Overview of the medical management of Crohn disease in adults

- The choice of therapy varies depending upon :
- the anatomic location of disease,
- the severity of disease,
- and whether the treatment goal is to induce remission or maintain remission.

Medical therapies that are used for Crohn disease include:

- Oral 5-aminosalicylates (eg, sulfasalazine, mesalamine)
- Glucocorticoids (eg, prednisone, budesonide)
- Immunomodulators (eg, azathioprine, 6-mercaptopurine, methotrexate

- Biologic therapies (eg, inɻiximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab, ustekinumab)

- **ASSESSING DISEASE ACTIVITY, SEVERITY, AND RISK**
- **Two** Crohn disease activity scoring systems ;
- Crohn Disease Activity Index (CDAI) .
- Harvey-Bradshaw Index (HBI) , which is a simplified derivative of the CDAI.

- In clinical practice, the following working definitions may be more useful :
  Clinical remission (CDAI <150); These patients are asymptomatic and without symptomatic inflammatory squeals .
- This status is achieved either spontaneously or after medical or surgical intervention.
- Patients requiring glucocorticoids to remain asymptomatic are **not** considered to be in remission but are referred to as being "steroid-dependent".

- Mild Crohn disease (CDAI 150-220) ;
- These patients are typically ambulatory and tolerating an oral diet.
- They have <10 percent weight loss,
- and no symptoms of systemic disease such as fever, tachycardia, abdominal tenderness,
- and no signs or symptoms of obstruction.

- Moderate to severe Crohn disease (CDAI 220-450) ;
- This group comprises patients who have failed treatment for mild to moderate disease ,
- or those patients with prominent symptoms such as ;
- fever, weight loss, abdominal pain and tenderness, intermittent nausea or vomiting, or anemia.

- Severe-fulminant disease (CDAI >450) ;
- Patients with persistent symptoms despite glucocorticoids or biologic agents (infliximab,adalimumab, certolizumab pegol, natalizumab, vedolizumab, or ustekinumab) as outpatients,
- or individuals presenting with high fever, persistent vomiting, intestinal obstruction, peritoneal signs, cachexia,
- or evidence of an abscess.

- **Low- versus moderate/high-risk patients**;
- In addition to the clinical parameters, the American Gastroenterological Association (AGA) ;
- stratifies patients into either a low or moderate/high risk category,
- by assessing inflammatory status with the following tests :

- Endoscopic evaluation for;
- mucosal ulcerations and stricturing and disease extent .
- Laboratory parameters:
- C-reactive protein and/or fecal calprotectin.
- Presence or absence of upper gastrointestinal involvement

- Low-risk patients with mild Crohn disease have the following features :
- No or mild symptoms,
- Normal or minimal elevation in C-reactive protein and/or fecal calprotectin levels,
- Diagnosis at age >30 years,
- Limited distribution of bowel inflammation,
- Superficial or no ulceration on colonoscopy,
- Lack of perianal complications,
- No prior intestinal resections,
- Absence of penetrating or stricturing disease

- There are two general approaches to the treatment of Crohn disease:
- **STEP-UP VERSUS TOP-DOWN THERAPY** ;

- **Step-up therapy –** Step-up therapy typically starts with less potent medications that are often associated with fewer side effects.
- Used in low risk patient.

- **Top-down therapy –**
- Top-down therapy starts with more potent therapies, such as;
- biologic therapy and/or immunomodulator therapy,
- relatively early in the course of the disease before patients become glucocorticoid dependent,
- and possibly even before they receive glucocorticoids .

- high-risk patients with moderate to severe Crohn disease;
- should be initiated on biologic or immunomodulator therapy in a top-down approach;

- **INDUCTION OF REMISSION**;
- Outpatient therapy with oral medications is appropriate for patients with mild Crohn disease,
- and choice of treatment will in part depend upon the distribution of disease.

- **Treatment goals**;
- The treatment goal for patients with Crohn disease is to achieve remission (endoscopic, histologic, and clinical remission) by demonstrating complete mucosal healing.

