REVIEW ARTICLE

Tertiary Peritonitis: Do we Know it Right?

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ABSTRACT

The term 'tertiary peritonitis' (TP) is poorly defined and seriously misunderstood. While a subset of researchers have dedicated their life work to defining and understand the pathophysiology of the disease. The others deny TP as a distinct entity. It is an intra-abdominal infection that persists or recurs ≥48 hours following successful and adequate surgical source control. This stands as a distinct entity because of its differences from secondary peritonitis in terms of complex etiopathogenesis, unusual microbiological profile, subtle presentation, and extremely high mortality. An integrated multidisciplinary approach is a basis for the successful management of a patient with TP. Targeted nutritional support, antimicrobial stewardship, well-structured anesthesia and sedation strategy, and timely intervention in cases of organ failures may fast-track patient recovery. Early, planned palliative care medicine consultation is a key element in supporting patient and family-centered care.

The true nature and exact characterization of this disease are still somewhat obscure. Is it a true entity, if yes then what are clinical, microbiological, and biochemical markers that will stamp a clinical entity as TP? Isn't the defined time limit of 48 hours too early to establish the diagnosis of tertiary peritonitis? Once this is elucidated, perhaps more relevant guidelines for the diagnosis and management can then be drawn.

Keywords: Immune paralysis, Inflammation, Infection, Intra-abdominal Infection, Peritoneum, Peritonitis, Sepsis.

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INTRODUCTION

In day-to-day practices, we often use the term peritonitis interchangeably with Intra-abdominal infection. Peritonitis i.e. inflammation of the peritoneum can be caused by several causes with infection being one of them. Non-infectious etiologies include foreign bodies, bile, pancreatic enzymes, and other irritants like barium. Peritonitis as an intra-abdominal peritoneal infection has been classified into primary, secondary, or tertiary (Table 1).[1]

Tertiary Peritonitis

The term 'tertiary peritonitis' (TP) is poorly defined and seriously misunderstood. While a subset of researchers have dedicated their life work to defining and understand the pathophysiology of the disease. The others are in constant denial of the existence of TP as a distinct entity. The former subset has struggled across its various definitions from failed surgical source control or inadequate antibiotic therapy of secondary peritonitis or even impaired host response to peritoneal infection. This heterogeneity of definitions invited clinicians and intensivists to work out the exact parameters to label a clinical situation as TP. However, there is a consensus that secondary peritonitis and TP exist in a continuum and the transition between both may be quite subtle.[2]

The most precise working definition of TP so far is an intra-abdominal infection that persists or recurs ≥48 hours following successful and adequate surgical source control.[3] This definition contains two essential conditions, which have to be met: The period of ≥48 hours and successful surgical source control. This is possibly the most acceptable definition and is used in various literature.

Epidemiology

Up to 20% of patients treated for secondary peritonitis may progress to the state of tertiary peritonitis, which is otherwise considered as a very rare complication. This state is characterized by organ dysfunction and prolonged systemic inflammation associated with recurrent peritoneal infection by multidrug-resistant organisms of low virulence. Mortality rates for TP vary between 30 to 64% as compared with secondary peritonitis 8–30%.[3-5]

Etiopathogenesis

Etiopathogenesis of TP revolves around the following five factors or processes that have been evident from the review of the literature (Figure 1).

- Immune Paralysis
- Colonization by MDRO with low virulence and nosocomial infections

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Table 1: Types of peritonitis: primary, secondary and tertiary peritonitis

Peritonitis	*Primary*	*Secondary*	*Tertiary*
Definition	SBP – bacterial invasion in ascitic fluid	Intra-abdominal Process – trauma, ischemia, GI inflammation, neoplastic, iatrogenic.	Persistent /Recurrent infection – 48 hours after successful source control in Secondary peritonitis
Source	Hematogenous/ lymphatic/ translocation from GIT	Exogenous / endogenous	Nosocomial infection
Microbiological profile	Mono-microbial, No anaerobic bacteria GNR - Escherichia coli, Klebsiella, GPC	Polymicrobial including Escherichia coli, Klebsiella , Enterobacter, Bacteroides -anaerobic bacteria	Polymicrobial , MDRO of low virulence and enterococci, coag. Neg. Staphylococci, Candida spp,
Classical feature of peritonitis #	Rarely present ± ascites	Features of Peritonitis ± iIleus ± shock	Absent
Mortality	2–6%	8–30%	30–64%

