ORIGINAL ARTICLE

Susceptibility pattern of bacteria isolated from blood cultures of neonates admitted with sepsis at a tertiary care hospital

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ABSTRACT

Background: Neonatal sepsis is one of the leading causes of neonatal mortality rate (NMR) in developing countries like Pakistan, where epidemiologic surveillance of organisms and their antimicrobial sensitivity patterns remains poor. The objective of this study is to identify common organisms implicated in neonatal sepsis and their susceptibility patterns as well as the emergence of antibiotic resistance at a tertiary care hospital.

Material and Methods: This Retrospective descriptive study, Blood culture reports of neonates admitted to the Nursery of Allama Iqbal Memorial Teaching Hospital (Khawaja Muhammad Safdar Medical College) with suspected sepsis from January 2020 to December 2022 were taken.

Results: Blood culture reports were positive in 303 (12.8%) out of 2368 neonates. The proportion of gram-negative and gram-positive micro-organisms were 278 (91.7%) and 25 (8.3%) respectively. *Acinetobacter baumannii* was the most predominant microorganism isolated (32.3%), followed by *E coli* (21.4%) and *Citrobacter freundii* (13.5%). Among the gram-negative microorganisms high level of resistance was seen with first-line agents, such as ampicillin (97.3%), third generation cephalosporins i:e cefotaxime (89.8%), while the majority of these organisms were sensitive to carbapenems (56.0%) and cefoperazone-sulbactam (53%). Methicillin resistant *Staphylococcus aureus* rate was 47.6% and no resistance to vancomycin and linezolid was detected.

Conclusion: This study shows the emergence of unusual gram-negative microorganisms causing neonatal sepsis and a high level of resistance to first-line empirical antibiotic therapy. This highlights the urgent need for the implementation of effective infections control program and antibiotics stewardship in neonatal ICU.

Keywords: Antibiotic susceptibility, Blood culture, Neonatal sepsis

BACKGROUND

Neonatal sepsis is a clinical syndrome in infants younger than 28 days of life manifested by nonspecific signs and symptoms due to invasion of microorganisms in the bloodstream.[2] Globally it is a common cause of morbidity and mortality among neonates with an estimated annual incidence of 22 per 1000 live births and an associated mortality rate of 11 to 19 percent.[2] It is accounted for an estimated 430,000 deaths worldwide which is approximately 15 percent of all-cause neonatal deaths in the year 2013[15], and 26 percent of neonatal deaths in resource-poor countries.[13] In Pakistan neonatal sepsis is one of the major causes of neonatal mortality rate accounting for 17.2 percent of total deaths.[4]

Microorganism causing neonatal sepsis are different among various regions of the world. In developed countries Group B *streptococcus* (a gram-positive organism) and *E. coli* are the most common organisms causing neonatal sepsis, [15,16,17,18] however literature from developing countries suggest that gram-negative organisms *including E. coli, Pseudomonas, Klebsiella pneumoniae, Acinetobacter species, Enterobacter species,* and *Neisseria meningitides predominate*.[3,4,7]

Early administration of broad-spectrum antibiotics is essential to decrease the morbidity and mortality associated with neonatal sepsis because blood culture and sensitivity takes time.[14] World Health Organization guidelines for suspected neonatal sepsis recommends empirical treatment with ampicillin combined with gentamicin as the first line therapy.[3,4,14] However antimicrobial resistance (AMR) has emerged globally rendering these first line regimens ineffective and is responsible for increase in morbidity and mortality.

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According to a study an estimated 31 percent of deaths in neonatal sepsis are attributed to this rising antimicrobial resistance.[12] Globally around 214,000 neonates die each year due to this antimicrobial resistance.[40] Injudicious use of antibiotics and lack of local antibiograms are among the causes of this rising trend of antimicrobial resistance.[4,12,14] Data from Pakistan shows that an estimated 25,692 neonates succumb to resistant sepsis each year.[4]

Predominant organisms and their sensitivity pattern differ among different regions and also in the same region over time.[1,14] Therefore, it is important to know the bacterial isolates and their sensitivity patterns not only at country level but also at local levels. Because neonatal mortality rate is very high in Pakistan (42/1000 live births)[4] and sepsis is one of the major causes, such evidence-based data will help clinicians to formulate effective empirical antibiotic regimen. Present study was conducted to describe the microbial pattern of neonatal sepsis as well as build the current antibiogram that will help the local practioners to use effective empirical antimicrobial treatment