- **Ileum and/or proximal colon involvement**;
- The ileum is the region of the small bowel most often involved in Crohn disease.
- Patients with mildly active ileitis and/or colitis typically present with diarrhea and abdominal pain.

- **Budesonide** ,
- several society guidelines recommend enteric-coated budesonide as;
- the first line treatment for inducing remission in ;
- low-risk patients with mildly active Crohn disease of the ileum and proximal colon .

- Budesonide is started at 9 mg per day for at least four weeks,
- but not more than eight weeks.
- Budesonide is then tapered by 3 mg increments every two to four weeks for a total of eight to 12 weeks of therapy.
- not recommend using budesonide for longer than 12 weeks per course .

- In patients who cannot successfully taper budesonide by three to six months,
- treatment escalation with either a thiopurine or biologic is indicated, similar to treatment of moderate to severe Crohn disease.

- **Alternative agents**
  Prednisone ,
- Prednisone can be given to low-risk patients who do not respond to budesonide,
- The initial dose of prednisone is 40 mg per day for one week,
- gradual tapering by 5 to 10 mg per week should be started with the goal of discontinuing the prednisone over one to two months.

- **5-aminosalicylates**;
- The use of 5-aminosalicylates (5-ASA) for Crohn disease is controversial,
- limit its use to patients with mild Crohn disease with limited ileocolonic involvement who prefer to avoid glucocorticoids.
- For such patients, a slow release, oral 5-ASA agent is suitable, such as mesalamine (eg, Pentasa) .

- sulfasalazine (the prodrug of 5-aminosalicylate) is less useful for ileitis,
- because colonic bacteria must cleave the drug to release the active 5-ASA moiety,
- so it is reserved for cases of colitis.

- **Diffuse colitis or left colonic involvement**;
- For patients with mild, diffuse Crohn colitis or left-sided colonic disease,
- initial therapy with oral prednisone 40 mg per day for one week.

- gradual tapering by 5 to 10 mg per week should be started with the goal of discontinuing the prednisone over one to two months .

- Sulfasalazine (3 to 6 g per day over a course of 16 weeks),
- can be an alternative option for initial treatment of patients with mild colonic (left sided) Crohn disease .

- **Asymptomatic patients diagnosed incidentally**,
- For asymptomatic patients who undergo a routine, screening colonoscopy,
- and are incidentally found to have very small, shallow aphthous ulcers,
- A repeat ileo colonoscopy is performed in six to 12 months in addition to clinical monitoring.

- **Other sites of disease**
  Oral lesions,
- Aphthous ulcerations, the most common oral lesions,
- occur in 20 to 30 percent of adult patients with Crohn disease .
- The lip and buccal mucosa are the most commonly affected oral areas by Crohn disease.

- other lesions have been described including ;
- buccal swelling, granulomatous masses, cheilitis, and granulomatous sialadenitis.
- Oral lesions usually coexist with intestinal disease ,
- therefore respond to treatment directed at the intestinal disease.
- Topical medications, such as triamcinolone acetonide, can provide local symptom relief.

- **Patients who required induction therapy**;
- After clinical remission has been achieved in a patient with mild Crohn disease,
- the goal of management is to prevent clinical and endoscopic relapse.
- For patients who achieved remission with a glucocorticoid (eg, budesonide or prednisone),
- tapering and then discontinuing the glucocorticoid Is recommended,
- followed by clinical observation and ileocolonoscopy in six to 12 months.

- Conventional glucocorticoids (ie, prednisone) should not be used to maintain remission given their side effect profile .
- For patients who achieved remission with a 5-ASA agent (or sulfasalazine),
- continue the same agent for long-term maintenance therapy,
- And perform an ileocolonoscopy in 6 to 12 months .
  (although some societies advise against 5-ASA) .

- Alternative approaches to preventing relapse of Crohn disease include the following:
- Budesonide – When using budesonide, our goal is to induce remission over a 12-week period and then to stop this medication.
- However, in some patients who have difficulty tapering budesonide,
- we continue budesonide at a dose of 6 mg daily for no longer than three to six months.
- In patients who require glucocorticoids to maintain remission, we also initiate a thiopurine.

