Treatment and Prevention of Respiratory Syncytial Virus Disease
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My institution has received support for research studies over the past 24 months from Novartis and Chimerix.

I have served as a consultant for GSK.
Potential populations who may need treatment for RSV

- Healthy Children
  - Infants < 6 months: Highest risk of hospitalization
  - Children < 2-3 years: Highest risk of disease
- Underlying lung disease
  - Preterm infants
  - All ages with chronic lung disease – cystic fibrosis, asthma
  - Older patients with chronic obstructive pulmonary disease (COPD)
- Elderly
- Immunocompromised patients
  - Children with congenital or acquired immunodeficiencies
  - Hematopoietic stem cell transplant (HSCT), lung and heart transplant or induction chemotherapy
PROPHYLAXIS/TREATMENT OF RSV IN THE YOUNG CHILD: KEY ISSUES

- Variable severity of infection
- Early diagnosis difficult, due to similar presentations with many viral infections
- Rapid onset of disease
- Requires drug that is easy to administer to young infants
- Studies must be done in children….

BUT:
- RSV is a common disease that occurs every year
- Quantitative viral load measurement and disease severity relatively straightforward
TREATMENT OF RSV IN THE ELDERLY OR IMMUNOCOMPROMISED PATIENT: KEY PROBLEMS

- Higher rates of severe disease in the immunocompromised and elderly compared to children
  - rates of mortality in HSCT remain ~20% during first months after transplant
  - Elderly complication rates similar to influenza
- May be difficult/expensive to diagnose early
- Both elderly and IC have multiple underlying medical conditions
- For Immunocompromised patients;
  - Placebo control not acceptable in some immunocompromised patients
  - Smaller studies may give answers as to efficacy
OUTLINE: PREVENTION AND TREATMENT

- Prevention
  - RSVIG: Respigam
  - Monoclonal Ab: Palivizumab

- Treatment
  - Ribavirin
  - Antibodies
  - Fusion Inhibitors
  - siRNA
  - Others
PREVENTION OF SPREAD OF RSV AND OTHER RESPIRATORY VIRUSES

- Isolate based on symptoms, not diagnosis
- Hand washing
- Hand washing
- Hand washing
- Consider gown and glove in certain conditions…
Correlation between RSV Antibody Concentration at Birth and Age at Time of Proven RSV Infection*

Passive Immunization: RSV-specific Antibody

- RSVIG (Respigam\textsuperscript{R}) - Hyperimmune RSV-IVIG product, licensed 1996 by MedImmune, Inc.

- Humanized monoclonal F-specific antibody, Palivizumab (Synagis\textsuperscript{R}) – licensed 1998; currently widely used for RSV prophylaxis in preterm infants

- R1-001 (ADMA, Inc) – Hyperimmune RSVIG under clinical investigation in 2010-2011

- Motovizumab (Numax\textsuperscript{TM}) – higher potency F-specific monoclonal antibody; not licensed in 2010 after FDA review of clinical studies in at-risk infants
Palivizumab: Humanized RSV Monoclonal Antibody

- Palivizumab (Synagis®; Medimmune, Inc., Gaithersburg, MD)
- Administered IM at a dose of 15 mg/kg monthly
- Approved for use in infants and children <2 years of age with chronic lung disease and babies born at <35 weeks gestation
- Cost ~$2800/100 mg vial at University of Washington in 2012 (cost for 3 kg infant: 5 doses = ~$14,000)
Palivizumab for RSV Prophylaxis in Children with Congenital Heart Disease

Palivizumab vs. placebo in children with CHD: (N=1287).

- Placebo (n=648)
- Palivizumab

RSV Hospitalization Rate (%) for Infants:
- Placebo: 9.7%
- Palivizumab: 5.3%

Pediatric Cardiology 2002; 23(6) 664
<table>
<thead>
<tr>
<th></th>
<th>2000/01 * Survey (n = 2,049)</th>
<th>1996/97 IMpact** (n = 1,002)</th>
<th>Placebo (n = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2.9%</td>
<td>4.8%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Premature</td>
<td>3.1%</td>
<td>1.8%</td>
<td>8.1%</td>
</tr>
<tr>
<td>All &lt;32 weeks GA</td>
<td>4.5%</td>
<td>5.8%</td>
<td>11.0%</td>
</tr>
<tr>
<td>All 32 - 35 weeks</td>
<td>1.6%</td>
<td>2.0%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Patients with CLD</td>
<td>5.8%</td>
<td>7.9%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

*Hudak M. Data on file, MedImmune, Inc.

