

Prevention of side-effects and complications:

Immunosuppressive drugs and anti-TNFs in IBD

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1. Specific side effects
 1. Immunosuppressive drugs
 2. Anti-TNFs
2. Prevention of severe/opportunistic infections
3. Prevention of tuberculosis
4. Prevention of HBV reactivation
5. Prevention of lymphoma and cancer
6. Pregnancy and lactation

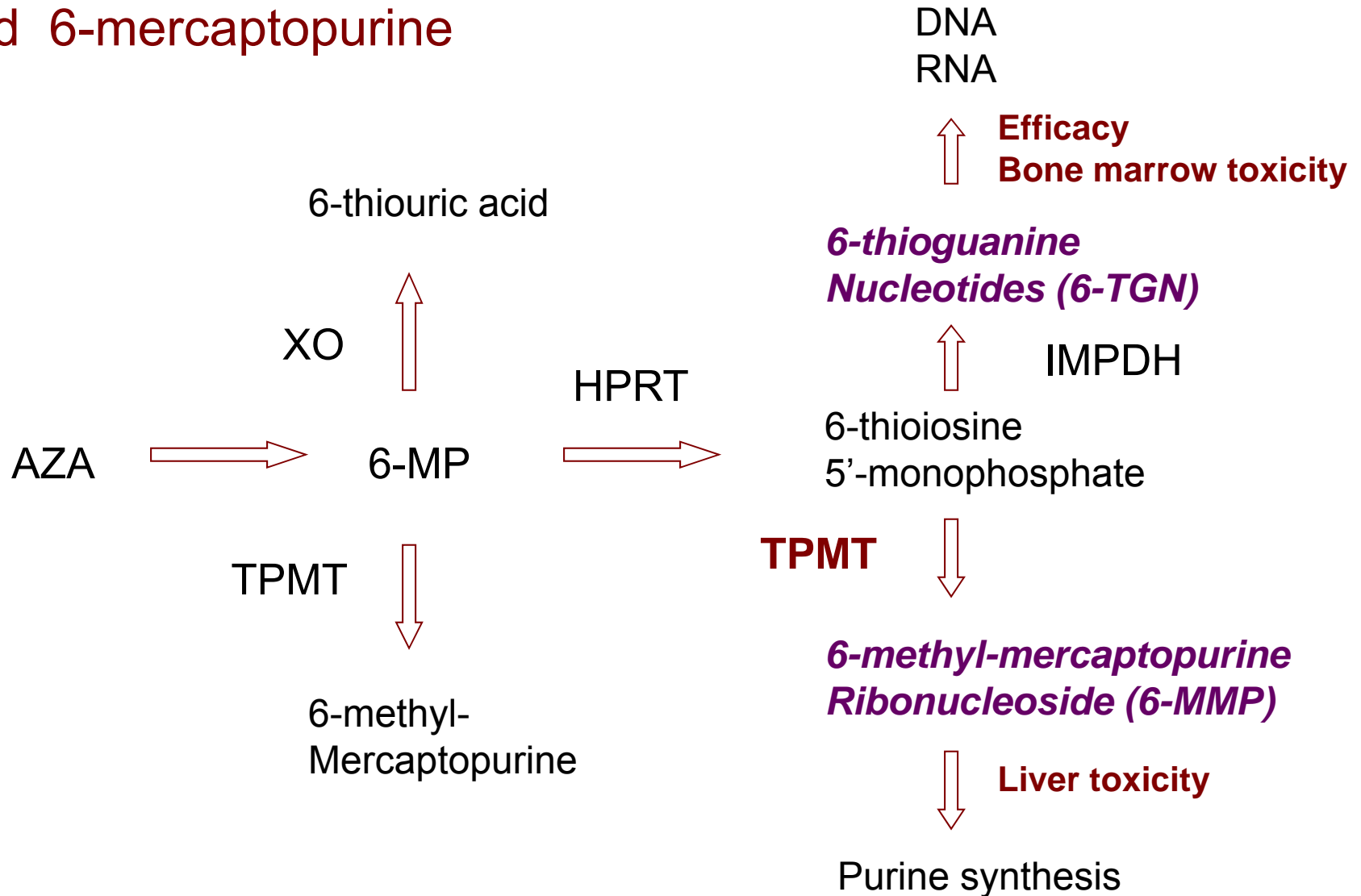
Will not be presented:

- List of side-effects/complications
- Treatments of complications

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Metabolism of azathioprine and 6-mercaptopurine



Azathioprine/6-MP

Bone marrow, liver and pancreas toxicity: check list

TPMT Genotype or Activity (phenotype) before starting therapy

- Predicts only 25% of leucopenia
- TPMT Activity is less reliable (drugs interactions)
- TPMT genotype* is robust
 - *Low methylator (0.3%)*
 - *Intermediate methylator (11%)*
 - *High methylator (88%)*

*TPMT 2,3A, and 3C = 95% of all mutations

CBCs, amyl/lipase and LFTs 1st, 3rd and 8th week
and then every 2-3 months

Azathioprine/6-MP

Tailoring dose according to TPMT phenotype (genotype)

