ORIGINAL ARTICLE

Therapeutic Options for Treating Cefotaxime-Resistant Escherichia coli & Klebsiella Species in Resource-Limited Tertiary Care Setup of Rawalpindi: A Retrospective Observational Study

Uzma Mussarat[1*], Shazia Taj[2], Amal Zahra[3], Nehaj Tariq[4], Amatul Naval[4], Saeeda Bano[5]

ABSTRACT

Objective: This study aimed to assess potential therapeutic options for Klebsiella pneumoniae and Escherichia coli isolates resistant to third-generation Cephalosporins.

Study Design: Retrospective observational study.

Place and Duration of Study: This study was conducted at the Department of Pathology, Pakistan Railway Hospital, Rawalpindi, Pakistan from January 2021 to December 2021.

Methods: Patient samples were congregated from the specified study period and processed in the microbiology laboratory using standard protocols. Pathogens were identified through Gram staining, biochemical tests, and antibiotic susceptibility tests via the disk diffusion method following Clinical and Laboratory Standards Institute (CLSI) guidelines. Data scrutiny was accomplished using Statistical Package for Social Sciences (SPSS) version 24.

Results: Out of 1,128 clinical specimens, Escherichia coli was recognized as the most recurrently isolated pathogen (34.66%, N=391), followed by Klebsiella pneumoniae (21.89%, N=247), with Enterococcus faecalis being the least common (3.10%). Escherichia coli exhibited notable decreased sensitivity to ampicillin (58%), amoxicillin-clavulanate (34%), cefotaxime (43%), ciprofloxacin (31%), and co-trimoxazole (24%). Similarly, Klebsiella pneumoniae showed resistance to amoxicillin-clavulanate (58.7%), cefotaxime (49%), and co-trimoxazole (24%). However, both pathogens remained susceptible to Carbapenems, ceftazidime, Cefoperazone-Sulbactam, tetracycline, Cloxacillin, erythromycin, Aztreonam, Nitrofurantoin, Fosfomycin, amoxicillin-clavulanate, and chloramphenicol.

Conclusion: The rising resistance of Escherichia coli and Klebsiella pneumoniae to third-generation Cephalosporins 92 (24%) and 89 (36%), respectively, has been revealed in the present study. Moreover, quinolones also present significant treatment challenges by showing high resistance among collected isolates. In contrast, Carbapenems, β-lactam/β-lactamase inhibitor combinations (Piperacillin–Tazobactam) (TZP), Ceftazidime, Cefoperazone-Sulbactam (SCF), Tetracycline, and Fosfomycin are found as effective alternatives to combat cefotaxime-resistant pathogens.

Keywords: *Cephalosporin Resistance, Drug Utilization, Escherichia Coli, Klebsiella Pneumoniae, Patient Safety.*

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[1]*Department of Pathology*
Islamic International Dental College
Riphah International University, Islamabad, Pakistan
[2]*Department of Pathology*
NUST School of Health Sciences, Islamabad, Pakistan
[3]*Akbar Niazi Hospital, Islamabad, Pakistan*
[4]*Department of Pathology*
Watim Medical & Dental College, Rawalpindi, Pakistan
[5]*Department of Pathology*
Al-Nafees Medical College & Hospital Islamabad, Pakistan

Introduction

Human health is at risk due to the rising incidence of antibiotic resistance (AR), especially for disadvantaged groups receiving care in hospitals and acute care settings. As a result, healthcare costs rise. It is expected that by 2050, the number of deaths associated with diseases due to resistant pathogens could increase from 700,000 to 10 million.[1] However,

Correspondence:
Dr. Uzma Mussarat
Assistant Professor, Pathology
Islamic International Dental College
Riphah International University, Islamabad, Pakistan
E-mail: uzma.mussarrat@riphah.edu.pk
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in developed nations, resistant pathogens are estimated to be responsible for 23,000 deaths yearly in the United States and 25,000 deaths in Europe. The year 2019 saw the continuation of Klebsiella pneumoniae, multidrug-resistant Pseudomonas aeruginosa, and extended-spectrum β-lactamases (ESBL) Escherichia coli as "serious threats".[2] As a whole, antibiotic resistance has grown. The annual cost of healthcare is more than $1 billion. Hospital expenses associated with treating patients with MDR infections are higher overall because of the more extended median stay and increased resource usage.[3] Multiple reasons are contributing to the rise in antimicrobial resistance. A major contributing factor is poor antibiotic stewardship, which encompasses the overuse of antibiotics, inadequate empirical coverage, erroneous diagnoses, delays, and insufficient therapeutic de-escalation. As the supply of potent antibiotics declines, the situation gets worse over time. To make matters more complicated, drug-resistant Gram-negative microbes are becoming more common in acute care and hospital settings.

