



UNIVERSITY IN KRAGUJEVAC  
FACULTY OF MEDICAL SCIENCES



# **ONCOLOGICAL TREATMENT COMPLICATIONS AND ADVERSE EFFECTS**

# **Oncological treatment complications and adverse effects**

## **Complications and side effects of chemotherapy treatment depend on:**

- type of drugs
- doses
- administration way

## **Side effects appearance**

- simultaneously with the application
- late (months or years after the treatment)
- There are side effects common to most cytostatics, but also specific, related to a group or an individual cytostatic

# **Oncological treatment complications and adverse effects**

- Side effects and complications of oncological treatment are increasingly common in the structure of morbidity
- The reporting time is extended to several years after the end of the treatment, that conditions cause misinterpretation or not diagnosing
- Potentially cause of the appearance of secondary malignancies (hematological usually in a period of two to ten years, and solid tumors in a period of up to thirty years after the end of treatment)

# Oncological treatment complications and adverse effects

## Local (related to one organ or organ system)

- pain
- redness
- phlebitis
- tissue necrosis

## Systemic

- Infusion reactions (most often when using monoclonal antibodies)
- fever
- febrility
- pain
- obstruction
- hypotension
- allergic reaction

# Nausea and vomiting

- The most common side effect
- It rarely seriously endangers health, but greatly compromises the quality of life and is often the reason for giving up treatment

## **According to the appearance time:**

- anticipatory emesis (before the start of treatment)
- acute emesis (within 24 hours from the start of treatment)
- delayed emesis (1-5 days after the start of treatment)

# Oncological treatment complications and adverse effects

Emesis → cytostatic drugs  
→ individual patient characteristics

## Mitigating factors

- Male
- Age >50 years
- Previous alcohol abuse
- Prior cytostatics treatment without nausea

## • Contributing factors

- Females
- Age <50 years
- Earlier treatment followed by nausea and vomiting
- History of vomiting during pregnancy
- "sea sickness"

## Oncological treatment complications and adverse effects

EMETOGENIC POTENTIAL	TYPICAL AGENTS	DEFINITION
High	Cisplatin Dacarbazine Nitrogen mustard	Emesis in nearly all patients
Moderate	Carboplatin Anthracyclines Cyclophosphamide Irinotecan	Emesis in >70% of patients
Low	Mitoxantrone Taxanes	Emesis in 10%– 70% of patients
Minimal	Hormones Vinca alkaloids Bleomycin	Emesis in < 10% of patients

# Nausea and vomiting treatment

- Metoclopramid
- Ondansetron - 5HT<sub>3</sub> antagonist
- Dexamethason
- Lorazepam
- Haloperidol
- Aprepitant
- Prochlorperazin



# Hematological toxicity

- Anemia
- Thrombocytopenia
- Leukopenia (granulocytopenia)
- A more frequent toxicity manifestation
- Gradus 4 is life threatening
- Febrile neutropenia (**emergency condition in oncology**)

# Anemia

- Life-threatening level - hemoglobin below 50g/L
- Often a reason for delaying treatment

## **Symptoms:**

- weakness
- easy fatigue
- palpitations
- drowsiness
- hypotension

## **Treatment:**

- iron preparations
- transfusions (values below 80g/L)
- administration of erythropoietin (?)

# Thrombocytopenia

- It occurs more often than anemia in a life-threatening degree (values below 20,000)

## Signs:

- petechial bleeding in the skin of the lower legs
- bleeding in tissues and organs
- suffusion
- epistaxis
- hematemesis
- melena
- rectoragia
- hematuria

## Treatment:

- substitution-transfusions of concentrated platelets

# Leukopenia/granulocytopenia

- It occurs frequently
- Reason for delaying or stopping treatment
- Values below 1000Le/500Gr require treatment

## Treatment:

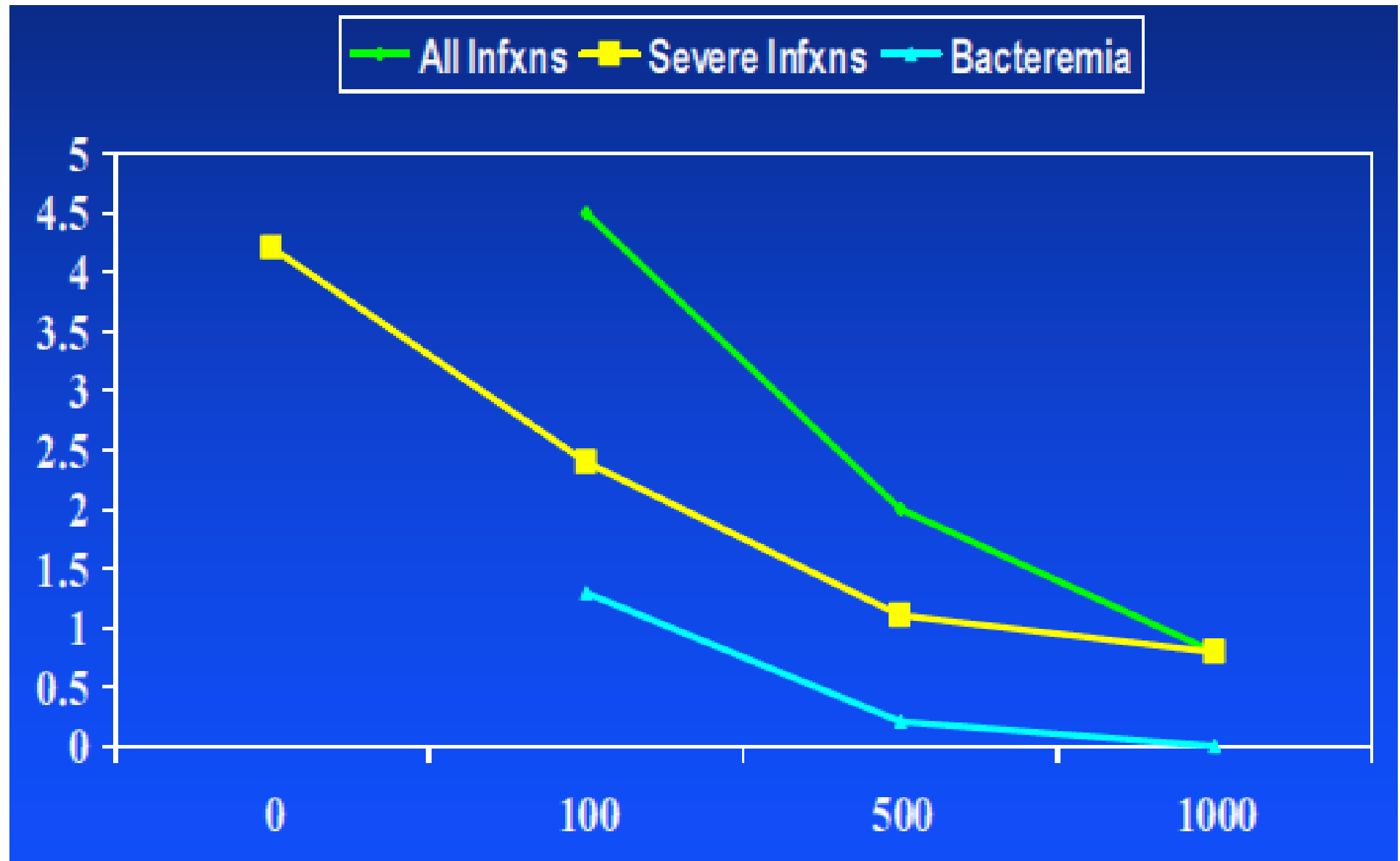
- antibiotic prophylaxis
- Granulocyte-Colony Stimulating Factor (G-CSF)

