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Antibiotic Prescription in Young Children With Respiratory Syncytial Virus-Associated Respiratory Failure and Associated Outcomes


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Disclosures

• I have nothing to disclose

• The paper we are reviewing was funded in part by
  – Accelerate Diagnostics
  – Genentech
  – Bristol Myers Squibb
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  – UpToDate

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Objectives

• Recognize statistically significant differences in outcomes between patients who receive early, late or no antibiotics for RSV bronchiolitis.

• Assess and apply results of this study and determine if there is a place in clinical practice.
Do you think we should use antibiotics in mechanically ventilated patients positive for RSV bronchiolitis who are < 2 years old in the PICU?

Why perform this study?

- RSV is the cause of over 80% of bronchiolitis admissions in young children worldwide.
- Lower respiratory tract infections in young children can lead to secondary bacterial pneumonia (PNA).
- It’s difficult to quickly diagnose and predict when a follow-up bacterial will occur.
- We need information to determine if antibiotics should be ruled in or out at 48 hours with cultures in the mechanically ventilated PICU patient population.
RSV Progression

- Peak time of viral shedding days 2-4
- Symptoms can last 2-8 day with persistent symptoms for up to 3 weeks

Risk Factors

- Neuromuscular Disorders
- Congenital Heart Disease
- Chronic Lung Disease
- Immuno-deficiency

Guidelines

- National Institute for Health and Care Excellence 2015 (NICE 2015)
  - Do not use any of the following to treat bronchiolitis in children: Antibiotics, hypertonic saline, adrenaline (nebulized), salbutamol, montelukast, epinephrine, systemic or inhaled corticosteroids, a combination of systemic corticosteroids and nebulized adrenaline.
  - Supplement if O₂ Sat. < 92%
  - Suctioning of airway secretions/chest PT (conditional)
  - Acquisition of capillary blood gas (conditional)
  - Provide fluid support (route conditional)

  "The Committee agreed that there might be a need to give antibiotic treatment to some children with a significant clinical deterioration. There might be a suspicion of an alternative infection in a child with an unexpectedly high temperature, for example above 39°C."

- American Academy of Pediatrics 2014 (APP 2014)
  - No: bronchodilator, inhaled epinephrine, inhaled hypertonic saline (conditional), steroids, oxygen when O₂ > 90%, Chest PT (conditional), antibiotics, fluids (route conditional)
  - Infants < 1 year with cardiac or respiratory disease or prematurity should receive palivizumab during RSV season for a maximum of 5 doses
  - "Antibiotic therapy may be justified in some children with bronchiolitis who require intubation and mechanical ventilation for respiratory failure"
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RSV prevention

- Synagis (Palivizumab)
  - < 2 y/o: 15mg/kg every month through RSV season (Max 5 doses) (AAP 2014)
  - Start administrations before the season starts
  - If active HSV occurs do not administer anymore doses that season.
  - Sd/fx: Skin rash (12%), Fever (27%), Antibody development (1-2%), Rare: angioedema, thrombocytopenia.

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Trial Design

- Retrospective Cohort Study: Pediatric Health Information System (PHIS).
  - 46 hospitals in only the US

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Time Line

- Hospital discharges from January 2012 to December 2016
  - The database was assessed for inclusion criteria and exclusion criteria
  - The results were sorted into:
    - Early antibiotic
    - No early antibiotic group
    - Late antibiotic group
    - Never antibiotic
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Recruitment

- Preexisting medical conditions
- LOS > 90 days
- Incomplete billing data
- Bacteremia, meningitis, or UTI
- MV before admission to PICU.
- ABX on just one of the first 2 days of MV
- Age < 2 years.
- RSV bronchiolitis or RSV pneumonia
- PICU level care

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Differences in baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole cohort</th>
<th>Early antibiotics</th>
<th>In early antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>11 (4-18)</td>
<td>11 (4-18)</td>
<td>11 (4-18)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>420 (69.8)</td>
<td>420 (69.8)</td>
<td>420 (69.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>420 (69.8)</td>
<td>420 (69.8)</td>
<td>420 (69.8)</td>
</tr>
<tr>
<td>Preoperative antibiotics, n (%)</td>
<td>401 (66.3)</td>
<td>401 (66.3)</td>
<td>401 (66.3)</td>
</tr>
<tr>
<td>Arterial pH, mmHg</td>
<td>7.39 (0.41)</td>
<td>7.39 (0.41)</td>
<td>7.39 (0.41)</td>
</tr>
<tr>
<td>Capillary refill delay, sec</td>
<td>7.5 (4.0)</td>
<td>7.5 (4.0)</td>
<td>7.5 (4.0)</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.8 (0.5)</td>
<td>37.8 (0.5)</td>
<td>37.8 (0.5)</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>96.1 (1.5)</td>
<td>96.1 (1.5)</td>
<td>96.1 (1.5)</td>
</tr>
</tbody>
</table>