Antibiotic resistance currently presents a significant obstacle to the treatment of bacterial illnesses and places a heavy financial strain on the country.[4] Antibiotic-resistant Escherichia coli, namely those resistant to Cephalosporins, pose a solemn hazard to worldwide public health. The emergence of resistance to third-generation Cephalosporins (3GCs), which are used worldwide to treat Escherichia coli infections such as urinary tract infections (UTIs), bloodstream infections (BSIs), and intra-abdominal infections, is particularly concerning.[4] The rise of Enterobacteriaceae that produce extended-spectrum beta-lactamases (ESBLs) is a serious concern because ESBL causes resistance to most Cephalosporins and all penicillins. Antimicrobial resistance to several antibiotics, including β-lactam drugs such as penicillins, Cephalosporins, Monobactams, and Carbapenems, has been interrelated to a novel family of ESBLs called CTX-M β-lactamases, which have become the most prevalent ESBL type worldwide. Furthermore, strains of Escherichia coli that produce CTX-M are habitually linked to co-resistance to other broad categories of drugs, including aminoglycosides and Fluoroquinolones.[5] In 2017 a surveillance report from China revealed that the overall resistance rates of Klebsiella spp. and Escherichia coli to cefotaxime were 45.6% and 59.3%, respectively.[6] According to a study, the global resistance rate for Escherichia coli that is resistant to third-generation Cephalosporins (3GC) and Klebsiella pneumoniae that is resilient to 3GC will be 77% and 58.2%, respectively, by 2030.[7] Additionally, Enterobacteriaceae species were at a higher probability of mounting resistance compared to other bacteria and were acorrelated with multi-drug resistance in some illnesses. For Klebsiella pneumoniae alone, the odds ratio (OR) for the emergence of resistance was 4.59. The mainstream of the Klebsiella pneumoniae isolates in this investigation were resistant to cephalosporin combinations, and 2% were also resistant to Colistin and quinolones.[8,9] Rendering to a dissimilar research, the probability of contracting a drug-resistant Klebsiella pneumoniae septicemia during a later hospital stay was amplified by 14% with each hospital-acquired infection.[10]

Without a doubt, the excessive and misapplication of antibiotics will undoubtedly encourage the evolution of bacterial resistance. The resistance pattern of Enterobacteriaceae and Klebsiella pneumoniae against third-generation Cephalosporins is not compared to the most recent data regarding the state of antibiotic usage in our study setup. The present study is planned to consider treatment options for third-generation cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae in the event of an emerging resistance.

Method

A retrospective, cross-sectional, observational study was carried out at the Department of Pathology, Pakistan Railway Hospital, Rawalpindi, Pakistan from January 2021 to December 2021 after taking approval from the Ethical Review Committee of Islamic International Dental College, Islamabad, vide letter no: IIDC/IRC/2020/001/015, dated: 10th

January 2020. Overall, 1128 cultures with bacterial growth were analyzed using convenient sampling techniques to comment on their antibiotic sensitivity pattern.

Inclusion Criteria: Non-duplicate clinical isolates were encompassed from patients of all ages and both sexes, obtained from both inpatients and outpatients. Positive culture samples were collected from urine, pus, high vaginal swabs (HVS), sputum, feces, blood, and other specimens such as tissue fluids, wound swabs, and catheter/cannula tips. The inclusion criteria comprised Escherichia coli and Klebsiella pneumoniae isolates resistant to cefotaxime, accounting for 92 (24%) and 89 (36%) strains, respectively.

Exclusion Criteria: Duplicate samples from the same patient devoid of culture growth were not included in the study.

