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Bacteriological profile and antibiotic susceptibility pattern of secondary peritonitis in correlation to the anatomical site of gastrointestinal perforation: A Retrospective Study

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ABSTRACT

Background

The mortality and morbidity due to secondary peritonitis is high. Timely surgical intervention of secondary peritonitis due to Gastrointestinal (GI) perforation and appropriate empirical antibiotic therapy are prerequisites for a good outcome in these cases. The study aims to investigate the bacterial profile and the antibiotic susceptibility pattern of bacterial isolates in cases of secondary peritonitis following GI perforation and the correlation of bacterial spectrum with the different anatomical sites of GI perforation.

Methods

The retrospective study includes 44 patients operated on for secondary peritonitis following GI perforation between Jan 2019 to March 2020. The peritoneal fluid samples from these patients were subjected to bacterial culture and sensitivity. The bacterial isolates were identified by standard microbiological techniques and antibiotic susceptibility pattern was determined by the Kirby Bauer disk diffusion method and E test. The clinical data about the anatomical site of gastrointestinal perforation was collected from the medical records of these patients and were analyzed.

Results

Out of 44 peritoneal fluid samples obtained from secondary peritonitis cases due to GI perforation, 58 bacterial strains were isolated. The majority of the bacterial isolates were Gram-negative bacilli; *Escherichia coli* 31/58 (53.44%), *Klebsiella pneumoniae* 16/58 (27.58%) and *Enterobacter spp*. 5/58 (8.62%). The Gram-positive bacteria accounted for 10.33% of the infections; *Enterococcus spp*. 4/58 (6.89%) and Staphylococcus aureus 2/58 (3.44%). The most common anatomical site of GI perforation was Appendix in 63% of the cases, followed by the stomach in 16% and the small intestine in 14% of the study cases. Meropenem was found to have the highest susceptibility rate among all Gram-negative bacteria. Vancomycin and Linezolid were effective in all localizations with a sensitivity rate of 100%.

Conclusion

By evaluating the microbial flora and its antibiotic susceptibility pattern in relation to the location of perforation and microbial flora, we recommend Meropenem and Linezolid as the choice for empirical antibiotic therapy in cases of secondary peritonitis following GI perforation.

Keywords: Intra-abdominal infection, Poly-microbial infection, Empirical antibiotics,Multidrug resistant Bacteria, Gastro intestinal perforation.

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INTRODUCTION

Intra – abdominal infections can present as uncomplicated or complicated infections. Un-complicated infections localize to a single organ with intact peritoneal lining.[1] The inflammation extending beyond the peritoneal space complicates the intraabdominal infection. [2] Secondary peritonitis is due to the spillage of bacteria into the peritoneal cavity secondary to Gastrointestinal (GI) perforation, laceration, or necrosis of gastrointestinal segment, the most common cause being GI perforation.[2] Mortality due to secondary peritonitis is 20% higher than other systemic infections as it leads to sepsis if not treated in time.[3] Due to increased morbidity and mortality, there is prolonged Intensive care unit stay which adds to more economic burden for the patients.[4]

Secondary peritonitis following GI perforation is a poly-microbial infection.[5] In case of secondary peritonitis, dysbiosis leads to excessive production of endotoxins and inflammatory mediators.[4] The absorption of endotoxins into the systemic circulation leads to sepsis, and multisystem organ failure (MSoF).[6] Inadequate source control, co-morbidities, and inappropriate antibiotic administration lead to poor prognosis in secondary peritonitis.[7] Many a times, the lack of response to the initial empirical antimicrobial agents by the resistant bacteria leads to mortality. Timely surgical intervention and appropriate antibiotic therapy are prerequisites for a good outcome in secondary peritonitis cases. [8,9]

