

PULMONARY HYPERTENSION MEDICATIONS

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DISCLOSURES

- No financial disclosures
- Only bosentan (over age 3) and inhaled nitric oxide (specifically for PPHN) have been approved by the FDA for the treatment of pediatric PAH
- Off-label medication use will be discussed

OBJECTIVES

- Discuss the goals of PH medications
- Explain the mechanisms of actions
- Review specific PH medications
- Address common side effects
- Identify special considerations when prescribing PH medications



KEEPING THE CLINICAL PERSPECTIVE

Our **WHY**

Our **FOCUS**

Our **PRIORITY**

WHAT ARE WE TREATING?

High blood pressure in the lungs which puts strain on the right ventricle



THE GOALS OF PH MEDICATIONS

Relax pulmonary vasculature

Lower pulmonary vascular resistance

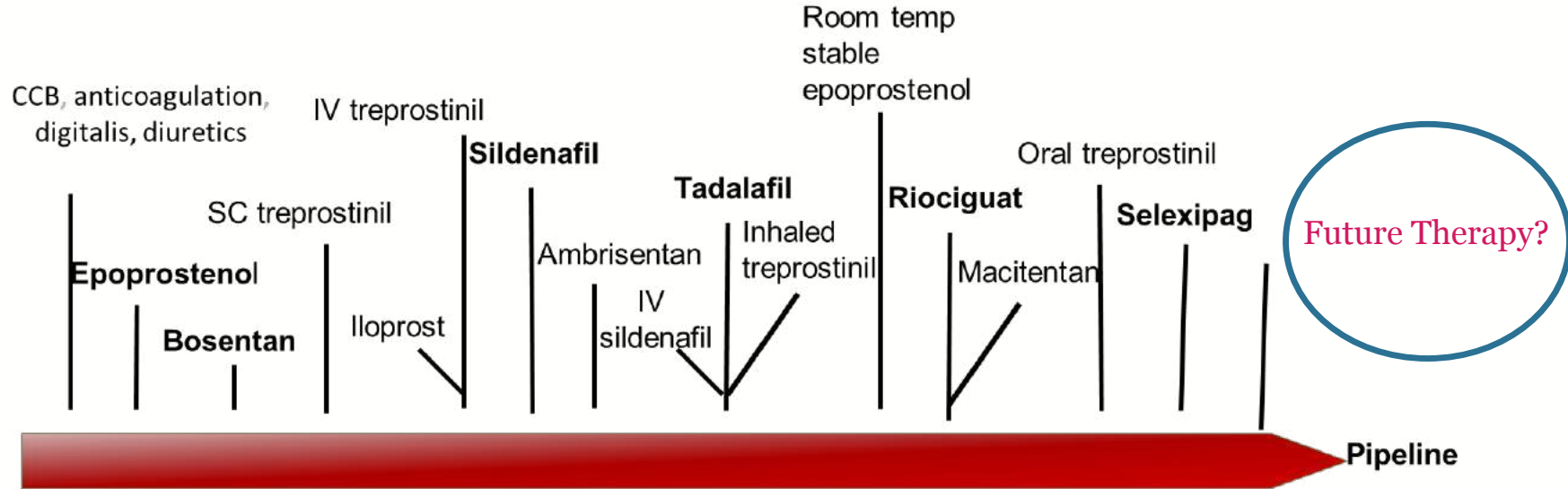
Preserve RV function

THE GOALS FOR OUR PATIENTS

- Improve quality of life
- Minimize symptoms associated with pulmonary hypertension
- Prevent clinical worsening



