Pharmacotherapy 2

Gout

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Gout

General Principles

الـ alcohol غني بالـ purine اللي موجود بمعظم خلايا الجسم وبصيره Metabolism والـ end product منه هوه الـ uric acid اللي اصلاً waste product والاصل يطلع by The Kidney in urine

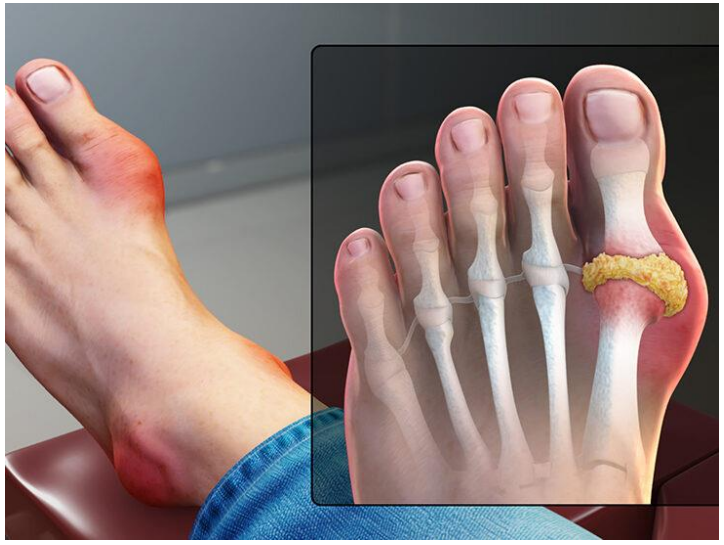
- ✓ Hippocrates described it as arthritis of the rich' due to the association with certain foods & alcohol.

اكل غني بالـproteins زي اللحوم والـsea food and alcohol

- ✓ Gout is caused by deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricaemia.

* الـ uric acid لما تزيد الـ Solubility الله لحد معين بالبلازما لما يوصل الـ saturation بصيره precipitation يترسب بالـ joints / soft tissues فبتين انها Mono sodium crystals هو نوع تحي من الـ crystals عشان نحكي انه الـ Pt تبعنا عنده gout

- ✓ Chronic hyperuricaemia is associated with disorders of purine metabolism due to under excretion or over production of uric acid.



- ✓ Gout usually presents as a monoarthritis in the first metatarsophalangeal joint (big toe) of the foot and is often referred to as podagra (from the Greek 'seizing the foot').

* هو منروح ازا فحصنا لـ Pt تبعنا وكان عنده Hyperuricemia انه يكون عنده gout. بس لو ما تعالج ممكن يؤدي انه يصير عنده gout

مشكلة

* يكون ال Pt اما عنده بال excretion of uric acid او production of uric acid

* مثلاً الناس اللي عندهم Leukemia او عندهم Hematolytic disease بال RBCs او خلايا الجسم يكونوا معرضين يصير عندهم Hyperuricemia ← Gout

* عادة بالبداية بيجي as single joint (Monoarthritis) بال Big toe of the foot اكثر شي

* يكون اسمها Podagra = لما يجي بال acute stage

inflammation in the acute stage

* متى يصير inflammation لما هاي ال crystals تصير تتوضع بال joints وتصير اقوى فأكيد لح تصير deep joint بال

Monosodium urate crystals preferentially form in cartilage and fibrous tissues where they are protected from contact with inflammatory mediators.

- ✓ The deposition of crystals may continue for months or years without causing symptoms; it is only when the crystals are shed into the joint space that inflammatory reaction occurs precipitating an acute attack of gout.
- ✓ The shedding of crystals can be triggered by a number of factors including direct trauma, dehydration, acidosis or rapid weight loss.

  ↳ Lactic acidosis, diabtec keto acidosis

  خبط المكان اصابا بالطارئة مثلاً
- ✓ The most appropriate time to measure serum urate for monitoring purposes is when the attack has completely resolved.

  عشان ناخد اصح قراءة
- ✓ Although the attack is extremely painful, it is usually self-limiting resolving spontaneously in 1–2 weeks.

