Pharmacotherapy for RSV in the Immunocompromised: When to Pull the Treatment Trigger

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Pharmacy Grand Rounds
April 19th, 2016
Objectives

• Identify risk factors for developing respiratory syncytial virus infection

• Review the current literature for the role of ribavirin in respiratory syncytial virus infections

• Describe a treatment strategy for treating an immunocompromised patient with a respiratory syncytial virus upper respiratory tract infection or lower respiratory tract infection
Respiratory Syncytial Virus (RSV)

- Paramyxoviridae family
- Subtypes A & B
- Seasonal: November - May

Dawson-Caswell and Muncie Jr. Am Fam Physician 2011; 83(2), 141-146.
Pathophysiology

- Replication in nasopharynx
  - Upper respiratory tract infection (URTI)
    - Self-limiting in immunocompetent patients
    - Flu-like symptoms
  - Lower respiratory tract infection (LRTI)
    - Edema, ↑ Mucus production, Necrosis, Infiltrate on X-ray
    - ~11% need ventilator support

Dawson-Caswell and Muncie Jr. Am Fam Physician 2011; 83(2), 141-146.
Image from http://afairgo.net/upper-respiratory-tract-infection/
Clinical Impact

- Poor prognosis if progression to LRTI
  - 38% in leukemia and HSCT patients
- High mortality rate
  - HSCT 32%
  - Lung transplant 10-20%

- Bronchiolitis Obliterans
  - Fibrogenic deposition in bronchioles and small airways
  - BOS: ≥20% decline in FEV₁ from baseline
  - RSV associated with BOS in lung transplant patients
Diagnosis

• Viral isolation
  • Historically considered “gold standard”
  • Time consuming

• Direct antigen testing
  • Results within 48 hours

• PCR assays
  • High sensitivity and specificity
  • Same day results
  • Specimen
    • Swab: throat or nasal
    • Bronchial or nasopharyngeal washings, BAL


BAL: Bronchoalveolar lavage
PCR: Polymerase chain reaction
## Risk Factors

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Progression to LRTI (HSCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;75 years of age</td>
<td>GVHD</td>
</tr>
<tr>
<td>Radiographic pneumonia</td>
<td>Pre-engraftment or &lt;1 month from transplant</td>
</tr>
<tr>
<td>Elevated WBC</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Bacterial superinfection</td>
<td>Transplant from mismatch, unrelated donor</td>
</tr>
<tr>
<td>Elevated urea level</td>
<td>Neutropenia</td>
</tr>
</tbody>
</table>

GVHD: Graft versus host disease  
WBC: White blood cell count  

Immunodeficiency Scoring Index-RSV

• ISI-RSV: stratify HSCT patients

• Based on results from single center study
  • RSV URTI (N=237)

• Treatment regimen
  • URTI – Aerosolized ribavirin
  • LRTI – above ± IVIG ± palivizumab

• Categories (Max 12)
  • Low: 0-2
  • Moderate: 3-6
  • High: 7-12

*Recent: Within past 30 days
ANC: Absolute neutrophil count
ALC: Absolute lymphocyte count
allo-HSCT: allogeneic hematopoietic stem cell transplant

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt; 500/µL</td>
<td>3</td>
</tr>
<tr>
<td>ALC &lt; 200/µL</td>
<td>3</td>
</tr>
<tr>
<td>Age ≥ 40 years</td>
<td>2</td>
</tr>
<tr>
<td>Myeloablative conditioning regimen</td>
<td>1</td>
</tr>
<tr>
<td>GVHD</td>
<td>1</td>
</tr>
<tr>
<td>*Recent corticosteroids</td>
<td>1</td>
</tr>
<tr>
<td>*Recent or pre-engraftment allo-HSCT</td>
<td>1</td>
</tr>
</tbody>
</table>

## ISI-RSV Results

<table>
<thead>
<tr>
<th>Group</th>
<th>LRTI Progression</th>
<th>RSV Associated Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARR, %</td>
<td>NNT</td>
</tr>
<tr>
<td>All Patients</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Low (0-2)</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Moderate (3-6)</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>High (7-12)</td>
<td>85</td>
<td>2</td>
</tr>
</tbody>
</table>

ARR: Absolute risk reduction  
NNT: Number needed to treat

ISI-RSV Validation at Mayo Clinic

- RSV-associated mortality (p<0.01)
- Risk LRTI progression was not significant (p=0.106)
- Need larger, multi-centered studies

Damlaj, et al. Transpl Infect Dis 2016; epub ahead of print
Question # 1

• 51 year old male admitted to ICU with respiratory distress
• PMH: multiple myeloma, allo-HSCT 18 months ago, history of GVHD 2 months ago, resumed chemotherapy last month due to progression
• Pertinent meds: Prednisone 30 mg MTuThF
• PCR from nasal swab: Influenza - , RSV +
• Labs: ALC – 1840, ANC – 3730
Question # 1

Which of the following are risk factors for RSV progression to LRTI?

