

Optimizing antibiotic prophylaxis choice and duration in lung transplantation

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Introduction

- Lung transplant recipients (LTR) are at high risk for early bacterial infections post-transplant^{1,2}
- Antibiotic prophylaxis is standard practice, but variation in choice and duration between transplant centers^{3,4}

Aim

To review our microbial epidemiology and antibiotic prophylaxis regimens, and examine relationships with early post-transplant outcomes

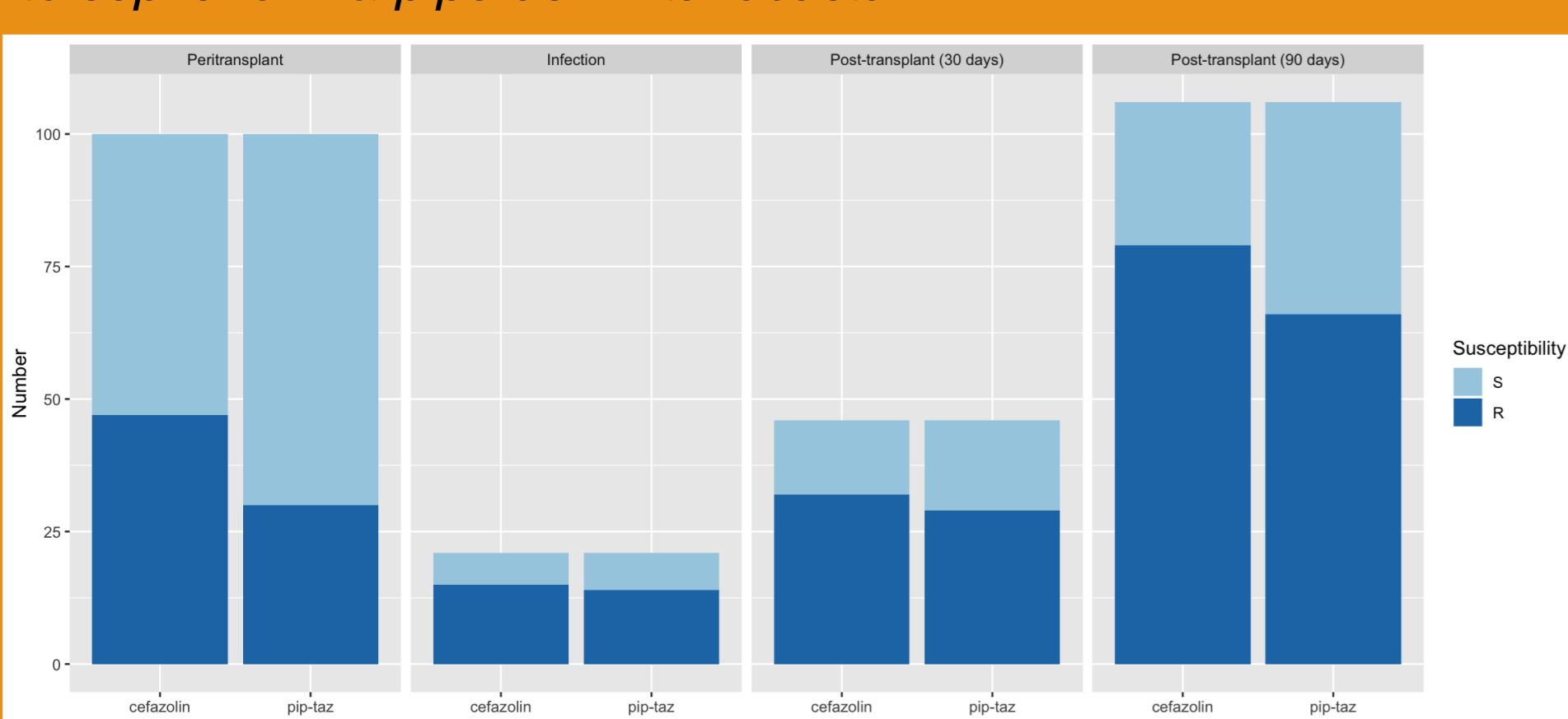
Methods

- Retrospective cohort study, Alfred Health, 2015-2017, originally recruited to evaluate the Quantiferon®-Monitor assay⁵
- 'Peritransplant' microbiology collated (recipient cultures 90 days pre- & 3 days post-transplant, donor cultures).
- Antibiotics administered within the first 30 days were recorded and classified as empiric/tailored prophylaxis and empiric/directed treatment.
- Exclusions:** Age <18, unable to provide informed consent, previous lung transplant, or follow-up planned elsewhere
- Primary outcome:** bacterial infection within 30 days post-transplant
- Secondary outcomes:** *C. difficile* infection, fungal infection, identification of a multidrug-resistant organism, rejection and death (all within 90 days)

Table 1: Individual bacterial isolated from donors & recipients within 90 pre- & 3 days post-transplant.

Recipient, <90d pre-transplant		Donor		Recipient, <72h post-transplant	
Organism	No. (%) (n=12)	Organism	No. (%) (n=63)	Organism	No. (%) (n=25)
<i>P. aeruginosa</i>	7 (58%)	MSSA	26 (41%)	MSSA	13 (52%)
<i>S. maltophilia</i>	2 (17%)	<i>E. coli</i>	5 (8%)	<i>P. aeruginosa</i>	5 (20%)
<i>B. cepacia</i>	1 (8%)	<i>Klebsiella</i> sp.	5 (8%)	<i>S. marcescens</i>	2 (8%)