  خلال 7-14 يوم الـ attack بتروح لحالها (self-limiting) بس احنا بنعالجها بـ anti-inflamatory agents
- ✓ Inappropriate management of gout can result in chronic tophaceous gout with polyarticular, destructive low-grade joint inflammation, joint deformity and tophi.

  affected joint تأثر على الـ Functions بيقلل

  Tophi → Chronic
  podgra → acute

✓ Risk factors:

- Hyperuricaemia is one of the main risk factors - occurs in about 15–20% of the population
- Genetics: Common primary gout in men often shows a strong familial predisposition (the genetic basis for this is not fully understood).

Men>women
بصيبهم الgout
خصوصاً قبل الmenopausal age
اما بعد هيك بتساو لانه ال estrogen بعطي protection

- Renal disease: Gout is frequently associated with kidney disease, each being a risk factor for the other.

Gout may lead to renal disease
والعكس كمان صح
Renal disease may lead to gout

بتكون kidney stones من ال Uric acid بترسبوا بال renal tissue بالتالي بأدي ل renal disease

- Co-morbidities

Box 54.1 Risk factors for gout
Genetics
Renal disease
Co-morbidities, for example, obesity, dyslipidaemia, glucose intolerance, hypertension
Diet
Alcohol consumption
Medication

[associated with each other]

- Studies have shown obesity, weight gain and hypertension all to be independent risk factors for the development of gout.
- Diet: Gout has often been associated with a rich lifestyle and excesses in diet (red meat, seafood, but not a diet high in purine-rich vegetables).

Animal source > Veg source

- Alcohol: Increased daily consumption of alcohol is associated with a higher risk of gout. Alcohol also raises lactic acid levels in blood, which inhibits uric acid excretion.

- Medication: A number of drugs are associated with increased uric acid levels - Table 109-2.

- Radiotherapy and chemotherapy in patients with neoplastic disorders can cause hyperuricaemia because of increased cell breakdown.

Thiazide diruices / aspirin indoses < 2g/day / niacin

بالنهايه رح metabolism of alcohol ال
ينتج عنها lactic acid الي بنتج عنه
inhibition of Uris acid excretion
purine غير انه كمان الكحول مصدر لل

Table 54.1 Causes of primary and secondary gout

Primary gout	Secondary gout
Idiopathic Rare enzyme deficiencies Hypoxanthine-guanine phosphoribosyl transferase deficiency (HPRT) Phosphoribosyl pyrophosphate synthetase super-activity Ribose-5-phosphate AMP-deaminase deficiency	**Increased uric acid production** Lymphoproliferative/ Myeloproliferative Chronic haemolytic anaemias Secondary polycythemia Severe exfoliative psoriasis Gaucher's disease Cytotoxic drugs Glucose-6 phosphate deficiency High purine diet overproduction **Reduced uric acid secretion** Renal failure Hypertension Drugs (diuretics, aspirin, ciclosporin) Lead nephropathy Alcohol Down's Syndrome Myxoedema Beryllium poisoning

اي شي بزيد او بقلل ال secretion of
Uris acid وما اله علاقه ب enzyme
deficiency or a defect in
enzymes
اله دخل بال metabolism of purine
يعتبر secondary cause

TABLE 109-2 Drugs Capable of Inducing Hyperuricemia and Gout

Diuretics	Ethanol	Ethambutol
Nicotinic acid	Pyrazinamide	Cytotoxic drugs
Salicylates (<2 g/day)	Levodopa	Cyclosporine

TABLE 109-3 Clinical Manifestations of Gout

Classic acute gout ("podagra")	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint, although other joints of the lower extremities are also frequently involved Affected joint is swollen, erythematous, and tender
Interval gout	Asymptomatic period between attacks
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues Complications include soft tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity May be confused with rheumatoid arthritis or osteoarthritis
Gouty nephropathy	Nephrolithiasis Acute and chronic kidney disease

