TUMOR NECROSIS FACTOR INHIBITORS IN IBD

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- The basis for use of anti TNF in IBD is that tumor necrosis factor (TNF)-alpha has several biologic activities that may be directly related to the pathogenesis of IBD and to the dysregulation of the immune system that occurs in patients with IBD

Table of contents

TNF-alpha inhibitors

PRETREATMENT SCREENING

Contraindication

Dosing and administration

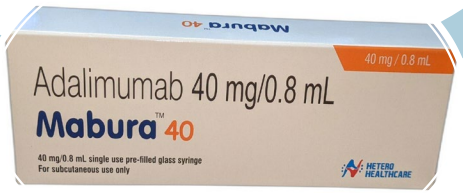
Follow up

Anti TNF Drug



cimzia®
(certolizumab pegol)





- The decision whether to use infliximab, adalimumab, or certolizumab pegol in patients requiring anti-TNF-alpha therapy is influenced by the
- Indication
- Patient preference
- Patient medical history
- vailability in individual countries

Infliximab

Infliximab is a chimeric monoclonal antibody comprised of 75 percent human and 25 percent murine sequences, which has a high specificity for and affinity to TNF-alpha.

Infliximab neutralizes the biologic activity of TNF-alpha by inhibiting binding to its receptors.

In contrast to some other TNF inhibitors (eg, etanercept), infliximab can also induce apoptosis of activated lymphocytes in the gut mucosa

Adalimumab

Adalimumab is a recombinant fully human monoclonal antibody that binds to TNF-alpha, thereby interfering with binding to TNF-alpha receptor sites and subsequent cytokine-driven inflammatory processes.

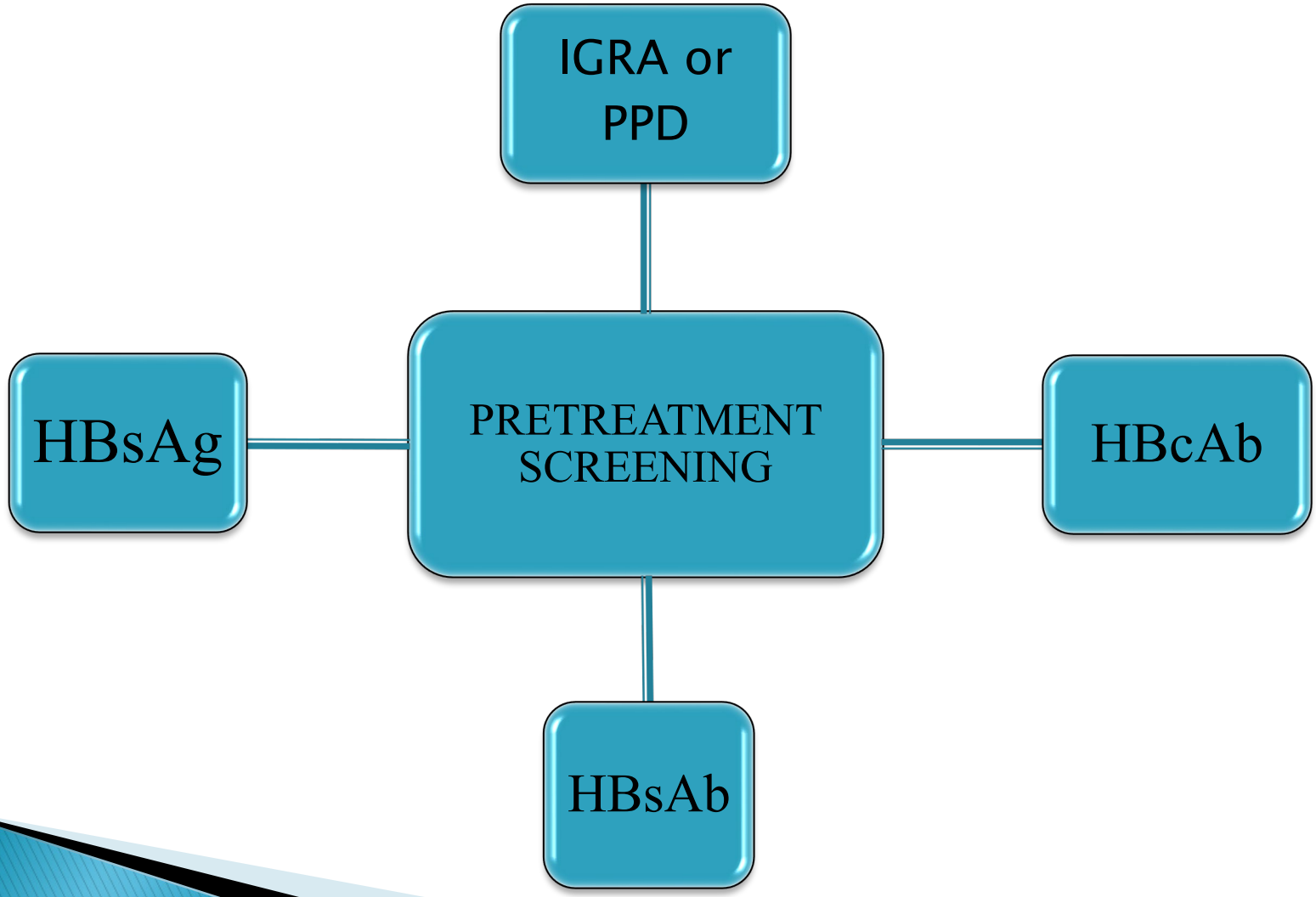
The humanized construction of adalimumab is presumed to lower the risk of forming anti-drug antibodies compared with infliximab.

