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

Shein SL. Pediatr Crit Care Med. 2019;20(2):101-109.

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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
  - La Jolla Pharma
  - 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.

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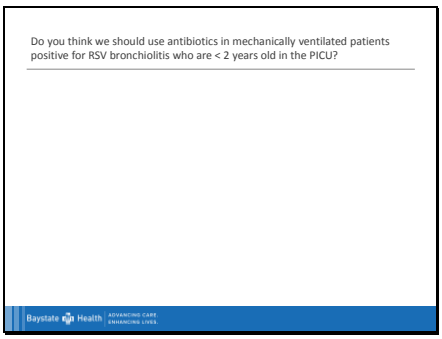

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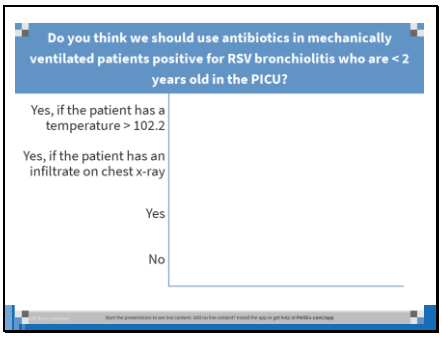

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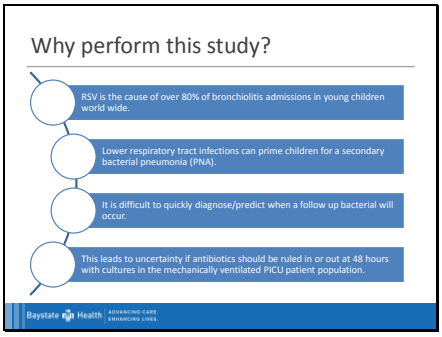

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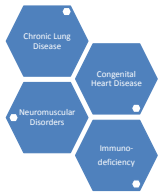
RSV Progression

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



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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, ipratropium, systemic or inhaled corticosteroids, a combination of systemic corticosteroids and nebulized adrenaline.

Supplement if O_2 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."

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Guidelines

- American Academy of Pediatrics 2014 (APP 2014)
  - No: bronchodilator, inhaled epinephrine, inhaled hypertonic saline (conditional), steroids, oxygen when O_2 > 90%, Chest PT (conditional), antibiotics, fluids (route conditional)
  - Infants < 1 year with cardiac or respiratory disease of 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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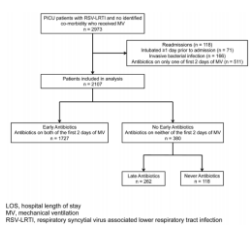
Recruitment



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Differences in baseline characteristics

TABLE 1. Demographics

Variables	Whole Cohort	Early antibiotics	No early antibiotics
Number of subjects	2,107	1,727	380
Age, median (IQR), mo	1 (1–4)	1 (1–4)	2 (1–4)*
Male, *n* (%)	1,272 (60.4)	1,044 (60.5)	228 (60.0)
Race, *n* (%)			
African–American	367 (17.4)	302 (17.5)	65 (17.1)
Caucasian	1,278 (60.7)	1,043 (60.4)	235 (61.8)
Other	462 (21.9)	382 (22.1)	80 (21.1)
Hispanic, *n* (%)	456 (21.6)	377 (21.8)	79 (20.8)
Private insurance, *n* (%)	586 (27.8)	489 (28.3)	97 (25.5)
Vasoactive medication on first day of MV, *n* (%)	251 (11.9)	238 (13.8)	13 (3.4)*
Apnea, *n* (%)	252 (12.0)	216 (12.5%)	36 (9.5%)
Duration of MV (d), median (IQR)	6 (4–9)	6 (4–9)	8 (6–11)*
Hospital length of stay (d), median (IQR)	12 (9–16)	11 (9–16)	13 (10–18)*

IQR = interquartile range, MV = mechanical ventilation.
*p<0.05 vs early antibiotics.
†p<0.001 vs early antibiotics.
Late antibiotics and no early antibiotics groups are not mutually exclusive. For 347 children whose ethnicity was "unknown", they were considered to be not Hispanic. For 33 children whose primary source of payment was unknown or "other", they were considered to be not private insurance.