* راحت توحت ال stage of gout اول

Presentation and diagnosis

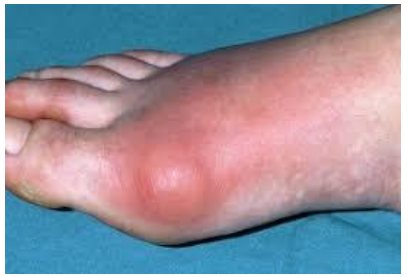
- ✓ An acute attack of gout has a rapid onset, with pain being maximal at 6–24 h of onset and spontaneously resolving within several days or weeks. → خلال 2 week تقريباً
- ✓ The first attack usually affects a single joint in the lower limbs in 85–90% of cases, most commonly the first metatarsophalangeal joint (big toe). Next most frequent joints: mid-tarsi, ankles, knees and arms.

↳ احد مفاصل قبل ال ankle بالرجل

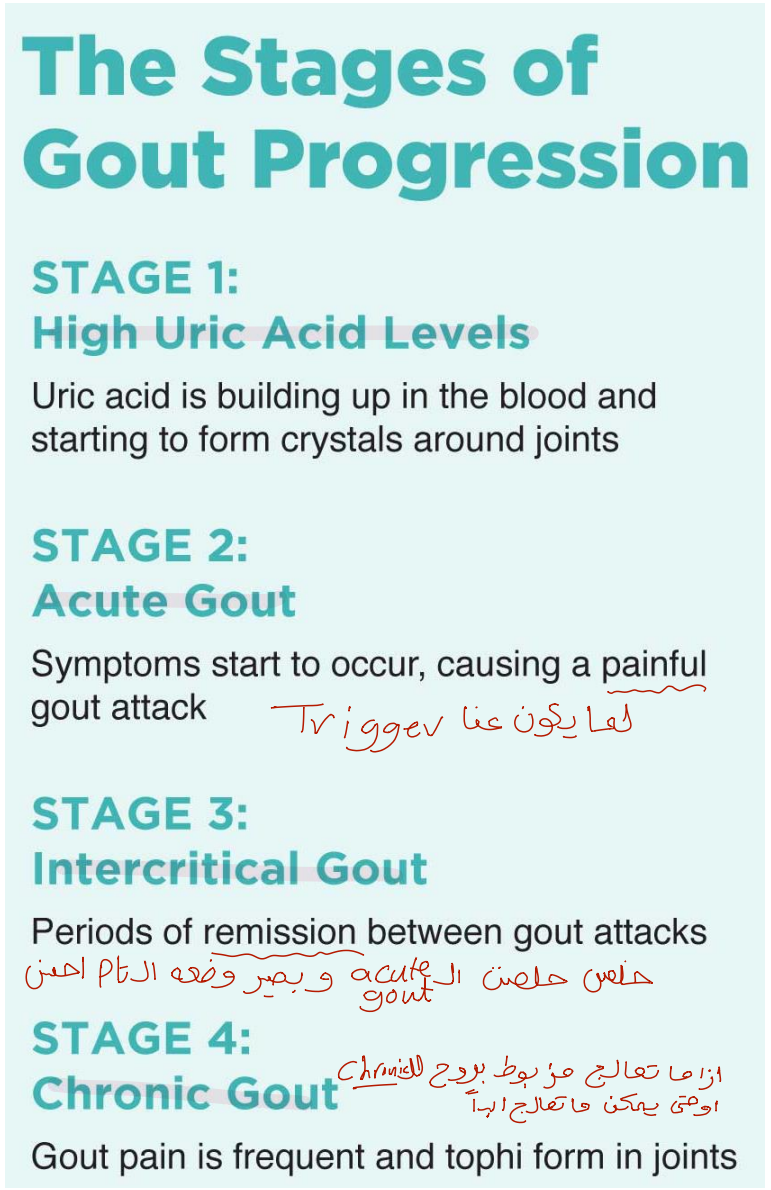
- ✓ The affected joint is hot, red and swollen with shiny overlying skin. Even the touch of a sheet on the affected joint is too painful for the patient to bear. → حاتحمل اي شي بسيط يلمس ال affected joint

- ✓ The patient may also have a fever, leucocytosis, raised ESR.
- ✓ The attack may also be preceded by prodromal symptoms as anorexia, nausea or change in mood.

