Peritonitis – Etiology and Treatment Options: A Systematic Review

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Abstract

Peritonitis is an infection with a substantial source of morbidity and death. The mortality rate is 10% to 60%. Its etiology may be infection of bacteria, viruses, or fungi. The objective of the current systematic review is to identify the causes of peritonitis and discuss available treatment options. A systematic review was conducted from the literature from January 2012 to December 2022. More than 60 articles were downloaded; after abstracting relevant information from the studies and assessing quality, data was synthesized and presented by PRISMA flow diagram. The most common cause was bacterial infection; followed by fungal and viral infections. Reported organisms were *E. coli, Klebsiella spp., Streptococcus spp., M. tuberculosis, C. trachomatis, Pseudomonas spss., C. albicans, C. glabrata, C. krusei, Cryptococcus spp.,* and *Aspergillus spp.,* and Feline-infectious-corona-virus. Empiric antibiotics therapy covers broad-spectrum antibacterials; antifungal and surgical interventions are treatment options. The acutely ill patient requires combined medical and surgical methods; culture sensitivity is highly advisable to reduce the chances of failure.

Keywords: *Peritonitis, bacteria, fungi, virus, empiric therapy, culture-sensitivity.*

INTRODUCTION

Peritonitis causes severe abdominal discomfort and is potentially fatal; morbidity and mortality rates are 10% to 60% [1]. Etiologies of peritonitis vary; depending on the geographic location, local environment, and genetic predisposition [1]. Appendicitis and typhoid ileal perforation are the most prevalent causes [1]. Other causes are; duodenal-perforation, ruptured appendix, tuberculosis perforation, tumor perforation, liver cirrhosis, gangrenous-gut, acute-pancreatitis, acute-diverticulitis and pelvic-inflammatory-disease [1]. Different layers of mucus, intestinal epithelia, gut-associated lymphatic tissue, and antimicrobial peptides work together to prevent microbial crossing from the gut lumen to the peritoneal cavity [2].

Human history is full of shreds of evidence of the dangers posed by peritonitis; peritonism refers to abdominal rigidity [3]. Most cases of peritonitis are caused by bacteria; contributing organisms are *E. coli, Klebsiella, Streptococcus, Staphylococcus,* and *Enterococci spss*. [4]. The peritoneum is a monolayer of mesothelial cells that protects the abdominal wall and viscera; lymphatic tubes are localized on the diaphragm between mesothelial cells and remove foreign matter; prompt expulsion of intra-abdominal bacteria *via* lymphatic tubes reduces the risks of bacteremia and sepsis [5]. When microorganisms break the gut wall into the peritoneal cavity from circulation or when the immune system is impaired, and there is no recognized intra-abdominal source of infection; most probably it is either *Chlamydia trachomatis* peritonitis or spontaneous bacterial peritonitis (SBP) in cirrhotic patients or tuberculosis (TB) peritonitis or pelvic dialysis-related peritonitis [6]. The most prevalent and potentially fatal infection in individuals with liver cirrhosis is spontaneous bacterial peritonitis (SBP) [7]. The utmost origin of SBP is bacterial translocation (BT) by invasive procedures; BT that spreads rapidly is pathological translocation and harmful to the patient [7].

In 2018, extra-pulmonary tuberculosis (EPTB) contributed to 15% of WHO-recognized tuberculosis (TB) cases; among them, almost 6% of EPTB cases were tuberculous peritonitis (TP) [8]. Tuberculous peritonitis is intra-abdominal tuberculosis with nonspecific symptoms; therefore, clinical knowledge and skills are required to diagnose the infection timely [8]. Nowadays; laparoscopic invasive peritoneal biopsy might confirm the condition histologically and offer a more sensitive diagnosis of TB [9]. T-SPOT (peripheral blood) and T-SPOT (peritoneal fluid) are IFN-γ release assays; extensively used for diagnostic purposes of tuberculosis [8].

Infection of the human peritoneum by a virus is very rare; literature reported only cytomegalovirus and coxsackievirus-B-virus [6]. Feline-infectious-peritonitis is a well-known veterinary disease; caused by coronavirus in cats [6]. Feline coronavirus (FCoV) has two serotypes; feline-enteric-coronavirus (FECV) and feline-infectious-peritonitis-virus (FIPV) [10].

