PULMONARY HYPERTENSION: INTRODUCTION
- PH = increase in pulmonary arterial pressure
- Progressive w/ poor prognosis if not treated
- Treatment with therapies in specialized pulmonary hypertension centres
  - Reductions in:
    - Patient sx
    - Disease progression
    - Mortality
  - Improved exercise capacity

WHY DOES PAH DEVELOP?
- Exact causes unknown
- Complex, multi-factorial condition
- Endothelial dysfunction occurs early in disease pathogenesis and leads to:
  - Endothelial & smooth muscle proliferation
  - Remodeling of the vessel wall
  - Impaired production of vasodilators (NO, prostacyclin)
  - Overexpression of vasoconstrictors (endothelin-1)

DRUGS & TOXINS THAT INDUCE PAH:

<table>
<thead>
<tr>
<th></th>
<th>Definite</th>
<th>Likely</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminorex</td>
<td>Amphetamines</td>
<td>Dasatinib</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>L-tryptophan</td>
<td>Methamphetamine</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>Interferon α or β</td>
<td>Interferon α or β</td>
<td>St John’s Wart</td>
</tr>
<tr>
<td>Toxic rapeseed oil</td>
<td>Amphetamine-like drugs</td>
<td>Some chemotherapeutic agents (mitomycine C, cyclophosphamide)</td>
<td></td>
</tr>
<tr>
<td>Benfluorex</td>
<td>SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SYMPTOMS OF PAH:
- High resistance to blood flow through the lungs causes right heart dysfunction, decreased cardiac output and produces:
  - Dyspnea
  - Fatigue
  - Dizziness
  - Syncope
  - Peripheral edema
  - Chest pain, particularly during physical exercise
- Early sx mild & non-specific
  - Commonly attributed to other conditions
  - Over time, sx become more severe & limit normal daily activities
- Delayed diagnosis common (> 2 years)
  - Frequently not recognized until the disease is relatively advanced

TREATMENT GOALS:
- Prevent disease progression
- Improve survival
- Improve quality of life
- Improve WHO FC to I
- Maintain good RV function

PULMONARY HYPERTENSION: INTRODUCTION

WHY DOES PAH DEVELOP?

DRUGS & TOXINS THAT INDUCE PAH:

SYMPTOMS OF PAH:

TREATMENT GOALS:
GENERAL MEASURES:
- Limit effects of external circumstances
  - Avoid pregnancy
  - Prevention & prompt txt of chets infections
    - Vaccine
  - Awareness of potential effects of altitude

SUPPORTIVE THERAPY:
- Provide symptomatic benefit
  - Supplemental oxygen
  - Oral anticoagulants (mainly for group 4 PH)
  - Diuretics
  - Calcium channel blockers

CCB VASOREACTIVITY TEST:
- Vasoreactivity test
  - Administration of short acting vasodilator
  - Positive result = mPAP decreases by at least 10 mmHg and to a value less than 40 mmHg
  - When: prior to initiation of advanced therapy
  - Who: all pts in group 1 (PAH)
  - What: positive results → start CCBs
    - Nifedipine for rapid titration, then to long acting form (30 mg/day)
    - Diltiazem ER (120 – 900 mg/day)
    - Amlodipine (10 – 20 mg/day)

PAH SPECIFIC THERAPY OVERVIEW:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>MOA</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial receptor antagonists (ERAs)</td>
<td>Blocks binding of ET to one (single antagonist) or both (dual antagonist) of its receptors</td>
<td>Bosentan (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambrisentan (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macitentan (oral)</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Cyclic guanosine monophosphate enhancer</td>
<td>PDE-5 inhibitors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sildenafil (oral &amp; IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soluble guanylate cyclase stimulant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riociguat (oral)</td>
</tr>
<tr>
<td>Synthetic prostacyclins and prostacyclin analogues</td>
<td>Help correct the deficiency of endogenous prostacyclin seen in pts with PAH</td>
<td>Epoprostenol (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treprostinil (IV, SC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selexipag (oral)</td>
</tr>
</tbody>
</table>

