Three-Year Experience of Antimicrobial Stewardship in a Tertiary Care Hospital in Pakistan: Successes and Challenges

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ABSTRACT

Background: Antimicrobial resistance (AMR) is on the rise globally. One strategy proposed by WHO to curtail AMR includes establishing antimicrobial stewardship (AS) programs. The objective of this study was to describe the practices of antimicrobial use at the Indus Hospital and Health Network (IHHN) and share their experience of establishing an AS program.

Methods: The Infectious Diseases (ID) department at IHHN, Korangi Campus, established an AS program in 2020. In the first phase (2020-2022), pharmacist-led reviews were performed on selected cases of injudicious antimicrobial use. In 2023, a prospective audit and feedback methodology was adopted. The data collected prospectively during these phases is analyzed in this paper**.** Frequencies and percentages were reported for categorical variables. SPSS 19 was used for data analysis.

Results: A total of 789 cases were analyzed across both phases. Overall compliance with AS recommendations was approximately 80%. Seven out of nine departments showed improved adherence over time, with cardiology and nephrology achieving over 90% compliance. The majority of antimicrobials reviewed (79%) were categorized in the WHO Watch group. In 2023 alone, AS interventions led to a direct cost saving of PKR 2,441,682 (approximately USD 12,000) and prevented administration of at least 1,765 antimicrobial doses. De-escalation or discontinuation of empiric therapy after 72 hours was the most frequent recommendation. Notably, 40% of cases reviewed did not require any antibiotics.

Conclusion: Implementing AS programs is crucial for monitoring and optimizing antimicrobial use. The IHHN model demonstrates the effectiveness of interdisciplinary collaboration, pharmacist-led reviews, and continuous education to promote rational antimicrobial use in a resource-limited setting.

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Keywords: Antimicrobial stewardship, compliance, antimicrobial resistance, cost savings.

INTRODUCTION

Infectious diseases were the major cause of death before the advent of antibiotics in the early 20th century [1]. However, we soon learned that some bacteria could survive these antibiotics through various resistance mechanisms [2]. In the last two decades, antimicrobial resistance (AMR) has gained further importance due to the development of resistance in most bacteria and lag in the discovery of new antimicrobials [3]. According to the World Health Organization (WHO), the global Cephalosporin-resistant E coli prevalence rate is more than 48%, while Methicillin-resistant Staphylococcus Aureus (MRSA) is 35% [3]. The Organization of Economic Cooperation and Development (OECD) predicts that the last resort antibiotic resistance will double by 2035 compared to 2005 [4]. The reported prevalence rates of MDROs from hospital-based studies in different cities of Pakistan range between 55% to 90% [5-7]. These Multidrug Resistant Organisms (MDROs) include Extensively Drug Resistant (XDR) Salmonella, Carbapenem-resistant Enterobacteriaceae (CRE), Carbapenem-Resistant Acinetobacter species, and MRSA [8, 9]. In 2015, the Global Action Plan (GAP) was proposed at the World Health Assembly, which suggests a One Health approach to address the problem of AMR with joint efforts from the Food and Agriculture, animal husbandry, and environment regulation sectors [3, 10]. As a result, the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) was developed in 2015 to inform strategies to contain AMR through WHO Regional offices [3].The National Institute of Health, Pakistan, proposed the National Action Plan for AMR in 2017 [11]. One of the key areas of action is Antimicrobial stewardship (AS), a multidisciplinary and coordinated program that promotes the appropriate use of antimicrobials, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms [12]. WHO also proposed a list of priority antimicrobials for prioritizing stewardship interventions called AWaRe [13].

The Infectious Disease (ID) Department at Iindus Hopitaland Health Network (IHHN) Karachi designed a stewardship program in 2020, starting with a pharmacist-led review of selected cases. The AS team consisted of ID physicians, microbiologists, clinical pharmacists, and the Infection Prevention and Control team. The aims of the AS program at IHHN include optimizing antimicrobial use, educating fellow practitioners on the growing burden of AMR and the need for

AS, developing institutional guidelines, and monitoring and evaluating the institutional practices related to AS. The objective of this paper was to describe the practices of antimicrobial use and share our experience of establishing an AS program. The primary outcome for this paper was compliance with AS recommendations.