WHERE WE STARTED & WHERE WE ARE HEADED

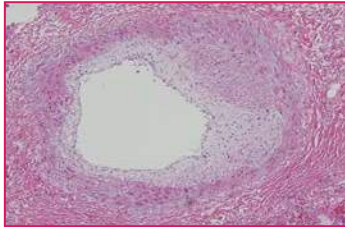


Before the 1990s

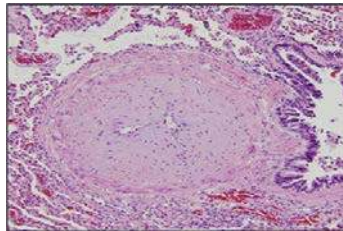
THREE CHIEF VASCULAR CHANGES WITH PH



- Vasoconstriction

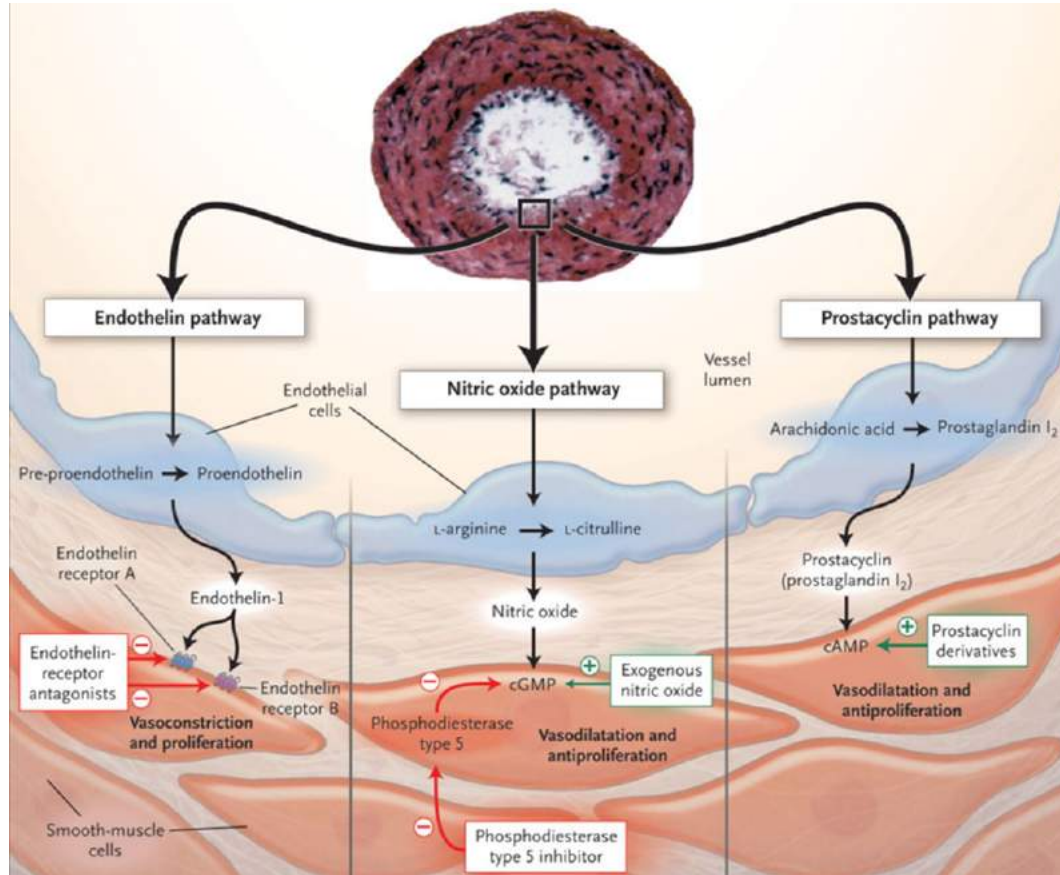


- Endothelial and smooth muscle cell proliferation

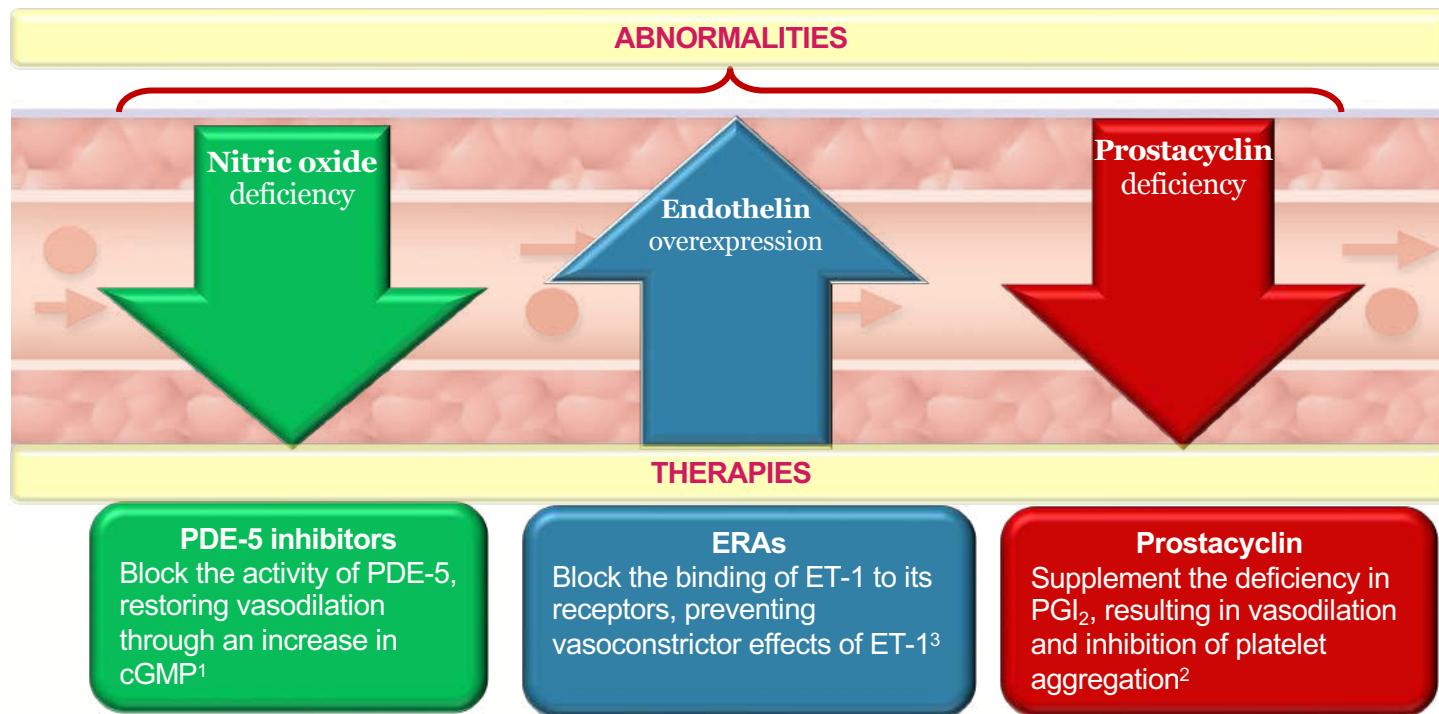


- Thrombosis in situ

MECHANISMS OF ACTIONS



TREATMENT IS AIMED AT THE 3 PATHWAYS



PH THERAPIES AND THEIR TARGETED PATHWAYS

Nitric Oxide Pathway	Endothelin Pathway	Prostacyclin Pathway
Inhaled Nitric Oxide	Ambrisentan (Letairis)	Treprostinil IV & SQ (Remodulin) Oral: (Orenitram) Inhaled: (Iloprost, Tyvaso)
Sildenafil (Revatio)	Bosentan (Tracleer)	Epoprostenol (Flolan, Veletri)
Tadalafil (Adcirca, Tadliq)	Macitentan (Opsumit)	Selexipag (Uptravi)

INHALED NITRIC OXIDE

- Advantage
 - Rapid and potent
 - Brief half life
 - Selective pulmonary vasodilation
 - Improves ventilation-perfusion matching
- Disadvantage
 - Not available at all facilities
 - Expensive
 - Risk for developing methemoglobinemia
 - Rebound PH with abrupt withdrawal



PDE-5 INHIBITORS

- Sildenafil
 - Advantage
 - Available in enteral and IV format
 - Disadvantage
 - Depending on route either 3 or 4 times a day administration
 - Main side effects noted are hypotension and worsening saturations due to VQ mismatching
 - Priapism is rare- but one of the most frequent concerns from patients/families
- Tadalafil
 - Advantage
 - Once a day administration
 - Less pharmacokinetic interaction with bosentan
 - Disadvantage
 - Often harder to obtain prior authorization approval



ENDOTHELIN RECEPTOR ANTAGONISTS

- Ambrisentan
 - Advantage
 - Once a day administration
 - Disadvantage
 - Only comes in tablet form
- Bosentan
 - Advantage
 - Available in tablet and liquid format
 - Pediatric dosing tablet of 32 mg
 - Disadvantage
 - Requires monthly LFTs given hepatotoxicity risks
 - May cause fetal harm