Legend:
- CCB: Calcium channel blockers
- PAH: Pulmonary arterial hypertension
- IV: Intravenous
- SC: Subcutaneous
**Endothelial Receptor Antagonists (ERA)**
- Elevated levels of Endothelin-1 (ET-1) seen in PAH
- Levels correlate with disease severity
- Deleterious effects mediated through ETA and ETB receptors
  - Fibrosis
  - Hypertrophy and cell proliferation
  - Inflammation
  - Vasoconstriction

> Endothelin receptor antagonists can block these effects

<table>
<thead>
<tr>
<th>ERA Type</th>
<th>Drug</th>
<th>Route</th>
<th>Dose Range</th>
<th>Drug Interactions</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual</td>
<td>Bosentan</td>
<td>Oral</td>
<td>62.5 – 125 mg BID</td>
<td>Minor substrate and moderate inducer of CYP2C9 and CYP3A4</td>
<td>Headache, Fluid retention / edema, Anemia, Increase in liver enzymes, Hepatotoxicity, ↓ sperm count</td>
<td>Pregnancy, Mod – severe hepatic impairment, Concurrent use with cyclosporine, glyburide</td>
</tr>
<tr>
<td>Macitentan</td>
<td>&gt; Oral</td>
<td>&gt; With or w/o food</td>
<td>3 – 10 mg once daily</td>
<td>Substrate of CYP3A4 and CYP2C19</td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Single (selective for ETA receptor)</td>
<td>Ambrisentan</td>
<td>&gt; Oral</td>
<td>5 – 10 mg once daily</td>
<td>Substrate of CYP3A4, CYP2C19, P-gp, UGT</td>
<td></td>
<td>Pregnancy, Severe hepatic impairment, Concurrent use with cyclosporine, Idiopathic pulmonary fibrosis (group 3)</td>
</tr>
</tbody>
</table>

**NITRIC OXIDE CYCLIC GUANOSINE ENHANCER:**
Nitric oxide:
- Potent vasodilator (mediated by cGMP)
- Rapidly degraded by PDEs -> PDE-5 inhibition reduces degradation
- Possesses anti-proliferative properties
- Impaired production in PAH

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug</th>
<th>Dose Range</th>
<th>Drug Interactions</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5 Inhibitor</td>
<td>Sildenafil</td>
<td>20 mg TID</td>
<td>Statins, Ritonavir, saquinovir</td>
<td>Visual effects, Sudden hearing loss</td>
<td>Severe hepatic failure, Drenapocytosis, Hypotension, in all 3 drugs</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>40 mg once daily (20 mg if hepatic or renal failure)</td>
<td>Nitrates, nicorandil</td>
<td>Headache, Flushing, Nasal congestion, Digestive disorders, Myalgia</td>
<td></td>
</tr>
<tr>
<td>sGC stimulator</td>
<td>Riociguat</td>
<td>0.5 – 2.5 mg TID</td>
<td></td>
<td>Hypotension, Feeling hot</td>
<td>Pregnancy, PDE-5 inhibitors</td>
</tr>
</tbody>
</table>

**PROSTACYCLINES**
- Potent vasodilator
- Inhibitor of platelet activation
- Low levels in pts with PAH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Route</th>
<th>Drug Interactions</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>Progressive up to titration based on efficacy and tolerance</td>
<td>Continuous IV</td>
<td>Anticoagulant, Platelet inhibitors</td>
<td>Infection, Headache, Jaw, Flush, nausea, diarrhea, Infusion site pain (treprostinil)</td>
<td>Chronic use in patients with heart failure</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Continuous IV</td>
<td>Continuous IV</td>
<td>Substrate of CYP2C8 or CYP3A4</td>
<td>Flushing, skin rash, NVD, Headache, Jaw, limb pain, Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Selexipag</td>
<td>200 – 1600 mg BID</td>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COMBINATION THERAPY:
> TRADITIONAL: sequential combination therapy
> EMERGING EVIDENCE: aggressive upfront combination

FOLLOW UP AND ROLE OF PHARMACISTS:
- How PH is different from systemic hypertension
- Self administration of medications
- Abrupt withdrawal of medications should be avoided
- Being aware of common SEs and report any AEs immediately
- Altitude and travel should be discussed with physician
- Pregnancy
- Vaccine – all age appropriate vaccines should be given
  - Influenza and pneumococcal
- Exercise