↳ To expect ليتوقع انه انه رح تيجي ال attack ليتجي قبل ال attack



- ✓ The gold standard for the diagnosis of gout is the demonstration of urate crystals in synovial fluid or in a tophus.
- ✓ Gout & septic arthritis may co-exist & in order to exclude septic arthritis synovial fluid is sent for Gram staining and culture.
- ✓ The course of gout follows a number of stages; initially, the patient may be asymptomatic with a raised serum uric acid level.
- ✓ Some patients may only ever experience 1 attack, but often a 2nd attack occurs within 6–12 months.
- ✓ Subsequent attacks tend to be of longer duration, affect more than one joint and may spread to the upper limbs.
- ✓ Untreated disease can result in chronic tophaceous gout, with persistent low-grade inflammation in a number of joints resulting in joint damage and deformity.



لما يجي الواحد بـ Monoarthritis و ال Joint inflamed
هل ممكن يكون احد ال differtial diagnosis انه يكون septic arthritis

* aseptic ← بغي حاش M.O
septic ← في M.O ← اطفال ملتهبين بطريقة جرثومية (صعبة الكلمة والله)

* بكون في M.O عل inflamm اطفال مو Monosodium crystales اللي

* عشان هيك ال standerd goal بعمل aspiration of affected joint

* بما انه اخذنا عينة عل الجهتين بنعمل culter و aspiration
عشان عادي ممكن يكونوا السببين للـ inflamation > M.O
Monosodium crystales

- ✓ Tophi deposition can occur anywhere in the body, but they are commonly seen on the helix of the ear, within and around the toe or finger joints, on the elbow, around the knees or on the Achilles tendons.

CLINICAL PRESENTATION Acute Gouty Arthritis

General

- Gout classically presents as an acute inflammatory monoarthritis. The first metatarsophalangeal joint is often involved ("podagra"), but any joint of the lower extremity can be affected and occasionally gout will present as a monoarthritis of the wrist or finger. The spectrum of gout also includes nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

Signs and Symptoms

- Fever, intense pain, erythema, warmth, swelling, and inflammation of involved joints.

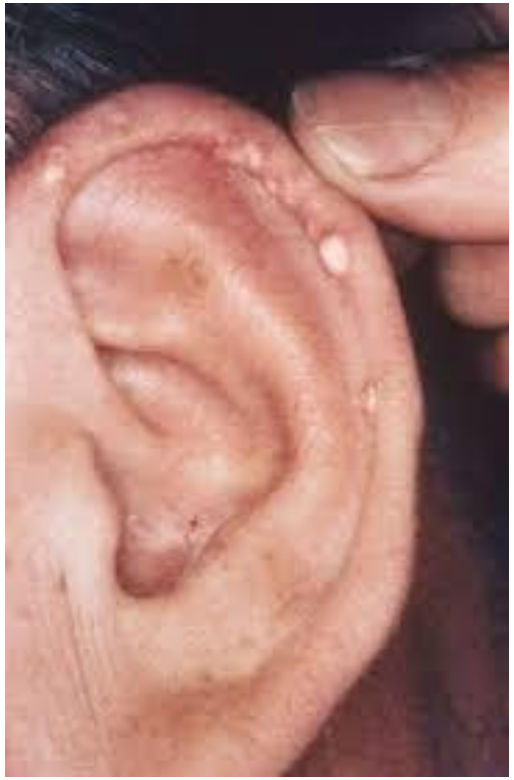
Laboratory Tests

- Elevated serum uric acid concentrations; leukocytosis.

Other Diagnostic Tests

- Observation of MSU crystals in synovial fluid or a tophus.
- For patients with long-standing gout, radiographs may show asymmetric swelling within a joint or subcortical cysts without erosions.

نفس الي قبل (بس زيادة سلايدات)



Treatment

- ✓ The management of gout can be split into the rapid resolution of the initial acute attack and long-term measures to prevent future episodes.

