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# Polypharmacy and Antibiotic-Steroid Interrelationships in Pulmonology Prescriptions: An Analysis from Pakistan

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**Abstract**

***Background:*** Polypharmacy and irrational prescribing are well-documented in Pakistan. However, the interrelationships between antibiotic use, steroid prescribing, and overall medication burden remain unexplored.

***Objective*:** This study aimed to analyze polypharmacy patterns, antibiotic-steroid associations, and the graded association between antibiotic use and medication burden in pulmonology outpatients.

***Methods:*** A cross-sectional study was conducted on 300 systematically sampled outpatient pulmonology prescriptions from Southern Khyber Pakhtunkhwa, Pakistan. Data on total medications, antibiotic use, and steroid prescribing were extracted. Polypharmacy was defined as ≥5 medications per prescription. Statistical analyses included descriptive statistics, chi-square tests, Fisher's exact test, and one-way ANOVA with post-hoc Tukey tests.

***Results:*** Polypharmacy was observed in 93.3% (280/300) of prescriptions (mean 5.96±1.20 medications). Notably, 66.1% contained ≥6 medications and 31.4% contained ≥7 medications, which identified a high-risk subgroup. Antibiotic prescribing showed no association with steroid use ($\chi^2$=3.976, p=0.409) or polypharmacy status (Fisher's exact, p=0.493). However, a significant graded association emerged between antibiotic use and medication burden (ANOVA: F=3.72, p=0.026). Prescriptions with ≥2 antibiotics had significantly higher medication counts (6.63±1.43) than antibiotic-free prescriptions (5.67±1.07; mean difference=0.96, p=0.003).

***Conclusion:*** This study demonstrates near-universal polypharmacy in Pakistani pulmonology practice, with one-third of patients receiving seven or more medications. While steroid prescribing operates independently of antibiotic decisions, antibiotic use exhibits a graded association with overall medication burden, which serves as a marker for prescription complexity. These findings identify high-risk subgroups for targeted medication review and support "antibiotic-triggered" deprescribing protocols to mitigate polypharmacy risks and antimicrobial resistance.

**Keywords:** Polypharmacy, anti-bacterial agents, steroids, drug utilization, pulmonology, Pakistan.

## 1. INTRODUCTION

Polypharmacy, defined as the concomitant use of five or more medications, is an emerging global health challenge. It has major consequences for patient safety, healthcare costs, and clinical outcomes [1, 2]. Beyond the well-documented risks of adverse drug reactions, drug–drug interactions, and treatment non-adherence [2, 4], polypharmacy leads to poor medication adherence, which results in treatment failure and thus prolong the duration of hospitalization [3]. The complexity of managing multiple medications often overwhelms patients. This leads to poor health outcomes and places an unsustainable burden on healthcare system's resources [4].

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These challenges are particularly common in low- and middle-income countries, where unique systemic pressures affect the healthcare system. In Pakistan, research indicates that irrational prescribing practices remain a concern in tertiary care settings. Among these the most notable problems are the excessive and often inappropriate use of antibiotics and injectable formulations [6, 8]. This trend is further compounded by widespread polypharmacy, and a persistent reliance on brand-name products [7]. Consequently, patients with chronic respiratory conditions, such as chronic obstructive pulmonary disease (COPD) have high exposure to complex, multi-drug regimens. Such regimens frequently deviate from international management standards like the GOLD guidelines [9, 10]. This reliance on empiric, multi-drug protocols complicate patient adherence, increase the incidence of adverse drug reactions and cost of treatment [6].

Preliminary data from Pakistani tertiary care settings indicate that average drug encounters often exceed five medications per prescription. Also, more than one-third of total orders contain at least one parenteral administration [6]. Such clinical trajectories necessitate a deeper analysis within the regional healthcare infrastructure to explore how these therapeutic choices align with established WHO prescribing indicators [11].

Despite this documented burden of antibiotic and injectable use, several important questions remain unanswered. It is unclear how antibiotic use relates to steroid prescribing decisions. Clinically, this is an important question because both antibiotics and steroids are commonly used in respiratory care but for distinctly different indications. Furthermore, the extent to which antibiotic use serves as a marker for overall prescription complexity and polypharmacy burden has not been systematically evaluated. The detailed distribution of polypharmacy severity in this population also remains uncharacterized. Understanding these broader interrelationships is essential for designing integrated stewardship interventions that address multiple prescribing patterns simultaneously rather than in isolation.