Certolizumab pegol

Certolizumab pegol is a humanized monoclonal antibody Fab fragment linked to polyethylene glycol that increases its plasma half-life and reduces the requirement for frequent dosing, possibly reducing immunogenicity as well.

In vitro studies suggest that certolizumab pegol also has a higher binding affinity for TNF as compared with adalimumab or infliximab

PRETREATMENT SCREENING



If IGRA or PPD was positive





CONTRAINDICATIONS



Active, uncontrolled infection	Latent (untreated) tuberculosis	Demyelinating disease	Heart failure (New York Heart Association class III/IV	Active lymphoma

ADMINISTRATION

The induction dose of Infliximab for treatment of patients with moderately to severely active Crohn disease, including fistulizing disease, is 5 mg/kg

Induction therapy with Adalimumab is given subcutaneously with the following regimen :Week zero, initial dose: 160 mg once

The recommended dose of certolizumab pegol for induction of remission in Crohn disease is 400mg subcutaneously at weeks zero, two, and four, and then every four weeks for maintenance therapy

Infliximab

Adalimumab

Certolizumab pegol

Golimumab

The recommended induction dose for golimumab is 200 mg subcutaneously at week zero, then 100 mg at week two, followed by weight-based maintenance therapy

1. For patients with actual body weight ≥80 kg – 100 mg every four weeks
2. For patients with actual body weight <80 kg – 50 mg every four weeks

Infliximab

Adequate response

- repeat infusions of 5 mg/kg, usually every eight weeks

Incomplete response

- Dose escalation can be accomplished by either decreasing the dosing interval or The maximal dose of Infliximab is 10 mg/kg every four weeks

alternative to intravenous

- Injection Infliximab 120 mg is given subcutaneously once every two weeks

Adalimumab

For patients who have a disease flare while on maintenance dosing, the dosing interval can be shortened to every week

A large number of factors predicted loss of response or need for dose escalation in patients treated with adalimumab

