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 couse 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

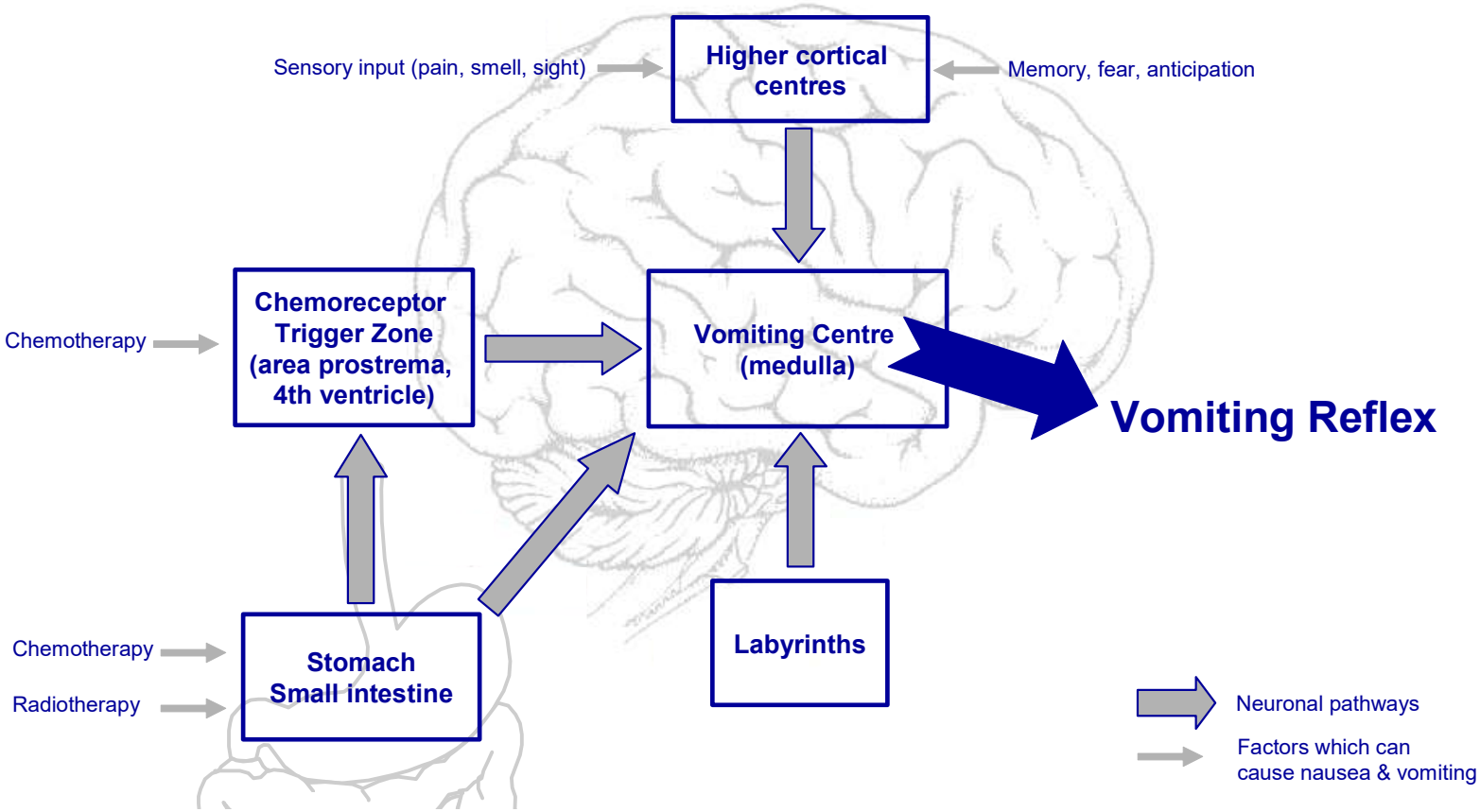
- Infusion reactions (most often when using monoclonal antibodies)
- fever
- febrility
- pain
- obstruction
- hypotension
- allergic reaction

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

<u>According to the appearance time:</u>

- 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)


Sensory input (pain, smell, sight)
Higher cortical centres
Memory, fear, anticipation
Chemotherapy
Chemoreceptor Trigger Zone (area prostrema, 4th ventricle)
Vomiting Centre (medulla)
Vomiting Reflex
Chemotherapy
Radiotherapy
Stomach Small intestine
Labyrinths
Neuronal pathways
Factors which can cause nausea & vomiting

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 - 5HT3 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:

