# Managing Adverse Events Associated with Immuno-oncologic Agents


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ICLIO eCourse 05

# Objectives

By the end of this e-course, participants will be able to:

- Understand adverse events and toxicities related to immunotherapy checkpoint inhibitors
- Understand how immune-related Adverse Events (irAEs) present in patients taking checkpoint inhibitors
- Understand ways of managing irAEs as it applies in real-world practice

# Adverse Events differ between cytotoxic agents and immuno-oncologic agents

*Differences in Mechanism of Action (MOA) between cytotoxic agents and immunotherapies result in different adverse event profiles*

## Cytotoxic Agents

- Directly kills or prevents cells from dividing (e.g. chemotherapy); lack of selectivity between normal cells and tumor cells causes unwanted toxicities

## Immunotherapy

- Stimulates an innate immune response against the tumor resulting in irAEs

*Novel immunotherapy agents are becoming the new standard of care in oncology; clinicians will need to understand and learn how to manage irAEs related to these agents*

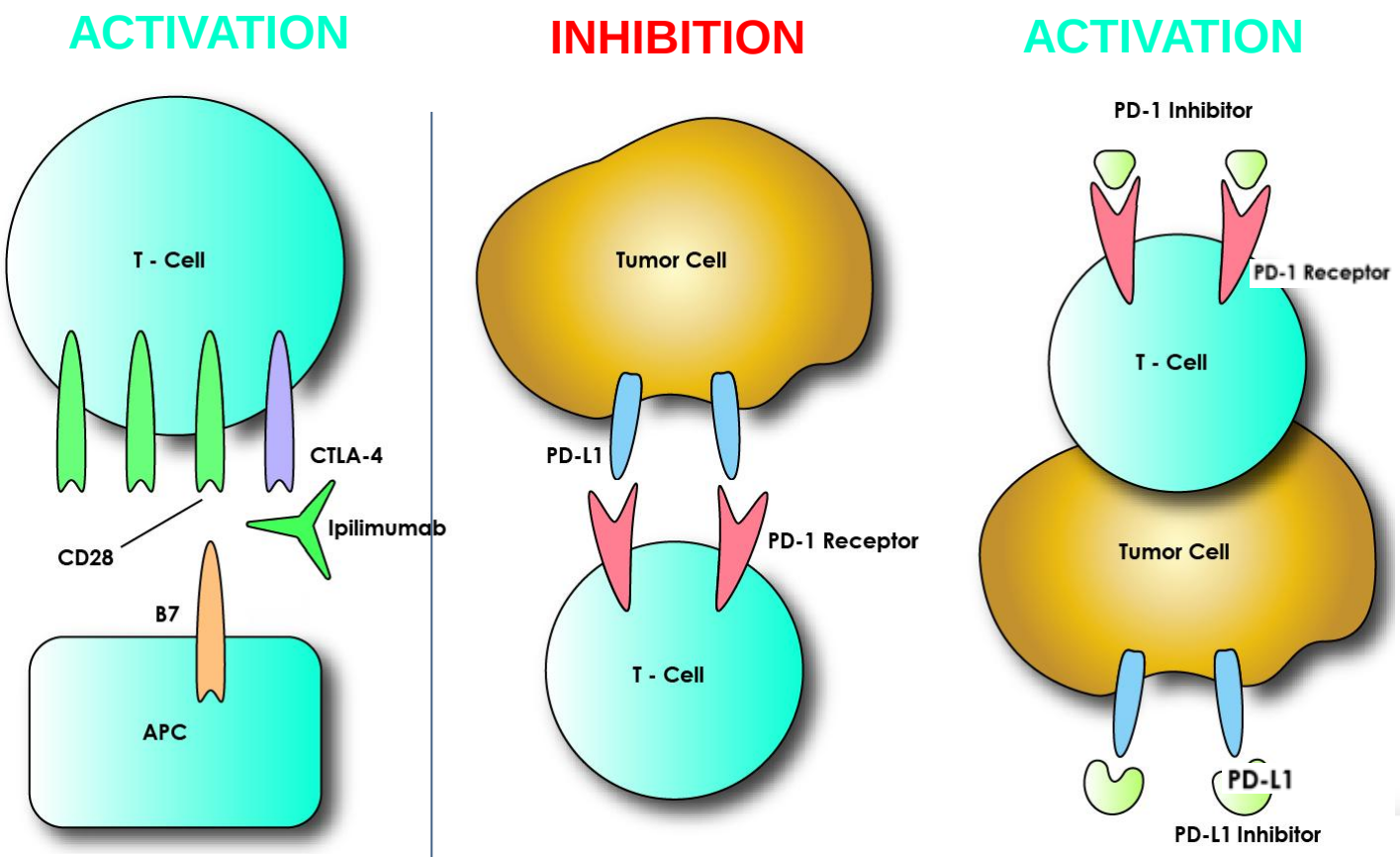
# FDA approved immunotherapy checkpoint inhibitors include ipilimumab, nivolumab, and pembrolizumab

