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Are Fungi Responsible For Higher Mortality In Perforation Peritonitis? Correlation of Mannheim Peritonitis Index (MPI) In Fungal Positive Cases

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Abstract
Background
Different species of microbes reside in the gastro-intestinal tract. On perforation of the GIT these microbes are released in the peritoneal cavity and cause peritonitis and its related manifestations. Early diagnosis and correct treatment may be helpful in improvement of the overall outcome of this serious condition. Fungi constitute between 8%-43% of cases in different studies of perforation peritonitis. Their role in the morbidity and mortality has not been exclusively studied in earlier studies. Our study was focussed on their role in the overall outcome of patients with perforation peritonitis.
Methods
Peritoneal fluid culture was taken at the time of Laparotomy, second culture from the abdominal drain on second post-operative day and third culture from the abdominal drain on fifth post-operative day. Bacterial and fungal cultures were done of the peritoneal fluid. Antimicrobial sensitivity was performed using Kirby–Bauer disk diffusion method.
Observations and Results
In our study Fungi were isolated in 95 (19.8%) cases (Candida species). Mean MPI score was higher in patients having both bacteria and fungi culture positive (MPI=27.3) and only fungal culture positive patients (MPI=27.1), compared to patients with only bacterial culture positive (MPI=26.8) and no growth (MPI=25).
Mortality was highest in patients having both bacterial and fungal positive cultures (27.7%) followed by positive for bacteria only (21.1%). Mortality in patients positive for fungi only was 16.7% and was least for patients having no growth (13%)
Conclusion
Patients with perforation peritonitis having fungal isolation had higher Mannheim Peritonitis Index (MPI) and higher morbidity and mortality.
KEY WORDS: *perforation peritonitis, Mannheim Peritonitis Index, microbial profile, Fungi, Candida, mortality*

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I. Introduction

Gastro-Intestinal tract is colonised by large number of bacteria[1,2], the perforation of the hollow viscus leads to the release of bacteria in the peritoneal cavity. Many of the bacteria are highly pathogenic. There is comparatively lesser number of microbial populations in upper GI tract (stomach, duodenum, jejunum and upper ileum). Most of these micro-organisms are translocated from the oropharynx with food. Due to acidic environment there is lesser number of microorganisms in the stomach and proximal part of intestine. Aerobic gram positive cocci are the predominant microorganisms in this part of GIT.[3] On the other hand, large intestine has a complex and dense population of microbes. Anaerobes (bacteroides, anaerobic streptococci and clostridia) are about 1000 times higher in colon than facultative anaerobes (e.g. *E. coli*).[3]
About 70% of the healthy individuals have fungi, mainly *Candida* species in their gut.[4]

During microbial profiling of cases of perforation peritonitis less attention is paid to fungal cultures. Few studies have focussed on the role of fungal isolates in the morbidity and mortality of the patients with perforation peritonitis.

The present study was conducted with the aim of studying the role of fungal isolates in relation to morbidity and mortality in perforation peritonitis.

Mannheim Peritonitis Index (MPI) developed by Linder and Wacha is a simple and easy tool to predict the outcome in perforation peritonitis patients. Maximum score possible is 47. (Table-1)

Total MPI score is calculated and allotted to one of the three score groups: <21, 21-29, >29. Higher the score poorer the outcome.

II. Material And Methods

The study was approved by institutional ethics committee and included 498 patients of secondary peritonitis. Peritoneal fluid culture were taken, for first culture, peritoneal fluid collected at the time of Laparotomy, second culture from the abdominal drain on second post-operative day, third culture from the abdominal drain on fifth post-operative day. Wound swabs for culture sensitivity were also taken if surgical site infection was present.

Peritoneal fluid was collected at the time of surgery in sterile syringe and transferred into two sterile pus culture containers. On second and fifth days, peritoneal fluid was collected from intra-peritoneal drains. For bacterial culture fluid was inoculated on 5% sheep blood agar, MacConkey agar and Trypticase soy broth (TSB) incubated overnight aerobically at 37^0C. Next day, the culture plates were observed for growth and identification of microorganism was done using Gram staining and biochemical tests using standard biochemical techniques. Cultures not showing growth on overnight incubation were sub-cultured from TSB on 5% sheep blood agar and MacConkey agar.