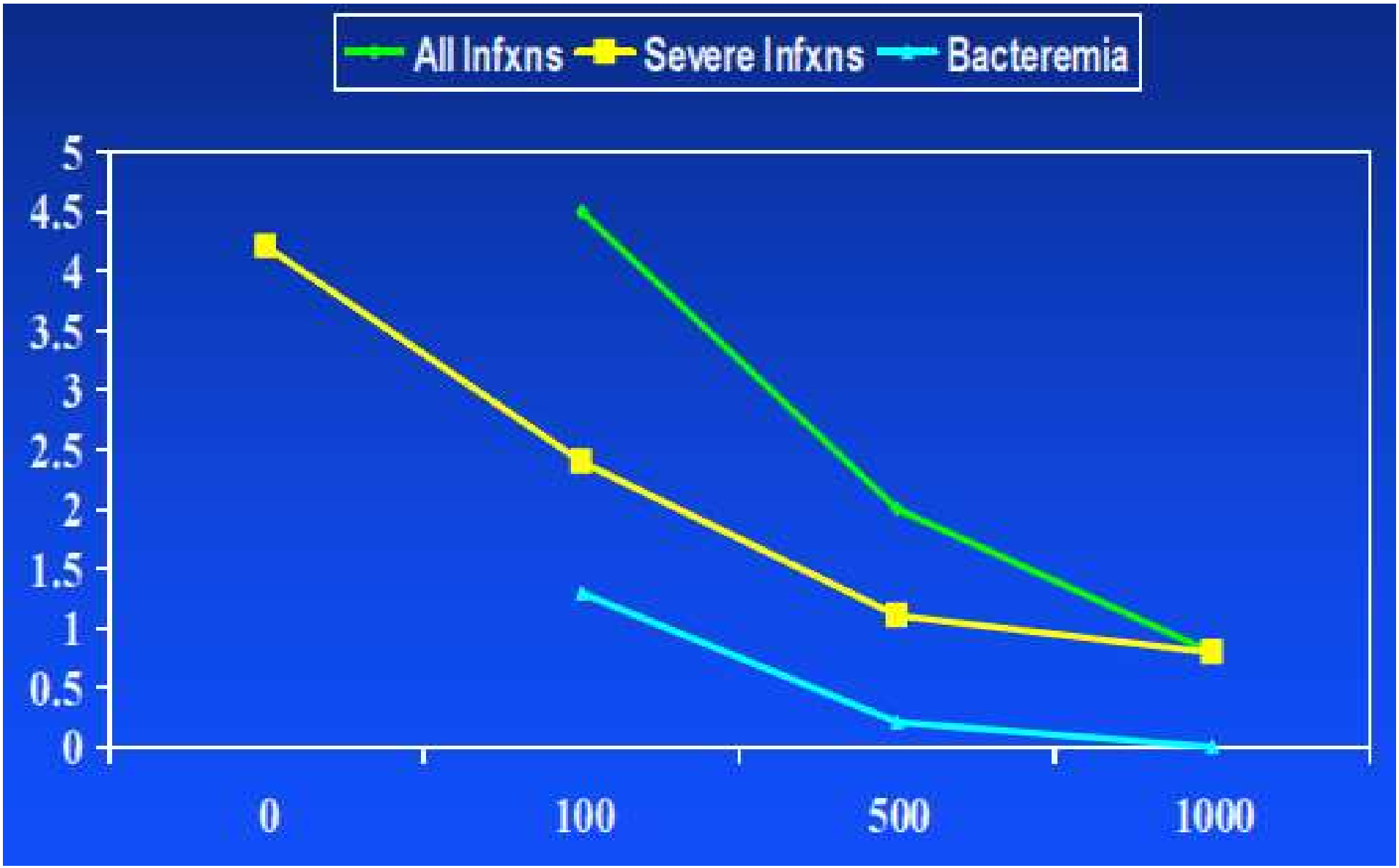
- antibiotic prophylaxis
- Granulocyte-Colony Stimulating Factor (G-CSF)

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^3
- Neutropenia: ANC < 1500 cells / mm^3
- Mild neutropenia: 1000-1500 cells / mm^3
- Moderate neutropenia: 500-999 cells / mm^3
- Severe neutropenia: < 500 cells / mm^3
- Profound neutropenia: <100 cells / mm^3

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)

