Recognizing , Monitoring and Managing Common unique Toxicities

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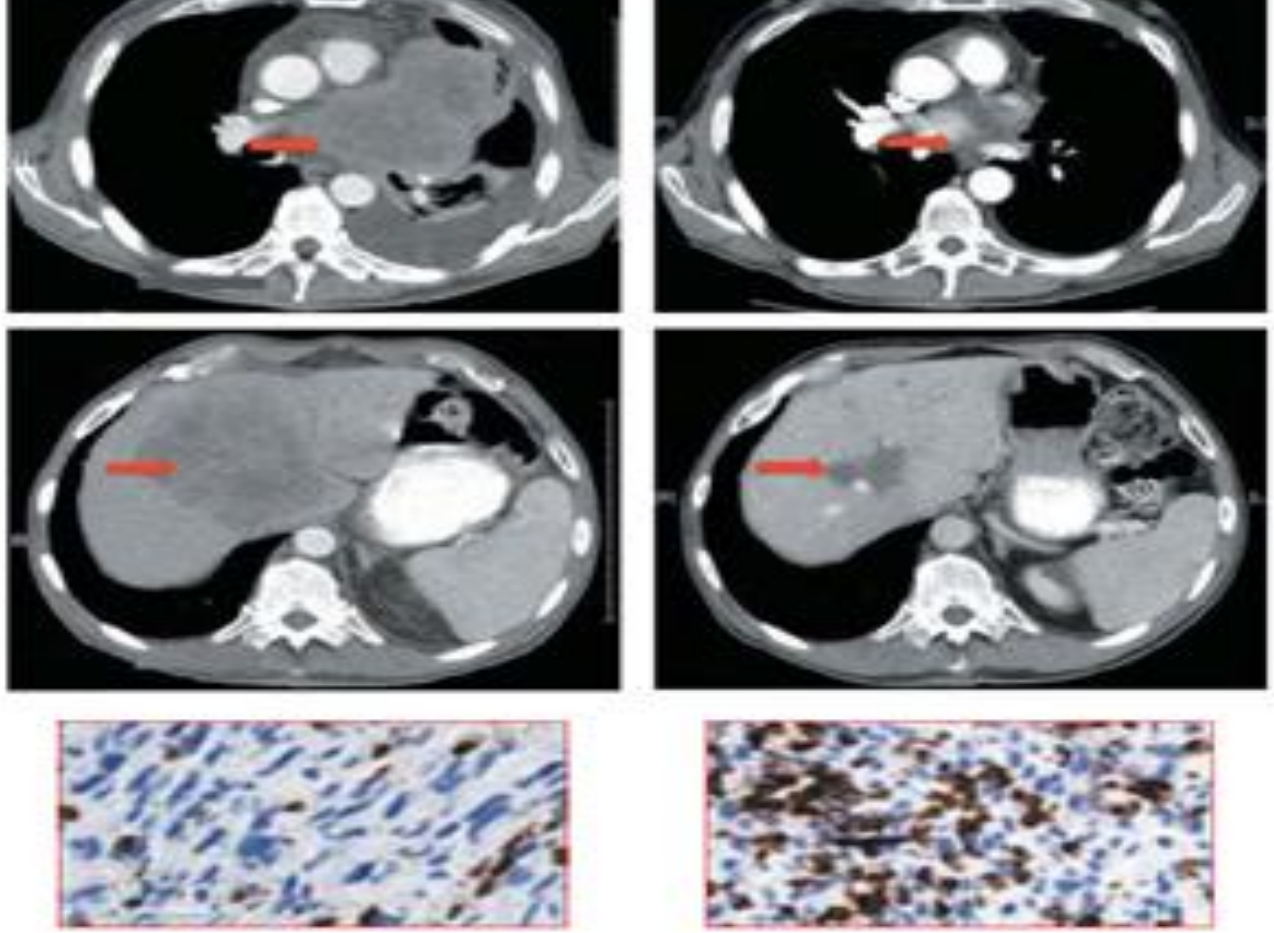
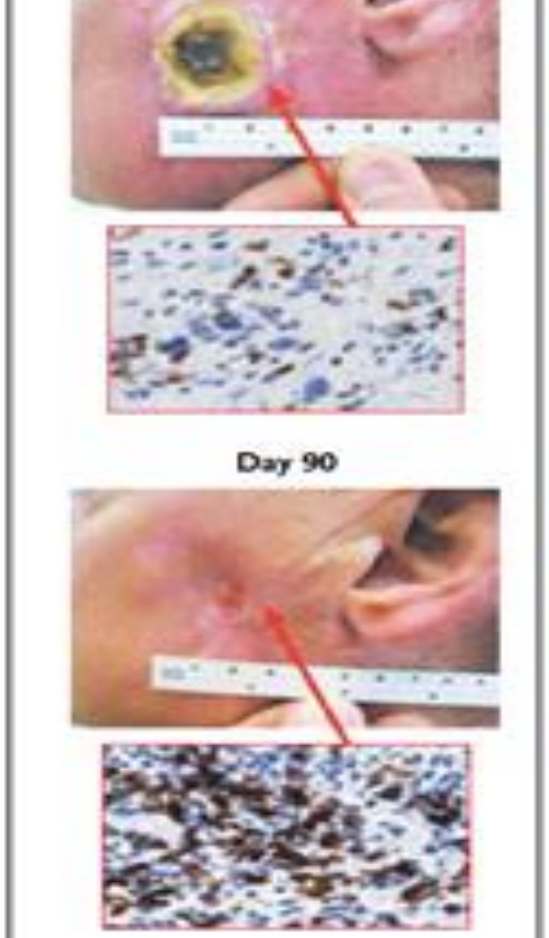
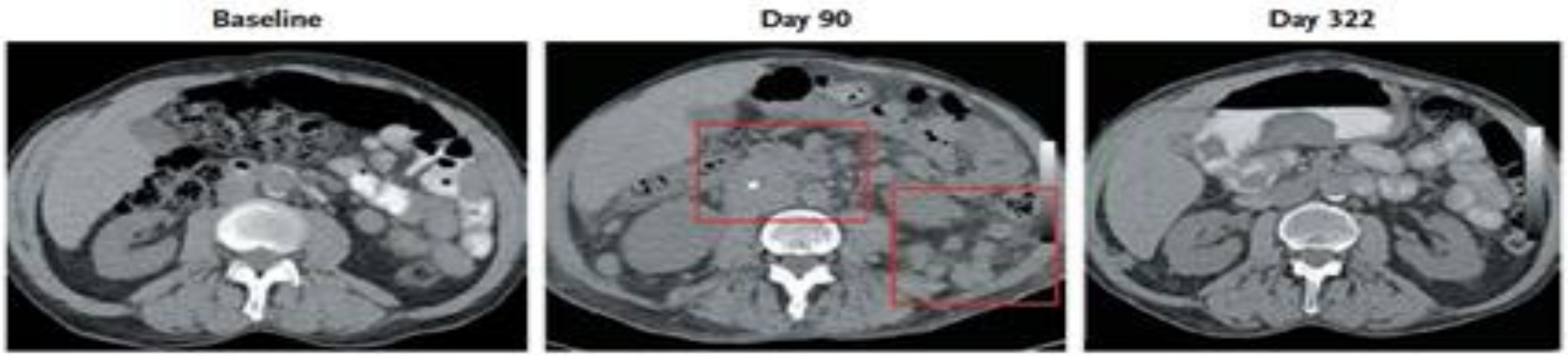
Aims

