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Real World Treatment of Multi-drug Resistant (MDR) or Extensively-drug Resistant (XDR) *Pseudomonas aeruginosa* Infections with Ceftolozane/Tazobactam (C/T) vs. a Polymyxin or Aminoglycoside (Poly/AG) based regimen: A Multicenter Comparative Effectiveness Study

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Background

- Clinicians rely on polymyxins and aminoglycosides to treat infectious caused by MDR/XDR *P. aeruginosa*, despite the limited efficacy and high toxicity
- C/T is a novel anti-pseudomonal beta-lactam with excellent *in vitro* activity against MDR/XDR *P. aeruginosa*
- Real world data on the outcomes of MDR/XDR *P. aeruginosa* infections treated with C/T are limited to small, non-comparative analyses
- The objective of this study is to compare the efficacy of C/T versus Poly/AG based regimens for serious infections due to MDR/XDR *P. aeruginosa*

Methods

- Retrospective cohort analysis at 5 medical centers in Michigan and Ohio
- Inclusion criteria: Infections due to MDR/XDR *P. aeruginosa*, Receipt of C/T or Poly/AG as "backbone therapy" for ≥ 48 hours
- Exclusion criteria: Creatinine clearance ≤ 20 mL/min or requiring RRT at baseline or receipt of both C/T plus an intravenous Poly/AG for > 48 hours

Definitions:

- Clinical cure: Resolution of the signs/symptoms of infection without needing to modify (escalate) therapy based on failure or toxicity
- Acute Kidney Injury (AKI): Defined per the RIFLE criteria
- Combination therapy was defined as use of a second agent directed towards *P. aeruginosa* for > 48 hours regardless of *in vitro* susceptibility

Statistical analyses:

- Bivariate comparisons between patients receiving C/T and Poly/AG based regimens for baseline characteristics and outcomes performed
  - Categorical Data: Chi-square or Fisher's Exact Test as appropriate
  - Continuous Data: T-test or Wilcoxon-Rank Sum as appropriate
- Multivariable analyses:
  - Multivariable analyses were performed to determine the independent effect of treatment on outcomes of interest (clinical cure, mortality, AKI)
  - Models were constructed including treatment group and any covariates associated with being treated with C/T at a p value ≤ 0.20
  - Adjusted odds ratios and 95% confidence intervals for C/T treatment were determined

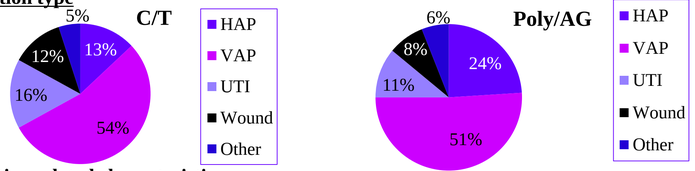
Results

Demographics and baseline characteristics

	C/T N = 94	Poly/AG N = 97	P value
Age, years*	61.3 ±16.2	55.8 ± 14.3	0.014
Female	30 (32)	28 (29)	0.65
Race, white	51 (54)	57 (59)	0.56
Admission from home	39 (42)	35 (36)	0.46
Admission from SNF/LTAC	33 (35)	33 (34)	0.88
Diabetes	37 (39)	30 (31)	0.22
Chronic Pulmonary Disease	40 (43)	43 (44)	0.81
Chronic Kidney Disease	22 (23)	10 (10)	0.02
Immunosuppression	19 (20)	14 (14)	0.29
Charlson Comorbidity Index**	3 (1 – 5)	2 (1 – 4)	0.55
Baseline Creatinine Clearance**	65.9 (36 – 110)	92.3 (56.4 – 132.0)	0.004

* Mean ± SD, ** median (interquartile range), otherwise n (%)

Infection type



Infection related characteristics

	C/T N = 94	Poly/AG N = 97	P value
Mechanical ventilation	59 (63)	64 (66)	0.64
Intensive care unit status	67 (71)	65 (67)	0.54
Severe sepsis/septic shock	37 (39)	44 (45)	0.40
SOFA score**	8 (6 – 10)	8 (5 – 10)	0.39
Bacteremia	5 (5)	7 (7)	0.59
ID consult	94 (100)	89 (92)	0.04
Time (hours) to appropriate therapy**	55.5 (24 – 79.5)	42 (3 – 72)	0.11
Time (hours) to study agent**	64.7 (45 – 93)	52.6 (5 – 94)	0.08

** median (interquartile range), otherwise n (%)

Results

Treatment

	C/T N = 94	Poly/AG N = 97	P value
Regimen backbone			
Polymyxin	N/A	56 (58)	N/A
Aminoglycoside		41 (42)	
Duration of therapy*	10 (7 – 14)	9 (6 – 14)	0.10
Combination therapy	14 (15)	69 (71)	< 0.0001
Combination agent susceptible	14 (100)	23 (33)	N/A
Combination agent intermediate	N/A	17 (25)	

*Median (interquartile range), otherwise listed as n (%)

Combination agents used – C/T: Ciprofloxacin (3), INH colistin (8), INH AG (3); Poly/AG: Beta-lactam (54), Ciprofloxacin (6), polymyxin (2) aminoglycoside (2), INH colistin (1), INH AG (4)

Outcomes

	C/T N = 94	Poly/AG N = 97	P value	Adjusted Odds Ratio (95% CI)**
Clinical cure	76 (81)	59 (61)	0.006	2.33 (1.14 – 4.75)
In hospital mortality	20 (21)	25 (26)	0.46	0.64 (0.31 – 1.32)
Acute Kidney Injury	6 (6)	33 (34)	< 0.001	0.08 (0.03 – 0.24)
Risk	2	7		
Injury	3	12		
Failure	1	14		
C. difficile on therapy	3 (3)	5 (5)	0.50	
Length of Stay* (from onset of infection)	15 (9 – 28)	14 (9 – 24)	0.94	

* Median (interquartile range), otherwise listed as n (%);
** aOR adjusted for age, baseline renal function, ID consult, time to appropriate therapy, infections in the past 90 days, and duration of therapy

Conclusions

- Treatment of serious infections caused by MDR/XDR *P. aeruginosa* with C/T is associated with higher rate of clinical cure and lower rate and severity of acute kidney injury than treatment with Poly/AG based regimens
- In hospital mortality rates were not different between treatment groups

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