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Association of trimethoprim-sulfamethoxazole with improved lung function in pediatric asthma

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Asthma affects over 300 million patients worldwide and is characterized by intermittent reversible airflow obstruction and airway inflammation. *Pneumocystis*, an opportunistic fungus, has recently been implicated in asthma pathogenesis. In preclinical models, *Pneumocystis* exposure causes goblet cell hyperplasia, bronchial hyperreactivity, and airway inflammation.[1,2] From a clinical perspective, patients with severe asthma have elevated anti-*Pneumocystis* antibody titers compared to healthy controls and higher levels of anti-*Pneumocystis* IgG are correlated with worsened lung function.[1] Furthermore, evaluation of the lung mycobiome identified that *Pneumocystis jirovecii* 18S rRNA was more abundant in the bronchoalveolar lavage fluid of patients with severe asthma compared to non-asthmatic controls.[3] Cumulatively, these studies suggest that *Pneumocystis* may represent an unrecognized contributor to asthma pathophysiology.

In this study, we sought to determine if *Pneumocystis* treatment improved lung function or exacerbation frequency in patients with asthma. We compared children who received trimethoprim-sulfamethoxazole (TMP-SMX), a standard therapeutic for *Pneumocystis*, with

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asthmatic patients who received clindamycin, an antibiotic without activity against *Pneumocystis* that is commonly used for similar indications (e.g. SSTI) as a control.[4] The electronic health record was queried for all patients from 2010-2018 who had an order/prescription for TMP-SMX or clindamycin and at least one spirometry. Each record was then manually reviewed for a diagnosis of asthma and for exclusion criteria (cystic fibrosis, ciliopathy, transplantation, malignancy, bronchiectasis, restrictive lung disease, prematurity <32 weeks, bronchopulmonary dysplasia, ventilator dependence, congenital heart disease, immunodeficiency, sickle cell disease, collagen vascular disorders and one-time doses of antibiotic). This study was approved by the Institutional Review Board (STUDY19010136).

Between 2010-2018, 79,047 orders of TMP-SMX and 86,033 orders of clindamycin were placed for 14,109 and 20,283 unique patients, respectively. Similarly, there were 46,215 spirometries performed on 16,444 unique patients. Among patients with spirometry data, there were 1,089 patients with an order for TMP-SMX and 937 patients with an order for clindamycin. After chart review and exclusion, 144 patients with asthma in the TMP-SMX group and 202 patients with asthma in the clindamycin group were included in the cross-sectional analysis (Table 1, right). Of those, 24 patients in the TMP-SMX group and 41 patients in the clindamycin group had both baseline and follow-up spirometry (+/− 12 months of antibiotic course) and were included in the longitudinal analysis (Table 1, left). Demographics between the TMP-SMX and clindamycin groups were similar, although TMP-SMX was prescribed more commonly for urologic indications (Table 1).

Baseline spirometry showed no differences in FEV1, FVC, FEV1/FVC, or FEF25-75 between antibiotic groups (Table 1). Similarly, there were no significant differences in the interval between baseline spirometry to antibiotics or antibiotics to follow-up spirometry. There were no differences in the proportion of patients requiring either an escalation or de-escalation in therapy between measurement of spirometry.

In patients that received TMP-SMX, there was a significant increase in FEV1 between baseline and follow-up spirometry (p=0.0023 by paired t-test, Table 1); in contrast, there was no significant FEV1 change in the clindamycin group (p=0.78). Of note, 79% of asthma patients receiving TMP-SMX had an increased FEV1 at the follow-up, compared to 44% in the clindamycin group (p=0.01). Similarly, there was a significant increase in FVC with TMP-SMX (p=0.016) but not clindamycin (p=0.54). After adjusting for age, sex, race, antibiotic indication, ICS dose, and the time intervals between spirometry and antibiotics, the improvements in FEV1 and FVC were again significantly higher in the TMP-SMX group than the clindamycin group. Furthermore, patients who received TMP-SMX had a significant reduction in the proportion and total number of ED visits for asthma exacerbations the 12 months following antibiotics (Table 1, right).