TPMT activity	AZA recommended dose	Major active metabolite	Mechanism of action	Therapeutic 6-TGN levels	Potential myelotoxicity
Very high (> 26.1 U/ml)	3.0 mg/kg/day	methylated ribonucleotides	Antimetabolic	Low	Delayed
High (> 18.1 -26 U/ml)	2.5 mg/kg/day	methylated ribonucleotides	Antimetabolic	Low	Delayed
Intermediate (13.8-18 U/ml)	1.5 mg/kg/day				
Low (5.1-13.7 U/ml)	0.5 mg/kg/day	6-Thioguanine nucleotides	Apoptotic	High	Acute
Very Low (< 5 U/ml)	0.125 mg/kg/day	6-Thioguanine nucleotides	Apoptotic	High	Acute

(adapted from Cara ; ref : 50)

Methotrexate

Bone marrow, lung and liver toxicity: check list

Rule out pre-existing liver (alcohol, obesity and liver diseases) and lung disease

Clinical evaluation of lung function (dyspnea, dry cough, fever, cyanosis, tachypnea, gazometry and chest xray)

CBC, albumine and LFTs every week during 2 months and then every 3 months

Add Folinic acid 15 mg PO /w

Liver biopsy: No! unless persistent ALFTs in patients with risk factors for hepatic toxicity (alcohol abuse, obesity, preexisting liver disease)

Cyclosporine

Nephrotoxicity, encephalopathy, HBP and PCP: Check list

- Check and follow creatinine, urea, K⁺, Uric acid, Mg⁺⁺ and cholesterol levels prior and during cyclosporine administration
 - cyclosporine dose should be decreased (25-50%)
 - if serum creatinine increases by 25% (neprotoxicity)
 - if the cholesterol level is below normal (seizures)
- Follow cyclosporine blood levels (<300 ng/ml)
- Follow blood pressure
- Clinical evaluation of lung function (dyspnea, dry cough, fever, cyanosis, tachypnea, gazometry and chest xray)
- PCP Prophylaxis
- Check for drug interactions

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Contraindications to anti-TNF therapies

- Allergy to mouse products (infliximab)
- Ongoing viral, fungal, bacterial or parasite infections
- Abscess
- TB
- Congestive heart failure
- Demyelinating diseases
- Lupus and (vasculitis)
- Previous history of cancer or lymphoma

Molecule specific complications

(related to antibodies) Immunogenicity

- Infusion reactions (type 1)
 - site injection reaction
- Serum sickness (type 3) and type 4 hypersensitivity
- Loss of response

Class specific complications

(related to TNF inhibition)

- Serious and opportunistic Infections (TB reactivation)
- Malignancies (non-hematological)
- Lymphoma
- Mortality
- Others (auto-immunity, vasculitis,..)

Disease specific

- Intra-abdominal sepsis

Recommendations to prevent immunogenicity

1. 3-dose instead of 1-dose induction (infliximab)
2. Scheduled maintenance
 1. Infliximab: Q8 weeks
 2. Adalimumab: EOW or EW
3. Combination with azathioprine/6-MP
 1. Infliximab: evidence-based
 2. Adalimumab: not evidenced based (no data)
4. Prophylaxis with IV hydrocortisone (infliximab)
Primary prophylaxis (if no combination therapy)
Secondary prophylaxis if infusion reactions
Primary prophylaxis in honey moon (re-treatment)

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Facts: prevention of severe and opportunistic infections with immunosuppressive drugs and anti-TNFs

- The average rate of severe infections is **1%** and opportunistic infections is **0.1%** with anti-TNF therapies
- There is **no increase of severe infections** in CD patients treated with anti-TNF (cohorts, registries, post-marketing surveillance and population based-studies)
- The risk of severe infections is related to **narcotics use, moderate- to-severe disease, and steroids use.**
- From RA data, there is a 2 fold increase in the risk of severe infections with anti-TNF therapies
- There is an obvious additive or synergistic risk for opportunistic infections with bi- or tri- combination therapy

Infections : how to avoid them ?

- Primary and secondary prophylaxis

TB, PCP, HBV, HSV, P. Jiroveci, fungal infection...

(i.e. Bactrim in patients treated with cyclosporine or bi- or tri- combotherapy)

- Special situation (travel): long term travelers

Tuberculin skin test or interferon-gamma release assay (IGRA) before departure.

If negative, it should be repeated approximately 8-10 weeks after returning

Blood test (eos) , stool cultures for ova/parasites and serology (strongyloidosis)

Precautions with food and water

- Food/ lifestyle

Avoid raw egg and vegetables, uncooked meat, and unpasteurized

milk/cheese (Salmonella and listeria) and direct contact with soil or inhalation of soil

contaminated dust (nocardia)

- Vaccination and work up before/during IM

General work up: history, TB testing and serology before starting IM therapy

- History of bacterial, fungal and parasite infections
- Risk of latent or active tuberculosis, TB testing and Xrays
- History of vaccination (vaccination card: Polio, DTP and MMR)
- History and serology of varicella-zoster virus infection (chickenpox/shingles)
- History and serology of herpes simplex virus infection
- History and serology for hepatitis B
- HIV serology
- History of travel and/or living in tropical area or countries with endemic infections / Future plans to travel abroad to endemic areas
- Eosinophil cell count, stool examination and strongyloidiasis serology (travel in developing countries)