- ✓ Gout is often associated with other medical problems including obesity, hypertension, excessive alcohol and the metabolic syndrome of insulin resistance, hyperinsulinaemia, impaired glucose intolerance and hypertriglyceridaemia. This contributes to the increased CV risk & deterioration of renal function seen in patients with gout.

- ✓ Management is not only directed at alleviating acute attacks and preventing future attacks, but also identifying and treating other co-morbid conditions as HTN and hyperlipidaemia.

- ✓ Pharmacological measures should be combined with non-pharmacological measures as weight loss, changes in diet, increased exercise and reduced alcohol consumption.

- ✓ The prior 2012 ACR Guidelines for the Management of Gout have been criticized due to low quality of evidence supporting treat-to-target recommendations.

- ✓ Since the 2012 ACR Guidelines for the Management of Gout were published, several clinical trials have been conducted that provide additional evidence regarding the management of gout, leading the ACR Guidelines Subcommittee to determine that new guidelines were warranted.

- ✓ The strength of each recommendation was rated as strong or conditional.

- ✓ Strong recommendations reflect decisions supported by moderate or high certainty of evidence where the benefits consistently outweigh the risks, and, with only rare exceptions, an informed patient and his or her provider would be expected to reach the same decision.

- ✓ Conditional recommendations reflect scenarios for which the benefits and risks may be more closely balanced and/or only low certainty of evidence or no data are available.

- ✓ As data continue to emerge supporting best practices in management, implementation of these recommendations will ideally lead to improved quality of care for patients with gout.

Mangment of gout 2 phases

→ resolution of Acute attack by anti - inflamatory agents

→ Maintenance to prevent further attacks

* ممكن انه ال gout ← associated with many other conditions ← زي ال DM / HTN / Metabolic syndrome

معناها بدنا ناخد بعين الاعتبار ال other conditions الموجودين عند مريض

* الكتاب الي جايبين منه ال algorithm عاملينه 3 institutions ← موجودين اسمائهم تحت ال algorithm

* بال 2020 علو تغيرات على ال algorithm وهي الي اعتمدوها بسلايداتنا

Strong recommendation → Benift outweigh Risk (بطريقة واضحة)

Conditional = → Benift = Risk بتأرجح موضح فيه recommend → Balanced → فش هاد evedince القوي عن الموضوع

→ معظم الدراسات الي درست هاي النقطة كانت ال Benifet > Risk → consistently

→ والي بزيد ال Strength انه انت لما تشرح للمريض انه انت لما تاخد مثلا ال allpurinol بال acute attack لتحكيله ال Benifit ← 1,2,3 وال risk ← 1,2,3 . بتسأله عن رأيه . قراره هوه والدكتور غالبا هيك لح يكون مطابق لهاي الدراسات

مثلا : عنا دوا safe بتاخده مره بالاسبوع not associated بأي ddI وما به Monitring بعطيكي anti-coagulate effect وبحميكي من امراض الجلطات مقارنة انه تاخذي ال warfrin الي اله many ddI وكمان narrow Therapeutic index ولازم كل يوم توخذي حبه وممكن مرات تكون جرعتك نص حبه (الطرح) مين تختاري ؟؟ الكيه الاول ممكن once weekly ← بس غالي او مثلا اله مشكلة ثانية بس بوضوح ال Binfeet < risk بشكل واضح

Management of an acute attack:

- ✓ Drugs used in the management of an acute attack include NSAIDs, colchicine and corticosteroids.
- ✓ Treatment should be continued until the attack is terminated, usually between 1 and 2 weeks.
- ✓ The affected joints should also be rested for 1–2 days and initially treated with ice which has a significant analgesic effect during an acute attack.
- ✓ A complete medication review should be performed, and ideally medication which is likely to have contributed to the attack discontinued.

* نادرًا ما يكون الوضع ideal عنا

* فعلياً في ادوية ماقيدر نتركهم . صون بنحكي عن الوضع المثالي ideally انه ازا في فجال To DC بنوقفله اياهم . بس هنه فعلياً فو CI

- ✓ Losartan has been shown to have uricosuric properties and is a suitable agent in hypertensive patients with gout.

