BPCA PULMONARY WORKING GROUP
Summary of Findings
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Pulmonary Working Group

“He’s a child” is not a diagnosis.

But it is an important part of his treatment plan

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Pulmonary Working Group Focus

- **Pulmonary Hypertension**
- **Asthma**
- **Cystic Fibrosis**

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Pulmonary Hypertension

- **Issues**
  - Pharmacology of New Therapeutic Agents.
    - » Sildenafil
  - Discriminatory Biomarkers.

Neonatal Off-label Drug Usage
10 Most Commonly Prescribed

Medication	% Exposed	FDA Labeling for Premature Infants
Ampicillin	74	None
Gentamicin	68	None
Cefotaxime	36	None
Caffeine citrate	19	None <29 wks
Furosemide*	19	None
Vancomycin	17	None
Beractant*	14	Yes
Metoclopramide	11	None
Aminophylline	11	None
Dopamine*	10	None

* Most commonly used for pulmonary disease.

Adapted from Clark RH, Bloom BT, Spitzer AR, Gerstmann DR; "Reported medication use in the neonatal intensive care unit: data from a large national data base"; Pediatrics 117: 1979-1987, 2006.

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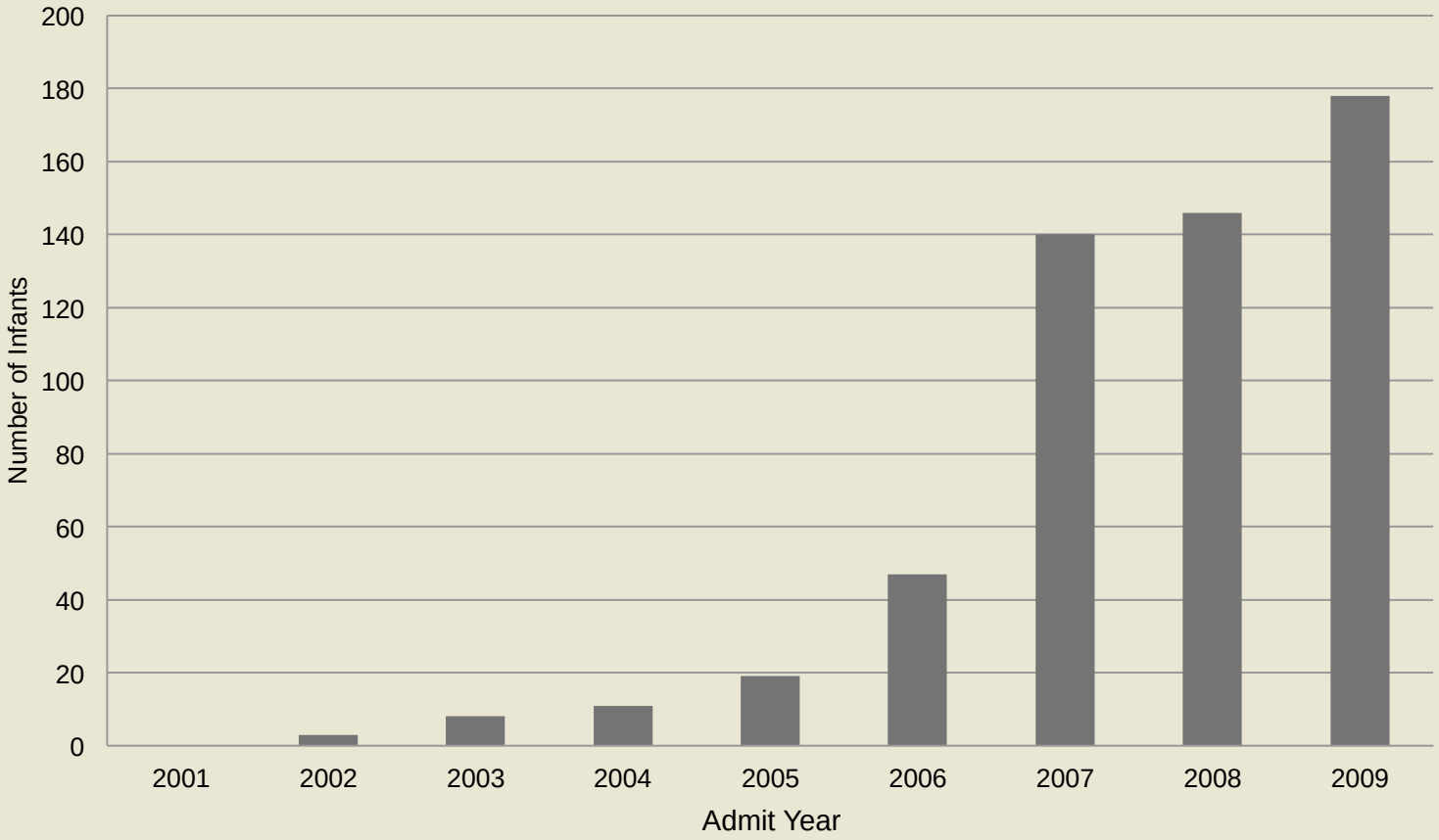
Neonatal Off-label Sildenafil Use (Pediatrix Medical Group)



R. Clark and B. Smith; Personal Communication to M.M. Laughon, M.D.; 2011

Pulmonary Hypertension Sildenafil

- **Issues:**
  - Up to 20% of infants with bronchopulmonary dysplasia (BPD) develop pulmonary artery hypertension (PAH)
  - Up to 40% of infants with PAH complicating BPD die.
  - Inhaled NO under study in BPD, with inconclusive and conflicting results.

