Managing Checkpoint Inhibitor Toxicities

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Approved Indications

	Ipilimumab	Nivolumab	Pembrolizumab*	Atezolizumab	Avelumab	Durvalumab	Ipi + Nivol
Metastatic melanoma	X	X	X				X
Adj stage III melanoma	X						
2nd line met NSCLC		X	X	X			
2nd line met RCC		X					
Classic Hodgkin lymphoma		X	X				
Recurrent or metastatic SCCHN		X					
Locally advanced or metastatic UCC		X	X	X	X	X	
MSI-H or MMR deficient metastatic malignancies			X				
Met Merkel cell carcinoma					X		

*also approved for 1st line metastatic NSCLC (PD-L1 $\geq$50% and 1st line metastatic NSCLC in combination with pemetrexed + carboplatin

Toxicities of Checkpoint Inhibitors

- 2 major types of reactions
  - Infusion reactions
  - **Immune-related adverse events (irAEs) or adverse events of special interest (AEoSI)**
    - Any organ or tissue can be involved
    - Most commonly affect skin, colon, endocrine organs, liver, and lungs
    - Infrequent but potentially lethal – neurological disorders and myocarditis

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Ipilimumab

- Anti-CTLA4 antibody at dose of 3 mg/kg
  - irAEs occur in 60-85% of patients
    - Mainly grade 1 and 2
    - 10-27% of patients develop grade 3 and 4 toxicities
    - 2.1% ipilimumab-related deaths reported in the first phase III trial
  - Onset generally within first 8 to 12 weeks of treatment
    - Skin toxicities generally first to develop

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Nivolumab & Pembrolizumab

- PD-1/PD-L1 blockade
- Fatigue most commonly reported
- High-grade toxicities less common for anti-PD-1 than CTLA4 blocking agent

	Nivolumab
Any treatment-related AE	74-85%
Grade 3-4 metastatic melanoma	12-20%
Advanced cisplatin-refractory squamous NSCLC	58%, 7%
Advanced cisplatin-refractory non-squamous NSCLC	69%, 10%
RCC	79%, 19%

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Timeline of Toxicities

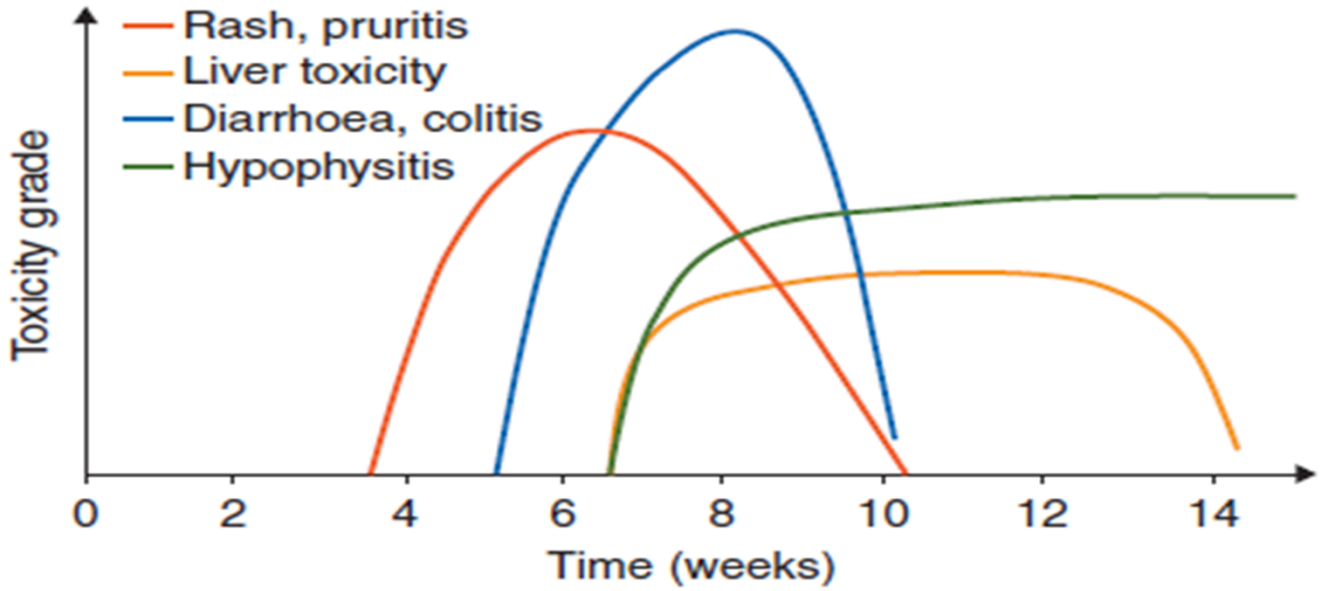

Figure 1. Timing of occurence of immune-related adverse events following ipilimumab treatment.
Reprinted from [86] with permission.