Classical features of peritonitis include characteristic abdominal pain and fever as symptom and tachycardia, tenderness, rebound tenderness and rigidity as signs
GNC: Gram Negative Rods; GPC: Gram Positive Cocci; MDRO: Multidrug Resistance organism

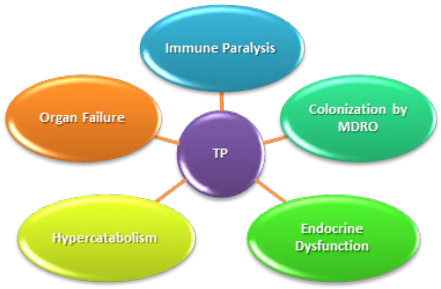

Figure 1: Events that play crucial role in etiopathogenesis of tertiary peritonitis (TP)

- Endocrine Dysfunction
- Hypercatabolism
- Organ Dysfunction

Immune Paralysis

Following infection or surgical trauma, the peritoneum produces cytokines. Proinflammatory cytokines recruit inflammatory cells to combat pathogens, clear necrotic tissue and facilitate wound repair. To protect the host from damage by this inflammatory response, the body simultaneously mounts an anti-inflammatory response where the ability of monocytes to produce inflammatory mediators and their antigen-presenting capacity (HLA-DR expression) is diminished. When the peritoneal defense mechanisms are unable to control the infection, a systemic immune response develops. Initially, a predominant proinflammatory reaction causes septic shock with organ dysfunction.

Even after all possible interventions, peritonitis persists then the anti-inflammatory cascade prevails, resulting in immune suppression. Owing to the inhibition of the synthesis of proinflammatory agents, peritoneal inflammation is lacking, and there is no tendency toward the healing of wounds or organ recovery. The immune system can be considered as one failing organ in the syndrome of multiple organ failure.[6]

The presence of several factors may result in immune paralysis. Patient-related factors include genetic immune deficiencies, age, and poor nutritional status while iatrogenic factors include surgery, blood transfusions, and immunosuppressive drugs. The presence of comorbidities or malignancy may in turn worsen the immune response.[5]

Immune paralysis can be defined by the critical level of deactivated monocytes with less than 30% HLA-DR expression.[7] This decreased cellular immunity has been demonstrated in trauma, burn-injured, and transplantation patients and is associated with high infection rates and mortality. Immune stimulation by removal of inhibitory factors (plasmapheresis) or by administration of hemopoietic growth factors such as GCSF, GM-CSF, and interferon-gamma (IFN-y) may be useful during this period.[8] Agnes et al. studied the effect of G-CSF substitution in 10 septic patients with immune paralysis (HLA-DR+ monocytes <30%) and found a persistently higher level of HLA-DR+ monocytes in the six survivors.[9] Docke et al. administered IFN-y to septic patients with low monocytic HLA-DR expression. The deficient HLA-DR expression, and in vitro LPS-induced TNF-alpha secretion was restored. Recovery of monocyte function resulted in the clearance of sepsis in eight of nine patients. Selective immunostimulatory therapy appears beneficial in the management of tertiary peritonitis and is worth pursuing.[10]

Colonization by MDRO with Low Virulence and Nosocomial Infections

Pathogens frequently cultured from the peritoneal cavity in tertiary peritonitis include multiresistant organisms, of low intrinsic pathogenicity and nosocomial origin. Pathogens associated with tertiary peritonitis include Gramnegative aerobes (e.g., *Pseudomonas, Enterobacter, Acinetobacter*), enteric anaerobes, Gram-positive bacteria (e.g., coagulase-negative species, methicillin-resistant *Staphylococcus aureus*, and *Enterococcus*), and *Candida* species.[11]

In a study by Ballus *et al*., microbiological results in isolates revealed higher number of patients with TP presenting with isolated GPC (26.2% vs.12.1% p = 0.007) and fungi (19.2% vs. 7.6%; p = 0.001) more frequently than those with SP.