Anti-microbial sensitivity testing was done using Kirby–Bauer disk diffusion method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines.

For Fungi, screening was done with direct microscopy on KOH mount, then culture was done in Sabroud's Dextrose Agar (SDA) tube and incubated at 25^0C and 37^0C, tubes were checked on alternate days for growth till 6 weeks. Cultures showing growth were identified using standard biochemical tests. Sensitivity testing was done using CLSI guidelines.

The data regarding the patient's particular, diagnosis, investigations, surgical procedures and outcome were transferred to a computer data base and individual Mannheim Peritonitis Index scores calculated for each patient.

III. Observations And Result

This study was conducted at Jawaharlal Nehru Medical College and Hospital Aligarh Muslim University, Aligarh, between November 2018 to October 2020. A total of 498 patients were included in the study. 377 were males (75.7%) and 121 were females (24.3%). Male to female ratio was **3.2:1.** Age range was between 18-65 years.

Peritoneal fluid cultures sent on the day of surgery showed monomicrobial growth in 228 (47.4%) cases, polymicrobial in 147 (30.6%) cases and no growth in 106 (22%) cases (Table-2). 280 (58.2%) patients were having peritoneal culture positive for bacteria only. 12 (2.5%) were positive for fungi only and 83 (17.3%) were having both bacteria as well as fungi culture positivity.

Fungi were isolated in 95 (19.8%) cases (*Candida* species). *Enterococcus*, *Citrobacter* and Staphylococcus were isolated in 67 (13.9%), 50 (10.4%) and 31(6.4%) cases respectively. *Pseudomonas*, *Corynebacterium* and *Proteus* were also isolated (Table-3)

On the second day, no growth was seen in 179 (39%) cases, most common organism was *Klebsiella* 99 (21.6%) whereas *E. coli* was isolated in 68 (14.8%) cases. Fungal culture was positive in 61 (13.3%) on second day. (Table-3)

On the fifth day, no growth was seen in 167 (37.3%) cases, most common organism was *E. coli* in 113 (25.2%) whereas *Klebsiella pneumonia* was isolated in 68 (15.2%) cases. Fungal culture was positive in 40 (8.9%) cases on fifth day. (Table-3)

Candida spp. isolated from the peritoneal cavity were sensitive to Fluconazole (100%), Clotrimazole (100%), Itraconazole (98.95%), Nystatin (94.74%), Amphotericin-B (94.74%) and Ketoconazole (97.89%). (Table-4)

Mean MPI score was higher in patients having both bacteria and fungi culture positive (MPI=27.3) and only fungal culture positive patients (MPI=27.1), compared to patients with only bacterial culture positive (MPI=26.8) and no growth (MPI=25).

Similarly, mortality was highest in patients having both bacterial and fungal positive cultures (27.7%) followed by positive for bacteria only (21.1%). Mortality in patients positive for fungi only was 16.7% and was least for patients having no growth (13%), although it was not statistically significant (p=0.0980).

Hospital stay was higher (>7 days) in patients having positive fungal culture (58.3% patients) and both bacterial and fungal positives (43.4%) than those with only bacteria positive (40.4%) or those who showed no growth (27.4%). But it was not statistically significant (p=0.207) (Table-5)

IV. Discussion

Gastrointestinal tract is a storehouse of a variety of microbial flora and thus is a source of peritoneal contamination and sepsis during its perforation.[1,2] Microorganisms isolated from peritoneal fluid vary depending upon the site of perforation of gastro intestinal tract. Prevalence of Aerobic Gram-Negative Bacilli (53.6%), Aerobic Gram-positive Cocci (47.2%) and *Candida* (53.6%) were found in perforations of upper GI Tract. In the lower GI Tract prevalence of Aerobic Gram-Negative Bacilli was in 100% and Gram positive cocci was in 37.5% patients.