<i>S. marcescens</i>	1 (8%)	<i>Enterobacter</i> sp.	5 (8%)	<i>E. coli</i>	1 (4%)
MRSA	1 (8%)	<i>Citrobacter</i> sp.	3 (5%)	<i>S. maltophilia</i>	1 (4%)
		<i>S. pneumoniae</i>	3 (5%)	MRSA	1 (4%)
		<i>H. influenzae</i>	3 (5%)	<i>C. koseri</i>	1 (4%)
		<i>A. baumannii</i>	2 (3%)	<i>E. aerogenes</i>	1 (4%)
		<i>Achromobacter</i> sp.	2 (3%)		
		<i>Bacillus</i> sp.	2 (3%)		
		MRSA	1 (1%)		
		<i>S. maltophilia</i>	1 (1%)		
		<i>P. aeruginosa</i>	1 (1%)		
		<i>P. agglomerans</i>	1 (1%)		
		<i>Chlamydiae</i> sp.	1 (1%)		
		<i>E. faecalis</i>	1 (1%)		
		<i>S. marcescens</i>	1 (1%)		

Figure 1: Susceptibility of peritransplant & post-transplant isolates to cephazolin & piperacillin-tazobactam.



Results

- 80 patients, median age 61, 60% male, 86% bilateral transplant, 38% receiving antibiotics before transplant
- 100 bacteria isolated from 53 donor-recipient patient pairs (Table 1)
- 28% and 18% of donors had cephazolin and piperacillin-tazobactam resistant isolates (Figure 2, p=0.19)
- 317 courses of antibiotics; 167 prophylaxis (108 empiric, 59 tailored) & 139 treatment (105 empiric, 34 directed)
- All patients received prophylaxis; 36% single drug, 64% multiple (Table 2). Similar choices with positive/negative microbiology.
- 31 (39%) had regimen tailored, 4 to narrow-spectrum agent
- Median time from prophylaxis dose to incision 2.5 hours, 48% received a dose <2 hours
- Median prophylaxis duration 10 days (IQR 8-13), longer if positive peritransplant microbiology (Figure 2, p=0.008)
- 30 patients developed bacterial infection <30 days (Figure 3, Table 3).
- Failure to receive a prophylactic dose within 2 hours of incision was associated with post-transplant infection (Table 4).

Table 2: Antibiotics used for prophylaxis.