METHODS

IHHN's Korangi campus is a 130-bed tertiary care facility that provides general medicine and allied services (cardiology, nephrology, gastroenterology, pulmonology) and general surgery and allied services (urology, head and neck surgery, orthopedics). The ID department at IHHN is composed of four ID physicians and at least three postgraduate fellow trainee physicians. Our study summarizes two periods of AS activities at our institute. In the first phase, i.e., 1st October 2020- 30th June 2022, we began AS with ID pharmacist-led weekly reviews of selected cases for injudicious antibiotic use. The data was collected prospectively as a part of AS interventions for this study. Sampling technique was non probability convenience sampling. The inclusion criteria was admitted adult patients (above 18 years of age) and receiving antimicrobial agents. Antimicrobials were chosen based on AWaRe classification by WHO (see below). The selection of antimicrobials for stewardship included a combination of indications for use, evidence of microbiological support, side effects, contraindications, etc. Data was collected on a predesigned performa which included demographic data, clinical information, indication for antimicrobial use and need for AS. The AS team met weekly at an AS 'Grand Round' to discuss cases and review AS data and progress. After review, the case was closed with the team's suggestions. Compliance with the recommendations was followed during the patient's admission, and basic demographic and relevant clinical details of the case were recorded. Recommendations included de-escalation, completely stopping antibiotics, or escalation to appropriate therapy and referral for official ID consultation. The AS team's recommendations were shared with the primary service providers through emails, detailed review notes in the electronic medical records (EMR), and verbally through physical meetings or phone calls if needed. Concerns were discussed and alleviated, and compliance with recommendations was measured as a binary outcome of yes/no.

During the next period, i.e., 1st October 2022- 31st October 2023, the AS program evolved and began daily AS reviews, providing prospective audits and feedback on inpatient antibiotic

utilization across all service lines. The antimicrobials were classified by WHO's AWaRe classification; hence, the clinical pharmacist obtained daily records of all adult patients receiving 'Reserve' drugs (which were assessed within 24 hours of being prescribed to judge for appropriateness), 'Watch' group (may be given up to 48 hours) and 'Access' group (up to 72 hours) were monitored less frequently (Table 1).

Table 1. Antimicrobials Reviewed According to the WHO AWaRe Classification

WHO AWaRe classification	Antimicrobials reviewed	Percentage
Reserve group	Acyclovir; Amphotericin; Aztreonam; Ceftaroline; Ceftazidime + avibactam; Colistin; Fosfomycin IV; Linezolid; Tigecycline	3%
Watch group	Azithromycin; Cefixime; Cefoperazone; Ceftazidime; Ceftriaxone; Cefuroxime; Ciprofloxacin; Clarithromycin; Ertapenem; Fosfomycin PO; Imipenem; Levofloxacin; Meropenem; Moxifloxacin; Piperacillin + tazobactam; Vancomycin	79%
Access group	Amikacin; Amoxicillin; Amoxicillin + clavulanic acid; Ampicillin; Benzathine penicillin; Benzylpenicillin; Cefalexin; Cefazolin; Chloramphenicol; Clindamycin; Cloxacillin; Doxycycline; Gentamicin; Metronidazole; Nitrofurantoin; Phenoxymethylpenicillin; Procaine benzylpenicillin; Sulfamethoxazole + trimethoprim	18%

Footnote: *WHO, World Health Organization; AWaRe, Access, Watch and Reserve; IV, intravenous; PO, oral. Percentages represent the distribution of antimicrobials reviewed according to their WHO AWaRe classification. The AWaRe classification categorizes antibiotics according to their importance for antimicrobial resistance and stewardship considerations.*

Each case selected by the ID pharmacist was reviewed through EMR for history, date of starting antimicrobial, indication mentioned, and microbiological data. Antibiotics were reviewed for the correct choice, dose, duration, adverse events, and drug-drug interactions, and recommendations were made accordingly. Where the indication for antibiotic usage was lacking, the primary team was advised to stop antibiotics. After reviewing the medical record and examining the patient at the bedside, AS feedback recommendations were provided to the primary team verbally and with a documented assessment note in the EMR. A formal ID consultation was recommended where indicated.