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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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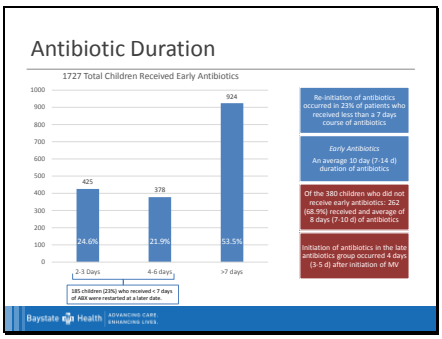

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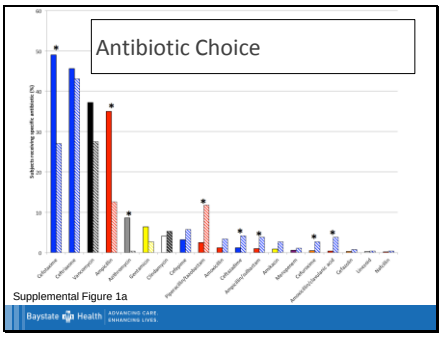

Supplemental Figure 1a

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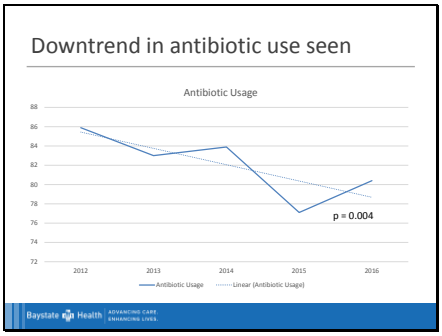

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Analyses

- Chi-Square analysis (χ^2)/Fisher's Exact test
  - Allows for determination of a significant difference between expected frequencies and observed frequencies.
  - Differences between antibiotic used between groups
- Wilcoxon Rank-Sum tests
  - Allows for comparison of two distinct data sets. Informing is 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 differences 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

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*gender, ethnicity, insurance type, vasoactive medication use on the first day of MV, apnea | $p \leq 0.10$

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Analysis adjusting for baseline factors

TABLE 2. Bivariate Analyses of Factors Associated With Clinical Outcomes

Variables	Duration of MV, Median (IQR)	*P*	Length of Stay, Median (IQR)	*P*
Female	6 (4–9)	0.41	12 (9–16)	0.06
Male	6 (4–9)		11 (8–16)	
Race		< 0.001		< 0.001
African-American	7 (5–10)		14 (9–18)	
Caucasian	6 (4–9)		11 (8–15)	
Other	6 (4–10)		12 (8–17)	
Hispanic	6 (4–8.5)	0.11	11 (8–16)	0.22
Not Hispanic	4 (4–9)		12 (9–16)	
Private insurance	6 (4–8)	< 0.001	10 (8–14)	< 0.001
Not private insurance	7 (5–10)		12 (9–17)	
Vasoactive medication on first day of MV	7 (5–10)	0.10	12 (9–18)	0.21
No vasoactive medication	6 (4–9)		11.5 (8–16)	
Apnea	6 (4–10)	0.297	12 (9–16.5)	0.283
No apnea	6 (4–9)		12 (8–16)	
Age (mo)	Coefficient: −0.021	0.341	Coefficient: −0.069	0.002

IQR = interquartile range, MV = mechanical ventilation.
Spearman coefficients shown for age. The negative values for the correlation coefficients indicate that age is inversely related to both outcomes.

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Bivariate Analysis (table 2)

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

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Results after adjustment (early vs. late)

TABLE 3. Patient-Level Variables Associated With Clinical Outcomes in Mixed-Effect Models Adjusted for Institution

Variables	Duration of MV		Length of Stay	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Intercept	7.63 (6.79–8.47)	< 0.001	14.01 (12.84–15.19)	< 0.001
Antibiotics on first 2 d of MV vs not	−1.21 (−1.68 to −0.75)	< 0.001	−2.07 (−2.89 to −1.26)	< 0.001
Admit age	−0.06 (−0.10 to −0.03)	0.001	−0.10 (−0.17 to −0.04)	0.003
Race				
African-American vs Caucasian	0.69 (0.20–1.19)	0.006	1.69 (0.82–2.55)	< 0.001
Other vs Caucasian	0.25 (−0.21 to 0.70)	0.299	0.66 (−0.13 to 1.45)	0.101
Female vs male	0.18 (−0.17 to 0.53)	0.320	0.40 (−0.22 to 1.01)	0.203
Vasoactive medication on day1 MV vs not	1.04 (0.50–1.58)	< 0.001	1.51 (0.56–2.45)	0.002
No private insurance vs private insurance	0.76 (0.36–1.17)	< 0.001	1.51 (0.81–2.22)	< 0.001

MV = mechanical ventilation.