The National treatment guidelines recommend beta-lactam and beta-lactamase inhibitors as the first line of antibiotics for the empirical therapy of Secondary peritonitis cases, followed by Carbapenem.[10]Antibiotic resistance patterns are ever-changing worldwide. Antimicrobial resistance is the main factor that reinforces the selection of appropriate empirical agents. While selecting an empirical antimicrobial agent for patients with secondary peritonitis, factors to be considered are the location of perforation, patient's risk profile, patient's past history of exposure to antibiotics and local antibiogram.[11] The data and the information on spectrum of microbial flora and its Antibiotic susceptibility pattern in relation to the location of perforation is essential for effective management and framing of the antibiotic policy. [11] Our study aims to evaluate the microbial profile and their antibiotic susceptibility pattern based on different anatomical site of GI perforation in cases with secondary peritonitis.The information will be helpful for clinicians in the selection of most appropriate empirical antibiotic based on the site of perforation.

Materials and Methods

The retrospective study was carried out at R L Jalappa Hospital & Research Centre, Tamaka, Kolar. The study period is from January 2019 to March 2020. During the study period at our Microbiology Laboratory, 90 peritoneal fluid samples were received for aerobic culture and sensitivity. The clinical details of these patients were fetched from the medical records department (MRD). The patients who had undergone surgery for secondary peritonitis with GI perforation were selected. Based on inclusion criteria, 44 out of 90 patients were considered for the study.

Microbiological diagnosis

Peritoneal fluid samples were obtained for bacteriological culture and sensitivity testing under aseptic conditions in a sterile wide-mouthed container. In case of a delay in transporting samples to the laboratory, samples were stored at 2 - 8°C. The macroscopic findings of peritoneal fluid were recorded as per the Standard operating procedures (SOP). [10] The peritoneal fluid samples were centrifuged at 3,500 rpm for 15-20 min. The peritoneal fluid samples were inoculated on the sheep blood agar, Mac Conkey agar, and Thioglycolate broth and incubated at 37°C for 48 hours. After 24-48 hours of incubation, colony morphology on the culture plates was noted. The bacterial isolates were identified by colony characteristics, gram stain, and standard biochemical tests. [10]

Antibiotic Susceptibility Testing

The Kirby Bauer disk diffusion method was used to determine the antibiotic susceptibility pattern of

bacterial isolates. The Broth culture of the test organism matching to 0.5 Mc Farland Standard was inoculated on the Muller Hinton agar (MHA) plate. Antibiotic disc panels were used based on CLSI guidelines.[12] The MHA plates were incubated for 18 hours at 37°C and the antibiotic susceptibility was recorded as sensitive and resistant as per CLSI guidelines. [12]

The retrospective data analysis included patients' gender, age, bacterial culture and antibiotic susceptibility findings in relation with the anatomical site of perforation. Data were analyzed using SPSS version 25. Descriptive statistics such as frequency, mean, and percentage were calculated to describe the demographic characteristics of the study population.Institutional ethics committee approval was obtained.

Results

Among the 44 patients with secondary peritonitis due to GI perforation, 70% were males, and 30% were females. The majority of the secondary peritonitis cases are seen in the age group 21-40 years (n=20, 45 %) followed by 0-20 years (n=10, 23%), 41-60 years (n= 8, 18 %), and >60 years (n=6, 14%). The characteristics of the study patients are shown in Table 1.

Table 1 Characteristics of the study patients (n=44)

Variables	Categories	Frequency	Percentage
Gender	Males	31	70%
	Females	13	30%
Age in years	0-20	10	23 %
	21-40	20	45%
	41-60	8	18%
	>60	6	14 %

In our study patients with secondary peritonitis, the most common site of GI perforation was Appendix found in 63% of the cases. Other sites accounted for 37% of the cases which included stomach in 16%, small intestine in 14% and colon in 7% of the cases. Distribution of cases of secondary peritonitis based on different sites of GI perforation is depicted in Fig. 1.