# Febrile neutropenia

- It is defined as a body temperature over 38.5 Celsius, measured axillary, lasting longer than one hour in the presence of less than 500 granulocytes
- Despite modern treatment options, mortality ranges from 1 (low-risk patients) to about 10% (high-risk patients)

- Normal ANC 1500 - 8000 cells/mm<sup>3</sup>
- Neutropenia: ANC < 1500 cells / mm<sup>3</sup>
- Mild neutropenia: 1000-1500 cells / mm<sup>3</sup>
- Moderate neutropenia: 500-999 cells / mm<sup>3</sup>
- Severe neutropenia: < 500 cells / mm<sup>3</sup>
- Profound neutropenia: <100 cells / mm<sup>3</sup>

# Risk of infection



# Multinational Association for Supportive Care in Cancer (MASCC) risk assessment criteria

Characteristic	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No active chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Burden of illness: moderate symptoms	3
Outpatient status	3
Age < 60 years	2

MASCC Risk Index score  $\geq 21$  indicates that the patient is at a low risk of complications and mortality, classified as low-risk febrile neutropenia.



# Diarrhea

- It often occurs
- Up to 60% of patients treated with irinotecan or fluorouracil, and 10% have a serious clinical condition
- It is often the cause of lowering the dose of the drug, delaying or treatment stopping
- When it occurs in combination with mucositis and neutropenia, it is often life-threatening

## **Risk factors for diarrhea**

- Older age
- Females
- Worse performance status (ECOG PS>2)
- Bowel diseases in the anamnesis
- Tumor in the intestines
- Irinotecan or fluorouracil in therapy
- Weekly treatment
- Infusion regimens
- Simultaneous application of radiotherapy

# Toxicity intensity assessment

Grade	Diarrhea	Colitis
1	Increase in stool frequency <4/day over baseline; mild increase in ostomy output compared to baseline	Asymptomatic; clinical or diagnostic observation only; intervention not indicated
2	Increase in stool frequency 4–6/day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Abdominal pain; mucus or blood in stool
3	Increase in stool frequency >7/day over baseline; severe increase in ostomy output compared to baseline; limiting self-care ADL	Severe abdominal pain; peritoneal signs
4	Life-threatening consequences; urgent intervention indicated	Life-threatening consequences; urgent intervention indicated
5	Death	Death

# Pulmonary toxicity of chemotherapy

- **Bronchospasm** presence of obstruction in the airways - wheezing
- **Allergic reactions**, bronchospasm, accompanied by other allergic manifestations
- **Infusion reactions** are hypersensitivity manifestations that occur during the infusion or a few minutes after
- **Interstitial pneumonitis**
- **Noncardiogenic pulmonary edema** - not associated with heart failure. Increased capillary permeability syndrome - non-cardiogenic pulmonary edema followed by diffuse edema and hypovolemia
- **Acute lung damage**
- **Acute respiratory distress syndrome** (ARDS)
- **Eosinophilic pneumonia**
- **Radiation recall pneumonitis**

# Pulmonary toxicity of chemotherapy

- **Bevacizumab** - pulmonary hemorrhage, hemoptysis, pulmonary embolism
- **Chlorozotocin** - interstitial pneumonitis
- **Erlotinib** - acute pneumonitis, ARDS
- **Etoposide** - acute pneumonitis, diffuse alveolar damage, bronchospasm
- **Gefitinib** - acute pneumonitis, diffuse alveolar damage, diffuse alveolar hemorrhage, pulmonary fibrosis
- **Gemcitabine** - diffuse alveolar damage, diffuse alveolar hemorrhage, increased capillary permeability syndrome, pulmonary edema, ARDS, pleural effusion
- **Ifosfamide** - interstitial pneumonitis
- **Imatinib** - acute pneumonitis, pulmonary edema, pleural effusion
- **Irinotecan** - pneumonitis, lung failure

# Pulmonary toxicity of chemotherapy

- **Oxaliplatin** - pulmonary fibrosis, pulmonary insufficiency, eosinophilic pneumonia
- **Mitoxantrone** - acute pneumonitis
- **Piritrexim** - acute pneumonitis
- **Taxanes** - acute pneumonitis, pleural effusion
- **Temozolomide** - acute pneumonitis
- **Thalidomide** - acute pneumonitis, pleural effusion, pulmonary embolism
- **Topotecan** - bronchiolitis, pneumonia with consequent fibrosis
- **Trastuzumab** - acute pneumonitis, acute lung injury, pneumonia with consequent fibrosis

# Chemotherapy cardiotoxicity

- Damage to the heart muscle by toxins represents cardiotoxicity

## **Characterized by:**

- Rhythm disorders
- Heart failure

# Cardiotoxic cytostatics

- Doxorubicin (Adriamycin)
- Epirubicin
- Idarubicin
- Cyclophosphamide
- Fluorouracil
- Mitoxantrone
- Paclitaxel
- Tyrosine kinase inhibitors
- Monoclonal antibodies



# Chemotherapy cardiotoxicity

- It occurs most often within a year of treatment, but it can also occur after several years
- Recent research shows that subclinical decline in heart muscle efficiency (by more than 10%) occurs in 10-50% of patients treated with anthracyclines
- Heart failure occurs in about 2% of patients treated with anthracyclines
- The prognosis of heart failure caused by cytostatics is significantly worse than heart failure of other etiology (it is resistant to treatment)