To address this gap, this study was designed to; 1) Determine the prevalence and distribution of polypharmacy in respiratory care, 2) Examine the association between antibiotic and steroid prescribing decisions, 3) Evaluate the relationship between antibiotic use and polypharmacy status and 4) Compare medication burden across different antibiotic prescribing categories.

Elucidating these interrelated prescribing patterns will provide critical evidence for targeted antimicrobial stewardship programs, context-appropriate guidelines, and stronger policy interventions. This is ultimately essential for improving patient safety and combating antimicrobial resistance in Pakistan and similar settings.

## 2. METHODOLOGY

### 2.1. Study Design and Setting

This retrospective, descriptive, cross-sectional drug utilization study analyzed 300 outpatient pulmonology prescriptions from Southern Khyber Pakhtunkhwa, Pakistan, collected between 15$^{th}$ November 2025 and 15$^{th}$ January 2026. This study was reported in accordance with the STROBE guidelines for cross-sectional studies. The study was exempted from ethical review by the Ethics Review Committee of Gomal University Dera Ismail Khan due to its retrospective and non-interventional nature. Patient confidentiality was maintained through anonymization of all prescription data.

### 2.2. Sample and Data Collection

Sample size was determined using the WHO sample size calculator, which indicated that a minimum of 296 prescriptions was required to achieve a 95% confidence level with a 5.7% margin of error, assuming a population proportion of 50%. To reduce selection bias and ensure representation of general prescribing trends, prescriptions were collected directly from community pharmacies across the study region using systematic random sampling, with the researcher present on-site to identify and select eligible paper-based prescriptions as they were presented. Data from selected prescriptions were extracted by a single reviewer into a structured Excel spreadsheet and subsequently imported into SPSS for analysis.

### 2.3. Inclusion and Exclusion Criteria

Prescriptions were included on the basis of the following criteria:

- Patients aged 14 years or older
- Documented respiratory-related diagnosis (asthma, COPD, pneumonia, bronchitis, allergic respiratory disorders, LRTI, URTI, tuberculosis, bronchiectasis)
- Prescribed by a pulmonologist or respiratory medicine specialist Prescriptions were excluded if they had:
- Incomplete or illegible diagnostic information
- Non-respiratory primary diagnosis
- Patients under 14 years of age

### 2.4. Variables and Data Extraction

Data were extracted using a structured, pre-piloted extraction form capturing patient demographics, clinical diagnosis, and complete medication listings, with injectable status recorded as a binary variable for each prescription.

### 2.5. Operational Definitions

- Polypharmacy: Prescription containing ≥5 medications (WHO definition)
- Antibiotic category: Categorized as no antibiotic, one antibiotic, or two or more antibiotics per prescription
- Steroid category: Categorized as no steroid, one steroid, or two or more steroids per prescription.

### 2.6. Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 27). Descriptive statistics summarized categorical variables as frequencies (n) and percentages (%), while continuous variables were reported as mean ± standard deviation. Polypharmacy prevalence and distribution were assessed using descriptive statistics on the total medication count. The association between antibiotic and steroid use was examined using Pearson's chi-square test, comparing antibiotic category (0, 1, 2+) with steroid category (0, 1, 2+). The association between antibiotic use and polypharmacy status was examined using Fisher's exact test, comparing antibiotic use (yes/no) with polypharmacy (yes/no). Medication burden across antibiotic categories (0, 1, 2+) was compared using one-way ANOVA with post-hoc Tukey tests; given the adequate sample size within each antibiotic category ($n \geq 30$), the ANOVA was considered reasonably robust to minor deviations from normality, although formal assumption testing was not performed and is acknowledged as a limitation of the analysis. Statistical significance was set at $p < 0.05$. Effect sizes were reported where applicable: Cramér's V for chi-square tests, Phi coefficient ($\varphi$) for 2×2 tables, and eta-squared ($\eta^2$) for ANOVA.

## 3. RESULTS

### 3.1. Study Population and Prescription Characteristics

A total of 300 outpatient pulmonology prescriptions were analyzed. The cohort consisted of 164 females (54.7%) and 136 males (45.3%). Patient age showed a bimodal distribution, with the largest proportions in the 45–54-year (25.3%) and 15–24-year (23.3%) age groups. Comorbidities were documented in 50 patients (16.7%). Asthma (26.0%) and pneumonia (20.0%) were the two most common primary diagnoses, followed by allergy (19.3%), COPD (9.3%), and bronchitis (9.3%). Less common diagnoses included lower respiratory tract infection (8.0%), upper respiratory tract infection (3.3%), influenza (2.0%), tuberculosis (1.3%), and bronchiectasis (1.3%) (Table **1**).

