Case Studies of Off-Label and Specialty Medication Use in Pediatrics: Considerations and Best Practices

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Robert J. Kuhn: Speakers Bureau (Genentech), Cystic Fibrosis Foundation Therapeutics DMSB Board

Hanna Phan: Consultant (Vertex Pharmaceuticals Inc.), Cystic Fibrosis (CF) Foundation Therapeutics DMSB Board, CF Foundation (Research Grant Support), NIH-NHLBI (Research Grant Support), MCHB (Training Grant Support)

NOTE: We will discuss the off label use of medications in children

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Review current specialty conditions in which off-label medication use is common and require addition medication management by pharmacists.
2. List key considerations when determining dose and monitoring for off-label medication use in pediatric patients.
3. Determine when off-label medication use is appropriate in a given pediatric patient.
4. Identify key evidence to support off-medication use in select pediatric chronic conditions.
5. Apply fundamental concepts in pediatric pharmacotherapy in the selection and monitoring of off-label drug therapy for specialty conditions.
Assessment Question 1

Key considerations that are important in determining dose and monitoring parameters for off label use of drugs in pediatrics include:
A. Pediatric medication dosing resources
B. Adult dose of the drug
C. Formulary issue
D. Cost
Assessment Question 2

FDA labeling of drug use is based on:

A. Data from clinical trials submitted to FDA for review  
B. Expert consensus panel recommendations  
C. National guidelines  
D. Adverse Reaction Reporting
Assessment Question 3

Which of the following conditions would often require the use of off label use of approved medications?

A. Otitis Media  
B. Cystic Fibrosis  
C. Spinal Muscular atrophy  
D. Vaccine administration
Assessment Question 4

Mary S is a 21 year old who is about to start Ivacaftor-lumacaftor therapy. She is on pancreatic enzymes, supplemental vitamins, dornase alfa, albuterol and oral contraceptive to prevent pregnancy. What important drug drug interaction should be discussed with the patient?

A. This new drug may require you to take more pancreatic enzymes for digestion
B. This drug may alter the effectiveness of your oral contraceptive
C. This new drug will require you to wait 2 hours to take your dornase alfa
D. This new drug will require you to double your vitamin requirements
Off Label in the Land of Pediatrics

- Estimates vary but as much as 80% of drug use in pediatrics is “off Label”

- What does that mean? Insufficient data for FDA to grant labeling

- Why is that?

- Difficulty in doing drug studies in children

- Lack of financial reason for drug manufacturers to invest in small populations exception Orphan drug status—under review
Off-Label: It’s Everywhere!

- Inpatient
- Outpatient
- Emergency Department

Off-Label Medication Use
Survey Says...

Prescribing a medication off-label for a pediatric patient is **not legal**.

A. True

B. False
Off-Label (OL) vs. Unlicensed

**OFF LABEL**
- Dose
- Age
- Indication
- Route of administration
- Contraindications

**UNLICENSED**
- Extemporaneous dispensing
- Drugs not licensed in US
- Chemicals
- “Specials” pharmaceutical manufacturer

FDA Pediatric Groups

- Neonatal period – first 30 days of life
- Infants- Toddlers- 31 days to 2 years
- Small Children- 2-6 years of life
- Children 6-12 years of life
- Adolescents 12-18 years of age
- Adult 18+
Hit and Miss: Data on OL in Pediatrics

- Various studies examining frequency of OL use based on setting, patient population
  - Hospitalized, outpatient, emergency department
  - Cardiac ICU, neonatal ICU, etc.
  - Types of medications: antiemetics, antiepileptics, gastrointestinal (GI), antidepressants

- ADR frequency reported, but limited data regarding:
  - Specific agents associated with ADEs
  - Severity of ADEs with OLs vs. label use
Emergency Dept. & Pediatric Patients

- Acute care + outpatient care mix
- Greater than 25% of ED visits are pediatric
  - Lack of safety and efficacy data in OL
- One of the 1st settings where possible ADE due to OL use present (home medications)
  - OL medications that lead to ED admission
  - OL medications used in ED that lead to ADE (and possibly subsequent inpatient admission)

Clinical Issues with Off-Label Medication Use

- Lack of appropriate formulations
- Limited dosing data
- Lack of information for patients/families
- Communication between providers (transition of care)
- Lack of postmarketing surveillance
- Medication errors
- Unanticipated adverse drug reactions

Lack of Formulations

- Generally children 6 yr+ should be able to swallow solid dosage forms...what about those kids who cannot?
  - Extemporaneous compounded liquid
  - Crush tablet
  - Open capsule