- **Ipilimumab:** human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells.
  - Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma

- **Nivolumab** or **pembrolizumab**: Human monoclonal antibodies directed against the programmed death-1 (PD-1) receptor of the T Cell
  - Nivolimumab has indications for use in patients with unresectable or metastatic melanoma and in patients with metastatic squamous or non- squamous non-small cell lung cancer (NSCLC).
  - Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic melanoma

# Immunotherapy checkpoint inhibitors

*Checkpoint inhibitors*: tumors express “checkpoint” proteins on their cell surface to escape detection from the immune system; targeted inhibition towards these receptors enhances T cell response towards the tumor



# Ipilumumab Adverse Events (melanoma)

*Phase II, randomized, double-blind, dose-ranging study, patients with pretreated advanced melanoma, ipilimumab monotherapy every three weeks for four cycles, followed by maintenance therapy every 3 months*

## Toxicities are dose-related

% Adverse Events (Grade 3-4) by Dose

| 0.3 mg/kg (n=72) | 3 mg/kg* (n=71) | 10 mg/kg (n=71) |
|---|---|---|
| 0% | 7.0% | 25.4% |

**Most common Grade 3-4 adverse events:**

| | 0.3 mg/kg (n=72) | 3 mg/kg (n=71) | 10 mg/kg (n=71) |
|---|---|---|---|
| Gastrointestinal | 0 | 2.8% | 15.5% |
| Skin | 0 | 1.4% | 4.2% |
| Endocrine | 0 | 2.8% | 1.4% |

**Adverse Events leading to discontinuation (drug-related, Any Grade)**

| 0.3 mg/kg (n=72) | 3 mg/kg (n=71) | 10 mg/kg (n=71) |
|---|---|---|
| 2.8% | 7.0% | 15.5% |

**Reasons for drug-related discontinuation include:**

- 0.3 mg/kg dose: Asthenia and bone pain
- 3 mg/kg dose : enteritis (Grade 2), hypopituitarism, hydrocephalus, confusion, respiratory tract infection, diarrhea (Grade 3)
- 10 mg/kg dose: most frequent was diarrhea (Grade 3)

** Ipilumumab's indicated dose is 3 mg/kg*

*(sources: Wolchok et al., 2010; Weber et al., 2015)*

# Nivolumab Adverse Events (melanoma)

*Patients with advanced melanoma who have received greater than 1 but not more than 5 prior systemic cancer therapies enrolled between 2008 and 2012 receiving nivolumab every 2 weeks for up to 96 weeks (n=107)*

**Toxicities do not appear dose-related**

% Adverse Events (Grade 3-4) by Dose

| 0.3 mg/kg (n=18) | 3 mg/kg* (n=17) | 10 mg/kg (n=20) |
|---|---|---|
| 16.7% | 35.3% | 25.0% |