# Toxicity of immunotherapy (irAE)

- Rash and other skin changes
- Diarrhea and colitis
- Endocrinopathies
- Hepatitis
- Pneumonitis
- Nephritis / renal dysfunction

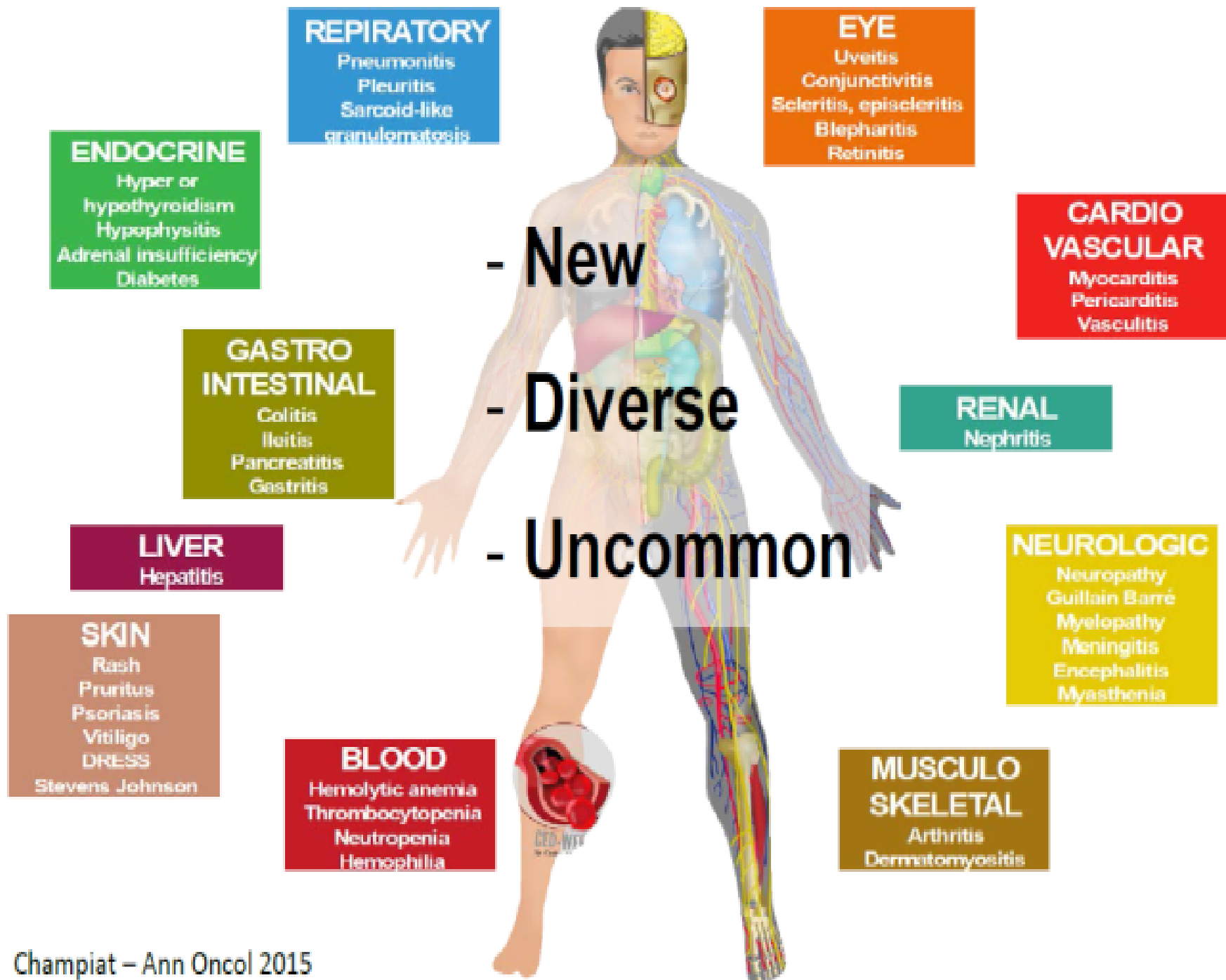
## **Treatment:**

- Corticosteroids are the mainstay of treatment
- Most toxic effects can be resolved, but endocrinopathies tend to result in lifelong treatment

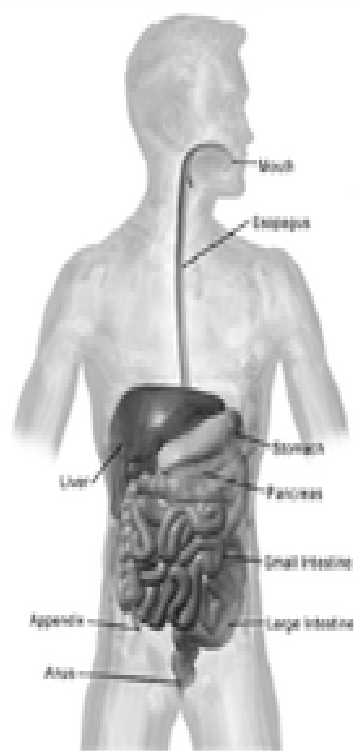
# Toxicities of Checkpoint Inhibition

- Choose an organ or body system, and add “itis”
  - Encephalitis, hypophysitis, ophthalmitis, thyroiditis, myocarditis, pneumonitis, hepatitis, pancreatitis, colitis, nephritis, arthritis, myositis, neuritis, dermatitis
  - Others are infusion reactions, fatigue, and adrenal insufficiency
- **These toxicities are NOT like our usual chemotherapy issues**