After sample collection, they were handled in the microbiology lab, where the causative pathogens were documented using standard microbiological techniques. Gram staining was performed and documented as part of the culture process. The stained slides were examined microscopically, and bacterial isolates were classified into Gram-positive and Gram-negative pathogens. Later on, conventional laboratory identification procedures for GNRs, such as TSI, Citrate utilization, motility, indole, urease, API 10E, oxidase test, and other pertinent biochemical tests, were accomplished in microbiology to distinguish pathogens. The Kirby-Bauer Disc Diffusion method was used to carry out the antibiotic susceptibility test procedure. By putting bacterial colonies into disinfected distilled water until it nearly reached the McFarland turbidity criterion of 0.5, a suspension from growth on a solid media plate was created. Using a sterile cotton swab, the resultant suspension was inoculated on Mueller-Hinton Agar (MHA). Antibiotic discs (mentioned below Table 1) to be tested were placed on these MH agar plates, and the plates were then inverted to prevent the dropping of condensation droplets from on the lid during incubation, which can cause the spread of antibiotic discs or bacterial colonies, leading to inaccurate zone of inhibition measurements. The plates then incubated at 37̊ C for 24hr. The zone of inhibition was considered in millimeters according to Clinical Laboratory Standards Institute (CLSI) guidelines.[11]

An Antibiogram encompassing the use of antibiotic discs (their name and concentrations mentioned below Table 1) was used to comment on the pathogens' susceptibility report. The collected data was investigated using the Statistical Package for the Social Sciences (SPSS) version 24. For categorical variables, such as patient gender, sample type, isolated organisms, ward distribution, and antimicrobial susceptibility, basic descriptive statistics, including counting frequencies and percentages, were calculated. Patient age (in years) wascalculated as Mean ± Standard Deviation (SD).

Results

A total of 391 (34.66 %) Escherichia coli and 247 (21.89 %) specimens of Klebsiella pneumoniae were collected in the study period of one year, including urine, pus, HVS, sputum cultures, stool, blood, and others (tissue fluid, wound, and cannula tip, etc. The percentages of distribution pattern are shown in Figure 1 and Figure 2.