1. highlight and review common toxicities
2. immunotherapy and toxicity
3. how to recognize and diagnose cardio-toxicity
4. manage and follow-up neuropathy



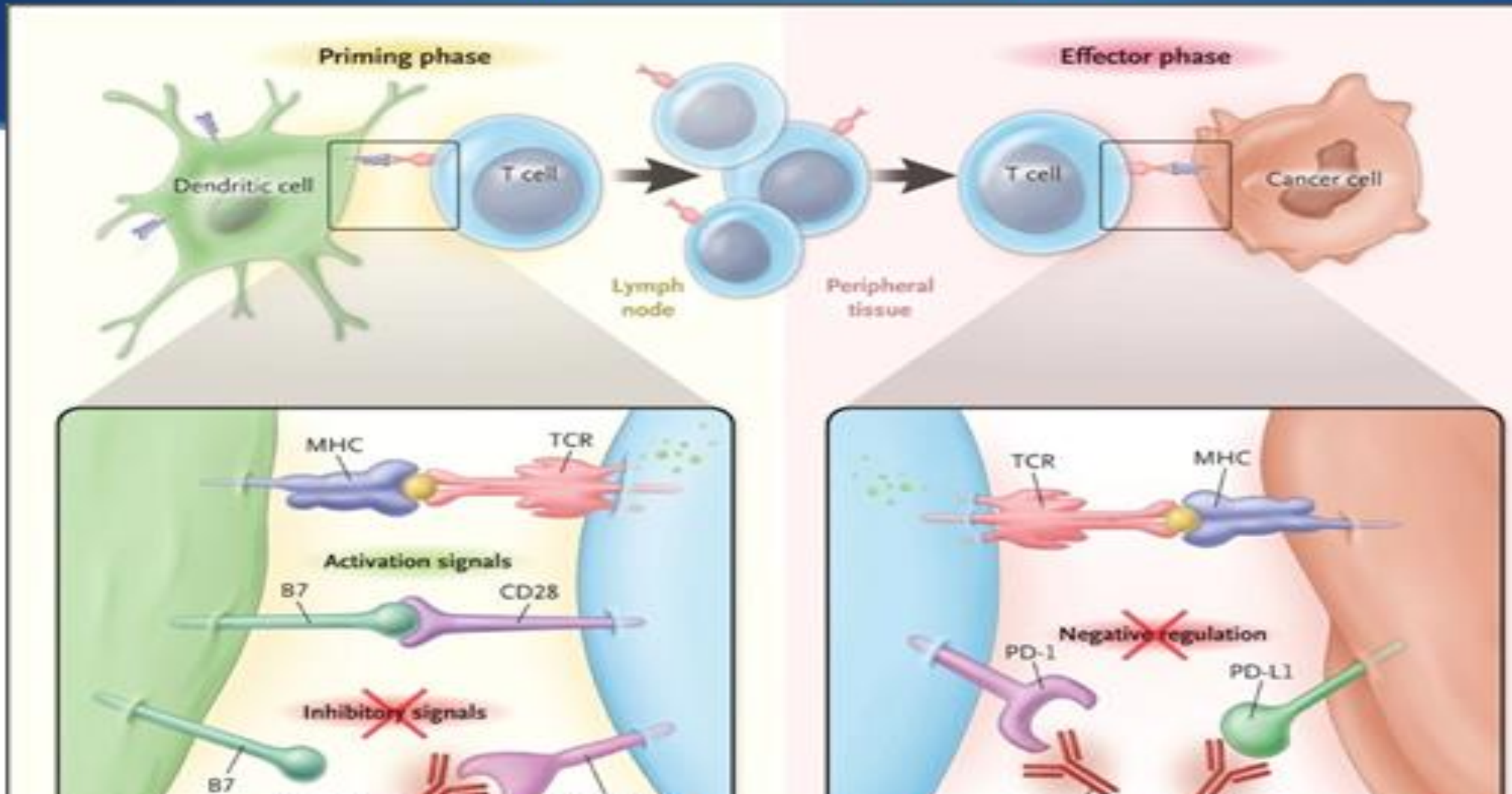


Pembrolizumab
Responders
NEJM 2013



Tumor Immunotherapy CTLA4 vrs PD1/PD

Antoni Ribas, NEJM epub June 2012



Agent	Target receptor	FDA-approved indications[b]
Ipilimumab	CTLA-4	Melanoma, MSI-H/dMMR CRC, intermediate- or poor-risk RCC (in combination with nivolumab)
Tremelimumab	CTLA-4	Not yet approved; under investigation
Nivolumab	PD-1	MSI-H or dMMR CRC, HNSCC, HCC, melanoma, cHL, NSCLC, RCC, urothelial cancer, SCLC
Pembrolizumab	PD-1	Cervical cancer, gastric cancer, HNSCC, HCC, cHL, melanoma, MCC, MSI-H/dMMR cancers, NSCLC, primary mediastinal DLBCL, urothelial cancer
Cemiplimab	PD-1	Cutaneous SCC
Atezolizumab	PD-L1	NSCLC, urothelial cancer
Avelumab	PD-L1	MCC, urothelial cancer