Baseline Assessment

- Patients with history of autoimmune disease, or actively being treated for autoimmune disease, at risk for worsening their autoimmune disease while on checkpoint inhibitor therapy
- Patients that have had irAEs on ipilimumab are at higher risk of developing irAEs following anti-PD-1 treatment and vice versa
- Consider long half-lives of monoclonal antibodies when switching therapy

Special Considerations

- In most cases, especially most severe cases, immunotherapy should be discontinued
  - Start immunosuppressive or immune modulating drugs
    - High-dose corticosteroids
    - Tumor necrosis factor alpha (TNFα) antagonists
      - Mycophenolate or tacrolimus
      - Carefully taper off these drugs
  - Long-term (>6 weeks) treatment with above drugs or infliximab increases chance of opportunistic infections
    - Consider pneumocystis prophylaxis

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Skin Toxicity

- Generally develops within first few weeks of initiation
  - Serious skin AEs rare, usually do not require dose reductions or treatment discontinuation
- Vitiligo associated with good clinical responses to anti-PD-1 MoAbs in melanoma patients

	Ipilimumab	Anti-PD-1	Combination
Rash	~24%	~15%	40%
Grade 3-4 rash	<3%	<3%	<5%
Pruritis	25-35%	13-20%	33%
Vitiligo	Rare	8%	8%

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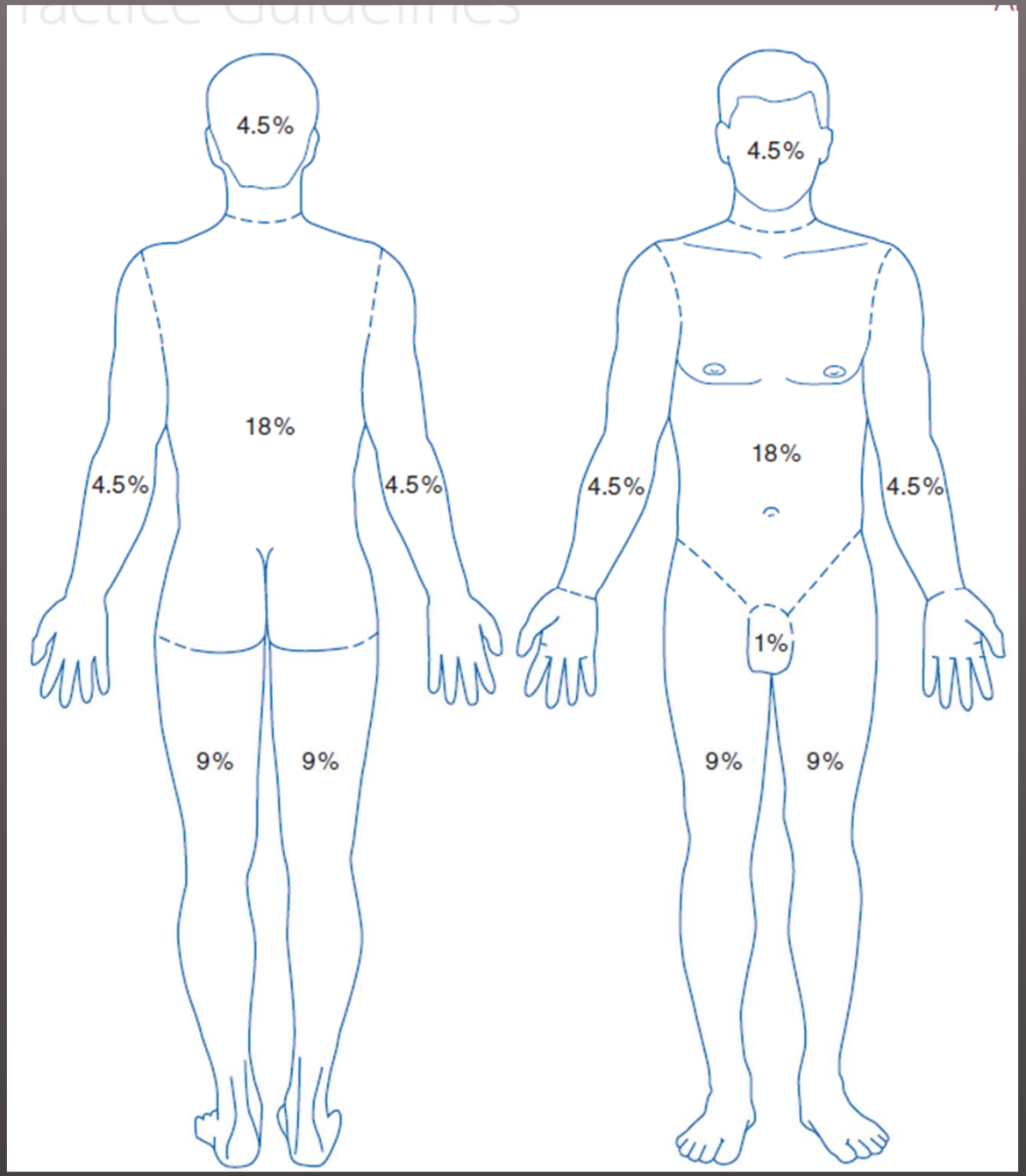
4.5%
18%
4.5%
4.5%
9%
9%
4.5%
18%
4.5%
4.5%
1%
9%
9%