To our knowledge, this is the first association between the use of an antibiotic active against *Pneumocystis* and the improvement of lung function and asthma control. The role of antibiotics in asthma pathogenesis has been evaluated previously. Any antibiotic use, including TMP-SMX, within the first 6 months of life is associated with development of atopic diseases including asthma.[5] Therapeutically, there is limited evidence for lung function improvement following antibiotic treatment in the setting of an exacerbation.[6] As a

long-term therapy used outside of exacerbations, however, macrolide antibiotics have been shown to increase peak flow measurements and correlate with improved symptoms without changes in lung function measures.[7] None of these studies, however, evaluated antibiotics with activity against *Pneumocystis* or assessed changes in pulmonary function or exacerbation rate after the antibiotic course.

The only known natural reservoir of *Pneumocystis jirovecii* is humans and near ubiquitous *Pneumocystis* prevalence has been demonstrated in infants on autopsy specimens. [8,9] The presence of *Pneumocystis* has been associated with increased MUC5AC expression, a mucin implicated in asthma pathogenesis.[9,10] The detection of subclinical *Pneumocystis* infection or *Pneumocystis* colonization is limited by the lack of a non-invasive biomarker. Future studies characterizing the natural history of *Pneumocystis* burden in the lungs of patients with asthma could be highly informative.

There are several limitations to the current study. Despite being at a large tertiary care pediatric hospital, the cohort of patients with baseline and follow up spirometry in the time frame of antibiotic exposure was relatively small. Second, while our hypothesis is that TMP-SMX would improve lung function due to activity against *Pneumocystis*, TMP-SMX is active against other human commensals and pathogens, and the impact of TMP-SMX on the human microbiota (e.g. lung, gut) cannot be excluded. Additionally, the retrospective nature of the current pilot investigation cannot demonstrate a causal or direct relationship between TMP-SMX and changes in lung function. Finally, although quite similar, the dose and duration of antibiotic exposure was not uniform across the patient population and warrants further investigation.

Despite the limitations of this retrospective study, the current study demonstrates an association between TMP-SMX use and improved lung function and reduced exacerbation rate in pediatric asthma. Further, the mounting animal model and clinical data linking *Pneumocystis* to asthma suggests that further study using a randomized, double-blind placebo-controlled trial evaluating the effects of TMP-SMX treatment in patient with asthma is warranted.

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Abbreviations:

TMP-SMX	Trimethoprim-sulfamethoxazole
PFT	pulmonary function test
EHR	electronic health record
FEV1	forced expiratory volume in the first second

FVC	forced vital capacity
FEF25-75	mid-expiratory flow rate

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Table 1.

Trimethoprim-sulfamethoxazole use in children with asthma is associated with improved FEV1 and reduced ED visits.

	Baseline/Follow up PFT cohort				Total cohort		
	TMP-SMX (n=24)	**Clindamycin (n=41)**	**p-value**		**TMP-SMX (n=144)**	**Clindamycin (n=202)**	**p-value**
Demographics							
Age							
Mean in years (+/− SEM)	10.7 (0.86)	11.2 (0.63)	0.59		10.6 (0.44)	10.7 (0.33)	0.73
Biologic sex, n (%)							
Male	10 (42%)	25 (61%)	0.20		68 (47%)	107 (53%)	0.33
Female	14 (58%)	16 (39%)			76 (53%)	95 (47%)	
Race, n (%)							
Caucasian	18 (75%)	21 (51%)	0.16		101 (70%)	122 (60%)	0.09
African American	5 (21%)	18 (44%)			40 (28%)	76 (38%)	
Other/declined	1 (4%)	2 (5%)			3 (2%)	4 (2%)	
Indication, n (%)							
ENT	7 (29%)	7 (17%)	0.02		26 (18%)	51 (25%)	0.03
Urologic	6 (25%)	1 (2%)			44 (31%)	1 (<1%)	
SSTI	9 (37%)	24 (59%)			71 (49%)	134 (66%)	
Respiratory	2 (8%)	9 (22%)			3 (2%)	16 (8%)	
Asthma therapy, n (%)							
No controller	3 (13%)	6 (15%)	0.99 *		75 (52%)	87 (43%)	0.09
Inhaled corticosteroid							
Low-dose ICS	9 (37%)	11 (27%)	0.49		28 (19%)	47 (23%)	0.51
Medium ICS	3 (13%)	7 (17%)			4 (3%)	14 (6%)	
High-dose ICS	9 (37%)	17 (41%)			39 (27%)	54 (27%)	
Systemic steroid	1 (4%)	2 (5%)	0.99 *		1 (<1%)	2 (<1%)	0.99 *
Biologic	1 (4%)	3 (7%)	0.99 *		1 (<1%)	3 (1%)	0.64 *