**Table 1: Patient demographics and clinical characteristics.**

| Characteristics | Number (n) | Percentage (%) |
|---|---|---|
| **Gender** | | |
| Female | 164 | 54.7 |
| Male | 136 | 45.3 |
| **Age Group (years)** | | |
| 15-24 | 70 | 23.3 |
| 25-34 | 28 | 9.3 |
| 35-44 | 36 | 12 |
| 45-54 | 76 | 25.3 |
| 55-64 | 64 | 21.3 |
| 65-74 | 26 | 8.7 |
| **Comorbidities** | | |
| Present | 50 | 16.7 |
| Absent | 250 | 83.3 |
| **Primary Diagnosis** | | |
| Asthma | 78 | 26 |
| Pneumonia | 60 | 20 |
| Allergy | 58 | 19.3 |
| COPD | 28 | 9.3 |
| Bronchitis | 28 | 9.3 |
| LRTI | 24 | 8 |
| URTI | 10 | 3.3 |
| Flu | 6 | 2 |
| Tuberculosis | 4 | 1.3 |
| Bronchiectasis | 4 | 1.3 |

### 3.2. Polypharmacy Prevalence and Distribution

Polypharmacy (≥5 medications) was observed in 93.3% (280/300) of prescriptions. Notably, 66.1% (198/300) of prescriptions contained six or more medications, and 31.4% (94/300) contained seven or more medications. Excessive polypharmacy (≥10 medications) was present in 2.0% (6/300) of prescriptions. Table **2** shows the complete frequency distribution of total medications per prescription. The median number of medications was 6 (IQR: 5-7), indicating that half of all patients received between five and seven medications. The 75th percentile of 7 medications means that one-quarter of patients received seven or more medications, which represents a particularly high-risk subgroup.

**Table 2: Distribution of total medications per prescription (N = 300).**

| Medicines | Frequency | Percentage (%) | Cumulative (%) |
|---|---|---|---|
| 1 | 2 | 0.7 | 0.7 |
| 2 | 0 | 0 | 0.7 |
| 3 | 6 | 2 | 2.7 |
| 4 | 12 | 4 | 6.7 |
| 5 | 82 | 27.3 | 34 |
| 6 | 104 | 34.7 | 68.7 |
| 7 | 50 | 16.7 | 85.3 |
| 8 | 32 | 10.7 | 96 |
| 9 | 6 | 2 | 98 |
| 10 | 6 | 2 | 100 |
| **Total** | **300** | **100** | **100** |

*Note: No prescriptions contained exactly 2 medications.*

### 3.3. Association between Antibiotic Use, Steroid Prescribing and Polypharmacy

Antibiotic prescribing showed no significant association with steroid use ($\chi^2 = 3.976$, df = 4, p = 0.409). The distribution of steroid prescriptions remained consistent across all antibiotic categories, with approximately 50% of prescriptions containing one steroid and 35-37% containing multiple steroids regardless of antibiotic status (Table **3**).

Similarly, no significant association was observed between antibiotic use and polypharmacy status (Fisher's exact test, p = 0.493, φ = 0.054). Although antibiotics were present in 94.2% of polypharmacy prescriptions compared to 60.0% of non-polypharmacy prescriptions, this difference was not statistically significant (Table **3**).

### 3.4. Medication Burden Across Antibiotic Categories

One-way ANOVA revealed significant differences in mean total medication count across antibiotic categories ($F(2,297) = 3.72$, p = 0.026). A graded increase in medication burden was observed with increasing antibiotic use: prescriptions with two or more antibiotics had the highest mean medication count (6.63 ± 1.43), followed by those with one antibiotic (6.03 ± 1.18), while antibiotic-free prescriptions had the lowest burden (5.67 ± 1.07) (Table **4**).