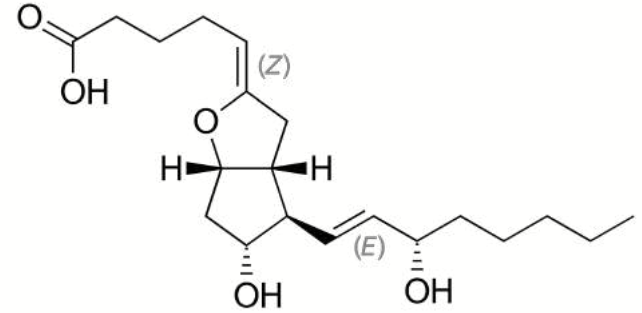
ENDOTHELIN RECEPTOR ANTAGONISTS

- Macitentan
 - Advantage
 - Once a day administration
 - Disadvantage
 - May cause fetal harm



PROSTACYCLINS

- Advantage
 - Most potent PH therapy
 - Several delivery modes
 - IV and SQ are continuous infusions
- Disadvantage
 - In the outpatient setting, cumbersome responsibility for patients and families
 - Side effect profile more prevalent



PROSTACYCLINS

- Inhaled
 - Iloprost - up to 9 times a day
 - Tyvaso - up to 4 times a day
- Advantage
 - Ideal for patients with tracheostomy
- Disadvantage
 - Mouthpiece size
 - Learned technique
 - Frequent administration



PROSTACYCLINS

- SQ Treprostinil
 - Delivered via CADD MS3 Pump or Remunity Pump
- Advantage
 - No need for central access
 - No risk for blood stream infections
 - Not emergent if SQ access is lost
 - More freedom
- Disadvantage
 - Site pain



PROSTACYCLINS

- IV Treprostinil
- IV Epoprostenol



COMPARATIVE DIFFERENCES BETWEEN IV THERAPIES

epoprostenol (Flolan)

- Half life of 3-6 minutes
- Because of short half life, patients can be titrated quickly
- Needs refrigeration
- Light sensitive
- Stable in room temperature for 8 hours
- Greater number and severity of side effects

treprostinil (Remodulin)

- Half life of 3-4 hours
- Because of longer half life, patients take longer to titrate
- Does not require refrigeration
- Not light sensitive
- Stable for 48 hours once mixed
- Fewer and less severe side effects but more caustic to peripheral veins



IP RECEPTOR AGONIST

- Uptravi
 - Advantage
 - Two times a day administration
 - Individualized titration
 - Disadvantage
 - Avoid in patients with severe hepatic impairment



CALCIUM CHANNEL BLOCKERS

- Advantage
 - Used for patients with + vasoreactivity
 - Minimal cost
 - Seldom requires a prior authorization
- Disadvantage
 - Contraindicated in children who are not vasoreactive
 - Not frequently prescribed to very young infant
 - Monitor for bradycardia, decreased cardiac output, gum hyperplasia



OXYGEN

- Advantage
 - Acts as pulmonary vasodilator
 - Valuable in preventing hypoxemia and associated vasoconstriction
 - Individualized titration to achieve targeted O₂ saturations
 - Available in concentrators and portable tanks
- Disadvantage
 - Depending on flow required may use tanks quickly
 - Too high flow can dry the nares
 - Free radical toxicity



SOLUBLE GUANYLATE CYCLASE STIMULATOR

- Riociguat
 - Advantage
 - Prescribed for chronic thromboembolic pulmonary hypertension (CTEPH)
 - Gradual up-titration
 - Disadvantage
 - May cause fetal harm
 - Hepatotoxicity



SIDE EFFECTS

- Nasal congestion
- Headache
- Jaw and extremity pain
- Diarrhea
- Nausea and vomiting
- Loss of appetite
- Fatigue
- Flushing
- Site pain (subcutaneous route)



CONSIDERATIONS WHEN PRESCRIBING PH MEDICATIONS

- Should combination therapy be considered?
- What route is best?
- Are baseline labs required?
- Is Risk Evaluation and Mitigation Strategy (REMS) enrollment required?
- Are we conducting a risk/benefit analysis on a routine basis?



CONSIDERATIONS WHEN PRESCRIBING PH MEDICATIONS

- Most insurance plans require prior authorizations
- Frequently denied and require appeal process
- Not all pharmacies supply PH medications
- PH medications are expensive



PATIENT ASSISTANCE PROGRAMS



CONCLUSIONS

- Goals of treatment
 - Relax pulmonary vasculature
 - Lower pulmonary vascular resistance
 - Preserve RV function
 - Slow disease progression
 - Improve quality of life



PH Therapies Have The Potential To Change Clinical Trajectories



Picture shared with permission from patient's parents