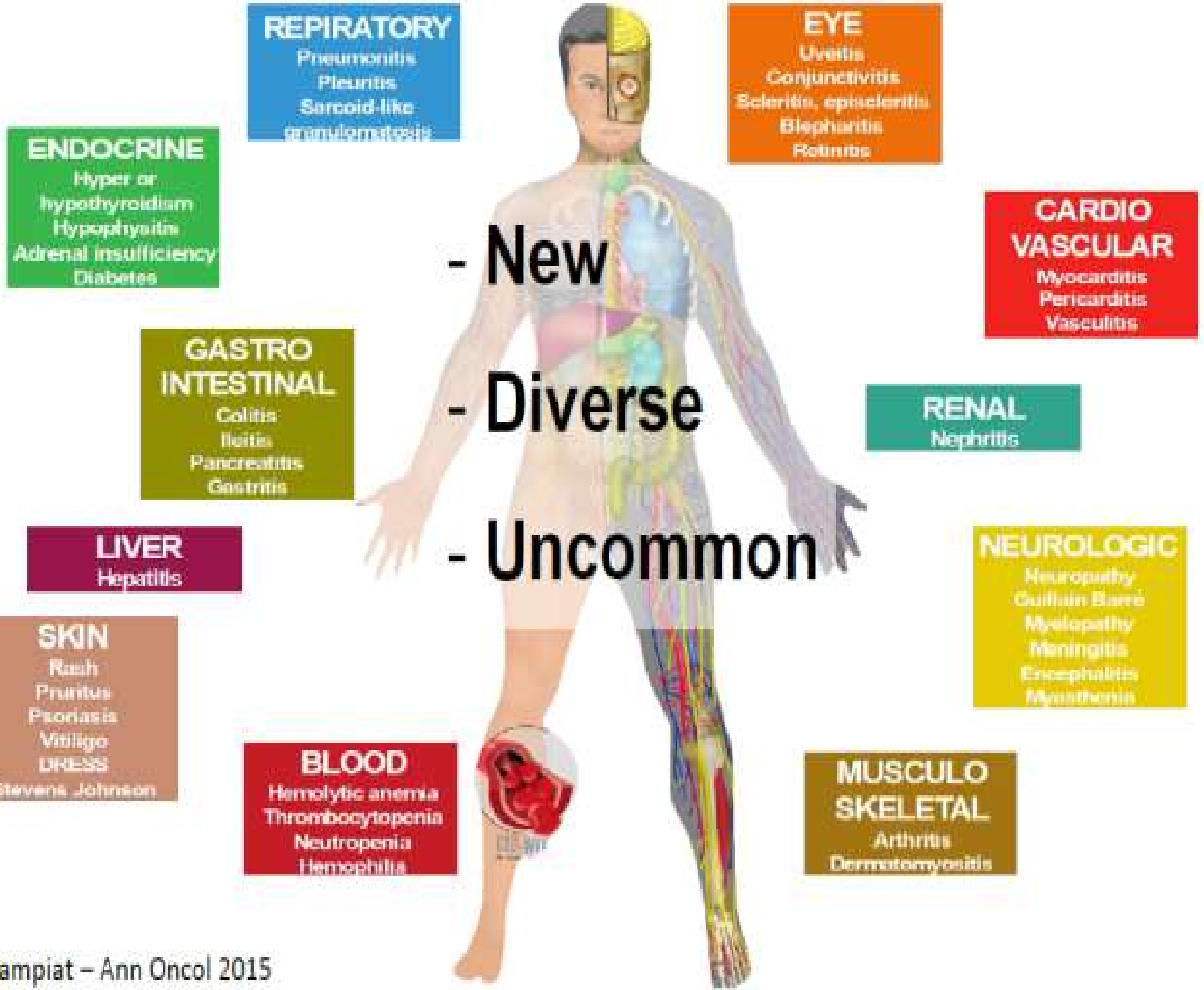
- Rash and other skin changes
- Diarrhea and colitis
- Endocrinopathies
- Hepatitis
- Pneumonitis
- Nephritis / renal dysfunction

Treatment:

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

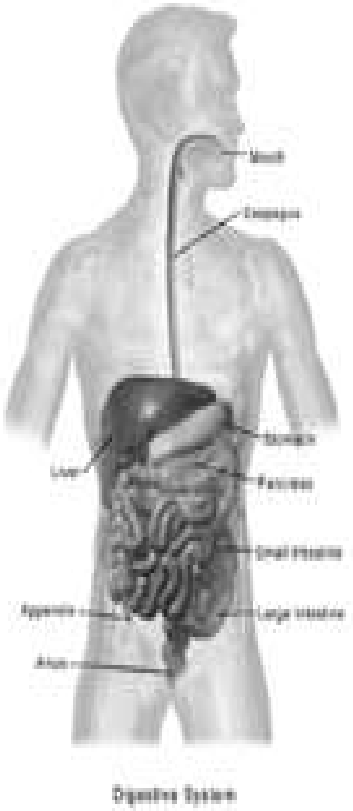
Toxicities of Checkpoint Inhibition

- 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
- **<u>These toxicities are NOT like our usual chemotherapy issues</u>**