- Lack of commercially available formulations
  - Extemporaneous compounding
    - Stability data
  - Limited safety and efficacy data

Lack of Post-Marketing Surveillance

- Most common with FDA approved medications
- Involves spontaneous reporting by prescribers
- **PROBLEM:** inhibition of reporting with OL or unlicensed medications use
  - Despite encouragement by regulatory bodies to report
Adverse Drug Events in Pediatric Patients

- Systematic Review
  - 17 prospective observational studies on ADEs in children, various settings
  - Inpatient incidence = 9.53%
    - ~ 12% severe reactions
    - ~ 2% of admissions due to adverse drug event
  - Outpatient incidence = 1.46%

- STUDY LIMITATION:
  No differentiation between label vs. OL use

Adverse Drug Events in Pediatric Patients

- One US pediatric institution, 1235 ADE reports reviewed
  - Small % outpatient data
  - Overall ADE reported incidence of ~1.6%
  - Most commonly reported by pharmacy
  - Majority lower level (1-3) severity ADEs
    - High severity (4-6) ADE → “definite” causality was common
  - Lower severity of ADE in NICU and general ward
- STUDY LIMITATION:
  No differentiation between label vs. OL use

CASE: JJ – A Child in Need

JJ is a 2 year old male who was diagnosed with CF at 1 month of age (F508del/G551D). He comes to CF clinic with a newly developed cough for the past 2 weeks. A cough swab reveals that he is now positive for *P. aeruginosa*. You and the physician decide to start tobramycin inhalation solution in an effort to eradicate the pathogen.
CASE: JJ – A Child in Need

FDA label for tobramycin inhalation solution:

“Safety and efficacy have not been demonstrated in patients under the age of 6 years”

Is it appropriate to prescribe this medication OL for JJ?
Important Sources: Day to day issues
My Take

- Pediatric Dosage Handbook
  - Harriet Lane Handbook/Neofax/Trissel
  - Specific Peer Reviewed Articles
- Clinical Practice
- ACCP-PPAG List serve
- Expert at other Hospital
  - FDA
Can’t Find it: Other Levels of Evidence

- Treatment Guidelines- e.g., Pediatric Asthma for the NHLBI guidelines 2008
- Section on Pediatric Asthma –complete with dosing and algorithms
- Few of these but look for them
- Standard of cares- from other organizations e.g. A.D.A or in our case Cystic Fibrosis Foundation Guidelines document use
What are Clinicians To Do?

- “Practitioner...is responsible for deciding drug and dosing regimen... and for what purposes”

- Decision based on:
  - Information from drug’s label
  - Other published data available
  - “Sound scientific evidence”
  - “Expert medical judgment”

What are Clinicians To Do?

- OL use of a drug should be:
  - “...done in good faith”
  - “...in the best interest of the patient”
  - “...without fraudulent intent”

- Potential for accountability for negligible use of any drug (OL, UL, licensed)

CASE: JJ – A Child in Need

Two years later, JJ is now 4 years old. He and his parents come to clinic for a quarterly visit and inquire about the use of the “miracle drug,” for CF patients with the G551D mutation (ivacaftor). His parents ask if he can be started on it, since he is able to swallow tablets now.
CASE: JJ – A Child in Need

FDA label for ivacaftor tablets:

“Safety and efficacy have not been demonstrated in patients under the age of 6 years”

AND

There is currently NO dosing, safety, and efficacy data in his age group

AND

It is known insurance will NOT pay for this medication at this time based on age (cost: $300K/year)...

Is it appropriate to prescribe this medication OL for JJ?
Necessity of Medication

- Serious or life threatening condition
- Long term or short term use
- Known toxicity of the drug
- No other alternatives
- Dosing of medication-mg/kg or mg/m²
Off Label Use for Unmet Need

- Difficult to treat Asthma
- Beyond the guidelines
- “Where the Rubber hits the Road”
Case: Julie

Julie is a 10 year old female (42 kg) with severe persistent asthma. She has required frequent, long taper prednisone courses over the last 18 months. Her work up for ABPA, immune panel (IgA, IgG, IgM) were negative. She has been on omalizumab for the last 3 years, however has presented with worsening asthma over the last year. No smoking, 1 cat (allergic, but bathes cat regularly), received immunotherapy for multiple allergies. Her current regimen is as follows:

- Albuterol/ipratropium or nebs 4x/day PRN
- Albuterol MDI HFA 2-4 puff every 4-6 hours PRN
- Fluticasone/salmeterol 230/21 HFA 2 puffs BID with spacer
- Epi Pen PRN anaphylaxis
- Montelukast 10mg po QHS
- Tiotropium 2.5 mcg inhaled daily
- Omalizumab 225mg subQ every 14 days
- Fexofenadine 180mg po daily
How do we help Julie?