The study was approved by the Indus Hospital and Health Network IRB under approval number IHHN IRB 2024-05-006. Informed consent was waived as data was retrospectively available from electronic medical records. Data was recorded on a pre-designed performa. Descriptive statistics were used to describe the data using frequency and percentage for

categorical variables. Data was analyzed using IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA) [14].

RESULTS

Two observation periods were described for 789 patients reviewed over 3 years. In the first period, 429 cases were reviewed, and in the second period, 360 cases were reviewed. Overall compliance with AS recommendations was 80.2% (344/429 cases) in the first period (Table 2) and 83% in the second observation period.

Table 2. Adherence to antimicrobial stewardship recommendations during the two study periods

Adherence to AS recommendations	Phase 1, n (%)	Phase 2, n (%)
Advice accepted	344 (80.2)	302 (83.8)
Advice not accepted	85 (19.8)	58 (16.1)
Total cases	429 (100.0)	360 (100.0)

Footnote: *AS, antimicrobial stewardship. Phase 1: 1 October 2020 to 30 June 2022; Phase 2: 1 October 2022 to 31 October 2023. Percentages represent the proportion of cases in each study period in which the AS team's recommendation was accepted or not accepted.*

In the first observation period (Oct 20-Jun 22), adherence was above 90% in Nephrology (Table 3), General Surgery, and Cardiology. In the second observation period (Oct 22- Oct 23), Nephrology continued to comply with AS recommendations in more than 90% of the cases.

Table 3. Distribution of cases by clinical discipline and adherence to antimicrobial stewardship recommendations during the two study periods

Clinical discipline	Phase 1: No. of cases, n (%)	Phase 1: Adherence, n (%)	Phase 2: No. of cases, n (%)	Phase 2: Adherence, n (%)
Ear, Nose and Throat (ENT)	15 (3.4)	8 (53.3)	5 (1.4)	4 (80.0)
Medicine	52 (12.1)	41 (78.8)	86 (23.9)	69 (80.2)
General Surgery	95 (22.1)	86 (90.5)	50 (13.9)	37 (74.0)
Nephrology	49 (11.4)	44 (89.8)	65 (18.0)	62 (95.3)
Urology	49 (11.4)	31 (63.2)	32 (8.8)	21 (65.6)
Orthopedics	76 (17.7)	59 (77.6)	70 (19.4)	65 (92.8)
Pulmonology	28 (6.5)	18 (64.2)	34 (9.4)	30 (88.2)
Cardiology	60 (13.9)	55 (91.6)	14 (3.9)	10 (71.4)
Gastroenterology	5 (1.1)	2 (40.0)	4 (1.1)	4 (100.0)
Total	429 (100.0)	344 (80.2)	360 (100.0)	302 (83.8)

Footnote: *AS, antimicrobial stewardship; ENT, ear, nose and throat. Phase 1: 1 October 2020 to 30 June 2022; Phase 2: 1 October 2022 to 31 October 2023. Adherence refers to acceptance of recommendations made by the AS team. Percentages in the "No. of cases" columns represent the proportion of total cases in that study period. Percentages in the "Adherence" columns represent the proportion of cases within each discipline in which AS recommendations were accepted.*

The direct cost saved from this AS program was PKR 2,441,682 (equivalent to 12000 USD) as per the manufacturer's retail price, with 1,765 doses of antimicrobials saved (Table 4).

Table 4. Antimicrobial doses discontinued and direct cost savings associated with antimicrobial stewardship interventions