- **Immunomodulator;**
- Start an immunomodulator such as ;
- azathioprine, 6-mercaptopurine, or methotrexate .
- these agents are reserved for patients with ;
- moderate to severe disease
- and patients with mild Crohn disease who become glucocorticoid-dependent.

- **MANAGING RELAPSE**,
- In patients who have clinical recurrence after achieving remission following glucocorticoid therapy,
- second course of a glucocorticoid is recommended .
- Initiation of athiopurine and/or biologic therapy is also recommended.

- **OTHER THERAPIES**
  Antidiarrheal medications,
- Symptomatic treatment with antidiarrheal drugs ,
- for patients not responding completely to first-line therapy who have mild Crohn disease,
- antidiarrheal agents should not be given to ;
- Patient with complications such as strictures ,
- or those at risk for bowel obstruction,
- Patients with moderate or severe Crohn disease,

- loperamide as needed in small doses (ie, 2 to 4 mg after an episode of loose stool) .
- Cholestyramine or other bile sequestrants are other options for chronic watery diarrhea.
- It is also indicated for patients with previous ileal resections who have bile salt diarrhea.
- The initial dose is 4 g per day, which is increased as needed to 12 g per day in three divided doses.

- **Probiotics**
- The available data do not support clinical effectiveness of probiotic therapy for either induction or maintenance of remission in patients with Crohn disease .

- High-risk patients with moderate to severe Crohn disease may have the following features :
- Diagnosis at a younger age (<30 years)
- History of active or recent tobacco use
- Elevated C-reactive protein and/or fecal calprotectin levels
- Deep ulcers on colonoscopy

Long segments of small and/or large bowel involvement .

Perianal disease .

Extra-intestinal manifestations .

History of bowel resections .

- **THE ACUTELY ILL PATIENT WITH CROHN DISEASE**;
- The ill patient due to a complication such as ;
- partial small bowel obstruction, peritonitis, or a disease flare that is not responding to outpatient therapy.
- Should be hospitalized .

- Management may include ;
- intravenous fluid and electrolyte replacement,
- intravenous broad spectrum antibiotics,
- nutritional assessment,
- consultation with a gastrointestinal surgeon.
- Some patients may also require treatment with intravenous glucocorticoids or biologic therapy.

- **Partial small bowel obstruction**;
- Medical management with ;
- intravenous hydration, nasogastric suction,
- And parenteral nutrition ,
- is often successful with a response seen within 24 to 48 hours .

- For patients who do not have proximal small bowel dilation and who have no evidence of long strictures (>10 cm) (on cross sectional imaging),
- parenteral glucocorticoids can be used.
- Surgery is reserved for those patients who do not respond to medical management ,
- or who have evidence of small bowel ischemia.

- **Localized peritonitis**,
- medical management is the initial approach,
- A response to intravenous antibiotic therapy is usually seen within three to four days.

- Most patients will then be transitioned to oral antibiotics,
- but some patients may require up to two weeks of intravenous antibiotic therapy.
- A subsequent two- to four-week course of outpatient oral therapy with a fluoroquinolone and metronidazole,
- or equivalent broad spectrum antibiotics, is suggested.
- Intestinal resection should be considered in non responders.

- **Abscess** ,
- Patients with an intra-abdominal abscess should receive
- antibiotic treatment ,
- and either percutaneous or surgical drainage of the abscess,
- followed by surgical resection of the involved bowel segment.

- **Risk of venous thromboembolism**,
- Patients with inflammatory bowel disease (IBD) are at increased risk of venous thromboembolism and pulmonary embolism .
- prophylaxis with low molecular weight heparin for venous thromboembolism in all hospitalized patients with IBD is recommend.

- **INDUCTION THERAPY**

  Selecting induction therapy for patients with moderate to severe Crohn disease takes into account several factors including;

- patient preferences,
- patient characteristics (eg, age),
- disease characteristics (eg, fistulizing or penetrating disease),
- and response to prior therapy for Crohn disease.