1. male sex
2. high body mass index
3. current/former smoking
4. family history of inflammatory bowel disease
5. isolated colonic disease
6. Extraintestinal manifestations
7. 80/40 mg induction therapy
8. longer disease duration
9. greater baseline Crohn Disease Activity Index
10. concomitant glucocorticoid use
11. absence of deep remission at week 12
12. low serum trough concentrations of adalimumab
13. Previous infliximab non-response
14. Prior treatment with an anti-TNF-alpha agent

Certolizumab pegol

For patients who have loss of response while on maintenance dosing and who are candidates for dose escalation, options include shortening the interval between doses (eg,every two to three weeks) or giving a single re-induction dose (ie, 400 mg) between scheduled four-week doses

MONITORING

- In addition to clinical observation
  - Monitoring the response to anti-TNF agents may include
- Therapeutic drug monitoring (checking drug trough levels, anti-drug antibodies) and levels of biomarkers CRP, fecal calprotectin.

Infliximab	• ≥5 mcg/mL for luminal disease. • Some but not all studies have reported that trough level of ≥10 mcg/mL has been suggested for patients with fistulizing disease
Adalimumab	• ≥7.5 mcg/mL.
Certolizumab pegol	• ≥20 mcg/mL
Golimumab	• ≥1 mg/mL

Therapeutic drug monitoring IN Patients with active disease despite maintenance therapy

A guideline from the AGA suggests that adult patients with active inflammatory bowel disease who are being treated with an anti-TNF agent receive reactive therapeutic drug monitoring using drug trough levels and anti-drug antibodies The drug trough level should be drawn no more than 24 hours prior to the next scheduled dose of the drug.

Therapeutic drug monitoring

- Therapeutic drug monitoring involves measuring serum drug trough concentrations and anti-drug antibodies to optimize the use of anti-TNF agents for patients with IBD
- Therapeutic drug monitoring can be used proactively by targeting specific drug trough concentrations for patients in remission
- Approximately 40 percent of patients who initially achieve remission will develop secondary loss of response during the first year of therapy

- Reactive drug monitoring in this setting can help the clinician decide whether a dose increase is needed or if switching to a different drug is preferred

Interventions based on therapeutic drug monitoring in patients with inflammatory bowel disease and loss of response to anti-TNF agents

Interventions based on therapeutic drug monitoring in patients with inflammatory bowel disease and loss of response to anti-TNF agents

Anti-drug antibody (ADAb)	Drug trough concentration*	
	Inadequate (subtherapeutic)	Adequate (therapeutic)
Undetectable	Non immune-mediated pharmacokinetic failure: Escalate dose of index drug ¶	Mechanistic failure: Switch to drug out of class Δ
Detectable	Immune-mediated pharmacokinetic failure: If low level ADAb: escalate dose of index drug ¶ If high level ADAb: switch to drug in class ◊	Mechanistic failure: Switch to drug out of class