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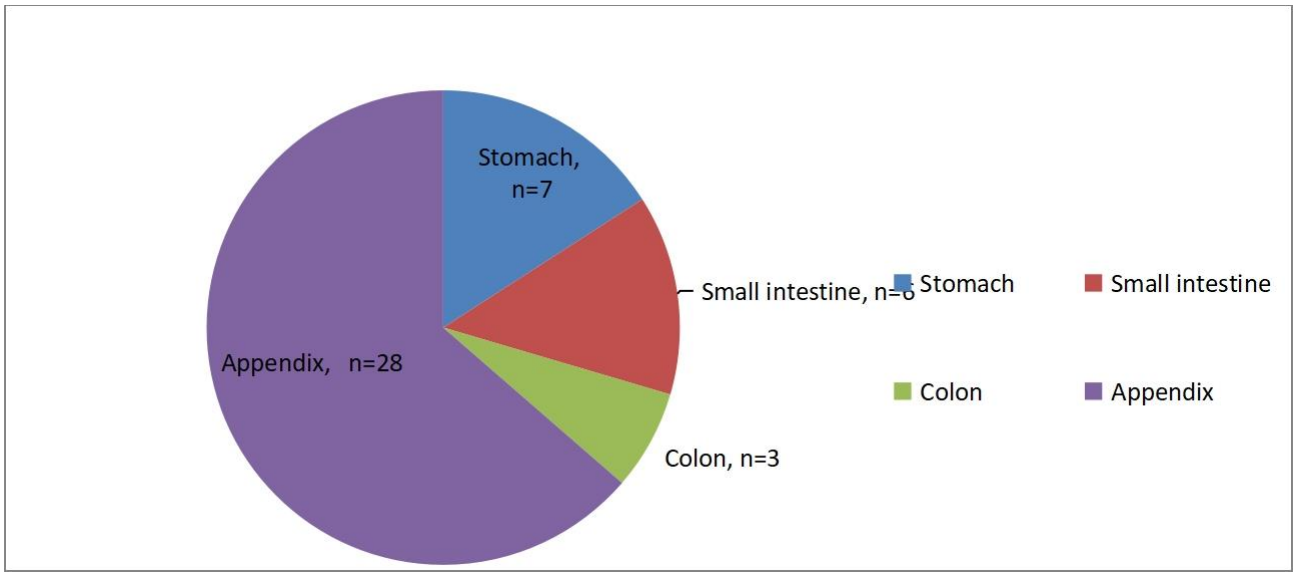
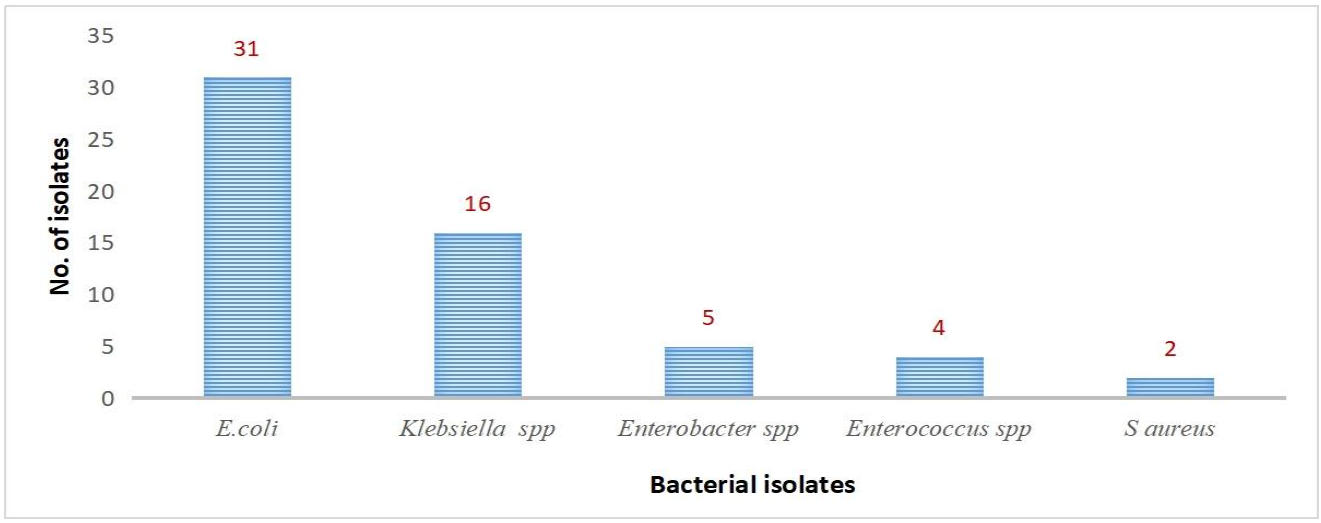
Fig. 1 Prevalence of Hollow viscus perforation based on different sites of GI tract