- Another Biologic off label
- Analysis of Guidelines
- Extrapolation of Adult Data
- Prior treatment with Omalizamab
### NHLBI EPR-3 Guidelines

#### Step-by-Step Treatment

**Step 1**  
**Intermittent Asthma**  
**Preferred Treatment**: SABA as needed

**Step 2**  
**Persistent Asthma: Daily Medication**  
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

**Step 3**  
**Preferred Treatment**: Low-dose ICS*  
**Alternative Treatment**: Cromolyn, LTRA,* or theophylline®

**Step 4**  
**Preferred Treatment**: Low-dose ICS* + LABA*  
**Alternative Treatment**: Medium-dose ICS* + LABA*

**Step 5**  
**Preferred Treatment**: Medium-dose ICS* + LABA*  
**Alternative Treatment**: High-dose ICS* + LABA* AND consider omalizumab for patients who have allergies**

**Step 6**  
**Preferred Treatment**: High-dose ICS* + LABA* AND oral corticosteroid® AND consider omalizumab for patients who have allergies**

Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.**

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**NHLBI EPR-3 -- pending future update**

- Listed for age 12 years and older at Step 5
- Guideline has not been updated since change in FDA labeling of omalizumab (age 6 years+) and release of newer biologics

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*Abbreviations: EIB, exercise-induced bronchoconstriction; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta2 agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2 agonist.

* If alternative treatment is used and response is inadequate, discontinue and use preferred treatment before stepping up.

* Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.

** Based on evidence for dust mites, animal dander, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens.

*** Children who administer immunotherapy or omalizumab should be prepared to treat anaphylaxis that may occur.

†† Dosing is less desirable because of limited studies as add-on therapy and the need to monitor liver function.

Before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton, may be considered, although this approach has not been studied in clinical trials.

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**NHLBI EPR-3 2004**
## GINA 2017 Guidelines

- Add-on omalizumab for age 6 years and older for severe allergic asthma
- Add-on mepolizumab for age 12 years and older for severe eosinophilic asthma

### Treatment Steps

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
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<tbody>
<tr>
<td>Low dose ICS</td>
<td>Consider low dose ICS</td>
<td>Leukotriene receptor antagonists (LTRA) Low dose theophylline*</td>
<td>Med/high dose ICS Low dose ICS+LTRA (or + theoph*)</td>
<td>Refer for add-on treatment e.g. Tiotropium,** Tiotropium, mepolizumab, omalizumab*</td>
</tr>
<tr>
<td>As-needed short-acting beta₂-agonist (SABA)</td>
<td>As-needed SABA or low dose ICS/formoterol#</td>
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*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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Pros and Cons of Biologics in Asthma

**ADVANTAGES**
- May reduce asthma health care resource costs
- Dosing frequency, may be suitable for poor adherence
- No issue with patient technique
- Can be systemic steroid sparing, helpful for patients with limited treatment options

**DISADVANTAGES**
- Cost of medication, payer coverage/formulary
- Requires clinic visit for dosing, requires injection
- Variable effect on asthma outcomes
- Challenge in identifying which patient would benefit most from given biologic (biomarker)
- Limited pediatric options

Mepolizumab: Clinical Questions

- Safety, efficacy, and dosing data in adolescents?
- Systemic glucocorticoid sparing effect?
- Biomarker(s) to help identify patients who may most benefit from mepolizumab?