Fungal peritonitis occurs infrequently but frequently in patients at high risk of immunodeficiencies; peritonitis may be a symptom of a *Cryptococcus neoformans* infection [6]. Prognosis is poor for Candida specie related fungal peritonitis; it is frequent in peritoneal dialysis (PD) patients; fungal peritonitis is more lethal in cirrhotic

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Received: March 25, 2023; Revised: May 30, 2023; Accepted: June 23, 2023
DOI: https://doi.org/10.37184/lnjpc.2707-3521.6.2

patients than in those on PD [6]. Candida peritonitis (CP) is rising in ICU patients and has significant mortality [11]. The potential risk factors of candida peritonitis are; hospital-acquired peritonitis, tertiary peritonitis, GIT (Gastro-intestinal Tract) perforation, heart failure, and surgery in the abdominal region [11]. Patients with liver cirrhosis also have a risk of fungal peritonitis; when ascitic fluid becomes infected; most common fungi were *C. albicans, C. glabrata, C. krusei, Cryptococcus spss.,* and *Aspergillus spss*. [4]. Late recovery of fungus in ascitic fluid cultures and clinical signs make it difficult to diagnose early; hence, delays in antifungal administration raise the risk of mortality [12].

Secondary Peritonitis

Secondary peritonitis is the second most prevalent cause of sepsis in Intensive-care-unit (ICU) patients [5]. It is the leading cause of death from surgical infections; accounting for up to 20% of deaths [13]. It is a poly-microbial illness; that causes gastrointestinal perforations due to direct bacterial spillage; secondary peritonitis can arise as a consequence of either ischemic gut, volvulus, or bleeding in the peritoneal cavity [3].

Tertiary Peritonitis

It is a recurrent intra-abdominal infection; that often develops within 48-72 hours following appropriate secondary peritonitis therapy in ICU settings; nonetheless, its fatality rate is 30-60% [14]. Tertiary and secondary peritonitis have very diverse bacterial ecology *e.g. Enterococci, Enterobacter, Candida albicans,* and *Pseudomonas* [15].

Sclerosing Encapsulating Peritonitis (SEP) leads to sclerosis membrane development and cocoon formation [16]. The etiology of SEP is assumed to be recurrent sub-clinical peritonitis [16]. Condition is characterized by a dense, greyish-white fibrotic membrane encasing the small bowel and other abdominal organs [16]. SEP can be primary or secondary; primary SEP is also known as abdominal cocoon while secondary SEP may be developed due to peritoneal dialysis (PD) or abdominal TB [16].

The main driving force to write a review on the current topic is to emphasize the significance of infectious peritonitis, which can be the main cause of death if not diagnosed early and properly treated. Therefore, the primary goal of the study is to provide an overview of the disease advancement, its etiology, and the development of therapeutic choices.

METHODS

To write a systematic review on peritonitis, etiology, and available treatment options; a literature survey has been conducted from 2012 to 2022 by two authors. Key-words and truncation techniques were used for the collection of relevant literature from PubMed, Directory of open access journals (DOJA), BioMed Central, Google Scholar, PakMediNet, National Database of Indian Medical Journals, African Journals Online (AJOL), Bioline International and Emerald. Sixty articles on peritonitis were downloaded; forty were chosen after abstracting relevant information from the studies and assessing quality, data synthesized and presented by following PRISMA (**Fig. 1**) flow diagram [17]. The PRISMA diagram details how studies were identified, the results of abstract screening, the results of full-text eligibility assessment; a breakdown of reasons for exclusion, and details of included studies [18]. Full-text eligible articles were forty. All the articles were evaluated for their quality; type of journal, data collection methods, statistical tests, significance values, and interpretations made.