Table 2: Organ dysfunction in sepsis

Target organ	Pathophysiology	Clinical features	SOFA score indices (other beneficial indices)	Available treatments
Lung (ARDS)	Vascular hyper-permeability, neutrophil accumulation	Impaired oxygenation	PaO_2/FIO_2 <400 (bilateral infiltration on CXR)	Mechanical ventilation with low tidal volume and PEEP
Liver	Disturbed intracellular and extracellular bile salt transport	Jaundice, cholestasis	Serum bilirubin ≥1.2 mg/dl	Not established
Kidney (AKI)	Tubular epithelial cell injury, dysfunction or adaptive response of tubular epithelial cells	Reduced GFR, reduced urine volume	Serum creatinine ≥1.2 Urine output <500 ml/day	Hemodialysis
Cardiovascular system	Myocardial depression, impaired intracellular calcium homeostasis, disrupted high energy phosphate production.	Ventricular dilatation, reduced ejection fraction, reduced contractility	Mean arterial pressure <70 mmHg	Inotropic agents, beta-blocker
Gastrointestinal tract	Epithelial hyper-permeability, altered microbiome	Mucosal bleeding, paralytic ileus	Not included	Proton pump inhibitor, early enteral nutrition, probiotics, SDD
Central nervous system (SAE)	Direct cellular damage, mitochondrial and endothelial dysfunction, neurotransmission disturbances, calcium dyshomeostasis	Altered mental status	GCS <15	Light sedation, early rehabilitation
Blood coagulation system (DIC)	Intravascular coagulation, microvascular damage, systemic thrombin generation, endothelial injury	Bleeding diathesis, microthrombi and tissue ischemia	Platelets $<150 \times 10^3/\mu l$ (prolonged prothrombin time, increased FDP)	Antithrombin, recombinant thrombomodulin, concentrated platelet preparation

SOFA sequential organ failure assessment, *ARDS* acute respiratory distress syndrome, *CXR* chest X-ray, *PEEP* positive end-expiratory pressure, *AKI* acute kidney injury, *GFR* glomerular filtration ratio, *SDD* selective digestive decontamination, *SAE* sepsis-associated encephalopathy, *GCS* Glasgow coma scale, *DIC* disseminated intravascular coagulation, *FDP* fibrin degradation product

Source: Fujishima S. Organ dysfunction as a new standard for defining sepsis. Inflamm Regener 36, 24 (2016).

Multivariable analysis between SP and TP showed a higher incidence of *Candida* spp. in TP group (OR: 1.275; p = 0.016), *Enterococcus faecium* (OR: 1.085; p = 0.002) and *Enterococcus* spp. (OR: 1.370; p = 0.047) in TP.[12]

Patients with higher co-morbidities, longer ICU admissions, and a hospital stay of more than a week are at a greater risk of colonization by MDR bacteria, and in these cases, the approach to TP is more complex. *Enterococcus* is associated with high death rates in peritonitis, even with adequate treatment, and is more frequently associated with severely ill and immunocompromised patients.[13,14]

However, these appear more as colonization rather than infection/disease. The main source of these pathogens is thought to be the patient's digestive tract. In critical illness intestinal starvation, hypoperfusion of intestine, and elimination of normal gut flora due to use of antimicrobial agents cause mucosal atrophy with subsequent loss of gut barrier function and microbial translocation. Toxins and microbes escaping from the gut lumen into the bloodstream and the peritoneal cavity activate the host's immune inflammatory defense mechanisms. However, as the target is undefined, the immune response will be both uncontrolled and unbalanced, leading to tissue destruction and multiple organ failure.[5]

Persistent Organ Dysfunction

The presence of any of the following criteria can suggest respective organ failure in a patient with tertiary peritonitis (Table 2).[15]

High morbidity and mortality seen in patients with TP have been attributed to non-resolving organ dysfunction in the setting of sepsis and septic shock. However, the specific mechanisms by which management of organ dysfunction hinders or enables host defense are not clearly defined and outcomes may be substantially driven by patient phenotype rather than a specific intervention.[16]

Endocrine Dysfunction

Endocrine pathways play an important role in the body's physiological response to peritonitis. Corticosteroids play an important role in metabolism, maintenance of vasomotor tone, and immune modulation which in turn is essential to restore homeostasis. In persistent stress, such as in complicated peritonitis, the adrenocortical response gets exhausted. When glucocorticoid production no longer meets the body's increased needs, a state of relative adrenal insufficiency (RAI) develops. Though the etiology of RAI is not fully understood but is thought to be caused by depletion of the adrenal cortex and glucocorticoid receptor resistance. Substitution of corticosteroids in patients with RAI can reverse the septic shock state dramatically.[17-19]