** nivolumab's indicated dose for melanoma is 3 mg/kg*

**Most common Grade 3-4 adverse events (n=107):**

| | |
|---|---|
| Fatigue | 1.9% |
| Diarrhea | 1.9% |
| Abdominal Pain | 1.9% |
| Lymphopenia | 2.8% |

*Discontinuation rate can vary - in a randomized, open-label trial with 268 patients with unresectable or metastatic melanoma receiving nivolumab 3 mg/kg every 2 weeks; discontinuation from adverse reactions was ~9%*

*(sources: Topalian et al., 2014; Weber et al., 2015; Opdivo (nivolumab FDA approved label))*

# Nivolumab Adverse Events (Non-Small Cell Lung Cancer)

*Phase I dose-escalation cohort expansion trial for Patients with advanced Non-Small Cell Lung Cancer (NSCLC) (squamous and non-squamous) heavily pre-treated to receive nivolumab once every 2 weeks in 8-week cycles for up to 96 weeks*

**Toxicities do not appear dose-related**

% Any Adverse Events* (Grade 3-4) by Dose

| 1 mg/kg (n=33) | 3 mg/kg** (n=37) | 10 mg/kg (n=59) |
|---|---|---|
| 15.2% | 13.5% | 13.6% |

** Patients were counted only once for "any adverse event"; data for only those events that were reported in at least 3% of the treated population was presented*

***nivolumab's indicated dose for NSCLC is 3 mg/kg*

**Most common Grade 3-4 adverse events (n=129):**

| | |
|---|---|
| Fatigue | 3.1% |
| Decreased CD4 Lymphocytes | 2.3% |
| Pneumonitis | 2.3% |

*For those patients experiencing treatment-related adverse events of any grade, the most common were fatigue (24%), decreased appetite (12%), and diarrhea (10%)*

*3 treatment-related deaths were associated with pneumonitis; authors did not observe a relationship between the occurrence of pneumonitis and dose level or treatment duration.*

*Higher grade select adverse events with immune etiologies were manageable in most cases through drug discontinuation, immune suppressive agents, and/or hormone replacement.*

*(source: Gettinger et al., 2015)*

# Pembrolizumab Adverse Events (melanoma)

*Phase I trial, patients with advanced melanoma who have progressed after prior ipilumumab therapy, treated with pembrolizumab every 3 weeks*

**Toxicities do not appear dose-related**

% Adverse Events (Grade 3-4) by Dose

| 2 mg/kg* (n=89) | 10 mg/kg (n=84) |
|---|---|
| 15% | 8% |

** pembrolizumab's indicated dose for melanoma is 2 mg/kg*

*Grade 3 fatigue reported in 5 patients in the 2 mg/kg pembrolizumab group, this was the only Grade 3-4 event reported in more than one patient*

*(sources: Robert et al., 2014; Weber et al., 2015)*

**Adverse Events leading to discontinuation (drug-related, Any Grade)**

| 2 mg/kg (n=89) | 10 mg/kg (n=84) |
|---|---|
| 7.0% | 11% |

**Most common drug-related adverse events include fatigue,**

| | 2 mg/kg (n=89) | 10 mg/kg (n=84) |
|---|---|---|
| Fatigue | 32.6% | 36.9% |
| Pruritis | 25.8% | 19.0% |
| Rash | 18.0% | 17.9% |

# Most irAEs occur within the first 3 months of treatment with an immunotherapy; some occur after the final dose of therapy

- Toxicities may be dose-dependent depending upon the immunotherapy (e.g. ipilumumab)
- irAEs can differ depending upon tumor types
- The severity of the toxicity (Grade 1 – 4) dictates how to manage the irAE
- In general, treatment is either withheld or discontinued in patients experiencing moderate or severe irAEs (Grade 2-4)
- Thyroid function, blood counts, liver function, and metabolic panels are tested/taken during treatment of checkpoint inhibitors

*The following slides will focus on the presentation and management of irAEs as they apply to ipilimumab, nivolumab, and pembrolizumab*

