
- ▶ X-rays and blood tests may be help to aid diagnosis → to rule out gout or RA



Learning Outcomes

- ▶ Define Arthritis
- ▶ Define Osteoarthritis
- ▶ Describe the impact of osteoarthritis on the population
- ▶ Detail the pathological changes in osteoarthritis
- ▶ Describe the risk factors and causes of osteoarthritis
- ▶ Describe how osteoarthritis is diagnosed
- ▶ **Discuss the pharmacological and non-pharmacological treatment options in osteoarthritis**

Management



Summary - Patient Care

- ▶ No pharmacological treatments to help prevent or cure
- ▶ Offer moderate symptomatic relief
- ▶ Lifestyle change is key in management
 - ▶ Exercise should be part of daily routine
- ▶ Limited role medication can play must be explained to patient

References

1. Versus Arthritis. [Arthritis](https://versusarthritis.org/about-arthritis/conditions/arthritis). versusarthritis.org/about-arthritis/conditions/arthritis (accessed 29 September 2020).
2. Drake RA, Vogl W, Mitchell A. Gray's Anatomy for Students. 2nd ed. London, UK: Churchill Livingstone;2009.
3. NICE. *Osteoarthritis: care and management*. <https://www.nice.org.uk/guidance/cg171/resources/osteoarthritis-care-and-management-pdf-3510974> (accessed 29 September 2020).
4. Arthritis Research UK. *Osteoarthritis in General Practice*. https://healthinnovationnetwork.com/wp-content/uploads/2017/01/Osteoarthritis_in_general_practice_July_2013_Arthritis_Research_UK_PDF_421_MB.pdf (accessed 29 September 2020).
5. NICE. CKS: *Osteoarthritis*. <https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fractures/paf-3510975/272517> (accessed 29 September 2020).
6. Versus Arthritis. *The State of Musculoskeletal Health 2019*. <https://www.versusarthritis.org/media/14594/state-of-musculoskeletal-health-2019.pdf> (accessed 29 September 2020).
7. HQIP. *National Joint Registry 15th Annual Report 2018*. <https://www.hqip.org.uk/resource/national-joint-registry-15th-annual-report-2018/#.X3M492xS2zw> (accessed 29 September 2020).
8. Whittlesea C, Hodson K. *Clinical pharmacology and therapeutics*, 6th ed. London: Elsevier; 2019.
9. Prieto-Antón D, Arden N, Hunter DJ. *Osteoarthritis: the Facts*, 2nd ed. Oxford: Oxford; 2014.

2A

W3L26

RA

Common Autoimmune Diseases

- Systemic autoimmune diseases
 - Rheumatoid arthritis
- Organ specific autoimmune diseases
 - Myasthenia gravis
 - Grave's disease
 - Autoimmune diabetes

RA pathophysiology

Prof Anja Mueller

Rheumatoid Arthritis (RA)

A chronic, progressive, systemic, inflammatory disorder affecting synovial joints



- 24 different types of arthritis, most common is osteoarthritis (joint wearing down/inflammatory-based) and rheumatoid arthritis (autoimmune)
- The inflammation may also affect eyes, lungs, heart
- RA can affect any joint but commonly hand, feet, knee, hip
- Affects between 0.3 and 1.5% of population
- It affects 600,000 (1%) of the UK
- Most sufferers develop RA between the ages of 25 and 50

Is it more common in males or females?



• Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, which is primarily characterized by proliferative synovitis and inflammatory arthritis with erosions.

- The prevalence of RA is estimated to be about 0.5-1% of the adult population
- The ratio of women to men in the RA patients is 2-3 to 1 *more women*
- The incidence of RA described in the literature is not racial or geographically different
- The pathogenesis of RA has not been elucidated but it is multifactorial. Genetics, environmental and immunological factors may affect this disease. RA has a specific genetic predisposition and approximately 70% of RA patients express **human leukocyte antigen (HLA)-DRA** *
- The concordance rate of twins is about 15-20% in RA [4]. There are other genes related to RA including **STAT4** (signal transducer and activator of transcription 4), **TRAF1/CS** (tumor necrosis factor-receptor associated factor 1/complement component 5), and **PTPN22** (protein tyrosine phosphatase, non-receptor type 22)
- It has been suggested that tobacco smoke, air pollution, occupational exposure to mineral oil and silica, infectious agents, and female hormones are involved in the disease
- Autoimmunity, including antibodies such as anti-citrullinated peptide antibodies (ACPs) and rheumatoid factors (RFs), is associated with RA. Immune dysregulation, antibody responses to modified peptides and increased production of cytokines and chemokines may contribute to pathophysiology of RA

* HLA - DRA
→ same as HLAB complex

* STAT4
* TRAF1/CS
* PTPN22

Rheumatoid Arthritis: Genetic & Environmental causes



- Tends to run in families, 15% among monozygotic twins
- MHC allele **HLA-DRB1***01/04/10 relative risk 4-12
- Hormones – more common in women than men (women who have taken contraceptive pill is around half of women who have never taken it) *less likely to get RA*
- Infections – definite associations lacking, but **Mycobacterium**, **Streptococcus**, **Mycoplasma**, **Epstein-barr virus** and **Parvovirus** have all been suggested
- Smoking
 - ↳ involved in onset of RA



Rheumatoid arthritis – Pathophysiology

1. **Initiator phase** – Initiating event unknown and reason for joint specific localisation is unknown.

Injury, infection, exposure to toxic substances.

APCs and citrullination of proteins → now seen as non-self

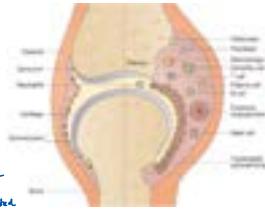
↳ trigger an immune response
posttranslational modification of protein on prolinearginine amino acid is converted into citrulline amino acid



Rheumatoid arthritis – Pathophysiology

- 2. Inflammation phase** – self antigens (citrullinated proteins) presented
- Clonal expansion of T and B cells
 - Insufficiently controlled by Tregs

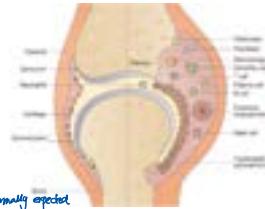
B & T cells activated in the joint where we don't want them to be activated.



Rheumatoid arthritis – Pathophysiology

- 3. Self perpetuating phase** – inflammatory damage in synovium causes self antigens previously 'unseen' by immune system to be exposed
- immune response against cartilage
 - infiltration of immune cells

Instead of going back to resolution as normally expected now even further self perpetuating



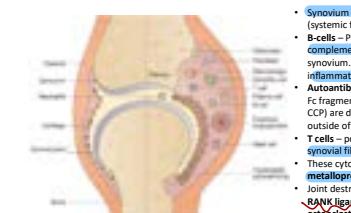
Rheumatoid arthritis – Pathophysiology

- 4. Destruction phase** – synovial fibroblasts and osteoclasts activated by cytokines (TNF, IL-6)
- destruction of bone and cartilage

→ real damage in tissue



Rheumatoid arthritis – Pathophysiology



- Synovium inflammation is key but systemic at all stages (systemic features link in with co-morbidities):
- B-cells – Produce autoantibodies which can activate complement and also bind to activated macrophages in synovium. Activated macrophages perpetuate inflammation.
- Autoantibodies (rheumatoid factor (RF) directed against IgM Fc receptors of B cells and anti-citrullinated peptides (anti-CCP) are directed against antigens commonly present outside of the joint. Other autoantibodies too.
- T cells – potentially activate monocytes, macrophages and synovial fibroblasts → produce TNF, IL-6 etc
- These cytokines induce the production of matrix metalloproteinases (MMPs) – which degrade the cartilage
- Joint destruction might be caused by CD4 T-cell cytokine: RANK ligand (belongs to TNF-family), this promotes osteoclasts (resorb bone)

To destroy bone as well

* Complement system

* Macrophages

* Monocyte

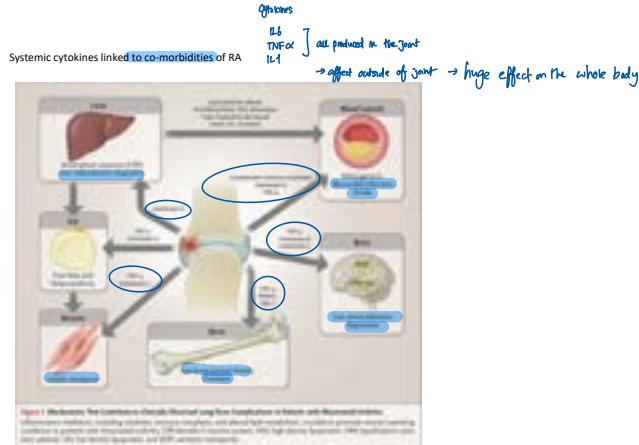
* MMPs

* CD4 T cell cytokines



Panel B: Inflammation. Initial activation of the (auto)immune system leads to an inflammatory cascade. Phagocytic cells release cytokines, chemokines and express adhesion molecules. These events, which involve APCs and the circulation of naïve T-cells, might accumulate within the joints as well as effector T-cells along with macrophages/mast cells via the synovium. Local survival factors, including fibroblasts, and macrophages, are involved leading to the release of proinflammatory cytokines of both the innate and adaptive immune systems. At inflammation phase, self antigens, namely citrullinated proteins, are presented in the context of MHC class II molecules that are characteristic of RA. This presentation leads to clonal activation of T cells in the cells, and the formation of granular lymphocytes. This process is predominantly conducted by T_{eff} cells, which are highly cytotoxic and secrete cytokines, which are highly cytotoxic to the immune system. B cells are exposed to damage and are activated, inducing the immune system against antigen using both surface antibodies such as IgM and IgG. Stimulation of bone and cartilage occurs. Adhesions, APCs, antigen-presenting cell (APC), granular lymphocytes, IgM, IgG, interleukin-6, IgA, rheumatoid arthritis, T_{eff}, effector T cell, T₁, T₂, Type 1 Helper T cell (Th1), T₂, Type 2 Helper T cell (Th2), T_{reg}, regulatory T cell.





Therapies

- Focus on anti-inflammatory and immunosuppressive drugs
- Currently
 - NSAIDs
 - (COX-2 inhibitors)
 - DMARDs
 - Biologics

25

W3L24

Rheumatoid arthritis

Nicola Moore
n.moore1@uea.ac.uk

Learning objectives:

By the end of this screencast, you should be able to:

- Recognise and identify the signs and symptoms of RA
- Explain how RA is diagnosed
- Describe how the disease is monitored

1)

Signs and Symptoms

All patients are different

- Insidious onset - gradual, subtle changes
 - Fever, malaise, weakness + arthralgia (joint pain)
 - **Symmetrical** – inflammation (pain), tenderness, swelling, stiffness, redness → visible and joint warmth
 - Usually in the small synovial lined joints of the hands and wrist or feet
 - Can affect any joint
- Progressive articular deterioration – loss of function
 - Inflammation, destruction of bone and cartilage
 - Deformity, limited motion, pain on motion → fixed or disabled joints
- General symptoms – weight loss, fatigue, mental health changes
- Extra-articular manifestations – including: lungs, heart, eyes, skin
 - RA nodules
 - ↳ form lumps that appear subcutaneously around the joints e.g. fingers / toes / elbows
 - ↳ poor prognostic factor - meaning patient's severity is high
 - pulmonary fibrosis
 - intestinal/lung disease
 - ↑ ESR
 - ↑ IgM antibodies
 - ↑ Raynaud's syndrome
 - ↓ eye dryness
 - ↑ carpal tunnel syndrome
 - ↑ cardiovascular risk
 - ↑ cognitive decline
 - ↑ fracture risk

hands, ankles,
wrists, feet
→ polyarticular



Signs and Symptoms

- **Clinical course**
 - Generally exacerbations/flares and remissions with general chronic progression
 - Less likely self-limiting
 - Can be chronic intermittent
 - ↳ some improve w/ each flare w/o general deterioration
- **Comorbidities** increase patients - cardiovascular risk, risk of infection, risk of respiratory disease, risk of osteoporosis, risk of malignancy and risk of depression
 - ↳ risk of death in RA
- Patient outcomes are compromised when treatment is delayed or inappropriate
- Appropriate treatments can alter the course of the disease

↳ Is drug therapy playing a role in these risks?
e.g.) methotrexate can increase risk of lung disease
some anti-TNF biologics can increase particular cancer e.g. colon
↓
↑ risk of infection

- 1) inflammation of the blood vessels - vasculitis
- 2) changes in the vessel function
- 3) changes in the clotting
- 4) changes to circulation due to inflammation

Signs and symptoms

- **Blood test:** measure of degree of inflammation among the joints
 - ↳ blood test (leucocytes in solution over 1 hour and measure distance moved)
 - increased fluid in the cavity indicates more inflammation
 - white blood cells move towards the inflamed area
 - RBC count decreases
 - not specific to RA
- **Inflammatory markers**
 - Erythrocyte sedimentation rate (ESR)
 - ↳ degree of inflammatory change
 - C-reactive protein (CRP) a protein that produces part of the innate immune response from the liver - increase after 1-6 h inflammation peak 8-50H
 - not specific to joint inflammation
- **Immunological parameters**
 - Rheumatoid factor (RF) presence of RF is poor prognostic factors and source disease
 - ↳ a type of autoantibody directed against components of the nucleus
 - also
 - Antinuclear antibody (ANA) present in less than 10% of patients w/ RA
 - ↳ more specific for RA than RF, but not all RA patient have it.
 - Anti-cyclic citrullinated peptide (anti-CCP) - autoantibody against the unusual amino acid citrulline, which is formed when arginine is altered
 - sign of more severe disease if present

Radiology

- ↳ damage & inflammation within joints
- are there changes?
- in early disease, not always visible

→ Also test patient haemoglobin levels to test for anaemia
→ quite common in RA & correlate to disease activity

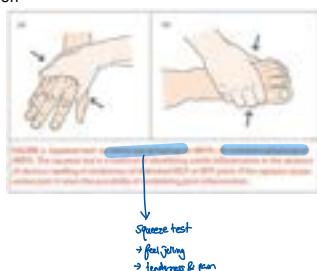
Positive result for RF or anti-CCP

- ↳ Seropositive
 - indicator that they have more severe disease

2)

On Examination - OE

- Limitation of motion
→ tight fat due to pain & stiffness
- Tenderness on palpation

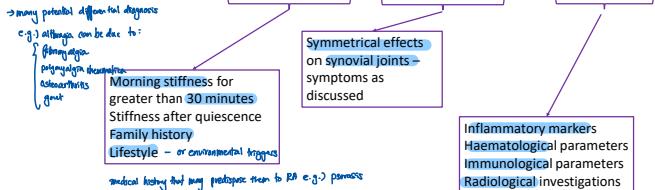


* stiffness
* tenderness
* pain on motion
* swelling

Diagnosis

* No one test will provide a diagnosis*

Dependent on complete history taking, clinical presentation and investigations



NICE guidance on diagnosis

National Institute for Health and Clinical Excellence (NICE) 2018 – Rheumatoid Arthritis in Adults: management.

Referral - Primary care to specialist- refer those with suspected persistent **synovitis**. → inflammation of synovial membrane

Urgently if : affecting small joints of hands and feet, more than 1 joint, **delay** of >3 months before seeking medical advice → worse if delayed treatment

Diagnosis - If found to have **synovitis** on clinical examination – Determine Rheumatoid Factor, consider **Anti-CCP antibodies** (if negative for RF), **x-ray hands and feet**.

↓ come back negative, don't do Anti CCP, but baseline bloodtest info for patients

Additional investigations – any of the above not done during diagnosis, plus **Health Assessment Questionnaire (HAQ)**.

↳ info about patient's functional ability + patient quality of life
→ disability, discomfort & pain, drug side effect, toxicity, cost

Management

Appropriate early therapy

- Improves symptoms
- Improves function
- Reduces mortality
- May reduce comorbidities

National Institute for Health and Clinical Excellence (NICE) 2018 – Rheumatoid Arthritis in Adults: management.

EULAR – European League Against Rheumatism
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update
(<https://doi.org/10.1136/annrheumdis-2019-216655> - accessed 30/9/2020)
Smolen JS, et al. Ann Rheum Dis 2020;79:685–699

treatment isn't always only pharmacological

- physical therapist: exercise, therapy
- occupational therapist: daily life
- orthotics: daily life activity
- SEVERE → surgery

B16 multidisciplinary mission?

3)

→ to monitor improvement and grade next steps/goods

Disease monitoring – DAS28

DAS28 → A measure of disease activity → 4 different measures

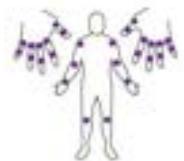
28 joints

- Number of swollen joints (out of 28)
- Number of tender joints (out of 28)
- Measure ESR or CRP → inflammatory marker
- 'Global assessment of health'
- Giving overall disease activity score

Scores:

- DAS 28 = >5.1 = active disease
- DAS 28 = <3.2 = low disease activity
- DAS 28 = <2.6 = remission

→ the score we get from monitoring help decide whether patient should move on to a particular therapy



• Allows disease/treatment monitoring, criteria for eligibility for biologic treatment

→ pitfalls: if joints affected on their foot

- not included!
- some patients don't see that chemotherapeutic increase in ESR or CRP
- patient may have lower score than actually how their disease are.
- most look at individual specifics

26

W3L25

Rheumatoid arthritis – Treatment guidelines

Nicola Moore

n.moore1@uea.ac.uk

Learning objectives:

By the end of this screencast, you should be able to:

- Describe and apply appropriate guidelines for the management of RA

Guidelines

Aims of treatment –

- Minimising joint pain and swelling
- Preventing deformity and radiological damage (i.e. erosion)
- Maintaining QoL *Quality of life*
- Controlling extra-articular manifestations

→ dependent on fast and appropriate diagnosis & treatment
 → close monitoring and drug adjustment crucial!

National Institute for Health and Clinical Excellence (NICE) 2018 – **Rheumatoid Arthritis in Adults: management.**

EULAR – European League Against Rheumatism

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update
 $(\text{https://doi.org/10.1136/annrheumdis-2019-216655} - \text{accessed 30/9/2020})$

• Smolen JS, et al. Ann Rheum Dis 2020;79:685–699

OVERVIEW OF MAIN TREATMENT

Treatments

- Analgesia – NSAIDs → symptom control → pain & stiffness
- Glucocorticoids → reduce inflammation & pain : given systemically orally or parenterally /locally into the joint
- DMARDs – Disease Modifying Anti-rheumatic Drug
 - Main goal of DMARD treatment = remission. → *center on underlying pathophysiology in RA*

Conventional DMARDs (cDMARD) – methotrexate, sulphasalazine, leflunamide [hydroxychloroquine, ~~azathioprine, penicillamine, gold, ciclosporin~~]
~~is discontinued in RA due to increased risk of cancer, but is no longer regularly used for certain types of RA~~

Biologic (bDMARD) - Anti-TNF - (Adalimumab, Etanercept, certolizumab, golimumab, infliximab)

Other biologics - Tocilizumab / sarilumab – IL-6 receptor inhibitor
 Rituximab – B-cell depletion of lymphocytes (*Anti B cell*) (anti CD-20 antibody)
 Abatacept – Antibody blocking T-cells

Anakinra – IL-1 receptor antagonist \hookrightarrow *lymphocyte activation*

Tofacitinib and baricitinib \hookrightarrow *cytostatic modulator CD39/86*

Targetted (tDMARD) – JAK inhibitors – tofacitinib and baricitinib
 \downarrow
 $=$ upadacitinib / filgotinib
 \downarrow
 $=$ *block on JAK 1/2/3/4 pathway*

NICE – NG 100

published July 2018
 updated October 2020

Guidelines – NICE - Treatment

- Treat to target** – a strategy which should include **frequent review, formal assessment of joints and escalation of therapy** if inflammation is still present until good control is reached.
 - Patients have an individual target (remission DAS28 < 2.6 or low activity DAS28 < 3.2)
 - Requiring **tight control** → **favorable outcome**

The target should be remission if there is increased risk of radiological progression (i.e. anti-CCP positive or erosion at baseline).

CRP and disease activity (i.e. with DAS 28) monthly in specialist care until target reached.

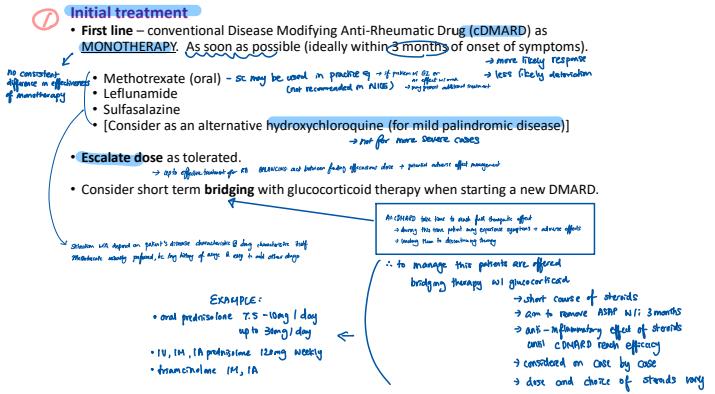
Monitoring:

 - blood test – ESR, CRP
 - disease state, activity

At least a monthly basis + 1 Rheumatologist

↑ disease & treatment

Guidelines – NICE - Treatment



Guidelines – NICE - Treatment

- (2) Step-up strategy** → even when optimised
- When the treatment target has not been achieved (despite dose escalation)
 - Offer **ADDITIONAL cDMARD** (oral) methotrexate, leflunomide, sulphasalazine or hydroxychloroquine)
 - better control & hopefully reach target
 - but ↑ risk of A.E.
 - more monitoring required
 - Symptom control**
 - Consider **NSAID** (traditional and COXII inhibitors) when control of pain and stiffness is inadequate.
 - Consider toxicities and **patients risk factors**
 - Lowest effective dose for shortest time
 - Offer PPI
 - Review risk factors regularly
 - If maintained for at least 1 year consider **step-down strategy** – **w/o corticosteroids used for flares**
 - Return to original regime if target no longer met
 - Consider cautiously reducing drug doses or stopping drugs
 - ↳ may cause flare up :: need to know who to contact and then return to

Goal should be short term
as DMARDs need to reach target

Guidelines – NICE – Monitoring

- Patients should be provided with information on **how and when to access specialist care**
 - Have rapid access during a flare
 - Ongoing drug monitoring → **disease monitoring**
↳ patient risk factors may change
- Review **6 months** after achieving target to ensure **maintenance**
- Annual review
 - Assess disease activity, damage and functional ability (i.e. with HAQ)
 - Check for development of comorbidities
 - Organise cross referral in the MDT
 - Assess the effect on personal life

↳ seasonal flu and pneumococcal vaccines

Guidelines – NICE - Treatment

- In severe disease (DAS 28 > 5.1) when not responded to combination cDMARD – **bDMARDs and tDMARDs may be considered**

bDMARD - Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept + MTX are options
tDMARD - baricitinib and tofacitinib

Guidelines – NICE - Treatment

- For those with **moderate disease** – they must have a **moderate response** (DAS 28 improvement of 0.6 units ≤ 1.2) at 6 months to continue.
- For those with **severe disease** – they must have a **moderate response** (DAS 28 improvement of ≥ 1.3) at 6 months to continue.
↳ treatment options after failure of a biological or targeted DMARD are not considered further

Guidelines – NICE - Treatment

- Flare management:**
 - For patients with recent onset or established RA - **short-term glucocorticoids** can rapidly reduce inflammation.
 - These should be – **STOPPED**
 - The only reason these may continue is = when **ALL** other treatment options have been offered.

EULAR – European League Against Rheumatism

Guidelines — NICE — Treatment

	Moderate disease (DAS 28 3.2 – 5.1)	Severe disease (DAS 28 >5.1)
Further pharmacological management:	<ul style="list-style-type: none"> • Anti-TNF <p>Adalimumab +/- MTX (TA 715) Etanercept +/- MTX (TA 715) Infliximab + MTX (TA 715)</p>	<ul style="list-style-type: none"> • Anti-TNF <p>Adalimumab <i>(+/- MTX)</i> (TA 375) <i>the - suggest MTX to be removed if patients can't take</i> Etanercept +/- MTX (TA 375) Infliximab + MTX (TA 375) Certolizumab + MTX (TA 375) Golimumab + MTX (TA 375)</p>
Biologics and targeted DMARDs	<ul style="list-style-type: none"> • Targeted DMARDs (Jak inhibitors) <p>Filgotinib +/- MTX (TA 676) Upadacitinib +/- MTX (TA 744)</p>	<ul style="list-style-type: none"> • Targeted DMARDs (Jak inhibitors) <p>Filgotinib +/- MTX (TA 676) Upadacitinib +/- MTX (TA 744) Baricitinib +/- MTX (TA 466) Tofacitinib +/- MTX (TA 480)</p>
	<ul style="list-style-type: none"> • Anti – IL-6 <p>X</p>	<ul style="list-style-type: none"> • Anti – IL-6 <p>Sarilumab + MTX (TA 485) Tocilizumab + MTX (TA 375)</p>
	<ul style="list-style-type: none"> • Antibody blocking T-cell activation (CD8-/86) <p>Abatacept + MTX (TA 715)</p>	<ul style="list-style-type: none"> • Antibody blocking T-cell activation (CD8-/86) <p>Abatacept + MTX (TA 375)</p>
	<ul style="list-style-type: none"> • Anti-B cell (anti-CD20 antibody) <p>X</p>	<ul style="list-style-type: none"> • Anti-B cell (anti-CD20 antibody) <p>Rituximab +/- MTX</p>

Other biologics

→ when treatment target is not reached w/ one CDARD, even w/ optimised doses we step up a therapy by adding additional CDARDs

→ we increase risk of AE, but hope to reach target ∴ intense monitoring is crucial

→ when the patients take 2 or more CDARDs but fail to reach target we select from above

① monotherapy → escalation

② Step up therapy → escalation

③ potential other therapies

these are the steps

Drug Selection Process

- if there is no clear indication of a specific agent to use, then the most cost effective ones are selected

- should also consider the staff on site time for drug administration

e.g.) IV drugs, we need nurses and a bed. on the other hand SC can be injected at home.

- dosing frequency should be considered

e.g.) adherence is difficult for some patients or the patient may have manual dexterity issues

→ then SC injections at home is a bad idea, rather IV therapy at the hospital is a better option

- Consider patients comorbidities i.e., maybe we could use one drug to treat 2 conditions or not use certain agents

↳ Golimumab licensed for RA and UC

↳ w/ severe heart failure do not use anti-TNF agent

Adalimumab licensed for RA, UC and Crohns

- Consider patients allergy e.g.) if patient allergic to latex, we got to use biosimilar of etanercept which is latex free

because some drugs use latex during manufacturing

- Storage - most biologics need to be stored in fridge → is it possible?

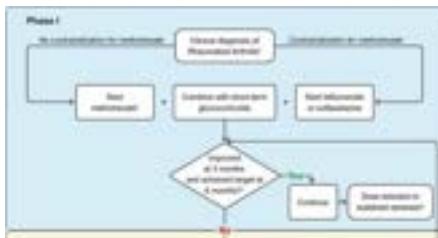
- ORAL THERAPY selected for patients w/ needle phobia, difficulty storing biologics, to minimise risk of site reactions from IV and SC

↳ JAK inhibitors

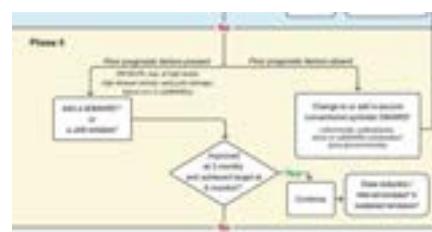
- Some JAK inhibitors e.g.) Upadacitinib & Baricitinib increase risk of UTE → DVT or PE

- Anti IL-6 can increase risk of GI perforation ∴ patient w/ or history of gastric ulcer should not be prescribed

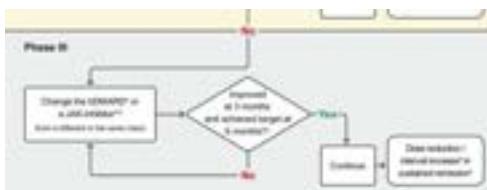
Guidance – EULAR (European League Against Rheumatism)



Guidance – EULAR (European League Against Rheumatism)



Guidance – EULAR (European League Against Rheumatism)



EULAR – treatment guidance

- Therapy with **DMARDs** should be started as soon as the diagnosis of RA is made.
- Methotrexate** should be part of the **first treatment strategy**.
- In those with contraindication to MTX, **leflunomide or sulfasalazine** should be considered as part of the treatment strategy.
- Short term **corticosteroids** should be considered when initiating or changing cDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
 - 'Treat-to-target'**
- If the treatment target is not achieved with the first cDMARD strategy, in the **absence of poor prognostic factors**, other cDMARDs should be considered.
- If the treatment target is not achieved with the first cDMARD strategy, when **poor prognostic factors are present**, addition of a **bDMARD or tDMARD should be added**.