Champiat – Ann Oncol 2015

GI Toxicity

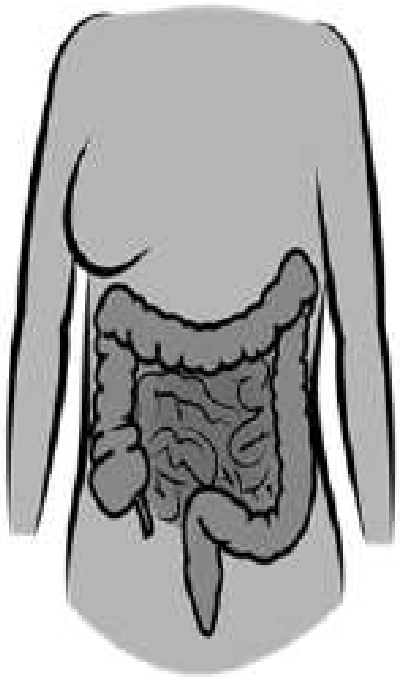


Digestive System

- 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

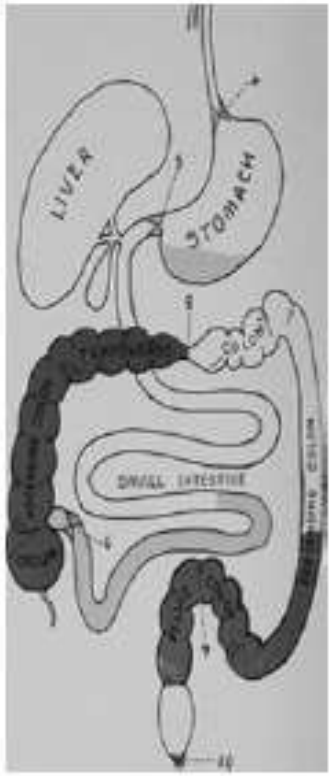
GI Toxicities

- 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



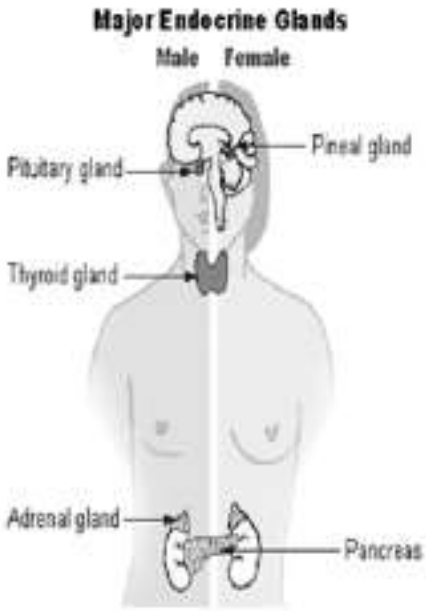
Diarrhea Management

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



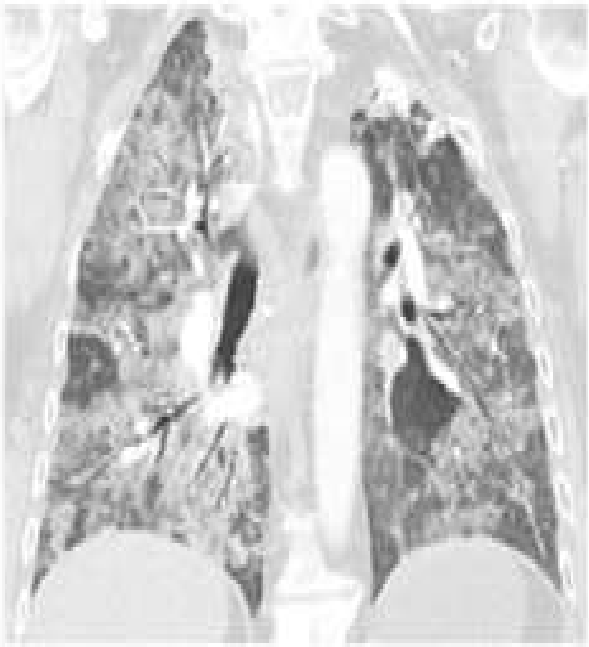
Endocrine Toxicity

- 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

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

Targeted Therapy Skin Toxicity

Acneiform

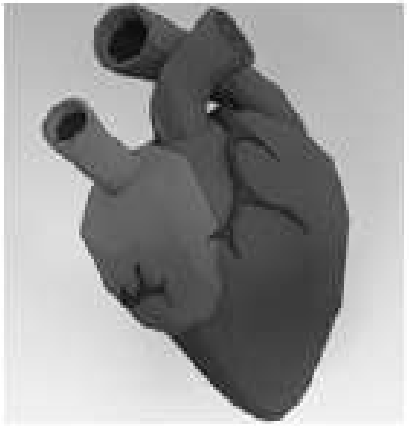
- Common with multiple targeted agents especially EGFR– TKI and mAB
- Tends to be dose dependent
- Signs and Symptoms:
  - Pruritis
  - Diffuse rash – commonly on face/chest/back
  - Often occurs in seborrheic areas
  - May be worsened by sun exposure
- Associated with increased risk of Staph super-infection