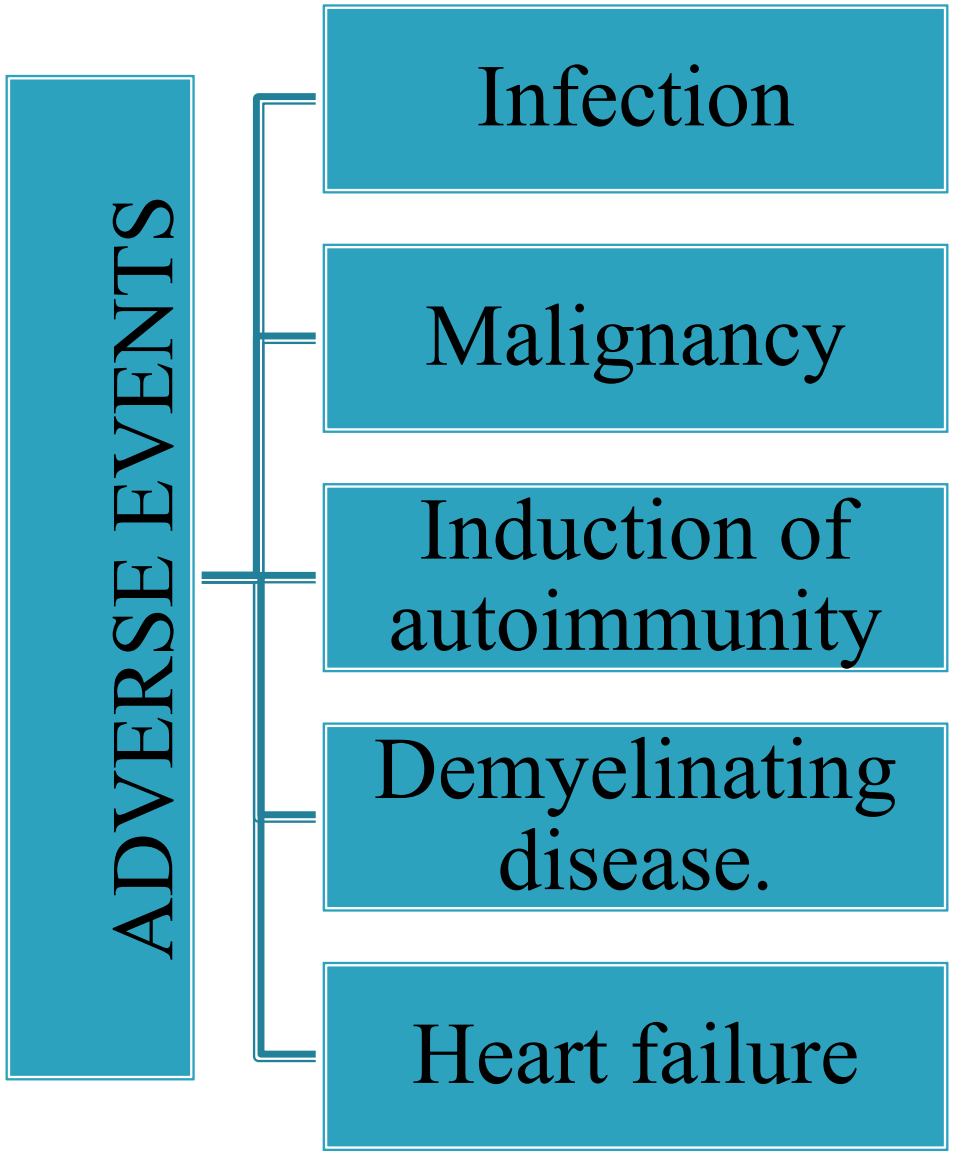
For patients with anti-drug antibodies who switch to a different biologic agent within the same class, the addition of an immunomodulator may be helpful.