- What if a patient was previously on omalizumab?
# Mepolizumab: Overview

| Mechanism of Action | Humanized mAb directed against IL-5 (IgG1 kappa)  
|                    | - Reduces # eosinophils in sputum and blood  
|                    | - Blocks cellular differentiation to eosinophil |
| FDA Approval       | Add-on treatment of patients with severe asthma, eosinophilic phenotype |
| Age Approval       | Includes adolescents; age 12 years and older |
| Dosing             | Standard dosing, 100 mg SubQ every 4 weeks |
| Considerations for Appropriate use | ✓ Response (and adherence to ICS regimen)  
|                    | ✓ Evidence of eosinophilic inflammation  
|                    | ✓ Varicella vaccination/immunity |
| Adverse Reactions  | Common: headache, local injection site reaction, back pain, fatigue  
<p>|                    | Severe: hypersensitivity reaction, immunogenicity (6%) |</p>
<table>
<thead>
<tr>
<th>STUDY &amp; DESIGN</th>
<th>POPULATION</th>
<th>MEDICATION(S)</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2012 Pavord ID et al. (DREAM study)</strong> Randomized, double-blind, placebo-controlled trial</td>
<td>N=621, patients ages 12-74 years (mean ~46-50 years) • At least 2 severe asthma exacerbations in the previous year • Signs of eosinophilic inflammation • Rapid deterioration of asthma control after reduction of 25% or less of regular inhaled or systemic steroid • Controller ICS equal to fluticasone propionate 880mcg/day + additional controller meds</td>
<td>Placebo Mepolizumab 75mg Mepolizumab 250mg Mepolizumab 750mg Every 4 weeks x 13 infusions</td>
<td>✓ Primary: 75 mg dose reduced # exacerbations by 48% (95% CI 31-61%; p&lt;0.0001) ✓ Secondary: ✓ Delayed time to next exacerbation ✓ No significant difference in FEV1, ACQ, AQLQ ✓ Correlation between baseline blood eosinophil count (300 cell/microliter or more) and rate of clinically significant exacerbations and # exacerbations in previous year</td>
</tr>
<tr>
<td><strong>2014 Ortega HG et al. (MESNA study)</strong> Randomized, double-blind, double-dummy study</td>
<td>N=576, patients ages 12-82 years (mean ~49-51 years) • Severe asthma • 2 or more exacerbations in previous year requiring systemic steroid • Controller equivalent to 880 mcg fluticasone propionate/day + additional controller • Eosinophil count of ≥ 150 cells/microliter at screening (or 300 in previous year)</td>
<td>Placebo Mepolizumab 75 mg IV Mepolizumab 100 mg SubQ Every 4 weeks x 32 weeks</td>
<td>✓ Primary: decreased exacerbation rate ✓ Secondary: ✓ Increased lung function (FEV1) Greater improvement with eosinophil ≥ 500 ✓ ACQ scores by week 4 (p&lt;0.001) ✓ Patients and clinicians global response to therapy ✓ Similar adverse event rates between groups</td>
</tr>
</tbody>
</table>
### Age Distribution Well-Represented?

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>DREAM (N=616)</th>
<th>MESNA (N=576)</th>
<th>TOTAL (N=1192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-17 years</td>
<td>1 (&lt;1%)</td>
<td>25 (4%)</td>
<td>26 (2%)</td>
</tr>
<tr>
<td>18-64 years</td>
<td>590 (96%)</td>
<td>471 (82%)</td>
<td>1061 (89%)</td>
</tr>
<tr>
<td>65 and older</td>
<td>25 (4%)</td>
<td>80 (14%)</td>
<td>105 (9%)</td>
</tr>
</tbody>
</table>

**Why approved...think about:**
- Pathophysiology of asthma
- PK of agents
- Surrogates
<table>
<thead>
<tr>
<th>Objectives</th>
<th><strong>Primary</strong>: percentage reduction in the daily oral glucocorticoid dose during weeks 20 and 24 vs. optimization phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomized, double-blind trial</td>
</tr>
</tbody>
</table>
| Population | N=135, severe eosinophilic asthma (age 16-74 y, mean ~50y)  
• 6 month history of maintenance with systemic glucocorticoid (prednisone 5-35mg/day or equivalent)  
• Eosinophil count of 150 cells/microliter at screening (or 300 in previous year)  
• Controller ICS equal to fluticasone propionate 880mcg/day + additional controller meds |
| Intervention | Mepolizumab 100 mg SubQ every 4 weeks vs. placebo x 20weeks |
| Results | • Mepolizumab patients had oral steroid dose reduction of 90-100% and 70-89%.  
• Median % reduction in oral steroid dose = 50% (p=0.007), significant reduction in exacerbation (1.44/year vs. 2.12/year, p=0.04), ACQ score reduction at week 2 through 24 (p=0.004)  
• No difference in change in lung function |
| Conclusion(s) | Mepolizumab has a significant glucocorticoid sparing effect, reduces exacerbations, improves asthma symptoms |
| Limitations | • Limited discussion of QOL scores, short duration of oral steroid withdrawal |
| Take Away Message(s) | Mepolizumab may help decrease need for oral steroids (steroid sparing effect), but limited pediatric specific data (age <16 years) |

