

Impact of Short versus Long Treatment Durations for Respiratory Tract Infections Caused by Non-fermenting Gram-negative Bacilli in Lung Transplant Recipients

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Background

- Infectious Diseases Society of America & American Thoracic Society (IDSA/ATS) 2016 guidelines recommend a treatment duration of 7 days for hospital acquired and ventilator-associated pneumonias¹
 - Chastre *et al* found shorter treatment durations of 8 days lead to increased recurrence in non-fermenting gram-negative bacilli (NFGNB) ventilator-associated pneumonia²
- Pulmonary infections in lung transplant recipients are associated with faster progression through stages of bronchiolitis obliterans syndrome (BOS) and to death³
- Limited data exist delineating optimal treatment durations for NFGNB respiratory tract infections (RTIs) in lung transplant recipients

Objective

- Evaluate the incidence of recurrent NFGNB RTI within 28 days following treatment for a short antibiotic duration (≤ 10 days) compared to a longer antibiotic duration (> 10 days)

Methods

Study Design: Retrospective, cohort study evaluating NFGNB RTI treatment durations and recurrent infection in lung transplant recipients from a period of July 1, 2010 to July 1, 2019. This study was IRB-approved.

Definitions:

- NFGNB RTI - Growth of *P. aeruginosa*, *S. maltophilia*, or *A. baumannii* from a respiratory specimen (e.g. bronchoalveolar lavage, tracheal aspirate, or sputum culture) and treated with systemic antimicrobials
- Clinically significant infection recurrence - NFGNB RTI microbiologically confirmed to be caused by the same NFGNB within a 28-day period following treatment completion of the previous episode, necessitating re-initiation of systemic antimicrobials
- Treatment durations - "short" is effective treatment for ≤ 10 days and "long" is effective treatment for > 10 days

Inclusion Criteria: ≥ 18 years of age at time of transplant, a positive respiratory culture specimen with the specified NFGNB and subsequently treated with systemic antimicrobials

Exclusion Criteria: Less than 28 days of follow-up data either due to death, lost to follow-up, or end of study surveillance period or insufficient information for investigator analysis

Primary Outcome: Clinically significant infection recurrence (NFGNB RTI recurrence) within 28 days following treatment course completion

Statistical Analysis:

- Bivariate analyses of continuous variables were performed using the Mann-Whitney U test
- Bivariate analyses of categorical variables were performed using the Chi-square test or the Fisher's exact test
- Multivariable analysis for NFGNB RTI recurrence was performed by binary logistic regression including bivariate variables with a *P*-value of ≤ 0.2
- A *P*-value of less than 0.05 was considered significant; all tests were two-tailed
- Four analyses were performed: all NFGNB RTIs, initial NFGNB RTIs only, and inpatient/initial NFGNB RTIs only (all RTIs treated as independent events)

Results

- Two-hundred seven patients were screened for inclusion; 157 patients were included with a total of 334 NFGNB RTIs over the surveillance period
 - Twenty patients had two different NFGNB in respiratory specimens, making 177 initial NFGNB RTIs by organism
 - Based on organism, NFGNB RTIs occurred up to one (98/177, 55%), two (41/177, 23%), three (19/177, 11%), four (5/177, 3%), five (8/177, 4%), six (5/177, 3%), or seven (1/177, 1%) times in a lung transplant recipient

Table 1: Patient and Transplant Characteristics for NFGNB RTIs (n=177)

Characteristic	Treatment for ≤ 10 days (n=75)	Treatment for > 10 days (n=102)	P-value
Age at time of transplant, median (IQR)	59 (53-64)	60 (52-65)	0.56
Indication for transplant, n (%)			
Alpha 1-Antitrypsin Deficiency	7 (9)	6 (6)	0.38
COPD	25 (33)	33 (32)	0.89
Cystic Fibrosis	7 (10)	17 (17)	0.16
Idiopathic Pulmonary Fibrosis	27 (36)	35 (34)	0.82
Other	9 (12)	11 (11)	0.80
Type of transplant, n (%)			
Single	13 (17)	22 (22)	0.48
Bilateral	62 (83)	80 (78)	0.48
Induction agent, n (%)			
Lymphocyte depleting*	45 (60)	51 (50)	0.24
Donor lung culture positive for NFGNB at time of transplant, n (%)	12 (16)	12 (12)	0.42
Native lung culture positive for NFGNB at time of transplant, n (%)	15 (20)	28 (28)	0.25