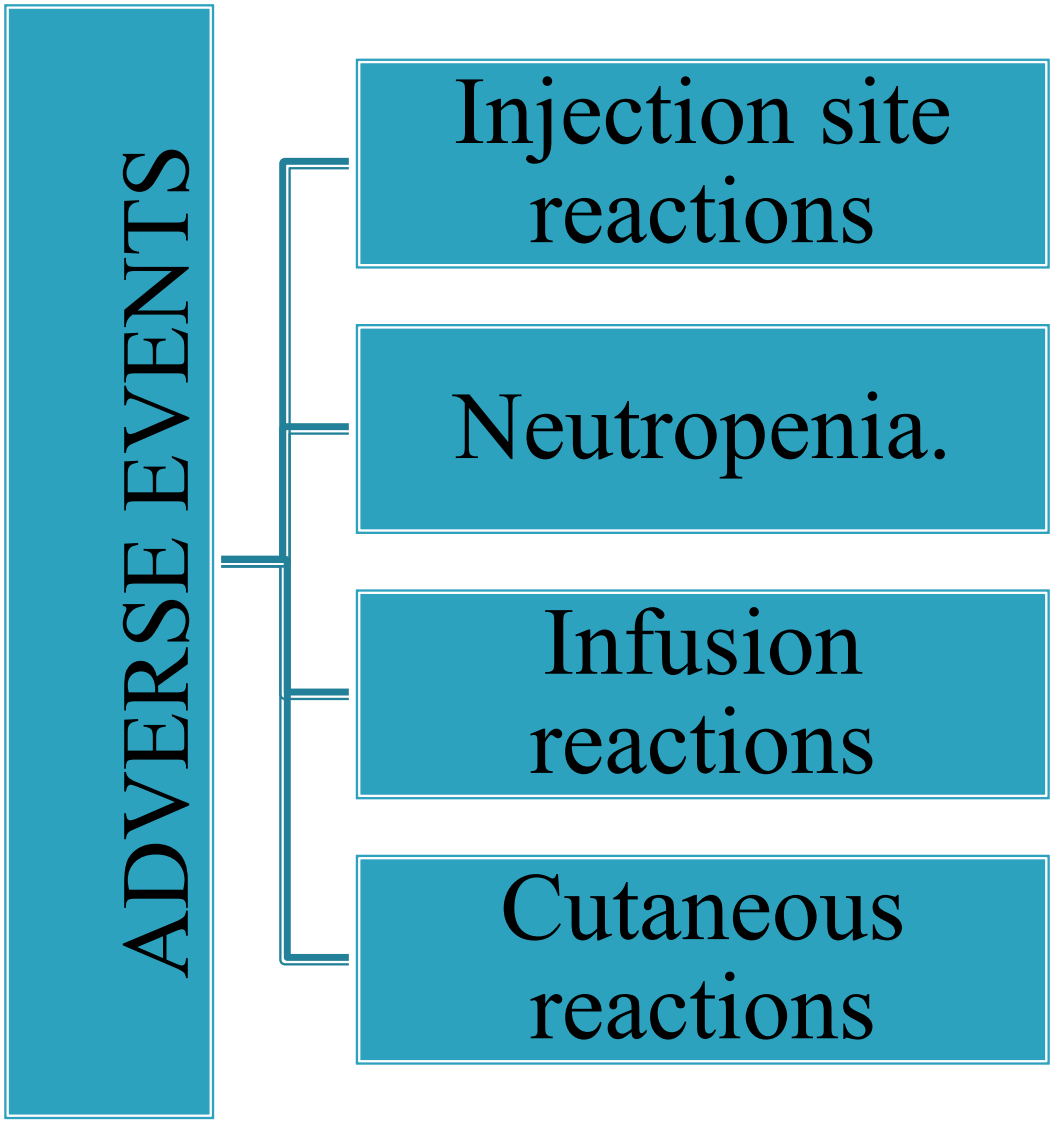
The use of immunomodulators (ie, azathioprine, 6-mercaptopurine or methotrexate) decreases the rate of formation of antibodies to anti-TNF agents and results in higher response and remission rates

Practical recommendation for proactive monitoring in remission

While therapeutic drug monitoring is useful in the setting of active IBD (ie, reactive drug monitoring), we do not routinely use therapeutic drug monitoring for patients in clinical remission (ie, proactive drug monitoring) because data from randomized trials suggested that proactive monitoring did not improve outcomes.

We reserve proactive monitoring for patients who are at higher risk of complications from a disease flare


ADVERSE EVENTS
Infection
Malignancy
Induction of autoimmunity
Demyelinating disease.
Heart failure


ADVERSE EVENTS
Injection site reactions
Neutropenia.
Infusion reactions
Cutaneous reactions