MATERIAL AND METHODS

This was a retrospective descriptive study conducted at Allama Iqbal Memorial Teaching Hospital (Khawaja Muhammad Safdar Medical College) from January 2020 to December 2022, after taking the approval of ethical review board via reference number 113/REC/KMSMC, that analyzed data of blood culture reports of neonates admitted in NICU with suspected sepsis. Culture and sensitivity reports were obtained from hospital record system. A total record of 2368 neonates with suspected sepsis was collected during the study period. All positive blood culture were included in the study however in the case of a new blood culture taken after 5 days from the initial culture, it was classified as a new episode of suspected sepsis and if a neonate medical record showed a positive blood culture for a different pathogen within 48 hours after the initial positive culture, and contamination has been ruled out, it was considered a new episode of Neonatal sepsis case. The initial control blood cultures reports taken within 5 days of the first positive blood culture to verify the effectiveness of treatment were excluded. Additionally, confirmatory blood cultures were excluded if taken to rule out or confirm contamination. Duplicate medical records of blood cultures for the same neonate at the same time of specimen collection, were also excluded. The total excluded medical records were 5950; Blood culture samples were positive in 303 (12.8%) neonates while remaining 2065 (87.2%) were culture negative.

Blood samples were inoculated in manual blood culture bottles and incubated at 37 degrees Celsius aerobically for 24 hours. Periodic subcultures were done on blood and MacConkey agar on day two, three and four followed by incubation at 37 degrees Celsius. The growth obtained was identified by colony morphology, gram staining and biochemical testing was done as per standard protocols. Antibiotic susceptibility testing of isolated microorganisms was performed by modified Kirby-Bauer disc diffusion method on Mueller Hinton agar plates as recommended by clinical Laboratory Standard Institute (CLSI) recommendations.

Data were presented as descriptive statistics (frequency tables, charts and percentages). Data analysis was carried out using Microsoft Excel 2023 version 16.72.

RESULTS

A total of 2368 neonates with suspected sepsis had their blood samples collected during the study period. Blood culture samples were positive in 303 (12.8%) neonates while remaining 2065 (87.2%) were culture negative (Figure-I). The number of isolated microorganisms were 278 (91.7%) gram negative, 25 (8.3%) gram positive and 6 (2.0%) fungal.

Among the gram-negative isolates *Acinetobacter baumannii* was the predominant organism (32.3% of the total isolates) followed by *E coli* (21.4%), *Citrobacter freundii* (13.5%), *Burkholderia Capacia* (8.3%), and *Enterobacter cloacae (*7.6%). Among gram positive isolates *Coagulase negative Staph (CoNS)* was predominant which constituted 6.9% of the total isolates followed by *Staph aureus* (1.3*%). Candida Albicans* was detected in 6 cultures which constitutes 2.0% of total isolates (Figure-II).

Antimicrobial susceptibility pattern of gram-positive isolates revealed that rate of *Coagulase negative staph* was 47.6% whereas all four *Staph aureus* isolated were methicillin resistant. No resistance to vancomycin and linezolid was detected in gram positive isolates however all the isolates were resistant to ampicillin. Sensitivity of gram-positive organisms to chloramphenicol, clindamycin and Amoxiclav was 83.3%, 63.7 % and 26.7 % respectively (Table-II). Sensitivity to tetracyclines was 92.9 percent but these antibiotics are not routinely used in neonatal sepsis.

Most of the gram-negative microorganisms were resistant to first line antimicrobial therapy (Table-II).

Overall sensitivity to fluoroquinolones was 42.3 % but it was very low for the most commonly isolated organism that is *Acinetobacter baumannii* (7.1%) however it was quiet sensitive for *Pseudomonas* (77.0%). Sensitivity to tetracycline group was between 22.0 to 25.0% which is better than third generation cephalosporins. Overall sensitivity to carbapenems was 56.0%, however it was very low for the most commonly isolated organism (*Acinetobacter*) which was 32.6%. The susceptibility to piperacillin-tazobactam was 49.0 % and to cefoperazone-sulbactam was 53.0%.