ARBs

- ✓ In patients with HF, diuretics are often essential and cannot be discontinued.

- ✓ Allopurinol should not be commenced during an acute attack as it may prolong or precipitate another attack. However, in patients already established on allopurinol therapy, allopurinol should always be continued during the attack.

- ✓ Aspirin at analgesic doses should be avoided as it blocks urate secretion. The continuation or initiation of low-dose aspirin (75–150 mg/day) is recommended in patients with cardiac disease as the benefits outweigh the minimal effect on serum uric acid levels.

- ✓ Maximum doses of an NSAID should be commenced rapidly after the onset of an attack and then tapered 24 h after the complete resolution of symptoms. The usual treatment period is 1–2 weeks.

- ✓ Overall, there is no convincing evidence to promote the use of one NSAID over another in the management of acute gout.

selective and non-selective ← nephropathy effect

selective ← worse on CV

non-selective ← gastropathy يعطوا

- ✓ COX-2 selective agents are recommended for use in patients who are at high risk of developing GI side effects, but they are not recommended for routine use. It should be noted that the selective benefit of COX-2 inhibitors is lost in patients taking low dose aspirin.

* ازا كان بياخد ال Pt aspirin بغير ياخد selective/non-selective هو ما بستفيد.

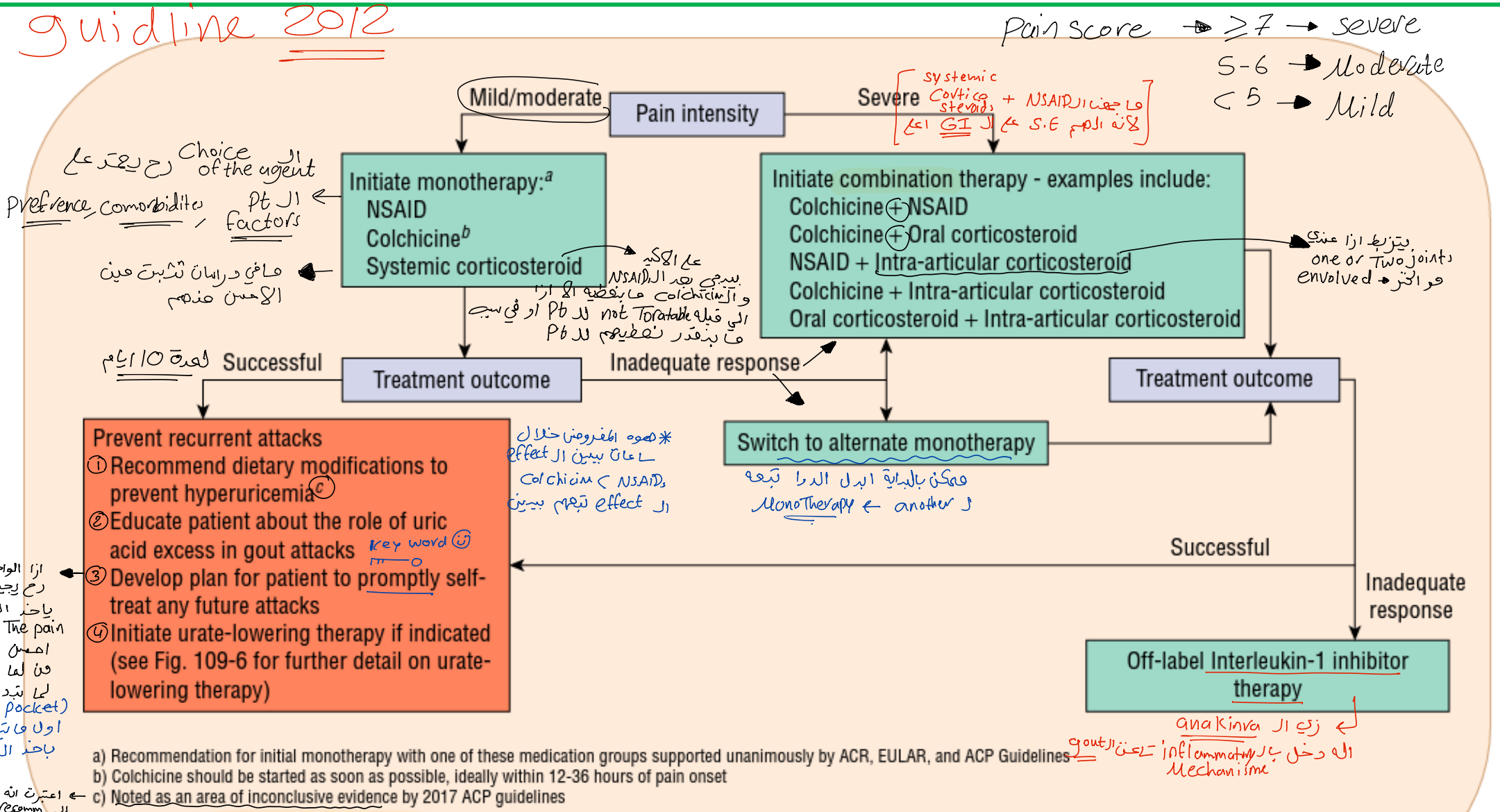
* ازا كان المريض عنده مشاكل بالGI بدنا مع aspirin ال PPI