**Table 4: Mean total medications by antibiotic category (N=300).**

| Antibiotic Category | n | Mean ± SD | 95% CI | Range |
|---|---|---|---|---|
| No antibiotics | 92 | 5.67 ± 1.07 | 5.45-5.90 | 3-8 |
| One antibiotic | 176 | 6.03 ± 1.18 | 5.85-6.21 | 3-9 |
| Two or more antibiotics | 32 | 6.63 ± 1.43 | 6.11-7.14 | 4-9 |
| Total | 300 | 5.96 ± 1.20 | 5.82-6.09 | 3-9 |

*One-way ANOVA: F(2,297) = 3.72, p = 0.026*

**Table 3: Associations between antibiotic use, steroid prescribing, and polypharmacy (N=300).**

| Outcome | No Antibiotics (n=92) | Antibiotics Present (n=208) | Statistical Test | p-value | Effect Size |
|---|---|---|---|---|---|
| **Steroid prescribing** | | | $\chi^2 = 3.976$, df=4 | 0.409 | Cramér's V = 0.115 |
| No steroid | 20 (21.7%) | 28 (13.5%) | | | |
| One steroid | 40 (43.5%) | 102 (49.0%) | | | |
| Two or more steroids | 32 (34.8%) | 78 (37.5%) | | | |
| **Polypharmacy** | | | Fisher's exact | 0.493 | φ = 0.054 |
| No polypharmacy | 8 (8.7%) | 12 (5.8%) | | | |
| Polypharmacy present | 84 (91.3%) | 196 (94.2%) | | | |

*Note: Steroid percentages are row percentages; polypharmacy percentages are column percentages.*

Post-hoc Tukey tests confirmed that prescriptions with two or more antibiotics contained significantly more medications than antibiotic-free prescriptions (mean difference = 0.96, 95% CI 0.28-1.64, p = 0.003). The difference between one antibiotic and antibiotic-free prescriptions approached but did not reach statistical significance (mean difference = 0.36, 95% CI -0.05 to 0.77, p = 0.098) (Fig. **1**).

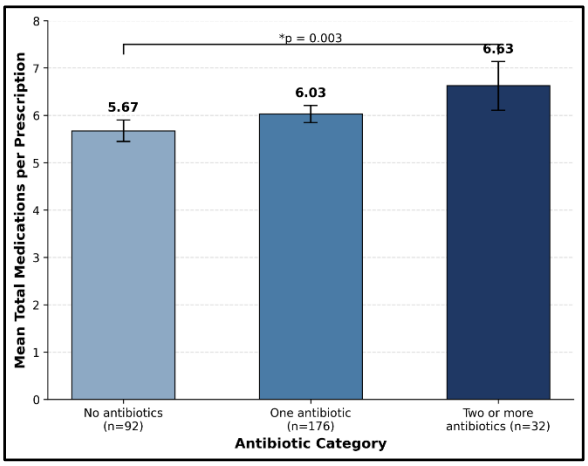



**Figure 1: Mean total medications per prescription across antibiotic categories (N=300).** Bars represent group means; error bars indicate 95% confidence intervals. Asterisk denotes a statistically significant difference (p = 0.003).

## 4. DISCUSSION

This study provides the first detailed characterization of polypharmacy distribution, antibiotic-steroid relationships, and graded associations between antibiotic use and medication burden in Pakistani pulmonology outpatients. This analysis reveals three key findings: first, near-universal polypharmacy with a distinct high-risk subgroup; second, complete independence of steroid prescribing from antibiotic decisions; and third, a significant graded association where increasing antibiotic use is associated with escalating medication burden. Together, these findings extend our understanding of prescribing complexity in this population beyond antibiotic selection alone.

The exceptionally high rate of polypharmacy observed in our cohort (93.3%) far exceeds the WHO's threshold of five or more medications. It is consistent with observations in other regions of Pakistan where irrational prescribing is prevalent [6, 12]. However, this study provides the first detailed distribution of polypharmacy severity in a Pakistani pulmonology cohort. It revealed that 66.1% of prescriptions contained six or more medications and 31.4% contained seven or more. This substantial medication burden, with a mean of 5.96 drugs per prescription, highlights a systemic issue that may contribute to adverse drug reactions, drug-drug interactions, and increased healthcare costs [6]. A particularly high-risk subgroup of patients receiving seven or more medications requires targeted intervention, because polypharmacy in older populations has been associated with increased hospitalization, although evidence for other adverse outcomes, including adverse drug events, is conflicting [13]. It is important to note, however, that polypharmacy as defined here is a numerical threshold rather than a direct measure of prescribing appropriateness; combination inhalers and multi-drug regimens are often clinically necessary in chronic respiratory disease, and this study did not assess indication-level appropriateness. Previous research in general outpatient settings in Pakistan has reported mean medication counts ranging from 2.8 to 3.56 drugs per prescription [7, 8]. A substantially higher average of 8.32 drugs per prescription was observed in another study, which specifically focused on evaluating respiratory tract infections [5]. Our findings address this gap by demonstrating that pulmonology prescribing in this region consistently exceeds the WHO numerical benchmark, with a distribution that has not been previously characterized. Polypharmacy was reported in 38.2% of elderly outpatients at a tertiary care hospital in India [14], a prevalence far below that observed in our cohort. The magnitude of polypharmacy observed in our cohort (one-third of patients receiving seven or more medications) suggests that non-clinical factors, including habitual prescribing patterns, patient expectations, or diagnostic uncertainty in resource-limited settings, may also be involved.