The most commonly isolated organism is *Acinetobacter baumannii* which has highest susceptibility to cefoperazone-sulbactam (45.0%) and carbapenems (32.6%), but it was least susceptible to third generation cephalosporins (1-3.0%). *E coli* was most Susceptible to carbapenems (83.0-87.0%) while its susceptibility to Cefoperazone-sulbactam, piperacillin-tazobactam and amikacin was 66.0%,65.0% and 64.6% respectively and it was least susceptible to third generation cephalosporins (cefotaxime 19.0%, ceftriaxone 29.2%). *Pseudomonas* and *klebsiella* were less commonly isolated bacteria. *Klebsiella* is most susceptible to carbapenems (66.0%) and aminoglycosides (45.0%) whereas susceptibility to Cefoperazone-sulbactam and piperacillin-tazobactam was low (22.0%). *Pseudomonas* is most susceptible to Cefoperazone-sulbactam (88.0%), piperacillin-tazobactam (88.0%) and amikacin (66.0%) whereas it is relatively low to carbapenems (56.0%). Carbepenem resistant *Enterobacter cloacae* were 35.0%.

Table-I: Antimicrobial susceptibility pattern among gram positive micro-organisms.

Antibiotics	*Staph. aureus (n=4)*	*Coagulase negative Staphylococci (n=21)*
Methicillin	0%	47.6%
Linezolid	100%	100%
Vancomycin	100%	100%
Chloramphenicol	100%	66.6%
Clindamycin	75.0%	52.3%
Amikacin	75.0%	85.7%
Minocycline	100%	85.7%
Doxycycline	100%	85.7%
Ciprofloxacin	50.0%	19.0%
Septran	25.0%	23.8%
Amoxyclav	25.0%	28.5%
Cephradine	25.0%	47.0%
Meropenem	25.0%	19.0%
Imipenem	25.0%	19.0%
Ampicillin/amoxicillin	0%	0%
Fusidic acid	100%	76.0%
Piperacillin-Tazobactam		23.8%

Table-II: Antimicrobial susceptibility pattern among gram negative organisms.

Antibiotics	*Acinetobacter baumannii*	*E. coli*	*Citrobacter freundii*	*Burkholderia cepacia*	*Enterobacter cloacae*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	Overall sensitivity
Meropenem	32.6%	87.0%	85.3%	0%	65.0%	66.0%	56.0%	56.0%
Imipenem	32.6%	83.0%	85.3%	4.0%	65.0%	66.0%	56.0%	56.0%
Piperacillin-Tazobactam	29.6%	65.0%	88.0%	44.0%	8.6%	22.0%	88.0%	49.0%
Cefoperazone sulbactam	45.0%	66.0%	0%	84.0%	13.0%	22.0%	88.0%	53.0%
Doxycycline	32.6%	47.6%	48.7%	12.0%	21.7%	11.0%	0%	24.8%
Minocycline	29.5%	44.6%	48.7%	12.0%	13.0%	11.0%	0%	22.6%
Ampicillin	0%	9.2%	7.3%	0%	0%	0%	0%	2.3%
Moxifloxacin	7.1%	49.2%	56.0%	76.0%	8.6%	22.0%	77.0%	42.3%
Amikacin	15.3%	64.6%	46.3%	56.0%	52.0%	45.0%	66.0%	49.3%
Ciprofloxacin/ Levofloxacin	7.1%	49.2%	56.0%	76.0%	8.6%	22.0%	77.0%	42.3%
Cotrimoxazole	17.0%	52.0%	66.0%	84.0%	13.0%	11.0%	0%	34.7%

Ceftriaxone	1.0%	29.2%	29.2%	4.0%	4.5%	11.0%	0%	11.3%
Gentamicin	14.2%	43.0%	36.5%	44.0%	52.0%	45.0%	55.0%	41.3%
Co-amoxiclav	8.1%	27.6%	14.6%	0%	8.6%	11.0%	0%	10.0%
Cefoperazone	1.0%	23.0%	7.3%	16.0%	4.5%	11.0%	22.0%	12.0%
Cefotaxime	3.0%	19.0%	19.0%	4.0%	4.5%	11.0%	11.0%	10.2%
Cefixime	1.0%	18.5%	7.3%	0%	4.5%	11.0%	0%	6.0%
Cefepime	3.0%	32.3%	14.6%	4.0%	4.5%	11.0%	22.0%	13.0%
Ceftazidime	2.0%	21.5%	9.7%	4.0%	4.5%	11.0%	22.0%	10.6%