- ✓ NSAIDs should be avoided in patients with HF, renal insufficiency and a history of gastric ulceration. Care should also be exercised in elderly patients with multiple pathologies.

- ✓ When prescribing an NSAID, the need for gastric protection should be considered in patients at increased risk of a peptic ulcer, bleed or perforation.

PPI ← ممكن نحتاج

guidline 2012



a) Recommendation for initial monotherapy with one of these medication groups supported unanimously by ACR, EULAR, and ACP Guidelines
b) Colchicine should be started as soon as possible, ideally within 12-36 hours of pain onset
c) Noted as an area of inconclusive evidence by 2017 ACP guidelines

Algorithm for management of an acute gout attack. (Algorithm derived from 2017 ACP, 2016 EULAR and 2012 ACR gout guidelines.)

Table 6. Gout flare management*

Recommendation	PICO question	Certainty of evidence
For patients experiencing a gout flare, we strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.	32	High†
For patients experiencing a gout flare for whom other antiinflammatory therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).	33	Moderate
For patients who may receive NPO, we strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.	32	High†
For patients experiencing a gout flare, we conditionally recommend using topical ice as an adjuvant treatment over no adjuvant treatment.	31	Low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; IL-1 = interleukin-1; ACTH = adrenocorticotropic hormone; NPO = nothing by mouth (nulla per os).

† High quality of evidence from network meta-analyses supporting canakinumab, which has superior mean pain score reduction and mean day-2 joint tenderness reduction. However, the Voting Panel raised concern that the comparator was weak (triamcinolone 40 mg) and that cost issues significantly favor other agents.

- ✓ **Colchicine** has a slower onset of action than NSAIDs but is recommended in patients where NSAIDs are contraindicated.

- ✓ It should be started as soon as possible after the onset of an attack.

- ✓ A substantially lower dose of colchicine (1.2 mg initially, followed by a single 0.6mg dose one hour later) was as effective as higher doses traditionally used (continued hourly dosing until symptoms subside or GI symptoms become intolerable).

- ✓ Common side effects associated with colchicine are abdominal cramps, diarrhea, nausea, vomiting, and rarely bone marrow suppression, neuropathy and myopathy.

- ✓ Side effects are more common in patients with hepatic or renal impairment.

- ✓ Colchicine is metabolised by CYP3A4 and excreted by p-glycoprotein; toxicity can be caused by drugs that interact with its metabolism and clearance, and this includes macrolides, cyclosporin and protease inhibitors.