Furthermore, anabolic agents play a modulating role in the immune response. They stimulate the proliferation and differentiation of T-lymphocytes and NK cells and augment the proliferation, chemotaxis, and phagocytosis of granulocytes. Positive effects of GH on metabolic parameters, wound healing, and immune competence are evident from the literature but no data exist concerning the effect of these agents in patients with tertiary peritonitis with multiple organ failure.[20]

Hypercatabolism

Prolonged critical illness is characterized by catabolism of whole-body protein stores, resulting in muscle wasting and a negative nitrogen balance. This has prompted research into the combined use of anabolic steroids such as growth hormone (GH) and insulin-like growth factor (IGF-1) to enhance protein metabolism in the critically ill.[5] Patients with chronic critical

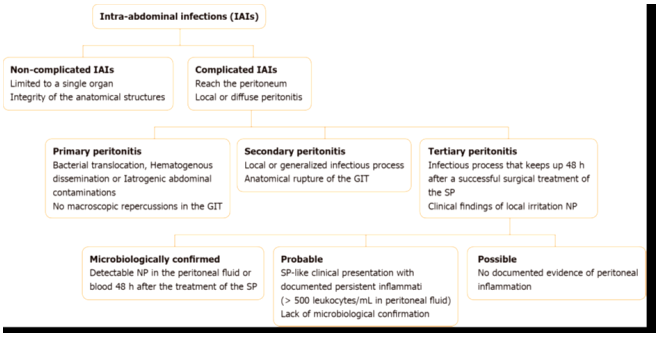

Figure 2: Stratification of intra-abdominal infections.

GIT: Gastrointestinal tract; NP: Nosocomial pathogens; SP: Secondary peritonitis.
Source: Marques HS, Araújo GRL, de Melo FF. Tertiary peritonitis: A disease that should not be ignored. World J Clin Cases 2021; 9(10): 2160-2169

illness (CCI) demonstrate suppressed pulsatile secretion of GH, TSH, and ACTH, resulting in low circulating levels of IGF-1, IGF binding protein-3, and thyroid hormones. Suppression of pulsatile secretion of these hormones may be partially responsible for the chronic fatigue and muscle weakness of CCI. The anti-catabolic and immunostimulatory actions of GH could be beneficial in these patients but lack substantial evidence.[20]

Clinical Presentation

The classic signs of peritonitis are the characteristic of secondary peritonitis and are usually absent in TP. TP is rather accompanied by an elevation in body temperature and is associated with progressive multiple organ failure and prolonged systemic inflammation. The differentiation between secondary and tertiary peritonitis becomes really difficult as there is usually a continuum between the two and the exact time point when secondary peritonitis turns into TP is often uncertain. Reoperation may be indicated in a subset of patients who show clinical signs of recurrent or persistent intra-abdominal infection despite apparently successful source control, which is referred to as TP.

It is essential to distinguish ongoing secondary peritonitis (failure of the surgical attempt of the source control) from TP where an obvious anatomical defect or perforation of the hollow viscus is characteristically absent. A planned or on-demand relaparotomy after an initial operation is probably the most frequent way to diagnose TP, but it is a late event to occur and may be too invasive just to establish a diagnosis.[2]

The ICU consensus conference has come up with three categories of the diagnostic certainty of TP, that is, microbiologically confirmed, probable, and possible (Figure 2). There are three practical stratifications for TP based on the different levels of clinical evidence. A microbiologically confirmed TP is characterized by detectable nosocomial pathogens in the peritoneal fluid or blood 48 hours after the treatment of the SP.[21]

Mannheim Peritonitis Index, Simplified Acute Physiology Score II (SAPS II), and C-reactive protein is three early and easily accessible parameters that may be utilized for identifying patients who might further develop TP.[2]

Table 3: Mannheim Peritonitis Index

Risk Factor	Points
Age >50 years	5
Female sex	5
Organ failure	7
Malignancy	4
Preoperative duration of Peritonitis >24 h	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, Purulent	6
Fecal	12
Definitions of Organ Failure	
Kidney Creatinine level >177 µmol/L	
Urea level >167 mmol/L	
Oliguria <20 ml/h	
Lung PO2 <50 mmHg	
PCO2 >50 mmHg	
Shock Hypodynamic or Hyperdynamic	
Intestinal obstruction Paralysis >24h or complete mechanical obstruction	

Source: Joshi, P., Poudel, R., and Chandra, K. (2018). Mannheim Peritonitis Index (Mpi) Score as A Predictor of Outcome in Patients with Secondary Peritonitis. *Journal of Universal College of Medical Sciences, 4*, 6-9.