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Primary: assess long term efficacy and safety of subcutaneous mepolizumab in severe eosinophilic asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Multicenter, open-label, Phase IIIb study (extension phases)</td>
</tr>
<tr>
<td>Population</td>
<td>Subjects from MESNA and SIRIUS studies (mean age 50y)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Mepolizumab 100 mg SubQ every 4 weeks x 48 weeks with study visits through week 52</td>
</tr>
</tbody>
</table>
| Results | • AE’s reported, similar between groups/placebo  
• No anaphylaxis reported with mepolizumab  
• Probability for exacerbation increased throughout treatment period (24.5% week 16; 49.1% week 52), similar to placebo (?)  
• ACQ and FEV1 maintained through open-label period  
• Lower oral steroid doses with mepolizumab than placebo period |
| Conclusion(s) | Mepolizumab has a favorable safety profile and durable/stable effect over time |
| Limitations | • Limited adolescents in sample  
• Carried limitations from other studies (SIRIUS) |
| Take Away Message(s) | • Available long term data, more applicable to adult patients  
• Longer treatment does not necessarily equal continued improvement (more stable effect of improvement) |
Case: Julie

Julie is a 10 year old female (42 kg) with severe persistent asthma. She has required frequent, long taper prednisone courses over the last 18 months. Her work up for ABPA, immune panel (IgA, IgG, IgM) were negative. She has been on omalizumab for the last 3 years, however has presented with worsening asthma over the last year. No smoking, 1 cat (allergic, but bathes cat regularly), received immunotherapy for multiple allergies. Her current regimen is as follows:

- Albuterol/ipratropium nebs 4x/day PRN
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- Epi Pen PRN anaphylaxis
- Montelukast 10mg po QHS
- Tiotropium 2.5 mcg inhaled daily
- Omalizumab 225mg subQ every 14 days
- Fexofenadine 180mg po daily

Can we start Mepolizamab? What Dose? Will it work?
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<tr>
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<tr>
<td><strong>Study Design and Population</strong></td>
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<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>MESNA</td>
</tr>
<tr>
<td>• Comparable exacerbation reduction +/- omalizumab history</td>
</tr>
<tr>
<td>• Greater improvement FEV1 and morning PEF without omalizumab history</td>
</tr>
<tr>
<td>SIRIUS</td>
</tr>
<tr>
<td>• Comparable OCS dose reduction and exacerbation rate based on +/- omalizumab history</td>
</tr>
<tr>
<td>• Higher proportion of patients with no decrease OCS, lack of asthma control, withdrawal higher with + omalizumab history</td>
</tr>
<tr>
<td><strong>Conclusion(s)</strong></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td>• Post hoc analyses - hypothesis generating study</td>
</tr>
<tr>
<td><strong>Take Away Message(s)</strong></td>
</tr>
</tbody>
</table>
### MEPOLIZUMAB
Outcomes Based on Current Evidence

<table>
<thead>
<tr>
<th>Age</th>
<th>Exacerbation Rate</th>
<th>FEV₁</th>
<th>ACT/ACQ</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 y</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>12-17 y</td>
<td>✔ (?)</td>
<td>✔ (?)</td>
<td>✔ (?)</td>
<td>✔ (?)</td>
</tr>
<tr>
<td>18 y +</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Rescue Therapy</th>
<th>ICS and/or systemic steroid dose</th>
<th>Time to 1&lt;sup&gt;st&lt;/sup&gt; Exacerbation</th>
<th>QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11 y</td>
<td>Not studied</td>
<td>Not studied</td>
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Advances in Special Populations- Scientific Breakthroughs – Game Changers

- Nusinersen- SMA
- Ivacaftor-CF
- Ivacaftor-Lumacaftor-CF
Spinal muscular atrophy...

Finally hope- Will this be the cure for my child?
What is SMA?

- Spinal Muscular Atrophy
  - A neuromuscular disease of infancy, childhood, and adulthood, that affects the survival and function of the anterior horn cells of the spinal cord.
  - It is characterized by progressive, predominantly proximal and symmetric muscle weakness
  - Sensation and cognition are preserved
  - Broad clinical heterogeneity across phenotypes
Epidemiology

- The spinal muscular atrophies are the second most common autosomal-recessive inherited disorders after cystic fibrosis. The acute infantile-onset SMA (type I) affects approximately 1 per 10,000 live births; the chronic forms (types II and III) affect 1 per 24,000 births.