IQR, interquartile range

*Lymphocyte depleting induction agents include alemtuzumab (99%) or anti-thymocyte globulin (1%)

Table 2: Treatment Characteristics of All NFGNB RTIs (N=334)

	Treatment for ≤ 10 days (n=129)	Treatment for > 10 days (n=205)	P-value
Duration of therapy in days, median (IQR)	10 (7-10)	14 (13-15)	< 0.001
Organism, n (%)			
<i>Pseudomonas aeruginosa</i>	99 (77)	167 (82)	0.30
<i>Stenotrophomonas maltophilia</i>	22 (17)	33 (16)	0.82
<i>Acinetobacter baumannii</i>	8 (6)	5 (2)	0.14
Antimicrobial treatment agent, n (%)			
Intravenous only	97 (75)	163 (79)	0.36
Intravenous transition to oral	2 (2)	4 (2)	1.00
Oral only	30 (23)	38 (19)	0.30
Time after transplant, n (%)			
Immediate (0-3 days)	23 (18)	43 (21)	0.48
< 30 days, not immediate	11 (8)	22 (11)	0.51
30 days - 1 year	58 (45)	57 (28)	0.001
> 1 year	37 (29)	83 (40)	0.03
Received lymphodepleting agent outside of induction period prior to RTI, n (%)	24 (19)	32 (16)	0.48
Location of treatment, n (%)			
Inpatient only	77 (60)	108 (53)	0.21
Outpatient only	42 (32)	61 (30)	0.59
Inpatient transition to outpatient	10 (8)	36 (17)	0.01
BOS Stage, n (%)			
Early (0, 0-p, or 1)	42 (33)	70 (34)	0.77
Advanced (2 or 3)	16 (12)	18 (9)	0.29
Not diagnosed	71 (55)	117 (57)	0.72
Invasive mechanical ventilation within 72 hours prior to RTI	39 (30)	64 (31)	0.85
Adjunctive therapy with inhaled antibiotics for full duration, n (%)	26 (20)	65 (32)	0.02
Inhaled suppressive antibiotics following treatment, n (%)	15 (12)	31 (15)	0.37
Recurrent RTI within 28 days of treatment end, n (%)	14 (11)	28 (14)	0.45

Figure 1: Comparison of Infection Recurrence in NFGNB RTIs Treated with Short versus Long Durations

