An Analysis of Weight-Based Dosing for Trimethoprim-Sulfamethoxazole in Skin and Soft Tissue Infections

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Background

- Skin and soft tissue infections (SSTI) are a common presentation to both the inpatient and outpatient settings[1-2]
- Guidelines recommend trimethoprim-sulfamethoxazole (TMP/SMX) as a potential agent for treating purulent SSTIs, with dosing recommendations of 1 or 2 double strength tablets by mouth twice daily[3]
- Studies suggest that weight-based dosing of TMP/SMX, based on the trimethoprim component, has a clinical impact in respect to treatment failures for SSTIs[4]
- There are no studies to date that assess the incidence of treatment failures in SSTIs with TMP/SMX dosed ≥ 5mg of trimethoprim/kg/day

Aim

- To determine if TMP/SMX dosed ≥ 5mg of trimethoprim/kg/day is associated with fewer treatment failures compared to TMP/SMX dosed < 5mg of trimethoprim/kg/day among patients with a SSTI

Methods

Design:	Observational, single health system, retrospective, chart review
Inclusion Criteria:	Patients aged 18 or older who were prescribed TMP/SMX for a SSTI based on ICD-9/10 codes
Exclusion Criteria:	Antibiotics in addition to TMP/SMX, ICD code did not match indication, calculated creatinine clearance < 30mL/min, receiving renal replacement therapy or dialysis, absolute neutrophil count < 500 cells/µL, pregnancy, inmates
Time period:	January 2009 through August 2021

Primary Outcome: incidence of treatment failure defined as one or more
- Admission due to same infection within 30 days from initial prescription
- Change in antibiotic within 30 days from initial prescription for the same indication
- Referral to infectious disease (ID) specialist within 30 days from initial prescription for the same indication

Secondary Outcome: incidence of adverse effects

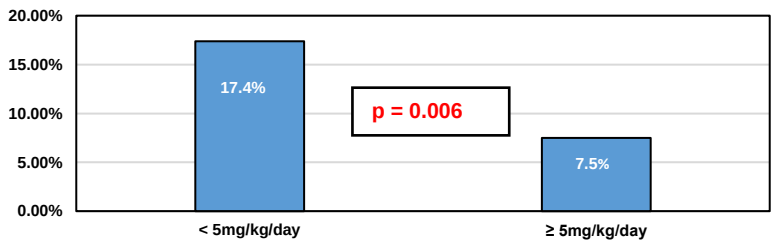
Statistical Analysis:
- 161 patients per group required to meet 90% power
- Alpha set at 0.05
- Continuous data: Mann-Whitney U Test or Student t-test
- Categorical data: Chi-squared test or Fisher's exact
- Univariate and multivariate analysis were conducted to identify variables associated with treatment failure