1. Infants and children with CLD who have received medical intervention within six months preceding onset of RSV season

2. Infants born 28-32 weeks gestation, without CLD, < six months old at onset of RSV season

3. Infants born at ≤ 28 weeks gestation, without CLD, <12 months old at onset of RSV season.

4. Infants without CLD born at 32-35 weeks who are < six months old at onset of RSV season and who have one or more risk factors for severe RSV infection
1. Infants and children with CLD who have received medical therapy within 6 months of season, < 24 months of age, maximum 5 doses

2. Infants born < 32 weeks, maximum 5 doses:
   a. 28 weeks gestation, if < 12 months of age
   b. 29-32 weeks gestation, if 6-12 months of age

3. Infants born at 32-<35 weeks gestation, maximum 5 doses
   a. <3 months of age at start of RSV season
   b. Born during RSV season

4. Infants with congenital heart disease that is hemodynamically significant (cyanotic or acyanotic)

5. Increased risk of exposure – max 3 doses until 3 months old
   a. Attends childcare
   b. Sibling < 5 years of age

http://redbookarchive.aappublications.org/cgi/content/full/2009/1/3.110
THERAPEUTIC OPTIONS FOR THE TREATMENT OF RSV PNEUMONIA TODAY

- Polyclonal high-titered RSV-IG: Not effective
- Monoclonal Anti-Fusion Ab:
  - Palivizumab - Not effective in children
  - ?Motavizumab – not available; not effective treatment-poster 118
- Ribavirin:
  - aerosolized
  - intravenous
  - IV + aerosolized
- Combination ribavirin therapy – currently most “popular”
  - Antiviral + immunoglobulin or monoclonal Ab
- New antivirals – not available
RSV RISK FACTORS IN IMMUNOCOMPROMISED PATIENTS

- Lymphocyte count
- Age
- Season of year
- Status of malignancy - relapse
- Graft versus host disease
- Transplant patients – especially bone marrow transplant patients
- Time since transplant – especially
- Immunosuppression
- Pneumonia/Respiratory failure

RSV Giant Cell Pneumonia in an Adult BMT Recipient
RIBAVIRIN

- Nucleoside analogue of guanosine
- Main mechanisms include alteration of cellular nucleotide pools and inhibition of viral mRNA formation, and well as interference with capping of mRNA.
- Multiple mechanisms of action postulated (possibly accounting for lack of development of clinical resistance)
- Licensed for aerosol treatment of RSV in children and orally, in combination with IFN-alpha, for treatment of hepatitis C
Randomized Controlled Multicenter Trial of Aerosolized Ribavirin for RSV Upper Respiratory Tract in Stem Cell Transplant Recipients (CASG)*

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Ribavirin</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Clinical pneumonia</td>
<td>1/9</td>
<td>2/5</td>
</tr>
<tr>
<td>RSV pneumonia</td>
<td>0/9</td>
<td>2/5</td>
</tr>
<tr>
<td>Maximum laboratory abnormalities (&gt;= grade 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>While blood count</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Platelets</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LDH</td>
<td>2</td>
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<tr>
<td>AST</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation of study drug due to toxicity</td>
<td>0/9</td>
<td>0/5</td>
</tr>
<tr>
<td>Survival at 28 days after Randomization</td>
<td>9/9</td>
<td>5/5</td>
</tr>
</tbody>
</table>

Bottom Line

* Boeckh et al, CID 2007
Aerosolized Ribavirin Improves Outcome in 118 Hematopoietic Cell TX Recipients with RSV Lower Respiratory Tract Disease (RSV meeting, Santa Fe, Waghmare, et al)

### Multivariable Analyses - Survival at Day 90

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HR 95% CI</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Ribavirin:</strong></td>
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<td></td>
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<tr>
<td>Systemic vs. None</td>
<td>0.71 (0.28-1.76)</td>
<td>0.454</td>
</tr>
<tr>
<td>Aerosolized vs. None</td>
<td>0.33 (0.17-0.64)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Oxygen at Dx:</strong></td>
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<tr>
<td>&gt;2L/Ventilator vs 0&lt;-2L</td>
<td>2.73 (1.58-4.71)</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Cell source:</strong></td>
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<tr>
<td>BM/Cord vs PBMC</td>
<td>2.44 (1.28-4.64)</td>
<td>0.006</td>
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<tr>
<td><strong>Steroid pre Dx:</strong></td>
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<tr>
<td>&gt; vs &lt;= 2 mg/kg</td>
<td>2.46 (1.24-4.92)</td>
<td>0.010</td>
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</table>

Overall HSCT Survival at Day 90

Log-rank test, p<0.001
Palivizumab in Addition to Ribavirin Not Beneficial for the Treatment of RSV LRTI in HSCT Recipients, FHCRC *

A. Probability of Overall Survival

B. Probability of Death Due to Respiratory Failure

*Seo et al— BBMT, in press, 2013
## Past “New” Antivirals for RSV
(adapted from Costello et al 2012)