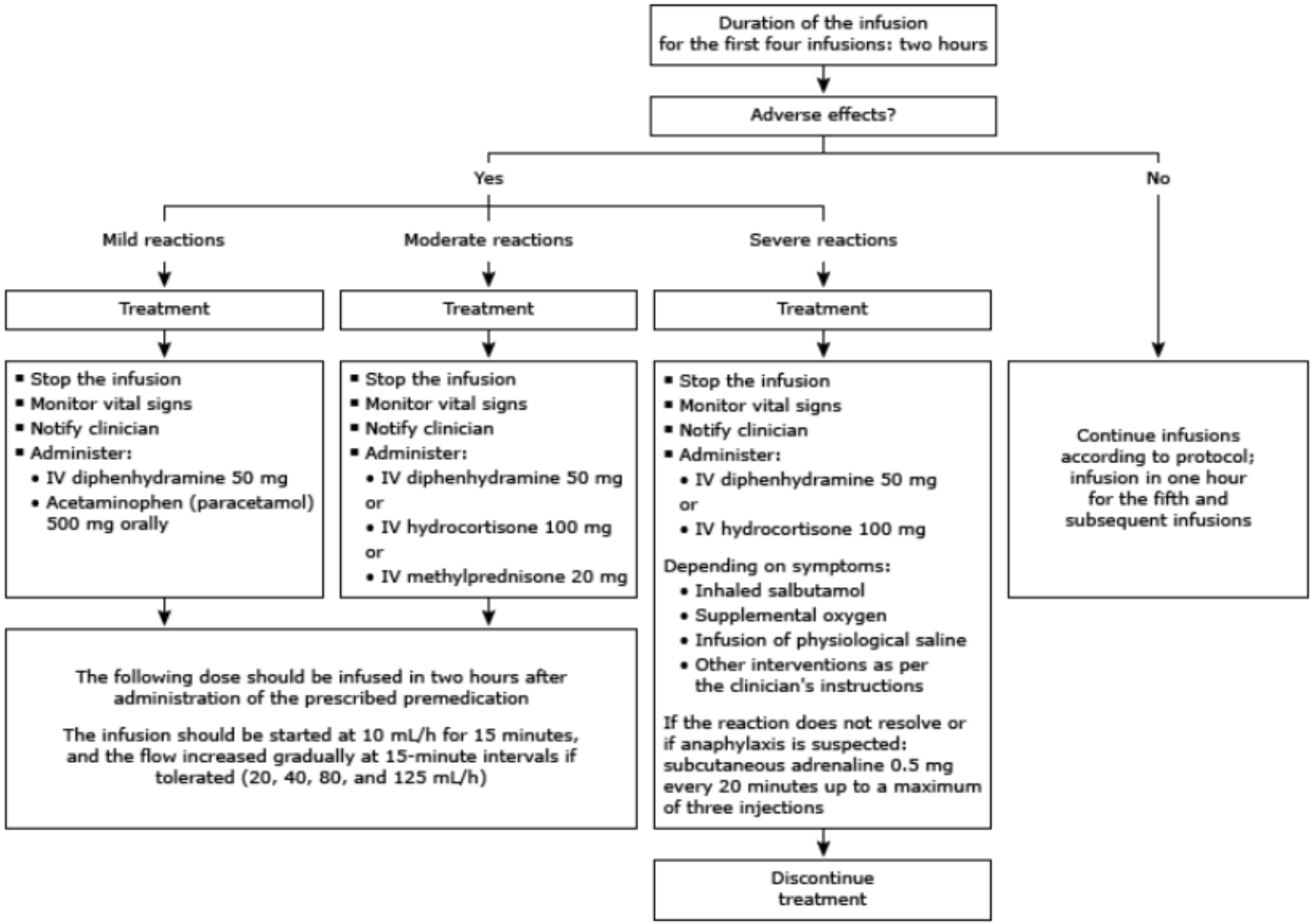
Risks with combination therapy

The risk of lymphoma in patients on infliximab (or other anti-TNFagents) in combination with an immunomodulator (azathioprine or 6-mercaptopurine), along with an increased incidence of infections in patientson more than one immunosuppressive agent, has led to the use of anti-TNF monotherapy in some patients with IBD