Skin Toxicity

- Grade 1: Skin rash, with or without symptoms, <10% BSA
  - Physical exam, exclude other causes (e.g., viral illness, infection, other drug rash)
    - Avoid skin irritants, avoid sun exposure, topical emollients recommended
    - Topical steroids (mild strength) cream once daily +/- oral or topical antihistamines for itch
    - Proceed with treatment
- Grade 2: Rash covers 10-30% of BSA
  - As for grade 1, consider dermatology referral and skin biopsy
    - Supportive management as for grade 1
    - Topical steroids (moderate strength) cream once daily or (potent) cream twice daily +/- oral or topical antihistamines for itch
    - Proceed with treatment

Skin Toxicity

- Grade 3: Rash covers >30% BSA or grade 2 with substantial symptoms
  - As for Grade 1, dermatology review, consider punch biopsy and clinical photography
    - Withhold treatment
    - Topical treatments as above (potent)
    - Initiate oral steroids:
      - Mild to moderate: 0.5-1 mg/kg prednisone once daily x 3 days, then wean over 2 weeks
      - Severe: IV (methyl)prednisolone 0.5-1 mg/kg and covert to oral steroids on response, wean over 2-4 weeks
      - Recommence treatment at G1/mild G2 after discussion with patient and consultant
- Grade 4: Skin sloughing >30% BSA with associated symptoms
  - As for Grade 1, dermatology review, punch biopsy, clinical photography
    - IV (methyl)prednisolone 1-2 mg/kg
    - Urgent dermatology review
    - Discontinue treatment