Time lines of immune toxicity

- Skin 2-4 weeks
- GI toxicity 4-6 weeks
- Hepato-toxicity 8-12 weeks
- Endocrine 12-24 weeks

endocrinopathies

- Severe mass effect symptoms headache, visual disturbance or hypoadrenalism- hypotension, severe electrolyte imbalance.
- Start methylprednisolone 1 mg/kg – refer to endocrine
- Moderate symptoms fatigue, altered mood, oral prednisone 0.5- 1 mg/kg

thyroid

- Elevated TSH normal T4 if no symptoms follow-up symptoms thyroxine if TSH > 10
- Normal TSH elevated T4 repeat
- Normal TSH low T4 no symptom check cortisol may hypopituitarism
- Low TSH elevated T4 hyperthyroidism treat with betablocker
- Low TSH low T4 check cortisol 9 am

Gastrointestinal toxicities

- Grade 1 less than 4 liquid stools Mild diarrhea antidiarrheal
- Grade 2 4-6 liquid stools persistent discontinuation of ICI prednisolone 0.5-1 mg/kg
- Response to steroid taper over 8-12 weeks
- Severe diarrhea- more than 7 liquid stools requires hospitalization Not responding to steroids infliximab 5 mg/kg
- Colon perforation emergency subtotal colectomy

pneumonitis

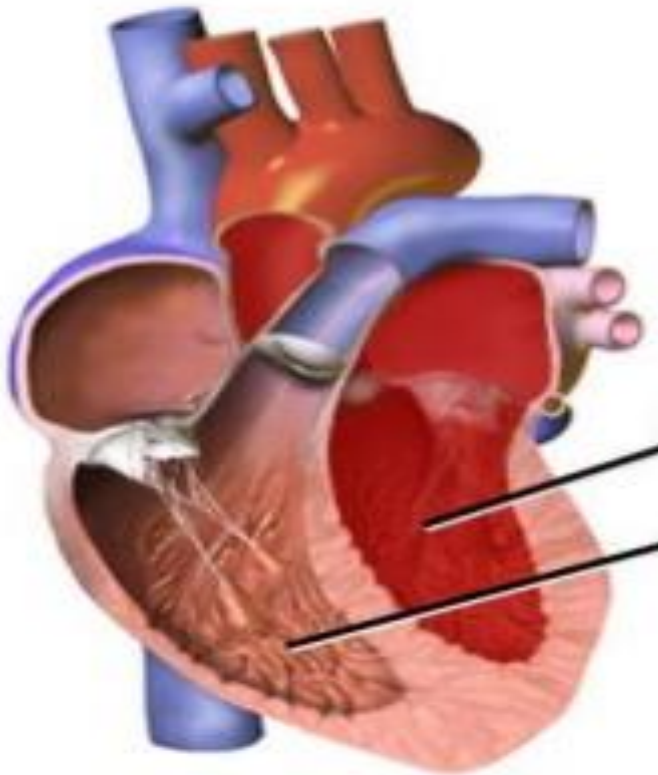
- Grade I ground glass change
- Grade 2 mild symptoms

Grade I-2 oral steroids, taper after stable

- Grade 3 new symptoms and worsening of hypoxia

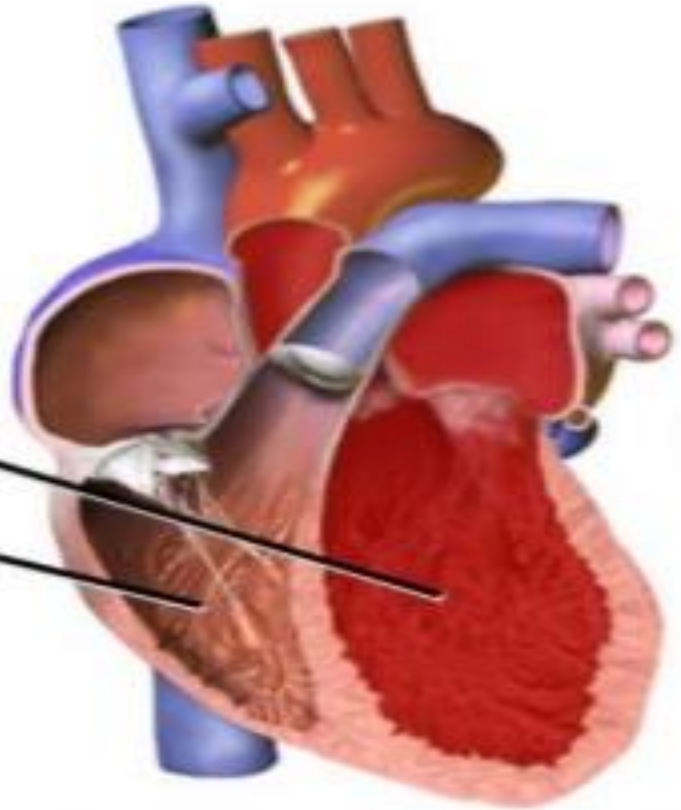
Grade 3-4 hospitalization methylprednisolone 2-4 mg/kg/day