# GI Toxicity

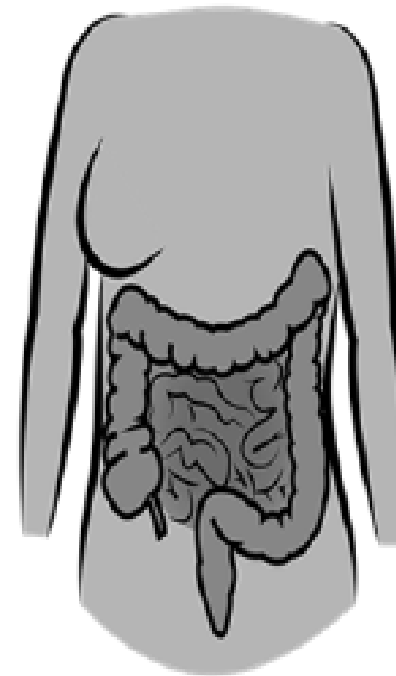


Digestive System

- **Colitis** is one of the most common toxicities
  - ✓ Any grade – 30%, severe cases <10%
  - ✓ Rule out infection, including C diff infection
  - ✓ Consider Colonoscopy for severe cases
- **Hepatitis**
  - ✓ Increased risk with combination therapy
  - ✓ Rule out infection, metastatic disease, steatohepatitis
- **Pancreatitis**
  - ✓ Amylase, lipase elevation
  - ✓ May be associated with hyperglycemia/diabetes

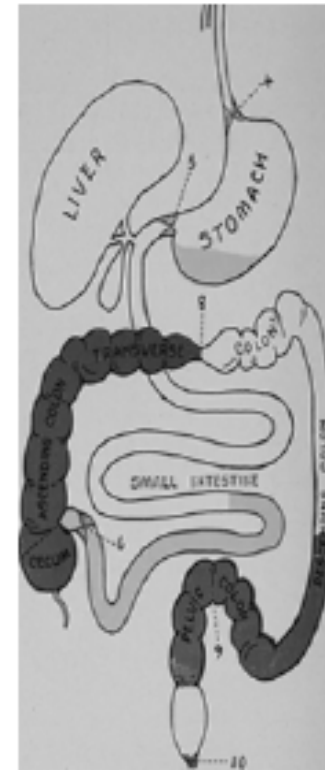
# GI Toxicities

- Diarrhea – very common with targeted therapy
  - ✓ EGFR inhibitors in particular
- Intestinal bleeding and perforations
  - ✓ Primarily with VEGF inhibitors
- Hepatotoxicity
  - ✓ Common with ALK inhibitors
- Elevated pancreatic enzymes



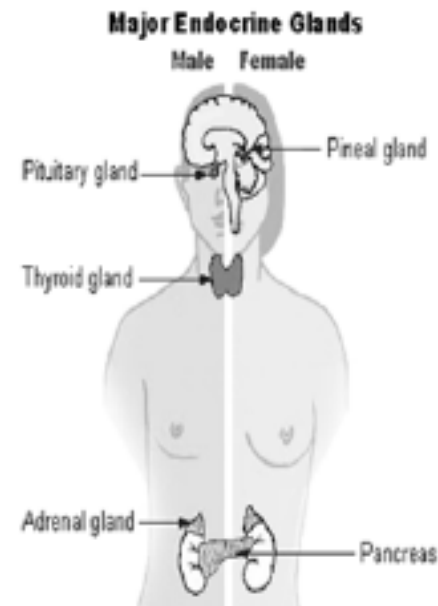
# Diarrhea Management

- First - Exclude other causes!
- Loperamide
- Octreotide (SC)
- Hold drug or dose reduction by oncology
- Severe diarrhea
  - ✓ Hospitalization
  - ✓ Replace electrolytes



# Endocrine Toxicity

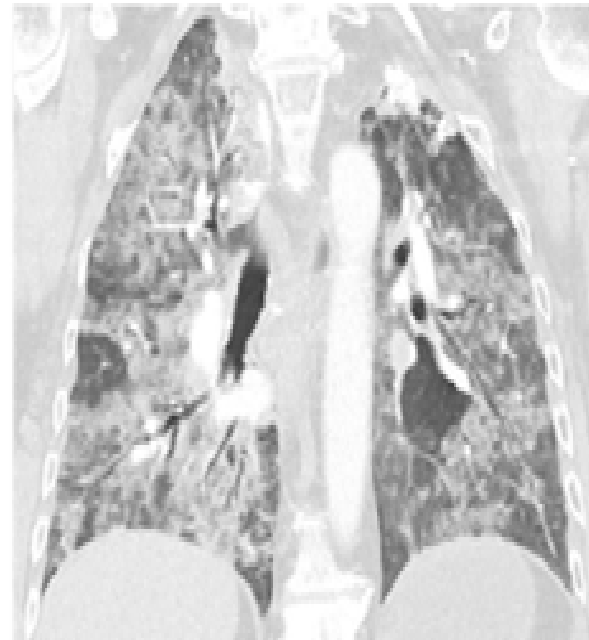
- **Thyroid dysfunction (>10%)**
  - ✓ Replacement therapy for hypothyroidism
  - ✓ Symptom control for Hyperthyroidism
- **Hypophysitis (<5%)**
  - ✓ Non-specific symptoms: headache, fatigue
  - ✓ Cortisol, ACTH, thyroid function testing
- **Adrenal insufficiency (rare)**
  - ✓ Dehydration, hypotension, hyperkalemia, hyponatremia
  - ✓ Steroid replacement
- **Diabetes (rare)**
  - ✓ Anti-GAD or anti-islet antibodies may be present
  - ✓ Insulin therapy may be required





# Pulmonary Toxicity - Pneumonitis

- Focal or diffuse inflammation of lung parenchyma
- Onset may be early or late
- Differential includes infection, COPD exacerbation, and disease progression
- Bronchoscopy may be helpful if patient is stable
- Empiric therapy: Steroids and antibiotics



# Immunotherapy Skin Toxicity

- **Rash/Inflammatory Dermatitis**
  - ✓ Variable: erythema, maculopapular rash, eczematous/ psoriasiform
  - ✓ *Differential:* drug rash, infection (cellulitis), autoimmune conditions, hand-foot syndrome
- **Bullous Dermatoses (rare)**
  - ✓ Bullae/blisters, sloughing possible
  - ✓ *Differential:* drug reaction, bullous pemphigoid, infection (esp. viral), friction/trauma

# Immunotherapy Skin Toxicity

- Stevens Johnson Syndrome (SJS), toxic epidermal necrosis (TEN),
  - ✓ Severe alteration to skin structure or function; mucous membrane involvement
  - ✓ *Differential*: drug reactions including paraneoplastic pemphigus, autoimmune blistering dermatoses
- Management: Moisturize, topical steroids, systemic steroids if severe

# Rare Toxicities

- **Cardiac**
  - ✓ May mimic heart failure or acute MI
  - ✓ Cardiac MRI may be helpful
  - ✓ High dose steroids may help
- **Neurologic**
  - ✓ Range of presentations including encephalitis, Guillan-Barre, or transverse myelitis
- **Ocular – Uveitis**
- **Rheumatologic**
  - ✓ Inflammatory Arthritis
  - ✓ Myositis
  - ✓ Sicca syndrome
- **Renal**
  - ✓ Kidney failure may be seen