Polymicrobial infection was seen in 10/44 patients and hence altogether, 58 bacterial isolates were found in 44 cases included for the study. As a whole, the predominant bacterial isolates were Gram negative bacilli. The most common Gram-negative bacterial isolate was *Escherichia coli* in 53.44% (n=31) of the cases followed by *Klebsiella pneumoniae* and *Enterobacter spp.* in 27.58% (n=16) and 8.62% (n= 5) of the cases respectively. Gram positive cocci accounted for only 10.33% (n=6) of cases; *Enterococcus spp.* in 6.89% (n=4) and *Staphylococcus aureus* in 3.44% (n=2) of cases as shown in Fig. 2.

Fig. 2 Bacterial profile in Secondary peritonitis cases (n=58)



Bacterial profile based on different anatomical location of perforation is shown in **Table 2.** Among patients with appendicular perforation, the most common organism isolated was *Escherichia coli* in 66% (n=23) of the cases followed by *Klebsiella pneumoniae*, *Enterobacter spp.* and *Enterococcus spp.* in 14% (n= 5), 11% (n=4), and 9% (n=3) of the cases respectively. In patients with perforation in Stomach, both *Escherichia coli* and *Klebsiella pneumoniae* were seen in 38% (n=3) of the cases each whereas

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Enterobacter spp. and *Staphylococcus aureus* were seen in 13% (n=1) of the cases each.In both the small intestinal and colonic perforations, *Klebsiella pneumoniae* was the predominant isolate seen in 50% (n=6) and 67% (n= 2) of the cases respectively, whereas *Escherichia coli* was the second most common isolate in 33% (n=4) and 33% (n=1) of the cases respectively. The other bacterial isolates in the remaining small intestinal perforation cases were *Enterococcus spp.* and *Staphylococcus aureus* contributing for 8% (n=1) of the cases each.

Table 2 Bacteriological profile of secondary peritonitis cases based on different anatomical location of perforation

Site of Perforation	Stomach	Small intestine	Appendix	Colon	Total isolates
***Escherichia coli* n (%)**	3(37.5%)	4(33.33%)	23 (66 %)	1(33 %)	31(53.44%)
***Klebsiella pneumoniae* n (%)**	3(37.5%)	6 (50%)	5(14 %)	2(67 %)	16(27.58%)
***Enterobacter spp.* n (%)**	1(12.5 %)	0	4 (11%)	0	5(8.62%)
***Enterococcus spp.* n (%)**	0	1(8.3 %)	3(9 %)	0	4(6.89%)
***Staphylococcus aureus* n (%)**	1(12.5 %)	1(8.3%)	0	0	2(3.44%)
Total	8	12	35	3	58 (100%)