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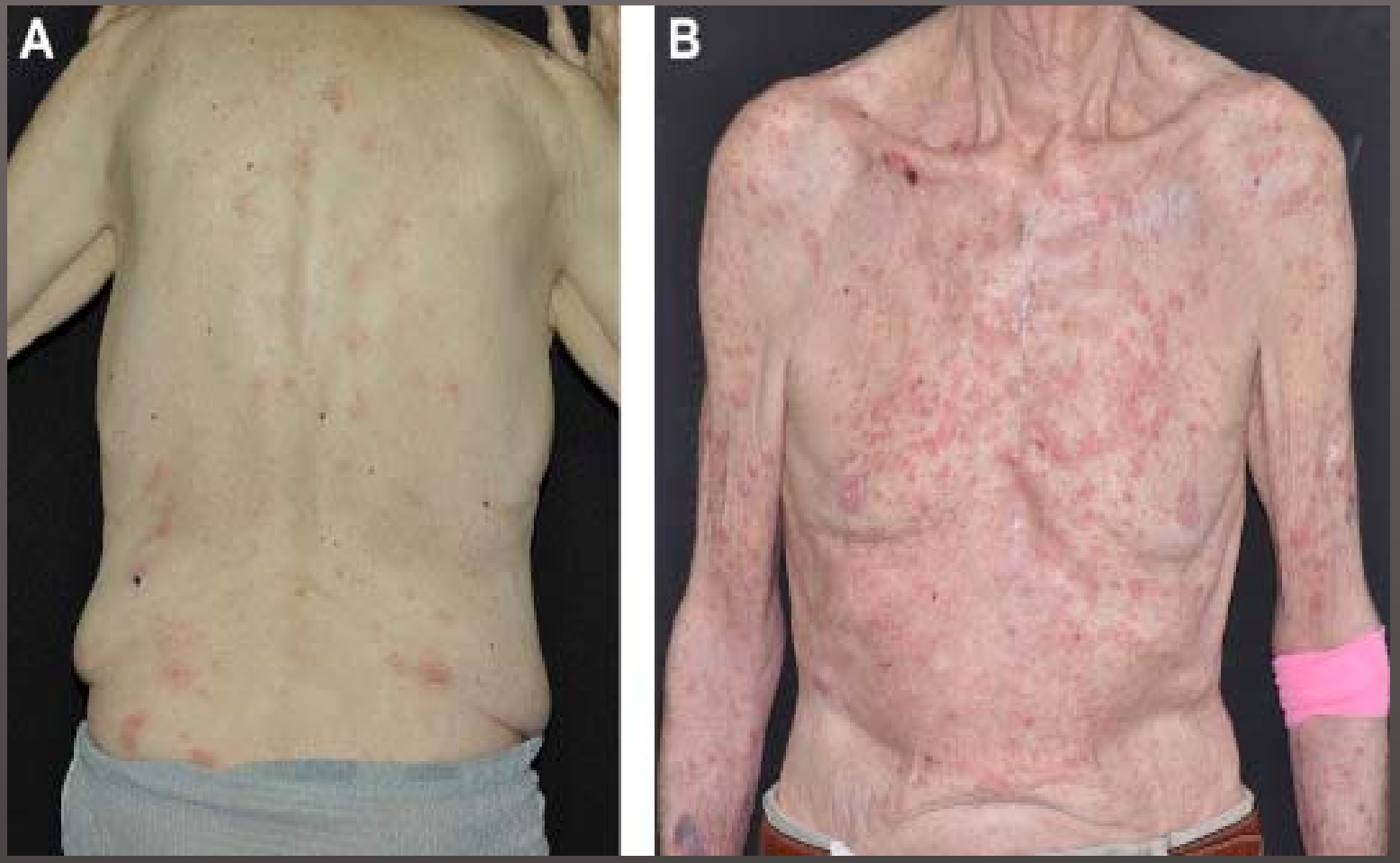
Skin Toxicity



Eur J Cancer 2016;60:12-25

GI Toxicity

- Diarrhea occurs in 27-54% of patients treated with anti-CTLA-4 MoAbs
  - Diarrhea in 33%
  - Colitis 8-22%
- Other presenting symptoms: Abdominal pain, hematochezia, weight loss, fever, and vomiting
- May occur at any time during 1-10 infusions
  - Enterocolitis has been reported several months after last ipilimumab infusion
- Stool analyses for bacterial enteropathogens and *Clostridium difficile* toxin should be carried out in every patient with diarrhea treated with anti-CTLA4

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GI Toxicity

- **Grade 1: Mild, <3 liquid stools per day over baseline, feeling well**
  - **Treatment can be continued**
- **Grade 2: Moderate, 4-6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes**
  - **Outpatient management if appropriate**
  - **If unwell, manage as per severe (i.e., grade 3/4)**
  - **Treatment to be withheld**
- **Grade 3/4: Severe, >6 liquid stools per day over baseline or if episodes within 1 hour of eating**
  - **Requires hospitalization and isolation until infection excluded**
  - **Treatment to be withheld**

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GI Toxicity

- Grade 1/2:
  - Symptomatic management: Oral fluids, loperamide, avoid high fiber/lactose diet
    - Grade 1 and persists >14 days or grade 2 and persists >3 days or worsens then:
  - Prednisolone 0.5-1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg once daily if no bloody diarrhea
    - Do not wait for sigmoidoscopy/colonoscopy to start
    - No improvement in 72 hrs or worsening or absorption concern then treat as grade 3/4 →
- Grade 3/4:
  - IV methylprednisolone 1-2 mg/kg, gastroenterology input and ensure sigmoidoscopy/colonoscopy is requested
    - No improvement in 72 hrs or worsening then:
  - Infliximab 5 mg/kg, can repeat 2 weeks later
  - Must have had sigmoidoscopy/colonoscopy prior
  - Other options:
    - MMF 500-1000 mg twice daily or tacrolimus

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GI Toxicity – Assessment & Investigations

- **Grade 1:**
  - Baseline investigations: FBC, UEC, LFTs, CRP, TFTs
  - Stool microscopy for leukocytes/ova/parasites, culture, viral PCR, *Clostridium difficile* toxin and cryptosporidia
  - Culture for drug-resistant organisms
- **Grade 2:**
  - As for grade 1 and:
  - Consider abdominal X-ray for signs of colitis in cases of abdominal discomfort
  - Exclude steatorrhea
  - Book sigmoidoscopy/colonoscopy (+/- biopsy)
  - Contact patient every 72 hours
  - Repeat baseline bloods at outpatient review
- **Grade 3/4:**
  - As for grades 1 & 2 above and:
  - Consider CT abdomen/pelvis, repeat abdominal X-ray as indicated
  - Daily FBC, UEC, LFTs, CRP
  - Review diet (e.g., nothing by mouth, clear fluids, TPN)
  - Early surgical review if bleeding, pain, or distention