Every patient with IBD should be considered for the 5
following vaccines:

VZV varicella vaccine (if there is no medical history of chickenpox, shingles, or VZV vaccination and VZV serology is negative)

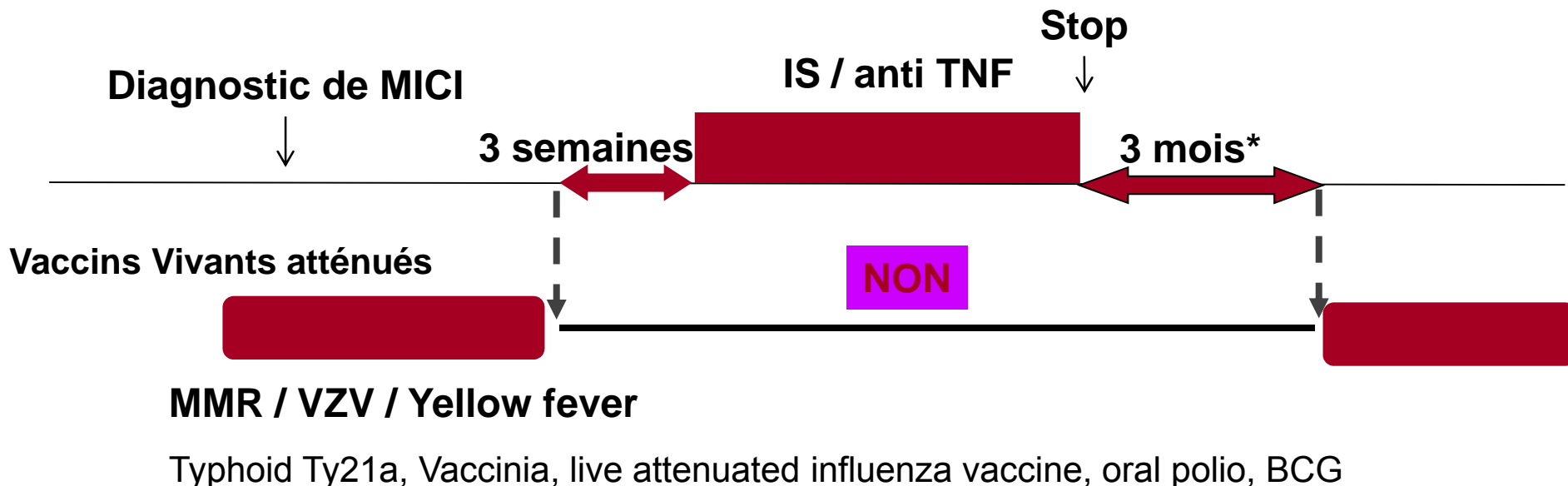
Human papilloma virus

Influenza (trivalent inactivated vaccine) once a year

Pneumococcal polysaccharide vaccine (single booster 3-5 years)

Hepatitis B vaccine in all HBV seronegative patients

Vaccins chez les patients MICI



Vaccins non vivants

DTP / Recombinant Hepatitis B vaccines / Influenza / Pneumococcal polysaccharide

HPV / Hepatitis A

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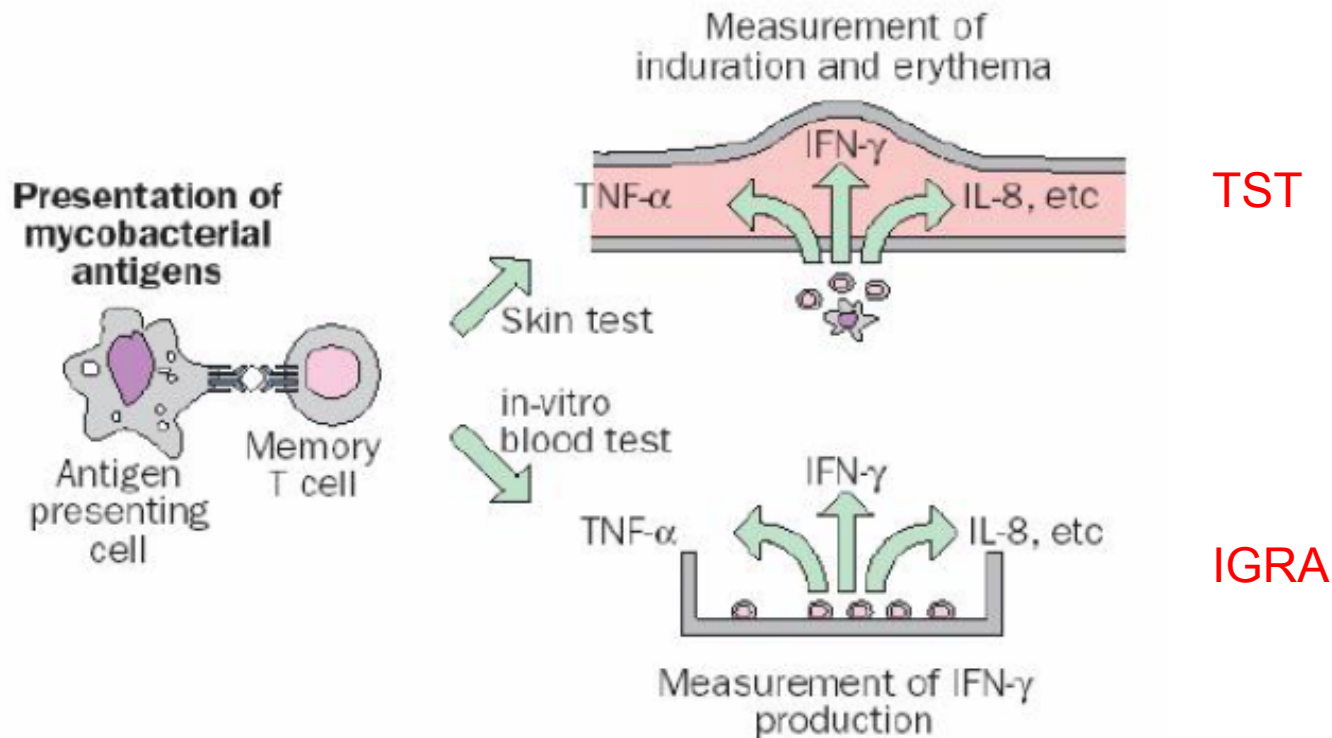
Problèmes liés au diagnostic de LTBI