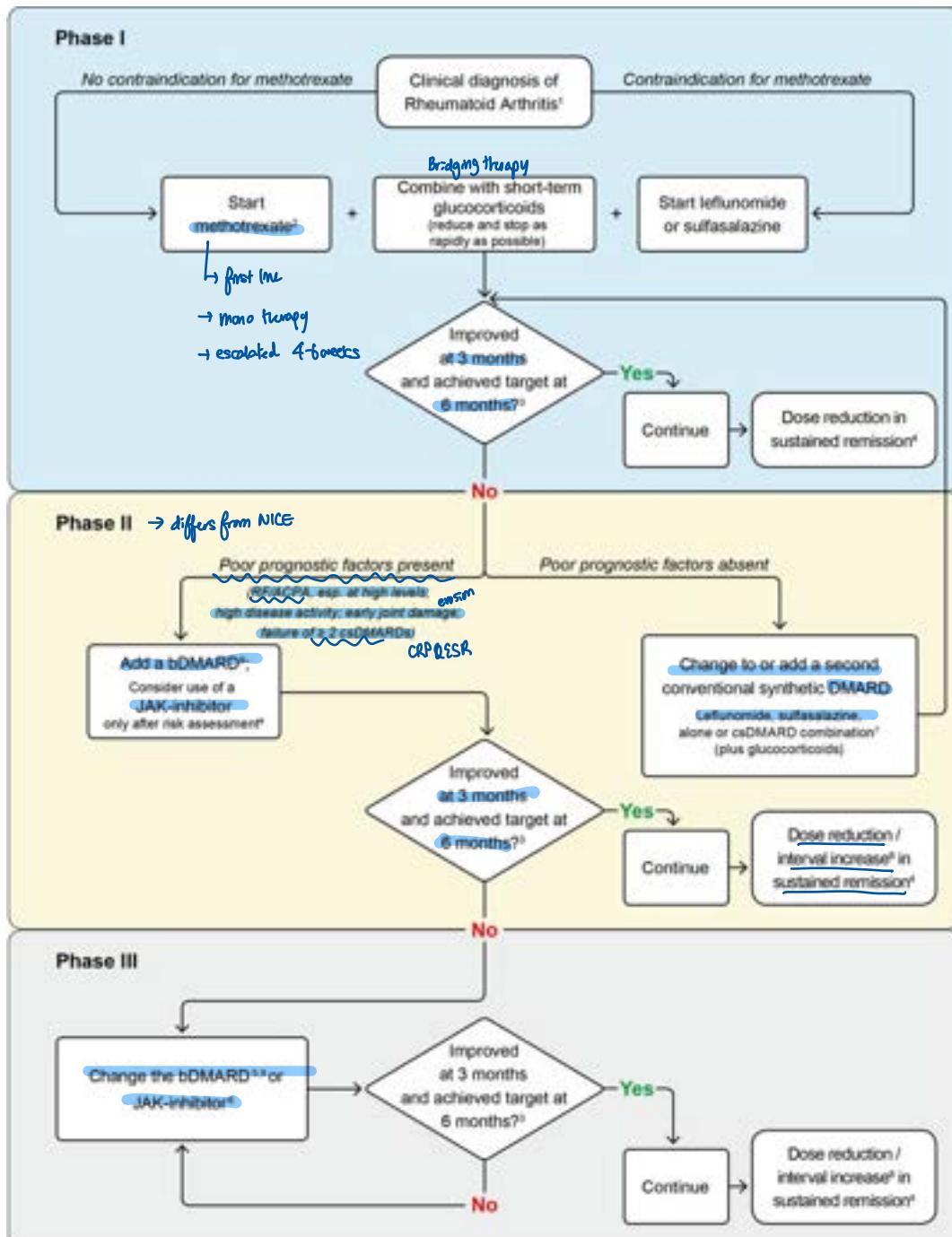
Initial therapy – Decision making

- EULAR Vs. NICE– not significantly different (EULAR uses MTX 'anchor drug')

- Drug choice becomes dependent on:

- Patient preference
- Patient specific characteristics Vs. treatment characteristics
 - i.e. co-morbidities Vs. cautions / contraindications / side effects / dosing / interactions / monitoring requirements etc

EULAR GUIDANCE



¹ 2010 ACR/EULAR classification criteria can support early diagnosis.

² Methotrexate should be part of the first treatment strategy². While combination therapy of csDMARDs is not performed by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs, although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.

³ The treatment target is clinical remission according to ACR/EULAR definitions³; if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted to changed/insufficient improvement (less than 30% of disease activity) as soon after 3 months.

⁴ Sustained remission > 6 months ACR/EULAR index based on Disease remission.

⁵ Consider contraindications and risks. TRP-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including ENBREL/INFRA approved csDMARDs), abatacept, IL-6R inhibitors, or olumiant (under certain conditions), in patients who cannot use csDMARDs as combination IL-6 inhibitor and csDMARDs have some advantages.

⁶ The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (e.g. history of previous history of malignancy after prior adequately treated NAMIC), risk factors for thromboembolic events (history of MI or heart failure, venous, arterial thrombo-embolic disorders or a history of stroke etc., as well as patients taking comedical contraceptives or hormone-replacement therapy, undergoing major surgery or immobilization).

⁷ The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.

⁸ Dose reduction or interval increase can be safely done with all csDMARDs and bDMARDs with little risk of flares, excepting a associated with high flare-rates, most but not all patients can re-acquire their good state upon re-introduction of the same (cs)DMARD/bDMARD, but before this glucocorticoids must have been discontinued.

⁹ From a different or the same class.

20

W3L20

Drugs used in immune diseases – Methotrexate

Nicola Moore
n.moore1@uea.ac.uk

DMARD

3 step precription
- prescription
- dispensing
- administration

Methotrexate – why is there so much to say?

- Between 1993 and 2002 – **25 deaths and 26 cases of serious harm from oral MTX (low dose)**
- NPSA – Alert in 2004 and reissue in 2006 (due to poor compliance to the guidance)
- 2 Cambridgeshire deaths –
 - 2000 – Inadvertent conversion of a weekly dose (**17.5mg**) to a **daily dose (10mg OD)** → **pharmacy dispensed 20mg tab OD**
→ **identified accident in hospital but no flushing**
 - 2009 – Patient prescribed weekly increasing dose up to a maximum of 25mg weekly
• However, patient continued to increase his dose every week over a 4 month period
→ **which went over the maximum dose**
- 2006 – 2020 – **11 yellow card reports of serious toxicity**
- September 2020 – Drug safety update
“**Methotrexate once-weekly for autoimmune diseases**: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing”

Methotrexate – low dose MTX - key points

- Time to effect** – generally it will take some time for MTX to start to have its effect and for that effect to be at a maximum → patient needs to know for good long term compliance
 - i.e. for RA it can take **6 weeks** to begin to work and **12 weeks** to feel the maximum effect
- In RA, dose escalation is required to reach the optimal dose
 - 2.5mg to 5mg increases every 1-3 weeks** → **7.5mg start**
 - Aim for optimal dose in 4-6 weeks
- Starting therapy – Baseline assessment → therapeutic / toxic monitoring purpose
 - Full blood count (FBC) – white cell count, neutrophil count, platelets, haemoglobin → info about bone marrow
 - Liver function test (LFT)
 - Urea and electrolytes (U&E)
 - Renal function (**creatinine**, Cr or **estimated glomerular filtration rate**, eGFR)
 - because greater than 80% of methotrexate is excreted unchanged in the urine ∴ need to know patient kidney function
 - monitor signs of pulmonary toxicity

Learning objectives

By the end of this screencast, you should be able to:

- Describe the therapeutics of the key medicines involved in the management of immune diseases
- Low dose methotrexate is used to treat immune diseases such as RA, psoriasis & IBD
- At high dose, used as part of cancer chemotherapy (not covered)

→ prescribing of any low dose methotrexate should only be undertaken by healthcare professional aware of benefits/risks
→ require expertise and prescribing competence
→ patients understanding and compliance crucial + patient pill burden should be examined by taking drug history

Methotrexate – low dose MTX - key points

- Oral (PO), intramuscular (IM), subcutaneous (SC) - parenteral route is generally not used first line.
Intramuscular of 25-50, but around 20 makes it more likely to absorb & to work.
- There are slight differences in **dosing** for different immune diseases and when using different routes – refer to BNF/SPC
 - Prior to therapy it is advisable for the patient to receive a **test dose** – to rule out **idiosyncratic adverse effects** → an adverse reaction that does not occur in most patients treated with the drug → no therapeutic effect. Sing as a single one off dose
- The **Frequency** of administration is –
 - ***** Once a week *****
 - On the **same day of the week** – documented in full on the prescription → write the day the patient would take
 - Patient should be appropriately **educated** about the dosing schedule → responsibility of all healthcare professionals never as directed!
 - Dose and frequency should be clear on the label! → specific direction required
- The **strength** of tablet should be prescribed as a **single strength of tablet**, only **2.5mg** should be used
 - 2.5mg → Cannot take 2 different doses FYI → 10mg
 - patient should complete to carry an alert card in packaging → changes made to packaging of methotrexate (over the next 4 years)
 - now would take 4x 2.5mg Once a week

will be different for different diseases

Methotrexate – low dose MTX - key points

- Monitoring therapy –
 - LFT, renal function, FBC → every 1-2 weeks until therapy stabilised → if abnormality is detected
 - Once stabilised → every 2-3 months
- Note: monitoring requirements can vary for different conditions and in local policies
- Patients and carers also have a responsibility for **self monitoring** → this could indicate some change
 - Signs of an **infection** i.e. sore throat, bruising, bleeding – indicating **blood disorders**
 - Nausea, vomiting, abdominal discomfort and dark urine – indicating **liver toxicity**
 - Shortness of breath – indicating **respiratory effects**

~~Methotrexate should always be co-prescribed w/ folic acid (5mg OD 1-6 days a week)~~

- methotrexate is an anti-folate medication
- can cause side effects @ hypofolicity

[Methotrexate Monday] Easy to remember
folic acid Friday

WAIT What role does folic acid have on the body?
Why is methotrexate an anti-folate?

Some patient may suffer w/ mouth ulcers
→ sore throat

check patient blood test (FBG)

as this is a sign of toxicity

→ if results come back normal

→ these symptoms may improve over time or w/ increased folic acid

Very common:

• Stomatitis

• Diarrhoea

• Nausea

these settle down

but if no improvement increase folic acid dose

→ or patient can take

anti-nausea for

short period of time

if side effects continued

reduce methotrexate

administration TO reduce

G2 side effect

Methotrexate – low dose MTX - key points

Key side effects:

- Bone marrow suppression
 - GI toxicity (↑ Inflammation, ↓ white blood cell count)
 - Liver toxicity (hepatitis, ↓ albumin, ↑ bilirubin)
 - Pulmonary toxicity
 - Skin reactions
- Key contraindications:
- Active infection
 - Severe renal impairment
 - Hepatic impairment
 - Bone marrow suppression
 - Immunodeficiency
 - Pregnancy and breast feeding
- male & female patient on methotrexate should not conceive bc teratogenic
→ can conception essential even 3-6 months after stopping
→ no breast feeding
- Signs of yellowing of skin part of the eye
• persistent nausea & vomiting
• Abnormal LFT tests
• increase in ALT (liver transaminases) → suggest need to decrease dose
→ but large increase in ALT he should stop drug

Key cautions:

- Surgery → methotrexate can be stopped
• Renal impairment → white cell count
 - Diarrhoea → caution in any condition that may affect stool frequency → diarrhoea to include more abdominal cramps & pain of renal impairment
 - Ascites (liver fluid in abdomen) → increase methotrexate accumulation as due to liver dysfunction
 - Peptic ulcer
- Do not mix w/ P2 family

Folic acid – Should be co-prescribed

→ can be increased to 60mg/week if required
5 mg OD (1 to 6 days a week, not MTX day)

Reduce the risk of hepatotoxicity and GI side effects

Methotrexate – low dose MTX - key points

Amount to supply –

- Supply only the required amount of MTX and folic acid i.e. if appointment in 4 weeks only supply 4 weeks

Missed doses

- Dose can be taken within 2 days i.e. Monday missed → Wednesday

Interactions

- Anti-folates – co-trimoxazole, trimethoprim
• NSAIDs → reduce excretion of methotrexate via the kidney
• Live vaccines → immunosuppressive so if they rely on immune response & potential to cause infection

- Recommended vaccines – pneumococcal and influenza (administered every year)
→ to reduce risk of contracting these infections

Additional counselling:

- Inform all HCP of MTX use
→ so they don't co-prescribe interacting drugs

• inform that MTX is not a pain killer, but is to treat underlying disease

• need to know dosing plan

• need to know side effects

• need to understand why blood tests are being done

• need to carry card

• monitoring booklet

• methotrexate overdose need to be notified & seek help

• alcohol effect (over – so not suggested only occasional)

• self-prescribing NSAIDc is a must no (if need pain relief speak to HCP)

Methotrexate – low dose MTX - key points

Patient Alert Card



Methotrexate treatment booklet

Every patient must own them

W3L21

Drugs used in immune diseases – leflunomide

Nicola Moore
n.moore1@uea.ac.uk

Learning objectives

By the end of this screencast, you should be able to:

- Describe the therapeutics of key medicines involved in the management of immune diseases

Leflunomide - DMARD *psoriatic arthritis & RA*

• RA – oral - 100 mg OD for 3 days (loading dose)

- Then, DECREASE to 10-20 mg OD → maintenance dose ↓
↳ if this is the case loading dose is omitted
- LD can increase the risk of adverse events – can be omitted

• Time to effect –

- The effect starts after 4-6 weeks and may further improve up to 4-6 months
→ patient must be aware so they continue therapy

• Monitoring – liver function tests (LFT), full blood count (FBC) and BP

- Prior to initiation
- Every 2 weeks for the first six months
- Then, every 8 weeks

⇒ if treating patient with child bearing potential, they should have pregnancy excluded

Link side effects to monitoring.

Leflunomide -

Side effects –

- Hepatic impairment** → LFT's
- Bone marrow suppression → increased when used w/ other drugs causing same problem
leucopenia, anaemia, thrombocytopenia, pancytopenia → require need to be stopped & wash out to be carried out
↳ signs of infection may be seen
- Increased BP (Common) → BP

Common –

- GI – pain, anaemia, diarrhoea, vomiting
- Alopecia (hair loss)
- Skin reactions – rash (rarely severe skin reaction)
- Dizziness

↳ increased when used w/ other hepatotoxic drugs → most cases occur in first 6 months
may require dose adjustment if slight increase
But if large increase, may require cessation → leflunomide has long half-life so it is okay to stop
↳ but patient require a wash out

Rare side effect – respiratory troubles → dyspnoea & cough

↳ could be severe & deadly
patient may be taking other drugs that affect the lung e.g. methotrexate

Leflunomide -

Contraindications –

- Hepatic impairment – accumulation
- Severe immunodeficiency – bc immunosuppressant
- Severe infection – bone marrow suppression
- Severe hypoproteinaemia
- Moderate to severe renal impairment – no data (we don't know its effect yet)
- Pregnancy
- Breastfeeding → active metabolite is toxicologic
contraception required ↓ after 2 years in women
+3 months in men
plasma concentration monitoring ↓
↳ required to ensure level is low enough before patients try to conceive
↳ waiting time can be reduced w/ hashing out
- patient metabolism in liver
- binary excretion (main): active secretion of drug molecules or their metabolites from hepatocytes into the bile
- active metabolite of the drug is highly protein bound
- ∴ low plasma protein concentration causes increased plasma levels, further causing more side effects

Cautions –

- Administration with haematotoxic or hepatotoxic drugs → bc side effects are similar & increase risk
- History of TB → potential of reactivation
- Bone marrow suppression – anaemia, leucopenia, thrombocytopenia

Leflunomide

↳ if a drug is not cleared from the body even after 5 half-lives
→ effect how long it takes for drug to gone

The active metabolite has a long half-life – 1-4 weeks

- Monitoring after discontinuation is required → effect of leflunomide continues even after cessation
- Washout procedure → if wanting to conceive, swap to another DMARD, or had severe side effects
 - Stop treatment
 - Give colestyramine 8 g TDS or activated charcoal 50g QDS
 - Treat for 11 days → can be repeated if required after monitoring levels left in system

Additional advice to patients –

- Avoid live vaccines due to the fact that the drug is immunosuppressant
- Avoid alcohol (increase risk of hepatic impairment)
- Can be taken with or without food

↳ mechanism is the interruption of enterocyte cycling or some G2 DNA synthesis process

22

W3L22

Drugs used in immune diseases – ciclosporin

Nicola Moore
n.moore1@uea.ac.uk

Learning objectives

By the end of this screencast, you should be able to:

- Describe the therapeutics of key medicines involved in the management of immune diseases

Cyclosporin

Calcineurin inhibitor : multiple effects on the immune system

• Indications –

- Inflammatory bowel disease – *gastroenterologist*
- Immunosuppressive therapy in transplant patients (SOT and bone marrow) *solid organ transplant*
- Psoriasis – *dermatologist*
- Severe atopic dermatitis
- Rheumatoid arthritis – *Rheumatologist*
- Capsules / liquids

• Dose – (PO/IV)

- Doses vary greatly for the different conditions – refer to the product SPC/BNF for details
- Often involve up titration
- Balance between effective treatment and tolerability/adverse effects

→ has lag phase to its full effectiveness

Cyclosporin

Contraindications –

- Abnormal baseline renal function
- Malignancy
- Uncontrolled hypertension
- Uncontrolled infection

Monitoring – (at baseline and throughout treatment)

- Renal function
- Hepatic function
- BP
- Lipids
- Electrolytes – potassium, magnesium, Uric acid

Therapeutic drug monitoring
→ monitoring of the actual levels of cyclosporin
→ done for non-transplant patients when there is unpredicted response
① for patients that are an interacting drugs (could alter drug levels)
② or if patient is showing signs of toxicity
→ In transplant patients, this is done extremely regularly

Cyclosporin

• Side effects

• Common – (bold very common)

- GI, fatigue, convulsions, **headache**, muscle cramps, myalgia, tremor, hyperglycaemia, hyperlipidaemia, hyperkalaemia, hyperuricaemia, hypomagnesaemia, **hypertension**, **hirsutism**/hypertrichosis, hepatic impairment, **renal impairment**, leucopenia

↓ normal hair growth

- Most side effects are dose dependent and respond favourably to dose reductions
- Side effects are more common where **higher doses** and **longer durations** of use are involved

↳ rare for transplant patients

• Other important side effects –

- Immunosuppression increases the risk of infections – screening of latent TB, important info when treating patients
- Immunosuppression increases the risk of developing lymphomas and malignancies (esp. skin)

→ its frequency + in intensity & duration

* barriers to skin cancer → worn out to have increased exposure to UV light

Cyclosporin is a potent immunosuppressant and a non mycophenolate, but is nephrotoxic.
→ usually reversible and dose dependent, however after prolonged use it can cause irreversible structural changes in the kidney

Cyclosporin ⇒ Always check for interactions

• Interactions –

- CYP450 inhibitors – macrolides, diltiazem, verapamil, lercanidipine, fluconazole, itraconazole, ketoconazole, grapefruit juice → ↑ blood cyclosporin levels

- CYP450 inducers – rifampicin, carbamazepine, phenobarbital, phenytoin, St. John Wort
→ ↓ blood cyclosporin levels

- Statins – avoid or dose reductions → cyclosporin markedly ↑ exposure of statin → increase risk of myopathy, muscle pain
→ leading to rhabdomyolysis & renal failure

- Nephrotoxic drugs – NSAIDs, MTX

- Any drugs causing effects as seen with cyclosporin → hypertension, bone + its side effects

- i.e. K⁺ sparing diuretics

- Cyclosporin inhibits CYP3A4, p-glycoprotein and Organic Anion Transporter proteins

↳ this can cause significant increase in certain other drugs e.g.) digoxin (for DVT)

→ can increase levels to harmful

mechanism for its interaction is related to CYP450, 3A4 inhibition, but also affects other transporters related to the handling of statins → specific guidance in SPC and BNF for each of different statins

 PHARMACISTS TO BE AWARE OF:

Ciclosporin

 significant difference in bioavailability?

- Differences in IV and oral preparations -
 - The oral dose of ciclosporin is approximately 3 times that of the IV formulation
- Specific information relating to the oral solution - → in transplant patients this is more significant, as inadvertent switching from brands to brands can cause change in bioavailability
 - Required dose should be mixed with orange or apple juice immediately before administration
not grapefruit juice, bc CYP3A50 inhibitor
 - oral preparation absorption is very poor
 - complicate transplant graft
 - Patient should stick to same brand
- Advice to patients –
 - Have blood tests done
 - Twice a day preparation
 - Should be maintained on the same brand of ciclosporin → check form
 - Consistency of administration – time of day and proximity to food → exposure can be increased w/ highly fat meals
 - Avoid live vaccines
→ decreased efficacy and potential infection

19

W3L16

Drugs used in inflammatory diseases - NSAIDs

Nicola Moore
n.moore1@uea.ac.uk

Paracetamol

- Mainly used for pain and as an antipyretic *(analgesic)* *(anti-fever)*
 - Paracetamol does NOT have significant anti-inflammatory effect (although central action on COX enzymes is postulated) *(contraindication)* + completely different drug profile
 - Generally well tolerated
 - Overdose:
 - Limited legal requirements of sale - tablets cannot be sold in packs of greater than 32
 - Inadvertent overdose - but pharmacists can sell up to 100 in justifiable situations
 - Check for duplicate prescribing. *(e.g. caution, contraindication, side effect)*
 - Special patient groups:
 - Children
 - Low body weight (<50 kg)**
 - Liver impairment (or those with risk factors for hepatotoxicity)
- at more risk of toxicity from paracetamol*

Aspirin

- able to inhibit thrombus formation in the arterial system*
(as in the risk of bleeding vessels, thrombi are composed mainly of platelets w/ little fibrin)
- Antiplatelet - 75 mg - 300 mg daily (loading dose dependent on indication)
 - No anti-inflammatory effect *∴ used for primary & secondary prevention of CVD*
 - Analgesic - Standard oral dose: 300-900 mg every 4 - 6 hours when required (max. 4 g per day)
 - Rarely used now in inflammatory conditions *: due to risk of side effects*
 - Special patient groups:
 - Contraindicated in children under 16 (except when specifically indicated - Kawasaki syndrome) *→ due to Reye's Disease (swelling in liver & brain)*
 - Contraindicated in patients with: previous or active peptic ulcerations, bleeding disorders, severe cardiac failure, previous hypersensitivity to aspirin or NSAID
 - Elderly *↑ risk of kidney side effects* *→ aspirin can increase risk of bleeding & GI irritation*
 - Caution in patients with: asthma *→ due to the risk of bronchospasm*

Learning objectives

By the end of this screencast, you should be able to:

- Describe and apply the therapeutics of paracetamol, aspirin and NSAIDs (traditional non-selective and COX-II selective)

Contents

- Paracetamol
- Aspirin
- NSAIDs
- GI side effects
- CV events
- Renal side effects
- Other considerations

Paracetamol

- BNF - "in single doses NSAIDs have analgesic activity comparable to paracetamol"
- Preferred analgesic over NSAIDs for:
 - Elderly (need to consider weight)
 - Patients with: hypertension, CVD, renal impairment, GI issues
 - Patients on medicines interacting with NSAIDs, i.e. warfarin
- Available preparations:
 - Tablet, caplet, capsule, orodispersible tablet (need to consider requirements of sale)
 - Suspension (need to consider the concentration and licensing)
 - Suppositories
 - Infusion *in standing care when patient NBM*
 - Compound preparations - co-codamol (paracetamol and codeine), co-dydramol (paracetamol and dihydrocodeine), OTC preparations - Tempsip etc.

Aspirin

- Interactions:
 - Drugs that increase the risk of GI irritation and bleeding - steroids, NSAIDs, SSRIs, anticoagulants
 - Drugs that increase the risk of renal side effect - Bisphosphonates
 - Drugs where aspirin can increase the toxicity of other drugs - Methotrexate *→ aspirin is known to reduce clearance of methotrexate*
- Available preparations:
 - Tablet, EC, dispersible (need to consider requirements of sale)
 - Suppositories
 - Compound preparations - Beechams powders (aspirin/caffeine), codis 500 (aspirin/codeine), Alka-seltzer (aspirin/sodium bicarbonate)

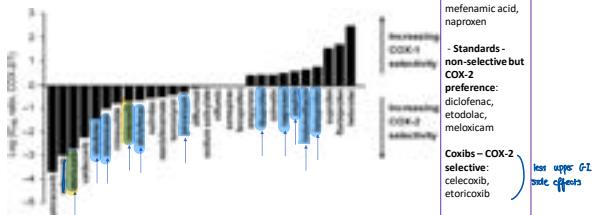
↑ GI side effects are thought to be due to inhibition of house keeping COX-1 enzyme and the production of prostaglandins

NSAIDs

- In regular full dosage, NSAIDs have **lasting** analgesic and anti-inflammatory effect
 - Analgesic effect starts soon after first administration and full effect obtained within a week
 - Anti-inflammatory effect may not be achieved for up to 3 weeks
- The difference in anti-inflammatory effect of the NSAIDs is small → detail found in BMF
 - Considerable variation in individual response and tolerance
- Selection of an NSAID should be based on the **characteristics of the drug** and individual patient risk factors for adverse effects
 - Key side effects:**
 - GI mucosa
 - Kidney
 - Cardiovascular system
 - If an NSAID is indicated, the **LOWEST effective dose** should be used for the **SHORTEST duration**

- diclofenac & naproxen has better efficacy to ibuprofen, but increased side effects
- cyclooxygenase 2 inhibitors (COX-2 inhibitors) have similar efficacy to Naproxen & diclofenac → but have less upper GI side effects associated → but have risk with CVD

Ranking of cyclo-oxygenase selectivity



Morten Schmidt, Morten Lamberts, Anne-Marie Schjerning Olsen et al. Cardiovascular safety of nonaspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. European Heart Journal – Cardiovascular Pharmacotherapy (2016) 2, 108–118

GI side effects

- For example: Epithelial damage, ulceration and bleeding
- Caused by:
 - Suppression of physiological homeostatic prostanoid (COX-1) inhibition
 - Reduced mucus production
 - Reduced bicarbonate production
 - Reduced mucosal blood flow
 - Topical irritation and direct epithelial damage**
- All NSAIDs are associated with GI issues
 - Highest incidence in the elderly
 - Consider cautions and contraindications → *more info*
- Selective COX-2 agents – coxibs – designed to **inhibit those prostanoids of COX-2 isoform (involved with inflammation and less important in GI homeostatic roles)**.
 - Lower risk of upper GI s/e than non-selective NSAIDs

GI side effects

- There are differences risk of serious upper GI s/e between the non-selective NSAIDs

Highest risk: piroxicam, ketoprofen, ketorolac

Intermediate risk: indometacin, diclofenac, naproxen

Lowest risk: ibuprofen (low dose, up to 1.2 g) → standard dose

(Lowest risk: Coxibs)

→ celecoxib
→ etoricoxib

Lowest risk agent preferred,
to start at lowest dose and
not used with another
NSAID

GI side effects

Key points

- Lowest risk agent preferred
- Start at lowest dose
- Use for the **shortest duration** (review need)
- Do not use more than one NSAID at a time**
- Advise medication to be taken with **food to reduce contact irritation** → *systemic effect & contact irritation is different*
- Co-prescribe with **gastroprotection** in those patients at risk of GI ulceration, i.e. **PPI** → *help protect G.I.*
- Monitor for adverse events
- Review patient for risk factors

GI side effects

- Interactions:
 - Aspirin
 - NSAIDs
 - Other drugs increasing the risk of GI ulceration and bleeding – **steroids, bisphosphonates**
 - Other drugs increasing the risk of bleeding: **serotonin reuptake inhibitors (SSRI's), anticoagulants**
- Monitoring
 - Reported symptoms of dyspepsia/GI irritation
 - Hb ↓ *haemoglobin level check*
 - Signs of GI bleeding – **haemoptysis, dark stools**

↓
Coughing blood

2)