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GI Toxicity

- Supportive care medication concerns:
  - Steroid wean duration:
    - Moderate – wean over 2-4 weeks
    - Severe – wean over 4-8 weeks
    - If steroids given over 4 weeks, consider PJP prophylaxis, regular random blood glucose, vitamin D level, start calcium/vitamin D supplement
  - Loperamide dosing:
    - 4 mg 1st dose, then 2 mg 30 min before each meal and after each loose stool until 12 hours without diarrhea (max dose 16 mg/day)

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Pneumonitis

- Variable onset and clinical, radiological, and pathological appearances
- More common with combination anti-CTLA4 and anti-PD-1 MoAbs
- Cough/dyspnea: 20-40%; grade 3-4 cough: 2-9%; grade 3-4 dyspnea: 1-2%

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Pneumonitis

- **Grade 1: Radiographic changes only, ground glass change, non-specific interstitial pneumonia**
  - **Baseline indications:**
    - **Chest X-ray**
    - **Bloods (FBC/UEC/LFTs/TFTs/Ca/ESR/CRP)**
    - **Consider sputum sample and screening for viral, opportunistic or specific bacterial (mycoplasma, legionella) infections depending on the clinical context**
  - **Consider delay of treatment**
  - **Monitor symptoms every 2-3 days**
  - **If worsens, treat as grade 2 or 3-4**

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Pneumonitis

Grade 2: Mild, moderate new symptoms; dyspnea, chest pain

- **Outpatient monitoring – monitor symptoms daily**
  - **Baseline indications as grade 1 plus:**
  - **Repeat chest X-ray weekly and baseline bloods**
  - **Lung function tests including TCLO**
  - **If no improvement after 48h of oral prednisolone, manage as per grade 3**
- **Withhold treatment**
  - **Start antibiotics if suspicion of infection (fever, CRP, neutrophil counts)**
  - **If no evidence of infection or no improvement with antibiotics after 48h add in prednisolone 1 mg/kg/day orally**
  - **Consider Pneumocystis prophylaxis depending on the clinical context**
  - **High resolution CT +/- bronchoscopy and BAL pending appearances**

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Pneumonitis

- **Grade 3/4: Severe new symptoms; new/worsening hypoxia; life-threatening; difficulty breathings/ARDS**
  - **Discontinue treatment**
  - **Admit patient, baseline tests as above methylprednisolone IV 2-4 mg/kg/day**
  - **High resolution CT and respiratory review +/- bronchoscopy and BAL pending appearances**
  - **Cover with empiric antibiotics**
  - **Discuss escalation and ventilation**
    - **If not improving or worsening after 48 hours:**
  - **Add infliximab 5 mg/kg or MMF if concurrent hepatic toxicity**
  - **Continue with i.v. steroids- wean as clinically indicated**

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Pneumonitis

- **Once improved to baseline:**
  - **Grade 2: wean oral steroids over at least 6 weeks, titrate to symptoms**
  - **Grade 3/4: wean steroids over at least 8 weeks**
  - **Steroid considerations:**
    - **Calcium & Vitamin D supplementation as per guidelines**
    - **PJP prophylaxis**

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Infliximab Considerations

- Chimeric monoclonal antibody that binds to TNFα, thereby interfering with endogenous TNFα activity
  - Biological activities of TNFα include:
    - Induction of proinflammatory cytokines (interleukins)
    - Enhancement of leukocyte migration
    - Activation of neutrophils and eosinophils
    - Induction of acute phase reactants and tissue degrading enzymes
- New biosimilar of infliximab just approved
- Infuse over 2 hours
  - Premedication with antihistamines (H_1-antagonist +/- H_2-antagonist), acetaminophen, and/or corticosteriods may be considered to prevent/treat infusion-related reactions
  - Evaluate HBV status in all patients prior to starting infliximab
    - May cause HBV reactivation, especially in patients receiving concurrent steroids
  - Evaluate patient for TB exposure prior to therapy initiation
    - Treatment of latent TB should be initiated before infliximab therapy, when possible

Remicade (infliximab) [prescribing information].
Horsham, PA: Janssen Biotech, Inc; October 2015.