In our study, Peritoneal fluid cultures sent on the day of surgery showed monomicrobial growth in 167 (33.5%) cases, polymicrobial in 225 (45.2%) cases and no growth in 106 (21.3%) cases. In subsequent cultures sent on 2nd and 5th days, number of samples having no microbial growth increased and less polymicrobial growth was seen.

Most common organism isolated in the peritoneal fluid on the day of surgery was *Escherichia coli*, seen in 170 (35.34%) cases of hollow viscus perforation, followed by *Klebsiella* which was isolated in 133 (27.6%) cases. Cultures showed no growth in 106 (22%) cases; fungi were isolated in 95 (19.7%) cases (*Candida* species). *Enterococcus*, *Citrobacter* and Staphylococcus were isolated in 67(13.4%), 50(10%) and 31(6%) cases respectively. *Pseudomonas*, *Corynebacterium* and *Proteus* were also isolated.

Kumar MP 2019 studied perforation peritonitis patients and found *E. coli* as the most common organism seen among the positive intraoperative fluid (47.9%) followed by *Klebsiella pneumonia*e (12.5%). Fungal culture positivity was seen in 4.2%. In our study, higher rate of fungal culture positivity was seen (18.47%).

Candida spp. isolated from the peritoneal cavity were sensitive to Fluconazole (100%), Clotrimazole (100%), Itraconazole (98.95%), Nystatin (94.74%), Amphotericin-B (94.74%) and Ketoconazole (97.89%).

De Ruiter et al observed prevalence of *Candida* to be 19.9% in hollow viscus perforation. Prevalence was 41% in Gastric perforation and 34.1% in Small Bowel Perforation. *Candida* was not isolated in appendicular perforation. Aerobic Gram-Negative Bacilli (AGNB) were found in 52.9% (45% were *E. coli*). AGNB were highest in colorectal perforations (68.6%) and lowest in Gastro Duodenal perforations (20.5%). Gram Positive Bacteria were found in 42.5% and most frequently in colorectal perforations (50%).[5]

Advait Prakash et al in their study of hollow viscus perforation observed that 50% were culture positive having *E. coli* as most common organism followed by klebsiella. *Candida* was associated in 31% of positive cultures. *Candida* was not present in isolation but was present along with other bacteria. Fungus was isolated more from ileal than gastro duodenal perforation.

Mortality was higher in patients with positive fungal culture ($p<0.001$).[6] Many studies have concluded that presence of fungus in peritoneal fluid is associated with higher mortality.[7–10]

Indra Singh Sahani et al found *E. coli* as the most common micro-organism isolated (50%) followed by klebsiella (24%) and streptococcus (12%). *Candida* was isolated in 10% cases. Sensitivity profile showed *E. coli* and *Klebsiella* to be sensitive to Meropenem.[11]

Neerja Jindal et al studied 140 patients of perforation peritonitis and found 73.5% to be positive whereas 26.5% showed no growth. Polymicrobial growth was found in 58.2%. 8.7% were having *Candida* as the only microbe in their peritoneal fluid.[12]

Shan YS et al in 2003 observed 43.4% fungal positive cultures in patients of Gastro Duodenal perforations. [8]

Jagannath Pramod et al from Puducherry in 2018 studied 407 patients and found 153 patients (37.6%) positive for fungus. He concluded that patients who received early anti-fungal therapy were having less complications than those who did not receive anti-fungal treatment.[13]

Wei-Sin Li et al in their study on 133 patients of perforated peptic ulcer observed that Antifungal therapy did not affect the outcome significantly in patients having positive *Candida* culture and antifungal therapy could be reserved in the immunocompromised and critically ill patients.[13,14]

Higher MPI score was associated with the positive fungal culture and higher mortality. Similar observations were made in our study and it was seen that fungal culture was positive in patients having high MPI score but it was not statistically significant. Mean MPI score of fungal positive patients was 29.4 whereas in fungal culture negative patients mean MPI score was 26.8.[13]

There is significant number of *Candida* species isolated (18%) in patients of perforated gastrointestinal tract. Antifungal treatment is not routinely provided to the patients as it is still an under diagnosed infection. This fact of fungal isolation should be considered while treating immunocompromised patients and in patient, who are not improving despite adequate anti-bacterial therapy and are having prolonged morbidities.