Table 3 shows the Antibiotic susceptibility pattern of isolates. The antibiotic susceptibility rate of Escherichia coli was more than 75% to Amikacin (87%), Meropenem (81%) and Tobramycin (77%). None of the Klebsiella pneumoniae isolates had >60% susceptibility rates to the antibiotics tested. Enterobacter spp. expressed 100% susceptibility to Meropenem, followed by Ertapenem, Piperacillin-Tazobactam and Levofloxacin at 80%.The prevalence of Extended spectrum beta lactamase (ESBL) producers among Gram negative bacteria was significantly noted in Escherichia coli and Klebsiella pneumoniae; ESBL producing strains among Escherichia coli was found to be 38.7% (12/31 isolates), in Klebsiella pneumoniae, it was 37.5% (6/16 isolates) and in Enterobacter 20% (1/ 5 isolates) of the isolates were ESBL producers.Among the Gram-positive isolates, Staphylococcus aureus (MRSA) expressed 100% susceptibility to Doxycycline, Gentamicin, Vancomycin, and Linezolid. Enterococcus spp. showed 100% susceptibility to Vancomycin and Linezolid.

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Table 3 Antibiotic susceptibility pattern of isolates

Antibiotics	*E. coli* n=31	*Klebsiella pneumoniae* n=16	*Entero-bacter* n=5	*S. aureus* n=2	*Enterococcus* n=4	Total n=58
Sensitivity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ampicillin (AMP)	5 (16 %)	0	0	0	2(50%)	7(12 %)
Amoxy-clavulanic acid (AMC)	7(23%)	0	1(20%)	-	-	8(14 %)
Cefotaxime (CTX)	12(39%)	5(31%)	1(20%)	-	-	18(31 %)
Ceftriaxone (CTR)	11(35%)	5(31%)	0	-	-	16(28 %)
Ceftazidime (CAZ)	11(35%)	5(31%)	0	-	-	16(28 %)
Piperacillin Tazobactum (PIT)	22(71%)	9(56%)	4(80%)	-	-	35(60 %)
Cotrimoxazole (COT)	14(45%)	6(38%)	3(60%)	2(100 %)	-	23(40 %)
Imipenem (IMP)	23(74%)	8(50%)	3(60%)	-	-	34(59 %)
Meropenem (MRP)	25(81%)	9(56%)	5(100%)	-	-	39(67 %)
Ertapenem (ETP)	23(74%)	9(56%)	4(80%)	-	-	38(66 %)
Amikacin (AK)	27(87%)	9(56%)	3(60%)	--	-	39(67 %)
Gentamicin (GEN)	23(74%)	9(56%)	3(60%)	2(100 %)	-	35(60 %)
Tobramycin (TOB)	24(77%)	9(56%)	3(60%)	-	-	36(62 %)
Ciprofloxacin (CIP)	11(35%)	6(38%)	3(60%)	0	0	20(34 %)
Levofloxacin (LE)	13(42%)	6(38%)	4(80%)	0	2(50%)	25(43 %)
Doxycycline (DO)	15(48%)	5(31%)	1(20%)	2(100 %)	1(25%)	24(41 %)
Clindamycin (CD)	--	-	-	1(50%)	2(50%)	3(5%)
Erythromyc	-	-	-	0	2(50%)	2(3%)

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Penicillin(P)	-	-	-	0	2(50%)	2(3%)
Tetracycline (TE)	13(42%)	9(56%)	4(80%)	1(50%)	2(50%)	29(50%)
Vancomycin (VA)	-	-	-	2(100%)	4(100%)	6(10%)
Linezolid (LZ)	-	-	-	2(100%)	4(100%)	6(10%)

In patients with appendicular perforation, the highest antibiotic susceptibility was found to Meropenem (82.3%) followed by Amikacin (75.4%) and 72.5% susceptibility was found to both Piperacillin – Tazobactam and Ertapenem. Isolates from small intestine perforation cases showed 70.8% susceptibility to Meropenem, Amikacin and Gentamicin. Isolates from patients with perforations in stomach and colon had the susceptibility rate of 66.7% only to Amikacin, Gentamicin and Tobramycin. Table 4