- Problème de l'absence de gold standard pour le diagnostic de LTBI
- Dépend de la détection d'une réponse de l'hôte plutôt que la présence/ activité du BK lui-même.
- Méthodes immunodiagnostiques
 - Moins performantes chez individus incapables de monter une réponse immune
 - Incapables de différencier individus qui vont développer une TB active
 - Ne distinguent pas les infections récentes / anciennes (risque moindre): Problème dans régions et/ou groupes d'âge ou prévalence élevée de LTBI

Diagnostic LTBI (infection tuberculeuse latente)

- Histoire clinique
 - Ethnie
 - Pays de naissance
 - Vaccination BCG
 - Histoire exposition récente à la TB
 - ATCD TB et traitement
 - Professions à risque ou voyage dans régions endémiques
- Radiologie (Rx ou CT)
- TST (intradermoréaction à la tuberculine)
- IGRA (Interferon γ release assay)

Méthodes de dépistage de l'infection latente: test tuberculinique et tests sanguins



IGRA (Interferon γ release assay)

- IRGA contient des antigènes + spécifiques de *M. tuberculosis*
 - ESAT-6 : Early Secretory Antigenic Target 6
 - CFP-10 : Culture Filtrate Protein 10
 - (TB 7.7)
 - Appartiennent à la région RD-1
 - Pas dans BCG et NTM (sauf *M.Kansasii*, *M.Marinum*, *M.Szulgai*, *M. Flavescens*, *M Gastrii*)
- Pros
 - Préférer IRGA en cas de vaccination BCG ou pour suivi si facteurs de risque (contact TB ou voyage zones endémiques ou profession à risque)
 - IRGA est plus sensible que TST pour LTBI chez les patients immunodéprimés (+/- sous traitements immunosupresseurs)
 - IRGA est plus spécifique mais un peu moins sensible chez les individus sains
- Con
 - TST est plus sensible que IRGA chez les individus sains
 - TST détecte mieux les LTBI passées

Sensibilité et spécificité TST et IGRA

- Estimation sensibilité IGRA déterminée essentiellement sur adultes avec TBC confirmée à la culture
- Sensibilité
 - TST: ± 95 %
 - T-Spot: ± 91 %
 - QFT-GIT: ± 84 %
- Spécificité
 - TST: ± 85 %
 - T-Spot: ± 88 %
 - QFT-GIT: ± 99 %

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Overt and occult HBV infection

- Overt infection:
positive HBsAg ± high replication
- Occult infection:
negative HBsAg, positive anti-HBc, positive or negative anti-HBs, low levels of HBV DNA (serum, liver)
(only the analysis of liver-tissue extracts can provide an exact evaluation of occult HBV infection)