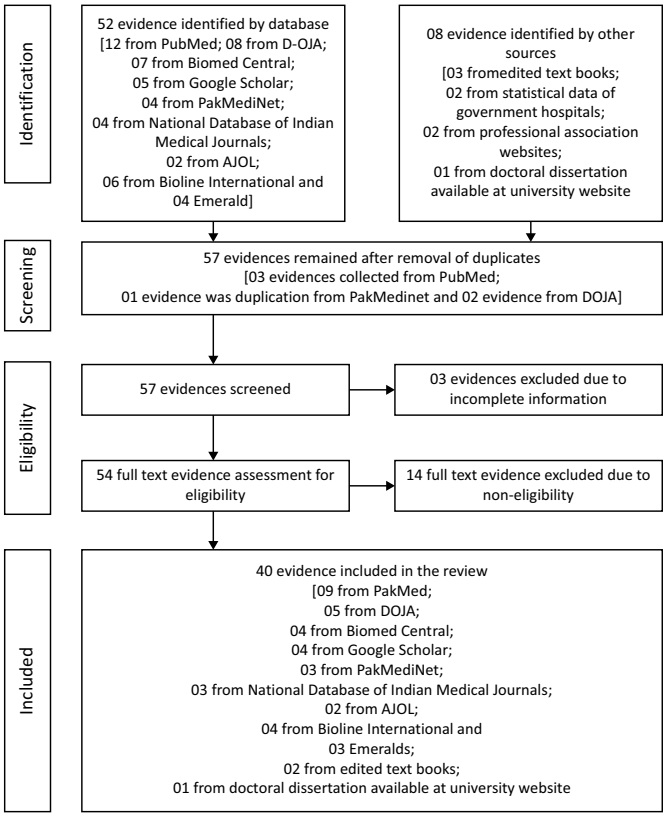

Fig. (1): PRISMA Diagram.

Quality of Literature Evaluation

GRADE (Grading of Recommendation Assessment, Development and Evaluation) criteria were employed for establishing the quality of literature. GRADE is an explicit and transparent system for decision-making regarding the best available literature [19]. The quality of literature by GRADE criteria can be determined by the risk of bias, imprecision, inconsistency, indirectness, publication bias and large magnitude of effect, dose-response gradients, and residual confounding in the published and non-published literature.

Evidence/Literature Inclusion Criteria

Pieces of evidence about primary, secondary, and tertiary peritonitis, and septic peritonitis in adults. Literature published from 2012 to 2022.

Table 1: Causes of different peritonitis and outcomes.

Types of Peritonitis	Study Year	First Author Name	Study Design	Sample Size (N)	Main Causes	Causative Organism	Outcome	Quality of Evidence [19]
Bacterial peritonitis [20]	2012	Guevara M.	Randomized Controlled Trial	110	Liver cirrhosis	*Klebsiella spp., Streptococcus spp., Staphylococcal spp.,*	Survival benefits were observed in patients with liver cirrhosis when antibiotics were administered with albumin.	High
Spontaneous Bacterial peritonitis [21]	2018	Niu B.	Cross-Sectional Study	88167	Variceal hemorrhage; hepatic encephalopathy; acute renal failure; coagulopathy	*Streptococcus spp., Staphylococcal spp.,*	Spontaneous bacterial peritonitis is a significant healthcare burden and is associated with in-hospital mortality.	High
Spontaneous Bacterial peritonitis [22]	2015	Piano S.	Randomized Controlled Trial	32	Liver cirrhosis and ascites	*Enterococci spp.,* and *Staphylococci spp.*	Found organisms were mostly resistant to cephalosporins; however, methicillin-sensitive particularly Enterococci spp.	Moderate
Acute peritonitis [1]	2012	Kumar D.	Longitudinal Study	309	Duodenal perforation (26.2%); ileal perforation (24.2%); appendicular perforation (16.8%); colonic perforation (4%); duodenal ulcer (52%).	*Helicobacter pylori*	Early surgical treatment; antibiotics administration and resuscitation yield improved outcomes.	Moderate
Acute peritonitis [23]	2017	Thirumalagiri V. R.	Case Series Study	50	Duodenal perforation (26.2%); ileal perforation (24.2%); appendicular perforation (16.8%); colonic perforation (4%); duodenal ulcer (52%).	*Helicobacter pylori*	Laparotomy with the closure of perforation by the omental patch is a comments method for the management.	Low
Primary Peritonitis or Spontaneous Bacterial peritonitis [4]	2018	Shizuma T.	Literature Review	339	Liver cirrhosis.	Gram-positive bacteria (16.6%-68.3%); Enterococci, gram-positive rods; *Listeria monocytogenes,* gram-negative; *Klebsiella spp., Streptococcus spp., Staphylococcal spp., E. coli and Streptococcus pneumonia* in ascitic fluid.	The mortality of septic fungal peritonitis is higher than septic bacterial peritonitis. Delays in antifungal treatment are usually occurring for the time taken in the differential diagnosis.	Moderate
Primary Peritonitis or Spontaneous Bacterial peritonitis [24]	2015	How J.	Case Report	01	Liver cirrhosis.	Gram-positive bacteria (16.6%-68.3%); Enterococci, gram-positive rods; *Listeria monocytogenes,* gram-negative; *Klebsiella spp., Streptococcus spp., Staphylococcal spp., E. coli* and *Streptococcus pneumonia* in ascitic fluid.	Outbreaks of Listeria septic bacterial peritonitis occur as foodborne. Its incidences are increasing; however, prevention is possible by control of food hygiene.	Very Low
Tertiary peritonitis [15]	2014	Mishra S. P.	Cross-Sectional Study	2676	Often occur by the failed management of secondary peritonitis.	Opportunistic and nosocomial facultative pathogenic bacteria and fungi (*e.g. Enterococci, Enterobacter,* and *Candida*)	It is appropriate to timely diagnose tertiary peritonitis after the operation and also the initiation of therapy to reduce the risk of worse outcomes.	High
Fungal peritonitis [25]	2012	Levallois J.	Cross-Sectional Study	288	Peritoneal dialysis	*Candida spp.*	Although fungal peritonitis is rare; however, if it occurs; usually caused by Candida spp. and may respond to empirical anti-fungal therapy	Moderate