A. Increased age (≥ 40 years)
B. allo-HSCT >30 days ago
C. Steroid use in the past 30 days
D. Both A and C
Pharmacotherapy

Antiviral Therapy (Ribavirin)

- Aerosolized
- Oral
- Intravenous (no trials with monotherapy)

Adjunctive Therapy

- Intravenous Immunoglobulin (IVIG)
- Palivizumab
- Corticosteroids
**Ribavirin**

- Purine analog – inhibits replication of RNA and DNA viruses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inhaled</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>6 gm over 18 hr</td>
<td>10-30 mg/kg/day divided into every 8-12 hours</td>
</tr>
<tr>
<td></td>
<td>2 gm (over 2 hr) every 8 hr</td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5-7 days</td>
<td>5-10 days or until symptom resolution</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Bronchospasm, psychologic distress, nausea, conjunctivitis</td>
<td>14% hemolysis, LFTs, lactic acidosis, declining renal function</td>
</tr>
<tr>
<td><strong>Pros</strong></td>
<td>Can give when NPO</td>
<td>↓$$$$</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Teratogenic \↑$$$$ Precipitation in vent tubing Scavenging tent</td>
<td>Teratogenic Variable absorption</td>
</tr>
</tbody>
</table>

Goss and Bryson. *Ann Pharmacother* 2015; 49(10), 1125-1135.
Shah et al. 2011

Data Summary

Mortality

Progression to LRTI

AR: aerosolized ribavirin, IR: intravenous ribavirin, OR: Oral Ribavirin

Aerosolized Ribavirin – Shah et al. 2013

- Performed due to limitations in previous review
- Retrospective review from 1996-2009
  - N=280, RSV confirmed infections in allo-HSCT
- Aerosolized ribavirin vs no antiviral therapy
- Endpoints:
  - All-cause mortality
  - LRTI progression

Aerosolized Ribavirin – Shah et al. 2013

- Antiviral therapy vs no antiviral therapy
  - Progression from URTI (n=237) to LRTI $p<0.001$ with log-rank test

Aerosolized Ribavirin - Summary

- Most evidence to support association with decreased LRTI progression and mortality
  - Effect of drug delivery or drug itself?

- Barriers to practice implementation

  - Cost
    - Increased from $6,105/day (2013) to $29,953/day (2015)
  - Administration

Oral Ribavirin in Immunocompromised Patients

- Retrospective review of PCR confirmed infections
- > 75 kg: 800 mg ribavirin PO BID
- < 75 kg: 600 mg ribavirin PO BID
- Elderly or renal insufficiency: option for 400 mg ribavirin PO BID
- Duration of therapy and use of IVIG
  - Physician discretion

### Immunocompromised State Definitions

2011-2013: 96 identified, 34 met criteria

<table>
<thead>
<tr>
<th>Moderately Immunocompromised (n=20)</th>
<th>Severely Immunocompromised (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid organ transplant &gt; 1 year from transplant</td>
<td>Allo-HSCT ≤6 months from transplant</td>
</tr>
<tr>
<td>Allo-HSCT &gt;6 months or with GVHD &lt; grade 2 or Autologous HSCT</td>
<td>Allo-HSCT w/GVHD ≥ grade 2</td>
</tr>
<tr>
<td>Hematologic malignancy receiving chemotherapy</td>
<td>Lung Transplant &lt; 1 year</td>
</tr>
<tr>
<td>Other immunosuppression (endogenous or exogenous)</td>
<td>Lung Transplant &gt; 1 year with augmented immunosuppression</td>
</tr>
</tbody>
</table>

Oral Ribavirin - Results

• Mean initial duration of therapy = 10 days
• 19 received IVIG (2.7 doses)
• Mortality = 2/34 (5.8%)
  • None attributed to RSV
• 2 adverse effects (hemolytic anemia, lactic acidosis)
• Overall: safe and potential treatment modality
  • Limitations
    • Single center
    • No comparative arm
    • Use of IVIG in select patients
    • Mostly HSCT patients