Normal Heart



Chambers relax and fill, then contract and pump.

Heart with Dilated Cardiomyopathy



Muscle fibers have stretched. Heart chambers enlarge.

5 fu
doxurubicin
paclitaxel
sunitinib
sorafenib
imatinib
ibrutinib
trastuzumab
proteosome inhibitor

cardiotoxic

CLINICAL MANIFESTATIONS

- Decreased exercise capacity
- Fatigue
- Dyspnea at rest
- Paroxysmal nocturnal dyspnea
- Orthopnea

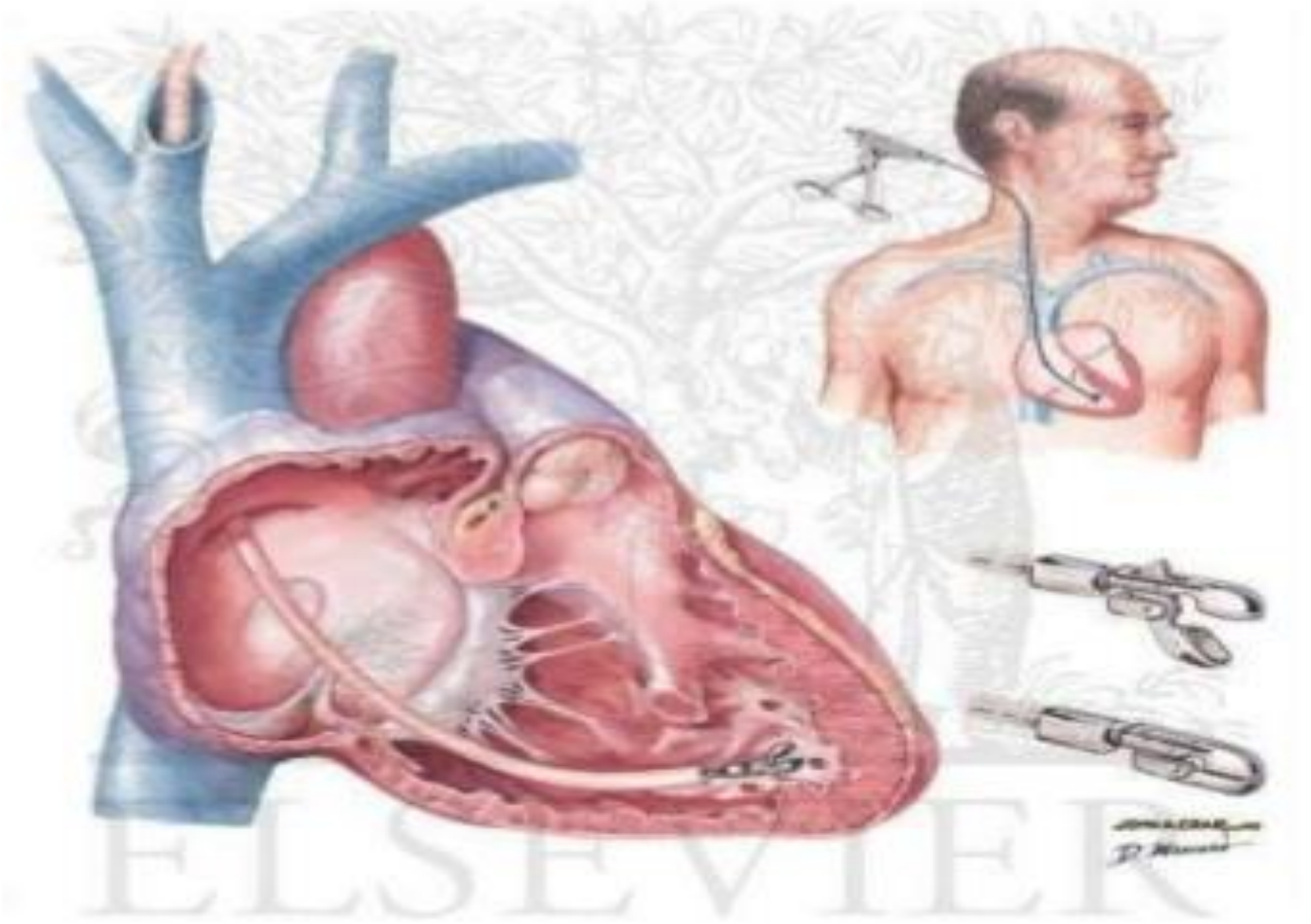
Signs

- Irregular heart rate with an abnormal S3 and/or S4
- Tachycardia or bradycardia
- Pulmonary crackles
- Edema
- Weak peripheral pulses

Diagnostic studies

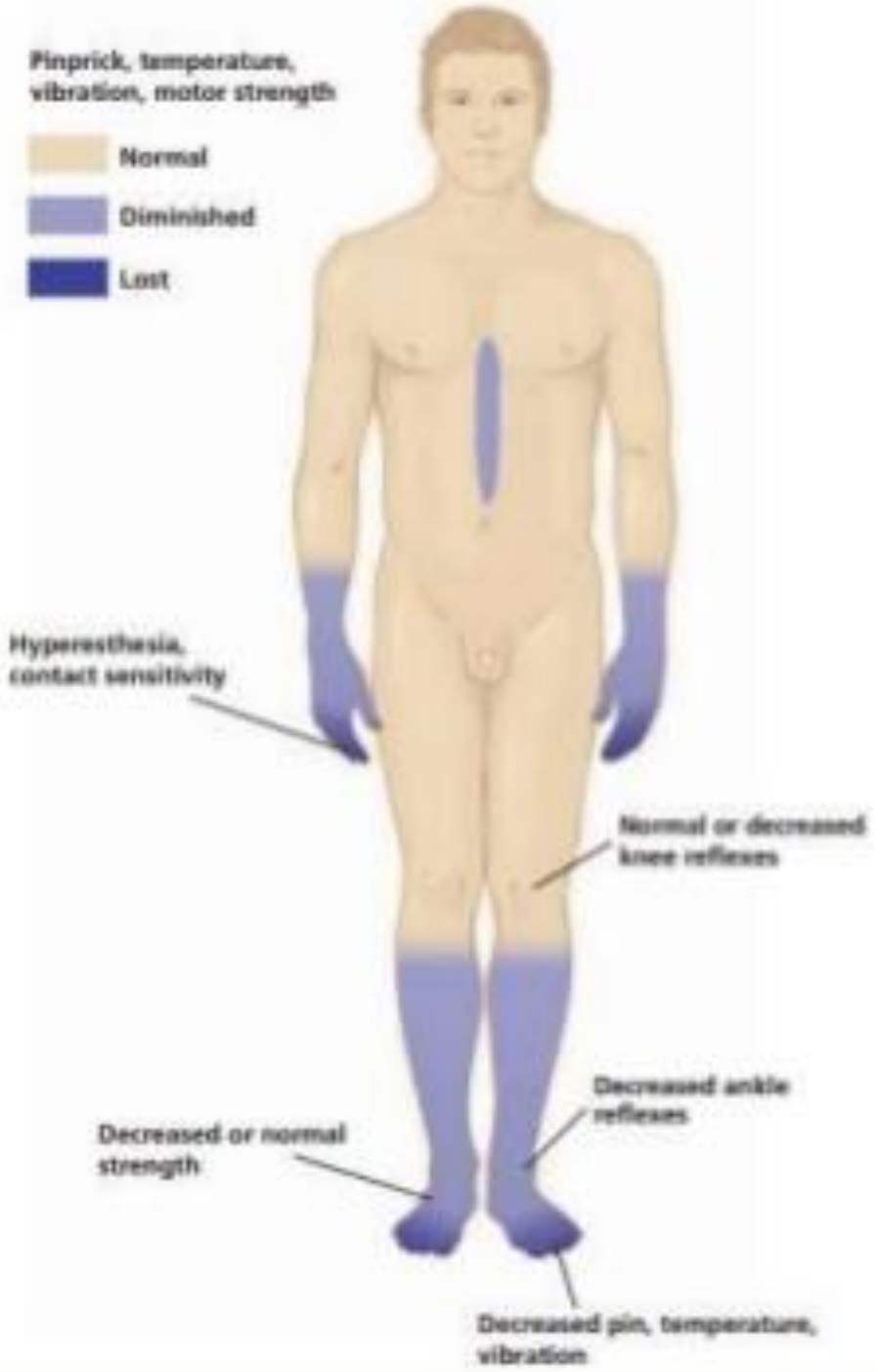
- History and physical examination
- Palpation and auscultation of the chest.
- ECG findings
- Echocardiogram
- Chest X ray
- Cardiac catheterization