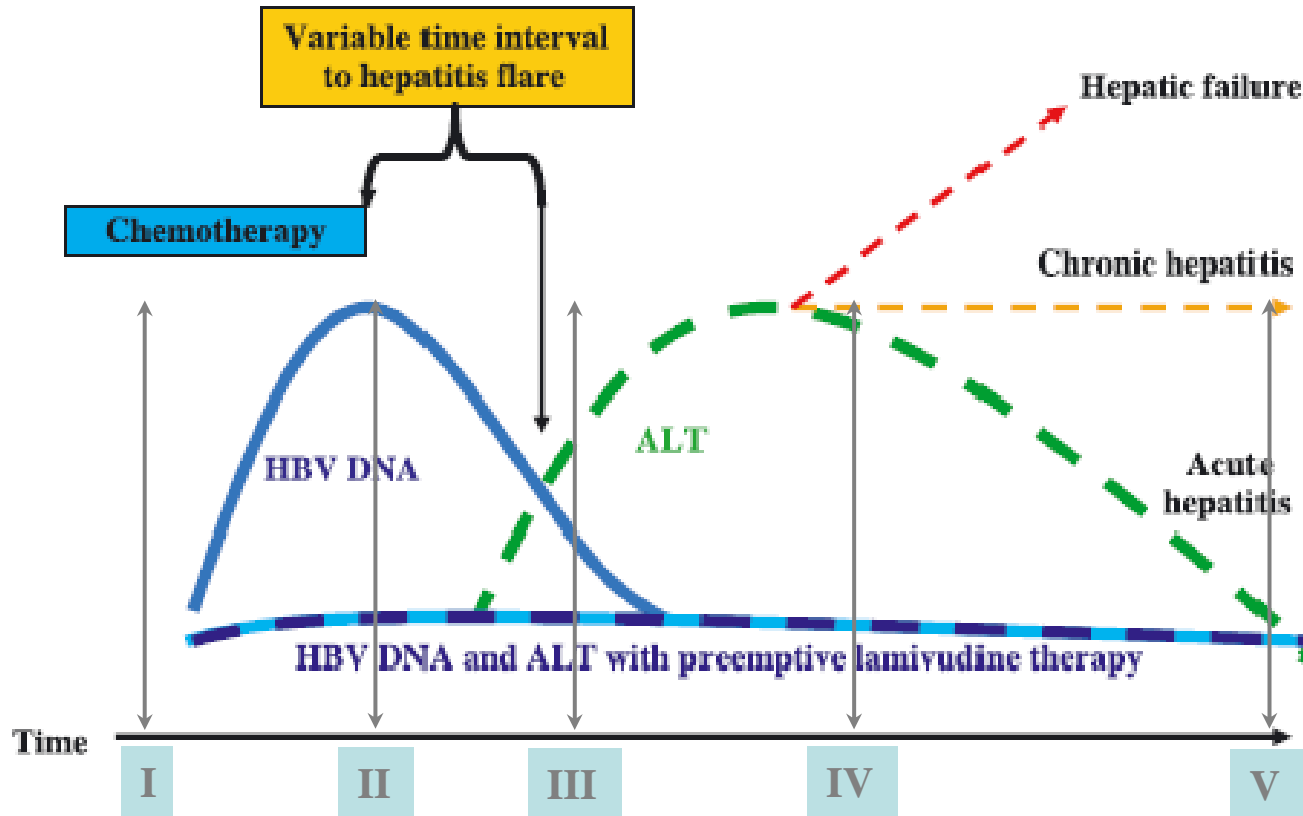
Definition of HBV reactivation

No internationally agreed criteria but usually:

- HBV DNA
 - $\geq 10x$ increase in HBV DNA or HBV DNA $\geq 6-9$ log copies/ml
 - detectable HBV DNA if initially negative

However, even in the absence of HBV DNA, hepatitis may be attributable to reactivation (phase IV).
- Laboratory or clinical features of "hepatitis".
- Exclusion of other causes (differential diagnosis of hepatic flare)
- HBsAg seroreversion: reappearance of HBsAg in HBsAg negative (anti-HBs positive and/or anti-HBc positive) patients due to dramatic reduction of anti-HBs titer induced by immunosuppressive therapy (14-50% based on reported series).

Time course of HBV reactivation



Phase	ALT	HBV DNA
I	N	N
II	N	↗
III	↗	↗
IV	↗	N
V	N	N

Dynamics of viral load and alanine amino transferase (ALT) during the course of hepatitis B virus (HBV) reactivation following chemotherapy-induced immune suppression.