CV events

- Many mechanism postulated, believed to be due to increased COX-2>COX-1 of vasculature, platelets and potential effects from the kidney
- 2004 – Rofecoxib withdrawn due to fears relating to increased CV risk
- 2005 – EMA identified increased risk of thrombotic events – myocardial infarction and stroke with COX-2 inhibitors
- 2006 – EMA identified that this may also be a problem for non-selective NSAIDs, such as diclofenac
- 2013 – Diclofenac prescribing advise changed massive ↓ in use of diclofenac
- 2015 – Diclofenac removed from P availability
- 2015 – EMA confirmed high dose ibuprofen (2.4 g daily or more) had increased CV risk comparable to COX-2 inhibitors and diclofenac

CV events

- All NSAID use can, to varying degrees be associated with increased risk of thrombotic events

- Independent of baseline or duration of use (however the greatest risk is with higher doses over longer periods)

Highest risk: COX-2 inhibitors, diclofenac (150mg daily), ibuprofen (2.4 g or more daily)

Lower thrombotic risk: Naproxen (1g daily)

No evidence for increased risk - ibuprofen (low does, 1.2 g or less)

lowest effective dose, for the shortest period, review long term use

CV events

Key points

- NSAID selection
- Use lowest effective dose
- Use for the shortest duration (review need of long term therapy)
- Monitor for adverse events
- Review patient for risk factors

COX-2 inhibitors, diclofenac and high dose ibuprofen are contraindicated in ischaemic heart disease, cerebrovascular disease and some stages of heart failure

Other non-selective NSAIDs have use **cautious** in patients with: heart failure, cerebrovascular disease, ischaemic heart disease, risk factors for CVD
→ use drug at lowest risk, lowest dose, shortest duration

CV event

- Interactions:
 - Antihypertensives (opposite effect)
 - Antiplatelet dose aspirin (75 mg)
→ effect may be reduced w/ long term use of NSAIDs
- Monitoring
 - Increase occurrence or first occurrence of CV event
 - Risk factors for increased CV risk – BP, medical history of diabetes/hypercholesterolaemia

3)

Renal side effects

in a healthy individual: prostaglandins play little role in how our kidneys work

- NSAID use can reduce renal function → lead to renal failure
- Mainly seen in individuals where **compensatory prostaglandins** are playing a role to maintain renal function, i.e. advanced age, renal impairment, heart failure, volume depletion, liver cirrhosis
 - Prostaglandin have a limited effect in healthy individuals
 - Through effects on the kidney, NSAID use can cause:
 - Decrease renal blood flow and increase the risk of acute kidney injury
 - Sodium and water retention – oedema and hypertension
 - Avoid in those patients with the above risk factors (patient characteristics)
 - Avoid in severe impairment/avoid or use with caution in other renal impairment
 - Use the **lowest effective dose** for the **shortest duration**
 - Close monitoring** of renal function

Renal side effects

- Interactions:
 - Co-prescribed nephrotoxic medicines – diuretics, ACE-inhibitors
 - Anti-hypertensive – (opposite effect) → effects of NSAIDs on the kidney: increase in fluid and blood pressure
 - Lithium and methotrexate – decreased renal elimination causing toxicity
→ in their narrow therapeutic windows & extensive side effects & toxicity profile
this can markedly increase risk of toxicity
- Monitoring
 - Renal function – GFR, urine output, urea
 - BP (glomerular filtration rate)
 - Electrolytes – sodium and potassium
 - Oedema (weight, visual signs)
 - Increased weight gain or swelling

4)

NSAIDs – other considerations

- **Bronchospasm** : cross sensitivity to NSAID : patient who had bronchospasm w/ one NSAID likely to another
→ patients should be cautious
- Topical therapies –
• Available OTC
• Systemic absorption can occur (if used over large area or heat therapy used alongside)
• Consider potential issues as previously discussed
- General interactions: (consider drug-drug and drug-disease interactions)
 - **Anticoagulants** –
• Patients should not self medicate → can increase risk of bleeding
• Close monitoring required (prescriber &)
- Counselling:
Take the lowest effect dose for the shortest period
Take with or after food
Self monitor for signs of GI disturbance – report
Do not self medicate with other NSAIDs or aspirin

Therapeutic Monitoring

- Effectively reducing pain & inflammation
- ↑ movement for patient w/ RA

Toxic Monitoring

- Signs of bleeding
- Signs of renal impairment
- Signs of GI events
- Signs of CVD events

27

W3L27

GOUT

GOOT

Screencast 1
(Epidemiology, aetiology, pathophysiology & clinical presentation)

Catherine Heywood
Hospital Teacher
Practitioner
catherine.heywood@uea.ac.uk

1

Objectives:

- Epidemiology
- Aetiology and risk factors
- Pathophysiology of hyperuricaemia and gout
- Clinical features

2

Introduction

- Group of diseases → HYPERURICAEMIA
↳ increased level of uric acid in the blood
↳ biochemical change in blood test result
and gout is the clinical manifestation of hyperuricaemia
- Caused by:
of uric acid
– ↑ production or ↓ excretion or both
- Deposition of monosodium urate monohydrate crystals in joints & soft tissues
→ acute inflammation & eventually tissue damage

3

EPIDEMIOLOGY¹

- Prevalence (UK 2012) of gout = 2.49%
- Incidence (UK) of gout = 1.77/1000/yr
- USA prevalence = 3.9% (2007-2008)
- More common in men (30-60years) and in older people (rare in those under 20 years)
– Ratio – 4.3 : 1 (M:F)
- More likely if FHx - genetic link
- Prevalence varies widely from country to country

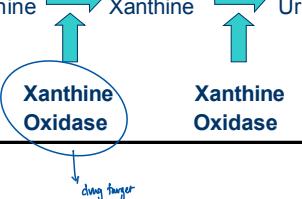
1. NICE – Gout, 2018 (available at: www.cks.nice.org.uk/topics/gout - accessed 28/9/20)

4

PHYSIOLOGY

Uric acid synthesis:

- Uric acid is end product of purine (adenine & guanine) metabolism
- Hypoxanthine → Xanthine → Uric acid



5

Uric acid excretion:

- Completely filtered by glomerulus
- 90-100% reabsorbed in proximal tubule (URAT-1 specific anion transporter)
- 50% actively secreted in distal tubule
- 40-45% post secretary reabsorption

→ ~5-10% of original glomerular load is excreted

6

Urinary excretion:

- 2/3 of urate excreted in urine
- 1/3 of urate excreted in gastrointestinal tract ^{through the bile}

7

AETIOLOGY

Gout caused by:

- ↑ rate of synthesis of purine precursors of uric acid (10%)
- ↓ elimination of uric acid by kidney (90%)

8

Classification:

- Primary:
 - Due to ~~rare~~ inborn errors of metabolism or renal excretion (not covered here)
- Secondary: ~~maturity!~~
 - Occur due to drugs or consequence of other disorder

9

Over consumption:

- Over consumption of foods high in purines:
 - Offal (liver, kidney, heart, sweetbreads), game, oily fish (anchovies, herring, mackerel, sardines, sprats, trout), seafood, yeast or meat extracts.

10

Over production:

- Only about 10% of cases ^{+tumour diseases}
- Excessive cell turnover (E.g: neoplastic disease, psoriasis, haemolytic anaemias)
- Cell lysis caused by cancer chemotherapy & radiotherapy
- Excessive synthesis of uric acid due to ~~rare~~ enzyme mutation defects

11

Under excretion:

- Occurs in remaining 90% of cases ^{> high levels of urea acid normally ~}
- Hyperuricaemia → large urate loads filtered through glomerulus → ↑ urate reabsorption to avoid dumping of insoluble urate into urinary tract ^{as a consequence of high levels in the blood}
↳ normal compensatory process
- Also ↓ tubular secretion in the distal tubule
due to this compensation, there is an overall reduction in the excretion of uric acid secondary to this high level in the blood

12

THIS HAPPENS

- Renal failure → cannot excrete uric acid normally
- Alcohol (beer, red wine) → cause itself, as it has high levels of purine
of under excretion caused by drugs → but also a secondary cause for under excretion
- Drugs:**
 - Diuretics - Especially thiazides, furosemide → loop diuretics
 - aspirin, ciclosporin, omeprazole, ethambutol, pyrazinamide, niacin, didanosine, levodopa, cytotoxics

↓
thiazide diuretic e.g.) bendroflumethiazide
↳ they cause volume depletion & cause reduction in tubular excretion of uric acid

In Year 1 we met a hypertension patient w/ gout

13

Other: TRIGGERS

- Physical Stress**
 - Tight shoes, hill walking, hiking, history of joint trauma
- Other independent risk factors:** hypertension, obesity & hypertriglyceridaemia

14

PATHOPHYSIOLOGY

Hyperuricaemia is the most important risk factor for gout

- Uric acid levels:**
 - Formation and deposition of monosodium urate crystals is more likely to occur when levels are persistently $> 360 \text{ micromol/L}$ (solubility limit)
- HIGHER plasma urate level** → ↑ incidence of gout
- PROLONGED DURATION** of ↑ urate levels → ↑ likelihood of developing gout.

15

- Uric acid = weak acid ($pK_a 5.8$)
 - At physiological pH → ionised → monosodium urate (MSU) ↳ in its raised form as wate
 - If supersaturation occurs → crystal formation
 - Solubility is influenced by:
 - Temperature, pH, cation concentration, articular dehydration and presence of nucleating agents (non-aggregated proteoglycans, insoluble collagens and chondroitin)
- ↳ environmental factors will affect

16

Urate crystals:

↳ long thin crystals
When seen under microscope, they are an important part of the diagnosis



BURSA

- Crystal deposition may continue for many months or years without causing symptoms
 - Only cause symptoms when shed into bursa (small sacs of synovial fluid surrounding joint) → inflammatory reaction
 - Shedding can be triggered by e.g:
 - Trauma, dehydration, rapid weight loss, illness & surgery
- Crystals ↳ small sacs of the synovial fluid

17

18

- Urate crystals are directly able to initiate, amplify and sustain inflammatory responses, through:
 - Humoral and cellular inflammatory mediators
 - Complement system
- Overall this causes:
 - a proinflammatory cascade of cytokines, chemotactic factors, TNF
 - Inflammatory cell accumulation (monocytes and mast cells in the early phase and neutrophils in the later phase)
- IL-1 β has been shown to be critically related to the inflammatory response in gout

19

IL 1 Beta

CLINICAL PRESENTATION

5 stages:

- Asymptomatic hyperuricaemia (long period before gout manifests)
 - Acute gouty arthritis
 - Interval gout/Intercritical gout
 - Chronic tophaceous gout
 - Gouty nephropathy

20

② Acute gouty arthritis

- 90% acute attacks monoarticular
- 80% first metatarsophalangeal joint of great toe (podagra)
- Others: small joints of feet/ankles, hands (distal interphalangeal), elbows & knees
- Caused by deposition of urate crystals in joints

21



- Severe pain with hot, red, swollen and extremely painful joints
- Begin abruptly – max intensity 8-12hrs
- Weight bearing impossible
- Erythema → redness of the area
- Synovitis → inflammation at the synovial lining
- Leucocytosis → ↑ in NBC count in blood test
- Confusion in elderly

22



- Attack at anytime but can be caused by trigger factors (E.g: food, alcohol, dehydration, starting diuretic)
- Left untreated last around 7 days → desquamation of overlying skin
↳ shedding of the outer layer skin

24

(3)

Intercritical gout

- Time between acute attacks of gout
- Variable intervals of months to years when there are no symptoms

25

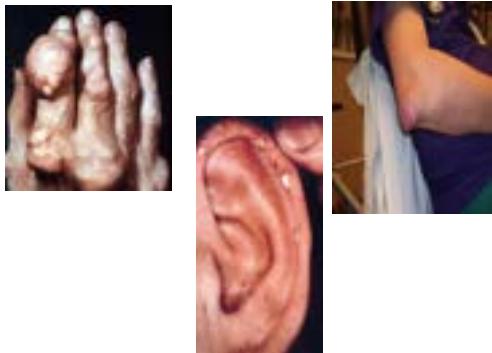
(4)

Chronic tophaceous gout

- Presence of tophi:
 - White deposits of monosodium urate
 - Nodule formation affecting joints → extended further than just swelling & pain
 - Subcutaneous and periarticular areas
 - Ear lobes, Achilles tendon, fingers

* usually had gout for 10 years or more before evidence of tophi

26



27

(5)

Gouty nephropathy/ Hyperuricaemia induced renal disease

- Crystals of urate deposited around renal tubules
 - inflammatory response (interstitial nephritis) → kidney damage
- Proteinuria & renal impairment
 - ↳ presence of protein in urine
- Renal stone formation
 - ↳ stones made up of monosodium urate

28

Diagnosis

- Has to be based on clinical history and examination.
- Uric acid levels can be useful but are not always raised when someone has an acute attack.
 - ↳ 1/3 of all patients
 - ↳ so test done 2/3 weeks after attack
- Joint fluid microscopy – presence of crystals and absence of infection (to rule out septic arthritis)
 - Not always done as it risks causing infection
- Joint X-ray
- Standard bloods – RF, lipids, glucose

29

Inflammation

28

W3L28

GOUT

Screencast 2
(Management & Drug Treatment)

Catherine Heywood
Hospital Teacher
Practitioner
catherine.heywood@uea.ac.uk

1

Objectives:

- Management:

- Treatment of acute gout
- Prophylaxis of gout
- Avoidance of trigger factors

- **Important pharmaceutical care issue****

2

TREATMENT

Aims of treatment:

- Relieve pain/inflammation of acute attack
- Terminate attack
- Prevent further attacks
- Prevent long term joint and organ damage
- Avoid precipitating factors

3

ACUTE ATTACK

- Rest
- Prompt treatment with **full dose NSAIDs**
** No particular first line choice*
- Avoid ASPIRIN:**
 - Competes with uric acid for excretion and can worsen attack

4

NSAIDs

- First line choice**
- Relieve pain & inflammation
- Can abort acute attack if commenced early enough (patients should carry supplies)
- Most important factor is how soon started rather than choice of NSAIDs *↳ more important*
- Full therapeutic high dose for 24-48hrs** then lower doses for 7-10 days until completely resolved
- Consider **gastroprotection** e.g. lansoprazole *→ ppz*

5

COLCHICINE

- Used **second line** when NSAIDs contraindicated or ineffective
 - Eg: CVD (HT, heart failure, diuretics)
Renal disease
Gastrointestinal toxicity
- Slower onset + high level of toxicity**
- Inhibits neutrophil migration into joint**
↳ mechanism of action

6

Neutrophil - WBC that act in innate immune system (first line defence)
- phagocytic cell and is able to phagocytose & destroy infectious disease

WBC
 ⌈
 granulocyte eosinophil
 lymphocyte basophil
 monocyte

- Administer ASAP → less effective over time
- Dose: 0.5mg 2-4 times a day until relief of joint pain or development of GI side-effects or total 6mg taken – do not repeat course within 3 days (12 tablets as maximum course)
- Lower dose of 0.5mg every 8 hrs in elderly and renal impairment

7

- Response after 6 hrs, pain relief after 12 hrs and resolution after 48-72 hrs (longer than NSAIDs)
- Interactions ++ → strong cytochrome P450 3A4 inhibitor (e.g. clarithromycin, erythromycin, verapamil, diltiazem)
- Side-effects:
 - Nausea & vomiting
 - Abdominal pain
 - **Diarrhoea** (stop therapy immediately) → colchicine can cause direct mucosal damage to the gut lining
 - Rashes, peripheral neuropathy, blood dyscrasias

(more rare, but need to monitor)

8

CORTICOSTEROIDS

- Oral: e.g. Prednisolone 30-35mg daily (or equivalent)
 - Pred 35mg daily for 5 days as effective as naproxen 500mg BD for 5 days for flare treatment
 - Pred 30mg daily for 5 days has analgesic effectiveness equivalent to indomethacin
- Articular: e.g. Triamcinolone = good safety profile
 - Consider particularly in monoarthritis of easily accessible joint (four digits in monoarthritis - one particular joints)

* Short course of oral steroids - prednisolone
or * injection directly to the site - Triamcinolone

9

Or COMBINATION THERAPY

- NSAID with colchicine or corticosteroid

10

// treatment of an acute attack

PROPHYLAXIS against acute attack of Gout (Urate Lowering Therapy – ULT)

- Important to prevent long term complications (development of tophi, development of nephropathy or kidney damage)
- Evidence of when to start controversial
- Initial attacks usually infrequent & self-limiting (so introducing the patient to continuing prophylaxis is not important)
- Consider when patient suffers **two or more acute attacks per year**, tophi, chronic gouty arthritis, joint damage, renal impairment, urolithiasis, diuretic use, young onset (formation of kidney stone known to cause gout)

they should be considered

11

- Traditionally, do not start during an acute attack
- Hyperuricaemic for several years → no need to treat hyperuricaemia immediately
- Changes (↓) serum uric acid levels → **mobilisation of uric acid stores** → may prolong attack or precipitate another (however small trials indicate allopurinol initiation did not prolong duration or worsen severity)

12

- **ULT**
 - Reduces frequency of flare
 - Once crystals dissolved avoids recurrence
 - Reduces size and number of tophi
 - Facilitates tophi disappearance
 - IMPROVED QoL
- All ULT should be started at a **low dose** and **titrated upwards**
 - Monitor and titrate to serum uric acid (sUA) target

13

With ULT potentially causing an acute gout attack due to mobilisation of uric acid
→ monitoring and risk management is essential

ULT – prophylaxis vs flares:

- Recommended during the first 6-months of **ULT** or during a dose titration
 - f for risk management*
- **Colchicine – first line**
 - 0.5-1mg daily
 - Reduce in renal impairment
- Where contraindicated or not tolerated
 - Low dose **NSAID** or **coxib** should be considered (consider cautions etc.)
 - With gastroprotection *PPI*

14

ALLOPURINOL

- First line choice
- Controls symptoms
- Some improvement in tophi (usually after about 6 months treatment)
- **Xanthine oxidase inhibitor** → controls the last two steps of purine breakdown
- Pro-drug → undergoes hepatic metabolism to active metabolite, **oxipurinol**

15

- Dose:
 - Start 100mg daily
 - ↑ every 3-4 weeks according to response to achieve ↓ serum urate levels (target sUA <300μmol/L)
 - Usual maintenance 300mg daily (100-600mg)
 - Accumulate in renal impairment (Dose 50-100mg daily)
 - If patient has renal impairment*

16

- Side-effects:
 - Rashes
 - Hypersensitivity reactions
 - Gastrointestinal disturbances

most people tolerate quite well

17

- Start 1-2 weeks **after** acute attack subsided
- If patient already on Allopurinol **at onset of** acute attack → **continue** & treat acute attack
- Allopurinol can be used for **prevention of** diuretic induced hyperuricaemia if no alternative
 - when you have no choice but to continue using a diuretic; e.g. for heart failure so we don't stop it → then we use allopurinol to treat hyperuricaemia associated with the diuretic

*Hyp : bendroflumethiazide → cause gout
↳ there are plenty of other Hyp drugs, so we swap
↳ but if used for heart failure, we don't have another choice*

Febuxostat

- Alternative to allopurinol if intolerant or C/I (NICE₂₀₀₈)
- Non-purine selective inhibitor of xanthine oxidase
- Dose: 80mg od (\uparrow to 120mg if uric acid levels $>357\mu\text{mol/l}$ after 2-4 weeks)
- Continue if acute attack occurs during prophylaxis
- Side-effects: G.I., headache, \uparrow LFTs, oedema, rash
- Rare but serious hypersensitivity reactions

19

These are the 2 firstline UCT →

URICOSURIC AGENTS

- Eg: **Sulfinpyrazone, Probenecid (unlicensed), Benz bromarone (unlicensed)**
- Second line alternative to Allopurinol/Febuxostat**
- \uparrow uric acid excretion by **direct action on renal tubule**
- Avoid in **urate nephropathy** → bc this can worsen incidence of kidney stone / crystaluria
↓ synthesis of urate in kidney
- Ineffective in poor renal function (CrCl $<20-30\text{ ml/min}$)
- Need to maintain **high fluid intake** to \downarrow risk of stone formation

20

↳ sometimes these can be used in combination w/ xanthine oxidase inhibitors
→ if we don't achieve appropriate SUA level with monotherapy

Canakinumab

→ incredibly expensive

- S/C injection
- Recombinant monoclonal antibody \times when gout not responded to any other therapy
- Severe, refractory tophaceous gout (NICE₂₀₁₃)
- Target interleukin-1 β associated with inflammatory response induced by urate crystals
- C/I in current infection – due to risk of sepsis
- Acute flares – not approved by NICE
 \rightarrow approved for UCT but not acute treatment

21

↳ associated in inflammatory response induced by urate crystal

Others:

just for reference purposes, drug w/ evidence → potential use in future

Pegloticase

- Pegylated uricase, catalysing the oxidation of uric acid into allantoin (more soluble end product)
- For those with crystal proven, severe debilitating tophaceous gout and poor QoL where the SUA cannot be reached at fully optimised treatment
- Not approved by NICE

Anakinra

- IL-1 receptor antagonist
- Not licensed for gout (licensed for RA)

Rilonacept

- IL-1 α/β antagonist and IL-1R antagonist
- Unlicensed in UK

22

PHARMACEUTICAL CARE ISSUES

IMPORTANT INTERACTION

ALLOPURINOL+AZATHIOPRINE

- ↑ first line agent for prevention of gout ↑ suppress auto immune system used IBD, Crohn's, UC, RA, kidney transplant
- Azathioprine metabolised to mercaptopurine
 - Mercaptopurine metabolised by Xanthine oxidase
 - Allopurinol causes accumulation →
- Potentially fatal bone marrow suppression**

23

Reference:

The British Society for Rheumatology Guideline for the Management of Gout, 2017

(available at: <https://academic.oup.com/rheumatology/article/56/7/e1/3855179>)

24

Upper Gastrointestinal Conditions

Jeremy Sokhi

j.sokhi@uea.ac.uk

[1]

Learning outcomes

- Outline the epidemiology, pathophysiology, aetiology & pharmacological treatments of common upper GI conditions
- Define gastro-oesophageal reflux disease, peptic ulcer disease, gastritis & functional dyspepsia
- List the alarm symptoms requiring referral
- Provide appropriate pharmaceutical and non-pharmaceutical advice for the management of common dyspeptic diseases

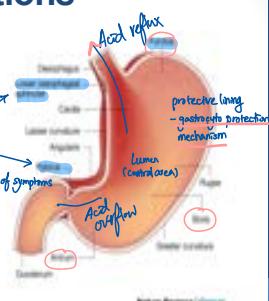
[2]

Upper GI Conditions

Due to Acid

- Wrong location
- Over-production
- Faults with protective mechanisms
- Dyspepsia - over production of acid (broad term of describing a range of symptoms in the upper GI tract)
- Treatment
 - Prevent acid from relocating
 - Reduce acid production or neutralise it
 - remove cause

Not a diagnosis or a disease
 Symptoms can include: upper abdominal pain & discomfort, heartburn (reflux and damage to oesophagus), nausea and vomiting & hiccups.
 - quality of life for person experiencing dyspepsia is lower bc it tends to present frequently
 Recurrent



[3]

Epidemiology

Prevalence varies from 20-40%

- Quarter of which will have peptic ulcer disease
- Majority of patients self-medicate (60 million pounds is spent annually on prescribed drug & medications)
 - 90% self treat (inpatient pounds)
 - 9% see a GP
 - 1% see a consultant

- Community pharmacy problem** → front-line contact for dyspepsia and gastro-oesophageal reflux disease
- Many patients self-select treatment
 - Mask potentially serious conditions → because of self-medication
 - lifestyle changes
 - correct OTC for relief of symptoms
 - review of prescribed meds (could be contributing factor of symptoms)
 - when do we refer patients
 - recording any adverse reactions to treatments

[4]

* self-medication cause masking of something more serious:

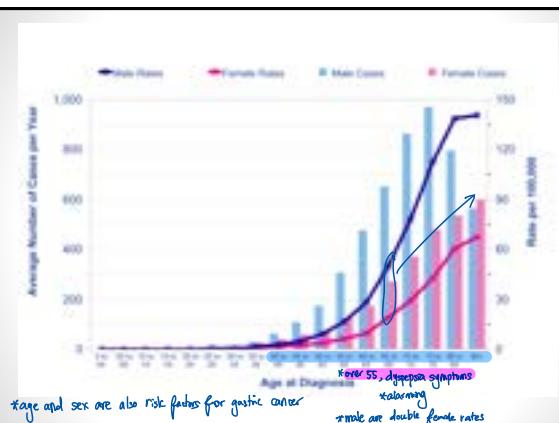
Gastric Cancer

- UK incidence rate 10 per 100,000 (UK is slightly higher)
 - EU 8.6 per 100,000
- 4,400 deaths from stomach cancer in the UK every year (2015-17)
- 17th most common cause of cancer death
- Responsible for over 3% of all cancer deaths
 - 1 year survival 42%
 - 5 year survival 19%
 - 7 in 10 cases diagnosed at a late stage
- 54% of cases are preventable
 - More common in smokers and drinkers → reduction in protective mechanism
 - Related to H.Pylori infection (32%) → in another sourcecast
 - Salt intake
 - Less common in vegetarians

* we are seeing a decline in cancer rates

- changes in diet and how we prepare food is starting to change e.g. salt intake
- 1970s there is less case of gastric cancer bc more jaffles available and more fresh food available.
- increased incidence can be due to deprivation
- + family history
- + previous gastric ulcer
- + more common in black ppl and less common in caucasian ppl
- : difference based on ethnic background

[5]



[6]

Common upper GI conditions

- Gastro-oesophageal reflux disease (GORD) 10-20%
GERD (american spelling)
- Duodenal and stomach ulcer disease (PUD) 10-25%
peptic ulcer disease
- Gastritis : inflammation of the stomach lining 30%
- Functional dyspepsia : dyspepsia of unknown cause 30%
- Oesophageal & gastric cancer 2%
small but significant!

[7]

3A

Upper Gastrointestinal Conditions

Jeremy Sokhi

j.sokhi@uea.ac.uk

[8]

Pathophysiology

(The science bit)



[9]

Gastric (stomach) secretions

- Pepsinogen from Chief cells
 - Break down proteins
 - Chief cells in gastric glands to mucus cells → secrete pepsinogens
 - We need a pH of less than 3 for pepsinogen to work (acidic condition)
- Hydrochloric acid from Parietal cells
 - Activate pepsinogen + kills bacteria
 - located in the glands found in the fundus (upper curvature of the stomach)
 - secretes hydrochloric or gastric acid (pH that kills your intestine should be at 2.5)
 - helps form the necessary acidic environment
- Intrinsic factor from Parietal cells
 - Aids absorption of vitamin B12 from small intestines
 - into this we can get pernicious anaemia which has an impact on red blood cell production

[10]

gastric activity with eating is divided into 2 stages!

Gastric physiology

*these phases can overlap and all can occur simultaneously.