A major contribution of this study is the demonstration that steroid prescribing operates independently of antibiotic use ($\chi^2 = 3.976$, p = 0.409). The study observed a uniform distribution of steroid use that was independent of antibiotic therapy. In both antibiotic and non-antibiotic groups, 50% of patients received one steroid and roughly 36% were prescribed more than one steroid. This suggests that antibiotic status was not associated with steroid selection, and that prescribers may be making separate, reasoned decisions about anti-inflammatory therapy. This finding is clinically reassuring and important. It suggests that steroid decisions may be driven by different clinical considerations than antimicrobial decisions, likely related to inflammatory status, control of asthma or COPD, and severity of exacerbation independent of infectious etiology. The independence observed here aligns with recommended GOLD guidelines that distinguish anti-inflammatory and antimicrobial therapy in respiratory conditions [9]. Steroid prescribing, by contrast, appears to follow independent clinical logic rather than tracking with antibiotic selection. This independence also has important implications for stewardship interventions: it reinforces that steroid should be prescribed based on inflammatory indications rather than added routinely to complex regimens. The fact that steroid prescribing does

not simply track overall polypharmacy suggests that prescribers are capable of selective, indication-based prescribing, an ability that could be leveraged to address other problematic co-prescribing patterns in this population, such as unnecessary injectable use.

Another clinically significant finding of this study is the graded association between antibiotic use and overall medication burden. One-way ANOVA revealed significant differences in mean total medication count across antibiotic categories ($F(2,297) = 3.72$, $p = 0.026$). A graded increase in total medication count was observed with increasing antibiotic use: prescriptions with two or more antibiotics showed the highest mean medication count ($6.63 \pm 1.43$), followed by those with one antibiotic ($6.03 \pm 1.18$), while the lowest burden ($5.67 \pm 1.07$) was observed in antibiotic-free prescriptions. Post-hoc analysis confirmed that prescriptions with multiple antibiotics contained significantly more medications than antibiotic-free prescriptions (mean difference = 0.96, 95% CI 0.28-1.64, $p = 0.003$). This difference of nearly one full medication, in a population already averaging six drugs per prescription, represents a clinically meaningful increase in regimen complexity. This graded pattern (more antibiotics associated with more total medications) suggests that antibiotic use may serve as a marker for overall prescription complexity. Importantly, this finding complements rather than contradicts the non-significant association between antibiotic use and polypharmacy status (Fisher's exact, $p = 0.493$): antibiotic use alone does not determine whether a prescription crosses the polypharmacy threshold, since 91.3% of antibiotic-free prescriptions already exhibited polypharmacy, but increasing antibiotic counts are associated with a gradual rise in medication burden. This distinction suggests that antibiotic use is not the primary driver of polypharmacy in this population, given that polypharmacy is already near-universal regardless, but may signal which patients have the most complex drug regimens. This association should be interpreted cautiously, however, as disease severity represents a plausible unmeasured confounder: more severely ill patients may independently require both a greater number of antibiotics and a greater number of overall medications, which could produce this graded pattern without antibiotic prescribing itself driving medication burden. Other possible explanations include more severe or polymicrobial infections requiring multiple antibiotics, empiric broad-spectrum therapy prescribed alongside other treatments, or prescribing practices in which multiple antibiotics simply co-occur with a generally more complex regimen [15, 16]. Distinguishing between these possibilities requires clinical severity data, which was not available in this retrospective analysis.

