Short versus prolonged course of therapy for ventilator-associated tracheitis caused by non-lactose-fermenting Gram-negative rods in children

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ABSTRACT (REVISED)

Background: Ventilator-associated consequences of endotracheal intubation in children admitted to pediatric intensive care units (PICU) include ventilator-associated tracheitis (VAT). The optimal duration of therapy (DOT) to prevent progression of VAT to pneumonia is undetermined.

Objective: This study sought to compare clinical characteristics and outcomes in PICU patients with non-lactose-fermenting Gram-negative rod (NLFGNR) VAT treated with >7 days (prolonged course group, PCG) vs ≤7 days (short course group, SCG).

Methods: This was a retrospective cohort in a single-centered 12-bed PICU at an 800-bed, urban, tertiary care, academic medical center. Treatment was at physicians' discretion. Patients were included if they were admitted between January 2009 and July 2016, mechanically ventilated for ≥48 hours, and treated with an antibiotic course of ≥96 hours for NLFGNR VAT.

Results: 50 patients were included (PCG n=27, SCG n=23). Median age was 1.6 years (0-18.8), PIM2 score was 1 (0.1-82.8), 62% of patients had a tracheostomy at baseline, and 70% had P. aeruginosa. More patients had an admission diagnosis of respiratory failure and mechanical ventilation and PICU stay were longer in PCG vs SCG (44% vs 13%, P=0.03; 12.5 vs 5 days, P<0.01; 16 vs 6 days, P<0.01; respectively). Median DOT was 10 days (8-30) in PCG vs 6 (3-7) in SCG. Clinical response at the end of treatment was 89% in PCG and 100% in SCG, P=0.2. Pulmonary infection-recurrence was 26% in PCG and 9% in SCG, P=0.2 at 17 days (1-29) and 9.5 days (4-15) P=0.5, respectively. Emergence of resistance or multidrug-resistant organisms occurred in 15% in PCG vs 0% in SCG, P=0.1. Readmission and in-hospital mortality were 7% vs 9%, P=0.9 and 7% vs 0%, P=0.5 in PCG and SCG, respectively.

Conclusions: Clinical courses were similar regarding treatment response, resistance, readmission, and mortality in short versus prolonged DOT for VAT. These findings suggest short DOT may be considered for less sick children including those with a tracheostomy at baseline.

BACKGROUND

- Ventilator-associated tracheitis (VAT)
  - Unintended consequence of mechanical ventilation in the pediatric intensive care unit (PICU)
  - May serve as a precursor to ventilator-associated pneumonia (VAP)
- Optimal duration for VAT caused by non-lactose-fermenting Gram-negative rods (NLFGNR) yet to be defined
  - Prior retrospective study of children diagnosed with VAT
    - Prolonged course of antibiotics does not protect against subsequent progression to VAP compared to a shorter course
    - Did not specifically evaluate VAT caused by NLFGNR
  - For adults with VAP
    - Clinical practice guidelines recommend a 7-day course of antimicrobial therapy
      - May be limited to VAP caused by organisms excluding NLFGNR
        - Data available to suggest longer courses of therapy to prevent recurrence
      - Lack of physical damage to the lungs in VAT compared to VAP

OBJECTIVE

- To compare outcomes for patients in the PICU with VAT due to NLFGNR who received prolonged (>7 days) versus short (≤7 days) courses of antibiotics

METHODS

Study Design

- Retrospective cohort in a 12-bed PICU between January 2009 and July 2016 at an 800-bed, urban, tertiary care, academic medical center

Inclusion Criteria	Exclusion Criteria
• Mechanically ventilated ≥48 hours • Diagnosed with 1st incidence of VAT • Treated with ≥96 hours of antibiotics for VAT due to a NLFGNR	• Radiographic evidence of a new lung infiltrate

Outcome Measures

- Primary
  - Rate of pulmonary infection-recurrence within 30 days of VAT treatment completion
- Secondary
  - Emergence of resistance or multidrug resistant organisms (MDRO) within 30 days of VAT treatment, 30-day readmission, all-cause in-hospital mortality

Definitions

VAT	• **Satisfying both of the following criteria**
	  • Fever (>38 C), hypothermia (<36 C), cough, rhonchi, wheezing, or new onset of purulent endotracheal secretions
	  • Sputum culture with ≥moderate polymorphonuclear cells and ≥moderate NLFGNR

Pulmonary infection-recurrence	• **Satisfying either of the following criteria**
	  • **Microbiologically documented** - sputum culture with ≥moderate polymorphonuclear cells and ≥moderate organism growth
	  • **Clinically suspected** - clinical signs and symptoms accompanied by the initiation of an antibiotic course of ≥48 continuous hours

Emergence of MDRO	• Newly identified colonization or infection by organisms resistant to ≥3 classes of antibiotics
Emergence of resistance	• ≥4-fold increase in minimum inhibitory concentration to the antibiotic that was used to treat VAT