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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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Bacterial Pneumonia (n = 579)

Variables	Duration of MV		Length of Stay	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Intercept	8.37 (6.94–9.79)	< 0.001	14.92 (12.67–17.18)	< 0.001
Antibiotics on first 2 d of MV vs not	−1.35 (−2.56 to −0.55)	0.003	−2.59 (−4.31 to −0.87)	0.003
Admit age	−0.04 (−0.12 to 0.05)	0.407	−0.07 (−0.21 to 0.08)	0.348
Race				
African-American vs Caucasian	0.49 (−0.52 to 1.50)	0.379	1.69 (−0.05 to 3.43)	0.057
Other vs Caucasian	1.04 (0.12–1.96)	0.027	1.06 (−0.52 to 2.64)	0.189
Female vs male	0.81 (0.07–1.55)	0.032	0.94 (−0.34 to 2.22)	0.151
Vasoactive medication on day1 MV vs not	2.12 (1.04–3.21)	< 0.001	3.28 (1.41–5.15)	< 0.001
No private insurance vs private insurance	0.71 (−0.12 to 1.53)	0.093	1.81 (0.39–3.24)	0.013

No Bacterial Pneumonia (n = 1,328)

Variables	Duration of MV		Length of Stay	
	Estimate	p	Estimate	p
Intercept	7.37 (6.49–8.25)	< 0.001	13.64 (12.33–14.94)	< 0.001
Antibiotics on first 2 d of MV vs not	−1.11 (−1.62 to −0.60)	< 0.001	−1.84 (−2.75 to −0.93)	< 0.001
Admit age	−0.07 (−0.11 to −0.03)	< 0.001	−0.12 (−0.19 to −0.04)	0.002
Race				
African-American vs Caucasian	0.73 (0.17–1.28)	0.010	1.65 (0.67–2.63)	0.001
Other vs Caucasian	−0.12 (−0.63 to 0.39)	0.645	0.50 (−0.40 to 1.39)	0.274
Female vs male	0.12 (−0.37 to 0.41)	0.935	0.27 (−0.42 to 0.96)	0.437
Vasoactive medication on day 1 MV vs not	0.56 (−0.06 to 1.17)	0.075	0.68 (−0.41 to 1.77)	0.219
No private insurance vs private insurance	0.75 (0.30–1.21)	0.001	1.33 (0.53–2.13)	0.001

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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 cultures[1])

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1 - Thorburn K, Harigopal S, Reddy V, et al. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax 2006; 61:611–615

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Authors Conclusions

There are significant variability in prescribing practices of antibiotics.

The effects of 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

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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).

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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

Levin D. Pediatr Crit Care Med. 2010;11(3):390-5.

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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

Thorburn K. Thorax. 2006;61(7):611-5.

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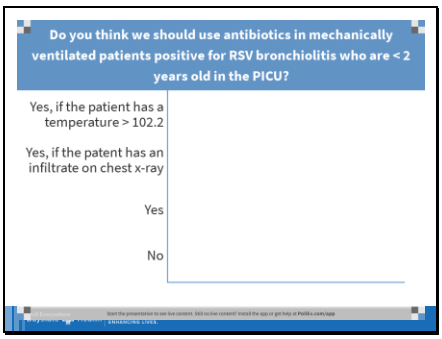

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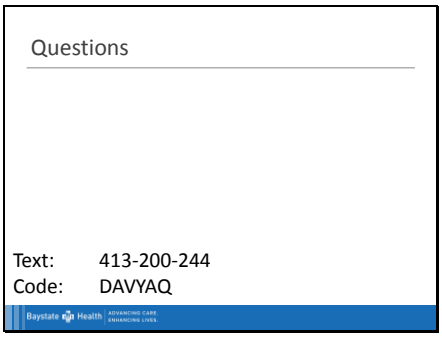

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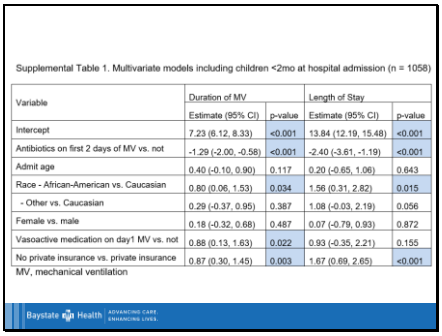

Supplemental Table 1. Multivariate models including children <2mo at hospital admission (n = 1058)