Pulmonary Hypertension Sildenafil

- **Issues:**
  - Dose-response studies of sildenafil conducted in term neonates with PAH show altered PK parameters compared to adults.
  - One retrospective study of enteral Sildenafil in 25 infants with lung disease.
    - » Hemodynamic benefit in 22; 5 deaths in follow up.
    - » No analysis of pharmacokinetics.
  - RCT of Sildenafil now underway in infants at risk of BPD (clinicaltrials.gov; NCT00431418).
    - » Dose unspecified.
    - » No PK samples or modeling.

Pulmonary Hypertension Sildenafil

- **Needs:**
  - Develop blood spot technology to measure Sildenafil concentrations.
  - Develop an enteral liquid formulation of Sildenafil.
  - Sildenafil pharmacokinetics trial in preterm infants.
  - Sildenafil pharmacodynamics trial in preterm infants.
  - Clinical pharmacology plan for phase I – III trials to determine optimal dose and effectiveness.

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Pulmonary Hypertension Biomarkers

- **Issues:**
  - Childhood disease layered on back drop of developmental programming.
    - » Significant, little recognized feature of PH in neonates and children compared to adults.
  - One recent classification scheme suggested to facilitate study of PH treatment options in children.*
  - Children and neonates with PH have differences in etiology, disease progression, genetic associations and treatment responses compared to adults.**

*** Del Cerro et al, Pulm Circ 2011**
**** Abman et al, Curr Opin Pediatr 2011**

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Pulmonary Hypertension Biomarkers

- **Needs:**
  - Physiology-based biomarkers:
    - » Alternatives to 6 minute walk for ambulatory age (less reliable) and non-ambulatory age (not useful).
    - » Determine the reliability of Pulmonary Vascular Resistance Index in pediatric or neonatal populations.
  - Plasma-based biomarkers:
    - » Several validated for adults; none for pediatrics/neonates.
    - » Identified plasma biomarkers should be validated against new physiology-based biomarkers.
  - Genetic-based biomarkers:
    - » Genetic risk factors for BPD, what about PAH?

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Asthma

- **Issues**
  - Pharmacology of existing therapeutic agents.
    - » Inhaled Corticosteroids
    - » Intravenous beta Agonists
    - » Omalizumab

Asthma
Inhaled Corticosteroids

- **Issues:**
  - Commonly used in children <5 years old – outside the age range of scientific evidence and FDA approval.
  - Usually delivered in these children by metered dose devices with spacers (MDI) but with no data on drug delivery to the lung.
  - Safety in these growing children unknown.
    - » Systemic absorption.
    - » Incidence of adverse effects.
  - Limited evidence of efficacy in these children.

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Asthma
Inhaled Corticosteroids

- **Needs for children <5 years old:**
  - Pharmacokinetics comparing nebulizer with MDI/ spacer delivery.
    - » Dose-response.
    - » Systemic absorption.
  - Efficacy - safety analysis of inhaled corticosteroids in this age group.
  - Improved outcome measures relevant to this age group.
    - » Improved technology for pulmonary function testing.

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Asthma
Intravenous beta Agonists

- **Issues:**
  - IV beta agonists commonly used in pediatric ICUs for severe refractory asthma.
  - Important gaps in clinical pharmacology of beta agonists in the pediatric population exist.
  - Uncertainty in efficacy.
  - Variability in clinical application (dose, indications).
  - Unknown dose-related risks of cardiovascular side effects .
  - Lack of appropriate pediatric formulations (e.g. Terbutaline formulation too dilute).

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Asthma
Intravenous beta Agonists

- **Needs:**
  - For conducting appropriate studies:
    - » Age-appropriate formulations of IV Terbutaline.
    - » Asthma assessment tool(s) appropriate to age and disease severity.
      - » For severe unstable asthma cared for in ICU.
      - » Correlation with physiologic parameters and robust measure of outcome
  - Age-related pharmacokinetics and pharmacodynamics of IV Terbutaline.
  - Age-related efficacy and safety of IV Terbutaline.

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Asthma
Omalizumab in Children < 5 Years

- **Issues:**
  - No therapy for disease modification or prevention in children.
  - Omalizumab (anti-IgE antibody) only approved for children >12 years age with IgE-triggered environmental antigen sensitivity.
  - Experimental data suggest use of Omalizumab early in childhood may prevent or modify the course of asthma.
  - Has potential for serious adverse effects including delayed anaphylaxis and malignancies.