# Presentation and Management of Dermatologic irAEs

- Dermatologic irAEs are the most frequently reported Adverse Events; they are typically mild to moderate in severity (<3% are Grade 3 or higher); types of irAEs include:
  - Maculopapular rash and pruritis
  - Vitiligo, alopecia

***Management:***

**Grade 1 – 2 :** symptomatic therapy such as moisturizers, ointments, low-dose topical corticosteroids, antihistamines
**Grade 3 – 4** : evaluate by a dermatologist, administration of systemic corticosteroids (prednisone or equivalent) and drug interruption

(sources: Tarhini, 2013; Yervoy (ipilimumab) Immune-mediated Adverse Reaction Management Guide; Postow M., Callahan, M., and Wolchok, J., 2015)

# Presentation and Management of Enterocolitis / Gastrointestinal irAEs

- Disregulation of GI mucosal immunity can result in diarrhea, colitis, abdominal pain, or blood/mucus in the stool without fever
- Diarrhea is a more common complaint with use of a CTLA-4 inhibitor vs. an anti-PD1

***Management:***

**Grade 1 – 2 :** treat symptomatically
**Grade 3 – 4** : discontinue treatment; rule out bowel perforation – if present do not administer corticosteroid; treat patient with high-dose intravenous methylprednisolone; other steroids can be used such as dexamethasone; with no improvement, consider single-dose infliximab

*(sources: Tarhini, 2013; Yervoy (ipilimumab) Immune-mediated Adverse Reaction Management Guide; Postow M., Callahan, M., and Wolchok, J., 2015)*

# Presentation and Management of Endocrinopathies

- Endocrinopathy irAEs include inflammation of the pituitary, thyroid, or adrenal glands and occurs in <5% of patients, with <3% being Grade 3 or higher; endocrinopathies can present with non-specific symptoms including:
  - Headache and fatigue (most common)
  - Visual field defects
  - Decreased libido
  - hypotension
  - Mental status change
  - Abdominal pain
  - Unusual bowel habits
  - Abnormal thyroid tests

***Management:***
**Grade 1 – 2 :** without adrenal crisis, may resolve spontaneously; monitor closely with potential endocrinological consultation; short-term, high dose corticosteroids if needed with relevant hormone replacement
**Hypophysitis**: high dose corticosteroids; supplementation of affected hormones
**Adrenal Crisis**: treat as medical emergency, give IV glucocorticoids and IV saline with dextrose

(sources: Tarhini, 2013; Yervoy (ipilimumab) Immune-mediated Adverse Reaction Management Guide; Postow M., Callahan, M., and Wolchok, J., 2015)

# Presentation and Management of Hepatotoxicities

- Inflammatory hepatitis has been reported in patients taking CTLA-4 inhibitors or PD-1 inhibitors. In patients taking ipilimumab, <2% present with hepatotoxicity, ~1% are Grade 3-4. Liver tests should be performed to determine AST (aspartate aminotransferase) or ALT (alanine aminotransferase) levels, most episodes are asymptomatic

***Management:***

Monitor transaminases and bilirubin prior to each dose to exclude other causes of hepatitis

**Grade 2 :** AST or ALT levels > 2.5 times but ≤ 5 times the upper limit of normal (ULN); total bilirubin > 1.5 times but ≤ 3 times the ULN; treatment should be withheld

**Grade 3 or greater**: AST or ALT >5 times the ULN, bilirubin >3 times the ULN; permanently discontinue treatment. Provide high-dose IV corticosteroid therapy; if refractory to corticosteroid treatment, mycophenolate mofetil is recommended

*(sources: Tarhini, 2013; Yervoy (ipilimumab) Immune-mediated Adverse Reaction Management Guide; Postow M., Callahan, M., and Wolchok, J., 2015)*

# Presentation and Management of Pneumonitis

- Pneumonitis can present as cough, chest pain, and shortness of breath; imaging should be considered; occurs with both CTLA-4 inhibitor and PD-1 inhibitor use, higher rate of occurrence with anti-PD-1s (~3%)