• Acid secretion via Parietal Cells controlled by:

- thought, smell, taste sight of food causes ① Control by brain
 - Nervous control - **cephalic phase** - parasympathetic
 - Thought, smell, taste or sight of food
 - 50% of acid is released during this phase ② Control by local
 - Local control - **gastric phase** - parasympathetic
 - Distension of stomach and chemical make up
 - stretching of the stomach
 - ③ Control by small intestine
 - Hormonal control - **intestinal phase**
 - Food in duodenum (chyme) causes secretion of somatostatin which inhibits acid production
 - a prostaglandin
 - serum fluid mass of partly digested food
 - negative feedback reflex which inhibits hypersecretion of the stomach

④ basal state (occurs between meals)

- intradigestive phase

- level of acid secretion during these times are regulated by:

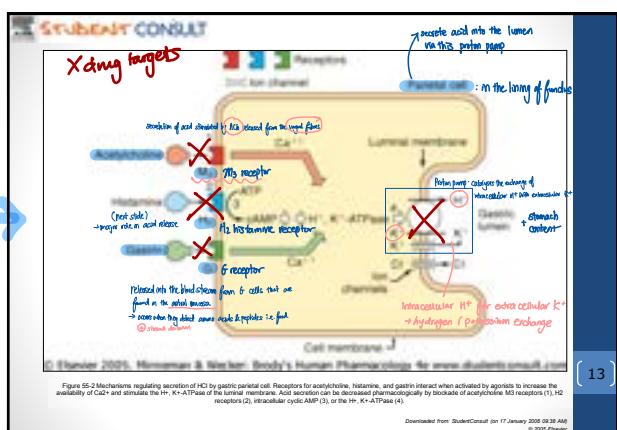
- body weight
- individual number of parietal cells
- time of day (circadian rhythm)

works of somatostatin negative feedback signal acid production to stop

Gastric physiology (II)

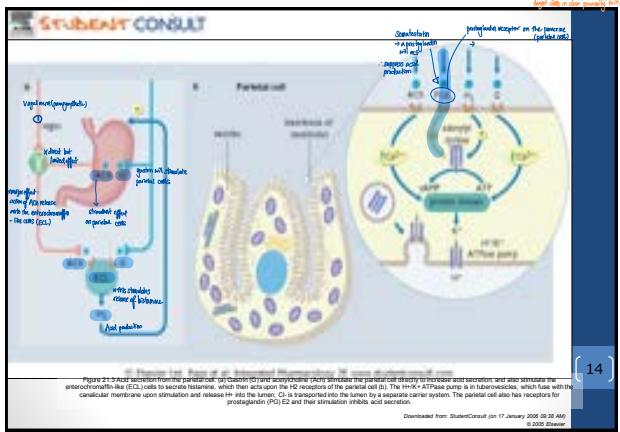
- "acid"**
 - Secretion of H⁺ from the parietal cells is stimulated by histamine, gastrin & acetylcholine (ACh)
- Gastrin
 - produced in response to vagal stimuli, rise in pH and ingested protein & calcium → chemical stimulation from food contents
 - stimulates growth of gastric mucosa → a protective function
 - negative feedback: gastrin production decreases in acid conditions
- Within the parietal cell H⁺ is produced via the proton pump, exchanges H⁺ with K⁺ in the gastric lumen

[12]



Xdrugs targets
acid secretion can be blocked pharmacologically by blocking these receptors or blocking the intracellular cyclic AMP (enzyme reaction) or by blocking the proton pump

[13]



Summary

- Parietal cell produces acid & directly stimulated by

- Vagus nerve – Acetylcholine (M_3 receptor)
 - Due to thought, sight, taste or smell
- Gastrin (G receptor)
 - Due to contents of stomach \rightarrow acidic P⁻
- Histamine (H_2 receptor)
 - Stimulation of ECL cells by Gastrin & Vagus nerve
- Somatostatin
 - Negative feedback due to contents of duodenum
 \rightarrow acid production should slow down and stop

15

35

Gastritis / PUD [GU / PV] / drug induced dyspepsia

Upper Gastrointestinal Conditions

- gastric cyto protection
- helicobacter pylori
- PUD - peptic ulcer disease
- dyspepsia

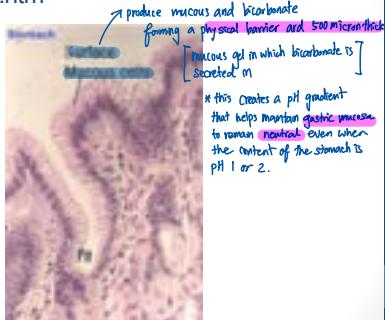
Jeremy Sokhi

j.sokhi@uea.ac.uk

[17]

[18]

<http://www.cytochemistry.net/microanatomy/digestive/stomach.htm>



[19]

[20]

* important feature bc or else we will end up digesting ourselves

Gastric cytoprotection

- Auto-digestion of the stomach is prevented by a thin layer above the mucosa surface
- Complex matrix of bicarbonate and mucus pH 7.0 - unstirred layer concentration of acid removed, taken away by sub-mucosal blood flow built up acid is taken away by sub-mucosal blood flow remove hydrogen ions diffused back from the lumen
- H+ taken away by sub-mucosal blood flow
 - ↓ blood flow → necrosis of mucosa by ↑ H⁺ conc & ↓ O₂
- Stress ulcer in shocked or critically ill patients
 - ↓ blood pressure, poor blood perfusion (decrease in blood flow)
 - this protective mechanism gets disrupted
 - necrosis of mucosa by H⁺ conc ↑ and O₂ ↓ causing stress ulcer

Gastritis → inflammation of the gastric mucosa

- Extremely prevalent amongst population
- Can be asymptomatic (80%) → symptoms would be dyspepsia or indigestion or a burning stomach or feeling sick or being sick
- Gastritis precedes ulceration
- Gastritis - inflammatory response of GI mucosa to H. Pylori → chronic gastritis → PUD → Gastric cancer (80% are caused by this bacteria)
- Gastritis → 40x ↑ risk of PUD & 6x ↑ Gastric cancer

[21]

[22]

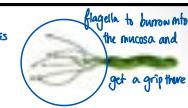
* adapted to survive a very acid environment

* prefer areas w/ moderate acidity : more favour via chemotaxis

* individual acid secreting status will determine the pattern of inflammation

* gastritis that develops

* Protect themselves by hydrolysing urea to produce ammonia, effectively buffer H⁺ ions



* colonisation beneath the mucus layer in the antrum → chronic inflammation, ↓ somatostatin → ↑ gastrin production → ↑ acid as a result of the interference of the colonisation of H. pylori

* ↑ stomach acid production → chronic inflammation in duodenum, H. pylori moves into duodenum and reduces local protection

* Duodenal Ulcer

* individual with this pattern are more likely to get duodenal ulcers

* H. pylori causes gastritis throughout stomach → damaged cells and ↓ acid production ↓ mucosa, which long term → Gastric Ulcer → Gastric cancer (decrease in protection)

* if acid remains in the stomach,

* Helicobacter will not affect a healthy duodenal mucosa, but it will affect if the stomach acid has passed through and damaged it. because it likes acidic conditions

* people with duodenal ulcers have 2x more parietal cells than the average

* normally producing more acid

* some acid will spill over into the duodenum

* and then get H. pylori infection - cause damage

* duodenal ulcer

* Two different types of infection/ulcer depending on your natural acid secreting status.

* for many H. pylori leads to acid secretion largely unchanged (80% are asymptomatic and does not develop either of these ulcers)

1

Helicobacter Pylori

- 50% of population over 60 infected
 - Almost all over 80 → age related
- Some strains more pathogenic than others
- Identified breath test or stool antigen test
 - Given radio labelled urea and CO₂ produced in breath - radio label urea then the CO₂ breath will also be radio labelled as its passing through the stomach
 - Stools need to be stored at -20°C before testing
 - Duodenal Ulcer - >90% H.Pylori infection
 - Stomach (Gastric) Ulcer - 70-80% H.Pylori infection
- Eradication of infection improves healing rates and reduces relapse rates
 - eradication is the cure for H.pylori associated ulcers?
 - >50% to <10% in 3 years
- Eradication is a cure for H.Pylori associated ulcers

individual need to avoid antibiotics over weeks before test to avoid false negativity (re-test should be weeks after treatment)

blood & urinary test
Best but not recommended.

↳ poor sensitivity, false negative don't differentiate w/ past infections (2 years)

[23]

Peptic Ulcer Disease

*important to be aware of when talking to patients presenting symptoms

• 10-15% of the population will suffer from peptic ulcer disease

① Gastric ulcers (GU) rare under 40

② Duodenal ulcers (DU) predominantly males between 20 - 50

Factors

- Gastric hypersecretion → genetic predisposition to produce more acid
- Reduced mucosal resistance - smoking → less natural protection (predispose to these conditions)

• DU - higher than average acid output

• GU - lower mucosal resistance

[24]

*patients can be healed but not cured by suppression of acid secretion. consider H.pyl.

→ DU is due to already due to predisposition to produce more acid than average

→ GU is due to lower mucosal resistance from damaged surface mucosa cells that cannot be replaced.

Prognosis

→ signs and symptoms leading to the disease.

- perforation (holes that develop through the wall of body organ)
 - Bleeding occurs in 10-15% of all patients with PUD
- 5-10% of patients with duodenal ulcer will perforate
 - 1 in 7 of these will die
- 5-10% of gastric ulcers eventually found to be malignant
- 60% of patients with DU relapse after 1 year
- 50% of patients with GU relapse after 2 years

[25]

Risk factors for PUD

↗ Contribution to relapse?

• H.pylori major cause of PUD

*relapse? due to self medication?
treated symptomatically only?
acid levels and the condition rather than eradicating the H.pyl.

• NSAIDS common cause of PUD

- some being treated w/ PUD is carried on w/ use of NSAIDs (ibuprofen, ibuprofen)

• More common in smokers

- ↑ no. cigarettes in a day → ↑ PUD prevalence
- Rate of healing slower in smokers and relapse twice as common
- salts: affect acid secretion - has suppressive effect on parietal cells. So salty diets end up cause a form of gastric atrophy → deal with

• Genetic link with people with parents with PUD 3x more likely

• Stress related to PUD? No strong evidence

[26]

↳ whilst antioxidants vitamins and fresh fruit might protect against specialised gastric cells

Drug Induced Dyspepsia

GI side effect from drugs

- NSAIDS, risk increased further if (aspirin as well)
 - Elderly
 - History of peptic ulcer
 - Smoker
 - Iron tablets
 - Sulfasalazine
 - Some antidepressants e.g. SSRIs
 - Iron preparations
 - Some antibiotics
 - Corticosteroids
 - Potassium (particularly modified release forms)
 - Bisphosphonates → used in treatment of osteoporosis
 - Theophylline
 - Calcium antagonists
 - Nitrates
- association w/ PUD
- may reduce the lower oesophageal sphincter pressure and therefore predispose patients to GORD

[27]

Drug Induced Dyspepsia (II)

• 1/3 of patients with rheumatoid arthritis suffer PUD

• Ibuprofen safest NSAID. ↳ anti-inflammatory / pain killers: need for NSAIDs?

what is the safest choice?

↳ Even patients on 162.5mg aspirin a day ↑ risk 1.5 times

• NSAIDS inhibit prostaglandin synthesis via COX pathway

↗ COX-1 pathway → protective prostaglandins (e.g. GI mucosa) → protect gastric mucosa

↗ COX-2 → inflammatory prostaglandins if we can selectively inhibit COX-2 these are associated w/ less GI side effects than non-selective NSAIDs.

• Safer NSAIDs less inhibitory effect on COX-1

• Celecoxib very little COX-1 activity

↳ this advantage may be lost when patient using low dose aspirin.

↳ safety profiles different on each NSAIDs

mucosa

[28]

Signs & Symptoms of PUD

- Gastric Ulcer
 - Pain on eating (timing important)
 - Epigastric pain → below the sternum and above the naval (the belly area)
 - Duodenal
 - Localised pain occurring between meals and at night (on an empty stomach) → may wake up
 - Relieved by eating (fatty foods may aggravate)
dull pain → pain in the upper abdomen and slightly right to the umbilicus (localized pain - can point painful area)
 - Other symptoms for both
 - Bloating, nausea, anorexia & belching
 - Haematemesis and melena present if bleed occurred
- Easy to prevent →
- blood in vomit dark sticky faeces

[29]

Summary

- Gastritis : inflammation of stomach lining
 - H.Pylori infection
- Gastric ulcer
 - Stomach
 - Prolonged exposure to H.Pylori causing inflammation & gastric atrophy
 - NSAIDs - reduce gastric cytoprotection
- Duodenal
 - Duodenum - post stomach (after the stomach)
 - Caused by → genetic predisposition to excessive acid secretion
 - Excessive acid secretion from stomach due to host factors/h.pylori
- Treatment?
 - www → remote causal agent? → treat the infection → manage acid production

[30]

36

GORD / Functional Dyspepsia

LOS does not close properly allowing acidic contents to flow back upwards.
GORD not treated it can lead to ulcers, bleeding, narrowing, Barrett's oesophagus

Upper Gastrointestinal Conditions

- GORD
- functional dyspepsia

Jeremy Sokhi
j.sokhi@uea.ac.uk

We think this is the cause:

[1]

GORD

reflux of their gastrointestinal/stomach contents into the oesophagus and causing symptoms

- 5-10% of western world adults have symptomatic reflux

<http://www.youtube.com/watch?v=9bnIuKiHdDE>

- Caused by gastric juice and occasionally duodenal contents in oesophagus

Defective Lower Oesophageal Sphincter (LOS) may be most important abnormality

- Factors lowering pressure of the LOS

- Dietary factors → sphincter relaxes
 - fat, chocolate, caffeine, alcohol, large meals
 - Cigarette smoking
 - Endocrine factors
 - from oral contraceptives
 - high levels of oestrogen and progesterone → HRT is associated with GORD (hormonal replacement therapy)
 - Drugs
 - ↓ look at more later



[2]

Reflux can cause symptom of heartburn, burning sensation in oesophagus

* sick burp sensation is quite normal but diagnosed condition GORD only present when it causes frequent severe symptoms or mucosal damage (oesophagitis - inflammation of the oesophagus)

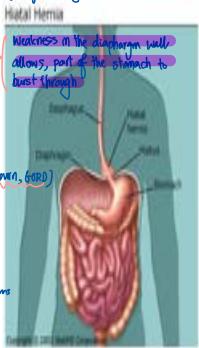
* severity of symptom is not related to the degree of inflammation

→ degree of mucosal damage needs to be checked

Hiatus Hernia

- Part of the stomach is pushed up through diaphragm
 - prevents LOS from closing
 - allowing stomach contents to escape up into the oesophagus
- Hiatus Hernia very prevalent
 - 30-50% of population (in patients w/ heartburn, GORD)
- Majority of patients asymptomatic
- May present as GORD or heartburn like symptoms

hiatal hernia: can affect LOS and worsen GORD
hiatal ring: where oesophagus passes the diaphragm of the lungs



[3]

Drugs & GORD

* important to investigate medication use which explains symptoms

- Drugs which lower the LOS pressure

- Anticholinergics
- Beta-2 agonists
- Calcium channel blockers
- Diazepam
- Nitrates
- Alcohol
- Progesterones
- Oral contraceptives
- Theophylline

[4]

Drugs & GORD (II)

↳ can cause ulceration in the oesophagus

- Drugs which can cause oesophageal ulceration
 - NSAIDs
 - Bisphosphonates
 - Clindamycin (capsule form)
 - Clotrimoxazole
 - Doxycycline
 - Potassium
 - Theophylline
 - Tetracycline
- Antibiotics responsible for 50% of drug induced oesophagitis
 - Esp. Clindamycin in capsule form

* consume drug with full glass of water to prevent prolonged contact with oesophagus
* contact w/ oesophageal wall



[5]

GORD

- Motility of oesophagus may be abnormal in patients with GORD

- Gastric emptying delayed in 40% patients with GORD food is staying longer in the stomach → more likely to move back up the oesophagus.

- Main symptom is heartburn

- May also suffer dysphagia or odynophagia (pain on swallowing)

- Complications include Barrett's oesophagus, haemorrhage, stricture

- Endoscopy only method of diagnosis
Upper GI?

* risk factor for cancer, it's when lining of the oesophagus changes looking more like the intestine

[6]

* key combination may patient need to sit or stand whilst taking and 30min after taking

Antibiotics: responsible for 50% of drug induced oesophagitis esp

esp

esp

esp

esp

* presence of symptoms is thought to originate in the gastro duodenal region in the absence of any organic, systemic or metabolic disease, which would otherwise explain the symptom.

formerly called non-ulcer dyspepsia (NUD)

Functional Dyspepsia (NUD)

→ this is dyspepsia that has been investigated but -

- Half of patients with chronic dyspepsia no evidence of organic disease
- Hypersensitivity to gastric acid? : suggestion
functional dyspepsia is the final diagnosis for more than half the patients with dyspepsia symptoms
- Four groups → aligns to the conditions where there are underlying cause
 - Ulcer like
 - Dysmotility like
 - Reflux like → overlap presentation of heartburn and reflux (had investigation for GORD)
but endoscopy didn't reveal any underlying organic cause
 - Non-specific (generalised symptoms)
physiological factors: anxiety, depression (check w/ patient) → functional dyspepsia
- Eradicate HP if present
- Neutralize acid or prevent acid production (symptomatic relief)
but ↑ would be main treatment
- Periodic monitoring → safety netting bc this could be precursor to a more serious condition at a later date: monitor long term

not necessarily distinct -
may overlap w/
other diseases or
conditions

Symptoms summary

* distinction between functional dyspepsia and the organic diseases are crucial!

	Symptoms	No organic disease	Organic disease
Heartburn → can be located in thorax	Pain immediately with or after food → but chronic, abattored → investigated		GORD
Epigastric pain	Pain immediately with or after food * timing check → investigation if needed Pain between meals or at night or pain relieved by eating * timing check → investigation if needed	Functional Dyspepsia	Gastritis or Gastric ulcer Gastritis or Duodenal ulcer

* ulcer like set of symptoms instead of an ulcer

8

→ not associated w/ risk of cancer, but symptoms are not pleasant and are chronic and thus has impact on quality of life.

31

Upper Gastrointestinal Conditions

Jeremy Sokhi
j.sokhi@uea.ac.uk

[9]

Management

[10]

* Peptic Ulcers

Stomach and Duodenal Ulcer

→ actually and ulcer present : there is an organic cause for the symptom
not to be treated over the counter

- Step 1:**
- Identify & eradicate H.Pylori
 - ↳ Today triple therapy : PPI and 2 antibiotics (omeprazole or clarithromycin)
 - * effective in eradication for 85% of cases
 - * check BNF
 - * alternative for allergy and resistance & interactions & contraindications
 - Stop inappropriate therapy
e.g. NSAIDs alternatives
 - Reduce acid production to reduce gastritis and enable mucosa to repair
 - Block H₂ or Proton Pump
 - may need to prescribe PPI or H₂ Antagonist for 4-8 weeks
 - once ulcer is healed, we test for H.pylori then offer eradication therapy

If no NSAID, no H.pylori → PPI or H₂ Antagonist prescribed

[11]

Management of GORD

→ recognized organic cause and has been diagnosed



[12]

* patients with ulcers untreated, why could that be?

- adherence check ! antacid course
- have they stopped NSAIDs or continued? - could be using OTC NSAIDs
- other disease present? such as crohn's disease or a malignancy

* patient heals but their symptoms recur

- lower dose PPI can be given to control the symptoms

Non-pharmacological management GORD

* they may already have a great diet so do not make assumptions.

- Diet → less pressure in stomach : reduction in gastric distension to help prevent reflux
 - Eat small meals (check what their portions are like)
 - Avoid food which lowers the LOS pressure → so alcohol, coffee, chocolate, salty food
 - Avoid fatty foods - slow gastric motility (delayed emptying of the stomach can aggravate symptoms)
- Avoid eating within 4 hrs & drinking within 2 hrs of going to bed
- Avoid drugs which lower the LOS pressure
- Avoid tight fitting clothes
- Lose weight



can all reduce symptoms

[13]

Non-pharmacological management GORD

- Attention to posture
 - Avoid bending from the waist : bend knees or better to squat to reduce pressure on Stomach Contents
 - Do not lie down after eating - increased exposure of food to oesophageal lining → aggravate that inflammation
 - Nocturnal heartburn symptoms raise the head of the bed (15-23cm)
 - ↳ raise the bed legs rather than using extra pillows (more likely to bend waist → more pressure not减轻)
- Stop smoking
- Reduce alcohol intake



[14]

Management of dyspepsia

→ can be managed OTC
when there are no alarm signs or symptoms present

- Symptomatic
 - Neutralise acid
 - Reduce flatulence (passing gas from the digestive system out of the body passage)
(farting)
 - Prevent dislocation of acid
- All treatments available over the counter

[15]

38 L40

Upper Gastrointestinal Conditions

- therapeutic options
- when to refer: alarming symptoms & signs

Jeremy Sokhi

j.sokhi@uea.ac.uk

[16]

Therapeutic options

[17]

Mechanism of gastric emptying mimicked by the salts

Antacids



→ are salts

when taken it combines w/ HCl or stomach acids and a CO₂ by product is released

- Aluminium, Magnesium, Sodium & Calcium Salts

• Neutralise acid → HCl stomach acid

• Eruption → by-product released gives relief → bring up gas (burp)

• Increase LOS pressure - by gastric alkalisation → possible mechanism of action

• Mucosal protection - stimulate prostaglandin synthesis

Liquids quicker but shorter acting → smaller particle size, greater surface area

• Rapid relief of symptoms of heartburn & indigestion → great neutraliser

• Avoid long term, frequent, continuous use: (NICE guidance)

• Only relieves symptoms in the short term, rather than prevention

• Rennies/Setters/Tums - chewed for best effect

Tablets → best to take 1 hour after a meal when gastric emptying is slow so they remain in the stomach longer (last up to 3hr)

* gastrin is a hormone produced by G-cells in the lining of stomach and the upper small intestine and released into blood circulation

→ food → gastrin stimulates → gastric acid HCl

gastric juice: water, mucus, HCl, pepsin, intrinsic factors

acidic protease

[18]

Antacids (II)

sometimes these side effects can be useful to treat constipation or diarrhoea

- Side effects include constipation with aluminium & diarrhoea with magnesium

• Aluminium binds phosphate in gut → osteoporosis

• Aluminium may be absorbed → neurotoxicity

Acid rebound: Rebound gastric acid secretion with prolonged use

Sodium avoided in patients with hypertension and cardiac problems → relative sodium content in indigestion remedies can be found BNF

- Important drug interactions to consider

• Generally safe in pregnancy

• Sodium content?

→ be mindful of this as it can contribute to fluid retention

.. best to go for no or low sodium product

for many medications not to be taken with indigestion remedies as it will damage the acidic coating

* another common interaction to be aware of is reduced absorption by bindings w/ such as tetracycline and iron based tablets

Well in practice
be mindful
and harmful
common in pregnancy

[19]

Alginates & Dimethicone



Gaviscon (the most famous)

- Alginates (formulated with antacid)

• Form a high pH viscous mass (Raft), trapping air bubbles and CO₂ from the reaction of antacid with the stomach contents

• Floats to top of stomach and protects oesophageal mucosa from stomach contents when reflux occurs.

• <http://www.youtube.com/watch?v=Y52p36qNUUo>

- Dimethicone (simeticone)

• Anti-foaming agent → comes as a tube or tablet

• Reduces surface tension of intragastric air bubble

• Allows bubbles to escape - reducing bloating feeling

→ good for bloating symptom

[20]

H₂ receptor antagonists

- Cimetidine, famotidine, nizatidine, ranitidine
- Compete for H₂ receptor on parietal cells → a larger cluster of cells than acid cells

- PUD

• high healing rates, no reduction in relapse

- GORD

• After 12 weeks, 80-90% of patients with mild oesophagitis improved

• Not effective in moderate to severe GORD

→ only use if inadequate response to PPI



[21]

Gaviscon youtube video: Excess acid from stomach can sometimes travel back up into the oesophagus causing inflammation and pain → acid reflux

The sodium alginate in Gaviscon forms a thick layer, known as raft on top of the stomach content as soon as it makes contact with stomach acid

CO₂ formed by the antacid in Gaviscon becomes trapped in the raft, enabling it to float to the surface of the stomach content

The calcium in Gaviscon links w/ the alginate to strengthen the raft

The raft act as a strong physical barrier to the forward upward pressure of the reflux

Gaviscon raft keeps all the aggressive components of stomach content in the stomach

H₂ Antagonists - Side effects

e.g.: Zantac (Brand) - ranitidine → moved from prescription to OTC

- 1-7% of patients suffer ADRs
 - Only headache and dizziness > placebo
 - Cimetidine - Gynaecomastia 0.2%, impaired libido
 - Ranitidine - Sweating, abnormal dreams
 - Confusional states in elderly
 - ↓ development of breast tissues in men
- Interactions
 - Cimetidine binds to P450 → inhibits metabolism of many drugs
 - phenytoin, theophylline, warfarin as a cytochrome P450 inhibitor
 - epilepsy treatment

we don't really see it prescribed any more

[22]

H₂ antagonists OTC

- Ranitidine (Zantac 75)

• Symptomatic relief of heartburn, dyspepsia & hyperacidity

• 6 days continuous treatment maximum

maximum dose of 2 tablets in 24 hours

• Sub-therapeutic dosages?

↓ before seeing doctor

→ Prescription only:
150mg twice a day
300mg at night

- Patients use them prophylactically

↓ take than before food if patient aware that food is going to cause a problem

[23]

4)

Proton Pump Inhibitors

takes a few days to work... given antibiotics together in the following

- Omeprazole, lansoprazole, pantoprazole, esomeprazole
 - ↑ because destroyed by stomach contents, but needs to reach small intestine
- Enteric coated preparations, absorbed in small intestine
- Blocks hydrogen-potassium ATPase enzyme
- Prolonged suppression of acid secretion
 - 20mg omeprazole causes 80%↓ of acid secretion for 24 hours, 40mg 100%
- Heal ulcers more rapidly than H₂ antagonists. Healing rate same at 8 weeks
- PPIs superior in the treatment of reflux/GORD

↓ licensed to prevent acid aspiration if patient is undergoing general anaesthesia
→ bc of that prolonged suppression of acid secretion

[24]

PPI - Side effects

- Short term side effects include nausea, diarrhoea, flatulence, epigastric pain, dry mouth & headache

• Arthralgia & myalgia → joint or muscle pains

• Concerns about bacterial overgrowth → because so effective on acid suppression

- May increase risk of salmonella or helicobacter

↓ slows absorption

- Lansoprazole before food - food ↓ bioavailability by 50%

- Rebound acid

↓ hypersecretion, protracted dyspepsia after stopping a prolonged treatment

∴ advice is to always use the lowest dose to control patient condition or use it on as needed basis

[25]

5)

Proton pump inhibitors OTC

Esomeprazole - hexamer more common now

- Omeprazole 10mg and 20mg
- Indicated for reflux symptoms in > 18 year olds
- Swallowed whole with plenty of liquid
- 20mg daily until symptoms improved then 10mg
- Refer to GP
 - If after 2 weeks still no relief
 - If treatment required continuously for 4 weeks then refer
- Patient is over 45 and present with new or changed symptom
 - ↓ fast presentation of gastric cancer in these age group :: red assessment



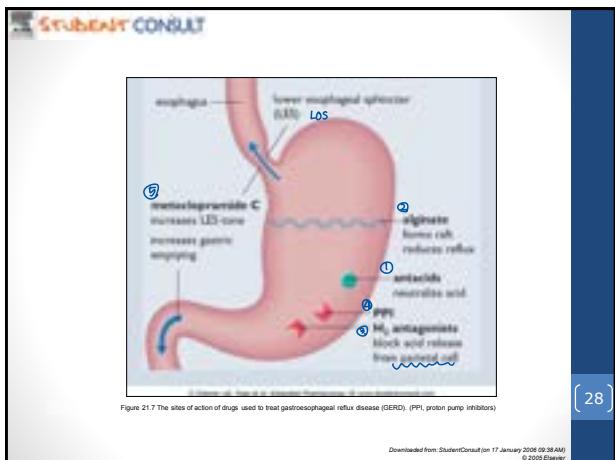
[26]

5)

Other Drugs

- Promotes gut healing by inhibiting the *H. pylori* receptor → can't prescribe as oral as S-100 receptors
- Metoclopramide & Domperidone → both have anti-fundamental dyspepsia, where there are many different set of symptoms → used for GORD
- Sucralfate
 - Polymerizes below pH 4 to form a sticky gel
 - Protective barrier over ulcer (adheres strongly)
 - Physical protection and allows bicarbonate to re-establish pH gradient
- Bismuth → used as 2nd line H. pylori regimen
 - May act similarly to sucralfate
 - Strong affinity for mucosa, especially in ulcer craters
 - May blacken teeth and stools
- Misoprostol
 - Promotes ulcer healing by stimulating protective mechanisms – sometimes used with NSAIDs

[27]



Which treatment - when?

- Functional dyspepsia, Gastritis or PUD
 - Removal of causative agents
 - Dietary changes
 - Symptomatic management
 - H_2 antagonists or Proton pump inhibitors

- GORD

- Lifestyle & dietary changes
 - Alginate products or Proton pump inhibitors
 - NOT H_2 antagonists

↳ not recommended firstline WHY?