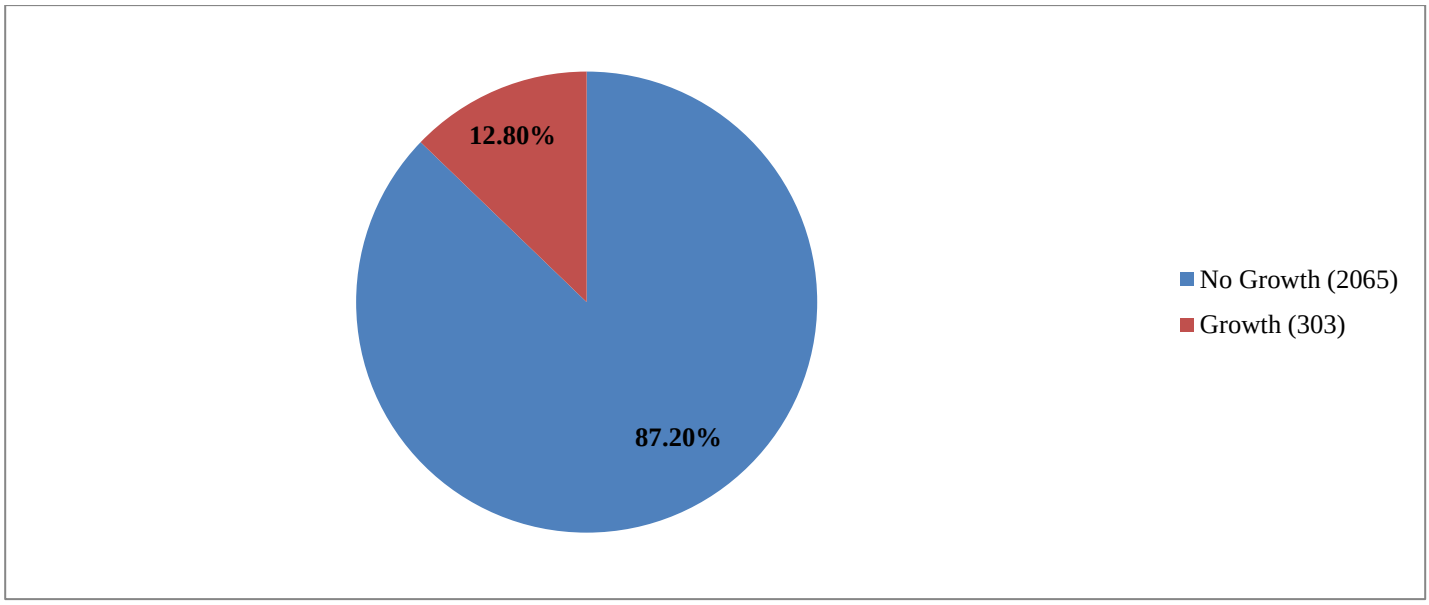

Figure-I: Growth pattern.