Results

Table 1: Baseline Characteristics n = 351

Characteristics (Mean)	< 5mg/kg/day (n = 190)	≥ 5mg/kg/day (n = 161)	p-value
Age (years) ± SD	47.7 ± 14.3	42.8 ± 14.9	0.002
Gender, n (%)			
Male	116 (61.1)	77 (47.8)	0.014
Female	74 (38.9)	84 (52.2)	
Race, n (%)			
African American	65 (35.7)	33 (21.9)	
Hispanic/Latino	4 (2.1)	6 (3.7)	
White	112 (61.5)	111 (73.5)	0.043
Other	1 (0.5)	1 (0.7)	
Weight (kg) ± SD			
Actual bodyweight	97.6 ± 28.6	69.2 ± 21.3	<0.001
Ideal bodyweight	66.3 ± 10.5	61.8 ± 11.1	
Adjusted bodyweight	80.1 ± 13.5	64.5 ± 13.5	
Body Mass Index (BMI) ± SD	33.1 ± 10	24.5 ± 7.3	<0.001
Insurance status, n (%)			
Commercial or government	113 (59.5)	67 (41.6)	
Self-Pay	13 (6.8)	13 (8.1)	
Medication Assistance	38 (20)	35 (21.7)	0.002
Not available	26 (13.7)	46 (28.6)	
Serum creatinine (mg/dL) ± SD	0.9 ± 0.4	0.7 ± 0.2	<0.001
Creatinine Clearance (mL/min) ± SD	121.4 ± 45.3	115.9 ± 38.6	0.226
Indication, n (%)			
SSTI	3 (1.6)	7 (4.3)	0.218
Cellulitis	146 (76.8)	124 (77)	1
Abscess	107 (56.3)	92 (57.1)	0.962
Prescribed duration (days) ± SD	9.4 ± 3.2	9.8 ± 4.5	0.312
Received inpatient treatment, n (%)			
Inpatient treatment	50 (26.3)	92 (57.1)	<0.001
Outpatient only	140 (73.7)	69 (42.9)	
IV antibiotic days ± SD	0.6 ± 1.3	2.1 (2.9)	<0.001
Total duration of therapy (days) ± SD	10 ± 3.4	11.9 (5.6)	<0.001
Surgical intervention, n (%)			
Incision and drainage	59 (31.1)	65 (40.4)	0.088
Irrigation and debridement	6 (3.2)	13 (8.1)	0.073
Amputation	1 (0.5)	1 (0.6)	1
Culture and Sensitivities obtained, n (%)	62 (32.6)	81 (50.3)	0.001
Antibiotics within last 90 days, n (%)	83 (43.7)	103 (64.4)	<0.001

Figure 1: Incidence of Treatment Failures



Results

Table 2: Primary & Secondary Outcomes

Primary Outcome	< 5mg/kg/day (n = 190)	≥ 5mg/kg/day (n = 161)	p-value
Treatment Failure, n (%)	33 (17.4)	12 (7.5)	
Admission within 30 days	26 (13.7)	8 (5)	0.006
Change in antibiotic within 30 days	26 (13.7)	6 (3.7)	
Referral to ID specialist within 30 days	2 (1.1)	2(1.2)	
Secondary Outcome			
Adverse Event, n (%)	5 (2.6)	11 (6.8)	
Nausea	4 (2.1)	5 (3.1)	
Vomiting	1 (0.5)	3 (1.9)	
Diarrhea	1 (0.5)	3 (1.9)	0.105
Nephrotoxicity	1 (0.5)	4 (2.5)	
Rash	-	1 (0.6)	
Other	-	1	

Table 3: Univariate and Multivariate Analysis

Variable	No Treatment Failure	Treatment Failure	OR (95% CI) Univariable	p-value	OR (95% CI) Multivariable	p-value
Dose, n (%)						
< 5mg/kg/day	157 (82.6)	33 (17.4)				
≥ 5mg/kg/day	149 (92.5)	12 (7.5)	0.38 (0.18-0.75)	0.007	0.39 (0.17-0.86)	0.023
Age, average ± SD	44.8 ± 14.8	49.5 ± 13.9	1.02 (1-1.04)	0.050	1.01 (0.99-1.04)	0.202
BMI, average ± SD	28.8 ± 9.8	31.4 ± 9.5	1.02 (0.99-1.05)	0.098	1.01 (0.97-1.05)	0.582
Adverse event						
No	295 (88.1)	40 (11.9)				
Yes	11 (68.6)	5 (31.2)	3.35 (1.10-9.74)	0.032	3.89 (1.09-12.6)	0.027

Discussion

- Patients who received < 5mg of trimethoprim/kg/day experienced significantly more treatment failures compared to those who received ≥ 5mg of trimethoprim/kg/day
- Patients who received ≥ 5mg of trimethoprim/kg/day did not experience more adverse events compared to those who received < 5mg of trimethoprim/kg/day
- Factors associated with treatment failure include TMP/SMX dose < 5mg of trimethoprim/kg/day and NOT experiencing an adverse event
- Limitations include retrospective design, randomization did not result in similar groups, adherence could not be assessed, no collection of comorbid conditions, and not powered to detect a difference in adverse events

References

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