- SMA types I and III each account for about one fourth of cases, whereas SMA type II is the largest group and accounts for one half of all cases.
Genetics

- SMN2 – production of alternative SMN protein
  - Differs from SMN1 by 11 nucleotides
  - C→T transition within exon 7 causing 80-90% of the transcripts to exclude exon 7
  - Unstable
  - Rapidly degrades
  - SMN2 copy number roughly proportional to clinical severity
- Limited amount of full length protein is insufficient to compensate for the loss of the SMN1 gene
## Phenotypic Variants

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Eponym</th>
<th>Age of onset</th>
<th>Highest Function</th>
<th>Natural Age of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 (profound)</td>
<td></td>
<td>Birth</td>
<td>Never sits</td>
<td>&lt;1 y</td>
</tr>
<tr>
<td>Type 1 (severe)</td>
<td>Werdnig-Hoffman</td>
<td>0 – 6 months</td>
<td>Never sits independently</td>
<td>&lt;2 y</td>
</tr>
<tr>
<td>Type 2 (intermediate)</td>
<td>Dubowitz</td>
<td>7-18 months</td>
<td>Never stands independently</td>
<td>&gt;2-7 y</td>
</tr>
<tr>
<td>Type 3 (mild)</td>
<td>Wohlfart-Kugelberg-Welander</td>
<td>&gt;18 months</td>
<td>Stands and walks</td>
<td>Adulthood</td>
</tr>
<tr>
<td>Type 4 (adult)</td>
<td></td>
<td>2\textsuperscript{nd} – 3\textsuperscript{rd} decade</td>
<td>Walks during adult years</td>
<td>Adulthood</td>
</tr>
</tbody>
</table>
nusinersen

- Modified antisense oligonucleotide, where the 2′- hydroxy groups of the ribofuranosyl rings are replaced with 2’-O-2-methoxyethyl groups and the phosphate linkages are replaced with phosphorothioate linkages.

- Nusinersen binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript.

- AKA ISIS 396443; BIIB058, ISIS SMNRx
Administration

- Nusinersen is administered intrathecally
- The recommended dosage is 12 mg (5 mL) per administration
- Initiate treatment with 4 loading doses; the first 3 loading doses at 14-day intervals; the 4th loading dose 30 days after the 3rd dose; a maintenance every 4 months thereafter
- Cost
  - $125,000 per injection
  - $750,000 for the first year and $375,000 per subsequent years
Open label Phase 1 Efficacy

- Hammersmith functional motor scale expanded (HFMSE) showed a significant increase with the 9 mg dose at 3 months post dose (mean increase of 3.1 points or 17.6% increase; p = 0.016), and 9-14 months post dose (5.8 points, P = 0.008)

- 7/10 (70%) participants exhibiting an increase of 3–7 points.
ENDEAR

- A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR)

- Primary Outcome Measures:
  - Percentage of participants who attained motor milestones as assessed by Section 2 of Hammersmith Infant Neurological Examination (HINE) [Time Frame: Up to Day 402]
  - Time to death or respiratory intervention [Time Frame: Up to Day 402]

- Secondary Outcome Measures:
  - Percentage of participants who attained Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) [Time Frame: Up to Day 402]
  - CHOP-INTEND tests includes 16 items structured to move from easiest to hardest with the grading including gravity eliminated (lower scores) to antigravity movements (higher scores). All item scores range from 0-4.

Finkel et al Lancet. 2016 Dec 17;388(10063):3017-3026
A phase 2 open label study in infants, assessment of safety, tolerability, pharmaceuticals and clinical efficacy (ENDEAR)

- 20 participants ages 3 weeks-6 months were between May 2013 and July 2014 with an interim analysis completed on January 26, 2016

- Patient’s received multiple intrathecal doses 6 mg (4,1) and 12 mg (16) on days 1, 15, 85, 253 and then every 4 months

- Clinical efficacy assessments including change from baseline of 2 assessments of motor Compound motor action potentials (CMAP) were measured

Finkel et al Lancet. 2016 Dec 17;388(10063):3017-3026
Endear Results

Baseline disease characteristics were similar in the nusinersen-treated patients and sham-control patients except that nusinersen-treated patients at baseline had a higher percentage of paradoxical breathing (89% vs 66%), respiratory symptoms (35% vs 22%), swallowing or feeding difficulties (51% vs 29%) and requirement for respiratory support (26% vs 15%).

- 22 percent of infants in the nusinersen group achieved full head control, 10 percent could roll by themselves, 8 percent could sit independently, and one infant could stand with minimal to moderate assistance.

- Forty-nine of the 80 children in the nusinersen group (61 percent) were alive without needing permanent ventilation, compared with 13 of 41 (32 percent) in the control group (p=.005).