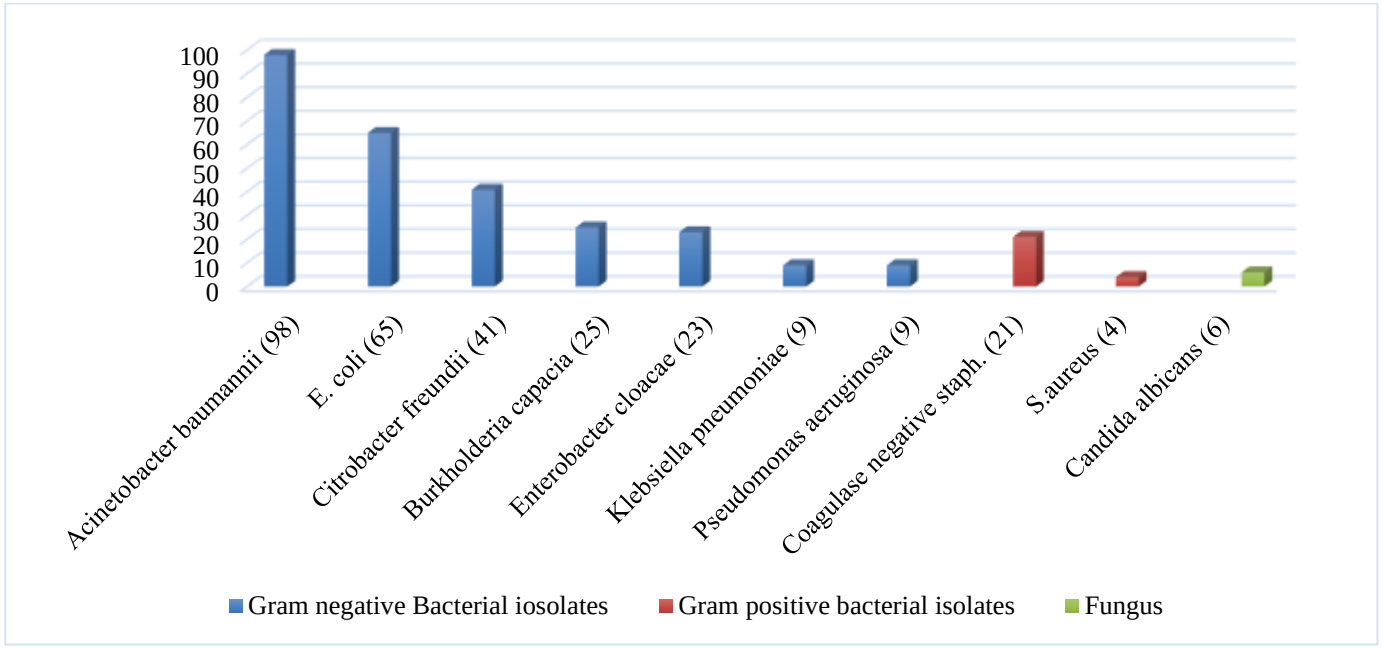

Figure-II: Frequency of bacteria isolated in blood cultures.

DISCUSSION

Blood culture yield varies among different laboratories depending upon the method used. In our study the blood culture positivity rate was 12.8 % which is comparable with the study conducted earlier at our hospital (13.7%),[1] Muhammad Almas *et alET ALF* (7.4%),[6] and Muhammad Atif *et al*. (8.9%).[4] This yield is slightly lower than that reported by studies conducted at Ghana (21%),[3] Nepal (20%),[11] and Nigeria (25%).[13] Some studies in India, and Nepal reported even higher

positivity rates of 46.7%,[10] 57%[5] and 42%.[8] The low blood culture positivity rate in our study could be due to low sample volume collected, technique of culture used and antibiotic therapy before referral to our hospital.

In our study, bacterial isolates were 98% while 2% were candida species. Isolation of gram-negative microorganisms was higher than gram positive in our study which is in accordance with that reported by Obaid *et al*[5], Dharshni *et al*[12], Shreshtha *et al*[10], and Bhishma *et al*. But studies from north India,[8] Germany, [14] Ghana[3] and east Nigeria[13] reported predominant growth of gram-positive microorganisms.

Among the gram-negative *Acinetobacter baumannii* emerged as the most common isolate (32.3%) in our study. Although a few recent studies from India (23.0%),[9] (3.0%),[8] and Pakistan (6%)[7], (17.7%)[6] did report it as one of the isolates, none has so far reported such a degree of dominance and resistance to commonly used antimicrobials. It was followed by *E. coli* as the second most common pathogen (21.4%). *Coagulase negative Staphylococcus (CoNS)* was the most common pathogen among the gram positives followed by S. aureus which is reported by Mudassar *et al*[1], Dharshni *et al*[9], Bhishma *et al*[11] and Belay *et al*[14] but other studies reported S. aureus[8,13,10,6] as the predominant one. Group *B. streptococcus* was not isolated in our study which along with Listeria monocytogenes and *E. coli* is the common pathogen implicated in neonatal sepsis in western countries[1,9]. This organism was also not reported by other studies in this region[4,5,6,7,8,10] *Acinetobacter species, coagulase negative staphylococci, Klebsiella and Pseudomonas species,* usually recognized as nosocomial pathogens were among the dominant pathogens in our study. This is possibly due to horizontal transmission from delivery rooms and NICUs or vertical transmission from maternal genital tracts colonized with these microorganisms after unhygienic personal and obstetric practices. [9]