Management of HBV reactivation

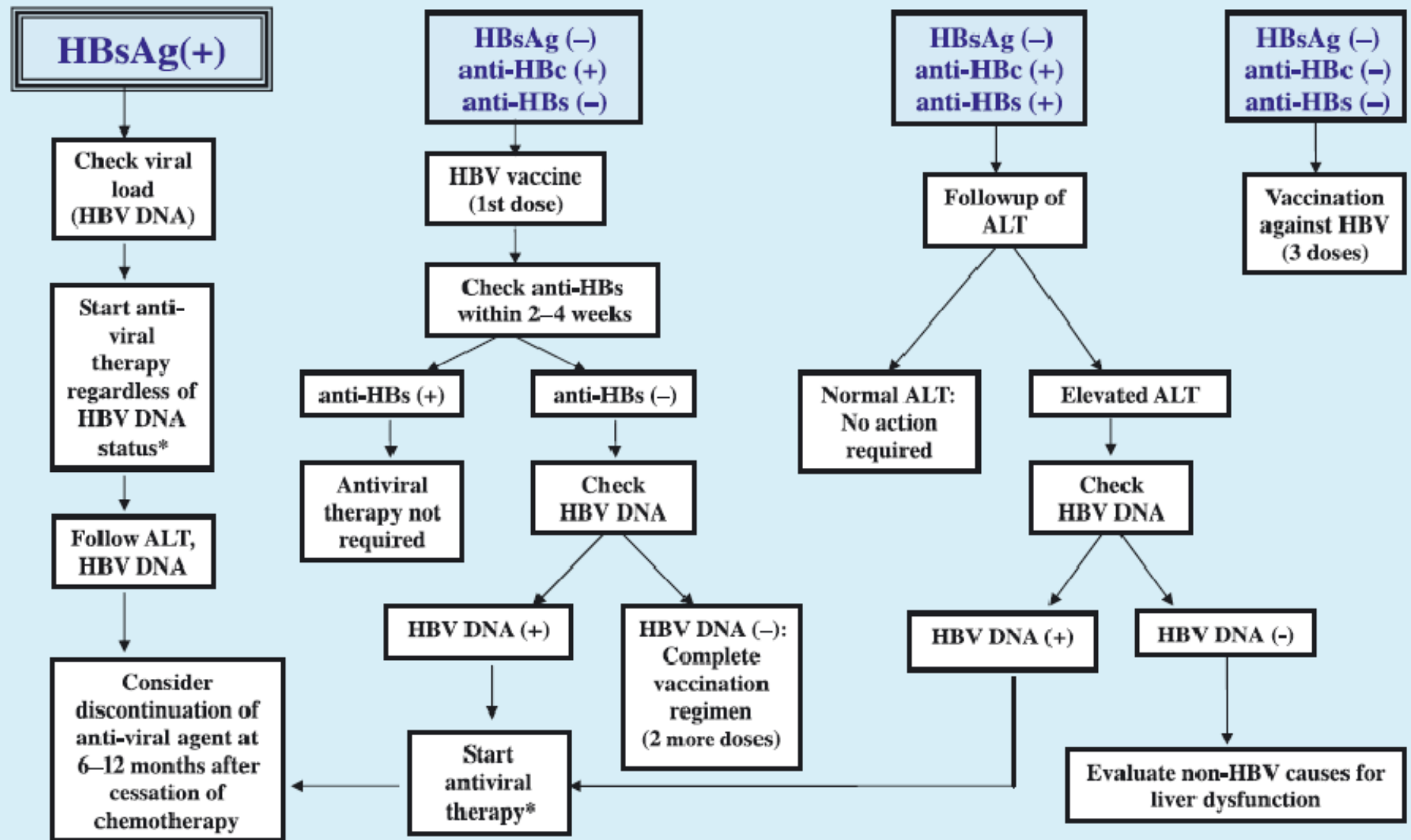
Scenario 1. Treatment of established HBV reactivation

- antiviral therapy (LAM 100 mg/d) once the flare is diagnosed may enable the continuation of immunotherapy without risking further hepatic deterioration.
- LAM less efficacious if hepatic deterioration has occurred (mortality as high as 40%).
- Reported efficacy rates of antiviral therapy probably overestimated as spontaneous resolution may occur.
- Other nucleos(t)ides analogues possible.

Management of HBV reactivation

Scenario 2. Prevention of HBV reactivation by early pre-emptive antiviral therapy (LAM)

- Reduction of HBV reactivation from 25-85% to 0-9% (12 studies in 208 patients).
- Early pre-emptive antiviral therapy with LAM 100 mg/d (other nucleos(t)ides analogues possible) in all patients with overt or occult HBV (irrespective of their HBV DNA status) treated with immunosuppressive therapy.
- Optimal duration remains unclear as premature discontinuation may lead to delayed HBV reactivation.



*Currently recommended first line treatment: lamivudine 100 mg/d. For YMDD mutant consider adefovir or entecavir.

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Facts: prevention of cancer/lymphoma with azathioprine and/or anti-TNF

- Azathioprine/6MP is associated with a 2-4 fold increase of lymphoma (Incidence in sporadic population is 1/10.000 -20.000)
- There is no increase of cancer or lymphoma in CD patients treated with anti-TNF (cohorts, registries, post-marketing surveillance and population based-studies)
- From RA data, anti-TNF therapies are associated with a 1.5 to 3 fold increase of cancer (including NMSC)
- HSTCL occurs in patient under combination therapy (mostly young and male CD patient)

Recommendations to prevent lymphoma/cancer

- Patients with **familial or personal history** of cancer/lymphoma
- Choose **monotherapy or combination therapy** depending on
 - Response to treatment,
 - Natural history of patient disease (low/high risk of complications)
 - Risk/benefit ratio of medications
- Avoid combination therapy in young male CD patients (HSTCL)

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Traitements et grossesse: Philosophie générale

- Dialoguer avec la patiente avant tout désir de grossesse
- Discuter du traitement médical et de la chirurgie avant la grossesse
- Essayer de choisir le bon moment pour la grossesse quand la patiente est en rémission
- Une patiente en rémission sous traitement médical devrait poursuivre son traitement (si possible monothérapie)
- Suivi clinique et biologique de la patiente sous IS et anti-TNF (arrêt des anti-TNF la semaine 22)
- Discuter la césarienne si MC périanale ou RCUH avec réservoir iléo-anal
- Discuter de l'allaitement et quand reprendre les médicaments (attention à la survenue d'une poussée après post-partum)

Médicaments, grossesse et allaitement

	Grossesse	Allaitement
5-ASA	Oui	Oui
Salazopyrine	Oui	Oui
Métronidazole	Oui	Non
Ciprofloxacine	Non	Non
Corticostéroïdes	Oui	Oui
Azathioprine	Oui	Oui/Non*
Méthotrexate	Non	Non*
Cyclosporine	Oui	Non
Infliximab	Oui (pas 3 ^{ème} trimestre)	Oui/Non*
Adalimumab	Oui (pas 3 ^{ème} trimestre)	Oui/Non*

* Si possible!