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

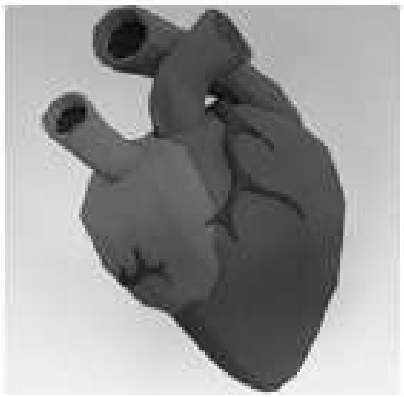
- Hypertension is one of the most common cardiac toxicities
  - ✓ Commonly associated with VEGF inhibitors
- HTN management: ACE-inhibitors are a preferred agent
- Dose reduction or holding drug may also be required
- Avoid these drugs in patients with uncontrollable HTN



- QT prolongation is another potential toxicity
- Thromboembolic disease and Bleeding are also possible

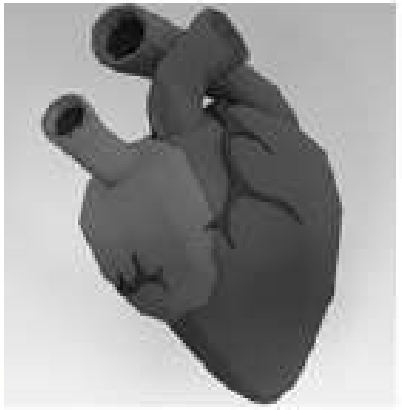
Cardiac Toxicity of Targeted Therapy

- 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

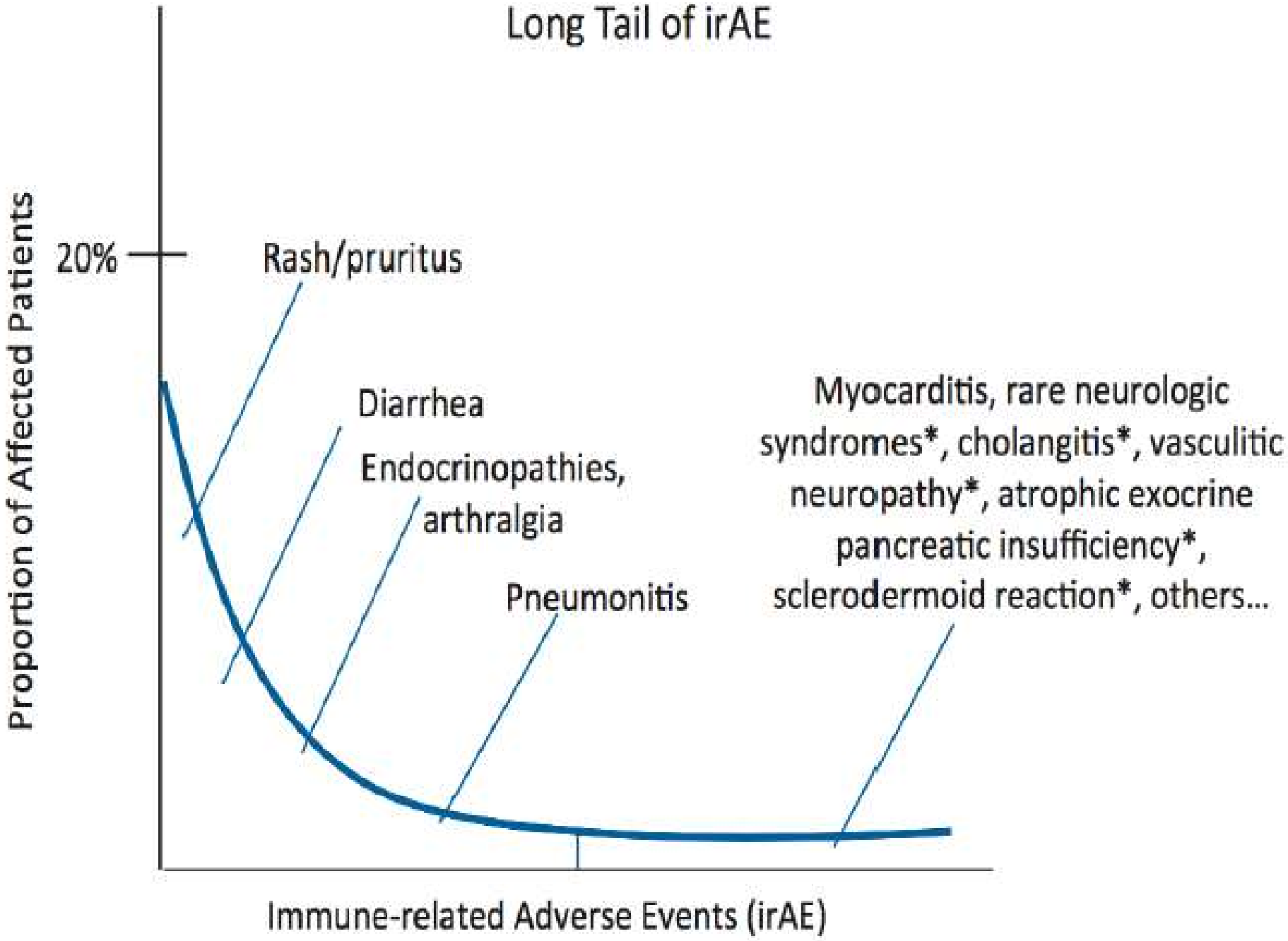


Renal Toxicity

- 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

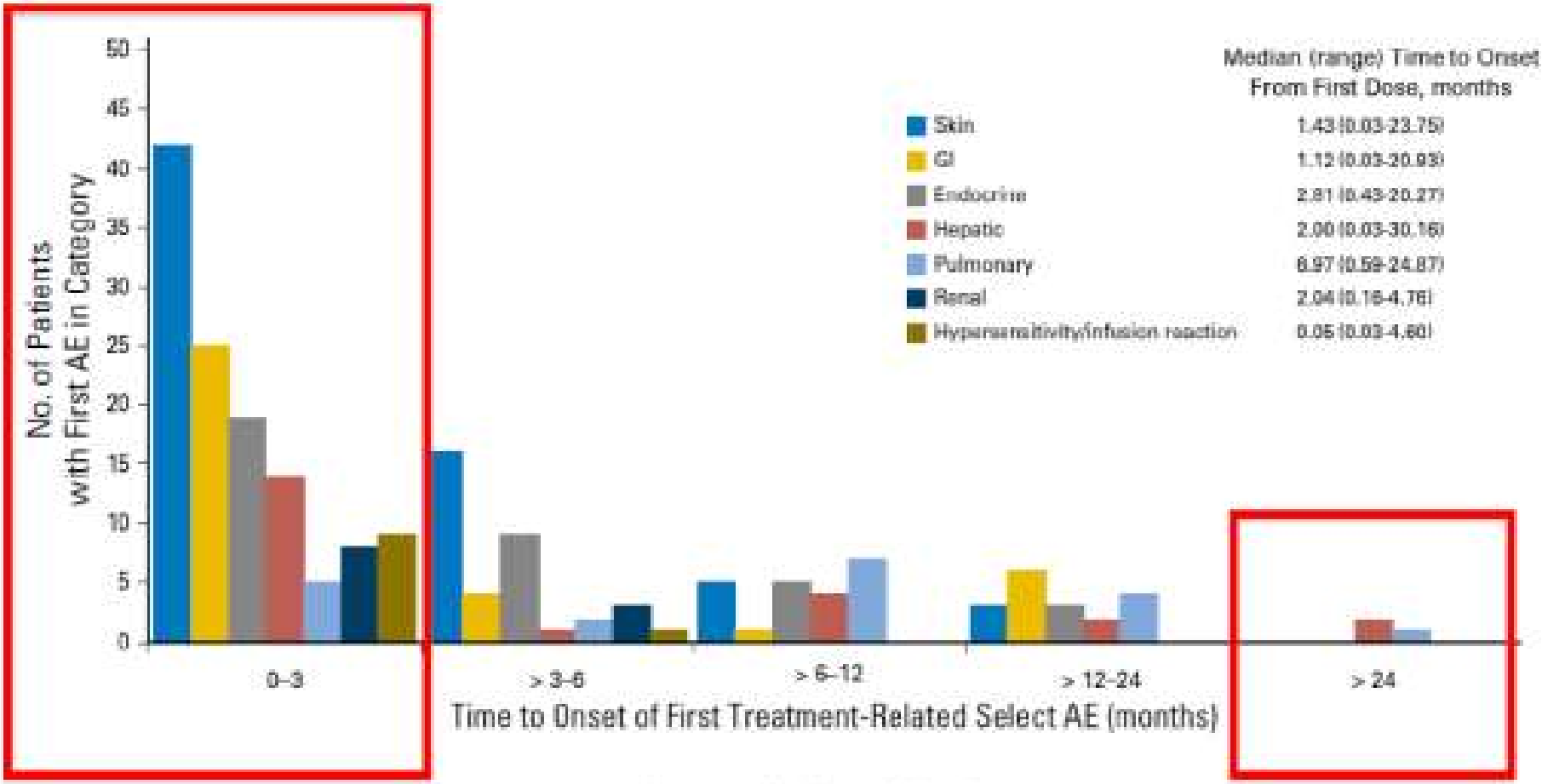
Examples of some targeted therapies and their renal toxicities