# Targeted Therapy Toxicity

Toxicity may be “on target” or “off target”

- ✓ “On target” toxicity: effect of the drug on a target that is expressed by both the cancer and normal tissue cell
- ✓ “Off target” toxicity results when a drug affects the target essential for normal tissue cells but not essential for cancer cell survival – “bystander effect”

Toxicity also depends on drug target

- Skin (rash)
- Gastrointestinal/Liver (diarrhea, hepatitis)
- Cardiac (cardiomyopathy, QT changes)
- Renal
- Others may also occur – ocular, endocrine, etc

# Other skin changes

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- Rash(acneiform,
  - Nail changes,
  - hand-foot syndrome,
  - Hyperpigmentation
  - Dry skin
  - Telangiectasia
-

# Targeted Therapy Skin Toxicity

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## Acneiform

- Common with multiple targeted agents especially EGFR- TKI and mAB
  - Tends to be dose dependent
  - Signs and Symptoms:
    - Pruritis
    - Diffuse rash – commonly on face/chest/back
    - Often occurs in seborrheic areas
    - May be worsened by sun exposure
  - Associated with increased risk of Staph super-infection
-

# Skin Toxicity: Prevention and Treatment

- Keep skin moist
- Avoid sun exposure or use sunscreen
- Apply emollient generously
- Topical steroids may be useful
- Topical Antibiotics: Clindamycin, metronidazole
- Oral minocycline, tetracycline and doxycycline may be necessary in some cases
- Antihistamines for itching not responsive to topical steroids

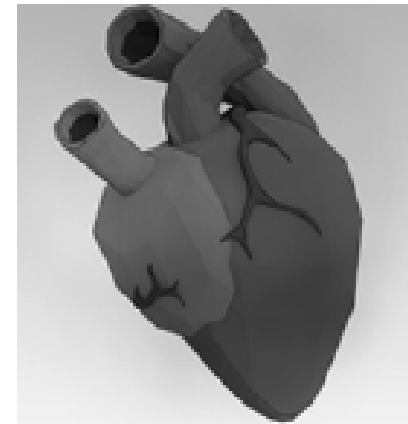




# Cardiovascular Toxicities

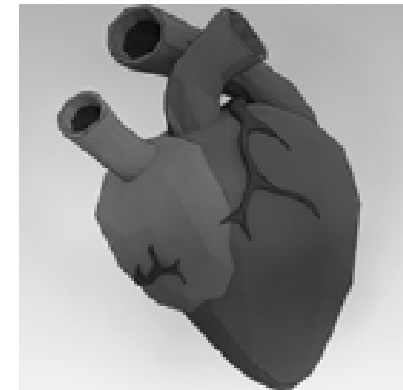
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- Hypertension is one of the most common cardiac toxicities
  - ✓ Commonly associated with VEGF inhibitors
- HTN management: ACE-inhibitors are a preferred agent
- Dose reduction or holding drug may also be required
- Avoid these drugs in patients with uncontrollable HTN
- QT prolongation is another potential toxicity
- Thromboembolic disease and Bleeding are also possible



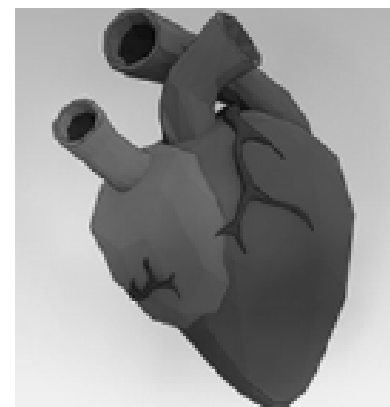
# Cardiac Toxicity of Targeted Therapy

- **Cardiomyopathy**
  - ✓ **Type I:** Kills cardiac cells but have minimal effects
  - ✓ **Type II:** Prevents coordinated contraction of cardiac myofibrils but do not kill cardiac cells
- **Cardiotoxic drugs require heart function monitoring**



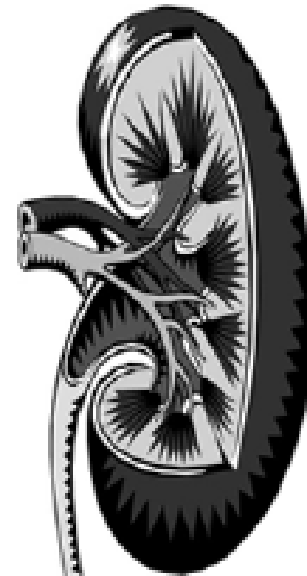
# Cardiac Toxicity of Targeted Therapy

- Cardiac myocytes express Human epidermal growth factors
  - ✓ Trastuzumab (anti-HER2 mAb) induces mitochondria apoptosis, thus affect cardiac contractility
  - ✓ Osimertinib (anti-EGFR TKI) may also cause cardiomyopathy
- Trastuzumab induced cardiotoxicity recovery ranges from months to > 1 year



# Renal Toxicity

- Multiple Renal Toxicities may be seen, particularly with VEGF inhibitors
- Glomerulonephritis: VEGF is expressed
- on nephrons – VEGF inhibitors are associated with proteinuria
- Minimal change, membranoproliferative and cryoglobulinemic /focal segmental nephritis
- Tubular acidosis, interstitial nephritis, Distal tubular dysfunction, Microangiopathy renal thrombosis
- Interstitial nephritis- allergic nephritis(fever, rash, proteinuria, eosinophilia and eosinophiluria)
- Acute tubular necrosis, crystal nephropathy, tubular atrophy, interstitial fibrosis



# Examples of some targeted therapies and their renal toxicities

## **Monoclonal antibodies**

Bevacizumab

Proteinuria  
Nephrotic syndrome  
Glomerulonephritis  
Interstitial nephritis  
Thrombotic microangiopathy