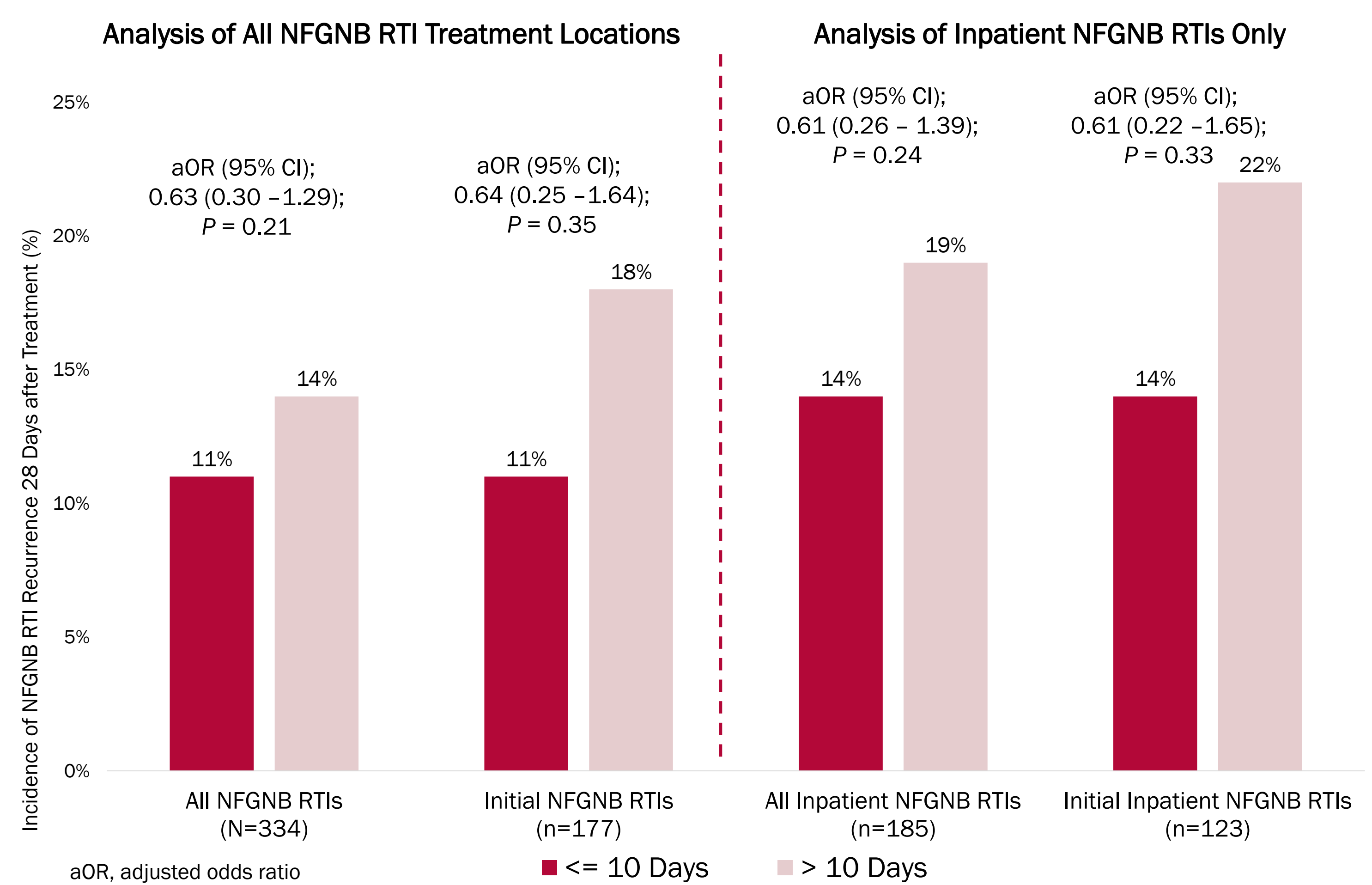


Table 3: Multivariable Analysis of Factors for Infection Recurrence Including Treatment Duration in All NFGNB RTI (N=334)

	Adjusted Odds Ratio	95% CI
Treatment for ≤ 10 days	0.63	0.30 - 1.29
Invasive mechanical ventilation within 72 hours prior to RTI	2.85	1.14 - 7.11
Location of treatment		
Inpatient only	3.05	1.24 - 7.5
Adjunctive therapy with inhaled antibiotics for full duration	0.38	0.16 - 0.92
BOS Stage		
Early (0, 0-p, or 1)	0.17	0.06 - 0.45

CI, confidence interval

Discussion & Conclusion

- No difference in infection recurrence was detected between NFGNB RTIs treated for short (≤ 10 days) or long (> 10 days) durations of systemic antimicrobial therapy at 28 days post-treatment
 - In analysis of all NFGNB RTIs, use of adjunctive inhaled antibiotics was associated with lower odds of infection recurrence
 - Infection recurrence was more likely in those receiving inpatient treatment or invasive mechanical ventilation within 72 hours prior to NFGNB RTI
- Overall incidence of infection recurrence was lower than in previous studies^{2,4}
 - However, use of adjunctive inhaled antibiotics were not evaluated
- Unable to evaluate current IDSA/ATS antibiotic treatment duration recommendation due to low utilization
- This was a hypothesis-generating, single-center, retrospective study needing future prospective validation in randomized controlled trials

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