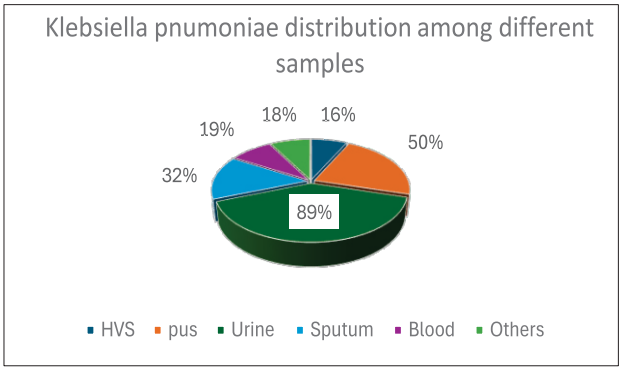

Fig.1: Distribution of Klebsiella spp. among different samples

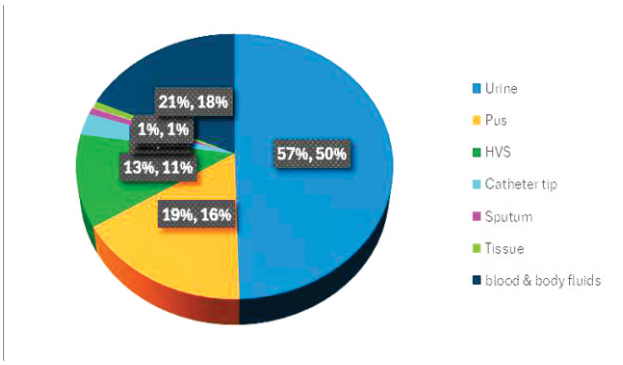

Fig.2: Distribution of Escherichia coli among different samples

The resistance outline of Escherichia coli & Klebsiella species isolates were analyzed using 24 selected antimicrobial drug disks of different classes. (Table 1). After applying statistical tests, the Mean of E.coli percentages was found to be 13.13 ± 15.03 (standard deviation), and the Mean of Klebsiella isolates was 15.17 ±16.47.The analysis of antibiotic resistance between E.coli & Klebsiella were calculated using Paired t-test and Pearson correlation. Paired t-test yielded the results as t-statistic: -2.2842 and P value = .0324 (significant result), and Pearson correlation coefficient was found to be 0/967. These isolates disclosed mutable results in their antibiotic sensitivity pattern in contradiction to commercial verified antibiotic discs. Escherichia coli revealed resistance against AMC (34%), CTX (43%), CIP (31%), and COT/SXT (24%), respectively. Klebsiella pneumoniae displayed (58.7%), (49%), and (24%) resistance against CTX & COT, respectively. According to the susceptibility pattern, Imipenem, Meropenem, Ceftazidime, Cefoperzone+Sulbactam (SCF), Tetracycline, Erythromycin, Aztreonam, Nitrofurantoin, Fosfomycin, and Chloramphenicol were the most effective antibiotics against Escherichia coli & Klebsiella Species as evidenced by Table 1. Among Escherichia coli and Klebsiella species, none of them were found to be sensitive to all antibiotics tested.

Table 1: Antibiotic resistance profile of isolated bacteria in culture-positive specimens N (%)

Names of Antibiotics	Percentages of Resistance among Isolates	
	Escherichia coli (N=391)	Klebsiella pneumonia (N=247)
AUG (Amoxicillin/Clavulanic acid)	131 (34%)	95 (38%)
AK (Amikacin)	40 (10%)	33 (13%)
AZT – Aztreonam	19 (05%)	29 (12%)
SCF-(Cefoperazone–Sulbactam	9 (02%)	7 (03%)
CTX- Cefotaxime	92 (24%)	89 (36%)
CRO- Ceftriaxone	168 (43%)	120 (49%)
CIP- Ciprofloxacin	121 (31%)	57 (23%)
COT/SXT- Cotrimoxazole (Trimethoprim–Sulfamethoxazole)	72 (18%)	60 (24%)
CN - Gentamicin	51 (13%)	35 (14%)
C-Chloramphenico	35 (09%)	33 (13%)
CE- Cephalexin,	7 (02%)	5 (02%)
CAZ-Ceftazidime	11 (03%)	3 (01%)
DOX-doxycycline	28 (07%)	17 (07%)
E-Erytromycine	18 (05%)	16 (06%)
FOS-Fosfomycine	30 (08%)	19 (08%)
F/NIT-Nitrofurantoin	22 (06%)	26 (11%)
IPM-Imepenem	4 (01%)	1 (00%)
MEM- meropnem	21 (05%)	9 (04%)
TET-tetracycline	2 (01%)	2 (01%)
TZP- Piperacillin–Tazobactam	17 (04%)	30 (12%)

**Amoxicillin/Clavulanic acid (AUG 20/10 µg), Amikacin (AK 30 µg), Azithromycin (15 µg), Aztreonam (AZT, 30 µg), Cefotaxime (CTX 30 µg), Ceftazidime (CAZ 30 µg), Ceftriaxone (CRO 30 µg), Ciprofloxacin (CIP 5 ug), Cefuroxime (30 µg), Trimethoprim/Sulfamethoxazole (1.25/23.75 µg), µg), Erythromycin (E 10 µg), Imipenem (IPM 10 µg), Gentamicin (CN 10 µg), Tetracycline (TET, 30 µg), Fosfomycin (FOX 50 µg), and Nitrofurantoin (F 300 µg), Clindamycin (DA, 15 µg), Meropenem (MEM 10 µg), Chloramphenicol (C, 30 µg)*

During the study period of one year, a total isolated bacterial pathogens were 1128, with the distribution of bacterial pathogens as mentioned in Table 1. This table displays Escherichia coli to be most habitually found pathogen (34.66%). The subsequent maximum common bacteria were Klebsiella pneumoniae, totaling 247 (21.9%) of total culture-positive specimens. The distribution pattern of Klebsiella spp. among isolates was revealed as; urine (35.2%), Pus (20.2%), HVS (2%), sputum (13%) and blood (7.4%). Antimicrobial sensitivity pattern of Escherichia coli and Klebsiella is shown in Figure 3 and Figure 4.