Cetuximab

Hypomagnesaemia

Panitumumab

Hypomagnesaemia

## **Tyrosine kinase inhibitors**

Sunitinib

Interstitial nephritis  
Thrombotic microangiopathy

Sorafenib

Interstitial nephritis

Vatalanib

Proteinuria

Vandetanib

Proteinuria

Axitinib

Proteinuria

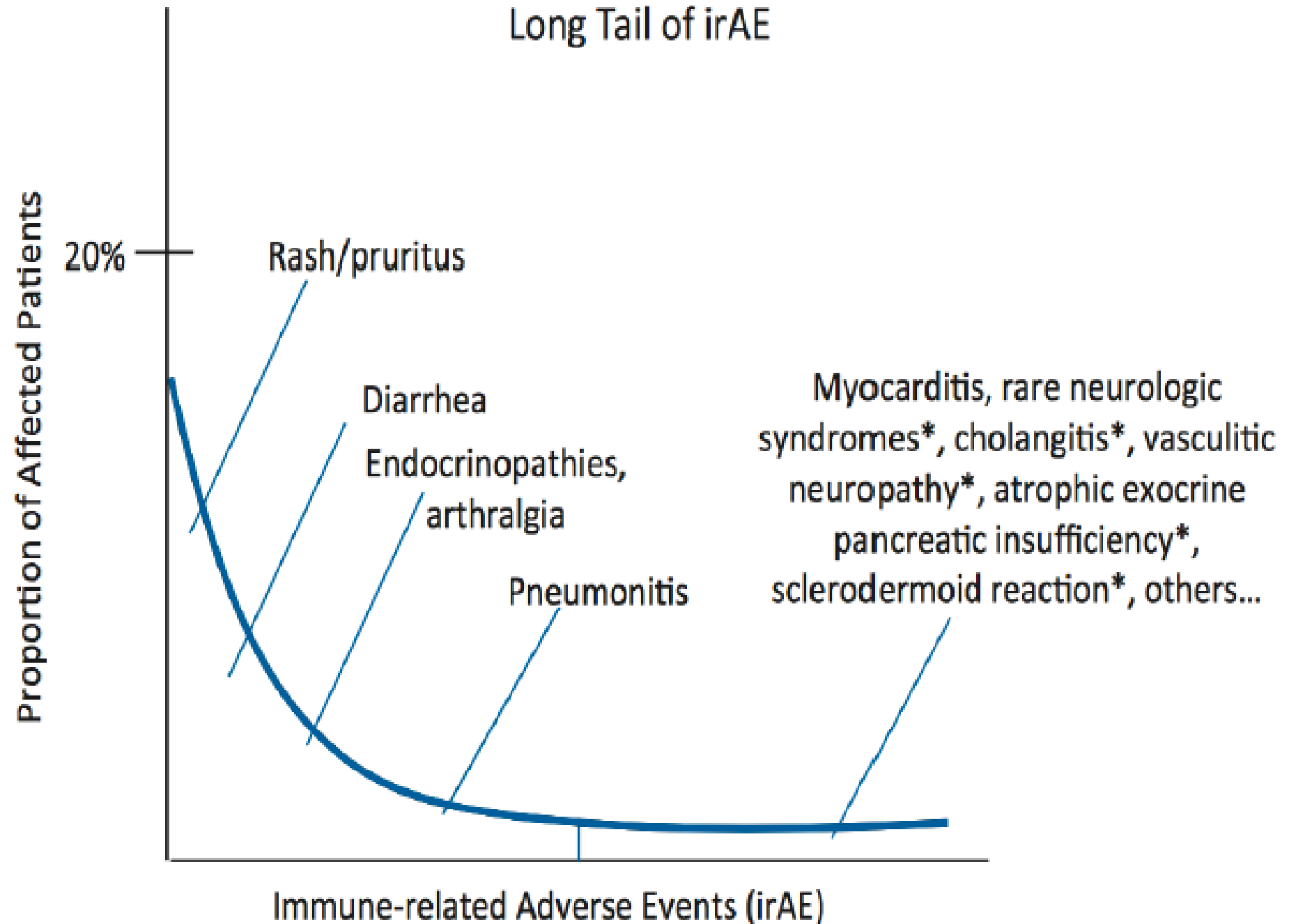
Imatinib

Fanconi Syndrome

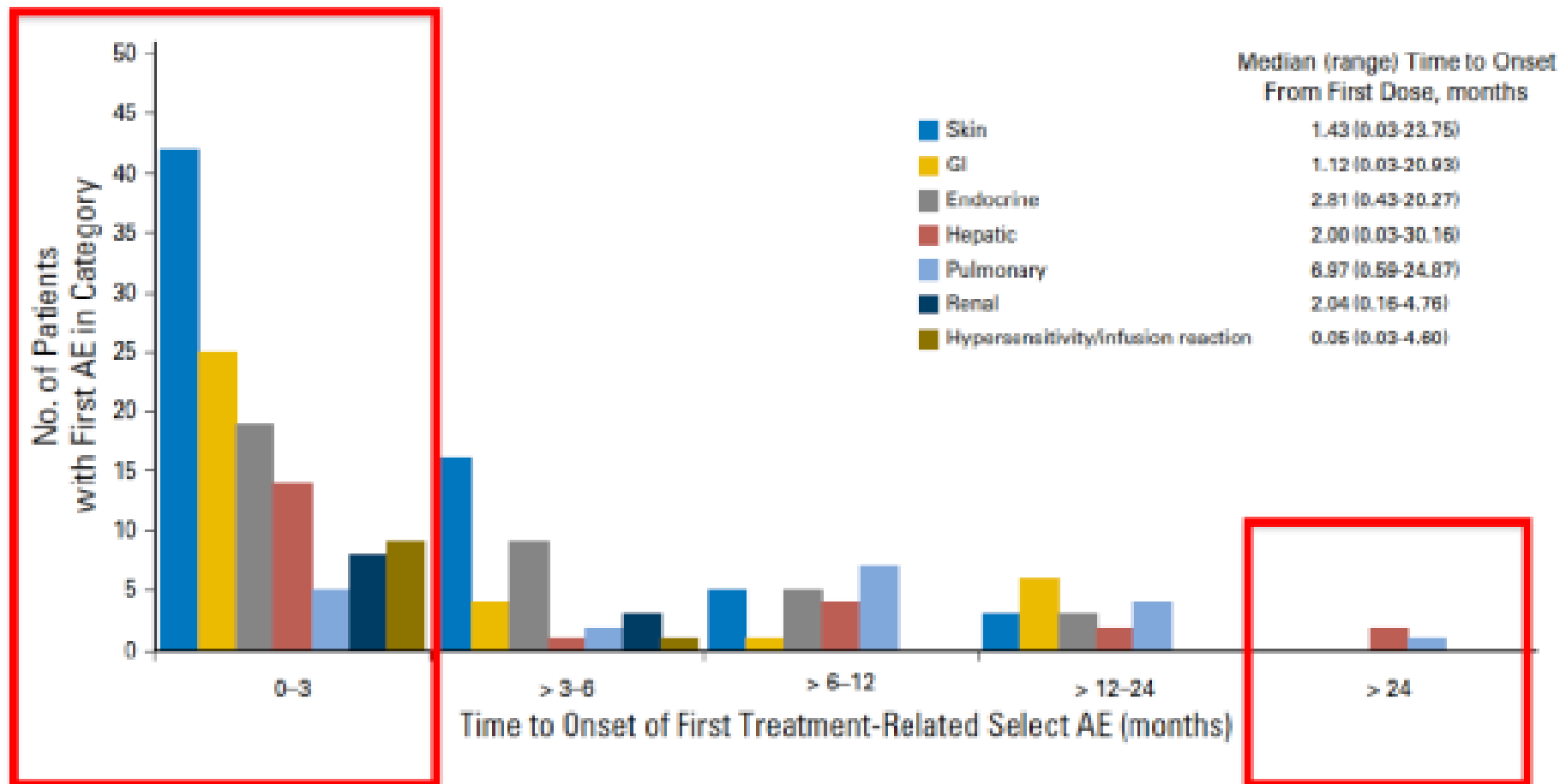
## **mTOR inhibitors**

Proteinuria  
Acute renal dysfunction  
Focal glomerulosclerosis  
Acute tubular necrosis  
Thrombotic microangiopathy