→ these are people that have diagnosed conditions with no organic cause
→ in CL, we can treat undiagnosed dyspepsia if no referral criteria are present
→ we just have to be cautious of gastric cancer symptom masking

[29]

When to refer

*if look at CP symptom books → Paul Potter
if product licence referral*

- Patient over 45 with a new/changed symptoms of heartburn or dyspepsia
- Continuous dyspepsia → persistent 5 days, recurrent symptoms. Used OTC 4 weeks
- Increasing severity
- Weight loss, loss of appetite, sign of anaemia
- Pain on exercise - cardiac origin?
↳ pain associated w/ arm - potential heart attack
- Dysphagia
 - Unexplainable pain on swallowing
- Blood in vomit or stools
- Child presenting dyspepsia

[30]

Summary

- Upper GI conditions common
- Most symptoms can be treated by community pharmacist
 - Antacids and H_2 antagonists
 - Rafting agents and PPIs
- Refer
 - When symptoms don't improve
 - Symptoms present for first time over the age of 45

[31]

Reading list

- Major Illness & Minor Disease
- Symptoms in the pharmacy
- Clinical Medicine
- Dyspepsia and GORD
- Guidelines in Practice
<https://www.guidelinesinpractice.co.uk/clinical-area/gastrointestinal>

Edwards
Blenkinsopp
Kumar & Clarke
<http://www.Nice.org.uk>

[32]

42

Constipation

Maria O'Connell

(presented by Evin Coogan)



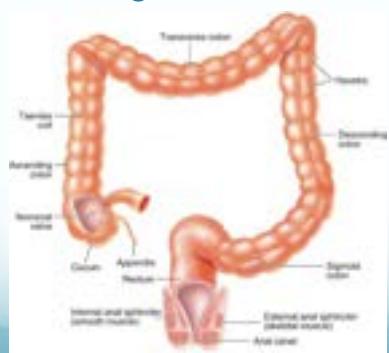
1

Learning Objectives

- Describe stool formation
- Describe epidemiology of constipation
- Describe aetiology of constipation
- Describe pathophysiology of constipation
- Describe symptoms of constipation in children
- Describe specific causes of constipation in older people

2

Large Intestine



3

Functions of the large intestine and formation of feces

- Food passes from **small intestine** and passes along **caecum**, **colon** and into **rectum** by **peristalsis**
- **Water and salts** reabsorbed, resulting in drying → excess dry → constipation
- **Bacteria**
 - ferment **non-digestible polysaccharides**, some metabolites absorbed
 - produce **Vitamin K** and **Biotin (Vit B7)**, which can be absorbed
 - Produce **gases** from undigested polysaccharides
 - Essential for **development** of **caecum** and **lymphatics**
- Stored in **rectum** until **urge for defecation**
- Stools hard when stored in rectum for longer than normal so more water absorbed

4

Constipation

- Definition:
 - "the passage of hard stools (faeces) less frequently than the patient's own normal pattern" → for its individual patient
- **SYMPTOM** – not a disease
- **Difficulty in opening bowels**
 - Going <3 times per week (less than 3a week - quantified as person experiencing constipation)
 - Straining to open bowels more than 25% of occasions
 - Hard or pellet-like stool on more than 25% occasions
- Chronic constipation – generally >12 weeks in preceding 6 months

5

Constipation

- **Common**, affects all ages
 - 1 in 7 adults
 - 1 in 5 older people
 - 1 in 3 children
 - **More common in women than men**
 - **Late pregnancy**
 - **Taking regular medicines** → lots of medication can contribute to the development
- Approx **10 million prescriptions for laxatives** written each year in England

6

Aetiology

Age : young & older more likely

- Diet
 - Low fibre
 - High animal fat - tend to also be low in fibre
 - Inadequate fluid intake - lower moisture in stool
 - Caffeine) substances are diuretics - stools contain less moisture
 - Alcohol
- Poor bowel habits
 - Ignoring urge to defecate → busy, public
- Imaginary constipation

↳ elderly - not eating as much, but still expect to go to toilet as frequently

7

Aetiology

side effect of:

- Medications - several
 - Antacids - Al and Ca salts → bind up the bowel
 - Antispasmodics → many of them contain anticholinergic ingredients, which reduce bowel motility
 - Antidepressants - eg amitriptyline, doxepin ↑
 - Iron tablets eg ferrous sulphate → also bind up the bowel
 - Diuretics e.g. furosemide, bendroflumethiazide → encourage patient to urinate
 - Painkillers - eg codeine, morphine
 - Ca channel blockers eg diltiazem, verapamil
 - ACE inhibitors eg enalapril, lisinopril
 - Anticholinergic eg hyoscine, tolterodine
 - Ulcer healing eg lansoprazole, omeprazole
 - Antipsychotics eg haloperidol, olanzapine
- Laxative abuse

8

Aetiology

- Irritable bowel syndrome → frequency is alternated between constipation and diarrhoea
- Intestinal obstruction
 - Scarring - from IBD, diverticulitis or post surgery
 - Adhesions
 - Intestinal cancers
 - Abdominal hernia
 - Gallstones wedged in intestine
 - Volvulus
 - Foreign bodies
 - Intussusception
 - Haemorrhoids
 - Fissures

9

Aetiology

- Other diseases causing constipation
 - Diabetic autonomic neuropathy → experience damage to the nerve conduction in the bowel area, it can contribute to inefficient bowel movements.
 - Spinal cord injury or tumors
 - Cerebrovascular accident
 - Multiple sclerosis
 - Parkinson's disease
 - Connective tissue disorders
 - Hirschsprung's disease

10

Aetiology

- Mechanical problems of the anus and rectum
 - Eg rectal prolapse → an anatomical issue making patients struggle to have regular bowel habits
- Poor thyroid function : key roles of thyroid hormone in maintenance of regular bowel habit
- Lead poisoning
- Pregnancy
- Travel
- Immobility - bed rest ↑ constipation
 - ↳ a contributing factor

11

Diagnosis

- Medical history
- History of symptoms
 - Normal patterns of defecation → Bristol stool chart
 - Other symptoms
 - Frequency and consistency, faecal impaction, incontinence
 - How long/intense are the symptoms?
 - Impact on daily life
- Medications
- Changes in diet and lifestyle
 - Change jobs
 - Holidays - flights, bus travels "periods of immobility"
 - Diet

12

Constipation in children

- Prevalent in 5-30% children
cause → could be change in diet → breast milk: lactose
- Aetiology often unknown
- Symptoms
 - Infrequent bowel activity**
 - Foul smelling wind and stools
 - Excessive flatulence
 - Irregular stool texture
 - Abdominal pain, distension or discomfort
 - Soiling/overflow**



<http://www.nice.org.uk/nicemedia/live/12993/48741/48741.pdf>

13

Constipation in older people

- Main causes:
 - Age-related decline in GI motility** *↑ GI loses some of its elasticity, less efficient*
 - Decreased mobility
 - Poor diet – low solid and liquid intake
 - Wasting of pelvic floor muscles
 - Side effects of medicines (see earlier)
- Faecal impaction may occur



14

Summary

- Constipation is a **symptom, not a disease**.
- It affects a **high** percentage of the population
- Many factors** can cause constipation
- When constipation has been confirmed **appropriate** steps need to be taken to manage the problem
 - Lifestyle and dietary changes *↑ fibre intake, fluid intake*
 - Short course of laxatives

15

Further reading

- <http://www.bsg.org.uk>
- <https://courses.lumenlearning.com/boundless-ap/chapter/the-large-intestine/>
- <https://cks.nice.org.uk/constipation>
- <http://cks.nice.org.uk/constipation-in-children>
- <http://www.worldgastroenterology.org/guidelines/global-guidelines/constipation>
- <http://www.nice.org.uk/guidance/ta211>
- <http://www.nice.org.uk/guidance/cg99>

16

43
L46

Constipation (Follow on)

TREATMENT IN PRACTICE: GUIDELINES AND CONSIDERATIONS

KYLIE FENWICK

Learning Outcomes

Summarise the [guidelines](#) for managing constipation.

Counsel a patient on appropriate [lifestyle changes](#) to help constipation symptoms.

Discuss the differences in the guidelines for [particular patient groups](#).

Distinguish the [key features](#) of each [laxative group](#).

Describe why one laxative is [chosen](#) over another.

Goals of Constipation Management

1. Achieve an individual's [normal frequency](#) of defecation
2. Establishing regular, comfortable defecation
3. Preventing [laxative dependence](#)
4. Relieving discomfort



Reminder...

(Common only)

Bulking Agents	Ispaghula husk Methylcellulose
Stimulant Laxatives	Bisacodyl (oral and rectal) Senna Dantron (in co-danthramer or co-danthrusate) Sodium picosulfate
Faecal Softeners	Docusate (oral and rectal) Glycerol (suppository) Arachis oil (enema) → mechanism of fluid to early bursts
Osmotic Laxatives	Lactulose Macrogols (inert polymers of ethylene glycol) Magnesium hydroxide and Magnesium sulphate Phosphate (suppository and enema) Sodium citrate (microenema)

What do the guidelines say?

Lifestyle advice: If you are constipated, eat more fruit and whole grain cereals. This improves bowel habit. [See accompanying diagram](#)

Acute (less than 4 weeks)	Chronic (more than 4 weeks)
1. Lifestyle advice and manage any underlying cause	Lifestyle advice and manage any underlying cause
2. Bulk Forming (e.g. Ispaghula husk for 1-3 days)	Bulk Forming
3. (+) Osmotic: Macrogol (if laxative averse , adults)	(+) Osmotic: Macrogol
4. Stimulant (e.g. sennosides)	Stimulant

* depending response:

Gradually reduce and stop after producing a soft, formed stool without straining at least three times per week

over a period of months (backwards treatment)

Review regularly depending on clinical judgement

returning stimulant fast + increasing osmotic laxatives

NICE CKS – last revised Sept 2020

What do the guidelines say?

<small>to optimise time to describe a history of faecal matter within the colon</small>	
Faecal Loading and/or Impaction → occurs when faecal material has remained for a longer period of time and body had greater time for fluid absorption	softening by fluid absorption
Hard Stools (impaction) e.g. senna or sennosides	Soft Stools (loosening) e.g. lactulose
① High dose oral macrogol (eg 40g) can be used to make it softer/stimulant	① Stimulant e.g. sennosides → softening of bowel in 1-2 days
② Stimulant e.g. sennosides → softening of bowel in 1-2 days	② Stimulant e.g. sennosides → softening of bowel in 1-2 days
Response inadequate or slow:	Response inadequate or slow:
Hard Stools	Soft Stools
③ Glycerol alone or glycerol plus bisacodyl suppositories → copious loose bowel movements (from = 15g)	③ Docusate or sodium citrate mini enema → softening bowel movements
④ Response still inadequate:	④ Laxatives (stimulant effects)
⑤ Sodium phosphate or Arachis oil retention enema (one of the most powerful osmotic laxatives)	⑤ Last step would be same as hard stool!
	Consider need for regular laxative to maintain bowel movements.

Lifestyle Advice

- High fibre diet** usually 15g/day (so normal bowel time is 1 day)
- 30g fibre/day with sufficient fluid
 - Caution: obstructive symptoms or fecal impaction (feels of hard)
 - Ineffective in slow-transit constipation or defaecatory disorders
 - Switch from 'white' to 'wholemeal'
 - Slow movement**: fluid softener
 - Limited evidence but also recommend...
 - Increased physical activity → let bowel move encephalically
 - Adequate fluid intake → more if sweating or loose motion
 - 2L water per day
- 

diarrhoea = stools due to pressure from inside

Patient Groups – Opioid Induced

- if patient is constipated**
- AVOID bulk forming laxative** → production of stool by increasing faecal mass [but could reduce bowel continuity] and could result in abdominal cramps & abdominal pain
- ideal laxative choice**
- Osmotic laxative (or docusate) and stimulant laxative
 - Naloxegol → acts upon μ and δ receptors [δ seems to be dominant]
 - Peripherally acting mu-opioid receptor antagonist (PAMORA)
 - Oral: Lubiprostone for constipation
 - If not effective → consider colectomy
 - Methyl-Nortriptiline: PAMORA
 - No evidence submitted to NICE (not recommended)
 - Naldemedine (NICE TA651) Sept 2020
 - PAMORA
 - Oral
 - A new option
- Other Medications**
- Example:**

Understanding PAMORA
 It's possible an antagonist of the opioid receptor in the bowel (constitutive effect)
 Not only effect of constipation it inhibits peripheral side effect

- helping pain in a broader network of the bowel
- blocking of the mu-opioid receptor in the G.I tract
- resulting in constipation

 Mechanism of action for PAMORA = block mu-opioid receptors in the G.I tract
 ... so helps the constipation effect
 ... perhaps the antidiarrhoeal effect for the patient

Antidiarrhoeal: stool passes = loose stools that develops in absence of large intestine near the anus

→ stool passes going to the toilet as long as pain
 → stool goes to the toilet, but delay in passing to the toilet can lead to diarrhoea (loose stools, and faecal, and stool) → bowel becomes too constipated

Patient Groups – Children

- pediatric version of constipation & toddler constipation version is common**
- 1st line → **macrogol** AND negotiated and nonpunitive behavioral interventions suited to persons stage of development
- 2nd line → **add lactulose** e.g. 2 sachets (or 1st line not tolerated) → change to stimulant laxative
- 3rd line → **add lactulose** (or other softening laxative) if macrogol not tolerated
- continuing at maintenance dose** (which may be several months)
 → we don't want to stop the bowels too quickly, as symptoms may reappear & the child may not have emerged from the bowel behaviour
- <http://www.bbc.co.uk/uchebbies/watch/get-well-soon-oh-poo?collection=get-well-soon-songs>

- Some paediatric laxatives are not licensed for children under 2 (e.g. commercial paediatrics informed and documented verbal consent recommended for prescribers)**
- Suppositories and enemas not recommended for use in young care (patients may come last for glycerin suppository)**
- (lavatives may be needed for several months to overcome the bowel behaviour)**

not however, products are dangerous, it is more because there is complexity in using these products

also do we provide them to patients if they have sufficient knowledge on using them?

Patient Groups – Pregnancy and Breastfeeding

- Pregnancy → 20% of patients suffer from constipation because progestrone relaxes the bowel smooth muscle (reduces the motility of the bowel)
- Offer a **bulk-forming laxative**
 - Add or switch to an **osmotic laxative**
 - Can consider a short course of a **stimulant laxative such as senna** → but note this close to term, bc it can stimulate labour contraction
 - Glycerol suppository.
 - [Laxatives in Pregnancy](#)

- Breastfeeding
- Offer a **bulk-forming laxative**
 - Add or switch to an **osmotic laxative**
 - Can consider a short course of a **stimulant laxative such as bisacodyl or senna**.
 - [Glycerol suppository](#)
 - [Laxatives in Breastfeeding](#)

- From here we will look at:
- Medications
 - Clinical considerations
 - Pharmacology/mechanism of action
 - Red flag when responding to symptoms

Bulk Forming

- Fragula husk** e.g. Fybogel 3.5g/sachet
- 1 sachet BD (over 12yrs)
 - Hi-Fibre is the same as original
 - Sachets must be poured into a full glass of water and take straight away
 - Probably after meals
 - Take ½ to 1 hour before or after other medicines
 - Remains effective despite long term use



Methylcellulose

- 500mg tablets e.g. Clevac
- 3-6 tablets BD with at least 300mls liquid
 - Break tablets in the mouth before swallowing.

Do not take just before bed

Ensure good fluid intake is maintained

2-3 days for effect

Adequate fluid intake is essential with osmotic laxatives.

Osmotic Laxatives and Faecal Softeners

- Macrogol** e.g. Movicol, Coarmol, Laxido
- 1-3 sachets daily, in divided doses
 - Sachets to dissolve in 125mls of water
 - Can be high in sodium
 - Do not take other oral medicines 1 hour before or after dose
 - Different flavours available – can mix with diluting squash if desired
 - 1-3 days for effect
- Lactulose**
- 15-45ml daily (single dose or in divided doses)
 - Very sweet tasting liquid – sickly sweet
 - Can cause bloating and colic
 - Caution if intolerance to lactose
 - NO ISSUE FOR DIABETES PATIENTS – not absorbed through gut wall
 - Up to 2 days for effect

- Magnesium hydroxide** e.g. Milk of Magnesia liquid, Dukloxyd chews
- Mainly seen as liquid: 30-45ml PRN
 - Dose to be given at bedtime
 - Can be abused as a purgative (strong effect)
 - Old fashioned – caution elderly
 - Commonly seen OTC (max. 3 days)
 - Research weak (no RCT)
 - Around 3-6 hours for effect

- Docusate** e.g. DulcoEase, Dicotyl
- Up to 500mg daily in divided doses
 - 1-2 hours for effect of tablets, suppositories ~15min
 - Side effects include constipation.
 - May be a cost alternative for people who find it hard to increase their fluid intake.
 - Generally well tolerated

Constipation (Follow on)

Screencast 2 of 2

- Medications
- Clinical considerations
- Pharmacology/mechanism of action
- Red flags when responding to symptoms

Evin Coogan

1

Bulk Forming

Ispaghula husk: e.g. Fybogel 3.5g/sachet

- Hi-Fibre is the same as original!
- 1 sachet BD (12yrs and over)
- Sachets which you pour into a full glass of water and take straight away
- Preferably after meals (but not just before bed)
- Take ½ to 1 hour before or after other medicines
- Remains effective despite long term use → don't act directly on the bowel itself



Methylcellulose: e.g. Clevac

- 500mg tablets
- 3-6 tablets BD with at least 300ml of liquid
- Break tablets in the mouth before swallowing → aids the process of absorbing water
- Do not take just before bed → bc. might swell when in contact w/ water by absorbing the fluid, bulks up the stool and the bulker stimulates distend the colon, which stimulates a bowel contraction
- Ensure good fluid intake is maintained
- 2-3 days for effect

no fluid, effectiveness reduced, may have opposite effects

& at night ppl don't have peristalsis so if taken before bed we are going against the natural peristalsis in the body

2

Adequate fluid intake is essential with osmotic laxatives.

Osmotic Laxatives and Faecal Softeners

- **Macrogol:** e.g. Movicol, Cosmocol, Laxido
 - 1-3 sachets daily in divided doses
 - Sachets to dissolve in 125ml of water
 - Can be high in sodium-Cl in hypertension, heart disease, renal
 - Do not take other oral medicines 1 hour before or after dose
 - Different flavours available – can mix with diluting squash if desired
 - 1-3 days for effect
- **Lactulose**
 - 15-45ml daily (single dose or in divided doses)
 - Very sweet tasting liquid – sickly sweet
 - Can cause bloating and constipation – having to go for a long time
 - Caution if intolerant to lactose – can trigger symptoms
 - NO ISSUE FOR DIABETIC PATIENTS – not absorbed through gut wall
 - Up to 2 days for effect

Magnesium hydroxide: e.g. Milk of Magnesia liquid

- Mainly seen as liquid 30-45ml PRN (over repeated)
- Dose to be given at bedtime
- Can be abused as a purgative (strong effect)
- Old fashioned! Caution elderly → may have rebound effect on an elderly patient
- Commonly seen OTC (max. 3 days)
- Research weak (no RCT)
- Around 3-6 hours for effect

Docusate: e.g. DulcoEase, Diocetyl

- Up to 500mg daily in divided doses
- 12-72 hours for effect of tablets, suppositories → 15min
- Softening agent and a stimulant
- May be a useful alternative for people who find it hard to increase their fluid intake
- Generally well tolerated

3

* they will last?

Suppositories and Enemas

typical counselling on use of:

• Suppositories:

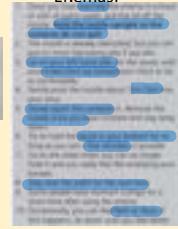
Reposition the rectum with the patient lying on their left side with their knee bent. Gently inserted is the least invasive route in respecting the suppository. When inserted, take the suppository well off the rectal wall and do not let it become dislodged. If it does, gently withdraw the rectal tube and reinsert it again. Gently withdraw the rectal tube and then coming out. Gently pull the rectal tube to the end of your fingers to dislodge the rectal tube. With this method, it is easier to insert the rectal tube.



- glyceryl suppository
- tricacydyl suppository
- docusate suppository



Enemas:



- Fleet enema
- microlax mini
- arachis oil enema (peanut oil)

* check allergy
it is also licensed for faecal impaction

4

* they have quick action, so useful when we need quick response
→ but not everyday choice
* explain why we made this selection instead of oral medication

Stimulant Laxatives (short term use)

- **Senna:** e.g. Senokot
 - Tablets and syrup
 - 7.5-15 mg daily (max. per dose 30 mg daily)
 - Onset of action 8-12 hours → 6-8pm so morning movement
 - Syrup is unpalatable

*patients now
nerves
→ changed
regularly*

- **Dantron:** e.g. co-danthramer or co-danthruse
 - Co-danthramer includes BEG → a macrolol
 - Co-danthruse includes docusate
 - Colours urine red (harmless)
 - Avoid prolonged contact with skin irritation
 - ONLY in terminally ill patients (potential carcinogen)
 - Oral solution *not commonly seen in CP
 - Onset of action 6-12 hours

- **Sodium picosulphate:** i.e. Dulcolax
 - 5-10mg once daily
 - Tablets and syrup
 - Syrup is palatable
 - Onset of action 10-14 hours
- **Bisacodyl:** i.e. Dulcolax (generic version available)
 - Acts on the small intestine
 - 5-10mg once daily, increased if necessary up to 20 mg once daily
 - Tablets act in 10-12 hours
 - Suppositories act in 20-60 minutes.
 - Suppositories can cause local inflammation

5

Prucalopride e.g. Resolor

* promotes good motility

- A selective serotonin 5HT₄-receptor agonist with prokinetic properties
- Should only be prescribed by clinicians experienced in treating chronic constipation after careful review
- 2 mg tablets once daily, review treatment if no response after 4 weeks (Reduced dose in elderly) → elderly - long available discontinued
- Side effects: headache and GI disturbances
- Increased doses will not improve response → max dose 2mg
- 1-2 weeks for effect

bc serotonin based activity
not discussed here

For use in IBS; see associated IBS material

6

~~study sympathetic, parasympathetic and all the possible receptors and its role~~

Peripherally acting mu-opioid receptor antagonists (PAMORA)

Other symptoms:
anxiety, headaches,
shakiness generally
feeling unwell
from getting off opioid

Naloxegol e.g. Movantik Tablets and syrup *tacts peripherally*

- 25mg once daily to be taken *in the morning*
- Counsel on risk of opioid withdrawal (shouldn't occur, but cases have been reported) → *rare cases but key counselling point*
- Tablets can be crushed, mixed with 120ml of water and taken immediately – mixture can be administered via a nasogastric tube, if required
- Take on empty stomach
- When naloxegol therapy is initiated, it is recommended that all *currently used maintenance laxative* therapy should be halted, until clinical effect of naloxegol is determined.
- Works within 12-72 hours

↳ to accurately assess
its benefit

Naldemedine e.g. Rizmolt

- 200mcg tablets OD

* Counsel on risk of opioid withdrawal

7

Pharmacology – bulk forming laxatives

Mostly of plant origin, including non-digestible polysaccharides
Cellulose and other components

- Mechanism of action depends on type
- Typically polysaccharides increase osmolality in gut when broken down, causing water retention
 - Retention of water in the GIT, so expanding and softening the stool
 - Bulkier stools distend the colon
 - Promotion of peristalsis via stimulating colonic mucosal receptors/stretch receptors
 - This leads to acetylcholine release (↑ parasympathetic drive) → better digestion
 - ACh activates muscarinic acetylcholine receptors (mostly M2 and M3 subtypes)
 - Increased peristalsis

Also creates mucus layer in intestinal lining, facilitating defecation

* retention of water in GI tract
leads to expansion and softening of the stool

8

Pharmacology – osmotic laxatives

* Poorly absorbed so act as osmotic agents and increase water retention in the gut lumen

- As hyperosmolar agents, they are absorbed into stool by osmosis, making it softer
- Softer stools are easier to pass!
- Many osmotic laxatives also contain Mg²⁺ (Magnesium)
- Mg²⁺ triggers release of cholecystokinin (CCK)
- CCK increases intestinal secretions and colonic motility

* Decreases transit time through gut

↳ less reabsorption of water fluids.

9

Pharmacology – stimulant laxatives

- Stimulate local reflexes of myenteric nerve plexus of the gut
- Irritate nerve endings in wall of intestine
- Motor effect on gut wall-increases propulsion (drive, push forward)
- Increase secretion of water into the bowel
- Increases gut motility and decreased transit time

Secondary effect

10

Pharmacology – stimulant laxatives

~~specific example~~
Senna

- Anthraquinone laxative → chemical structure
- Combine with sugars to form glycosides
- Glycosides are molecules where the sugar is attached to a functional group via a glycosidic bond.
- Glycoside bond hydrolysed by colonic bacteria to release irritant anthracene glycoside derivatives, specifically sennosides A and B.
- Absorbed and have direct action on myenteric nerve plexus, increasing smooth muscle activity
- Also postulated to increase PGE₂ secretion (which increases gut motility).
- Also reduce colonic water absorption

11

Pharmacology – stool softeners

- Sometimes known as emollient laxatives
- Some work as surface wetting agents/surfactants (e.g. Docusate)
- Reduced surface tension allows water/fats to penetrate stool
- This softens the stool, making it easier to pass
- Docusate also has some stimulant activity (intense)
- Araucaria oil and Paraffin creates a barrier between stool and intestinal wall
- This eases the passage of stool through intestine
- Paraffin no longer popular due to concerns over carcinogenicity

12

Pharmacology – other agents

PAMORAs are **competitive antagonist at intestinal mu-opioid receptors**

Prevent opioid activation of intestinal mu-opioid receptors

Targeting underlying opioid induced side effects ie **reduced GI motility, hypertonicity, increased fluid absorption**

This results in **normal propulsion and peristalsis**

Prucalopride is a **5HT₄-receptor agonist**

5HT₄ receptors are present in **GI tract**, especially **myenteric plexus**

5HT₄ activation leads to increased release of ACh

↑ rest and digest/parasympathetic drive

This increases peristalsis and propulsion

13

Responding to Symptoms

- Children – although there are laxatives licensed for children OTC, they require **initial referral to a GP to have a physical examination**.

- Remember: **Macrogol is 1st line**

- Paediatric dose Macrogol is a **POM** (people will ask to purchase it as **adult** **Macrogol products are P**). → **cannot so refer**

- RED FLAGS:**

- Pain on defecation – **causing suppression of reflex**

- Patient over **40 years** with sudden **change in bowel habits** (no obvious cause)

- Greater than **14 days' duration** (no obvious cause)

- Associated fatigue**

- Presence of blood in stool

- Repeated failure of laxatives

- Suspected laxative abuse



14

Benign prostate enlargement

- Remember **70% of men over 70 have some degree of prostate enlargement.**

- The below image demonstrates the proximity between the prostate (in red) and the rectum beneath.

- Unwitting men may seek to treat the symptom of constipation.

- You will refer repeat requests anyway (and **unexplained constipation in the over 40s**), but refer for **prostate checks**.



* men treat symptom of prostate enlargement
→ constipation
→ they will use long term
(so refer)

15

Summary

- Been through the guidelines
- Discussed lifestyle advice
- Considered specific patient groups
- Focused on specific counselling for each drug class
- Discussed OTC use.

16

References

- Bumps - best use of medicine in pregnancy [Internet]. Medicines in pregnancy. 2020 [cited 14 October 2020]. Available from: <https://www.medicinesinpregnancy.org.uk/Medicine-pregnancy/Treating-constipation-during-pregnancy/>
2. Safety in lactation: Laxatives [Internet]. SPS - Specialist Pharmacy Service. 2020 [cited 14 October 2020]. Available from: <https://www.sps.nhs.uk/articles/safety-in-lactation-laxatives/>
3. Guidance for using an enema: Information for patients [Internet]. Ktbs.nhs.uk. 2020 [cited 14 October 2020]. Available from: <https://www.ktbs.nhs.uk/Information-for-patients/Information-for-patients/Using-an-enema.pdf>
4. How to use Glycerine Suppositories [Internet]. Uhd.nhs.uk. 2020 [cited 14 October 2020]. Available from: <https://www.uhd.nhs.uk/Downloads/pdf/PtGlycerineSuppositories.pdf>
5. Constipation Treatment summary [Internet]. British National Formulary. 2020 [cited 14 October 2020]. Available from: <https://bnf.nice.org.uk/therapeutic-area/constipation/treatment-summary.html>
6. Dealing with over-the-counter stimulant laxatives in community pharmacy | RPS [Internet]. Rpharms. 2020 [cited 14 October 2020]. Available from: <https://www.rpharms.com/resources/pharmacy-guides/dealing-with-over-the-counter-stimulant-laxatives-in-community-pharmacy/>
7. Constipation: Topic A to Z [Internet]. Ckss.nice.org.uk. 2020 [cited 14 October 2020]. Available from: <https://cks.nice.org.uk/topics/constipation/>
8. TAG51: Naldemedine for treating opioid-induced constipation [Internet]. Nice.org.uk. 2020 [cited 14 October 2020]. Available from: <https://www.nice.org.uk/guidance/tag51>
9. TAG39: Naldemedine for treating opioid-induced constipation [Internet]. Nice.org.uk. 2018 [cited 14 October 2020]. Available from: <https://www.nice.org.uk/guidance/tag39>
10. TA211: Prucalopride for the treatment of chronic constipation in women [Internet]. Nice.org.uk. 2014 [cited 14 October 2020]. Available from: <https://www.nice.org.uk/guidance/ta211>
11. CG99: Constipation in children and young people: diagnosis and management [Internet]. Nice.org.uk. 2017 [cited 14 October 2020]. Available from: <https://www.nice.org.uk/guidance/cg99>

17

Diarrhoea

Maria O'Connell

(presented by Evin Coogan)

1

Learning Objectives

- Describe the epidemiology of acute diarrhoea (plus aetiology and pathophysiology)

2

The Bristol Stool Form Scale

	Type 1	Type 2
Long transit (e.g. 100 hours)	Separate hard lumps, like nuts hard to pass	
Type 2	Sausage shaped but lumpy	
Type 3	Like sausage but with cracks on its surface	
Type 4	Like sausage or snake, smooth and soft	
Type 5	Soft blobs with clear cut edges (passed easily)	
Type 6	Raggy pieces with ragged edges, a mushy stool	
Type 7	Watery, no solid pieces	ENTIRELY LIQUID

3

Diarrhoea

- Definition:
 - A change in normal bowel habit resulting in increased frequency of bowel movements and the passage of soft or watery stools
 - May be accompanied by colicky pain
→ as body try expell material, there is increased contraction of the smooth muscle and additional gas causing pain
 - SYMPOTM** – not a disease

4

Diarrhoea

- Acute diarrhoea
 - Abrupt onset of >3 loose stools/day and lasts no longer than 14 days
 - Dietary insults : food, substance struggle to tolerate e.g. alcohol, spicy food
 - Bacterial/viral infection
 - Majority resolve within 2-3 days without specific treatment
** hydration important
* rehydration salt if necessary*
- Chronic diarrhoea
 - Pathological cause
 - Lasts >14 days
 - Possibly flare up of previously diagnosed condition eg IBS
 - Needs further investigation
or inflammatory conditions such as UC or CD

5

How common is diarrhoea?