Variable	Duration of MV		Length of Stay	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Intercept	7.23 (6.12, 8.33)	<0.001	13.84 (12.19, 15.48)	<0.001
Antibiotics on first 2 days of MV vs. not	-1.29 (-2.00, -0.58)	<0.001	-2.40 (-3.61, -1.19)	<0.001
Admit age	0.40 (-0.10, 0.90)	0.117	0.20 (-0.65, 1.06)	0.643
Race - African-American vs. Caucasian	0.80 (0.06, 1.53)	0.034	1.56 (0.31, 2.82)	0.015
- Other vs. Caucasian	0.29 (-0.37, 0.95)	0.387	1.08 (-0.03, 2.19)	0.056
Female vs. male	0.18 (-0.32, 0.68)	0.487	0.07 (-0.79, 0.93)	0.872
Vasoactive medication on day1 MV vs. not	0.88 (0.13, 1.63)	0.022	0.93 (-0.35, 2.21)	0.155
No private insurance vs. private insurance	0.87 (0.30, 1.45)	0.003	1.67 (0.69, 2.65)	<0.001

MV, mechanical ventilation

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Supplemental Table 2. Multivariate models including children ≥2mo at hospital admission (n = 1049)

Variable	Duration of MV		Length of Stay	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Intercept	7.87 (6.87, 8.88)	<0.001	14.01 (12.40, 15.63)	<0.001
Antibiotics on first 2 days of MV vs. not	-1.24 (-1.87, -0.61)	0.001	-1.70 (-2.82, -0.57)	0.003
Admit age	-0.07 (-0.12, -0.02)	0.003	-0.13 (-0.22, -0.05)	0.003
Race - African-American vs. Caucasian	0.68 (0.00-1.35)	0.0499	1.81 (0.61, 3.02)	0.003
- Other vs. Caucasian	0.15 (-0.48, 0.79)	0.632	0.36 (-0.76, 1.49)	0.525
Female vs. male	0.26 (-0.24, 0.75)	0.313	0.77 (-0.12, 1.65)	0.091
Vasoactive medication on day1 MV vs. not	1.23 (0.44, 2.02)	0.002	2.16 (0.75, 3.58)	0.003
No private insurance vs. private insurance	0.62 (0.05, 1.19)	0.032	1.35 (0.33, 2.36)	0.009

MV, mechanical ventilation

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Supplemental Table 3. Multivariate models including children with non-RSV disease

Variable	Duration of MV		Length of Stay	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Intercept	7.43 (6.73, 8.12)	<0.001	13.50 (12.45, 14.55)	<0.001
Antibiotics on first 2 days of MV vs. not	-1.01 (-1.41, -0.62)	<0.001	-1.57 (-2.28, -0.87)	<0.001
Admit age	-0.10 (-0.13, -0.07)	<0.001	-0.19 (-0.24, -0.13)	<0.001
Race - African-American vs. Caucasian	0.26 (-0.14, 0.66)	0.208	1.14 (0.43, 1.86)	0.002
- Other vs. Caucasian	-0.02 (-0.40, 0.37)	0.935	0.30 (-0.38, 0.98)	0.391
Female vs. male	0.24 (-0.06, 0.53)	0.112	0.47 (-0.06, 0.99)	0.084
Vasoactive medication on day1 MV vs. not	0.90 (0.45, 1.35)	<0.001	1.41 (0.60, 2.21)	<0.001
No private insurance vs. private insurance	0.64 (0.30, 0.98)	<0.001	1.31 (0.70, 1.92)	<0.001

MV, mechanical ventilation
Note: In order to adjust for institutional variation, each center's difference from the overall average proportion of early antibiotic administration (i.e. center usage rate minus overall usage rate for children with RSV or non-RSV disease) was included in the mixed-effect models as a random effect.

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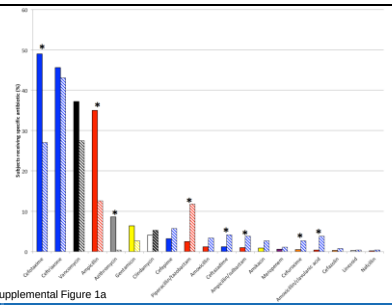

Supplemental Figure 1a

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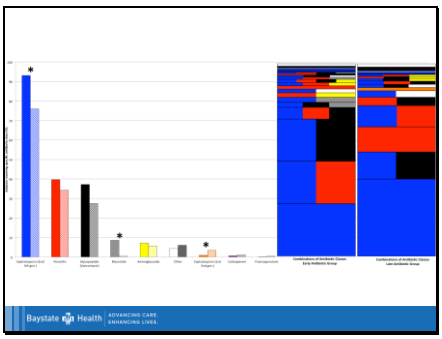

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