Table 4 Antibiotic susceptibility pattern of Microbial flora related to location

Site of Perforation	Colon (n=3)	Appendix (n=28)	Stomach (n=7)	Small intestine (n=6)
Antibiotic Sensitivity	(%)	(%)	(%)	(%)
Ampicillin (AMP)	25	5.8	0.0	0.0
Amoxy-clavulanic acid (AMC)	0	15.6	16.7	12.5
Cefotaxime (CTX)	25	36.2	16.7	29.2
Ceftriaxone (CTR)	25	27.8	0.0	29.2
Ceftazidime (CAZ)	25	34.5	0.0	29.2
Piperacillin Tazobactum (PIT)	25	72.5	50.0	37.5
Co trimoxazole (COT)	25	60.9	33.3	37.5
Imipenem (IMP)	25	64.4	50.0	62.5
Meropenem (MRP)	50	82.3	50.0	70.8
Ertapenem (ETP)	50	72.5	50.0	58.3
Amikacin (AK)	66.665	75.4	66.7	70.8
Gentamicin (GEN)	66.665	69.6	66.7	70.8
Tobramycin (TOB)	66.665	65.9	66.7	58.3
Ciprofloxacin (CIP)	25	52.8	33.3	29.2
Levofloxacin (LE)	25	47.6	33.3	29.2
Doxycycline (DO)	25	33.8	33.3	29.2

Discussion

In our study, we evaluated the bacterial profile of Secondary peritonitis cases in relation to different anatomical sites of GI perforation and analyzed the antibiotic susceptibility pattern of the isolates to obtain appropriate empirical antibiotic treatment options. In the era of antimicrobial resistance, empirical antibiotic therapy guidelines are to be re-evaluated frequently for better clinical outcome of the patients. The recommended empirical antibiotic treatment for patients with secondary peritonitis following GI perforation should be based on bacterial profile in relation to site of perforation, as well as on local epidemiology, and clinical severity. Among 44 cases of secondary peritonitis included in the study, the majority were male patients, similar to other studies done in India.[13] Most of the study patients belonged to 21–40-year age group which is in concordance with a study done by Srivastava et al.[14] The factors responsible for higher incidence of secondary peritonitis in the patients with middle age group, could be probably due to lifestyle changes, consumption of street food, stress and usage of more analgesics. Few scientific reports state that perforation in males is higher due to less adherence of males to hygienic measures and a greater propensity to eat raw or undercooked foods.[15] The most common site of GI perforation in our study patients was the appendix in 63 % of the cases. Studies from the western world have reported appendicular perforation as the common cause of perforation. [16] The inappropriate treatment for acute appendicitis leads to perforation. The inappropriate treatment may be due to delay in consulting the doctor by the patient, poor access to health care and misdiagnosis.[17] As our study population is from rural area, the probable reason for higher incidence of appendicular perforation could be because of poor access to healthcare facilities as well as delay in reporting by the patient.Peritonitis is a poly-microbial disease. [8] In our study, Poly-microbial growth was seen in 22.7% of the cases. In a study done by Manju Singh et.al, Poly-microbial growth was seen in 12.6% of cases. [18] In our study, Gram-negative bacilli were the most common causative agents of secondary peritonitis in 89% of the cases. Our findings are comparable with a study done by Manju Singh et al. [18] As the bacterial profile differs in cases based on different sites of GI perforation, the antibiotic of choice also varies.[13] We found that in cases with appendicular perforation, *Escherichia coli* was the most common isolate, followed by *Enterobacter* spp. In the study by Lohith et al, *Escherichia coli* was seen in 100% of cases with appendicular perforation. [19] In another study by Vishnu et al, *Escherichia coli* was found in 47.24% of appendicular perforation cases. [20] In cases of perforation in stomach, again *Escherichia coli* and *K.pneumoniae* were the most common isolates, whereas in small intestinal and colonic perforations *K.pneumoniae* was the predominant isolate. The study by Lohith et al reports *Escherichia coli* as a common isolate in the small intestine and colonic perforations in almost 100% of the cases. [19] Other studies on small intestinal perforation also report *Escherichia coli* as a common isolate among the Enterobacteriaceae family. [20] Empiric antibiotic treatment for secondary peritonitis should cover commonly isolated pathogens.[21] The antibiotic susceptibility pattern of the most prevalent isolate *Escherichia coli* showed significant susceptibility rates of >75% only to Tobramycin, Amikacin and Meropenem. This is in concordance with a study done by Manju Singh et al. [18] However, Amikacin is not suitable for empirical therapy in intraabdominal infections as it has decreased activity in an acidic environment like pus. [22]

