Persistent Pulmonary Hypertension of the Newborn

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Outline

- Background –
  - Epidemiology
  - Presentation & Diagnosis
  - Pathophysiology
- Treatment –
  - Goals of treatment
  - Guidelines & first line options
  - Other alternatives
- Conclusion

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Objectives

- Gain understanding of PPHN and underlying pathophysiology
- Learn the established treatments for PPHN and their mechanisms
- Analyze treatment options for resistant PPHN

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Abbreviations

- FiO_2 – fraction of inspired oxygen
- iNO – inhaled nitric oxide
- ECMO – extracorporeal membrane oxygenation
- MAP – mean airway pressure or mean arterial pressure
- OI – oxygenation index
- PaO_2 – arterial partial oxygen pressure
- PAP – pulmonary arterial pressure
- PDA – patent ductus arteriosus
- PGI_2 - prostacyclin
- PH – pulmonary hypertension
- RVP – right ventricle pressure
- SBP – systemic blood pressure

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Patient Case

- BC is a ex-33 week baby boy, born via Caesarean section after prolonged rupture of membranes in mother
- Mother is 32 y/o, G2 P1, chronic hypertension, denies any alcohol, tobacco or drug use
- Mother received standard prenatal care and was admitted in antenatal unit
- Now 11 days old, BC develops respiratory problems and he is ventilated
- An echocardiogram is ordered showing patent ductus arteriosus (PDA) and right to left shunting

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PPHN - Epidemiology

- Estimated at roughly 2 cases per 1000 live births
- Typically affects late preterm (≥34 weeks) or term infants
- Increased risk associated with:
  - Maternal use of SSRI/SNRIs or salicylates
  - C-section delivery
- Mortality has improved from 50% over past decades and is now believed to be about 8-10%
- Long-term neurological effects are frequent

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Steinhorn et al, *J Pediatr.* 2016., Van Marter et al, *Pediatrics 2013*., Reece et al, *Obstet Gynecol* 1987., Steinhorn et al, *Early Hum Dev* 2013.

PPHN – Presentation & Diagnosis

- Presentation:
  - Labile oxygen saturation
  - Severe hypoxemia despite oxygen and ventilation
- Diagnosis:
  - Clinically by pulse oximetry differential between thumb and great toe of >10%
  - Echocardiogram (gold standard) will show evidence of right to left shunting and allows grading severity

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Abman et al, *Circulation* 2015

PPHN – Presentation & Diagnosis

- Severity:
  - Oxygenation Index (**OI**) = 100*(mean airway pressure x FiO_2)/PaO_2 with larger OI indicating higher severity
    - OI < 25 is typically managed by supportive care
    - OI ≥25 usually requires higher level care: iNO, high-frequency oscillatory ventilation, ECMO
  - Percentage of right ventricle pressure (RVP) vs. systemic blood pressure (SBP)

Severity	RVP vs. SBP	Oxygenation Index
Mild	RVP 50-75% of systemic BP	OI ≤15
Moderate	RVP >75% of systemic BP	OI = 15-25
Severe	RVP >100% of systemic BP	OI >25; (very severe: OI>40)

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Sharma et al. *Matern Health Neonatol Perinatol.* 2015

Pathophysiology

Four basic causes of PPHN in lungs:

- Maladaptation – e.g. meconium aspiration syndrome
- Maldevelopment – a.k.a. idiopathic
- Underdevelopment – hypoplasia caused by oligohydramnios due to amniotic fluid leakage
- Intrinsic Obstruction – due to hematologic disorder resulting in elevated PVR