Antimicrobial agent	No. of doses saved	Price per dose (PKR)	Direct cost saved (PKR)
IV Piperacillin + tazobactam 4.5 g	510	1,106	564,060
IV Meropenem 1 g	452	2,748	1,242,096
IV Vancomycin 1 g	274	1,509	413,466
IV Cefoperazone + sulbactam 2 g	72	496	35,712
IV Cefuroxime 750 mg	70	213	14,910
IV Clindamycin 600 mg	69	322	22,218
IV Ciprofloxacin 400 mg	55	290	15,950
IV Amoxicillin + clavulanic acid 1.2 g	49	271	13,279
IV Colistimethate sodium 1 MIU	42	1,800	75,600
IV Ceftriaxone 1 g	40	350	14,000
IV Ceftazidime 1 g	27	363	9,801
IV Ampicillin 500 mg	24	53	1,272
IV Levofloxacin 500 mg	22	350	7,700
IV Amikacin 500 mg	20	310	6,200
IV Metronidazole 500 mg	15	130	1,950
Capsule Cefixime 400 mg	11	60	660
IV Azithromycin 500 mg	6	268	1,608
Capsule Doxycycline 100 mg	5	10	50
IV Co-trimoxazole 80 mg	2	575	1,150
Total	1,765	11,224*****	2,441,682

Footnote: *IV, intravenous; PKR, Pakistani rupees. Direct cost savings were calculated as the number of doses saved multiplied by the corresponding price per dose. *The total in the "Price per dose" column represents the sum of the listed unit prices and should not be interpreted as the total expenditure. The reported total direct cost saving was PKR 2,441,682.*

Among the antimicrobials, 79% belonged to the Watch group as per the AWaRE classification (Table 5), with Carbapenems, Vancomycin, 3rd generation Cephalosporins, Piperacillin-tazobactam, and fluoroquinolones being most prevalent (Fig. 1).

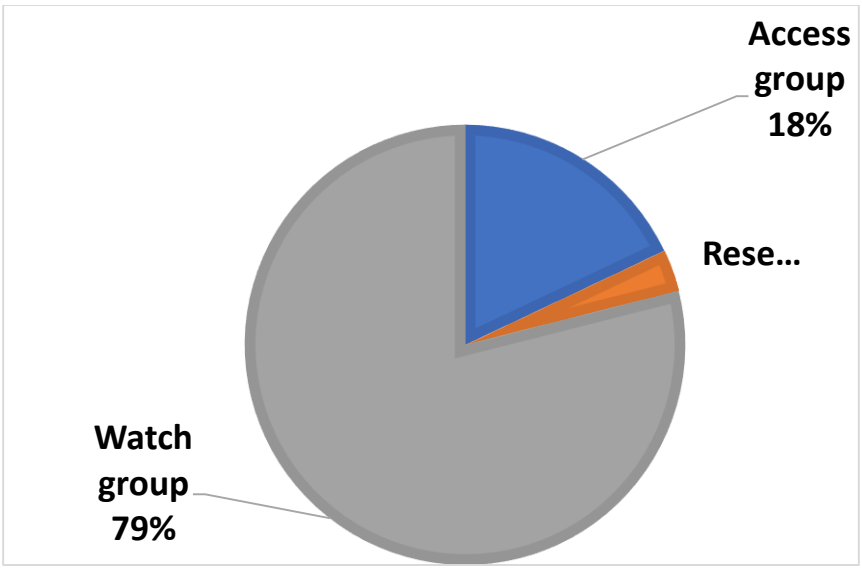

Figure 1: Antimicrobials reviewed by AWaRE classification

These AS reviews identified 15 broad areas of antimicrobial stewardship (Fig. 2). Among the reasons for intervention, 22% needed de-escalation of therapy with narrow-spectrum agents, 16% had used empiric therapy beyond 72 hours and needed re-evaluation, and in 11% therapy was not needed.