Antibiotic	Number of courses (%)	Median (IQR) duration (days)
Piperacillin-tazobactam	66 (40%)	8 (6-11)
Meropenem	24 (14%)	7 (4-10)
Cephazolin	23 (14%)	1 (1-1)
Vancomycin	22 (13%)	2 (1-4)
Tobramycin (IV)	5 (3%)	3 (1-13)
Ciprofloxacin	4 (2%)	8 (4-10)
Amoxicillin-clavulanate	3 (2%)	5 (4-6)
Trimethoprim-sulfamethoxazole	3 (2%)	10 (8-15)
Ceftazidime	3 (2%)	22 (14-26)
Tobramycin (inhaled)	3 (2%)	10 (10-18)
Cefepime	2 (1%)	4
Ceftriaxone	2 (1%)	2
Flucloxacillin	2 (1%)	8
Azithromycin	1 (1%)	7
Aztreonam	1 (1%)	1
Benzylpenicillin	1 (1%)	14
Moxifloxacin	1 (1%)	10
Tigecycline	1 (1%)	11

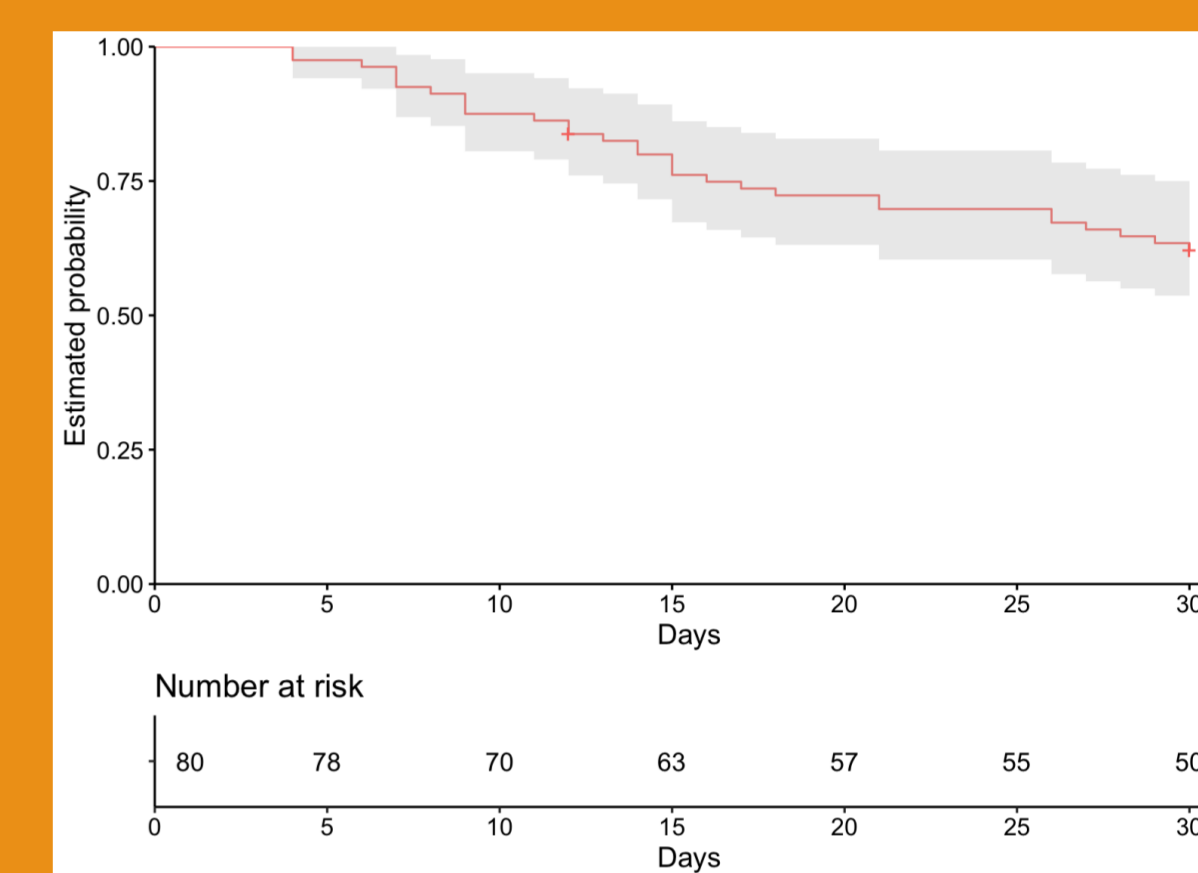
Table 4: Factors associated with bacterial infection within 30 days post-transplant.