Baseline/Follow up PFT cohort					Total cohort		
	TMP-SMX (n=24)	**Clindamycin (n=41)**	**p-value**		**TMP-SMX (n=144)**	**Clindamycin (n=202)**	**p-value**
Spirometry				Emergency Department Visits			
Days from baseline spirometry to antibiotics Mean (+/−SE)	177 (+/−43)	194 (+/−26)	0.71 *	Total ED visits			
				12 months prior	60	71	0.04
				12 months after	32	66	
Days from antibiotics to follow up spirometry Mean (+/−SE)	164 (+/−33)	131 (+/−19)	0.36 *	Change in ED visits after antibiotics			
				Fewer	22 (15.1%)	28 (13.9%)	0.05
Escalation in therapy n (%)	2 (8%)	6 (15%)	0.70	Same	6 (4.2%)	10 (5.0%)	
				More	9 (6.3%)	32 (15.8%)	
De-escalation in therapy n (%)	1 (4%)	3 (7%)	0.99	None	107 (74.3%)	132 (65.3%)	
FEV1 Mean (95% CI)							
Baseline	90.3 (82.8-97.9)	93.6 (89.3-98.5)	0.42				
Follow-up	96.4 (89.5-103)	93.3 (88.6-98.1)	0.44				
Change	6.04 (2.4-9.7)	−0.56 (−2.8-1.7)	0.002, 0.001 ‡				
FVC Mean (95% CI)							
Baseline	97.8 (91.0-104.5)	102.3 (97.4-107.1)	0.29				
Follow-up	102.5 (96.6-108.3)	101.4 (96.2-106.5)	0.78				
Change	4.71 (0.96-8.5)	−0.93 (−3.1-1.3)	0.006, 0.001 ‡				
FEV/FVC Mean (95% CI)							
Baseline	81.3 (77.5-85.1)	80.4 (77.8-83.0)	0.68				
Follow-up	82.6 (79.2-86.0)	80.7 (78.1-83.4)	0.78				

Baseline/Follow up PFT cohort					Total cohort		
	TMP-SMX (n=24)	**Clindamycin (n=41)**	**p-value**		**TMP-SMX (n=144)**	**Clindamycin (n=202)**	**p-value**
Change	1.33 (−1.4-4.1)	0.34 (−1.3-1.9)	0.49, 0.335‡				
FEF25-75 Mean (95% CI)							
Baseline	79.8 (61.9-97.7)	83.2 (72.4-94.0)	0.46				
Follow-up	83.1 (69.5-96.8)	75.4 (67.7-83.1)	0.38				
Change	4.35 (−8.8-17.5)	−7.80 (−17.4-1.8)	0.13, 0.065‡				

Categorical variables analyzed via Chi-square test or Fisher's exact test (for analyses with n<5, denoted by *).

Continuous variables analyzed by unpaired t-test unless noted otherwise.

‡denotes multivariable linear regression analysis.