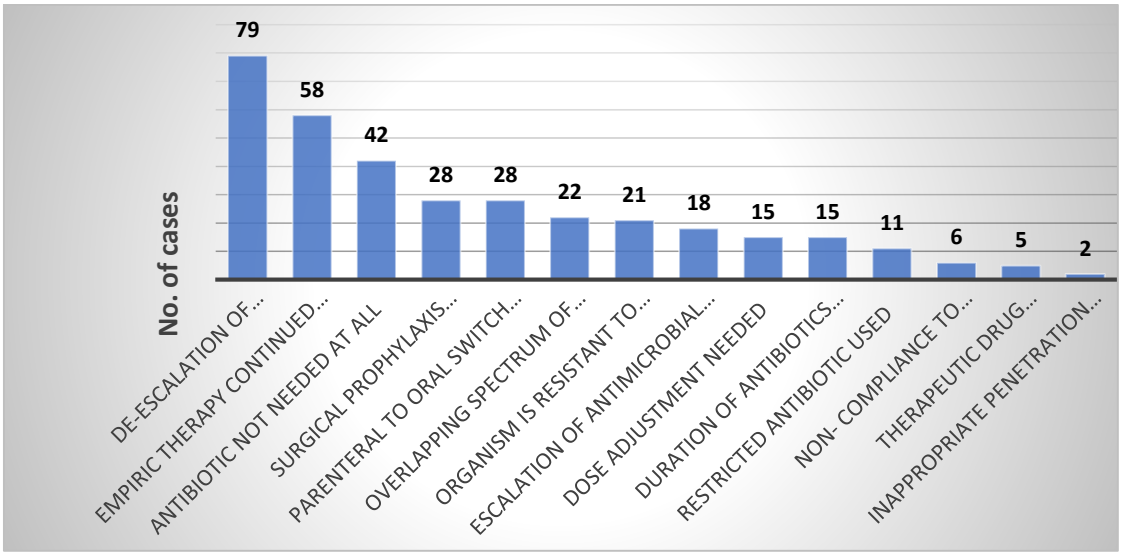

Figure 2: Reasons for Antimicrobial Stewardship Intervention

Most interventions were targeted toward broad-spectrum antimicrobials, including piperacillin-tazobactam (23.4%), Meropenem (22.2%), and Vancomycin (15.7% (Table 5).

Table 5. Antimicrobial stewardship interventions by antimicrobial agent and WHO AWaRe classification

Antimicrobial agent	Number of interventions, n (%)	WHO AWaRe classification
Piperacillin + tazobactam	98 (23.4)	Watch
Meropenem	93 (22.2)	Watch
Vancomycin	66 (15.7)	Watch
Ceftriaxone 1 g	25 (5.9)	Watch
Cefoperazone + sulbactam	22 (5.2)	Watch
Cefuroxime	22 (5.2)	Access
Clindamycin	21 (5.0)	Access
Ciprofloxacin	15 (3.5)	Watch
Amoxicillin + clavulanic acid	11 (2.6)	Access
Amikacin 500 mg	9 (2.1)	Access
Colistimethate sodium	6 (1.4)	Reserve
Tigecycline	5 (1.1)	Reserve
Levofloxacin 500 mg IV	4 (0.9)	Watch
Doxycycline 100 mg capsule	4 (0.9)	Access
Metronidazole 500 mg IV	3 (0.7)	Access
Cefixime 400 mg capsule	3 (0.7)	Access
Azithromycin 500 mg IV	3 (0.7)	Watch
Ceftazidime 1 g	2 (0.4)	Watch
Ampicillin 500 mg	1 (0.2)	Access
Co-trimoxazole 80 mg IV	1 (0.2)	Access
Fluconazole	1 (0.2)	Watch
Linezolid	1 (0.2)	Reserve
Teicoplanin	1 (0.2)	Watch
Voriconazole	1 (0.2)	Reserve
Total	418	—

Footnote: *IV, intravenous; WHO, World Health Organization; AWaRe, Access, Watch and Reserve. Percentages represent the proportion of all antimicrobial stewardship interventions (n = 418). Antimicrobials were classified according to the WHO AWaRe classification framework. "Reserve" agents are considered last-resort options for treatment of multidrug-resistant infections.*

DISCUSSION

Antimicrobial Stewardship has shown to reduce antimicrobial utilization globally. A Chinese study showed a significant reduction in injudicious surgical prophylaxis after the establishment of AS programs [15]. A study from a Czech Republic hospital showed reduced AMR over a decade after the introduction of an AS

program [16]. AS interventions led to a 43% reduction in hospital-acquired infections in India [17]. A qualitative study from Pakistan showed that only 2 out of 7 tertiary care hospitals included in that study had an AS program [18].