- **Combination therapy**,
- For most patients with fistulizing moderate to severe Crohn disease (eg, perianal or intestinal fistula),
- combination therapy consisting of tumor necrosis factor-alpha (TNF) inhibitor (eg, infliximab) ,
- and an immunomodulator (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate) ,

- The dose of azathioprine can be gradually increased to a maximum of 2.5 mg/kg per day (6-MP can be increased to a maximum of 1.5 mg/kg per day).

- **Glucocorticoids**
- Glucocorticoids are commonly used for primary initial medical treatment for patients with moderate to severe Crohn disease
- who require more immediate symptom relief .
- A limited course (eg, eight weeks) of glucocorticoid therapy ,
- should serve as a "bridge" to a long-term maintenance treatment (usually with a thiopurine or a biologic agent).
-

- intravenouse glucocorticoids for patients who are hospitalized for an exacerbation of IBD.
- methylprednisolone 60 mg intravenously daily,
- if there are no contraindications such as;
- a bowel-related infection (eg, *Clostridioides* [formerly *Clostridium*] *difcile* or cytomegalovirus).
- If the patient responds to treatment and can tolerate oral intake,
- transition therapy to oral prednisone 40 mg daily.

- **MAINTENANCE THERAPY**

  Once clinical remission is achieved,

- an ileocolonoscopy is performed in 6 to 12 months.

- **Following remission achieved with anti-TNF agent regimen**,
- patients achieve remission following induction with combination therapy,
- then continue long-term treatment with a biologic agent and immunomodulator for one to two years.

- After one year of combination therapy ;
- patients are reassessed using markers of disease activity (eg, endoscopic evaluation of mucosal inflammation),
- prior to deciding if the immunomodulator can be discontinued .

- **Duration of maintenance therapy**,
- Generally The optimal duration of biologic or immunomodulator therapy as maintenance therapy is unclear,
- but many high-risk patients with moderate to severe Crohn disease will require life-long therapy with at least one agent.

- screen all patients for latent tuberculosis before starting anti-TNF therapy.
- annual testing for tuberculosis to patients on anti-TNF therapy who live in endemic areas.
- For those with new exposure to tuberculosis;
- a tuberculin skin test or interferon-gamma release assay such as QuantiFERON-TB Gold In-Tube assay is performed ,
- at that time and then annually.

- **Patients who lose response to anti-TNF therapy**,
- Immunogenicity failures ,
- Pharmacokinetic failures,
- Pharmacodynamics failures ,

- **Patients with low drug levels and positive anti-drug antibodies,**
- Immunogenicity failures :
- are characterized by low or absent drug trough levels in the presence of anti-drug antibodies.
- These patients should be switched to an alternative anti-TNF agent, especially in the presence of high anti-drug antibody titers.

- **Patients with low drug levels and negative anti-drug antibodies;**
- Pharmacokinetic failures :
- are characterized by low or absent drug trough levels in the absence of anti-drug antibodies.
- These patients require dose optimization by either dose escalation ,
- or shortening the dosing interval.

- **Patients with a normal drug level and negative anti-drug antibodies**;
- Pharmacodynamics failures :
- are characterized by adequate drug levels with absent anti-drug antibodies.
- These patients are managed by switching outside the anti-TNF class to another agent (eg, anti-integrin antibody).

- **Methotrexate**
- Methotrexate is an alternative for maintenance therapy for the patient ;
- who does not tolerate thiopurines,
- and may be preferable to azathioprine or 6-MP in patients with Crohn disease-related arthropathy.

- Methotrexate is initiated intramuscularly or subcutaneously,
- at a dose ranging from 12.5 mg once weekly (when used in combination with a biologic agent) ,
- or 15 mg once weekly (when used as monotherapy) to 25 mg once weekly .
- A clinical response is expected within three months.
- For patients on glucocorticoid therapy, the glucocorticoid should be continued during this period with a gradual tapering of the dose.
- Once a response to methotrexate is achieved,

- **Less effective therapies**
  — Although thiopurines are used as maintenance therapy,
- Thiopurine monotherapy is not recommended for induction of remission of Crohn disease .
- The slow onset of action of azathioprine (AZA) and 6- mercaptopurine (6-MP) results in a delayed clinical response.