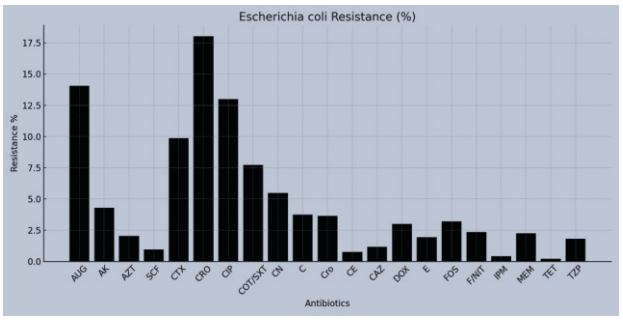

Fig.3: Antimicrobial Resistance Pattern of Escherichia coli

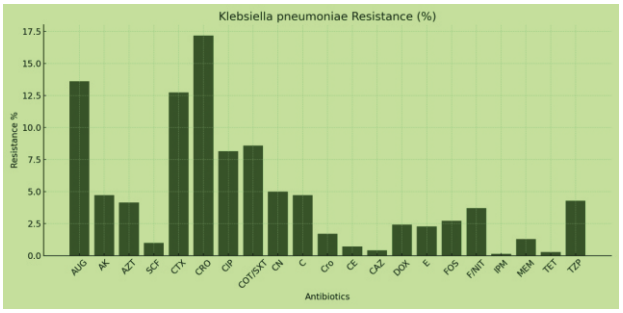

Fig.4: Antimicrobial Resistance Pattern of Klebsiella pneumoniae

Discussion

The emergence of multi-drug-resistant Escherichia coli and Klebsiella pneumoniae poses a significant challenge for clinicians in managing various infections acquired by the human body. The development of these new resistances diminishes the effectiveness of existing antibiotics, presenting a therapeutic challenge even for the most experienced physicians.

The present study revealed emerging resistance against Augmentin (34%, 38%), Cefotaxime (24%, 36%), Ceftriaxone (43%, 49%), Ciprofloxacin (31%, 23%), and Gentamycin (18%, 24%), revealed by Escherichia coli and Klebsiella species. This finding is parallel with the narratives of Liu G et al. and Karuna et al., who commented that the majority of these pathogens in his study (77.5%) were resistant to ampicillin and almost half of the drugs in the cephalosporin group.[12,13] A tertiary hospital in Pokhara, Nepal, and a study from Egypt reported similar results.[14,15] The synthesis of several β-lactamase enzymes may be the cause of this kind of resistance. The frequency of genes encoding 3rd generation Cephalosporins (3GC-resistant) beta-lactamases was also found to be significantly interrelated with high mortality rate in a cross-sectional examination of 143 tertiary hospitals in China.[16] The results of this investigation contrast those of a study carried out in Iraq, which illustrated that all strains of Escherichia coli unveiled resistance to each antibiotic tested, with resistance vacillating from 80 to 95%.[17] Our study revealed increased susceptibility to Imipenem & Amikacin, and these findings are in contrast with the verdict led by Karuna et al. and Alqasim A et al., who stated that the Maximum isolates (>80%) of their study were inclined to Imipenem, Piperacillin/Tazobactam, and Amikacin.[13,18] Studies carried out at various teaching hospitals in Nepal have revealed the high effectiveness of Imipenem and Amikacin against Klebsiella and Escherichia coli.[12] In addition, present data is very close to a study carried out in Lebanon, which claims 100 % susceptibility of Escherichia coli and Klebsiella to Imipenem (100%) and Meropenem (100%).[19] In comparison, an analysis of data from China revealed emergent resistance rates of Klebsiella pneumoniae to Imipenem, which poses an enormous challenge to clinical treatment.[20] Furthermore, given our findings of a high percentage of third-generation cephalosporin resistance for Klebsiella pneumoniae and Escherichia coli, Carbapenems must be used as a last possibility to treat severe infections that are acquired in hospitals and the community and are bacterial in origin in many situations. Our results are also harmonized with a study carried out in Thailand, which reported that Escherichia coli and Klebsiella pathogens were more susceptible to Carbapenems and aminoglycosides. Additionally, they showed a projected resistance rate to trimethoprim/

Sulfamethoxazole, ampicillin, Cefazolin, cefotaxime, and Fluoroquinolones.[21] The updated facts that Carbapenems are the most suitable empiric antibiotic combating these two microbes are also supported by studies conducted in Zambia. In addition, this study reveals that bulbous resistance to third-generation Cephalosporins proposes an outstanding level of β-lactamase production.[22,23]