***Management:***

**Grade 1:** May present without symptoms, but shown on scans
**For moderate to severe symptoms or radiographic findings**: Pulmonary consultation is suggested as well as a bronchoscopy to evaluate for infectious etiology; severe cases may warrant use of IV methylprednisone and the possible consideration of other immunosuppressant agents (e.g. infliximab, mycophenolate mofetil, cyclophosphamide)

*(sources:* Postow M., Callahan, M., and Wolchok, J., 2015*; Kudchadkar, R. Winship Cancer Institute, Emory University Presentation, https://winshipcancer.emory.edu/files/presentation-files/11.20-Kudchadkar-Immune-theapy-AE.pdf*

# Other irAEs

## Ocular irAEs:

- Eye inflammation from episcleritis, conjunctivitis, uveitis, ophthalmopathy associated with Graves disease
  - Symptoms: photophobia, pain, dryness, blurred vision
  - Recommended to consult with an ophthalmologist if experiencing visual disturbances
  - Topical corticosteroids may be useful; for Grade 3-4 events, oral corticosteroids may be used

## Neurologic irAEs:

- Guillain-Barre Syndrome, inflammatory myopathy, posterior reversible encephalopathy syndrome, aceptic meningitis, enteric neuropathy, transverse myelitis are a few neurologic irAEs associated with checkpoint inhibitors
  - Symptoms: muscle weakness, sensory neuropathies, or motor neuropathies confirmed by examination
  - Serious events are treated with corticosteroids; consultation with a neurologist recommended

*Additional irAEs in patients taking immunotherapy checkpoint inhibitors can also include adverse events related to the Kidneys and Pancreas, and can be Hematologic*

*(sources: Tarhini, 2013; Postow M., Callahan, M., and Wolchok, J., 2015)*

# Key Takeaways

- Adverse Events differ in patients taking cytotoxic agents versus patients taking immunotherapy checkpoint inhibitors; this is a result of the Immunotherapy's unique MOA
  - Clinicians need to understand how irAEs present as well as how to manage them to maintain effective use in patients

- Three checkpoint inhibitors are approved by the FDA. irAEs occur including, but not limited to, Dermatologic Toxicities, Enterocolitis / Gastrointestinal irAEs, Endocrinopathies, Hepatotoxicities, and Pneumonitis

- Severity of the toxicity (Grade 1-4) dictates how to manage the irAE; in general, treatment is either withheld or discontinued in patients experiencing moderate or severe irAEs (Grade 2-4)
  - Less severe irAEs can be treated symptomatically; with more severe irAEs often requiring steroid use (e.g. corticosteroids, glucocorticoids)
  - Consultation with a specialist is often recommended

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- A 67 year old male with stage IV melanoma (lung, adrenal, liver) on a clinical trial utilizing sequential ipilimumab followed by PD1 AB- randomized to receive ipilimumab first.

- Week 7
  - Previously tolerating treatment well
  - Presents for dose 3 ipi
  - Continues to feel well: active, walking, playing golf 2-3 times a week
  - No complaints of diarrhea, cramping abdominal pain or blood per rectum
  - Reminded to call for adverse effects- fatigue, rash, itching, diarrhea, shortness of breath or cough
  - RTC 3 weeks or call for issues

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 8 (phone call)
  - (5 days post treatment)
  - Patient calls stating he has had diarrhea x 4 days . He is unsure how many episodes per day and he has been taking Imodium sporadically

- Contact MD-
  - Instructions:
    - Imodium- 2 tabs po with first diarrhea of the day, 1 tab with each additional diarrhea , up to 8 tabs a day
    - Lomotil- 1 tab po QID on days with diarrhea
    - Budesonide – three 3 mg tabs po q am x 10 days ( take all 10 days- even if diarrhea stops)
    - Call MD if no improvement