Statistical Analysis

- All continuous variables presented as median (range)
- Fisher's exact test was used for categorical variables
- Mann-Whitney U test was used for continuous variables

RESULTS

Figure 1. Patient Screening

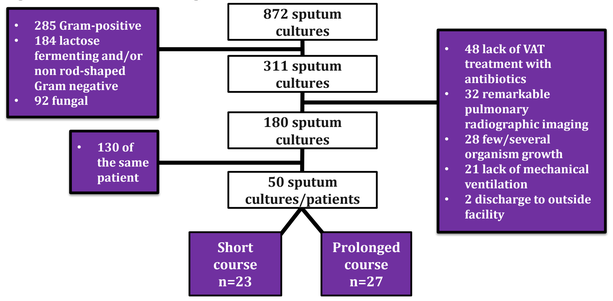

Table 1. Patient Demographic Characteristics

Patient Demographic Characteristic	Prolonged Course (N=27)	Short Course (N=23)	*P*-Value
Female	11 (41)	13 (57)	0.395
Age	1.7 (0-18.8)	1.6 (0-17.7)	0.823
LOS			
Hospital	32 (3-764)	18 (4-77)	0.005
PICU	31 (3-764)	11 (4-77)	0.001
Preexisting conditions			
Prematurity	7 (26)	5 (22)	1.000
Neuromuscular	11 (41)	14 (61)	0.256
Cardiovascular	8 (30)	7 (30)	1.000
Genetic/Metabolic	10 (37)	8 (35)	1.000
Respiratory	18 (67)	19 (83)	0.332
Tracheostomy	16 (89)	15 (79)	0.773
Trauma	1 (4)	1 (4)	1.000
Gastrointestinal	18 (67)	16 (70)	1.000
Admission diagnosis			
Respiratory failure	12 (44)	3 (13)	0.029
Shock/circulatory support	1 (4)	3 (13)	0.322
Metabolic derangements	1 (4)	0 (0)	1.000
Elective surgery	10 (37)	8 (35)	1.000
Seizure	2 (7)	4 (17)	0.395
Other	1 (4)	5 (22)	0.082
Elective admission	10 (37)	10 (44)	0.596
MV at any time during 1st hour in PICU	18 (67)	15 (65)	1.000
Total duration of MV (days)	20 (3-746)	9 (2-66)	0.003
PIM2 score (%)	0.8 (0.2-44.4)	1.2 (0.1-82.8)	0.585
LOS prior to VAT diagnosis (days)	9 (2-70)	5.5 (2-26)	0.183

Data presented as n (%) unless continuous variable

Figure 2. Microbiology

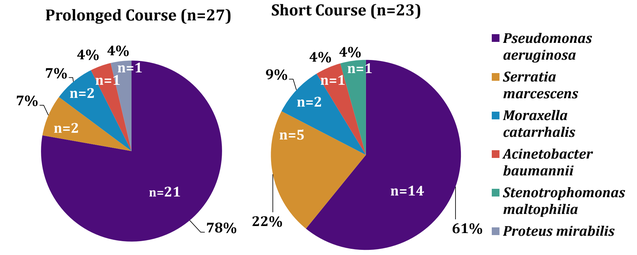

Table 2. Treatment Characteristics

Treatment Characteristic	Prolonged Course (N=27)	Short Course (N=23)	*P*-Value
Duration of antibiotics (days)	10 (8-30)	6 (3-7)	0.0005
Clinical response	24 (89)	23 (100)	0.240
Duration of MV[a] (days)	12.5 (3-735)	5 (1-55)	0.001
LOS[a]			
Hospital	18 (3-735)	6 (2-66)	0.001
PICU	16 (2-735)	6 (2-66)	0.0005

Data presented as n (%) unless continuous variable; [a] From time of antibiotic initiation for VAT

Table 3. Outcomes

Outcome	Prolonged Course (N=27)	Short Course (N=23)	*P*-Value
Pulmonary infection recurrence	7 (26)	2 (9)	0.152
Microbiologically documented	6 (86)	0 (0)	0.083
Tracheitis	4 (67)	-	-
Pneumonia	2 (33)	-	-
Clinically suspected	5 (71)	2 (100)	1.000
Tracheitis	3 (60)	2 (100)	1.000
Pneumonia	2 (20)	0 (0)	-
Time to subsequent infection (days)	17 (1-29)	9.5 (4-15)	0.500
Emergence of resistance or MDRO	4 (15)	0 (0)	0.100
30-day readmission	2 (7)	2 (9)	1.000
All-cause in-hospital mortality	2 (7)	0 (0)	0.493

Data presented as n (%) unless continuous variable

CONCLUSION

- Pulmonary infection-recurrence was not observed in patients who received short course compared to prolonged course therapy for VAT caused by NLFGNR
- Emergence of resistance and MDRO were not detected in patients who received shorter antibiotic courses
- These findings suggest that short antibiotic courses may be considered in children with a lower severity of illness, including those with a preexisting tracheostomy at baseline