<table>
<thead>
<tr>
<th>TARGET</th>
<th>NAME</th>
<th>MANUFACTURER</th>
<th>Human efficacy trials?</th>
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<tbody>
<tr>
<td>F target-Y198</td>
<td>BMS-433771</td>
<td>BMS</td>
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<tr>
<td></td>
<td>VP-14637</td>
<td>Viropharma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMC353121</td>
<td>Janssen, Tibotec</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI3/C15</td>
<td>Lundin et al</td>
<td></td>
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<tr>
<td>F drugs-other</td>
<td>RFI-641</td>
<td>Wyeth</td>
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<tr>
<td></td>
<td>BTA-9981</td>
<td>Biota, Astra Zeneca</td>
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<tr>
<td>F-peptides</td>
<td>T-67, T-118</td>
<td>Tibotech</td>
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<tr>
<td>G target</td>
<td>MBX-300</td>
<td>Microbiotix</td>
<td></td>
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<tr>
<td>N target</td>
<td>RSV-604T</td>
<td>Arrow/Novartis</td>
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<tr>
<td>siRNA</td>
<td>ALN-RSV01,02</td>
<td>Alnylam</td>
<td>YES- lung tx</td>
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</table>
siRNA

- Small-interfering RNA’s (si-RNA): short lengths of double-stranded RNA that regulate gene expression through posttranscriptional gene silencing mechanisms

- RSV-specific siRNAs (ALN-RSV01; Alnylam Pharmaceuticals, Cambridge, MA):
  - Targets two nucleocapsid protein genes, the P protein and N protein genes and nonstructural protein gene, NS1
  - ALN-RSV01 targets the synthesis of the viral nucleocapsid (N) protein.
  - Only siRNA therapy undergoing clinical trials, with phase II trials completed:
    - Associated with reduction of RSV infection among healthy adult volunteers (deVincenzo et al Antiviral Ther 2008)
Fusion inhibitors: Most Common Antiviral Target

- Importance of fusion in RSV disease pathogenesis well studied
- Conservation of F protein and function among RSV strains well documented
- Impact of monoclonal Ab on prevention of RSV disease clinically documented

Figure:
mdtx.com/pipeline/proprietary-products/mdt-637/
EXAMPLE:  Antiviral Drugs under investigation


- Gilead Sciences-5806: Phase 2, placebo-controlled study listed in Clinicaltrials.gov, using healthy volunteers infected with RSV starting in Nov., 2012. Drug given as oral solution in apple juice once daily for 4 days.
Other Approaches to RSV Antivirals

- MBX-300 (Microbiotix, Worcester, MA, USA): Targets the **RSV G protein** as an attachment inhibitor.
  - Safety and antiviral efficacy in animal models demonstrated

- YM-53403 (Yamanouchi Pharmaceutical, Tokyo, Japan): Targets the **RSV L (polymerase) protein**
  - Shown in *in vitro* studies to target the RSV nucleocapsid protein to prevent viral replication.

- RSV604 (Arrow Therapeutics/AstraZeneca Corp., London, UK): Targets the **RSV polymerase**
  - Oral benzodiazepine broadly protective against both A and B subgroups
  - Appears to inhibit viral replication after mucosal entry in in-vitro studies
# UPDATES ON RSV THERAPEUTICS – 2012 RSV Meeting

<table>
<thead>
<tr>
<th>CLASS</th>
<th>NAME</th>
<th>MODEL</th>
<th>Company/Institution</th>
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<tbody>
<tr>
<td>Antibodies</td>
<td>Motavizumab</td>
<td>Children</td>
<td>MedImmune</td>
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<tr>
<td></td>
<td>ALX-0171 “Nanobody”-F</td>
<td>Cotton rat</td>
<td>Ablynx</td>
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<td>Nicotiane-derived anti RSV F-Ab</td>
<td>Cotton Rat</td>
<td>Mapp</td>
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<td>Fusion Inhibitors</td>
<td>R170591, TMC353121</td>
<td>In vitro</td>
<td>Ohio State</td>
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<td></td>
<td>MDT637</td>
<td>Adult/safety</td>
<td>MicroDose Therapeutix</td>
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<td>TMC353121</td>
<td>In vitro, vervet monkey</td>
<td>U. Leuven/Janssen</td>
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<td>siRNA</td>
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<td>Lung Tx</td>
<td>Alnylam</td>
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<td>Receptor Inhibitor</td>
<td>Anti-Neucleolin, AS 1411</td>
<td>114</td>
<td>In vitro, mice</td>
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<tr>
<td>MISC.</td>
<td>Pulmonary Surfactant POPG</td>
<td>112</td>
<td>In vitro, mice</td>
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<tr>
<td></td>
<td>L-polymerase Inhibitor AZ27</td>
<td>113</td>
<td>In vitro</td>
</tr>
<tr>
<td></td>
<td>Nuceloside Analogues to inhibit RSV</td>
<td>119</td>
<td>In vitro</td>
</tr>
<tr>
<td></td>
<td>polymerase</td>
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RSV antiviral therapy remains an important unmet medical need.

Even if successful vaccines were to become available, there will still be a need.

Advances in diagnostics, improved molecular understanding of RSV, and experience with other antivirals improve the outlook for RSV antiviral.

Potential therapies may differ for different populations:
  - Oral therapy – for children, elderly?
  - Aerosolized, IV for immunocompromised?

Road to licensure will not be simple - but it is possible.
Thanks-

• Questions?