ECCO Statement 11G

Medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risk of medication.

FDA Categories for use of medication in pregnancies

FDA category	
A	Controlled studies in animals and women have shown no risk
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester
C	No controlled studies in humans have been performed and animal studies have shown adverse events or studies in humans and animals not available give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease
X	Studies in animals or humans show fetal abnormalities; drug contra-indicated

Conventional drugs and risks during pregnancy

Drug	FDA category	Recommendations
Aminosalicylates	B	No increased risk Folate supplements with Sulphasalazine
Metronidazole	B	No birth defects 1 population-based case-control study found that infants of women exposed to Metro in 2nd to 3rd months of pregnancy had higher rates of cleft lip with or without cleft palate
Anti-TNF	B	No transfer in first 2 trimesters
Corticosteroids	C	Use during the first trimester associated with increased risk of oral cleft in the newborn Increased risk of adrenal insufficiency
Cyclosporine	C	Does not appear to be a major teratogen
Quinolones	C	Should be avoided due to potential increased risk of arthropathy
Azathioprine	D	These agents can be continued to maintain remission during pregnancy.
Methotrexate	X	Contraindicated in pregnancy
Thalidomide	X	Contraindicated in pregnancy

Medication during lactation

Drug	Recommendation	Remarks
5-ASA	safe	
Prednisone and prednisolone	safe	Low concentrations in breast milk 4 hour delay after oral intake recommended to minimize exposure Adrenal insufficiency possible in infant after stopping breast feeding during high dose therapy
Thiopurines	Probably safe	Low levels detected in breast milk
Anti-TNF	Probably safe	No or very low levels detected although limited data

Take home message:

General recommendations

- Check appropriate indication
- Inform the patient about risks and benefits
- Check contraindications
- Prevention of side effects and complications
 - TPMT genotyping and surveillance blood test
 - Prevention of opportunistic infections
 - History of previous infectious diseases
 - TB (history, PPT, IRGA, RX or CT, Pneumologist)
 - Serology (all the virus: HBV....)
 - PCP or TB Prophylaxis
 - Vaccination
- Prevention of cancer and lymphoma: patient history
- No MTX during pregnancy and biologics in the third trimester

LES MESURES INDISPENSABLES

Pathologies	Données cliniques	Examens complémentaires	Conduite à tenir concernant l'anti-TNF	OK
INFECTION EVOLUTIVE	Fièvre, signes d'appel.	NFS, CRP et selon contexte.	Contre-indication temporaire, jusqu'à guérison de l'infection.	<input type="checkbox"/>
ABCES ABDOMINAL	Rechercher des signes cliniques d'abcès.	Imagerie si suspicion.	Contre-indication temporaire, jusqu'à guérison de l'abcès.	<input type="checkbox"/>
ABCES PERINEAL	Rechercher des signes cliniques d'abcès.	Imagerie si suspicion.	Contre-indication temporaire, jusqu'à guérison de l'abcès.	<input type="checkbox"/>
TUBERCULOSE	Rechercher un antécédent de tuberculose latente ou active chez le patient ou son entourage proche, et un séjour en zone d'endémie. Préciser si vaccination BCG et réalisée. Si oui, date :	IDR à la tuberculine (Tubertest) Un test de production d'interféron (Quantiféron ou Elispot) peut être réalisé si disponible. Il peut : 1) détecter une tuberculose latente à IDR négative et 2) éviter un traitement chez un sujet vacciné par le BCG ayant une IDR positive Radiographie pulmonaire de face ; si besoin : TDM thoracique et avis pneumologique.	Contre-indication temporaire - si tuberculose latente, le traitement est possible après au moins 3 semaines de traitement antituberculeux - si tuberculose active, après guérison et au moins 2 mois de traitement antituberculeux.	<input type="checkbox"/>
VIH	Rechercher infection VIH ou facteurs de risque.	Sérologie VIH avec accord du patient, à renouveler si facteurs de risque. Avis de l'infectiologue si nécessaire	Contre-indication relative. A discuter au cas par cas avec l'infectiologue.	<input type="checkbox"/>
HEPATITE B	Rechercher une infection VHB, des facteurs de risque et préciser si vaccination déjà réalisée. Si oui, date :	Sérologie B incluant Ag Hbs, Ac Hbs, Ac Hbc. ADN viral si Ag Hbs+.	Si Ag Hbs+ : traitement anti-TNF possible, si indispensable. Un traitement pré-emptif antiviral doit être instauré. Proposer vaccination si sérologie négative.	<input type="checkbox"/>
CANCER	Rechercher un antécédent de cancer ou lymphome. Si oui, date :	Avis du cancérologue si nécessaire	Contre-indication si cancer évolutif ou récent (moins de 5 ans pour la plupart des cancers) sauf cancer cutané spino- ou baso cellulaire et cancer <i>in situ</i> du col utérin traité.	<input type="checkbox"/>
MALADIE DEMYELINISANTE	Rechercher un antécédent personnel de névrite optique ou de sclérose en plaque.	Avis d'un neurologue si nécessaire	Utilisation non recommandée	<input type="checkbox"/>
INSUFFISANCE CARDIAQUE	Rechercher une insuffisance cardiaque.	Avis d'un cardiologue si nécessaire	Contre-indication si insuffisance cardiaque modérée à sévère (grade III ou IV de la NYHA).	<input type="checkbox"/>
GROSSESSE	Interroger sur les désirs de grossesse.	Test de grossesse si suspicion de grossesse	Utilisation actuellement non recommandée à discuter au cas par cas.	<input type="checkbox"/>