- Difficult to determine as many cases self-limiting and not reported
→ home treatment
- Children under 5: most common?
• Acute gastroenteritis most common
• Between 1-3 bouts per year
** other habits
* under developed GI tract*
- Adults
 - Just under 1 episode/yr
 - 22% food related
• wrongely treated
 - Traveller's diarrhoea → countries where sanitation the same as we are used to

6

Mortality/morbidity

- Mortality from acute diarrhoea **declining globally** *better treatment access to rehydration salts etc*
- Second highest cause of childhood mortality**
- Age and nutritional status are most important host factors in determining severity and duration *age & nutritional status*
- The younger the child, the higher risk for severe, life-threatening dehydration \rightarrow smaller body \therefore less fluid in body in first place
 \rightarrow more prone to develop more complication from acute diarrhoea
 \rightarrow immune system more prone

7

Pathophysiology

- Change in the balance between the absorption and secretion of water and electrolytes *fine balance*
- Due to
 - Osmotic force that drives water into the gut lumen, eg after ingestion of nonabsorbable sugars e.g. foods that contain inositol, xylitol, sorbitol **celiac disease, cystic fibrosis, pancreatic insufficiency*
 - Proportional to the intake and **responsive to fasting** *\downarrow condition will improve*
- OR
- Enterocytes actively secreting fluid eg **enterotoxin-induced** diarrhoea *\downarrow gut cells lining the mucosal*
 - Not responsive to fasting
 - Ion transporters activated by eg bacteria resulting in pathogens
 - Invasive enterocytes or *(mucosal lining)*
 - producing enterotoxins which damage cells or
 - inducing cytokine secretion to produce prostaglandins which stimulate secretion \rightarrow extra secretion of fluids and electrolyte

\rightarrow examples of conditions where patient digestive symptoms are explained
- reducing sugars that are non-absorbable
 \rightarrow build up of non-absorbable sugar in GI tract \therefore ↑ osmotic force
Severity of the Symptom is proportional to the intake

8

Mechanism of diarrhoea

- Bacteria causing diarrhoea
 - Invasive
 - Directly attack mucosal cells** which causes diarrhoea
 - Stools may contain **blood and pus**
 - Fever** *\checkmark \rightarrow usually cooked chicken*
 - Eg **Shigella, Salmonella, Yersinia, Enteroinvasive E coli**
 - Non-invasive
 - Do not directly damage gut**
 - Bacteria **produce enterotoxins** that disrupt secretion of water and electrolyte
 - Watery diarrhoea** *\times different reason*
 - Eg **S aureus, B cereus, C perfringens, Enterotoxigenic E coli**
- Virally-induced diarrhoea
 - Mechanism not fully understood
 - Enterocytes become secretory** resulting in watery diarrhoea

9

Diagnosis

- Symptoms
 - Accompanying symptoms *temperature/fever, presence of blood in the stool, how quickly was the onset, total absence of stool formation?, trigger factor?, excessive alcohol?, drugs?, consuming contaminated water, time, intensity*
 - Rapid onset
 - Absence of stool formation?
- Trigger factors
 - "bad"/unusual food; alcohol; drugs; contaminated water
- Time/intensity *
 - Dehydration in major risk groups *very young or very old or other medical condition \rightarrow dehydration status zones*
- Fecal studies
 - Identify pathogen** *came back from a foreign country \rightarrow maybe after antibiotics*
 - Serum albumin
 - Fecal alpha 1 antitrypsin *tests to check presence of any protein loss as part of the diarrhea be it would suggest damage to GI tract*
 - Intestinal biopsy *\times not a specific test but can help assist diagnosis*

10

Common causes of diarrhoea

- Infants
 - Infectious gastroenteritis, toddlers diarrhoea, food intolerance, coeliac disease** *brought due to very children play (underground tick them)*
- School age children
 - Infectious gastroenteritis, Drugs (Antibiotics)**
- Adults
 - Infectious gastroenteritis, IBS, IBD, Drugs, XS alcohol and spicy food, coeliac disease**
- Older people
 - Infectious gastroenteritis, large bowel cancer, faecal impaction, drugs, ischaemic colitis** *more with age*

11

pseudo diarrhoea:
watery diarrhoea can split over the sides of the impacted material
 \rightarrow actually patient suffering from constipation

Typical organisms causing diarrhoea

- Children < 5 yrs
 - Rotavirus** most common: onset 12-48 hr
- Adults
 - Campylobacter** (onset 2-5 d) most common, followed by rotavirus
- Other causes
 - E.coli** (1-6 days), **Salmonella** (12-24 hours), **Shigella** (1-7 days), **Clostridium difficile** (usually starts during AB therapy), **Clostridium perfringens** (12-18 hours), **Bacillus cereus** (1-16 hours), **Staphylococcus aureus** (1-7 hours)

For more information on the typical organisms that cause diarrhoea visit
<https://www.fda.gov/food/consumers/what-you-need-know-about-foodborne-illnesses>

12

Examples of drugs that can induce diarrhoea

- Antibiotics – most common- broad spectrum
→ bc. disruption of natural balance of bacteria within GI tract
- Laxatives
- Metformin
- Ferrous sulphate (iron)
- NSAIDs
- Colestyramine
- Antacids – Mg Salts → has laxative effects unlike aluminium & calcium antacids
- Beta blockers
- Digoxin
- Misoprostol

13

Preventing diarrhoea

- Good hygiene: Wash hands
 - After visiting the toilet
 - Before touching food
 - After gardening
 - After playing with pets
 - Between handling raw and cooked food

Ejemot, R et al. (2015). "Hand washing promotion for preventing diarrhoea." Cochrane database of systematic reviews 9 (Art no:CD004265).

14

Summary

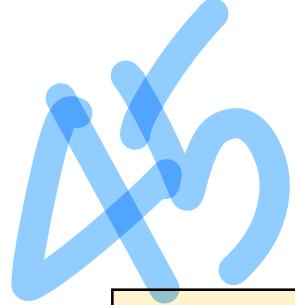
- Diarrhoea is a change in normal bowel habit resulting in increased frequency and soft or watery stools
- Considerations in treatment include
 - Age, frequency, duration
 - Assess dehydration risk
- Anti-motility drugs have a role in the management of diarrhoea

15

Further reading

- Food Standards Agency : www.foodstandards.gov.uk
- Health Protection Agency: www.hpa.org.uk
- <http://www.neli.org.uk/IntegratedCRD.nsf/e67b3914fbe8da658025755c0062cd62/154ec3f29da593f9802573cb00395e08?OpenDocument&Highlight=0 diarrhoea>
- <http://www.pharmaceutical-journal.com/learning/learning-article/treating-acute-diarrhoea-in-adults/10027800.article>
- <http://cks.nice.org.uk/diarrhoea-adults-assessment>
- <http://cks.nice.org.uk/diarrhoea-prevention-and-advice-for-travellers>
- <http://www.who.int/mediacentre/factsheets/fs330/en/>
- <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC152597/>
<https://medlineplus.gov/ency/patientinstructions/000121.htm>
<http://www.nhs.uk/Conditions/Diarrhoea/Pages/Treatment.aspx>

16



DIARRHOEA (FOLLOW ON) SIMPLE DIARRHOEA (NOT LINKED TO IBS)

Evin Coogan

1

LEARNING OUTCOMES

- List treatment options for different patient groups
- Describe the pharmacology of the treatment options
- Describe counsel points for patients on the common treatment options
- Describe how to apply the guidance to over the counter requests
- List appropriate non-pharmaceutical advice
- Detail and identify the signs of dehydration
- Describe the cause, symptoms and treatment of Clostridioides difficile infection (C. Diff)

2

TREATMENT – ACUTE (ADULTS)

- Treatment aims:
 - Prevention and reversal of fluid and electrolyte depletion
 - Management of dehydration (if present)
- Most settle spontaneously (at around 3 days) *72h*
- Oral rehydration therapy (ORT) → *rehydration salt*
- Rapid control of symptoms required:
 - Loperamide *opiate agent, reducing gut motility*
 - Prescribed dose* >12 years: Initially 4 mg, followed by 2 mg after each loose stool (for up to 5 days max); usual dose 6–8 mg daily; maximum 16 mg per day (**8 caps**)
 - GSL/P dose* > 12 years: Initially 4mg, followed by 2 mg after each loose stool (for up to 48 hours max); usual dose 6–8 mg daily; maximum *12 mg* per day (**6 caps**). *different times all same*

3

TREATMENT – ACUTE (ADULTS)

- Eat as soon as able (bland) – soups, bread, pasta, rice, potatoes
- Avoid coffee, alcohol, carbonated drinks → *these are diarrhoeas*
- Avoid anti-motility drugs in severe gastroenteritis or dysentery
- These are more serious – *blood/mucus in stools, fever*.
- The concern is that Loperamide can prolong the infection
 - Prevention and treatment of fluid and electrolyte depletion is primary importance

4

ORAL REHYDRATION THERAPY

- I.e. **Dioralyte** (if under 2 years only *under medical supervision*).
- Mainstay of treatment for acute diarrhoea
- To prevent or correct dehydration
- Maintain appropriate fluid intake once rehydration established
- Mix sachet with 200ml water. *gradually if more or less, during balance* *.. not some level of hydration we are aiming*
- Dioralyte Relief: Contains *rice starch* (bulks)
- If under 1 year old only under *Doctor*
 - Sachets not contain *bulks* *.. return more water with coffee*
- Severe cases require hospitalization for IV fluids.

prescription doses, not OTC

5

TREATMENT – CHRONIC (>4 WEEKS)

- Determine underlying cause and treat as appropriate
- Foreign travel
- Laxative abuse
- Medications-PPIs, antibiotics *ORT and Loperamide while investigations ongoing*
- Immunocompromised → *diarrhoea prolonged*
- Family history of IBS/coeliac disease
- Lactose intolerance (if worsened by dairy), excess caffeine/sorbitol
- Refer for specialist investigations

6

PREGNANCY AND BREASTFEEDING

Lack of evidence of harm doesn't mean it's okay

- Loperamide manufacturers advise to avoid in pregnancy (no info available).
- Weigh up risks to both baby and mum (if severe enough refer)
- Loperamide appears in breast milk \rightarrow may need IV fluids
- Amount probably too small to be harmful \rightarrow not enough evidence
- ORT and fluids essential – avoid dehydration
- If symptoms warrant Loperamide, refer in both instances from community pharmacy

* not to supply OTC (not licensed)
* pharmacist prescribers could supply & should refer to option

7

CHILDREN

- Feeding babies: continue with normal milk feeds \rightarrow antibiotic or breast milk with help to babies many pathogens
- Children: encourage plenty of fluids
- Use ORT \rightarrow loperamide
- Anti-diarrhoeals not recommended by NICE (BNF states doses for children, but not licenced in <12 year olds for most products, so never sell from community pharmacy).
- Preventing spread of diarrhoea
 - Careful washing and drying of hands after using toilet, nappy changing and before meals
 - Don't share towels
 - 48h exclusion from school following cessation of symptoms
- Avoid swimming for 2 weeks following last episode of diarrhoea

8

OTHER MEDICINES TO NOTE

- Co-Phenotrope
 - Atropine and Diphenoxylate (anti-cholinergic and opioid).
 - Licensed as adjunct to rehydration in acute diarrhoeas
 - Initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled.
- Kaolin and Morphine
 - Not evidence based: such small amounts of Morphine
 - No evidence for Kaolin in acute diarrhoeas
 - Historical use – elderly patients
 - Potential for abuse
- Bismuth subsalicylate \rightarrow pink solution / tablets seen in CP
 - E.g. Pepto-Bismol (never in less than 16 years old due to Reye's syndrome)
 - Limited evidence – not recommended in BNF or by NICE
 - Inhibits intestinal fluid secretion
 - Suppresses intestinal inflammation
 - Bactericidal action

Probiotics	Live bacteria
Compete for available nutrients with pathogen	Insufficient evidence for use on NHS

9

HOW LOPERAMIDE WORKS?

PHARMACOLOGY-LOPERAMIDE

- Synthetic opioid analogue – pethidine congener which doesn't readily pass BBB \rightarrow no primary ^{chemical structure} \rightarrow ^{chemical structure}
- Binds to mu-opioid receptors in gut wall
- This inhibits Acetylcholine (ACh) and Prostaglandin release
- ACh is the main excitatory neurotransmitter in the GI tract
- ACh binds to muscarinic/nicotinic ACh receptors, increasing parasympathetic activity \rightarrow less output

10

PHARMACOLOGY-LOPERAMIDE

- ACh inhibition leads to:
 - Decreased propulsive peristalsis
 - Decreased sensitivity to rectal distension
 - Increased sphincter tone of the ileocecal valve and anal sphincter
- Prostaglandin inhibition leads to:
 - Reduced gut secretions
 - Reduced gut motility (both mainly via inhibition of PGE2)
- Increases intestinal transit time (enhancing water and electrolyte reabsorption)
- Morphine/codeine are also sometimes used to treat diarrhoea
- As opioids, they share this mechanism of action
- Problems with abuse/dependence

readily cross BBB as this zone remains

11

The Large Intestine

Junction of small intestine & large intestine
 → role is to limit the rate of food passage, but the colon
 → prevent reflux of digestive material. If large intestine back into small intestine
 → fails, leading to constipation. If no normal muscle tone it leads the rate of passing of digestive material
 → reduce gut motility, slowing reabsorption of water/electrolytes

12

PHARMACOLOGY OF CO-PHENOTROPE

↳ opioid + antimuscarinic

- 100 parts diphenoxylate HCl to 1 part atropine sulphate
- Diphenoxylate (exactly the same mechanism as loperamide)
 - Synthetic opioid – pethidine congener; does not readily pass BBB
 - Does not usually have CNS activity; large doses lead to typical opioid effects
 - Insoluble salts mean that there is no potential for misuse by injectors
- Atropine – anti-cholinergic action
 - Muscarinic ACh receptor antagonist
 - Reduction in ACh reduces parasympathetic drive
 - GI motility is inhibited
 - Effect not marked as several excitatory transmitters, including Ach are important in the function

13

RESPONDING TO SYMPTOMS

- RED FLAGSTO REFER
 - Recent travel abroad (especially to intermediate/high risk areas)
 - Blood or mucus in stools
 - Associated with severe vomiting and fever
 - Severe or persistent abdominal pain
 - Pregnancy or breastfeeding
 - Signs of dehydration (covered later)
- Referral to GP when duration exceeds:
 - >1 day: Infants under 1 year
 - >2 days: Children under 3 and frail/older people
 - >3 days: Children over 3 and otherwise healthy adults

14

NON-PHARMACOLOGICAL ADVICE

- ANote: Absorption of medicines may be affected (sick day rules) → advised to stop taking them
- Drink plenty of clear fluids,
- Avoid drinks high in sugar, alcohol or caffeine
- Avoid carbonated drinks – cause bloating
- void milk and milky drinks
- Eat light, easily digested food
- Advise not to return to work until they have been symptom-free for 48 hours.
- Close attention to hygiene,
 - Hand washing
 - Cleaning of toilet seats, flush handles and basin taps

15

TRAVELLER'S DIARRHOEA

- Definition
 - Three or more loose stools in 24 hours with or without at least one symptom of cramps, nausea, fever, or vomiting
- Causes
 - Bacteria (most common, esp E coli); viruses; protozoan parasites
 - Comparatively lower food hygiene and sanitation facilities in destination →
- Prevention
 - Food, water, and personal hygiene →
 - Vaccines (hepatitis A, typhoid and cholera)
- Treatment →
 - Maintain hydration
 - Loperamide
 - Antibiotic treatment? → e.g.) ciprofloxacin (broad spectrum antibiotic)
- National Travel Health Network and Centre (NaTHNaC) website → www.natnac.org

↳ can be used to communicate w patients

16

SIGNS OF DEHYDRATION

Sign	Definition	Severity
Decreased urine output	Decreased urine output for age	Mild
Decreased turgor	Decreased skin turgor	Mild
Dry mucous membranes	Dry mucous membranes	Mild
Decreased skin elasticity	Decreased skin elasticity	Mild
Decreased oral secretions	Decreased oral secretions	Mild
Decreased眼泪 (tears)	Decreased tears	Mild
Decreased skin turgor	Decreased skin turgor	Moderate
Decreased skin elasticity	Decreased skin elasticity	Moderate
Decreased oral secretions	Decreased oral secretions	Moderate
Decreased眼泪 (tears)	Decreased tears	Moderate
Decreased skin turgor	Decreased skin turgor	Severe
Decreased skin elasticity	Decreased skin elasticity	Severe
Decreased oral secretions	Decreased oral secretions	Severe
Decreased眼泪 (tears)	Decreased tears	Severe

17

A

when dehydrated these can further impair patient kidney function

not exhaustive
there are other meds e.g.) the anti-diabetics

↳ dehydration increases the risk of misfrom causing basic actions

18

C. DIFF INFECTION

- C.Diff bacterium usually present in gut
 - Broad spectrum antibiotics upset microbiome-allowing C.Diff to flourish
 - Toxins damage lining of colon
 - Highly contagious diarrhoea can develop, can be fatal
 - Risk factors include broad spectrum Abx use, >65 years old, prolonged stay in hospital care home, immunocompromised etc
 - Vancomycin 125mg-500mg every 6 hours for 10 days
- extensive producing bacteria & toxin
it produce can delay the long of the
body to recover the bacteria*
- bacteria not good bacteria*

SUMMARY

- Describe treatment for different patient groups
- Counsel patients on the common treatment options
- Apply the guidance to over the counter requests
- Give appropriate non-pharmaceutical advice
- Detail and identify the signs of dehydration

19

20

REFERENCES

- <http://cks.nice.org.uk/diarrhoea-adults-assessment>
- <http://cks.nice.org.uk/diarrhoea-prevention-and-advice-for-travellers>
- <https://www.medicines.org.uk/emc/>
- <https://bnf.nice.org.uk/>
- <https://www.pharmaceutical-journal.com/learning/learning-article/treating-acute-diarrhoea-in-adults/10027800.article?rnpass=false>
- <https://pathways.nice.org.uk/pathways/diarrhoea-and-vomiting-in-children/diarrhoea-and-vomiting-in-children-overview#content=view-node%3Anodes-advice-for-parents-and-carers>
- <https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/2...-Covid-19-Diabetes-Sick-Day-Rules-Type-1-MD-06042020.pdf>
- <https://www.nihseneca.org.uk/guidance/cg84/chapter/Recommendations - dehydration assessment.html>

21

Irritable Bowel Syndrome

Evin Coogan
e.coogan@uea.ac.uk

1

Learning objectives

- Describe the epidemiology of irritable bowel syndrome (IBS)
- Describe the aetiology of IBS
- Describe the pathophysiology of IBS
- Describe the symptoms
- List the common treatments
- Describe the pharmacology of the common treatments
- Describe red flag symptoms for IBS

2

Epidemiology

- Onset most common ages 20-30
- X2 more common in females than males
- Estimated to affect 10-20% of population (but is under-reported)
- X2 the risk among 1st degree relatives
- Lack of reliable prevalence data

self managed

3

Aetiology

- Exact cause of IBS is not understood
- Food intolerances (eg Lactose/Gluten) are precursors to IBS
- No lesions are present (i.e. gut is not damaged/diseased)
- Post infective bowel dysfunction, gut hypersensitivity, altered colonic motility and heightened pain sensation all implicated.
- Stress commonly implicated

Infection of bowel e.g. gastroenteritis 1 in 6 cases

4

Pathophysiology

- Structurally the gut is normal
- IBS is a 'functional' GI disorder
- No detectable pathology using standard tests
- Blood tests/stool samples/colonoscopy may be used to rule out other conditions → differential diagnosis
- Functional conditions require symptom management

5

Symptoms

- Abdominal cramping
- Diarrhoea/constipation/alternating
- Flatulence
- Bloating
- Urgency to defecate
- Acid indigestion
- Nausea
- Lethargy
- Eating may worsen symptoms
- Passing mucus in stools

6

Diagnosis

- Abdominal pain present for at least **6 months**
- **Relieved by defecation**, or:
- **Increased/decreased bowel frequency or stool form**
- Plus at least 2 of the following:
 - **Abdominal bloating/distension**
 - **Altered stool passage (straining, urgency, incomplete evacuation)**.
 - **Worsened by eating**
 - **Passing mucus**

7

Diagnosis

- In secondary care, the Rome IV criteria are sometimes used
- Abdominal pain **1 day per week in last 3 months**
- Symptoms began at least **6 months prior**
- Alongside >2 of the following:
 - **Related to defecation**
 - Change in **stool frequency**
 - Change in **stool form**

8

IBS classifications (Rome IV criteria)

- IBS-C
more
≥25% of stools are types 1/2, *less*
≤25% are types 6/7
 - IBS-D
 - IBS-D
more
≥25% of stools are types 6/7, *less*
≤25% are types 1/2
 - IBS-M (*mixed*)
more
≥25% of stools are types 1/2 AND ≥25% of stools are types 6/7
 - IBS-U
- Person has IBS, but bowel habits can't be categorised as above

9

Treatments

- Antispasmodic drugs
- Antidepressants
- Laxatives
- Loperamide
- Linaclootide

10

Antispasmodic drugs

for IBS-D & abdominal pain

- Preferable to use direct acting **smooth muscle relaxants**:
- **Alverine Citrate** 60-120mg up to TDS
 - **Mebeverine** 135mg TDS (20 mins before food) or 200mg BD for MR preps
 - **Peppermint oil capsules**, 1-2 caps up to TDS
- Hyoscine butylbromide** and **Dicycloverine** can also be used but tend to have more **antimuscarinic effects** → *try to avoid where possible*
- C/I in intestinal obstruction or paralytic ileus
- ↳ be strong down mobility can be maine problem if patient already got an intestinal obstruction or paralytic ileus (rare will be meeting already)*

11

Antidepressants

Use is **unlicenced**, for people with **IBS pain**
People usually **not responded to typical treatments**
Doses given are **lower** than you would see for mental health uses
TCA, e.g. **Amitriptyline** 10-30mg at night
SSRI 2nd line (Sertraline, Citalopram, Fluoxetine)
**All off label*
BSG doesn't specifically recommend one
Pain **modulatory effects/****peripheral effects** on GI function
COUNSEL patients as they may be shocked when reading PIL!

12

Laxatives

- For IBS-C
- Laxatives from any class may be used (aside from Lactulose) *(can increase gas)*
- Lactulose can increase gas production and worsen symptoms
- Dose should be titrated according to symptoms
- Review laxative advice from constipation screencast
- Avoid prolonged stimulant laxative use!

13

Loperamide

- For IBS-D
- All material covered in diarrhoea screencast *>12 years old w/o IBS ✓*
 - Remember, P/GSL versions of Loperamide can be used for acute diarrhoea in IBS, but only for patients **>18 years old**
 - Must** have been diagnosed with IBS
 - Only for attacks lasting up to 48 hours (refer if longer)
 - Can be used for 2 weeks maximum, as long as **individual bouts** are less than 48 hours

14

Linaclotide

- For moderate to severe IBS-C in adults
- Person must have had IBS-C for at least **12 months**
- Should only be used if max tolerated doses of laxatives haven't helped
- 290mcg once daily 30 minutes before food**
- Avoid in **GI obstruction/IBD** *↳ be laxative effect*

15

Pharmacology

- Laxative pharmacology covered in constipation screencast
- Loperamide pharmacology covered in diarrhoea screencast
- Antidepressant pharmacology covered in mental health materials
- We will focus on **antispasmodics** and **Linaclotide**

16

Pharmacology-antispasmodics *IBS-D*

- Exact mechanism of action for **Mebeverine** unknown
- It specifically acts on smooth muscle cells
- Blocks voltage operated sodium channels
- This prevents build up of intracellular calcium *→ will have reduction in contractility of smooth muscle*
- This **reduces symptoms of colonic hypermotility**

17

Pharmacology-Linaclotide *IBS-C*

- Guanylate cyclase-c (GC-C) agonist
- GC-C activation leads to increased production of cyclic guanosine monophosphate (cGMP)
- Increased cGMP stimulates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel
- CFTR ion channel increases **secretion of chloride and bicarbonate into the intestinal lumen** *→ increase moisture content of GI lumen*
- GI transit increased
- GC-C → ↑ cGMP → ↑ CFTR action → ↑ intestinal chloride+bicarb

18

Red flag referral criteria

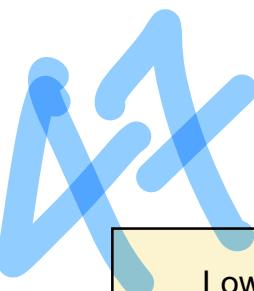
- Unintentional weight loss
- Unexplained rectal bleeding *diagnosed hemorrhoids, anal fissure → explained bleeding*
- Family history of bowel/ovarian cancer
- Loose stools for >6 weeks in patients >60 years old
- Anaemia
- Elevated inflammatory markers (?IBD)
- Abdominal/rectal masses → suggestion of malignant tumor

19

References

- <https://cks.nice.org.uk/topics/irritable-bowel-syndrome/prescribing-information/linaclootide/>
- <https://theromefoundation.org/rome-iv/rome-iv-criteria/>
- <https://go.drugbank.com/drugs/DB08890>
- <https://patient.info/doctor/irritable-bowel-syndrome-pro#nav-5>

20



Lower Gastrointestinal Diseases

Diverticular Disease

Evin Coogan



1

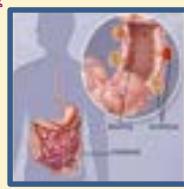
Learning outcomes

- Describe the epidemiology of diverticular disease
- Describe the aetiology
- Describe the pathophysiology
- Describe the symptoms
- Describe the management of diverticulosis and diverticulitis

2

Diverticular disease

- Presence of diverticula (plural diverticulum)
 - pouches protruding outwards from the large intestine wall
 - small mucosal herniations protruding through intestinal layers and smooth muscle
- [\(2.11\)](http://www.youtube.com/watch?v=6kg5wZQfADQ)
- Diverticulosis
 - condition where uninflamed diverticula
 - Usually asymptomatic
- Diverticular disease
 - symptomatic
- Diverticulitis
 - condition where one or more inflamed/infected diverticula



3

Epidemiology

- Diverticular disease is very common, particularly in industrialised countries
 - Westernisation increases incidence
 - Lack of fibre
- Prevalence
 - similar in males and females
 - increases with age
 - rare in people aged <40 years
 - 1/3 people >65 years, >65% people >85 yrs
- 80–85% patients with remain asymptomatic



4

Epidemiology of diverticulitis

- Approx 5% patients with diverticulosis develop diverticulitis
- 15-25% patients with diverticulitis develop complications requiring surgery. Mortality associated with these
 - Abscess formation → localized collection of pus
 - Intestinal rupture
 - Fistulas (inflammation/abscess causes passageway) *(e.g. from one part of an anatomy to another part that shouldn't be connected e.g. large intestine to bladder to vagina)*
 - Peritonitis (lining abdominal wall and organs in abdomen) → infection/inflammation
 - Massive bleeding
- More common in patients who are immunocompromised, on anti-inflammatories or have severe co-morbidities