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Differences in baseline characteristics

- Early Antibiotics
  - Younger average age -> higher rate of early antibiotic use
  - Vasopressors on the first day of mechanical ventilation (MV) -> higher rate of early antibiotic use
  - Shorter course of MV -> with use of early antibiotics
  - Shorter length of stay -> with use of early antibiotics
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Antibiotic Duration

- 425
- 378
- 924

- 0
- 100
- 200
- 300
- 400
- 500
- 600
- 700
- 800
- 900
- 1000

2-3 Days 4-6 days >7 days

1727 Total Children Received Early Antibiotics

24.6% 21.9% 53.5%

Reinitiation of antibiotics occurred in 23% of patients who received less than a 7 days course of antibiotics.

Early Antibiotics

An average 10 day (7-14 d) duration of antibiotics

Of the 380 children who did not receive early antibiotics: 262 (68.9%) received an average of 8 days (7-10 d) of antibiotics.

Initiation of antibiotics in the late antibiotics group occurred 4 days (3-5 d) after initiation of MV.

185 children (23%) who received < 7 days of ABX were restarted at a later date.

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Antibiotic Choice

Supplemental Figure 1a

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Downtrend in antibiotic use seen

Antibiotic Usage

- 2012
- 2013
- 2014
- 2015
- 2016

Linear (Antibiotic Usage) p = 0.004
Analyses

- Chi-Square analysis ($\chi^2$) / Fisher’s Exact test
  - Allows for determination of a significant difference between expected frequencies and observed frequencies.
  - Difference between attributes used between groups
- Wilcoxon Rank-Sum tests
  - Allows for comparison of two distinct data sets, informing us there is a similar distribution between the two.
  - Differences in primary outcomes and population data*
- Kruskal-Wallis analysis of variance (ANOVA)
  - Allows for testing for difference between 2 or more averages.
  - Used to correlate race
- Spearman’s rank-order correlation
  - Allows for assessments of the strength and direction of a relationship between two variables
  - Association in outcomes with age

*gender, ethnicity, insurance type, vasoactive medication use on the first day of MV, apnea

Analysis adjusting for baseline factors

Factors that were included as a fixed effect in the multivariate analysis (table 3)

- Fixed Effects
  - Gender: Females (increased LOS)
  - Race: African American (increased MV and LOS)
  - Not private insurance: (increased MV and LOS)
  - Vasoactive medication: (increased MV)
  - Increased Age: (decreased LOS)
- Random Effect
  - Treatment center
Table 3

- Adjusted results based on above characteristics.
  - Admit age: presumably increased age of some amount yields shorter MV and LOS (clinically insignificant)
  - All races have increased MV and LOS as compared to Caucasians.
  - Patients on MV who require vasopressors on day one of admission (increased MV and LOS)
  - No private insurance (increased MV and LOS)
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Discussion

- Antibiotic use was common (94.3%) even though incidence of documented bacterial PNA was (27.4%)
- Timing and selection of antibiotics was inconsistent
- 48 hour rule out was inconsistently followed. (75% > 3 days of ABX, 40% had positive cultures¹)


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Authors Conclusions

- There are significant variability in prescribing practices of antibiotics.
- The effects of early antibiotic exposure (asthma, allergies) must be evaluated.
- Effective implementation of rapid diagnostic/development of accurate biomarkers are essential.
- Early prescribing of antibiotics during an RSV bronchiolitis was associated with shorter MV durations and shorter LOS.

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Limitations

- Only applicable to PICU population
- Only applicable in patients requiring intubation
- Not applicable to patients with chronic health conditions, or other risk factors
- Not supported by guidelines
- Retrospective analysis
- Populations across several centers
  - Inconsistent practices (ABX choice/duration) across centers
Other Literature

- NICE (2015) list of important factors to monitor:
  - Hospital admission rate
  - Length of hospital stay
  - Duration of cough
  - Change in respiratory rate
  - Change in O2 saturation
  - Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
  - Adverse effects (including mortality).

Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: A prospective study and evidence review*

- Design: Prospective
- Setting: PICU
- Patients: 23 infants (< 12 mo., 1.5 mo. ave. age) 2004-2007
- Exclusions: Pre-existing conditions
- Conclusions: High prevalence of bacterial co-infection (39%), may justify use of antibiotics until bacterial pneumonia is ruled out


High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis.

- Design: Prospective microbiological analysis
- Setting: PICU
- Patients: 165 children (1.6 mo. Ave. age)
- Results:
  - 42.4% positive cultures for bacteria
  - Bacterial co-infection lead to increased MV duration (p<0.01)
  - WBC, CRP, neutrophils not different between groups
- Conclusions: RSV infections are associated with high rates of bacterial PNA

Questions

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