Monoclonal antibodies	
Bevacizumab	Proteinuria Nephrotic syndrome Glomerulonephritis Interstitial nephritis Thrombotic microangiopathy
Cetuximab	Hypomagnesaemia
Panitunimab	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



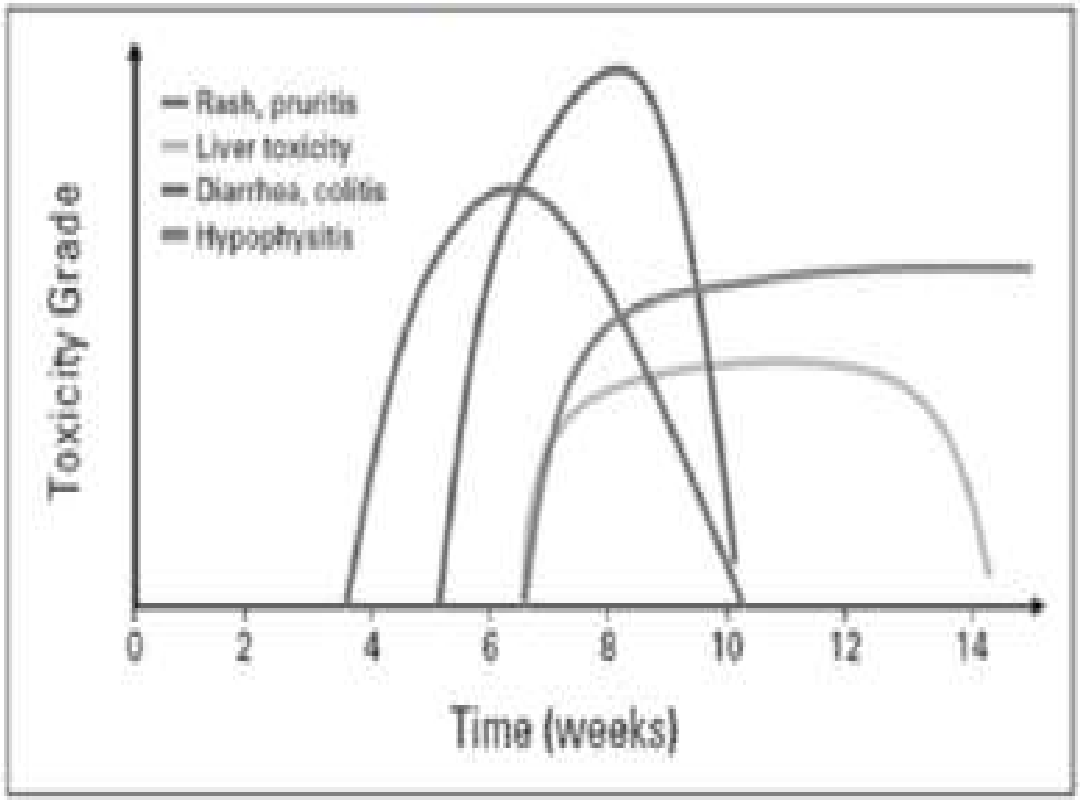
Friedman - Ann Oncol 2017

Onset of irAE's in NSCLC patients



Horn – J Clin Oncol 2017

Immunotherapy Toxicity Timing is Variable

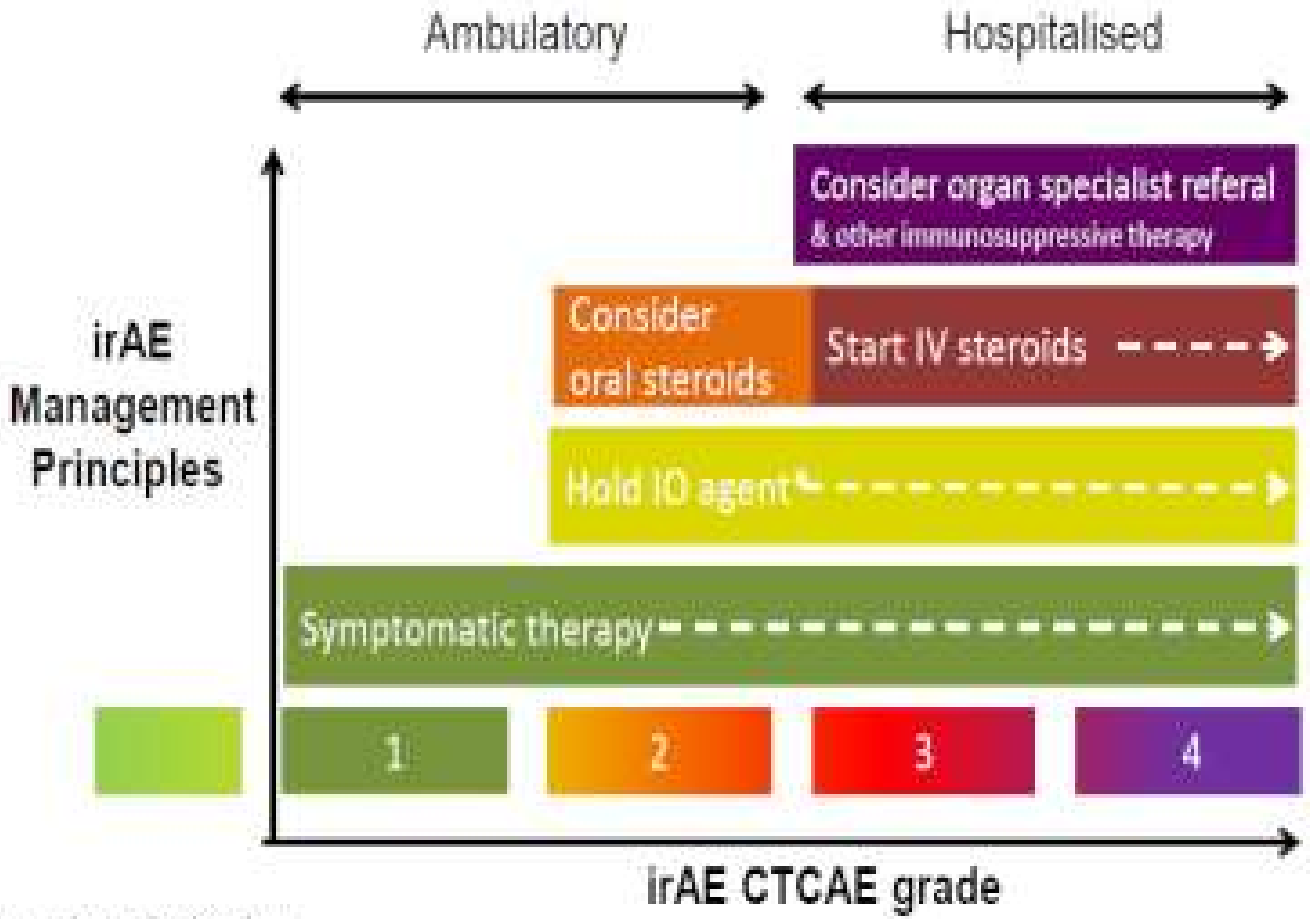


Immune-related adverse advents associated with immune checkpoint inhibitors treatment (including incidence and onset of presentation)

Toxicity	Incidence	Onset after initiation of treatment
Skin	• Amongst the most frequent • Almost ¼ of patients experience rash — >G3 rashes are rare (<3%) • 26-35% of patients experience pruritis — severity greater with combination therapy	2–3 weeks
Endocrine	• Hyper and hypothyroidism have been reported; the latter is more common • Incidence varies from 6%-10%, up to 20% observed (depending on dose and mono/combination therapy) • Rarely higher than Grade 2	6–7 weeks
Hepatotoxicity	• Occurs in up to 10% of patients — 1-2% is Grade 3 with ICPI monotherapy • Occurs in up to 30% of patients with combination therapy — of which 16% is Grade 3	6–14 weeks
Gastrointestinal	• Most common associated IrAE — 27-54% of patients treated experience diarrhoea and 9-22% experience colitis (when treated with anti-CTLA-4 monotherapy) • Often most frequent/severe of IrAEs associated with ICPI therapy as compared to other toxicities • Incidence much less for anti-PD-1/PDL1 treatments	5–10 weeks
Respiratory	• Pneumonitis is 1.5-2.0-times more frequent with anti-PD-1 therapy compared to anti-CTLA-4 monotherapy • Combination therapy — up to 3 times more likely to experience IrAE (Grade 3)	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