Characteristic	No infection (n=50)	Infection (n=30)	Odds ratio (95% CI)	p-value
Age, mean ± SD	60 ± 8	60 ± 9	0.99 (0.94-1.05)	0.69
Diabetes	7 (14%)	1 (3%)	0.21 (0.01-1.28)	0.16
Pre-transplant antibiotics	20 (40%)	9 (30%)	0.64 (0.24-1.66)	0.37
Bronchiectasis	24 (48%)	15 (50%)	1.08 (0.44-2.69)	0.86
Bilateral transplant (vs. single)	43 (86%)	26 (87%)	1.06 (0.29-4.36)	0.93
No prophylaxis dose within 2 hours of incision	21 (42%)	21 (70%)	3.22 (1.26-8.75)	0.02
Surgery duration, minutes, median, IQR	232, 185-278	239, 185-271	1.00 (1.00-1.01)	0.39
Basiliximab induction	29 (58%)	11 (37%)	0.42 (0.16-1.05)	0.07
Required ECMO post-transplant	3 (6%)	4 (13%)	2.41 (0.50-13.03)	0.27
Hours intubated	22, 15-47	23, 15-50	1.00 (1.00-1.01)	0.36
Initial ICU LOS	4, 3-6	4, 3-9	1.03 (0.96-1.12)	0.38
Readmission to ICU	7 (14%)	3 (10%)	0.68 (0.14-2.69)	0.60
Return to surgery	6 (12%)	3 (10%)	0.81 (0.16-3.36)	0.78
Duration drains remained in situ	8, 5-9	8, 6-11	0.92-1.15	0.65
Positive donor/recipient microbiology	35 (70%)	18 (60%)	0.64 (0.25-1.67)	0.36
Antibiotic allergy	8 (16%)	9 (30%)	2.25 (0.76-6.83)	0.14
Rejection in first 30 days	4 (8%)	2 (7%)	0.82 (0.11-4.50)	0.83

Table 3: Primary & secondary outcomes.

Outcome	Number (%), n=80
Early bacterial infection (within 30 days)	31 in 30 patients
Pneumonia	22 (38%)
Bronchitis	3 (4%)
Central line associated bloodstream infection	2 (3%)
Empyema	1 (1%)
Urinary tract infection	1 (1%)
Surgical site infection (chest wall)	1 (1%)
Gastroenteritis	1 (1%)
Other outcomes (within 90 days)	6 (8%)
<i>Clostridium difficile</i> colitis	16 in 14 patients (18%)
MDRO isolation	23 in 20 patients (25%)
Fungal infection	6 (8%)
Any rejection	3 (4%)
Steroid-treated rejection	1 (1%)
Death	1 (1%)