Sharma et al. *Matern Health Neonatol Perinatol.* 2015

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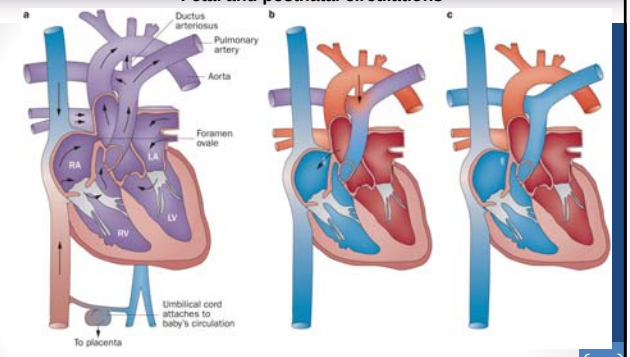
Fetal and postnatal circulations



Hunter, L. E. & Simpson, J. M. (2014) Prenatal screening for structural congenital heart disease *Nat. Rev. Cardiol*

nature REVIEWS CARDIOLOGY

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Pathophysiology

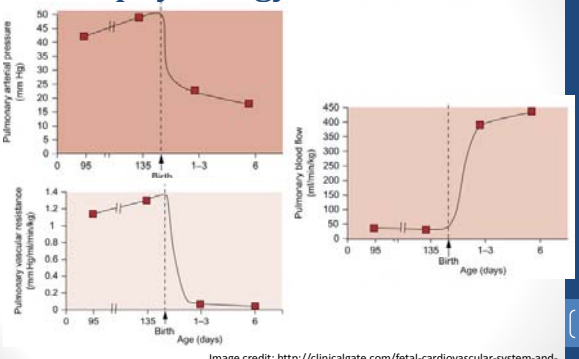

Image credit: http://clinicalgate.com/fetal-cardiovascular-system-and-congenital-heart-disease/

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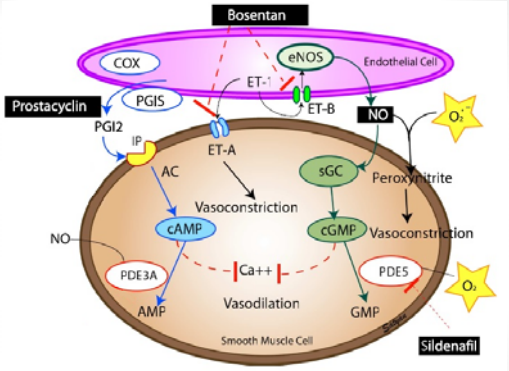

Image: Sharma et al. *Matern Health Neonatol Perinatol* 2015.

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Patient Case - Diagnosis

- Has failed to maintain O_2 saturation despite ventilation
- Echocardiogram reveals right-to-left shunting across PDA
- Oxygenation index:
  - FiO_2 (%)= 100%
  - Mean airway pressure (cm H_2O) = 22 cm H_2O
  - PaO_2 (mm Hg) = 45 mmHg *[normal: 70-75]*
  - OI = 48.9
- Diagnosis: PPHN, severe
  - Risk Factors: prolonged membrane rupture, C-section
- *How should BC be treated?*

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Treatment - Goals

- Primary Goal: Selectively reduce pulmonary pressure
- Reduction in pulmonary pressure helps…
  - Maintain oxygenation
  - Buys time for lungs to develop normal function, when possible

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Treatment Approach

- All Patients:
  - Supportive Care
- Severe Patients:
  - Inhaled nitric oxide (iNO)
  - Extracorporeal membrane oxygenation (ECMO)
  - Sildenafil
  - Other options

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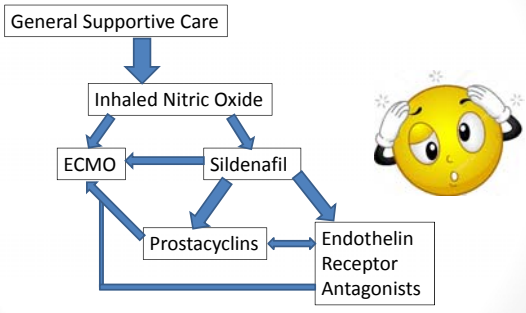
Treatment Approach



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Supportive Care

- Oxygen – target pre-ductal O_2 saturation 90-95%
- Assisted ventilation – goal to minimize acidosis and promoting alveolar recruitment
- Sedation and limiting stimulation
- Hemodynamic support –
  - Maintenance of adequate volume in vasculature
  - Maintenance of systemic vascular resistance
- Surfactant – in cases of respiratory distress

Abman et al. *Circulation* 2015.