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 8 ½ (phone call)
  - Patient continues with diarrhea
  - Stools are firmer, not as watery as last week
  - Had 3 stools yesterday ( continues with Imodium, Lomotil and budesonide) but probably up to 7 stools the day before.
  - Lab report received from PCP-stool  positive for occult blood

- Contact MD
  - Instructions- continue Imodium, Lomotil and budesonide
  - Add prednisone taper starting at 80 mg a day , decrease by 10 mg every 3 days. ( 24 days)
  - Patient to call if no improvement

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 10 clinic visit on schedule ( for dose 4 Ipilimumab)
  - 15 days into steroid taper
  - Diarrhea completely resolved within days after starting steroids
  - Patient feeling well, energy 80-90%, played golf twice last week

- Plan
  - Continue steroid taper
  - Will skip dose 4 ipilimumab
  - Get rescanned as planned and RTC in 3 weeks

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 13 clinic visit ( post scans, pre PD1 AB)
  - Off steroids for 10 days
  - 1 episode of diarrhea last week controlled with Imodium
  - Scans show stable disease

- Plan
  - Proceed on trial with PD1 AB

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 26 clinic visit-
  - Has been tolerating PD1 AB without toxicities so far
  - CT scans show a partial response
  - Grade 1 diarrhea – controlled with Imodium
  - Grade 1 elevated Lipase

- Plan
  - Proceed with PD1 AB

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Over next 5 months patient had occasional grade 1-2 elevated amylase and/or lipase (asymptomatic)
- Patient was treated on schedule

- Week 47 Clinic visit
  - Patient presents to clinic for PD1 AB on schedule
  - Grade 3 amylase ( 2-5 x ULN)
  - Grade 4 lipase (> 5 x ULN) – asymptomatic

- Plan-
  - hold PD1 AB
  - Medrol dosepak
  - RTC 2 weeks on schedule ( after CT scans)
  - Call asap for indigestion, abdominal pain or discomfort, nausea and/or vomiting or proceed to ER

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 49 clinic visit
  - Scans show confirmed PR
  - Grade 2 lipase ( 1.5-2 x ULN) asymptomatic

- Plan
  - proceed with PD1 AB

- Week 51 clinic visit
  - Grade 3 lipase –asymptomatic

- Plan
  - proceed with PD1 AB

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 64- (ER visit)
  - Presents to ER with abdominal pain, bloating and nausea ( no vomiting)
  - Patient had called MD and was instructed to proceed to ER if it did not clear up soon
  - Findings in ER
    - Lipase was 1348
    - CT ABD shows inflammation surrounding pancreatic head consistent with pancreatitis
  - Treatment :
    - IV solumedrol in house x 2 days
    - D/C home 2 days after admit on a medrol dosepak
    - Amylase at discharge 69, lipase at discharge 300

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 65 clinic visit
  - Patient feels much better
  - Grade 1 lipase

- Plan
  - Due to admit for acute pancreatitis decision was made to discontinue therapy and continue to monitor patient on trial but off active treatment
  - Complete medrol dosepak
  - Avoid fatty foods and ETOH intake
  - RTC 2 weeks
  - Call clinic for any issues

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 67 clinic visit
  - Following bland low fat diet with decreased ETOH
  - Back to usual activity (golf 4 times a week)
  - Lipase 197 (grade 3)
  - Amylase 98 (grade 3)

- Plan
  - Check labs at PCP in 2-3 weeks
  - Call asap for any abdominal symptoms

- Week 69
  - Labs at PCP-Lipase 54 , amylase 45 (WNL)

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 84
  - Scans stable
  - Symptoms- new chronic dry cough; no SOB, hemoptysis , increased sputum or DOE

- Findings
  - O2 saturation 99% at rest and after activity
  - CT scan shows possible pneumonitis

- Plan-
  - RTC in 6 weeks for an interim CT scan
  - Call asap for worsening pulmonary symptoms or any other issues

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

- Week 90
  - Patient feels good with 90% energy
  - Playing golf daily
  - Cough is the same without change in sputum production
  - Patient denies SOB at rest but does have some DOE