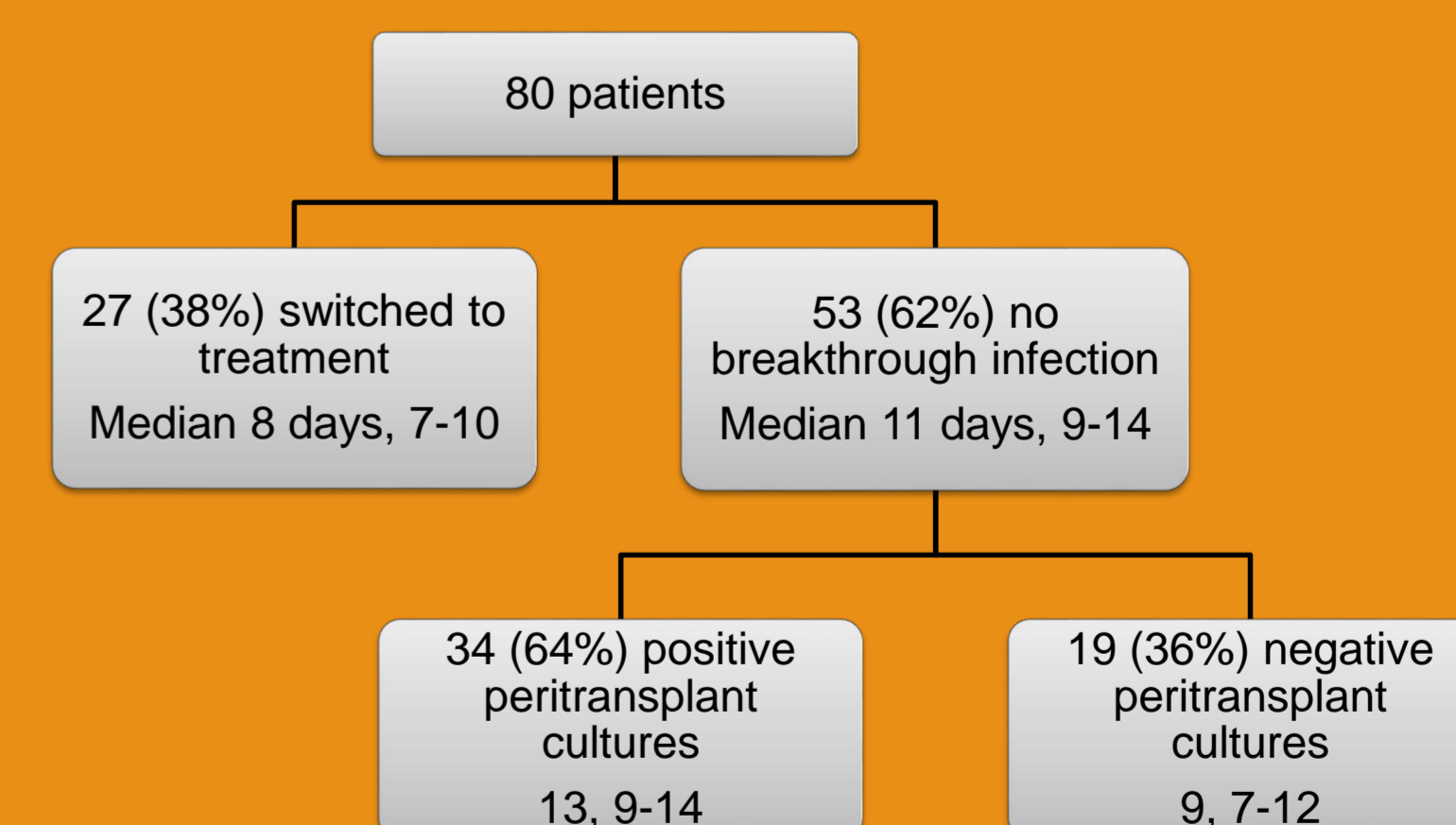
Figure 3: Infection-free survival within first 30 days post-transplant.



Conclusions

- Most patients received prolonged courses of antipseudomonal beta-lactams post-transplant
- Prophylaxis tailored in 1/3 but rarely to narrow-spectrum agent
- Many received first dose too early; associated with higher rates of early bacterial infection
- 34% donor/recipient cultures negative, but if positive, 1/3 cephazolin resistant
- C. difficile*, MDRO common post-transplant
- Risks and benefits of antibiotics need to be carefully weighed in this patient population at high risk of both early bacterial infection but also complications of antibiotic exposure

Figure 2: Antibiotic prophylaxis duration (median, IQR) in patients who did not develop breakthrough infection by peritransplant microbiology results.



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