Types of Peritonitis	Study Year	First Author Name	Study Design	Sample Size (N)	Main Causes	Causative Organism	Outcome	Quality of Evidence [19]
Secondary Peritonitis [26]	2014	Doklestić S.	Case Series Study	204	Appendicitis (22.06%); cholecystitis (7.35%); gastrointestinal perforation (29.4%); anastomotic leak and gastro perforation	Bacterial (Poly-microbial)	Outcomes of secondary peritonitis depend upon three clinical parameters; duration of abdominal infection, site of perforation, and overall clinical condition of the patient. To reduce the morbidity and mortality in such types of patients; sepsis therapy, intensive care, and surgical source controls are required.	Low
Tertiary peritonitis [3]	2012	Clements T.	Review	77	Often occur by the failed management of secondary peritonitis.	Opportunistic and nosocomial facultative pathogenic bacteria and fungi (*e.g. Enterococci, Enterobacter,* and *Candida*)	The team approached techniques discussed in this piece of literature and assumed that; these techniques reduce the risk of abdominal sepsis and multi-organ failure; it would be a truly impactful surgical strategy.	Low
Peritoneal dialysis-related peritonitis [27]	2018	Salzer W. L.	Cross-Sectional Study	3000	Peritoneal dialysis technique failure.	Streptococci, coagulase-negative *Staphylococcus spp., Corynebacteria,* Non-Pseudomonas Gram-negative, *Escherichia coli* gram-negatives	Prevention and prompt appropriate action are required for peritonitis in patients of peritoneal dialysis. Patients should also be educated and trained in the prevention of infection. Antibiotic prophylaxis should always be considered before any procedure.	High
Tuberculous peritonitis [6]	2021	Pörner D.	Cross-Sectional Study	71	Patients at high risk include End stage renal disease (ESRD), HIV/AIDs, and liver cirrhosis.	Hematogenic dissemination of mycobacteria.	Secondary peritonitis requires surgical or extensive interventional treatment.	Moderate
Outcomes of fungal peritonitis [28]	2015	Nadeau-Fredette A.-C.	Retrospective Cohort study	671 patients-month (13 Years Follow-up)	Peritoneal dialysis	*Candida spp.*	Fungal peritonitis is highly associated with death and technique failure.	Moderate
Peritonitis due to chlamydia trachomatis [6]	2021	Pörner D.	Cross-Sectional Study	71	Pelvic inflammatory disease (PID)	Obligate intracellular bacteria; *Chlamydia trachomatis*	In the case of peritoneal dialysis; antibiotics should be given as empiric therapy to cover gram-positive and gram-negative microbes by the intra-peritoneal route.	Moderate
Fungal peritonitis [29]	2016	Lahmer T.	Retrospective Cross-Sectional study	205	Liver cirrhosis and spontaneous bacterial peritonitis	*Candida albican, Candida glabrata, Candida krusei, Candida kefyr, Candida parapsilosis, Candida tropicalis, Fusarium spp.*	C. albican was found in 60% of cases; while C. glabrata in 13%; C. krusei in 13%; C. kefyr in 9%; C. parapsilosis in 4%; C. tropicalis in 4% and Fusarium spp. in 4%	High
Peritonitis due to infection with Clostridioides difficile [6]	2021	Pörner D.	Cross-Sectional Study	71	Diarrhea and colitis.	Anaerobic bacterium; *Clostrium difficile.*	To prevent bacterial peritonitis, antibiotics should be given intravenously with albumin	Moderate
Coxsackievirus B1peritonitis [30]	2012	Pauwels S.	Case report	01	Ambulatory peritoneal dialysis	*Coxsackievirus B1*	Rare cases reports of viral cause of peritonitis. To avoid unnecessary use of antibiotics; it is advisable to confirm the diagnosis by virology tests.	Moderate

Table 2: Treatment options of peritonitis.