Long-term thiopurine use (more than two years) appears to be a common denominator in cases of hepatosplenic T-cell lymphomas


THANKS FOR YOUR ATTENTION

Procedure to be followed in the case of an acute reaction to infliximab infusion



NYHA and other classifications of cardiovascular disability

Class	NYHA functional classification [1]	Canadian Cardiovascular Society functional classification [2]	Specific activity scale [3]
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.	Patients can perform to completion any activity requiring ≥7 metabolic equivalents (ie, can carry 24 lb up 8 steps; do outdoor work [shovel snow, spade soil]; do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.	Patients can perform to completion any activity requiring ≥5 metabolic equivalents (eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance foxtrot, walk at 4 mph on level ground) but cannot and do not perform to completion activities requiring ≥7 metabolic equivalents.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight in normal conditions.	Patients can perform to completion any activity requiring ≥2 metabolic equivalents (eg, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping) but cannot and do not perform to completion any activities requiring >5 metabolic equivalents.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.	Patients cannot or do not perform to completion activities requiring >2 metabolic equivalents. Cannot carry out activities listed above (specific activity scale III).

Interventions based on therapeutic drug monitoring in patients with inflammatory bowel disease and loss of response to anti-TNF agents

Anti-drug antibody (ADAb)	Drug trough concentration*	
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Detectable	Immune-mediated pharmacokinetic failure: ▪ If low level ADAb: escalate dose of index drug¶ ▪ If high level ADAb: switch to drug in class◇	Mechanistic failure: ▪ Switch to drug out of class

Administration of infliximab: Guidelines for drug administration and the recognition and initial approach to infusion reactions

Description
Intravenous (IV) administration of infliximab, a tumor necrosis factor-alpha antagonist biologic therapy. Infliximab, a chimeric antibody, is administered in the form of periodic infusions (zero, two, and six weeks and, depending on the subsequent course of the disease, every six to eight weeks thereafter).
Contraindications to treatment
Known hypersensitivity to the drug or murine proteins
Active systemic or localized infections
History of infection related to a prosthesis that remains in place
Infection with human immunodeficiency virus
Active infection with hepatitis B virus
Congestive heart failure classified on the New York Heart Association scale as functional class III/IV
History of demyelinating disease
History of cancer (except when there has been no recurrence in the preceding five years and in the case of patients with basal cell carcinoma)
Patients with a history of systemic lupus erythematosus
Live vaccines should not be administered during treatment: yellow fever, German measles, measles, polio, or bacillus Calmette-Guérin (BCG)

Patient care during IV administration of infliximab

Patient care during IV administration of infliximab
Objectives
To prepare patients physically and psychologically so that they undergo treatment in the best possible conditions
To ensure the patient's safety throughout the infusion process
To prevent treatment-related problems and ensure prompt detection of any such problems
Preparation of the patient before the procedure
Ascertain what the patient knows about the treatment they are about to receive
Patients may eat breakfast or lunch and take their usual medication unless they have a history of moderate to severe infusion reactions (risk of vomiting)
Make the patient comfortable in a seat or bed, depending on the preference and physical state of each individual
Check whether the patient's chart includes an order for laboratory testing before the procedure, and whether premedication has been prescribed
Personnel: nursing staff
Procedure
Personnel: nursing staff
Materials: ▪ Esmarch bandage ▪ Cotton ▪ Antiseptic ▪ 20 G catheter ▪ Catheter securement dressings ▪ Pump ▪ Filter (pore size ≤1.2 microns) ▪ Infusion pump ▪ 10 mL syringe ▪ 21 G needle ▪ 10 mL of double-distilled water for each vial of infliximab ▪ Infliximab (store in refrigerator at between 2 and 8°C) ▪ 250 mL of 0.9% saline solution

Implement laboratory testing order, if any, prior to infusion
Administer prescribed premedication, if any. This can only be diphenhydramine or hydrocortisone.