- Findings
  - O2 saturation 97% at rest and 90% after activity
  - CT scan shows progression in pneumonitis
  - PE exam reveals rhonchi bilaterally
- Plan-
  - Prednisone 30 day course with a decline by 10 mg every 3 days until finished
  - Add Zantac to Protonix due to known reflux with steroid therapy
  - RTC 2 ½ week for PE and labs

# Case Study 1
# Colitis Followed by Pancreatitis and Pneumonitis

Week 93

- Feels much better
- Patient is currently at dose of 40 mg in prednisone taper
- Patient has minimal cough but denies SOB, increased sputum, hemoptysys or DOE

- Findings
  - O2 saturation 96% at rest and 95% after activity
  - PE exam reveals lungs clear to auscultation

- Plan-
  - Continue Prednisone 30 day course with a decline by 10 mg every 3 days until finished
  - Continue Zantac and Protonix due to known reflux with steroid therapy
  - RTC 4 weeks for restaging scans on protocol

# Case Study 2: Enteritis Then Nephritis

- A 42 year old male with a history of stage IIIC resected melanoma from the right groin with 10/24 positive nodes received 6 doses of nivolumab on an adjuvant trial, then had a re-staging evaluation/scans showing no disease

- 2 weeks later, just prior to the scheduled 7$^{th}$ dose, he came to clinic complaining of 2 days of anorexia, nausea, one episode of vomiting and one episode of diarrhea. The temp was 101.5 degrees F, creatinine was 1.2, and he mentioned that he had dark urine.

# Case Study 2: Enteritis Then Nephritis

- He was admitted to the hospital, had blood cultures, was started on broad spectrum antibiotics and had another diarrheal stool just after admission

- C Diff titres were taken, and he was hydrated. KUB/upright showed an ileus. CT scan showed no colitis, but some small bowel stranding. The C Diff was positive

# Case Study 2: Enteritis Then Nephritis

- The patient was treated for C diff with vancomycin, but the ileus did not improve, with requirement for narcotics for pain relief
- The patient had 7 diarrheal BMs the next day
- Steroids were instituted 48 hours after admission, with 125 mg Solumedrol given twice a day IVPB, then 125 mg once IVPB

# Case Study 2: Enteritis Then Nephritis

- The patient improved rapidly, the diarrhea disappeared, and he was discharged on a 100 mg prednisone taper orally on the 5$^{th}$ day after admission, eating normally

- He was better when seen a week later, and then 2 weeks later felt well.

- The steroids finished in 40 days, and he returned to work as a PE instructor and coach 2 weeks after discharge, on steroids

# Case Study 2: Enteritis Then Nephritis

- 2 weeks after finishing the steroids, he began to have nausea and anorexia
- 2 days later he developed a fever and contacted the on call physician; he was told to come to be seen at the hospital
- He had a fever to 102 degrees F, Cr of 1.3, dark urine and severe nausea
- The abdominal exam showed minimal diffuse tenderness without rebound noted
- CT scan showed no changes of enteritis or colitis, but stranding around both kidneys

# Case Study 2: Enteritis Then Nephritis

- The patient was hydrated and treated with empiric antibiotics; there was no clear diagnosis
- The next morning he still felt poorly, with low grade fevers, and Cr 1.4, taking nothing by mouth. KUB/abdomen upright were unrevealing
- 48 hours after admission, Cr=2.0, with less than 1 liter of urine, feeling a bit improved, with low grade fevers
- The next day his creatinine was 2.8, BUN 12, with continued anorexia, nausea, and vomiting controlled with zofran

# Case Study 2: Enteritis Then Nephritis

- He was started on IV solumedrol at 125 mg BID for 2 days; the next day the creatinine was 2.4, then 1.9 the day after.

- He started to take fluids by mouth and was afebrile. He was switched to 120 mg prednisone PO tapering over 48 days, and was discharged home 6 days after admission, tolerating a bland full diet

# Questions?

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