EMB (Endomyocardial biopsy)



MANAGEMENT

- Nitrates (eg: Nitroglycerin)
- ACE inhibitors(Eg: captopril)
- β adrenergic blockers(Eg: metoprolol)
- Aldosterone antagonists (Eg: spironolactone)
- Diuretics to maintain the volume balance.
- Cardiac glycosides(Eg: Digoxin)



Features of CIPN

- CIPN is primarily polyneuropathic, with symmetric stocking-glove "dying back" distribution, with the earliest symptoms developing at the finger tips and toes

Assessment of PN

- **Subjective assessment:** Symptoms related to PN
  - Evaluate sensory, motor and autonomic symptoms
- **Objective assessment:**

-Touch, Pinprick, vibration, & proprioception

  - Reflexes, muscle strength, Gait and balance.
  - Autonomic: assess bowel sounds, orthostatic blood pressures, pulse regularity
  - Difficulty with fine motor skills: opening jars, buttoning

Diagnostic Studies

Serum:

- HIV, herpes, Vitamin B12 deficiency, B6 toxicity, CBC diff

Radiology

- X-ray, CT, MRI

Neurodiagnostic studies

- EMG
- NCV
- QST

These are only a few of the available tests and procedures to diagnose PN

Subjective and objective assessments are important to correctly diagnose PN

Table 5 Common Agents for Pain Management in Neuropathy

Drug	Starting Dose	Titration	Maximum Dose	Duration of Adequate Trial	Potential Side Effects
Duloxetine	20–30 mg/d	No evidence that higher dose is more effective	120 mg/d	2 wk	Nausea, xerostomia, constipation, diarrhea
Gabapentin*	100–300 mg nightly or 100–300 mg 3 times/d	increase by 100–300 mg 3 times/day, every 1–7 days	3600 mg (depending on absorption)	1–2 wk at max tolerated dose	Somnolence, dizziness, GI symptoms, mild edema, cognitive impairment (elderly), exacerbation of gait problems
5% Lidocaine patch	Maximum of 3 patches daily	Non-applicable	3 patches	2 wk	Rash/erythema
Opioids (oxycodone, morphine, methadone)	5–15 mg every 4 h	Convert to long-acting after 1 wk, titrate based on breakthrough use	No ceiling effect	4–6 wk	Constipation, nausea, vomiting (self-limited), sedation, confusion, respiratory depression
Pregabalin	25–50 mg 3 times/d	Increase by 50 mg/dose after 1 wk	200 mg 3 times/d	Unclear (likely 2–4 wk)	Dizziness, somnolence, xerostomia, edema, blurred vision, decreased concentration
Tramadol	50 mg 1–2/d	Increase by 50-100 mg/d, individual doses every 3-7 days	400 mg/d (100 mg 4 times/d); elderly 300 mg/d	4 wk	Dizziness, constipation, nausea, somnolence, orthostatic hypotension, increased risk of seizure, serotonin syndrome
Tricyclic antidepressants (amitriptyline,* nortriptyline,* desipramine)	Starting dose: 10-25 mg nightly	Increase by 10-25 mg every 3-7 days	75–150 mg; may increase if blood level of drug plus metabolite <100 ng/mL	6-8 wk; 1-2 wk at max dose	Cardiovascular disease (needs screening), anticholinergic effects, interact with drugs metabolized

Thank you

Adapt it with your needs and it will capture all the audience attention.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