Aetiology

- Causative agents unknown
 - ↑ tone is the opening inside large intestine*
 - ↑ increased intraluminal pressure and weakening of muscle wall thought to be a primary cause*
 - Abnormal colonic motility e.g. IBS, use of opioid
 - Defective muscular structure
 - Changes in collagen structure eg in aging.
- Factors thought to be involved:
 - Genetics
 - Left-sided diverticula predominate in the west (sigmoid colon)
 - Right-sided predominant in Asians
 - Dietary factors
 - Associated with a low fibre diet and constipation
 - Associated with obesity → in younger population

5

6

Pathogenesis



- Colonic muscular hypertrophy results in narrowing of lumen and formation of small chamber with high pressure and subsequent diverticula
→ generally take place at an area of weakness along the lining of the intestine
↳ means weakened wall - increased pressure will cause lumen to expand → herniation will develop from lumen & formation of diverticular pouch
- Diverticulitis**
 - fecal material or undigested food collect in diverticula and cause obstruction
 - mucus secretion and normal bacterial overgrowth lead to distension of diverticula
 - results in vascular compromise and perforations → hives developing
 - increase in intraluminal pressure and stuck food particles may also damage diverticula wall, resulting in inflammation and necrosis and perforation
 - recurrent attacks lead to scar tissue formation and lumen narrowing

7

Diverticulosis management

- Asymptomatic
- No need for routine follow ups
- Maintain healthy balanced diet, high in fibre ↗ 30g of fibre /day ↗ aug UK intake is 18g/day
- Maintain adequate fluid intake → affect hardness of stools
- If overweight, advise about benefit of weight loss, exercise and also smoking cessation to prevent progression.
- If constipated-offer bulk forming laxatives
c.g.) ispaghula husk

8

Diverticular Disease

- Intermittent pain in lower left quadrant (with constipation, diarrhoea, rectal bleeds)
- Abdominal pain worsened by eating, relieved by passing stool or wind
- Flatulence
- Lower left quadrant tenderness on palpation
- Asian populations symptoms may present right sided
- Symptoms can overlap with other conditions, such as IBS
- No systemic symptoms

9

Diverticular Disease Management

- High fibre diet minimum 30g/day
- Bran supplements/Bulk-forming laxatives
- Lifestyle advice as per diverticulosis ↗ adequate fluid intake of 2L/day ↑ exercise
→ ↓ weight
→ ↑ exercise + smoking cessation
- Anti-spasmodics when colic eg alverine, mebeverine, peppermint oil etc ↗ like IBS patients
↳ if patient presenting w/ cramping & colicky symptoms
- Avoid NSAIDs
- Anti-motility drugs to slow transit time eg codeine and loperamide should **NOT** be used
because ↗ risk of diverticular perforation

10

Diverticulitis

- Constant lower left abdominal pain with:
 - Fever
 - Sudden bowel change
 - Blood/mucus in stools
 - Lower left quadrant tenderness (right in ascra)
 - Palpable abdominal mass/distension
 - Malaise → discomfort w/ exact cause difficult to identify
 - Nausea and vomiting
 - ↑ WBC, if bleeding occurs ↑ platelets, anaemia, ↑ CRP (non-specific marker of inflammation)
-) signs that patient is becoming systemically unwell
② may also have toxic colon

11

Diverticulitis management

- Refer for hospital assessment if:
- Patient **> 65 years** ↗ increased risk in complicated diverticulitis
- Co-morbidities/immunosuppressed**
- Can't take oral Abx at home → admitted to hospital for IV abx
- Dehydrated/at risk, can't rehydrate sufficiently from home
- Uncontrollable abdominal pain plus signs of complicated acute diverticulitis:

12

2

Diverticulitis management

- Signs of complicated acute diverticulitis:
 - **Intra-abdominal abscess** (mass on examination)
 - **Diverticular haemorrhage** → *blood in stools*
 - Peritonitis (rigidity/guarding upon examination)
 - Stricture (**reduce GI motility, constipation, cramping**)
 - **Fistula formation** (**faecaluria, pneumaturia**, passing faeces through vagina)
fecal matter ↑ bubbles in urine (gas from fistulae from bursts)
fistula causing rise to urine from large intestine to bladder
 - Intestinal obstruction (**cramping, absolute constipation, distension**)
 - **Sepsis** (\uparrow resp, \uparrow HR, \downarrow systolic BP, no urine output, skin discolouration, cognitive impairment)

13

Diverticulitis management

fever, tachycardia, ↑ respiratory rate, ↓ systolic B.P + nausea, vomiting, malaise

- Acute + systemically unwell (but doesn't need admission)
- **Co-amoxiclav 500/125 TDS x 5 days** (Cefalexin if penicillin allergy) + **Metronidazole 400mg TDS x 5 days**, OR
- **Trimethoprim 200mg BD x 5 days** + **Metronidazole 400mg TDS x 5 days**
- Acute + systemically well
 - Consider **no Abx** strategy (antimicrobial stewardship)
 - Analgesia e.g. **Paracetamol** (avoid **NSAIDs/opioids**)
 - Re-present if symptoms worsen

14

References

- <https://cks.nice.org.uk/topics/diverticular-disease/>
- <https://www.nice.org.uk/guidance/ng147/resources/diverticular-disease-diagnosis-and-management-pdf-66141784856005>

15

Learning Objectives

- Define "Stoma"
 - Describe different types of stoma
 - Describe some of the types of appliances available
 - Summarise the psychosocial impact for stoma users
 - Summarise the impact of foods and drugs on stoma output
- e.coogan@uea.ac.uk

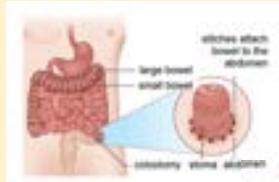


<https://www.coloplast.co.uk/stoma/people-with-a-stoma/before-stoma-surgery/>

1

What is a Stoma?

- Opening in front of abdomen
- Surgically created
 - Bowel or bladder
 - Enables elimination of contents



<https://www.bupa.co.uk/-/media/images/HealthManagementTopics/Bowels-the-large-and-small.png>

2

Indications

- Why may a patient need a stoma?
- Some diseases predispose patients:
 - Inflammatory bowel diseases (IBD)
 - Diverticular disease
 - Cancer of the Large Intestine
- Volvulus (twisted bowel)
- Perforation of colon
- Toxic Megacolon (Inflammation-bowel wall thick-colon bloated with gas-fever/GI pain)
 - <https://www.cancer.gov/live/CDR41500-750>
- Colonic Polyps



<https://www.cancer.gov/live/CDR41500-750>

3

Stoma Types



Colostomy



Ileostomy



Urostomy

https://www.coloplast.co.uk/stoma/people-with-a-stoma/before-stoma-surgery/#section=ileostomy_385589

4

Colostomy

- Most common
- Large intestine used
- End colostomy
 - Descending → firmer stool
 - Ascending or Transverse → more fluid stool
- Permanent or temporary

Ileostomy

- End of small intestine becomes the stoma
- Large intestine removed
- Right-hand side
- Generally more fluid contents



<https://www.nhs.uk/conditions/ileostomy/Pages/introduction.aspx>

5

6

Urostomy

- Formed following bladder removal
- Output is urine
- Ileal Conduit Urinary Diversion
 - Small piece of bowel connected to the ureters
 - Acts as a channel for urine
- Not reversible
- Continuous flow
- **Urostomy Association

7

Colostomy Bags

- Generally closed bag (Disposable)
 - Change once - twice a day
 - Opaque/beige more discrete
 - Normally use one- or two-piece system
- Two Piece
 - Base plate (change every 3-7 days)
 - Pouch

<https://www.coloplast.co.uk/products/stoma-bags-accessories>

8

Ileostomy Bags

- Generally drainable bags (Reusable)
 - Change every 3-5 days
- Also one- or two-piece systems
- Integrated clip, or no closure system
- Integrated tends to be preferred

<https://www.coloplast.co.uk/Products/Stoma-bags-accessories>

One and Two piece example with integrated clips

9

Urostomy Bags

- Many different types available
 - Also one- or two-piece systems
- Tap outlet bag needs changing every 1-3 days
- Specialist stoma nurse involvement
- Night drainage bags can be used at home

<https://www.coloplast.co.uk/products/stoma-bags-accessories/>

Night Drainage Bag

10

Other Items Available

- Adhesives
- Adhesive Removers
- Deodorants
- Skin Fillers and Protectives
- Stoma Caps

<http://www.stomawise.co.uk/ostomy-accessories>

11

Psychosocial Dimensions

- Diet
 - Fluids
 - Fibre-rich food
 - Dispelling gas
 - Reducing odour
- Clothes
 - Discrete
 - Special designs
- Swimming/Sports
 - Stoma caps can be helpful, perfect for stable patients who need to use a smaller capacity bag for a short time.
- Travel
 - Forward planning
 - Plenty of supplies
 - ORS and anti-diarrhoea medicines
- Personal life
 - Most resume normal sex life
 - Smaller bag or stoma cap

12

Common Problems - Food

Gas-producing	Acid-producing	Water-absorbing	Fatty	High protein
Alcohol	B vitamins	Apples	Beef	Butterfat
Asparagus	Some cheeses	Bran	Broccoli	Strawberries
Bananas	Cauliflower	Figs	Celery	Tomato sauce
Beans	Fish	Prunes	Cottage	
Broccoli	Garlic	Spicy food	Grapes	
Beef	Green vegetables	Wholegrain cereals	Lamb	
Cucumber	Onions		Mushrooms	
Eggs	Pancakes		Nuts	
Mushrooms	Turnips		Sweetcorn	
Onions			Popcorn	

13

Common Problems - Drugs

Antibiotics	Anticholinergics	TCA	Aspirin
Fusarium	Diazepam	Ca channel blockers	NSAIDs
Gold compounds	Iom	Opiates	Ca channel blockers, (verapamil, diltiazem)
Iron compounds	Opioids	Loperamide	Antacid
Misoprostol	TCA		Nitroates
NSAIDS	Verapamil		Prednisolone
Theophylline	Aluminosilicates		Ferric sulphate
Laxatives	Fluoxetine / Paroxetine		
Magnesium	Fluoxetine		

14

Diarrhoea & Constipation

- Constipation
 - Diet and medicines review
 - Increase fluid and fibre
 - Consider use of Ispaghul Husk
 - NOT ileostomy patients
 - Increases water and salt loss
 - Refer to ileostomy nurse
- Diarrhoea
 - Diet and medicines review
 - ORS use
 - Loperamide (liquid or disp tab)
 - Caps may pass too quickly to be absorbed (check stoma output to check)
 - [https://pharmaceutical-journal.com/article/id/pharmaceutical-considerations patients-with-stomas](https://pharmaceutical-journal.com/article/id/pharmaceutical-considerations-patients-with-stomas)



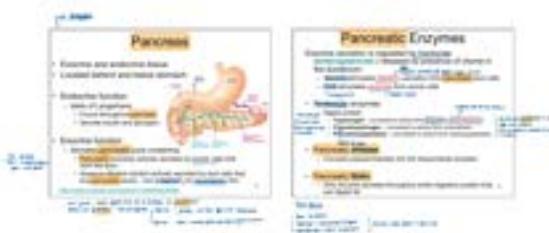
<https://www.chemistdirect.co.uk/imodium-instant-tabs/prd-13p>

15

References

- http://www.pjonline.com/files/rps-pjonline/pdf/pj20101106_cpd.pdf
- <http://www.coloplast.co.uk/Stoma/People-with-a-stoma/Living-with-a-stoma/>
- <http://www.hollister.com/uk/ostomy/resource/booklets.html>
- <https://www.bupa.co.uk/health-information/directory/s/stoma-care>
- <http://www.stomawise.co.uk/types-of-stoma/overview>
- <https://urostomyassociation.org.uk/information/urostomy/>
- <https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/urostomy>

16

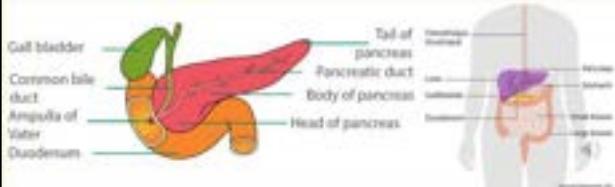


Maria O'Connell's week 4 material on Pancreas physiology

Exocrine pancreatic insufficiency

- Describe the cause(s) of pancreatic insufficiency.
- Describe the symptoms of pancreatic insufficiency.
- Describe the aims of drug treatment.

This session builds on the Pancreas teaching by Maria O'Connell in Lower GI physiology-small intestine and accessory organs.



1

Causes of pancreatic exocrine insufficiency

- Ultimately, the cause is a lack of pancreatic digestive enzymes being secreted into duodenum.
- Specifically lack of amylase, lipase, protease.

Digestive enzyme	Macronutrient digested
Amylase	Carbohydrate
Lipase	Fats
Protease	Protein



2

Causes of pancreatic exocrine insufficiency

- Some underlying causes of lack of digestive enzymes include:
- Pancreatic resection → surgical removal of pancreas, unable to carry out exocrine function of pancreas.
- Pancreatitis → inflammation of the pancreas ↴ reduce size and function
- Diabetes (lack of insulin atrophies the pancreas, diabetes is also inflammatory-can lead to pancreatic inflammation).
- Celiac disease (pancreatic fibrosis, fewer secretory granules).
- Pancreatic tumours ↴ a form of pancreatitis
- Cystic fibrosis (pancreatic duct becomes blocked with mucus)

3

Symptoms of pancreatic exocrine insufficiency

- This is where the overlap with other conditions can be seen.
- Macronutrients (fats, carbs, protein) are malabsorbed.
- Malnutrition, lack of energy, low blood levels of fat soluble vitamins (A, D, E, K).
- In children this can lead to lack of growth rates (weight loss in adults).
- Low blood levels of Zinc, Selenium can show up as reduced immune function, poor wound healing, thyroid function.
- General signs of malnutrition can present-lethargy, depression, concentration, muscle loss, dry skin, brittle nails etc

4

Symptoms of pancreatic exocrine insufficiency

- Physical symptoms arise from the inability to digest macronutrients properly.
- Diarrhoea → overlap w/ other liver G2 lectures
- Cramping/bloating/flatulence
- Steatorrhoea (fatty, foul smelling stools, usually light in colour) ↴ floating stools
due to undigested food → flatulence

5

Aims of drug treatment

- Pancreatic enzyme replacement (amylase, lipase, protease). nutrient supplement
- See medicinal forms section of the Pancreatin monograph in BNF.
- Pancrex V
- Creon
- Nutrizym 22
- Pancrease HL

varying strength of pancreatic

6

Aims of drug treatment

- Dose will be **tailored according to meal**
 - **Higher doses for main meals**
 - **Smaller doses for snacks**
 - **Physical symptoms should ease** *↑ muscle mass due to absorbed necessary amino acids*
 - **Clinical manifestations such as lethargy, muscle loss, low blood levels of fat soluble vitamins and nutrients should also improve.**
- A,D,E,K*

7

References

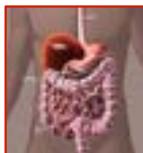
- <https://www.macmillan.org.uk/cancer-information-and-support/pancreatic-cancer/the-pancreas>
- <https://www.cancerresearchuk.org/about-cancer/pancreatic-cancer/about>
- <https://classnotes123.com/what-is-the-function-of-digestive-enzymes/>
- <https://bnf.nice.org.uk/treatment-summaries/exocrine-pancreatic-insufficiency/>

8

e.coogan@uea.ac.uk

Lower Gastrointestinal Diseases

Maria O'Connell



Inflammatory Bowel Disease

Epidemiology, Aetiology and Pathogenesis

1

Learning Objectives - IBD

- To understand and discuss the definition, epidemiology, aetiology, pathogenesis, clinical symptoms and diagnosis of inflammatory bowel disease
- To be able to differentiate between ulcerative colitis and Crohn's disease

2

Inflammatory Bowel Disease (IBD)

- 2 inflammatory disorders of the gastro-intestinal tract
 - Crohn's Disease (CD)
 - Ulcerative Colitis (UC)
- Chronic disease
 - Follows an unpredictable relapsing & remitting course, varying severity
 - Extra-gastrointestinal manifestations
- In 10-15% cases - UC and CD may be difficult to distinguish

3

What are they?

Crohn's Disease

- Affects any part of the G.I. tract from mouth to rectum
- Inflammation extends through all layers of the gut wall
- Inflammation is patchy in distribution

Ulcerative Colitis

- Affects the colon and rectum only
- Only affects the mucosa (and submucosa)
- Inflammation is diffuse in distribution

4

Epidemiology

- World-wide distribution of IBD
 - More common in industrialised countries
 - Affects all races & both sexes
- Peak incidence occurs between 10 - 40 years
 - Can occur at any age
 - 15% - over 60 years old
- 1/250 people are affected by IBD in UK
- Rapid increase in incidence between 1955-1975, particularly Crohn's disease
 - Now stabilised

www.nacc.org.uk

5

Who are they?



President Eisenhower
diagnosed with Crohn's disease
while in office, had obstruction
and colostomy

Beth Orton
diagnosed with Crohn's disease
at 17, serious relapses

Steve Redgrave
suffers from ulcerative
colitis and diabetes

Mike McCready
suffers from
Crohn's disease

6

Incidence

- | Crohn's Disease | Ulcerative Colitis |
|-----------------------------------------------------|------------------------------------------------------|
| • 5-10 per 100,000 population per year | • 10-20 per 100,000 population per year |
| • Prevalence of 50-100 cases per 100,000 population | • Prevalence of 100-200 cases per 100,000 population |

7

Male:Female Ratio

- | Crohn's Disease | Ulcerative Colitis |
|-----------------------------------|---------------------------------|
| • Slightly more common in females | • Slightly more common in males |
| • M:F = 1:1.2 | • M:F = 1.2:1 |
| • Occurs at a younger age | • Occurs at an older age |
| • Mean age at onset: 26 years | • Mean age at onset: 34 years |

8

Aetiology

- Causative agents of IBD are unknown
- Numerous factors are thought to have a role e.g.
 - Environmental
 - Diet
 - Smoking
 - Infection
 - Drugs
 - Genetic

9

Aetiology - Environmental Factors

- **Diet**
 - Several factors have been associated with IBD
 - e.g. **fat** intake, **fast food** ingestion, **milk** and **fibre** consumption, **total protein** and **energy** intake and **refined carbohydrates**
 - Evidence is inconclusive
- Many patients are able to identify foods that aggravate or exacerbate their symptoms
 - e.g. cow's milk or spicy foods

10

Aetiology - Environmental Factors

- **Smoking**
 - Worsens the clinical course of the disease
 - Increases the risk of relapse & need for surgery
- 40% of CD patients are smokers (10% UC)
- Smoking may help to prevent the onset of UC
 - Chemicals affect colon smooth muscle
 - Alters gut motility & transit time

11

Aetiology - Environmental Factors

- **Infection**
 - Some evidence that exposure to *Mycobacterium paratuberculosis* can cause CD
 - UC can occur after episode of infective diarrhoea,
 - No definite association with a single infective agent
 - Association with measles & mumps infections
 - Possibly immune system does not switch off after infection leading to autoimmunity

12

Aetiology - Environmental Factors

- **Enteric Microflora**

- IBD patients - loss of immunological tolerance to intestinal microflora
- Can be manipulated by antibiotics, probiotics and prebiotics to balance favourably

13

Aetiology - Environmental Factors

- **Drugs**

- NSAIDs can exacerbate IBD
 - Inhibit the synthesis of cytoprotective prostaglandins
- Antibiotics can change enteric microflora
 - Precipitate a relapse
- Oral contraceptive pill
 - Increase risk of developing CD
 - Possibly caused by vascular changes
- Isotretinoin – for acne – possible risk factor

14

Aetiology - Environmental Factors

- **Appendectomy**

- Has a protective effect in CD & UC
- ? immunologically based

- **Stress**

- Can trigger a relapse in IBD
- Activates inflammatory mediators at enteric nerve endings in gut wall

15

Aetiology - Genetic Factors

- Genetic factors influence the risk of IBD by causing:
 - Disruption of epithelial barrier integrity
 - Deficits in autophagy
 - Deficiencies in innate pattern recognition receptors
 - Problems with lymphocyte differentiation, especially CD
- Inappropriate response of the immune system in the mucosa of the G.I. tract to normal enteric flora
- Mutations of the gene CARD15/**NOD2** located on chromosome 16
 - Associated with small intestine CD in white populations
- The genes **OCTN1** on chromosome 5 and **DLG5** on chromosome 10 have also been linked to CD

16

Aetiology – Genetic Factors

- 70% of UC patients

- Have anti-neutrophil cytoplasmic antibodies (p-ANCA)

- ? Autoimmune component

- Association between IBD, ankylosing spondylitis & histocompatibility antigen HLA-B27

17

Aetiology - Genetic Factors

- **Ethical factors**

- Jews are more prone than non-Jews
- IBD incidence is lower in non-white races

- **Familial factors**

- First-degree relatives of those with IBD have up to 20-fold increase in developing the disease
- 15-fold greater concordance for IBD in identical twins than non-identical twins

18

Pathophysiology

- IBD is a severe, prolonged & inappropriate inflammatory response to trigger factors
 - Alters the normal architecture of G.I. Tract
- Could be due to:
 - Increased activity of effector lymphocytes & pro-inflammatory cytokines that override normal control mechanisms
 - Primary failure of regulatory lymphocytes & cytokines
 - In CD, T cells are resistant to apoptosis after inactivation

19

Pathophysiology - CD

- Affects any part of the gut
 - Involving one area or multiple areas
 - Usually the **terminal ileum & ascending colon**
 - Discontinuous
- Affected areas are thickened, oedematous & narrow
 - Deep ulcers can appear
 - Mucous membrane between fissures has a **cobblestone** appearance
 - Can progress to deep fissuring ulcers, fibrosis & strictures
- Also, can lead to bowel obstructions, abscesses and gut perforations

20

Crohn's Disease



<http://www.youtube.com/watch?v=-oa65IEb8-0>

21

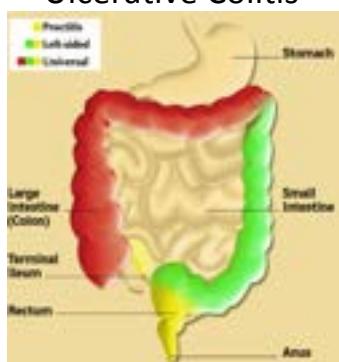
Pathophysiology - CD

- Microscopically:
 - Non-specific **granulomatous** inflammation
 - Inflammation extends throughout all layers of the bowel (**transmural**)
 - Inflammatory cells are seen throughout – **lymphocytes and plasma cells**
 - **Th1-associated**
- Chronic inflammation leads to an increased risk of cancer



22

Ulcerative Colitis



23

Pathophysiology - UC

- At first presentation:
 - 40% - rectum (proctitis)
 - 40% - sigmoid & descending colon (left-sided colitis)
 - 20% - whole colon
- Only the mucosa & submucosa are affected
- Continuous, starting in rectum
- Formation of crypt abscesses & mucosal ulceration
- Mucosa looks red, inflamed & bleeds easily
 - Purulent & granular with superficial ulceration
 - Pseudopolyps in severe inflammation

http://www.youtube.com/watch?v=FEL_LngIY20

24

Pathophysiology - UC

Microscopically:

- Inflammatory cells infiltrate the lamina propria & crypts
- Th2-associated
- Dysplasia can be seen from biopsies
 - Can progress to carcinomas

25

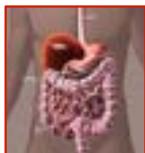
Ulcerative Colitis



26

Lower Gastrointestinal Diseases

Maria O'Connell



Inflammatory Bowel Disease

Clinical symptoms, Complications and Diagnosis

1

Clinical Features

- IBD – depends on site, extent & severity of active disease
- Symptoms of both diseases
 - Diarrhoea
 - Fever
 - Abdominal pain
 - Nausea and vomiting (more common in CD)
 - Malaise
 - Lethargy
 - Weight loss (more common in CD)
 - Malabsorption
 - Growth retardation in children

2

Clinical Features - CD

- Tends to be more disabling than UC
- Onset can be acute or insidious
- Other symptoms can include:
 - Pain (particularly LRQ)
 - Anaemia
 - Palpable masses
 - Small bowel obstructions
 - Abscesses
 - Fistulas
 - Gut perforation

3

Clinical Features - UC

- Symptoms
 - Diarrhoea – possibly with blood/mucus
 - Up to 10-20 liquid stools a day
 - Abdominal pain (cramps) with fever
 - Constipation
- 50% of UC patients have a relapse each year
 - Severe attacks can be life-threatening

4

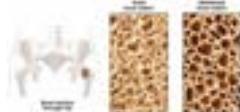
Distinguishing Features of CD vs UC

Features	CD	UC
Skip areas	Common	Never
Cobblestone mucosa	Common	Rare
Transmural involvement	Common	Occasional
Rectal sparing	Common	Never
Perianal involvement	Common	Never
Fistulas	Common	Never
Strictures	Common	Occasional
Granulomas	Common	Occasional

5

Complications of IBD -10-20%

- Joints & Bones
 - Arthropathies & Osteopenia
- Skin
 - Erythema nodosum
 - Tender, hot, red nodules – subside over a few days to leave brown skin discolouration
 - Pyoderma gangrenosum
 - Pustule – develops into an ulcer



6

Complications of IBD

- Ocular
 - Episcleritis
 - Intense burning & itching of blood vessels involved
 - Uveitis
 - Headache, burning red eye, blurred vision
- Sclerosing Cholangitis
 - Chronic inflammation of the biliary tree
 - Leads to progressive fibrosis & biliary strictures



Morbidity

- Quality of life generally lower in CD vs UC, especially because of recurrences after surgery
- Increased risk of peritonitis and malignancy
- Malnutrition and chronic anaemia common in long-standing CD

8

Diagnosis of IBD

- Confirmed by clinical evaluation & a combination of investigations:
 - Biochemical
 - Endoscopic
 - Radiological
 - Histological
 - Nuclear medicine based

9

History of Disease

- Full history including:
 - Recent travel
 - Medication
 - Smoking
 - Family history
- Details of symptoms including:
 - Stool frequency & consistency
 - Urgency
 - Rectal bleeding
 - Abdominal pain
 - Fever

10

Examinations

- Physical signs
 - General well-being
 - Pulse
 - Blood pressure
 - Temperature
 - Weight loss
 - Abdomen tenderness or distension
 - Right iliac fossa mass
 - Anus
 - Oedematous anal tags, fissures or perianal abscesses

11

Initial Investigations

- Blood tests
 - Anaemia is common
 - Deficiency of iron and/or folate also occurs
 - Raised ESR & CRP & a raised WCC
 - Hypoalbuminaemia
 - LFTs may be abnormal
- Microbiological testing for infectious diarrhoea
- Serological tests
 - *Saccharomyces cerevisiae* antibody usually present in CD
 - p-ANCA antibody
 - -ve in CD & +ve in UC

12

Abdominal Radiography

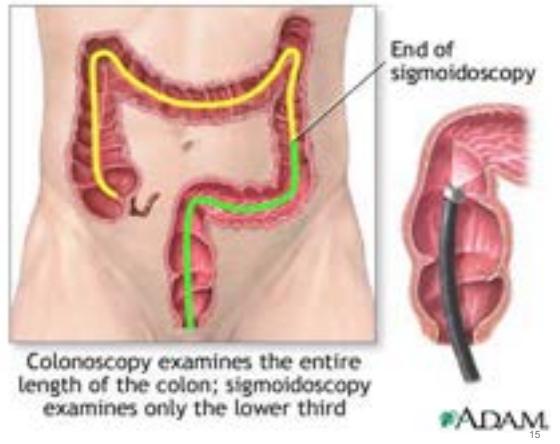
- Essential in the **initial assessment** of suspected severe IBD
- Excludes colonic dilatation
- Helps assess **disease extent** in UC
- Identifies proximal **constipation**
- Gives an impression of **right iliac fossa mass** in CD
- Can show evidence of **small bowel dilation**

13

Investigations

- **Sigmoidoscopy**
 - Internal examination of the colon (lower third) using a sigmoidoscope.
 - Used for all patients presenting with diarrhoea
 - Used to confirm diagnosis of UC
- **Rectal Biopsy**
 - Detects non-specific histological changes in the mucosa
- **Colonoscopy**
 - Internal examination of the colon (entire length) using a colonoscope
 - Used for mild or moderate disease to assess extent of disease
 - Biopsy can be performed as well

14



Other Investigations

- Double contrast barium enema
 - Inferior to colonoscopy
 - Can detect early mucosal changes
- Small bowel radiology
 - Current standard for assessing small intestine
- Ultrasound
 - Sensitive & non-invasive
 - Identifies thickened small bowel loops in CD
- Computer tomography & magnetic resonance imaging
 - Evaluates activity & complications of the disease

16



ULCERATIVE COLITIS CLINICAL THERAPEUTICS

NICOLA MOORE

CUH TEACHER PRACTITIONER

N.MOORE1@UEA.AC.UK

1

LEARNING OUTCOMES

- By the end of this screencast (and accompanying workshop), you should be able to:
 - State the current medical guidance used in clinical practice
 - Recall the NICE guidance and be able to apply that to a variety of clinical care situations

2

WHAT GUIDANCE IS USED IN PRACTICE?