Types of peritonitis	Study Year	First Author Name	Study Design	Sample Size (N)	Sub-Types	Treatment Options	Quality of Evidence [19]
Primary peritonitis or SBP [6, 22, 31]	2021; 2015; 2016	Pörner D.; Piano S.; Montravers P.	Cross-Sectional Study; Randomized Controlled Trial; Multi-panel discussion	71; 32; 12	Community-acquired	3rd generation cephalosporin for at least 5 days; Amoxicillin/Clavulanic acid, Piperacillin/Tazobactam, or Ciprofloxacin	Moderate; Moderate; Low
					Healthcare-related and nosocomial SBP	Piperacillin/Tazobactam; resistant to Piperacillin/Tazobactam or septic patient: Carbapenems in combination with antibiotics targeting multidrug-resistant gram-positive pathogens (*e.g.* Vancomycin, Linezolid, or Daptomycin)	
Secondary Peritonitis [6, 14, 20, 31]	2021; 2015; 2012; 2016	Pörner D.; Ballus J.; Guevara M.; Montravers P.	Cross-Sectional Study; Cross-Sectional Study; Randomized Controlled Trial; Multi-panel discussion	71; 305; 110; 12	Non-severe Community-acquired	Amoxicillin/Clavulanic acid and Cefuroxime or Fluoroquinolone combinations with Metronidazole. Piperacillin/Tazobactam.	Moderate; High; High; Low
					Severe patients suspected and non-severe instances of healthcare-related and nosocomial infections	Antibiotic therapy for 5-7 days; in most cases, surgical intervention is necessary. In situations of secondary peritonitis, delaying surgical consultation raises mortality and morbidity.	
Peritoneal dialysis-related peritonitis [21, 27]	2018; 2018	Niu B.; Salzer W. L.	Cross-Sectional Study; Cross-Sectional Study	88167; 3000	Gram-positive bacteria	1st generation Cephalosporin (Cefazolin) or Vancomycin.	High; High
					Gram-negative bacteria	3rd generation Cephalosporin, Aminoglycosides, and oral therapy of Ciprofloxacin as an alternative.	
					On identification of the specific organism	International Society for Peritoneal Dialysis (ISPD) guidelines recommended different treatment options for specific organisms.	
Tuberculous peritonitis [6]	2021	Pörner D.	Cross-Sectional Study	71	Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol were administered orally for two months; followed by Isoniazid and Rifampicin for the next four months	Moderate
Chlamydia trachomatis infection peritonitis [6]	2021	Pörner D.	Cross-Sectional Study	71	Antibiotic therapy for complicated cases of PID: IV therapy	Ceftriaxone, Doxycycline, and Metronidazole.	Moderate
					Antibiotic therapy for complicated cases of PID: Oral therapy	Doxycycline and metronidazole for a total of 14 days after clinical improvement.	
Clostridioides difficile infection peritonitis [6]	2021	Pörner D.	Cross-Sectional Study	71	Fulminant infections	Generally enteral Vancomycin or Fidaxomicin	Moderate
					Non-severe cases	Metronidazole	
Candida peritonitis [32-34]	2020; 2015; 2013	Gioia F.; Grau S.; Hall R. G.	Clinical Pharmacokinetic Study; Population Based Clinical Study; Prospective Pharmacokinetic Study	69; 10; 18	Infection caused by: *C. glabrata; C. parapsilosis; C. albican; C. krusei; C. tropicalis*	Anidulafungin: Higher plasma concentration; however, clinical response is evident	Moderate; Low; Moderate
						Caspofungin: Lower plasma concentration; resistance is expected.	
						Micafungin: Moderate plasma concentration; however, clinical response is evident	
Viral peritonitis [30]	2012	Pauwels S.	Case report	01	*Coxsackievirus B1*	Immuno-globulin	Moderate

Evidence/Literature Exclusion Criteria

Literature reported the cases of any type of peritonitis in children and adolescents (13 to 18 years), literature published before 2012.

RESULTS

After careful review and evaluation of the literature; findings refer to many causes and causative organisms for peritonitis (**Table 1**).