Together, these findings paint a broader picture of prescribing complexity in this cohort. Antibiotic use is associated with overall medication burden but not with steroid prescribing, suggesting that polypharmacy here clusters specifically around antibiotic-driven regimens, while anti-inflammatory therapy follows separate clinical logic. This suggests that the polypharmacy observed here is not random and appears to cluster specifically around antibiotic use, while anti-inflammatory therapy follows separate clinical logic. These patterns suggest that stewardship programs should target the antibiotic-prescribing complex as a unit, while maintaining appropriate autonomy for steroid decisions.

This study has several notable strengths. It provides the first detailed characterization of polypharmacy distribution in Pakistani pulmonology practice, moving beyond mean values to identify high-risk subgroups. The analysis of antibiotic-steroid relationships addresses a clinically important question not previously examined in this population. The demonstration of a graded association between antibiotic use and medication burden provides novel evidence that antibiotic prescribing may mark prescription complexity. The use of multiple complementary statistical approaches with effect size reporting strengthens confidence in our findings.

Several limitations should be considered when interpreting these results. The cross-sectional design cannot establish cause and effect, nor can it evaluate the clinical appropriateness of the prescribed medications. As a single-center study from Southern Khyber Pakhtunkhwa, findings may not generalize to other settings. The lack of clinical severity, treatment duration, and outcome data limits evaluation of whether the observed patterns represent appropriate care or unnecessary polypharmacy, and, as noted above, disease severity in particular cannot be ruled out as a confounder of the antibiotic-medication burden association. Reliance on prescription records precluded assessment of actual medication adherence. The WHO polypharmacy threshold of five medications may not fully capture appropriateness in respiratory care, where combination inhalers are appropriately counted as separate medications. Finally, both this and our previous work derive from the same dataset, requiring validation in independent cohorts. Despite these limitations, our findings have practical implications. The identification of a high-risk subgroup (31.4% of patients receiving seven or more medications) supports tiered intervention strategies, with those receiving $\geq 7$ medications, and those receiving multiple antibiotics, prioritized for comprehensive medication review [17]. The independence of steroid prescribing from antibiotic use is reassuring and should be reinforced through educational initiatives that leverage prescribers' apparent capacity for indication-based prescribing. Finally, the near-universal polypharmacy documented here calls for systemic policy interventions such as mandatory prescription audits, feedback mechanisms, and incentives for guideline adherence.

Several research priorities emerge from this work. To validate these patterns nationally, multicenter studies

across Pakistan should be conducted. Longitudinal research is needed to determine whether the graded association between antibiotic use and medication burden predicts patient outcomes such as hospitalization or treatment failure. Studies incorporating clinical severity data could help distinguish appropriate escalation from unnecessary polypharmacy and clarify the confounding role of illness severity. Qualitative research could explore why antibiotic use tends to mark prescription complexity. Intervention studies should prospectively evaluate whether using antibiotic count as a trigger for medication review reduces polypharmacy. Finally, similar analyses in other specialties would clarify whether these patterns extend beyond pulmonology.

## 5. CONCLUSION

This study provides the detailed characterization of polypharmacy distribution, antibiotic-steroid relationships, and graded associations between antibiotic use and medication burden in Pakistani pulmonology outpatients Near-universal polypharmacy (93.3%), with a mean of 5.96 medications per prescription and nearly one-third of patients receiving seven or more medications, far exceeds the WHO's numerical polypharmacy threshold; whether this reflects appropriate multi-drug regimens or unnecessary prescribing cannot be determined from this study. Steroid prescribing operates independently of antibiotic decisions, indicating that prescribers differentiate between anti-inflammatory and antimicrobial therapy. Most importantly, antibiotic use demonstrates a significant graded association with overall medication burden, which may serve as a marker of prescription complexity even in a population where polypharmacy is already widespread, though this association should be interpreted with caution given the potential confounding role of disease severity. These findings identify patients receiving multiple antibiotics as a priority group for medication review and suggest that antibiotic count could serve as a practical trigger for prioritizing such review, warranting prospective evaluation before adoption as a formal deprescribing protocol. These patterns may continue to expose patients to unnecessary risk and contribute to antimicrobial resistance in Pakistan unless addressed through antimicrobial stewardship and comprehensive medication review.

## ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was exempted from routine ethical review by Gomal University, as confirmed by author with letter Ref. No. 1126/Pharm/GU.

As this was a retrospective study involving no intervention and no direct collection of data from individual participants, informed consent was not required.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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## AUTHOR CONTRIBUTIONS

All authors contributed equally to the study.

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