LES MESURES RECOMMANDÉES

Pathologies	Données cliniques	Examens complémentaires	Action à proposer	OK
PNEUMOCOQUE	Préciser si vaccination anti-pneumococcique. Si oui, date :		Vaccination polysaccharidique, possible en cours de traitement anti-TNF. Rappel tous les 3-5 ans.	<input type="checkbox"/>
HERPES SIMPLEX	Rechercher un antécédent d'herpès oral ou génital.		Pas de contre-indication sauf infection sévère. Anthraxal oral si herpès récidivant.	<input type="checkbox"/>
VARICELLE/ZONA	Rechercher un antécédent de varicelle et/ou zona ; préciser si vaccination réalisée. Si oui, date :	Sérologie varicelle/zona en l'absence d'antécédent connu.	Pas de contre-indication sauf si infection VZV évolutive. Vaccitrader éventuelle, au moins 3 semaines avant anti-TNF.	<input type="checkbox"/>
HEPATITE C	Rechercher infection VHC ou facteurs de risque.	Sérologie C	Pas de contre-indication. Surveillance conseillée.	<input type="checkbox"/>
CYTOMEGALOVIRUS	Rechercher un antécédent d'infection à CMV.	Pas de test de détection sauf si colite sévère. Dans ce contexte, rechercher une colite à CMV par des biopsies coliques si sérologie ou PCR sanguine positive.	Contre-indication temporaire si infection tissulaire à CMV.	<input type="checkbox"/>
EPSTEIN-BARR VIRUS	Rechercher un antécédent d'infection à EBV.		Contre-indication temporaire si infection EBV cliniquement évolutive.	<input type="checkbox"/>
GRIPPE SAISONNIERE	Préciser si vaccination annuelle contre la grippe saisonnière.		Proposer la vaccination anti-grippale (possible en cours de traitement anti-TNF).	<input type="checkbox"/>
GRIPPE H1N1	Préciser si vaccination contre la grippe H1N1.		Proposer la vaccination anti-H1N1 (possible en cours de traitement anti-TNF).	<input type="checkbox"/>
PAPILLOMAVIRUS HUMAIN (HPV)	Rechercher antécédent dysplasie du col utérin, condylomes.	Examen gynécologique avec frotis cervical.	Pas de contre-indication. Proposer la vaccination chez la jeune femme.	<input type="checkbox"/>
FIÈVRE JAUNE	Préciser si vaccination fièvre jaune au cours des 10 dernières années ou si voyage en zone d'endémie envisagé.		Contre-indication si vaccination contre la fièvre jaune réalisée il y a moins de 3 semaines.	<input type="checkbox"/>
STRONGYLOÏDOSE	Préciser si voyage en zone d'endémie (passé ou futur).	Eosinophiles ; sérologie de la strongyloïdose ou traitement par ivermectine.	Traitement par ivermectine avant anti-TNF.	<input type="checkbox"/>
PNEUMOCYTOSE	Préciser les associations d'immunosuppresseurs.		Traitement par co-trimoxazole si utilisation de 3 immunosuppresseurs incluant l'anti-TNF.	<input type="checkbox"/>
LUPUS	Rechercher un antécédent de lupus.	Si orientation clinique.	Utilisation non recommandée.	<input type="checkbox"/>

Azathioprine/6-MP

Efficacy according 6-TGN and 6-MMP blood levels

Metabolite measurements are indicated in patients not responding or experiencing adverse events to adequate weight-based doses of TP

Group 1	Group 2	Group 3	Group 4
Low/Absent 6-TGN and Low/Absent 6-MMP = Non-Adherence = Education	Low 6-TGN and Low 6-MMP = Under-dosing = Increase TP dosage	Low 6-TGN and High 6-MMP = Thiopurine resistance = Add Allopurinol ?	High 6-TGN and High 6-MMP = Thiopurine refractory = Change to another drug

(Adapted from M Sparrow, UEGW 2009 task force of thiopurine).

Methotrexate

Hypersensitivity pneumonitis

- No relationship with cumulative dose (Daily dose > weekly) and Risk factors (male, smoking, preexisting pulmonary disease and NSAIDs)
- Symptoms: dyspnea, dry cough, fever, cyanosis, tachypnea
- Gazometry: Hypoxemia
- X-rays: normal to widespread alveolar filling
- Treatment: withdrawal MTX \pm corticosteroids
- $\Delta\Delta$: opportunistic infections (Pneumocystis carinii)