Implement laboratory testing order, if any, prior to infusion. Administer prescribed premedication, if any. This can only be diphenhydramine or hydrocortisone.
Check arterial blood pressure, heart rate, respiratory rate, and temperature at the start and after completion of infusion and whenever required by the patient's physical condition
Preparation of the drug
Aseptic technique
Reconstitute each 100 mg vial of infliximab with 10 mm of double-distilled water
Aim the double-distilled water against the side of the vial to prevent foaming
Ensure that the contents of the vial have dissolved completely, but avoid prolonged and energetic movements
Allow the solution to stand for five minutes
The solution should be colorless to slightly yellowish and may contain translucent particles (protein) ▪ The solution should not be administered if it is inappropriately colored or contains visible opaque particles
From the bottle of saline solution, withdraw a volume of saline equal to the volume of infliximab solution to be used in order to obtain a final volume of 250 mL and a concentration of between 0.4 and 4 mg/ml
The solution must be infused within three hours of reconstitution
Never dissolve infliximab in dextrose solution
Cannulate the venous line
Administer the drug using a volumetric infusion pump ▪ The first, second, third, and fourth infusions should be administered over two hours (125 mL/hour) ▪ Starting with the fifth infusion, the dose can be infused in one hour (250 mL/hour)
Assess response to treatment; if the patient does not present any anomalous symptoms, he or she can be discharged and return to normal daily activity
Patients must be instructed to telephone their clinician or the nursing staff if they experience any reaction symptoms after the infusion
Observations
Infusion time can be modified by the clinician responsible for the patient

Description of problems related to the procedure and remedial action

Acute infusion reactions		
Mild in the presence of	**Moderate in the presence of**	**Severe in the presence of**
▪ Headache ▪ Diaphoresis ▪ Throat irritation ▪ Lumbar pain ▪ Hyperemia ▪ Nausea ▪ Palpitations ▪ Itching ▪ Cutaneous eruption ▪ Flushing ▪ Vertigo ▪ Vomiting	The same symptoms as mild reactions and ▪ Dysphagia ▪ Hypotension or hypertension (± 20 mmHg with respect to baseline) ▪ Chest pain or tightness ▪ Edema of the face, hands, or lips ▪ Suffocating sensation ▪ Hyperemia (accompanied by a sensation of heat or fever) ▪ Hyperthermia (<39°C) ▪ Palpitations, tachycardia ▪ Urticaria	The same symptoms as moderate reactions and ▪ Severe hypotension or hypertension (± 40 mmHg with respect to baseline) ▪ Hyperthermia and chills (≥39°C) ▪ Swelling of the larynx or pharynx with stridor ▪ Dyspnea ▪ Severe bronchospasm ▪ Convulsive seizure ▪ Clinically significant chest pain
Action to be taken: ▪ Stop the infusion ▪ Monitor blood pressure, heart rate, respiratory rate, and temperature ▪ Notify the treating clinician ▪ If the reaction does not resolve, follow appropriate procedures for management of an acute reaction to infusion of infliximab ▪ If extravasation occurs, stop the infusion immediately, notify the treating clinician, attempt to aspirate the extravasated fluid with a 10 to 20 mL syringe, withdraw the IV line, mark the affected area, and follow the hospital's treatment protocol covering such events		

Important points

To ensure early detection of infusion reactions, monitor the patient's response to treatment
Ensure that the intravenous line is open
Assessment indicators
The nursing record should include details of the results of vital signs monitoring before and after treatment
The nursing record should provide details of the assessment of tolerance to treatment, that is, the occurrence or absence of incidents
Records
The following information should be recorded: ▪ Vital signs ▪ The assessment and preparation of the patient prior to treatment ▪ Incidents (presence or absence) related to the procedure ▪ Assessment of the patient's condition after treatment