- **Ulcerative colitis: management. NICE guideline, NG 130, May 2019**
- British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease. Gut, 2019, 1-106.
- ECCO Third European-based consensus on diagnosis and management in ulcerative colitis. Part 2 : current management. Journal of Crohn's and Colitis, 2017, 769-784.

3

WHAT IS THE AIM OF THERAPY?

- Reduce symptoms
- Induce remission
- Maintain remission
- Improve (maintain) the quality of life
- Minimise toxicity related to drugs (short and long-term)

Distinguish ACUTE treatment and MAINTENANCE therapy:

- ACUTE treatment is often termed INDUCTION treatment - i.e. to induce remission
- MAINTENANCE therapy is that used to maintain remission/prevent relapse

4

WHAT IS THE TARGET OF THERAPY?

- ??? the problem...
- There is no fully agreed or validated definition of remission
 - Montreal classification – Extent - E1=proctitis, E2=left sided, E3=extensive
 - Severity - S0=clinical remission, S1=mild, S2=moderate, S3=severe
 - Truelove and Witts severity index (see article) (NICE)
 - Mayo score
 - Treat-to-target
 - Adjustment to therapy based on assessment (control of asymptomatic inflammation)

5

WHAT AFFECTS THE CHOICE OF THERAPY?

- Disease severity
- Disease extent
- Disease location (see article)
- Previous response to therapy
- Presence of complications
 - Risk factors for progression and complications, patient characteristics, risk:benefit, cost

6

NICE 130

- Inducing remission – mild to moderate ulcerative colitis - PROCTITIS
 - Topical aminosalicylate** (first presentation or inflammatory exacerbation)
 - If remission not achieved in 4 weeks consider adding **oral aminosalicylate**
 - If further treatment needed consider adding **topical or oral corticosteroid**
 - Time limited
 - For patients that decline topical treatment – consider **oral aminosalicylate** (not as effective)
 - For patients that cannot tolerate aminosalicylates consider **time limited oral or topical corticosteroid**



7

NICE 130

- Inducing remission – mild to moderate ulcerative colitis
 - PROCTOSIGMOIDITIS AND LEFT-SIDED COLITIS (DISTAL COLITIS)
- Topical aminosalicylate** (first presentation or inflammatory exacerbation)
 - If remission not achieved in 4 weeks consider
 - adding a **high-dose oral aminosalicylate**
 - Switching to **high-dose oral aminosalicylate and time limited topical corticosteroid**
 - If further treatment needed, stop topical treatment and offer **oral aminosalicylate and time limited oral corticosteroid**
 - For patients that cannot tolerate aminosalicylates, consider **time limited topical or oral corticosteroid**

8

**NICE 130**

- Inducing remission – mild to moderate ulcerative colitis – EXTENSIVE
 - Topical aminosalicylate and high-dose oral aminosalicylate** (first presentation or inflammatory exacerbation)
 - If remission not achieved in 4 weeks, stop topical treatment and offer a **time-limited course of oral corticosteroids**
 - For people who cannot tolerate aminosalicylates, consider a **time limited oral corticosteroid**



9

NICE 130

- Inducing remission – moderate - severe
 - Oral corticosteroid**

10

NICE 130

- Inducing remission – Moderate to severely active disease
 - Biologics and Janus kinases**
 - Infliximab, adalimumab, golimumab(TA 329) – after failure of conventional therapy
 - Vedolizumab – (TA 342) – inadequate response/loss of response (or intolerance) to either conventional therapy or TNFalpha antagonists
 - Tofacitinib (TA 574) – when the disease has responded inadequately/response been lost, to conventional or biological therapy

NICE 130

- Inducing remission – Acute severe - Hospitalised (all areas)
 - IV corticosteroids** and assess likelihood of requiring surgery
 - Consider **IV cyclosporin** or surgery in those intolerant/decline/Cl corticosteroids
 - If symptoms worsen or little/no improvement within 72 hours, consider adding **IV cyclosporin to the corticosteroid**
 - If cyclosporin Cl/clinically inappropriate, **infliximab** is an option (NICE TA 163)

11

12

NICE 130

- Maintaining remission – mild to moderate
 - PROCTITIS and PROCTOSIGMOIDITIS
- Consider the following options:
 - Topical aminosalicylate alone (daily or intermittent)
 - Oral aminosalicylate plus topical aminosalicylate (daily or intermittent)
 - Oral aminosalicylate – explaining that this may not be as effective as combined treatment or intermittent topical aminosalicylate alone

**NICE 130**

- Maintaining remission – mild to moderate
 - LEFT-SIDED and EXTENSIVE
- Offer low maintenance dose of **oral aminosalicylate**



13

14

NICE 130

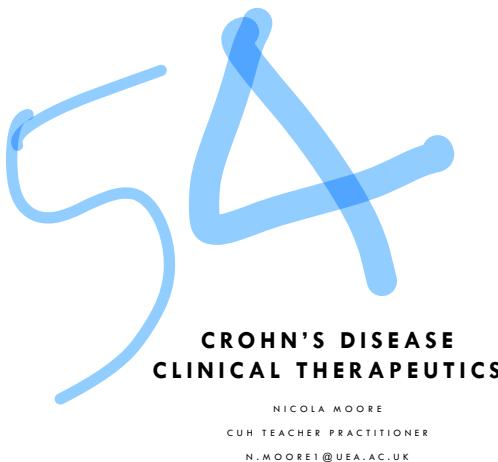
- Maintaining remission – all areas
- Consider mercaptopurine or azathioprine:
 - After 2 or more inflammatory exacerbations in 12 months that require systemic corticosteroids
Or
 - If remission is not maintained by aminosalicylates
- Consider azathioprine or mercaptopurine (**or oral aminosalicylate if aza/merc CI**)
 - To maintain remission after a single episode of acute severe UC

• You should be able to:

- State the current guidance used in clinical practice
- Recall the NICE guidance and be able to apply that to a variety of clinical care situations

15

16

**LEARNING OUTCOMES**

- By the end of this screencast, you should be able to:
 - State the current guidance used in clinical practice
 - Recall the NICE guidance and be able to apply that to a variety of clinical care situations

1

2

WHAT GUIDANCE IS USED IN PRACTICE?

- [Crohn's disease: management. NICE guideline, NG 129, May 2019](#)
- British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease. Gut, 2019, 1-106.
- ECCO Guidelines on Therapeutics in Crohn's disease: Medical Treatment. Journal of Crohn's and Colitis, 2020, 4-22.

3

WHAT IS THE AIM OF THERAPY?

- Reduce symptoms
- Induce remission
- Maintain remission
- Improve (maintain) the quality of life
- Minimise toxicity related to drugs (short and long-term)

Distinguish ACUTE treatment and MAINTENANCE therapy:

- ACUTE treatment is often termed INDUCTION treatment - i.e. to induce remission
- MAINTENANCE therapy is that used to maintain remission/prevent relapse

4

WHAT IS THE AIM OF THERAPY?

Unfortunately, it is a bit more complicated than that...

- Poor outcomes are associated with:
 - Untreated inflammation (even if asymptomatic)
- Tight control
 - Achievement of clinical and endoscopic remission
- Treat-to-target
 - Adjustment to therapy based on assessment

5

WHAT AFFECTS THE CHOICE OF THERAPY?

- Disease location
- Disease activity and severity
- Previous response to therapy
- Presence of complications
 - Risk factors for progression and complications, patient characteristics, risk:benefit, cost

6

NICE 129

• Inducing remission

- Monotherapy with traditional glucocorticosteroid (at first presentation or a single inflammatory exacerbation in a 12 month period)
 - Prednisolone, methylprednisolone, hydrocortisone (IV)
- Budesonide may also be considered in certain circumstances, including
 - Contraindication to/refusal of conventional glucocorticosteroids
 - NOT for severe presentations

7

NICE 129

• Inducing remission – Add-on therapy

- Consider adding azathioprine or mercaptopurine to glucocorticosteroid or budesonide to induce remission (if 2 or more inflammatory exacerbations in 12 months or if glucocorticosteroid dose cannot be tapered)
- Consider adding methotrexate to glucocorticosteroid or budesonide in those who cannot tolerate azathioprine or mercaptopurine or low TPMT activity (if 2 or more inflammatory exacerbations in 12 months or if glucocorticosteroid dose cannot be tapered)

8

NICE 129

• Infliximab and Adalimumab

- Licensing – for adults with moderately/severely active disease, whose disease has not responded to conventional therapy
- Should be given as a planned course until treatment failure or 12 months after initiation
- Continue if there is clear evidence of ongoing active disease (symptoms, biological markers and investigations – endoscopy)
- You may also see this therapy given with an immunosuppressant

Severe = very poor general health and 1 or more of the following – weight loss, fever, severe abdominal pain, usually frequent 3-4 stools/day

9

NICE 129

• Ustekinumab

- TA 456 – Recommended as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.

• Vedolizumab

- TA 352 - Recommended as an option for treating moderately to severely active Crohn's disease only if: a tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated. Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme

10

NICE 129 - MAINTAINING REMISSION**Treatment**

- Offer azathioprine or mercaptopurine when previously used in induction strategy; or consider in those not previously receiving this
- Consider methotrexate only in those who needed it at induction, tried and did not tolerate/Cl azathioprine or mercaptopurine

No treatment – follow-up

- Share plans for follow-up (frequency and what it should be with)
- Symptoms of relapse are known and action required (unintentional weight loss, abdo pain, diarrhoea, ill-health)
- Knowledge of how to access healthcare
- Smoking cessation

Do NOT offer conventional glucocorticosteroids or budesonide to maintain remission

11

NICE 129

• Maintaining remission after surgery

- After complete macroscopic resection (in ileocolonic Crohn's disease) within the last 3 months, consider azathioprine in combination with metronidazole (for up to 3 months post operatively)
- Azathioprine alone in those who are unable to tolerate metronidazole

(Do NOT offer biologics or budesonide)

12

- You should be able to:
 - State the current guidance used in clinical practice – NICE, BSG, ECCO
 - Recall the NICE guidance and be able to apply that to a variety of clinical care situations – induction of remission / add-on therapy / maintenance of remission



13



PHARMACEUTICAL CARE CONSIDERATION IN PATIENTS WITH IBD

NICOLA MOORE

CUH TEACHER PRACTITIONER

N.MOORE1@UEA.AC.UK

1

WHAT GUIDANCE IS USED IN PRACTICE?

- [Ulcerative colitis: management. NICE guideline, NG 130, May 2019](#)
- [Crohn's disease: Management. NICE guideline, NG 129, May 2019](#)
- [NICE guidance on osteoporosis: assessing fragility fractures. CG 146, Aug 2012](#)
- British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease. Gut, 2019, 1-106.
- Crohn's and Colitis UK – www.crohnsandcolitis.org.uk

3

IMMUNOSUPPRESSIVE THERAPY – PREVENTION OF INFECTION

- Assess at diagnosis –
 - Infection history – HSV (oral/genital), VZV (chicken pox, shingles)
 - Immunisation status – BCG, tetanus, diphtheria, pertussis, *Haemophilus influenzae*, polio, meningococcus, measles, mumps, rubella, pneumococcus, HPV, rotavirus, influenza
- Serology should be tested if the history is unclear
- Treat active HBV, latent/active TB, HCV or HIV prior to initiating immunosuppressive therapy

5

LEARNING OUTCOMES

- By the end of this screencast (and the accompanying workshop), you should be able to:
 - Identify potential and actual care issues in patients with IBD
 - Describe how they are managed
 - Apply this to patient care situations

2

INFECTIONS AND IBD

- Although data can be conflicting, it appears that the risk of enteric infections is higher in IBD patients than in controls.
 - Norovirus, *Campylobacter*, *E. coli*, *C. difficile*
 - IBD patients with *C. diff* show increased colectomy and mortality
 - *C. diff* treatment required
 - Careful consideration of IBD treatment
 - In acute severe disease, corticosteroids can remain and MDT review of other treatment is required.
 - Cytomegalovirus (CMV) – risk potentially associated with refractory disease, immunomodulatory therapy, corticosteroids
 - IV ganciclovir followed by PO valganciclovir treatment

4

CORTICOSTEROID RELATED ISSUES

- Effective at inducing clinical remission but no role in maintenance
 - Important to reduce dose to cessation
- Approximately, 14.9% of UK IBD patients have steroid excess or dependence
- Prolonged steroid use is associated with: increased infection risk, osteoporosis, adrenal suppression, diabetes, weight gain, cardiovascular disease
- Monitoring of the following is important before and during therapy: FBC, Glucose/HbA1c, lipids, BP, eyes (cataracts, glaucoma), mood, sleep

6

MONITORING BONE HEALTH

- Approximately 35 – 40% of patients with IBD have osteopenia
- Approximately 15% from osteoporosis
- Risk factors include: uncontrolled inflammation, malabsorption, weight loss, prolonged/high dose steroids, lack of physical exercise (weight bearing and muscle building), alcohol intake
- All patients on corticosteroids – 800mg-1000mg calcium and 800 IU vitamin D daily
- Patients should have their risks assessed check calcium and vitamin d levels
 - Low risk – retest in 3-5 years
 - High risk – bisphosphonate (alendronate, risedronate, ibandronate, zoledronate)

7

NUTRITIONAL DEFICIENCIES

- Malnutrition is common in IBD – it comprises over and undernutrition
 - Multidisciplinary approach involving dietitian input
- Specific deficiencies, (difficult to interpret as influenced by disease activity):
 - 13-88% suffer with magnesium deficiency, due to intestinal losses
 - PO or IV magnesium – care PO can worsen diarrhoea
 - Calcium/vitamin D - as previously discussed
 - Potassium
 - IV or PO potassium

8

NUTRITIONAL DEFICIENCIES

- Specific deficiencies, (difficult to interpret as influenced by disease activity):
 - 1/3 of IBD patients have iron deficiency anaemia
 - Fatigue, reduced QoL, delayed recovery
 - Annual FBC, ferritin and CRP monitoring
 - Dietary improvements – iron fortified foods, non-haem iron, haem-iron foods, promoters of iron absorption (vit-C-rich)/avoiding inhibitors (tannins, caffeine, calcium)
- Pharmacological intervention
 - IV iron (iron sucrose, ferric carboxymaltose) – active IBD
 - PO up to 100mg (elemental iron) – mild anaemia in those with clinically inactive disease

9

SMOKING

- Always check status – advise of widespread harm – offer smoking cessation
- Smoking is more common in Crohn's disease patients
 - Continuation of smoking is linked to worse disease course, higher risk of surgery and worst outcomes after surgery
- UC is more common in non-smokers and is more likely to arise in those who quit
 - Smoking is linked to reduced surgery rates, less extensive disease, reduced need for therapy
- Should be encouraged to stop, inform of potential increase in treatment

10

NSAIDS

- Data is conflicting regarding non-specific NSAIDs
 - May lead to increase disease activity – esp. in Crohn's colitis
 - May precipitate a relapse
- Short term, low dose, in patients with controlled disease in remission - is potentially safe
- No evidence that COX-II inhibitors are safer than non-specific NSAIDs
- Further studies are required

11

COLORECTAL CANCER SURVEILLANCE

- IBD is a known risk factor for bowel cancer (colon and rectal cancer)
- In UC the risk factors include, duration of disease, amount of bowel affected and severity of the inflammation
 - Cancer risk begins to develop 8-10 years after the start of symptoms
 - Extensive > Distal >> Proctitis
 - Cumulative incidence ~1% at 10yrs, 2-3% at 20 yrs and 5-7% at 30 yrs
- Crohn's disease – Risk similar to UC if colon main area of disease
 - Small bowel, intestinal lymphomas, anal cancers – risk potentially increased

12

COLORECTAL CANCER SURVEILLANCE

Reducing the risk:

- Receive and take appropriate treatment to manage inflammation
- Regular specialist reviews – at least annually
- Regular colonoscopy – frequency dependent on presence of additional risk factors (FHx) and specific disease characteristics (disease activity/presence of stricture)
 - Usually 1-5 yearly
- Additional ways to reduce risk – physical activity, high fibre, reducing red/processed meat, limiting alcohol, ?supplementing vitamin D if deficient

13

VACCINATION

IBD patients on immunosuppressants should not take live vaccines

Covid-19:

- Patients should receive a covid vaccine – currently all vaccine (oxford/AZ, Moderna and Pfizer) are considered safe
 - Aminosalicylate or no treatment the vaccine should work as well as in the general population
 - Those on immunosuppressants are thought to have a reduced antibody response – CLARITY study showed this to improve with 2nd dose – ongoing research
- Influenza injection – especially if on immunosuppressants (but general increased risk) –annually
Pneumococcal – 2 weeks before immunosuppressant initiation

14

ADHERENCE

• The issues...

- Chronic disease with long term medical treatment
 - Remission
 - Topical treatments
 - Need for monitoring
 - Adverse effects
 - Patients beliefs
- = Worse patient outcomes – increased disease activity, relapse, loss of response, higher morbidity and mortality, poor QOL, higher disability

15

OTHER PHARMACEUTICAL CONSIDERATIONS

- Stoma – Output monitoring, knowledge of the site and functioning bowel remaining
- 'Short gut syndrome' – Lack of functioning small bowel
 - May affect nutritional absorption – consider review and replacement
 - May affect oral medication absorption – review absorption profiles and alter therapy accordingly
- Drug considerations-Pain control (non-opioid), EC/MR preparations, loperamide/codeine to reduce motility, antisecretory drugs (PPI)/somatostatin, fluids (sodium losses)/rehydration solutions, digoxin/diuretics, iron preparations, laxative (avoid in ileostomy patients/colostomy can cause bulk forming), sorbitol, s/e diarrhoea

16

OTHER PHARMACEUTICAL CONSIDERATIONS

Anxiety and depression

- It is common and associated with increased hospitalisation and poorer outcomes

Pain and fatigue

- Pain – common (even when asymptomatic), more common in females and those experiencing anxiety and depression
- Need to rule out inflammation, structuring, adhesions, abscesses
- Long term opiate use is associated with poor outcomes for IBD and addiction
- Consider other options / low dose for short periods / additional therapies
- Fatigue – common = poor QOL (review for subclinical disease and modifiable factors)

VTE prophylaxis – hospitalised patients

• You should be able to:

- Identify potential and actual care issues in patients with IBD
- Describe how they are managed
- Apply this to patient care situations

17

18



PHARMACEUTICAL CARE – DRUGS USED IN IBD

NICOLA MOORE

CUH TEACHER PRACTITIONER

N.MOORE1@UEA.AC.UK

LEARNING OUTCOMES

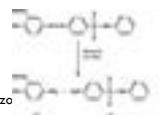
- By the end of this screencast (and accompanying workshop), you should be able to:
 - State the common side effects, cautions and contraindications for certain drugs used in IBD
 - Consider drug characteristics in decision making about treatments in IBD and apply them to patient scenarios
 - Recommend appropriate drug monitoring for patients with IBD

1

2

AMINOSALICYLATES

- Sulfasalazine
 - Mesalazine (5-ASA) bound to sulfapyridine via an azo
 - Colonic bacterial azoreductase breaks the bond
 - Sulfapyridine is absorbed by colon, metabolised by the liver and excreted in the urine
 - Mainly responsible for adverse effects
 - Mesalazine exerts therapeutic effect through topical effects on the mucosa
 - 30% of free mesalazine is absorbed
 - Metabolised locally and in the liver to an inactive form and free/conjugated drug is excreted in the urine or faeces



AMINOSALICYLATES

- Sulfasalazine
 - Contraindication - Hypersensitivity to sulfapyridine/sulfonamides or 5-aminosalicylate/salicylates
 - Cautions – History of asthma
Risk of haematological toxicity
Renal and hepatic impairment
Glucose-6-dehydrogenase (G6PD) deficiency
Slow acetylator status

3

4

AMINOSALICYLATES

- Sulfasalazine
 - Side effects - Headache, nausea, fever, rash, raised temperature, reversible infertility in men, reduced WBC
 - Pancreatitis
 - Hepatitis, pneumonitis, skin reaction (i.e. Stevens-Johnson syndrome), haemolysis, inflammation of the kidney

AMINOSALICYLATES

- Sulfasalazine
 - Monitoring - FBC] before initiation and every second week for first 3 months, then monthly for three months then every 3 months
Creatinine/eGFR – Monthly for 3 months then as indicated
 - Patient to report – sore throat, fever, malaise, jaundice and unexpected non-specific illness - may indicate myelosuppression, haemolysis or hepatotoxicity
 - It may colour urine and stain contact lenses yellow

5

6

AMINOSALICYLATES

- Different delivery mechanisms exist to change the release of mesalazine to the GIT
 - Attachment to other carrier molecules (olsalazine – mesalazine dimer; Balsalazide – aminobenzoyl-beta-alanine)
 - pH dependent formulations (Asacol, Mesren, Salafalk/granules, Mesalal)
 - Time dependent formulations (Pentasa/granules)
 - Multi-matrix system (Mezavant)

7

AMINOSALICYLATES

- There is uncertainty whether individual mesalazine formulations have differential effects on IBD patient subgroups.
- However, an appropriate formulation must be chosen for the patient
 - Dependent on disease distribution, efficacy, s/e profile, patient preference
- Agent selection may be important...

8

AMINOSALICYLATES

- Enteric coat** - with a specific agent to release at specific PH – prevent early disintegration in the stomach and upper GIT
 - Eudragit S – methyl acrylate copolymer coating – dissolves > or equal to 7
 - Eudragit L – methyl acrylate copolymer coating – dissolves > or equal to 6
 - Potential issue, pH reduced in IBD / other factors can change pH
- Time dependent** – microspheres of mesalazine encapsulated in ethylcellulose semi-permeable membrane = time and moisture dependent release (pH independent)
 - Theoretically releasing throughout the GIT, stomach/duodenum to rectum
- Multi-matrix** – Mesalazine incorporated into lipophilic matrix and enterically coated (dissolution pH >7)
 - Matrix swells to form a gel (potentiating slow diffusion) – terminal ileum and entire colon release

9

AMINOSALICYLATES

Brand	Formulation	Optimal drug release pH	Site of release
Asacol MR / Mesren	Enteric coat with Eudragit S	>7	Terminal ileum and large bowel
Salafalk	Enteric coat with Eudragit L	>6	Mid - terminal ileum and colon
Salafalk granules	Matrix core with Eudragit L and coating	>6	Mid - terminal ileum and colon
Octasa	Enteric coat with Eudragit S	>7	Terminal ileum and large bowel
Pentasa/granules	Ethylcellulose semi permeable membrane microspheres	Time dependent	Duodenum to rectum
Mezavant XL	Film coated with Eudragit S and L	>6-7	Terminal ileum and colon

10

AMINOSALICYLATES

- Licensing is different for the different preparations (doses and administration different)
 - Difference in formulation should allow different release profile
 - Comparisons in efficacy and safety (mild-mod UC) = well tolerated and equally effective
 - Systemic exposure from all oral formulations is comparable
- Monitoring – Renal function (creatinine/eGFR), urea, electrolytes, LFTs, FBC – prior to initiation and periodically (until stabilised and routinely)
- Renal function – 6-monthly
- Urea, electrolytes, LFTs, FBC – 6-monthly to annually

11

AMINOSALICYLATES

Brand	Pentasa (D)	Solashield (K)	Solashield (S)
Formulation	Foam enemas in single use bottles	Foam enemas in a preservative container containing 14 doses.	Foam enemas in single use bottles
Strength	1g in 150ml	1g per actuation	2g in 5ml
Licensed indications	Proctitis and mild UC affecting the distal colon and rectum	Proctitis and mild UC of the sigmoid colon and rectum.	Prophylaxis of acute attacks of mild UC in the distal colon and rectum & descending colon.
Adult dose frequency	1g (one enema) once daily at bedtime	Two morning applications (2g) once daily at bedtime for 4-6 weeks followed by one administer in divided doses (1g) once daily and 1 during the night or in the morning if symptoms persist and has difficulty in holding in defaecation.	2g (one enema) once daily at bedtime
Use in children	Not recommended.	Little experience, only limited documentation for an effect in children.	Little experience, only limited documentation for an effect in children.
	BNFC: Not licensed for use in children under 18 years of age.	BNFC: Not licensed for use in children under 18 years of age.	BNFC: Not licensed for use in children under 18 years of age.
	12-17 years doses as for adults (unlicensed use) (10).	12-17 years doses as for adults (unlicensed use) (10).	12-17 years doses as for adults (unlicensed use) (10).
Adverse effects related to administration	Pruritus, rectal irritation and urge to defecate.	Abdominal distension, abdominal pain and urge to defecate, application site irritation, painful rectal tenesmus.	None listed in Summary of Product Characteristics.

12

AMINOSALICYLATES

Medicines Q&A. What are the differences between the non-oral mesalazine preparations? www.sps.nhs.uk

- Topical –Suppositories
- Indicated for use in disease up to the rectosigmoid junction.
- Deliver drug more effectively to the rectum than enemas

Brand	Pentasa (S)	Salsalate (S)	Sulphas (T)
Strength	500mg	500mg	500mg
Licensed indications	Treatment of ulcerative proctitis.	Treatment of acute mild to moderate UC of the rectum.	Moderate or mild and moderate episodes of UC of the rectum.
Adult dose frequency	Take one rectal 500mg suppository daily for 2-4 weeks then reduce to maintenance treatment 1 suppository daily.	Take one rectal 500mg suppository daily for 2-4 weeks then reduce to maintenance treatment 1 suppository daily.	Duration of use to be determined by the physician. Usage should be withdrawn if no improvement in the condition.
Use in children	Not recommended. Little experience, only limited documentation for an effect in children.	Little experience, only limited documentation for an effect in children.	Little experience, only limited documentation for an effect in children.
	BNFC: Not licensed for use in children under 15 years. Child 12-17 years. Dose same as for adults. Dose licensed for children 12-14 years.	BNFC: Not licensed for use in children under 15 years. Child 12-17 years. Dose same as for adults. Dose licensed for children 12-14 years. (10)	BNFC: Not licensed for use in children under 15 years. Child 12-17 years. Dose same as for adults. Dose licensed for children 12-14 years. (10)
Adverse effects related to administration	Perforation, rectal bleeding and urge to defecate.	None listed in Summary of Product Characteristics.	None listed in Summary of Product Characteristics.

13

THIOPURINES

• Mercaptopurine and Azathioprine

- Azathioprine dose usually – 2-2.5mg/kg daily
- Mercaptopurine dose usually – 1-1.5mg/kg daily

• Prior to initiation –

FBC, U&E and LFT

Screen for HCV, HIV, HBV / VZV

Vaccinate – influenza and pneumococcal

Ensure cervical screening up to date

Check TPMT (ThioPurine MethylTransferase) – dose altered dependent on result

• Avoid in patients with very low TPMT

• Ongoing monitoring – FBC, U&E and LFT – at least at 2, 4, 8 and 12 and then 3-monthly

14

THIOPURINES

• Mercaptopurine and Azathioprine

- Contraindications – Hypersensitivity, serious infection, pancreatitis, impaired bone marrow
- Cautions – Reduce TPMT
Renal and hepatic impairment
- Patients to inform the doctor of: ulceration of the throat, fever, infections, bruising, bleeding = signs of myelosuppression
- Interaction with allopurinol – reduce azathioprine dose to 1/4 of the usual dose
- Reduce exposure to the sun, due to increased risk of skin cancers
- Take with meals to reduce the risk of nausea – Reduce dose and give with allopurinol/switch to mercaptopurine

15

• You should be able to:

- State the common side effects, cautions and contraindications for certain drugs used in IBD
- Consider drug characteristics in decision making about treatments in IBD and apply them to patient scenarios
- Recommend appropriate drug monitoring for patients with IBD

16