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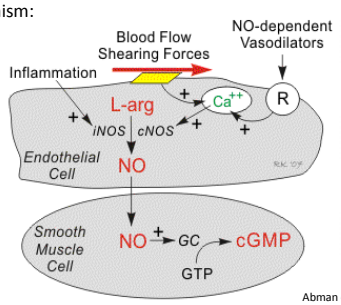
Inhaled Nitric Oxide

- First line treatment for severe PPHN (OI>25) [Class IA evidence]
- Mechanism:



Abman et al. *Circulation* 2015

Image credit: Dr. Richard Kalbunde, PhD

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Inhaled Nitric Oxide

- Pros:
  - Selective pulmonary vasodilator
  - Inhalation route direct to site of action
  - FDA approved for PPHN in near-term & term infants
  - Extensively studied in several large RCTs
  - Reduces need for ECMO
- Cons:
  - Does not reduce mortality vs. ECMO
  - Does not reduce hospital stay
  - 30-40% of infants do not respond to iNO
  - Expensive

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Inhaled Nitric Oxide

- Initiate treatment at 20 ppm
- Continue treatment up to 14 days or until oxygenation rebounds
- Check methemoglobinemia at 2h, 8h and daily
  - Target – methemoglobin <5%
- Weaning is recommended due to rebound hypertension – <u>even in non-responders</u>

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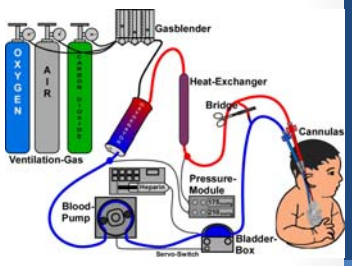
ECMO

- Used when iNO fails
- Goal: maintain oxygenation while allowing PH to resolve
- Requires very specialized personnel and equipment
- 1-2 weeks may be needed
- PPHN survival rate on ECMO was 81%



Lazar DA, et al. *J Surg Res. 2012.*

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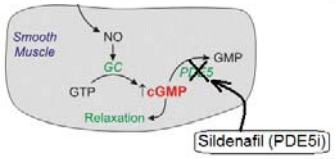
Sildenafil

- Phosphodiesterase-5 inhibitor (PDE-5i)
- Metabolized in liver (Major: CYP3A4 / Minor: 2C9)
- *Selectively* reduces PVR
- Used for infants not responding to iNO
- PO or IV



- FDA Clarification (2014): Revatio not approved in children, but health care professionals must weight benefits vs. risks for each patient

Image credit: Dr. Richard Kalbunde, PhD

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Sildenafil - PO

Study	Design	Population & PPHN Severity	Intervention	OI Change	Mortality
Baquero et al (2006)	Blinded RCT n=13 (6 placebo)	>35.5 weeks gestation; OI>25 (mean=56)	1 mg/kg q6h until OI <20	vs. baseline: -34.71 (p=0.04) vs. control: -45.46 (p=0.03)	Control: 5/6 Sildenafil: 1/7 (p<0.05)
Vargas-Origel et al (2010)	Blinded RCT n=40 (20 placebo)	Term infants; OI>20 (mean=45)	3mg/kg q6h until OI <10	vs. baseline: -30.4 (p<0.05) vs. control: -25.0 (p<0.05)	Control: 40% Sildenafil: 10% (p<0.05)

Baquero et al. *Pediatrics* 2006.
Vargas-Origel et al. *Am J Perinatol.* 2010

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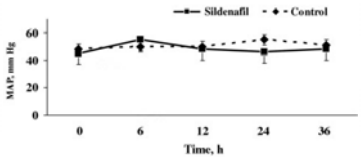
Sildenafil - PO

- Adverse Reactions:
  - Not powered to find adverse effects
  - Severe reactions not attributed to sildenafil
  - No evidence of drop in systemic BP



Baquero et al. *Pediatrics* 2006.