The Mannheim Peritonitis Index (MPI) was instrumented by Linder *et al.* (1987) and validated in several studies for secondary peritonitis.[22] The MPI was historically used to predict mortality and risk of post-surgical complications in patients with peritonitis (Table 3). However, recent literature has found it to be effective in the prediction of the development of TP and a score greater than 32 has been associated with a higher risk of mortality. Since it can be estimated based on clinical parameters during the index operation, MPI can be considered for the diagnosis of TP.[23]
SAPS II is a disease-independent tool based on 17 variables and has prognostic importance for TP.

The APACHE II is based on 12 physiological variables such as blood pressure, heart rate, temperature, age, biochemical parameters, etc. It has also been studied and found helpful in predicting mortality (a score greater than 15 is associated with higher mortality rates) and multiple organ failure in ICU patients. Weiss et al studied all three scores and found that MPI (25.9 vs 31.4, $p < 0.001$), SAPS II (31.9 vs 45.6, $p < 0.001$), and APACHE II (12.4 vs 20.7, $p < 0.001$) were significantly higher in TP patients compared with SP individuals.[24]
C-reactive protein is not specific for abdominal infections.[2] However, a study on 69 patients observed significantly higher values of C-reactive protein (265 mg/dL vs 217 mg/dL, $p < 0.05$) as well as of SAPS II (45.1 vs 28.4; $P < 0.005$) and MPI (28.6 vs 19.8; $p < 0,001$) among individuals who progressed to TP compared to those with SP.[25]

Diagnostic Challenges - Work Up

Recurrent / persistent peritonitis duration of > 48 hours following successful source control in secondary peritonitis

Table 4: Panel of investigatory workup in a patient with possibility of tertiary peritonitis.

Hematological and biochemical investigations	*Microbiological*
Leukocytosis / leukocytopenia	C/s of peritoneal fluid
Anemia	Blood culture
Hypoprotenemia	
Derranged lft / rft (organ failure)	Adjunct -
Derranged coagulation profile	Urine culture
Crp raised	Catheter tip culrure
Procalcitonin raised (marker of sespsis)	
Peritoneal fluid for wbc count and protein	Immunology: (not routinely available)
Urine routine and microscopy	Hla-dr + monocyte < 30%
Arterial blood gas analysis	

is the working definition for TP. Scoring system mentioned above has been used to predict the development of TP in a patient treated with SP, disease severity and risk of death once diagnosis of TP has been established. These scoring system therefore, in other words do not contribute in establishing the diagnosis. Moreover, There has been no consensus till date regarding value of clinical and laboratory parameters and scoring systems for sufficient diagnosis and monitoring of TP. [2]

Routine microbiological workup of intraperitoneal fluid may reveal nosocomial pathogens and may serve as a basis for the search for an infectious focus and for the appropriate antimicrobial choice. White blood counts, procalcitonin and CRP can be altered as a consequence of the inflammatory respons or due to the initial surgery; however, persistently high or rising values may indicate a persistent or recurrent infection. Although these parameters can increase the accuracy of the diagnosis, their usefulness may be reduced in patients who present with sepsis, multiple organ failure, and recurrent inflammations (Table 4).[26]

Prevention of Tertiary Peritonitis

Aggressive management of SP forms the foundation in prevention of development of TP. Table 5 delineates outline of strategies regarding the same. Table 4 enlists crucial considerations regarding the same.[27-29]

Treatment of Tertiary Peritonitis

An integrated multidisciplinary approach is the basis of successful management of a patient with tertiary peritonitis. While the intensivist and the surgeon forms the centre of the team, there is definitive role of specialists from other disciplines including microbiologist, physician, dietician, physiotherapist, endocrinologist, etc (Figure 3).[30]

By far no standard protocol or guidelines to approach and manage a patient of TP has been published. But from current knowledge of underlying etiopathogenesis and presentation, an outline can be drawn regarding the same (Table 6).

