BPCA PULMONARY WORKING GROUP
Summary of Findings 2011

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“He’s a child” is not a diagnosis.

But it is an important part of his treatment plan.
Pulmonary Working Group

Focus

- Pulmonary Hypertension
- Asthma
- Cystic Fibrosis
Pulmonary Hypertension

- Issues
  - Pharmacology of New Therapeutic Agents.
    » Sildenafil
  - Discriminatory Biomarkers.
Neonatal Off-label Drug Usage
10 Most Commonly Prescribed

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Exposed</th>
<th>FDA Labeling for Premature Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>74</td>
<td>None</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>68</td>
<td>None</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>36</td>
<td>None</td>
</tr>
<tr>
<td>Caffeine citrate</td>
<td>19</td>
<td>None &lt;29 wks</td>
</tr>
<tr>
<td>Furosemide*</td>
<td>19</td>
<td>None</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>Beractant*</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>10</td>
<td>None</td>
</tr>
</tbody>
</table>

* Most commonly used for pulmonary disease.

Neonatal Off-label Sildenafil Use
(Pediatric Medical Group)

Number of Infants

Admit Year

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

Sildenafil

- 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

- 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.
**Pulmonary Hypertension Biomarkers**

- **Issues:**
  - Childhood disease layered on backdrop 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
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?
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.
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.
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).
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.
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.
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.
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 intermittent 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 3\textsuperscript{rd} and 4\textsuperscript{th} 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.
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.
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.
**Cystic Fibrosis**

**Colistin / Colistimethate**

- **Issues:**
  - Increased multi-drug resistant gram negative pathogens in CF
  - Sensitive to IV Colistin / Colistimethate, but IV phamokinetics 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.
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.
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.
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.
Sub-group leaders:
- Pulmonary Hypertension
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  » Louis Chicoine
- Asthma
  » Thomas Green
  » Christopher Newth
- Cystic Fibrosis
  » Hanna Phan
  » Michael Reed
  » Greg Kearns
  » George Retsch-Bogart

All members of the Pulmonary Workgroup
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- Carol Blaisdell (NHLBI)
- Brandy Weathersby (Circle Solutions)
- Ayesha Navagamuwa (Circle Solutions)