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Sildenafil – IV (Steinhorn et al. 2009)

- Unblinded and uncontrolled trial;
  - n=36, term infants, Ave. OI = 27.7
- Dose escalation design
  - Loading dose ranged 0.008 – 0.427 mg/kg
  - Maintenance infusions ranged 0.07 – 1.64 mg/kg/day
- iNO used concurrently in 29/36 infants
- Discussion:
  - Very difficult to draw conclusions on efficacy of IV sildenafil alone
  - No significant drop in systemic blood pressure during observation does provide some safety evidence for concurrent iNO & sildenafil

Steinhorn et al. *J Peds* 2009.

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Patient Case - Update

- BC has been treated with:
  - General supportive measures
  - iNO at 20 ppm
  - Sildenafil 1.5 mg/kg q6h
- But his OI remains at = 43.1
  - FiO_2 (%)= 92%
  - Mean airway pressure (cm H_2O) = 22 cm H_2O
  - PaO_2 (mm Hg) = 47 mmHg
- What options remain?

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Beyond sildenafil…

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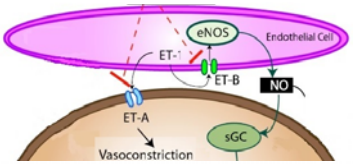
Endothelin Receptor Antagonists (ERA)



- ET-1 is most active of 3 endothelin (ET) factors which activate ET-A & ET-B receptors
- Higher levels of ET-1 in PPHN vs. healthy infants
- ET-1 is smooth muscle mutagen

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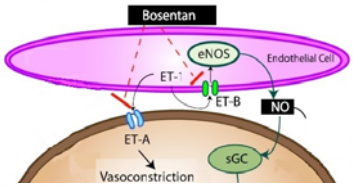
Endothelin Receptor Antagonists (ERA)



- **Bosentan** – non-selective ERA
  - Route: oral
  - Metabolism: CYP2C9 and 3A4 (inducer), one active metabolite
  - REMS program required for access due to hepatotoxicity and teratogenicity
  - Liver function must be monitored
  - Adverse reactions: edema, headache, decrease in Hgb

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Bosentan Studies

	Mohammed et al (2012)	Steinhorn et al - FUTURE-4 (2016)
Trial Design	Single center 1:1 double-blind RCT	Multi-center 2:1 double-blind RCT
n	47 (24 treatment)	21 (13 treatment)
Dose	1 mg/kg per tube BID	2 mg/kg per tube BID
Control:	Placebo	Bosentan + iNO
Add'l Ther.	Supportive, surfactant	Supportive + milrinone, vasopressors, surfactant, sodium bicarbonate
Inclusion:	Infants>34 weeks GA Ventilated w/FiO2>0.5 PPHN confirmed w/echo (R-->L shunt + PAP>40)	Infants >34 weeks GA OI>12 PPHN confirmed w/echo
Baseline disease:	Median: PaO2 ~ 37 OI ~44	Median: OI (bosentan) = 18.3 OI (placebo) = 13.2 Median iNO dose = 20ppm x 20 hrs
Primary outcomes:	Composite "favorable" if all criteria below met by day 3: - OI <15 (main outcome) - PAP <20mmHg - No discontinuation d/t adverse effects	- Need for ECMO or alternate vasodilator - Time to complete weaning from iNO & mechanical ventilation