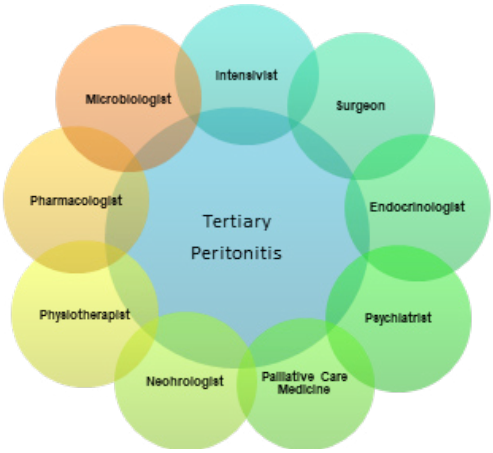

Figure 3: Multi-disciplinary approach in management of tertiary peritonitis

Initial Resuscitation Strategy

Intravenous fluids are an essential component of the multimodal resuscitation strategy. Fluid resuscitation is the mainstay in the initial treatment of sepsis, but the choice of fluid remains unclear. The aim is to restore intravascular volume while minimizing edema. While edema and related complications limits the use of crystalloids, colloids with superior hemodynamic properties and plasma volume expanding capacity lacks survival benefit and have high costs.

A consensus committee of 55 international experts recently proposed the new guidelines for management of sepsis. The recommend for fluid resuscitation is at least 30 mL/kg of intravenous crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).[38] They also recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status. Mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors and normalization of serum lactate levels are two important target parameters. Though urine output of >0.5–1 mL/kg/hour is often considered as one of the parameters to curtail fluid therapy but this may not be achievable in patients with AKI/CKD. In any case, foley's catheterization is essential for urine output monitoring.

Whenever clinicians decide to prescribe intravenous fluids, they need to weigh the risks and benefits of giving fluid and also the advantages and side effects of each fluid type in order to optimize patient outcomes. Acidosis and correction of electrolyte imbalance (hypokalemia/hyperkalemia, hyponatremia, hypocalcemia) needs to be corrected before subjecting the patient to stress of operative intervention and anesthesia. Regular Arterial Blood Gas study should be used to dictate and evaluate an ongoing corrective measures. Respiratory support in the form of oxygen inhalation via face mask to need for invasive ventilatory support is often required. NG tube placement for gastric decompression and USG guided percutaneous drain placement often helps to reduce respiratory distress secondary to grossly distended abdomen compressing against diaphragm.[26]

Table 5: Measures that should be taken at various steps in management of secondary peritonitis in order to prevent progression of secondary peritonitis into tertiary peritonitis[27-30, 32-34]

<table>
<tr><td colspan="2">Preoperative preparations:
Fluid resuscitation and monitoring
Broad spectrum systemic antibiotic therapy
Correct serum electrolyte and coagulopathy
Adequate analgesia
Adequate oxygenation and Ventilatory support
Preparation of GIT</td></tr>
<tr><td colspan="2">Goals of exploratory laparotomy in secondary peritonitis:
3 goals of operative treatment of secondary peritonitis:
To eliminate the source of contamination
To reduce the bacterial inoculums
To prevent recurrent or persistent sepsis</td></tr>
<tr><td colspan="2">Intra and post-operative drainage:
Thorough lavage reduces the microbial content and debris. Electrochemically activated solution of sodium chloride (0.05% sodium hypochlorite).
Decompression of intestine, peritoneal lavage and early initiation of enteral nutrition.
Drain placement</td></tr>
<tr><td colspan="2">Abdominal closure</td></tr>
<tr><td>Open abdomen: (OA)
GOAL: Easy and direct access to the affected area, Damage control (preliminary drainage and removing necrotic tissue) in extensive peritonitis → ICU resuscitation and stabilization → definitive drainage and source control.
Pros: Helpful if high risk of ACS because in OA approach compartment is decompressed, visceral perfusion is maintained, pulmonary ventilation is optimized.
Easy access for Re-Exploration
Regular inspection and drainage
Cons: Early complication: Evisceration, fluid and electrolyte loss, loss of protein in effluents, contamination with nosocomial pathogens.
Late complication: Enterocutaneous fistulae, ventral hernia</td><td>Total abdominal closure:
GOAL: definitive surgical treatment at the initial opertation with primary fascial closure.
Pros: Reduces risk of heniation and contamination
Cons: Drain Blockage
Loculated collections