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Asthma
Omalizumab in Children < 5 Years

- **Desirable studies:**
  - Controlled clinical trials in children <5 years developing:
    - » Safety data.
      - » Immunologic effects.
      - » Long-term outcome.
    - » Efficacy data.
      - » Prevention or amelioration of asthma.
      - » Genetic markers.
- **Needs for successful studies:**
  - Validated asthma predictive index.
  - Physiologic pulmonary function testing.
  - Age-appropriate immunologic testing.

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Cystic Fibrosis

- **Issues**
  - Pharmacology and Use of Existing Drugs.
    - » Antibiotics
    - » Antifungals
    - » Colistin / Colistimethate
    - » Ibuprofen
    - » Proton pump inhibitors

Cystic Fibrosis Antibiotics

- **Issues:**
  - Need for more effective antibiotic regimens with multi-drug resistant *Pseudomonas*
    - » With increasing MIC's in multi-drug resistant strains, traditional intermittant dosing – even high doses – may be sub-optimally effective.
    - » Little pharmacokinetic and/or safety data on high dose infusions of beta Lactams, 3rd and 4th generation Cephalosporins, Carbapenems, and Monobactam.
  - New regimens of extended (over 4 hrs) or continuous infusions being tried with insufficient data.

Cystic Fibrosis Antibiotics

- **Issues:**
  - Important to note that current continuous infusion studies of beta Lactams and 3rd and 4th generation Cephalosporins are not specific to the CF population.
  - CF population known to have different pharmacokinetics.

Cystic Fibrosis Antibiotics

- **Needs:**
  - Studies to be carried out with beta Lactams, 3rd and 4th generation Cephalosporins, Carbapenems, and Monobactam:
    - » Pharmacokinetics, efficacy and safety comparisons of high dose, extended infusion and continuous infusion.
    - » Evaluation of potential interference with clearance of aminoglycosides.
  - Development of a uniform clinical assessment tool for clinical response.

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Cystic Fibrosis Antifungals

- **Issues:**
  - Fungal endobronchitis and allergic bronchopulmonary aspergillosis (ABPA) an emerging serious problem in cystic fibrosis related to increased use of inhaled, oral and IV antibiotics.
  - Particular problem in younger age groups as these antibiotic regimens are being extended into these children.
  - Voriconazole and Itraconazole currently used; no approval for children < 12 yrs age and no approval for use in CF.

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Cystic Fibrosis Antifungals

- **Needs:**
  - Establish therapeutic ranges in CF children.
  - Establish conditions making enteral absorption more reliable and predictable.
  - Establish long-term safety in CF children.
    - » Recommendations for drug and safety monitoring.
  - Efficacy studies in both Endobronchitis and ABPA
    - » Reduction in exacerbations.
    - » Reduction in prednisone usage during exacerbations.

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Cystic Fibrosis
Colistin / Colistimethate

- **Issues:**
  - Increased multi-drug resistant gram negative pathogens in CF
  - Sensitive to IV Colistin / Colistimethate, but IV pharmokinetics in younger children inadequately studied.
  - Common practice to deliver via nebulized / aerosolized / inhaled route using IV formulation.
  - No data on pharmacokinetics, safety, efficacy of this mode of delivery.
  - Serious Colistin / Colistimethate toxicity possible.

Cystic Fibrosis
Colistin / Colistimethate

- **Needs:**
  - Pharmacokinetics, safety and efficacy of Colistin / Colistimethate in children <12 yrs age with CF.
    - » IV use.
    - » aerosolized / nebulized / inhaled use.
  - Standardized clinical assessment tool(s) for efficacy.

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Cystic Fibrosis Ibuprofen

- **Issues:**
  - Strong evidence that high dose long term Ibuprofen slows the progression of CF.
  - Age-associated adverse effects on high dose long term therapy in CF not known.
  - Possible protective effects of adjuvant therapy not known.
  - Used with invasive/intense monitoring to optimize dosing.

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Cystic Fibrosis Ibuprofen

- **Needs:**
  - Development of dose scheme requiring less intensive ibuprofen therapeutic monitoring.
  - Data on safety of high dose ibuprofen relative to the age of treatment initiation across the pediatric age spectrum.
  - Determination whether concurrent acid suppressive therapy benefits ibuprofen efficacy, safety, and pharmacokinetics.

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Cystic Fibrosis
Proton Pump Inhibitors (PPIs)

- **Issues:**
  - Potential value as adjuvant therapy with enzyme replacement drugs to enhance their bioavailability.
  - Need for episodic treatment of gastro-esophageal reflux disease (GERD).
    - » Lack of approved product labeling for GERD in neonates and young infants.
  - Potential value of normalizing duodenal pH to reduce intestinal permeability and stress on the exocrine pancreas.
  - Pharmokinetics well-studied in pediatric populations.

Cystic Fibrosis
Proton Pump Inhibitors

- **Needs:**
  - Development of an exposure-controlled paradigm (i.e. a target Area Under Curve) to evaluate value of concomitant PPI therapy on bioavailability / bioactivity of enzyme replacement therapy.
  - Determination of CF phenotype and CYP2C19 phenotype on PPI treatment / response relationships in CF.
  - Determination of effect of PPIs on magnesium metabolism.

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Pulmonary Working Group Acknowledgements

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