Finkel et al Lancet. 2016 Dec 17;388(10063):3017-3026
Adverse Effects

- The most common adverse reactions that occurred in the controlled study in at least 20% of nusinersen-treated patients and occurred at least 5% more frequently than in control patients were
  - upper respiratory infection (39% vs 34%),
  - lower respiratory infection (43% vs 29)
  - constipation (30% vs 22%).
- Serious adverse reactions of atelectasis were more frequent in nusinersen-treated patients (14%) than in control patients (5%).
- In the open-label studies, the most common adverse events in later onset patients were headache (50%), back pain (41%) and post lumbar puncture syndrome (41%).
Pharmacokinetics

- Absorption -- Intrathecal injection of nusinersen into the cerebrospinal fluid (CSF) allows nusinersen to be distributed from the CSF to the target central nervous system (CNS) tissues.
  - Following intrathecal administration, trough plasma concentrations of nusinersen were relatively low, compared to the trough CSF concentration.
  - Median plasma Tmax values ranged from 1.7 to 6.0 hours. Mean plasma Cmax and AUC values increased approximately dose-proportionally up to a dose of 12 mg.

- Distribution Autopsy data from patients (n=3) showed that nusinersen administered intrathecally was distributed within the CNS and peripheral tissues, such as skeletal muscle, liver, and kidney.

- Elimination Metabolism -- Nusinersen is metabolized via exonuclease (3′- and 5′)-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes.

- Excretion The mean terminal elimination half-life is estimated to be 135 to 177 days in CSF, and 63 to 87 days in plasma. The primary route of elimination is likely by urinary excretion for nusinersen and its chain-shortened metabolites. At 24 hours, only 0.5% of the administered dose was recovered in the urine.
Anti-drug Antibodies

- The immunogenic response to nusinersen was determined in 126 patients with baseline and postbaseline plasma samples evaluated for anti-drug antibodies (ADAs).
  - Five (4%) patients developed treatment-emergent ADAs, of which 3 were transient and 2 were considered to be persistent.
  - There are insufficient data to evaluate an effect of ADAs on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.
Monitoring

- Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose of nusinersen. For urinary protein concentration >0.2 g/L, consider repeat testing and further evaluation.
  - Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.

- Platelet count and coagulation testing at baseline and prior to each administration of nusinersen

- Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications.
CASE: JJ – A Child in Need

FDA label for ivacaftor tablets:

“Safety and efficacy have not been demonstrated in patients under the age of 6 years”

AND

There is currently NO dosing, safety, and efficacy data in his age group

AND

It is known insurance will NOT pay for this medication at this time based on age (cost: $300K/year)…
Necessity of Medication

- Serious or life threatening condition
- Long term or short term use
- Known toxicity of the drug
- No other alternatives
- Dosing of medication-mg/kg or mg/m²
CFTR Modulators

The attack on the basic defect of CF
The beginning of a cure
CFTR Modulators

- Understanding the mutation and the mechanism of the defect guides therapy development

- First treatment available to target the underlying cause of cystic fibrosis
• Class Mutation of CF

Adapted from CFTR Modulators http://www.umd.be/CFTR/W_CFTR/gene.html
# CFTR Modulators

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Form</th>
<th>Dose</th>
<th>Administration Instructions</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivacaftor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygous for G551D</td>
<td>50 mg oral granule</td>
<td>2 to 5 years and &lt; 14 kg: 50 mg</td>
<td>Every 12 hours with a fat containing food</td>
<td>CYP3A substrate—dose adjustments may be warranted!</td>
</tr>
<tr>
<td>G1224E, G1349D, G178R,</td>
<td>75 mg oral granule</td>
<td>2 to 5 years and ≥ 14 kg: 75 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G551S, S1251N, S1255P,</td>
<td>150 mg tablet</td>
<td>6 years and older: 150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S549N, S549R, R117H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lumacaftor/Ivacaftor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous for F508del</td>
<td>100 mg/125 mg tablet</td>
<td>6 to 11 years of age: 200 mg/250 mg</td>
<td>Every 12 hours with a fat containing food</td>
<td>CYP3A substrate—dose adjustments may be warranted!</td>
</tr>
<tr>
<td></td>
<td>200 mg/125 mg tablet</td>
<td>12 years and older: 400 mg/250 mg</td>
<td></td>
<td>Lumacaftor is an inducer</td>
</tr>
</tbody>
</table>
Ivacaftor

- Administration Instructions:
  - Dosed every 12 hours with a fatty meal/snack
    - Oral granules are mixed in with 5 mL of soft food or liquid

- Side effects:
  - Headache
  - Rash
  - Abdominal pain
  - Gastrointestinal upset
  - Dizziness
Ivacaftor: Monitoring

- Liver function
  - Baseline
  - Every 3 months for the first year of therapy
  - Annually thereafter