Is there direct evidence comparing oral and inhaled ribavirin?
### Oral Versus Inhaled Ribavirin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Hospital LOS (p-value)</th>
<th>Mortality</th>
<th>BOS Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 patients received OR</td>
<td>Oral: 11±15.1 days</td>
<td>30-day mortality 0 and no difference at end of follow-up (p=0.42), deaths in both groups at end of follow up not reported</td>
<td>Oral: 0</td>
</tr>
<tr>
<td>(400 mg TID 5-10 days)</td>
<td>Aerosolized: 5±1.5 days (p=0.37)</td>
<td></td>
<td>Aerosolized: 2 (p&gt;0.99)</td>
</tr>
<tr>
<td>15 patients received AR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6 gm over 12 hours for 3-5 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Lung/Heart-Lung transplant
- Retrospective comparative study
- Bias to treatment allocation, median follow up 1.5 years for OR and 2.9 years for AR

Li, et al. *J Heart Lung Transplant* 2012; 31(8), 839-844.
Oral Ribavirin Summary

• Reasonable to use oral over aerosolized
• Prospective and comparative trials needed
• Current studies
  • Ongoing trial comparing OR vs AR
  • Anticipated results 12/2016

IVIG in RSV

• Mechanism
  • Prevent replication in lungs
  • Reduce viral load in tissues
  • Promote antibody response

• Gap in literature, no direct comparator trials
  • Commonly a part of other regimens for immunocompromised adults

• Not unreasonable for adjunctive therapy
  • 500 mg/kg every other day

Palivizumab in RSV

- Prevention of LRTI in pediatric patients at high risk
  - MOA: Bind to RSV fusion protein
  - 15 mg/kg body weight per month
  - Combination therapy in retrospective trials/case series
- Retrospective, single centered, allo-HSCT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Palivizumab (n=19)</th>
<th>Control (n=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRTI Progression</td>
<td>5/9</td>
<td>5/9</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Mortality (1 year)</td>
<td>7/19</td>
<td>5/19</td>
<td>0.71</td>
</tr>
</tbody>
</table>

- Would not routinely recommend palivizumab monotherapy in adults

Corticosteroids in RSV for Immunocompromised

- Viral infections trigger inflammatory cytokine surges
  - Mitigate sequelae
    - Steroids may play a role in attenuating this
  - Increased length of stay, secondary infections

- HSCT patients (n=45) 2008-2014
  - Underwent PFTs 100 days postoperatively
  - Concurrent treatment with oral ribavirin ± IVIG

- Steroid use: ↑ dose or addition ≤ 7 days of diagnosis

Damlaj, et al. Transpl Infect Dis 2016; epub ahead of print
Corticosteroids in RSV

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Steroids</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>16/19</td>
<td>11/26</td>
<td>2.05 (1.24-3.37)</td>
<td>0.005</td>
</tr>
<tr>
<td>ICU admission</td>
<td>8/19</td>
<td>1/26</td>
<td>2.91 (1.89-5.01)</td>
<td>0.034</td>
</tr>
<tr>
<td>Progression to LRTI</td>
<td>8/15</td>
<td>3/20</td>
<td>2.49 (1.21-5.13)</td>
<td>0.016</td>
</tr>
<tr>
<td>BOS incidence</td>
<td>4/11</td>
<td>5/22</td>
<td>-</td>
<td>0.69</td>
</tr>
<tr>
<td>Overall Survival*</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
<td>0.26</td>
</tr>
</tbody>
</table>

• No benefit seen with corticosteroids
  • Would consider if other indication
  • Potential confounding since given to sicker patients?

*Median not reached in either group with follow-up
NA: Not available
RR: Relative risk

Damlaj, et al. Transpl Infect Dis 2016; epub ahead of print
Question #2

Decompensated patient, requiring mechanical ventilation. BAL positive for RSV. Patient currently has normal renal function. Weight = 80 kg, RSV-ISI score = 4. Which of the following ribavirin-based strategies would be appropriate to initiate in this patient?

1. Oral 10 mg/kg/day with IVIG 500 mg/kg IV QOD
2. Oral 800 mg BID
3. Aerosolized 6 gm nebulized over 18 hours with IVIG 500 mg/kg IV QOD
4. Oral 800 mg BID, IVIG 500 mg/kg IV QOD with Palivizumab 15 mg/kg IV x one dose
Question #3

Which of the following is true regarding ribavirin for RSV infections?

A. Aerosolized has been shown to be superior to oral ribavirin in terms of efficacy

B. Hemolytic anemia is a side effect of the oral formulation

C. Aerosolized can be easily given through the ventilator without complications

D. Both aerosolized and oral formulations require dosage adjustment in renal insufficiency
Conclusion

Diagnosis, identification of risk factors, stratification

- PCR: Swab, nasopharyngeal washing, BAL
- ISI-RSV in HSCT patients
- Consider treatment if high RSV-ISI score

RSV URTI
- Oral ribavirin ± IVIG

RSV LRTI
- Oral ribavirin + IVIG
- Aerosolized considered for select patients (severe RSV-ISI score and cannot tolerate OR)
- Would not routinely recommend other adjunct therapies