The study showed overall 80% compliance to AS recommendations (Table 1), which is similar to reported figures from Canada and Singapore [19, 20]. Compliance with the AS team's recommendation was seen to improve in the second study period. It is concerning to note that General Surgery and Cardiology services had a fall in the level of compliance to AS. On the other hand, all other disciplines improved or maintained their compliance levels (Table 2), which may be related to the induction of new trainees. A South African study showed 71% compliance to AS recommendations among surgical patients, which correlates with our second study period [21]. A study from Singapore showed approximately 81% compliance with AS recommendations within 48 hours of the recommendation [22]. There was a surge in cases selected from Internal Medicine in the second study period. This maybe explained by the induction of new trainees requiring sensitization to the principles of stewardship.

Among the antimicrobials used, Piperacillin-Tazobactam and Meropenem (Table 3) were the most common in our study, similar to other Pakistani and Indian studies [23, 24]. Similarly, another Bangladeshi study saw 54% use of ceftriaxone, followed by 41% of meropenem [25]. However, a survey from eight different hospitals in Bangladesh showed that among 1417 admitted patients, 78% received at least one antibiotic, mostly a 3rd generation cephalosporin (44%) [26]. In our study, most (79%) of the antimicrobials belonged to the 'Watch' group (Fig. 1), similar to a study by Rashid et al. from Bangladesh [26]. The most frequent reasons for AS in our patients were "de-escalation of therapy", "empiric therapy continued beyond 72 hours," and "antibiotic not needed at all" (Fig 2) which is in accordance with data shared from an Australian hospital study where most reviews were carried out for stopping inappropriate therapy or de-escalation to simpler agents [27].

Our study revealed substantial direct cost savings of PKR 2 million over one year due to stewardship. Cost reduction is a strong incentive for institutional commitment in terms of AS programs, as shown by a Chinese study where antimicrobial utilization dropped from 60% to 33% in a tertiary care center in China [15]. Another benefit was the shortened hospital stay, which further reduced the expenditure on antimicrobials [17, 24]. An Iranian study posted a 41% drop in the monthly expenditure of

approximately 18,0000 USD [24]. Switching from parenteral to oral antibiotics with similar bioavailability obviates the need for intravenous access or extended hospitalization, further reducing the expenditure by approximately 8.2% [28].

Our study describes the antibiotic stewardship intervention at a large tertiary care hospital, which can serve as a model for other institutions. We conclude that with targeted interventions and focus on antimicrobials through AWaRe criteria can reduce the burden of AS. Injudicious antimicrobial use can be reduced through education and awareness, along with a strict AS program. The challenges we faced during this period were all worth it when we look at the cost reduction alone.

One of our limitations was not being able to measure the AMR burden without an automated software-based AS program, which incorporates antibiotic time-outs, and flags injudicious use of antimicrobials by following an in-built algorithm. Our hospital is expanding to a 1500-bed center where automated reminders and filters for antimicrobial authorization will be needed to manage AS. Further, we were not able to measure the indirect cost saved through this AS program, as the study relied on existing data. These include reduced hospital stay, side effects, and cost of managing side effects like acute kidney injury and need for hemodialysis, etc. If these costs were included in the analysis, the magnitude of effect may be exponential.

CONCLUSION

This study highlights the need for Antimicrobial Stewardship to reduce the burden of AMR in Pakistan. Establishing AS programs at health facilities is a simple and cost-effective strategy to curtail AMR. Classifying antimicrobials by AWaRe class is a simple strategy to prioritize effective antimicrobial agents for stewardship. Over the past 3 years, we learned that compliance with AS improves with constant education and feedback. It is the need of the hour to educate physicians and health care workers, control the sale of antimicrobials, and regulate the use of these agents at health facilities to avoid the impending catastrophe of antimicrobial resistance globally. Pakistan should develop a National Antibiotic Stewardship Program that can help reduce the rise of other life-threatening microorganisms.

DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

*The study was approved by the Institutional Review Board (IRB) of The Indus Hospital and Health Network (IHHN) under approval number **IHHN IRB 2024-05-006**. The IRB granted a waiver of informed consent; therefore, informed consent was not required from the study participants.*

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

No specific funding was received for this study.

AUTHOR CONTRIBUTIONS

Conceptualized and supervised the antimicrobial stewardship program and manuscript preparation: *Naseem Salahuddin*

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Contributed to case identification, data collection, and preliminary analysis*: Muhammad Hamid Hanif, Mujahid Hussain*

All authors: *Read and approved the final manuscript.*

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