## Long Tail of irAE

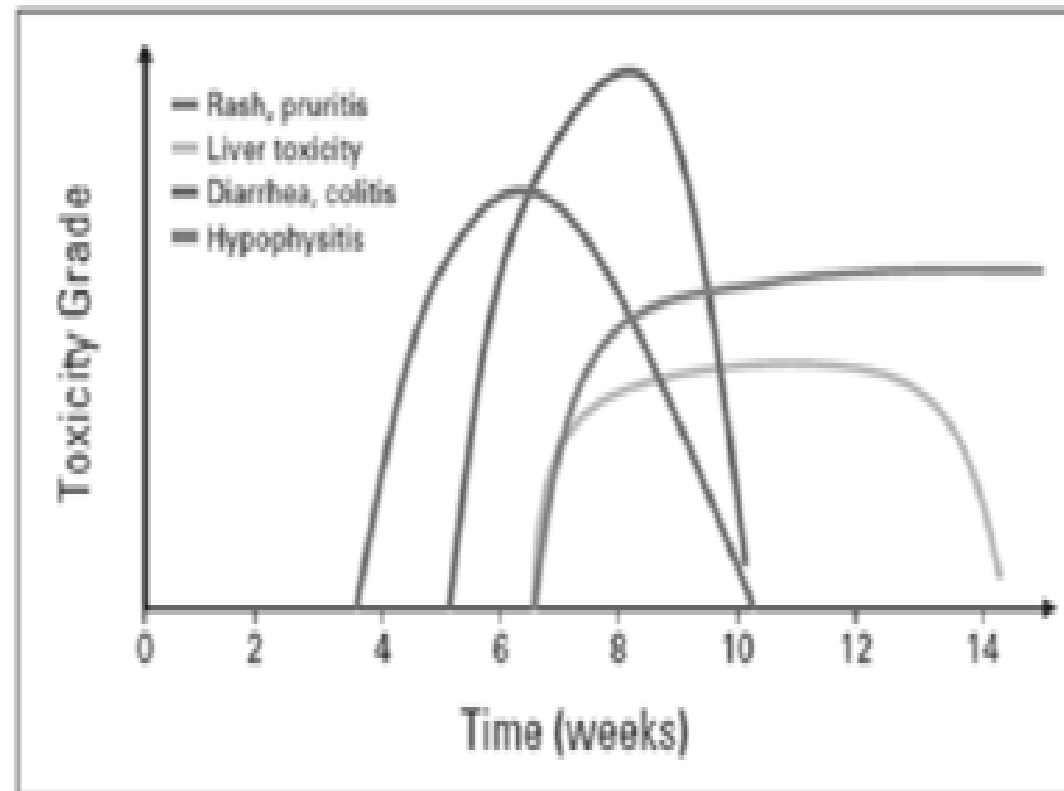


# Onset of irAE's in NSCLC patients



Horn – J Clin Oncol 2017

# Immunotherapy Toxicity Timing is Variable

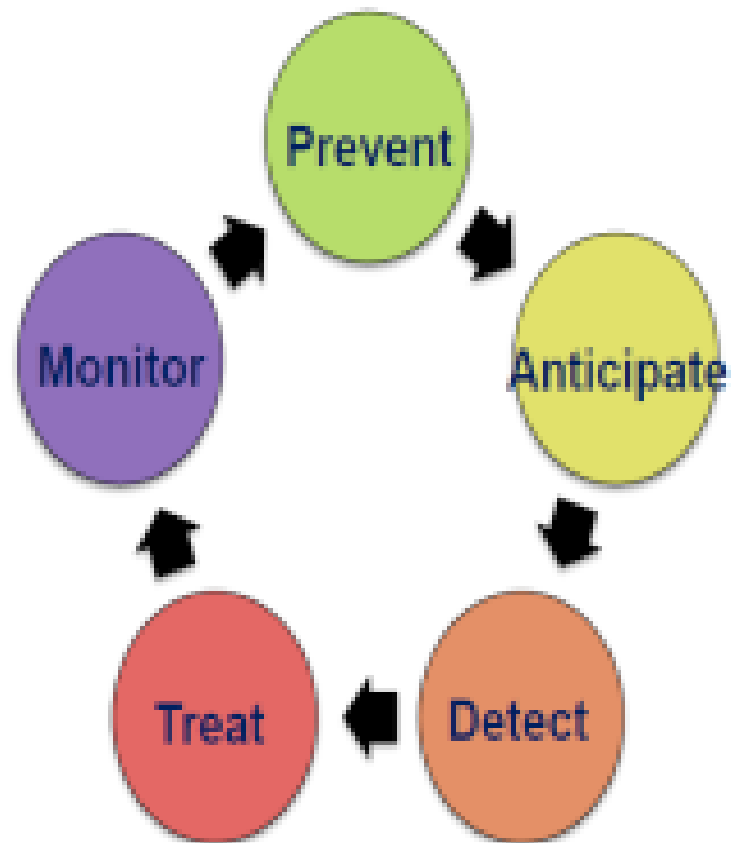




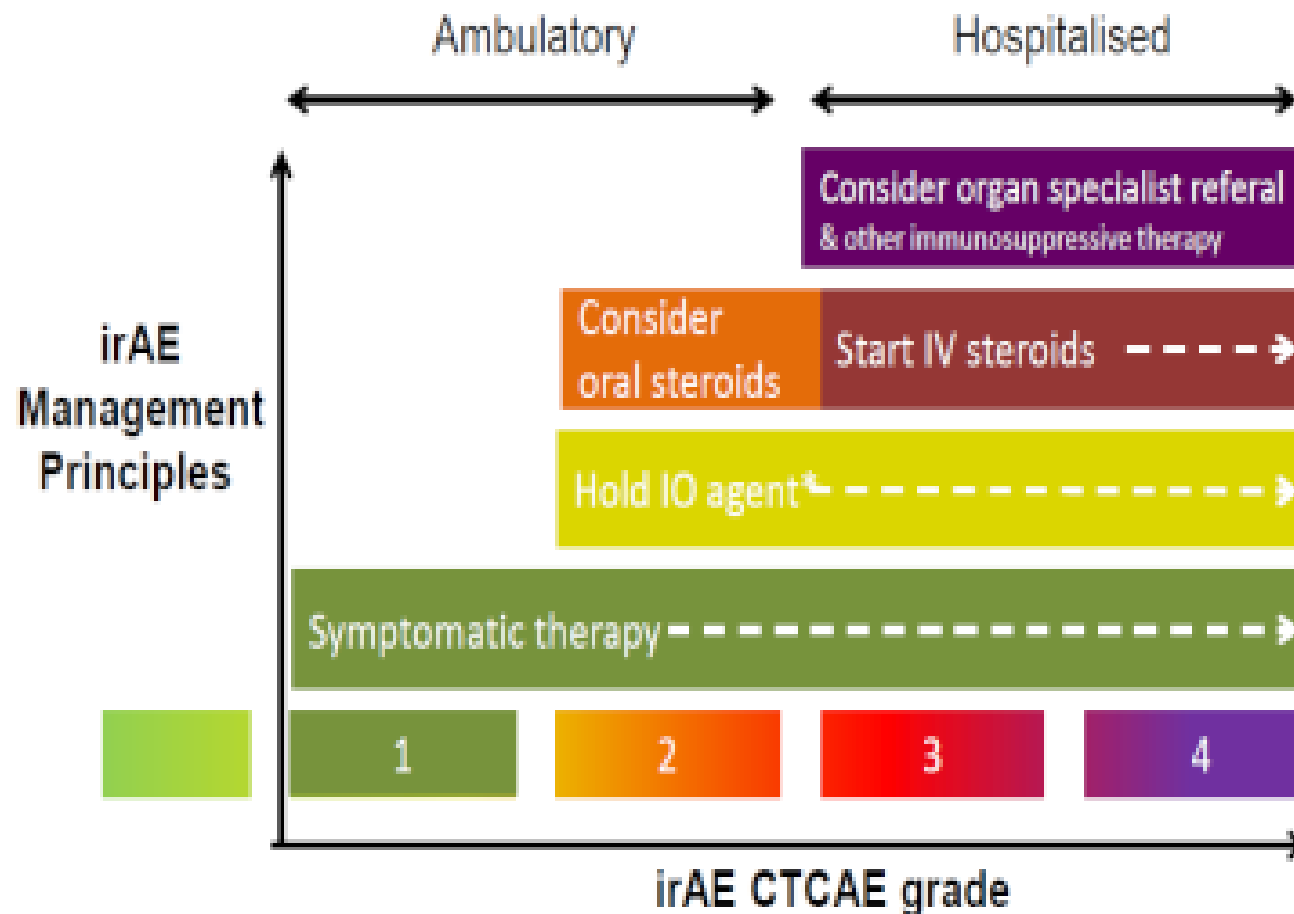
**Immune-related adverse events associated with immune checkpoint inhibitors treatment  
(including incidence and onset of presentation)**

<b>Toxicity</b>	<b>Incidence</b>	<b>Onset after initiation of treatment</b>
Skin	<ul style="list-style-type: none"> <li>● Amongst the most frequent</li> <li>● Almost 1/4 of patients experience rash — &gt;G3 rashes are rare (&lt;3%)</li> <li>● 25-36% of patients experience pruritis — severity greater with combination therapy</li> </ul>	2-3 weeks
Endocrine	<ul style="list-style-type: none"> <li>● Hyper and hypothyroidism have been reported; the latter is more common</li> <li>● Incidence varies from 6%-10%, up to 20% observed (depending on dose and mono/combination therapy)</li> <li>● Rarely higher than Grade 2</li> </ul>	6-7 weeks
Hepatotoxicity	<ul style="list-style-type: none"> <li>● Occurs in up to 10% of patients — 1-2% is Grade 3 with IOPI monotherapy</li> <li>● Occurs in up to 30% of patients with combination therapy — of which 16% is Grade 3</li> </ul>	6-14 weeks