TABLE 109-8 Colchicine Dosing in Special Situations/ Colchicine Drug Interactions

	Treatment of Acute Gout Flares	Prophylaxis of Gout Flares
Impaired Kidney Function[a]		
Mild/moderate (creatinine clearance = 30-80 mL/min [0.5-1.33 mL/s])	Dose adjustment not required	Dose adjustment not required
Severe (creatinine clearance <30 mL/min [<0.5 mL/s])	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	0.3 mg daily (starting dose)
Dialysis	Single 0.6-mg dose; treatment course should not be repeated more than once every 2 weeks	0.3 mg twice weekly (starting dose)
Hepatic Impairment[b]		
Mild/moderate	Dose adjustment not required	Dose adjustment not required
Severe	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	Dose reduction should be considered

Colchicine Drug Interactions		
Strong CYP3A4 Inhibitors • Atazanavir • Clarithromycin • Darunavir/ritonavir • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Nefazodone • Nelfinavir • Ritonavir • Saquinavir • Telithromycin • Tipranavir/ritonavir	Single 0.6-mg dose followed by 0.3 mg 1 hour later; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily
Moderate CYP3A4 Inhibitors • Amprenavir • Aprepitant • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice and related citrus products • Verapamil	Single 1.2-mg dose; dose to be repeated no earlier than 3 days	0.3-0.6 mg daily (0.6-mg dose may be given as 0.3 mg twice daily)
P-glycoprotein Inhibitors • Cyclosporine • Ranolazine	Single 0.6-mg dose; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily

a Treatment of gout flares with colchicine is not recommended in patients with impaired kidney function who are receiving colchicine for prophylaxis.

b Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis.

IV colchicine has resulted in fatalities and is no longer available.

- ✓ **Corticosteroids** are usually considered where use of an NSAID or colchicine is contraindicated or in refractory cases.

- ✓ They may be given intravenously, intramuscularly or direct into a joint (intra-articular) when only one or two joints are affected.

- ✓ In patients with a monoarthritis, an intra-articular corticosteroid injection is highly effective in treating an attack.

- ✓ Two different dosing strategies for oral corticosteroid therapy (prednisone or prednisolone) in the treatment of acute gout:
  - 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation or
  - 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days

- ✓ A hypothetical risk exists for a rebound attack upon steroid withdrawal; therefore, gradual tapering is often employed when discontinuing steroid therapy.

- ✓ The adverse effects of corticosteroids are generally dose and duration dependent.

- ✓ **Interleukin-1 inhibitors:** IL-1β is critically associated with the inflammatory response induced by monosodium urate crystals.

- ✓ Anakinra and canakinumab, have demonstrated efficacy in the treatment of acute gout. → Moderate evidance عليهم

- ✓ The EULAR and ACR guidelines suggest that IL-1 inhibitors can be considered for treatment of severe acute gout attacks refractory to other treatments.

Management of chronic gout:

- ✓ The presence of hyperuricaemia is not an indication to commence prophylactic therapy. → اذا عندك ال uric acid ب High level لا يعني انه نعطيه allopurinol

- ✓ Some patients may only experience a single episode and a change in lifestyle, diet or concurrent medication may be sufficient to prevent further attacks.

- ✓ Patients who suffer one or more acute attacks within 12 months of the first attack should normally be prescribed prophylactic urate-lowering therapy.

هاي الجملة عامة (رح نحكي عنها بالتفصيل قدام)

* ال urate lowering Therapy الي بنزلوا ال uric acid ياما بكونوا بقللوا ال production لل uric acid او بزيدوا ال excretion الها. همه 3 classes

* هدول مو indicated بحالة ال Hyperuricemia وحالها هوه indicated بحالة ال gout.

* طبعاً indicated بال gout لو في حاجة لاستعمالهم اصلاً ← زي مثلاً حد صابه gout مرتين بالسنة بكون indication انه ابلش معه urate lowering Therapy

- ✓ There are, however, some groups of patients where prophylactic therapy should be instigated after a single attack. These include individuals with uric acid stones, the presence of tophi at first presentation and young patients with a family history of renal or cardiac disease.

- ✓ Prophylactic treatment should not be initiated until an acute attack of gout has completely resolved.

- ✓ Once started, prophylactic treatment should be continued indefinitely even if further acute attacks develop.

- ✓ Drugs that lower serum uric acid can be classified into three groups according to their pharmacological mode of action.