In our study, an increased number of Escherichia coli and Klebsiella revealed resistance against Cefotaxime (24%, 36%) and Ceftriaxone (43%, 49%), but less resistance against ceftazidime (3%, 1%). These outcomes are consistent with analogous studies from Nepal, but in contrast to the study conducted in the Kathmandu valley, which reports an extraordinary occurrence (>60%) of MDR bacteria in medical specimens.[20,21] Moreover, among MDR isolates, half of the isolates were ESBL producers that were declared to be less sensitive toward cefotaxime, ceftriaxone, ceftazidime, and ampicillin.[24]

The results of this study underscore the substantial challenge presented by antimicrobial resistance. (AMR), particularly among Escherichia coli and Klebsiella pneumoniae isolates, which are commonly implicated in clinical infections. The occurrence of Escherichia coli as the leading pathogen, constituting 34.66% of total isolates, followed by Klebsiella pneumoniae at 21.9%, underscores the dominance of these Gram-negative bacteria in healthcare-associated infections. The least common isolate, Enterococcus faecalis (3.10%), adds to the complexity of pathogen diversity encountered in clinical settings. The observed resistance patterns, particularly against third-generation Cephalosporins such as ampicillin (AMP), amoxicillin-clavulanate (AMC), and cefotaxime (CTX), are concerning, as these antibiotics are frequently used in empirical therapy. The growing resistance trends of commonly used drugs in primary care reflect an alarming signal, and these findings necessitate a reconsideration of experiential treatment approaches, as sustained reliance on these antibiotics may deteriorate AMR and compromise treatment efficacy. Moreover, the updated resistance pattern in resource-limited settings highlights the critical need for alternative options in combating common infections. Fortunately, the study identifies a range of antibiotics that remain effective, including Carbapenems, ceftazidime, Cefoperazone-Sulbactam (SCF), Tetracycline, and Fosfomycin, which showed high susceptibility. These findings reinforce the efficacy of these antibiotics in cases of multidrug-resistant infections, particularly those caused by Escherichia coli and Klebsiella pneumoniae. However, the growing concern of resistance even to advanced antibiotics like Carbapenems in some regions underscores the importance of continual surveillance and judicious antibiotic use to prevent further resistance development.

Our study limitations are that the collected data represent records from one hospital, and the results may not reflect community trends or other healthcare facilities (restricted generalizability). Sampling Bias and clinical outcomes (treatment response, mortality, and complications) were not studied. The study is revealing phenotypic resistance patterns while resistance genes (e.g., ESBL, Carbapenems) were not confirmed genotypically, which limits mechanistic insights. Additionally, Progressive trends or seasonal stratification of resistance patterns have not been explored, which may mask changing resistance patterns over time.

Conclusion

The present study highlights the cumulative resistance of *Escherichia coli* and *Klebsiella pneumoniae* to third-generation Cephalosporins, reported in 24% (92 isolates) and 36% (89 isolates) of cases, respectively. A considerable level of resistance was also noted against quinolones, posing further therapeutic challenges. Conversely, Carbapenems, β-lactam/β-lactamase inhibitor combinations (Piperacillin–Tazobactam) (TZP), Ceftazidime, Cefoperazone-Sulbactam (SCF), Tetracycline, Fosfomycin, Nitrofurantoin, as well as Tigecycline and Colistin, demonstrated promising activity against cefotaxime-resistant strains. These findings underscore the importance of continuous surveillance of antimicrobial resistance patterns and the adoption of individualized antibiotic regimens. Furthermore, utilizing local epidemiological data can significantly aid in optimizing treatment strategies

within primary healthcare settings.As AMR continues to evolve, integrating local epidemiological data into clinical decision-making is critical to optimizing patient outcomes and preserving antibiotic efficacy. The study's findings emphasize the importance of routine susceptibility testing and alternative treatment regimens, which are vital in combating AMR and ensuring patient safety in primary care settings.

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Author Contributions

UZ: Manuscript writing for methodology design and investigation
ST: Conception and design of the work
AZ: Writing the original draft, proofreading, and approval for final submission
NT: Data acquisition, curation, and statistical analysis
AN: Validation of data, interpretation, and write-up of results
SB: Revising, editing, and supervising for intellectual content