Gastrointestinal	<ul style="list-style-type: none"> <li>● Most common associated irAE — 27-54% of patients treated experience diarrhoea and 8-22% experience colitis (when treated with anti-CTLA-4 monotherapy)</li> <li>● Often most frequent/severe of irAEs associated with IOPI therapy as compared to other toxicities</li> <li>● Incidence much less for anti-PD-1/PDL1 treatments</li> </ul>	6-10 weeks
Respiratory	<ul style="list-style-type: none"> <li>● Pneumonitis is 1.5-2.0-times more frequent with anti-PD-1 therapy compared to anti-CTLA-4 monotherapy</li> <li>● Combination therapy — up to 3 times more likely to experience irAE (Grade 3)</li> </ul>	8-14 weeks

# Immunotherapy toxicity management



# General management strategies for irAEs



- outside skin or endocrine disorders where immunotherapy can be maintained

## Treatment irAE

- The patient should receive and carry a card with information about the medicine he is receiving, so that he can show it to the doctor if necessary
- **Grade 1/2 (mild to moderate toxicity)**: withhold drug until toxicity returns to grade 1. Oral corticosteroids may be started if symptoms do not improve after seven days
- **Grade 3/4 (severe or life-threatening toxicities)**: permanently stop the drug, give high doses of corticosteroids. When symptoms are grade 1 or lower, begin tapering corticosteroids