The notable finding of significant antibiotic resistance by *K.pneumoniae* is a matter of concern. There was no significant susceptibility to any of the antibiotics tested including carbapenems. *Klebsiella pneumoniae* is an ideal vehicle for transfer of drug resistance genes from the environment to clinically significant bacteria.[23] Through the plasmids and mobile genetic elements, pathogens accumulate the antimicrobial resistance genes.[23] *Klebsiella pneumoniae* disseminates antibiotic-resistant genes through vertical transfer to its daughter cells and horizontal transfer between organisms of varying strains, genera, and species.[24] The increase in the dissemination of acquired antimicrobial resistance (AMR) genes occur following the increase in

antimicrobial use.[23] Although, *Enterobacter spp.* prevalence was less in our study, they expressed good susceptibility to Piperacillin-Tazobactam, Levofloxacin, Meropenem and Ertapenem.

Though Piperacillin-Tazobactam is the recommended first line antibiotic as per few studies, our study showed a cumulative sensitivity of only 65%. [13]

Only 11% of our cases yielded Gram positive cocci as the causative agents which showed better antibiotic susceptibility pattern than Gram negative bacilli. Both *Staphylococcus aureus* and *Enterococcus spp.* expressed 100% susceptibility to Linezolid and Vancomycin.There is a considerable antibiotic resistance noted in *Escherichia coli, K. pneumoniae* and *Enterobacter spp.* in our study. Antibiotic resistant bacteria are the greatest threat to human survival and in the recent times, there is increased incidence of antibiotic resistant bacteria worldwide. [25]Extended Spectrum Beta Lactamase (ESBL) producing Enterobacteriaceae are a threat in intestinal infections. ESBL strains have beta-lactam hydrolyzing enzymes and plasmids encoding resistance to aminoglycosides and fluoroquinolones. [26-27]According to the report issued by the Asia-Pacific SMART Group, the rates of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* were 34 % and 22.3% of all these organisms, respectively. [28] The Enterobacter ales pose increasing resistance to Amoxicillin – clavulanic acid; however, most isolates are susceptible to Piperacillin- Tazobactam in few studies.[29] In our study, ESBL producers were susceptible to Piperacillin-Tazobactam in 87% of the ESBL isolates and susceptibility to Amoxicillin clavulanic acid was found in 23% of ESBL producers. Least susceptibility was found to Cephalosporin and fluoroquinolones.

Overall, Meropenem and Amikacin showed susceptibility results of 72%. In recent years, raising Extended Spectrum Beta-Lactamase (ESBL) infections has emphasized Carbapenem-preserving antimicrobial stewardship. [30]

The recent guidelines recommend the use of high-end antibiotic like Meropenem and vancomycin or Linezolid as adjuvant antibiotic for empirical treatment of adults with intraabdominal infections. [31]Taking into consideration, to formulate empirical antibiotic therapy based on cumulative bacterial profile and antibiogram related to the site of GI perforation as well as the most common site of GI perforation, we recommend Meropenem as the empirical antibiotic of choice in our study.

Conclusion

In managing intra-abdominal infections, key components are source control and antibiotics. In the era of increasing antimicrobial resistance, optimization of empirical therapy is required for better clinical outcomes and restriction of excessive use. On comparing antibiotic susceptibility patterns to the location of perforation and microbial flora, we recommend the combination of Meropenem and Linezolid as better choices for empirical antibiotics.

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