Large multicentre studies are needed in different countries to study the role of fungal infections and its effects on the patient's outcome in cases of perforation peritonitis, as this aspect has not yet been studied extensively.

Further should antifungal treatment be a part of Antibiotic treatment in patients with perforation peritonitis having fungal isolates, need to be studied in larger studies and accordingly guidelines to be framed.

V. Conclusion

The present study has concluded that fungal isolates constitute about 18% of the total microbiological load in perforation peritonitis. Further those with the fungal isolates have higher Mannheim Peritonitis Index (MPI) score and higher morbidity and mortality. We recommend addition of Antifungal treatment in addition to Antibacterial therapy in seriously ill patients of perforation peritonitis to improve the overall outcome.

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Table-1: Mannheim Peritonitis Index

Study Variable	Adverse factor	Points	Favourable factor	Points
1.Age	>50 years	5	< 50 years	0
2.Sex	Female	5	Male	0
3.Organ Failure	Present	7	Absent	0
4.Malignancy	Present	4	Absent	0
5.Evolution time	>24 hrs	4	<24 hrs	0
6.Origin of sepsis	Non-colonic	4	Colonic	0
7 Extension of peritonitis	Generalized	6	Localized	0
8.Character of exudate	Purulent	6	Clear	0

	Faecal	12

Table-2: Microbial profile in patients with perforation of hollow viscera

POST-OP DAY	NO GROWTH	MONOMICROBIAL	POLYMICROBIAL
Day 0	106 (22%)	228 (47.4%)	147 (30.6%)
Day 2	179 (39%)	201 (43.8%)	79 (17.2%)
Day 5	167 (37.3%)	209 (46.6%)	72 (16.1%)

Table- 3: Microbial profile in patients of perforation of hollow viscera

ORGANISM	Day 0		Day 2		Day 5	
Bacteria	**n=481**	**%**	**n=459**	**%**	**n=448**	**%**
Escherichia coli	170	35.3	68	14.8	113	25.2
Enterococcus fecalis	67	13.9	47	10.2	56	12.5
Citrobacter species	50	10.4	42	9.2	12	2.7
Klebsiella pneumonia	133	27.7	99	21.6	68	15.2
Staphylococcus aureus	31	6.4	24	5.2	39	8.7
Pseudomonas species	8	1.7	3	0.7	13	2.9
Corynebacterium species	6	1.2	10	2.2	1	0.2
Acintobacter species	0	0.0	2	0.4	0	0.0
Proteus species	6	1.2	2	0.4	10	2.2
Fungi	95	19.8	61	13.3	40	8.9
No Growth	106	22.0	179	39.0	167	37.3

Table- 4*:* Sensitivity of *Candida species* to antifungal agents

ANTIFUNGAL AGENT	SENSITIVITY
Fluconazole	100% (95/95)
Clotrimazole	100% (95/95)
Itraconazole	98.95% (94/95)
Nystatin	94.74% (90/95)
Amphotericin B	94.74% (90/95)
Ketoconazole	97.89% (93/95)

Table- 5: Peritoneal fluid culture and outcome

PERITONEAL CULTURE	NUMBER OF CASES	HOSPITAL STAY		MORTALITY	MEAN MPI SCORE
		<7 DAYS	>7 DAYS		
BACTERIA AND FUNGI	83	31	29	23 (27.7%)	27.3
BACTERIA ONLY	280	104	117	59 (21.1%)	26.8
FUNGI ONLY	12	3	7	2 (16.7%)	27.1
NO GROWTH	106	53	39	14 (13.2%)	25
Chi square value		4.5592, p=0.207		6.295, p=0.0980	

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