- Eye exam
  - Baseline
  - Follow up
## Ivacaftor: Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential Effect on Drug Exposure</th>
<th>Ivacaftor Dosing* and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong CYP3A Inhibitor</strong></td>
<td>Clarithromycin</td>
<td>Increased ivacaftor exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg twice weekly</td>
</tr>
<tr>
<td><strong>Strong CYP3A Inhibitor</strong></td>
<td>Itraconazole</td>
<td>Increased ivacaftor exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg twice weekly</td>
</tr>
<tr>
<td><strong>Strong CYP3A Inhibitor</strong></td>
<td>Voriconazole</td>
<td>Increased ivacaftor exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg twice weekly</td>
</tr>
<tr>
<td><strong>Strong CYP3A Inducer</strong></td>
<td>Rifampin</td>
<td>Decreased ivacaftor exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-administration is NOT recommended</td>
</tr>
</tbody>
</table>

* Dosing for the 150 mg tablets

Note: NOT an all inclusive list; please see package insert for complete list of drug interactions
Ivacaftor - Results

- Absolute change in Percent predicted FEV₁ - 10.6%

- 55 % less like to have a pulmonary exacerbation

# CFTR Modulators

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<tbody>
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<td>50 mg oral granule</td>
<td>2 to 5 years and &lt; 14 kg: 50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 mg oral granule</td>
<td>2 to 5 years and ≥ 14 kg: 75 mg</td>
<td></td>
<td>CYP3A substrate—dose adjustments may be warranted!</td>
</tr>
<tr>
<td></td>
<td>150 mg tablet</td>
<td>6 years and older: 150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumacaftor/Ivacaftor</td>
<td>100 mg/125 mg tablet</td>
<td>6 to 11 years of age: 200 mg/250 mg</td>
<td>Every 12 hours with a fat containing food</td>
<td>CYP3A substrate—dose adjustments may be warranted!</td>
</tr>
<tr>
<td></td>
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<td>12 years and older: 400 mg/250 mg</td>
<td>Every 12 hours with a fat containing food</td>
<td>Lumacaftor is an inducer</td>
</tr>
</tbody>
</table>

**Indication:**

- **Lumacaftor/Ivacaftor:** Homozygous for F508del
Lumacaftor/Ivacaftor

- Administration Instructions:
  - Dosed every 12 hours with a fatty meal/snack

- Side effects:
  - Headache
  - Rash
  - Gastrointestinal upset
  - Dizziness
  - Shortness of breath/chest tightness
Lumacaftor/Ivacaftor: Monitoring

- Liver function
  - Baseline
  - Every 3 months for the first year of therapy
  - Annually thereafter

- Eye exam
  - Baseline
  - Follow up
## Lumacaftor/Ivacaftor: Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential Effect on Drug Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Contraceptives</td>
<td>Decreased hormonal contraceptive exposure</td>
</tr>
<tr>
<td>Proton Pump Inhibitors (omeprazole, esomeprazole)</td>
<td>Decreased proton pump inhibitor exposure</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Co-administration is <strong>NOT</strong> recommended</td>
</tr>
</tbody>
</table>

Note: NOT an all inclusive list; please see package insert for complete list of drug interactions
Ivacaftor-Lumacaftor Results

- Absolute Increase in FEV1- 2.6-4%
- Reduction in Pulmonary exacerbation 30-39%

Summary: What do I need to have access to for the Essential Part of Practice for Children

- At least one Tertiary Pediatric Reference
- With at least every other year update
- On line or hardback - with references
- Pediatric Dosage Handbook - Takeトomo et al. Lexi-Comp
- Pediatric Drug labeling on FDA website
Assessment Question 1

Key considerations that are important in determining dose and monitoring parameters for off label use of drugs in pediatrics include
A. Pediatric medication dosing resources
B. Adult dose of the drug
C. Formulary issue
D. Cost
Assessment Question 2

FDA labeling of drug use is based on:

A. Data from clinical trials submitted to FDA for review
B. Expert consensus panel recommendations
C. National guidelines
D. Adverse Reaction Reporting
Assessment Question 3

Which of the following conditions would often require the use of off label use of approved medications?

A. Otitis Media
B. Cystic Fibrosis
C. Spinal Muscular atrophy
D. Vaccine administration
Assessment Question 4

Mary S is a 21 year old who is about to start Ivacaftor-lumacaftor therapy. She is on pancreatic enzymes, supplemental vitamins, dornase alfa, albuterol and oral contraceptive to prevent pregnancy. What important drug drug interaction should be discussed with the patient?

A. This new drug may require you to take more pancreatic enzymes for digestion
B. This drug may alter the effectiveness of your oral contraceptive
C. This new drug will require you to wait 2 hours to take your dornase alfa
D. This new drug will require you to double your vitamin requirements