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Bosentan Studies

	Mohammed (2012)	Steinhorn - FUTURE-4 (2016)
Results:	By day 3, 83.3% bosentan had favorable response vs. 13.0% placebo group (p<0.05)	No significant differences in primary or secondary outcomes after correction for difference in baseline OI
Secondary outcomes:	p<0.0008 for overall major sequelae @ 6 months with significance in neurological outcomes but not 28-day mortality	Change in OI, FiO2, restart of iNO - none statistically different b/w groups
Notes:	- 8 patients dropped out of placebo group d/t clinical worsening and were excluded from analysis - Resource limited setting	- Study terminated d/t difficulty enrolling pts after 2 years - Much higher use of vasoactive agents in bosentan arm vs. placebo (9/13 vs. 1/8)
Author's conclusion:	Effective vs. placebo, well-tolerated, useful in resource-limited setting	No evidence to support clinical efficacy, well-tolerated. Authors speculate erratic PK may be reason for lack of efficacy. Low number of treatment failures generally.

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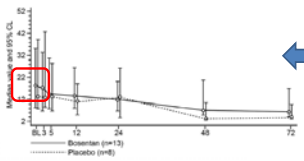
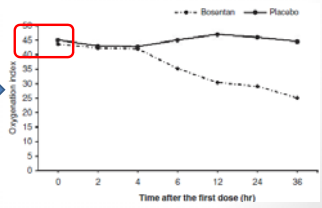
Bosentan study – OI outcomes



FUTURE-4

Mohamed et al.



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Bosentan - Conclusions

- Very small enrollments limit conclusions
- Impossible to compare/combine studies directly due to very different settings and approaches to treatment
- Baseline OI in FUTURE-4 trial is very close to OI level deemed treatment success in other PPHN studies
- Bosentan was considered well-tolerated in both studies, though small size limits statistical significance
- Given the outcomes in Mohammed et al, bosentan may be a reasonable salvage option in patients with OI levels that remain in the severe category despite established care with iNO +/- sildenafil

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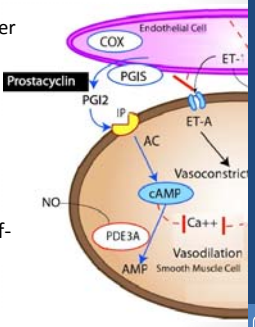
Prostacyclins

- Complementary pathway to other treatments
- Several products with different routes:
  - Iloprost
  - Epoprostenol
  - Treprostinil
- Most products have short half-life and are administered via continuous infusion pumps in adults
- Stability is also problem



Mubarak et al. *Respir Med.* 2010.

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Prostacyclins

- IV prostacyclins are a cornerstone of treatment in pediatric and adult pulmonary hypertension

	epoprostenol	treprostinil	iloprost
Route:	IV, inhaled	SC, IV, inhaled	IV, inhaled
Metabolism:	rapid hydrolysis	hepatic (CYP2C8)	hepatic (β-oxidation)
Half-life:	6 minutes	3 hours	20-25 minutes
Interactions:	Antiplatelet agents, anticoagulants, antihypertensives		
Adverse Effects:	**Severe**: systemic hypotension, bleeding. Chronic IV treprostinil associated w/Gr(-) bloodstream infections, epoprostenol associated w/Gr(+) infections **Other**: Diarrhea; flushing; pain at injection site, foot and jaw		

- PPHN guidelines are generally dismissive of prostacyclins due to lack of evidence
- Generally, limited to older case series reports and safety studies

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Prostacyclins

Safety and efficacy with SC, IV and inhaled therapy has been reported in infants:

- Safety of epoprostenol and treprostinil in children less than 12 months of age (McIntyre et al. *Pulm Circ.* 2013)
  - Case series (n=36) of children <1 year old receiving IV epoprostenol or treprostinil initiated @ 1-2ng/kg/min
  - 50% of patients experienced at least 1 ADE
  - Majority of ADEs were minor or transient – hypotension (managed by dose reduction), pain, flushing
  - 2 events each of significant bleeding and associated cyanosis leading to drug discontinuation
  - Conclusion: while unable to compare to placebo, PGI_2 agents are safe & tolerable in children <1 year of age

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Prostacyclins

- Efficacy:

Study:	Kelly et al (2002)	Ferdman et al (2014)
Type:	Case series n=4	Case series n=5
Disease:	PPHN	Chronic Lung Disease (CLD)
Drug:	epoprostenol	treprostinil
Dose:	50 ng/kg/min	1.25 ng/kg/min, titrated up
Route:	Inhaled	SC
Outcome:	Death OI	Est. PH severity (via echo) Supp. O2
Results:	Death: 1 OI baseline: 29 +/- 5 OI @ 12 hrs: 10 +/- 4 (in 3 surviving pts)	- PH severity improved in 3/4 surviving infants - Supp. O2 reduced or unneeded in 3/4 surviving infants
Notes:	- Death due to alveolar capillary dysplasia - No ADEs noted	- No pain noted from SC route - No ADEs recorded

Kelly et al. *J Pediatr*. 2002; Ferdman et al. *Pediatrics* 2014.

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Prostacyclins – Iloprost vs. Sildenafil

Oral Sildenafil and Inhaled Iloprost in the Treatment of Pulmonary Hypertension of the Newborn (Kahveci et al. *Pedi Pulm*. 2014)

Type:	Single-center (Turkey), retrospective study, tracking patients over 8 days
n:	47 (20 iloprost, 27 sildenafil)
Population:	Term infants, echocardiographic diagnosis of PPHN, OI>25, ventilated (no statistical differences in population)
Baseline OI:	Sildenafil: OI (ave)= 48.2 Iloprost: OI (ave) = 43.9
Intervention:	Sildenafil: 0.5 mg/kg q6h initial up to 2 mg/kg per tube Iloprost: 1-2.5 mcg/kg q2-4h nebulized
Additional Treatments:	inotropes (dopamine, dobutamine) MgSO4

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Prostacyclins – Iloprost vs. Sildenafil

Kahveci et al. *Pedi Pulm*. 2014

	Sildenafil (n=27)	Iloprost (n=20)	p-value
Mortality (n):	4	3	p=1
Inotrope use (n):	7	0	p<0.05
Mean duration of mech. vent:	10.03 days	6.23 days	p<0.05
Systemic hypotension (n):	9	0	p<0.05

No side-effects attributed to iloprost during period of study

- Study positives:
  - Active comparator
- Study limitations:
  - Sildenafil dose lower than other studies
  - Final OI comparison not done on full groups (n=9 in iloprost, n=22 in sildenafil)
  - OI difference between groups not significant
  - Limited generalizability to US setting

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Prostacyclins – New Trial

Remodulin (treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn

- NCT02261883; Estimated Primary completion date: Dec 2017
- Phase 2, multicenter, double-blind RCT
- Remodulin initiated @ 1ng/kg/min and titrated up 2ng/kg/min q2h until OI <10 or not tolerated;
- Primary Outcomes:
  - Composite of initiating additional pulmonary vasodilators, ECMO or death
- Secondary Outcomes (selected):
  - Change in OI
  - Time to discontinue iNO
  - Safety & adverse events
  - Pharmacokinetic analysis
- Note: Sponsored by United Therapeutics

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Conclusion & Recommendations

- For patients refractory to iNO, there are a number of options to consider:
- Sildenafil should be the first choice for refractory PPHN
- If OI does not recover with sildenafil, bosentan is the next choice
  - Mohammed et al, not perfectly generalizable to US medical setting but it was a blinded RCT that indicates efficacy
  - Consider bosentan particularly if OI remains stubbornly elevated
- Prostacyclins should be considered a last option if all other therapies fail.
  - Unclear if any particular route or agent is superior to others; allow patient specifics to guide choice of inhaled vs. IV vs. SC
- Results of SC treprostinil study may provide evidence that shifts salvage therapy sequence towards prostacyclins

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Patient Case

- What further therapies would be appropriate for JC?
- JC was eventually given:
  - Treprostinil 15ng/kg/min SC into the left thigh
  - Bosentan 2mg/kg Q12H

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