An appropriate pharmacological treatment and antibiotics recommendations in the guidelines are mentioned below in Table **2**:

DISCUSSION

Peritonitis sufferers need early surgical and medicinal treatment; suitable anti-infective therapy and adequate surgical intervention are the main cornerstone treatments [31]. Patients with systemic peritonitis and localized

peritonitis; hemodynamically unstable, require immediate surgical intervention [35]. Bacterial peritonitis requires antibiotics [6]. Initial antibiotic treatment should cover all predicted microorganisms [6]. Directed antibiotic therapy should be targeted; once culture-sensitivity results are available; it avoids adverse effects, hospitalization, unnecessary expenditures, and resistance [36]. Thus, speedier diagnosis enables antibiotic selection. Empiric antibiotic selection is also challenging; it should cover the estimated bacterial range and take MDR risk into account [37]. The recommendation is to use antibiotics carefully, and reserves antibiotics for special clinical circumstances to avoid MDR selection and resistance induction [37]. Adjuvant therapy should manage sepsis; since peritonitis often occurs with systemic inflammation [37]. Bacterial peritonitis mortality may be reduced by peritoneal immune system-balancing drugs [38]. The gut barrier is maintained by FXR (Farnesoid X receptor); a nuclear bile acid receptor located mostly in the liver and small intestine [38]. FXR also modulates immunological response [39]. It is noted that FXR deficiency increases the likelihood of bacterial translocation or peritonitis [40]. FXR agonists; used to treat liver illnesses such as primary biliary cholangitis and nonalcoholic steatohepatitis (NASH); can prevent peritonitis by regulating the functional and physical response of the intestinal microbiota [41].

Peritonitis treatment is still missing the evidence base practices; many deviations have been seen in clinical practice, such as not prescribing Vancomycin in MRSA peritonitis [42]. Similarly, in some clinical situations; only one antibiotic is prescribed rather than two for treating pseudomonas species; in addition, failing to prescribe antifungal drugs in case of fungal peritonitis [42]. The main reason behind the above issue is that interventions and practices are not properly evaluated through clinical studies [42]. However, randomized controlled trials (RCTs) are considered the gold standard for the evaluation of such evidence base interventions; it requires high numbers of patients usually 1000 or more in the case of peritonitis for the powered outcome of intervention [42]. A more accurate evaluation of the relative effectiveness of therapies for peritonitis may be achieved by the use of standardized criteria for accounting for peritonitis and related outcomes [43].

Peritonitis is frequently treated with vigorous fluid resuscitation and immediate surgical intervention [1]. However, despite significant advancements in surgical techniques, antimicrobial drugs, and intensive care support; peritonitis management remains challenging and complicated [1]. Treatment becomes increasingly challenging; due to the increased prevalence of concomitant disorders and the rise in the occurrence of multidrug-resistant (MDR) bacteria [31]. Regarding peritonitis caused by *Coxsackievirus B1*; a new technique is under experimental status; the technique may neutralize *Coxsackievirus B1* binding sites [44].

LIMITATIONS

The current guidelines for the treatment of peritonitis are not up-to-date. Many microorganisms now develop resistance to currently available most of the antibiotics. Antibiotics such as Linezolid, daptomycine, and tigecycline are no more recommended in SBP [45]. Misuse of antibiotics led to the development of MDR bacteria. Meropenem is now weakly effective against gram-positive cocci. Vancomycine treatment failures are also reported in many institutions worldwide. Another limitation of the current review is that protocol of the current systematic review was not registered on PROSPERO or any other database.

CONCLUSION

The current review focused on the causative organism and the pharmacological management of different types of peritonitis. It is recommended; acutely ill patient requires combined medical and surgical methods, before the deliberate use of any anti-microbial; microbiological sampling is important to identify the causative organism; to reduce the chances of failure. Antibiotics should be used carefully to avoid MDR selection and resistance induction; particularly in prophylaxis of sepsis.

RECOMMENDATION

Recent evidences based management guidelines require clarity regarding peritonitis management. Stewardship programs for antibiotic use must be implemented. Risk factors-based evaluation for empiric therapy must be considered to preserve antibiotic sensitivity against micro-organisms. Antibiotic recommendations for community-acquired and healthcare-associated infections have been developed; early empirical therapy should target all microorganisms including MDR (Multi-Drug Resistant) bacteria to limit sepsis; critically ill patients need broad-spectrum therapy [31]. Recently; national and international guidelines for choosing an antibiotic have been reviewed; risk factors should be considered [5].

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

None.

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