Ampicillin and third generation cephalosporins are mostly used as empirical treatment in neonatal sepsis at our hospital but they were found to be least susceptible to pathogens isolated in this study. All gram-positive organisms isolated were resistant to ampicillin while only 2.3% gram-negative pathogens were sensitive to it. All gram-negative pathogens showed sensitivity of 13% or lower to all cephalosporins tested. This is in comparison to earlier study in this institute (14%)[1] and other studies done in this region (5.0%)[6], (9.5%) [11], (37.0%),[3] (23.0%),[8] (13.0%).[10] Although third generation cephalosporins have broad coverage, their injudicious use has made them less effective. Fortunately, amikacin which is also used as first line has very good sensitivity against gram-negative pathogens (49.3%). This is lower than that reported by Edna *et al* (79%),[3] Obaid *et al* (61.5%)[5] and Muhammad Atif *et al* (61.0%).[4] Methicillin resistance (MRSA) rate was showed at 47.6 percent against Coagulase negative Staphylococci (CoNS) (n=21) while all Staphylococci (n=4) isolated were resistant to it.

Linezolid and Vancomycin both were found to be most effective against gram-positive pathogens with sensitivity of 100%, followed by minocycline/ doxycycline (92.9%), fusidic acid (88.0%), and chloramphenicol (83.3%). This trend is similar to that reported earlier in our setup[1], by Kenechi *et al*[13] and multiple other authors.[6,8,10,12,9] This is because these antibiotics are not in routine use for the management of neonatal sepsis. Carbapenems showed susceptibility of only 56% against gram negative bacteria, followed by cefoperazone-sulbactam (53.0%), piperacillin-tazobactam (49.0%), and amikacin (49.0%). This is even lower than that reported by multiple other authors in this region[4,9,10,8,11] and other regions of the world [3,12,13,14].

As mentioned earlier *Acinetobacter* emerged as the most common pathogen implicated in neonatal sepsis in present study, is found to be highly resistant to all the antibiotics tested, with highest sensitivity to cefoperazone-sulbactam of only 45.0%. It has resistant rate of 100% against ampicillin, 97% against third generation cephalosporins while 84.3% against amikacin. Isolation of this unusual pathogen and such a high level of resistance to first line antibiotics and even to highly reserved antibiotics is an alarming situation for us and if steps are not taken to curb this resistance pattern, then we will not be left with any choice, and morbidity and mortality from neonatal sepsis will be even worse.

Our study carries a few limitations. First, this study was conducted at only one tertiary care hospital of the province Punjab, Pakistan. Therefore, the findings cannot be generalized for whole of Pakistan as type of pathogens and antibiotic use may vary across the country. Second, it was a retrospective study due to which we were unable to identify some of the

confounding variables, for example prior use and duration of antibiotics by the neonates, maternal variables and risk factors etc. which may have affected the results. Third, small sample and low culture yield rate at our setup was an important limitation of the study. Hence multi center prospective studies with larger sample size and latest blood culture isolation techniques are required to validate our findings.

CONCLUSION

The most commonly isolated organisms were *Acinetobacter baumannii* followed by *E. coli* and *Citrobacter* species. Among the gram-positive organism's resistance to commonly prescribed first and second-line agents was very high however no resistance was documented to vancomycin and linezolid. Among the gram-negative organism's resistance to commonly used antibiotics like ampicillin, third generation cephalosporins and cefepime was alarmingly high. The overall sensitivity to aminoglycosides is high however resistance to commonly isolated organism is still high. Carbapenems, piperacillin-tazobactam, and cefoperazone-sulbactam has highest susceptibility in our study but resistance documented to these drugs is alarming.

To curb the high resistance to antimicrobials found in our study comprehensive approach consisting of improvement of laboratory techniques to increase culture yield, evaluation of antibiotic consumption, rational use of empirical treatment, de-escalation of therapy when suitable along with continuous monitoring and surveillance of local epidemiology is need of the hour.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Saqib Munir: Idea conception, manuscript writing, revisions

Mudassar Hussain, Shahid Rashid: Data analysis, data interpretations

Salman Arshad: Literature review, critical review

Sidra Ijaz, Nadia Qamar: Data collection

Abdul Sattar: Overall supervision

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