Planned relaparotomies refer to repeated operations at fixed intervals (24–72 hours) irrespective of the patient's condition. Its purpose is to anticipate the formation of infectious collections and to preclude their systemic effects. Re-laparotomies are discontinued when the peritoneal cavity has become macroscopically clean. Adverse effects include damage to the often fragile viscera, necrosis of the abdominal fascia, and complications related to general anesthesia.</td></tr>
<tr><td colspan="2">Post-operative care:
Vigilant monitoring is the heart of post operative care with watchfulness regarding the adequacy of volume resuscitation, electrolyte imbalance, resolution/persistence of sepsis and development of organ system failure. Patient's overall condition should improve significantly and progressively within 24–72 hours of source control.
Those admitted to ICU, malnourished, with co-morbidities, subjected to prolonged course of antibiotics, immune-compromised, underwent multiple invasive procedures and re-exploration surgeries are at higher risk of developing infection with MDRO and tertiary peritonitis.
Early mobilization, initiation of enteral feeding, judicious use of antibiotics, early diagnosis and supportive intervention for organ dysfunction can prevent progression to TP.</td></tr>
</table>

Pre-operative Evaluation and Decision-making

A focused history and physical examination is essential, with attention to the patient's cardiopulmonary concerns, available laboratory reports (e.g., complete blood count, baseline arterial blood gas analysis, serum electrolytes and renal function tests), airway and vascular access. Consent should be discussed with the patient's health care proxy decision-maker, in case of critically ill patients or those on life supports. Such conversation should emphasize on the nature of the surgical procedure being performed and potential risks involved from both surgical as well as anesthesia point of view as well as possible outcomes (Figure 4).[31]

Intra-operative Management? Source Control in Tertiary Peritonitis

In tertiary peritonitis where definitive foci of infection is typically absent, rather replaced by a generalized colonization with MDRO with low virulence after successful management of Secondary peritonitis is primarily surgical that involves source control and reduction of intraperitoneal debris and bacterial load. In the majority of cases this is achieved by a single operation. However, when there is extensive contamination with or without profound systemic toxicity, repeated surgical interventions may deem necessary to clear the infectious source(s).[32]

Operative strategies in such cases include either planned relaparotomies or open management. A clear advantage of either treatment over the other remains intangible. As the incidence of complications is higher with the open management approach, the current consensus recommends its use only in patients who may require >2 laparotomies, or in patients who are at higher risk of abdominal compartment syndrome.[28,29]

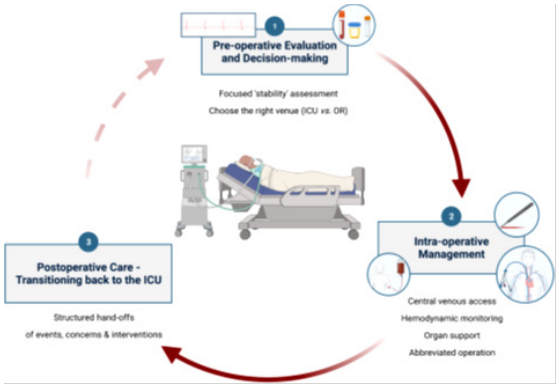

Figure 4: Triphasic approach to anesthesia considerations in tertiary peritonitis.

1. Focused evalution of cardiopulmonary stability, airway access history, and vascular access; 2. Planned plasma volume expansion, or pre-emptive administration of vasopressor agents, vigilant cardiovascular monitoring and intervention; 3. Structured hand-offs so that all team members are present at the same time has been evaluated and serves as a best practice to ensure information fidelity. (HATRICC Trial)

Source: Lane-Fall MB, Beidas RS, Pascual JL et al. Handoffs and transitions in critical care (HATRICC): protocol for a mixed methods study of operating room to intensive care unit handoffs. BMC Surg. 2014 Nov 19;14:96.

Table 6: Outline of management of TP

- Initial resuscitation
- Preoperative evaluation and decision making
- Intra-operative management - ? Source control and role of surgical intervention
- Post-operative care - role of intensivist
- Management of organ failure

Supportive and antibiotic management in tertiary peritonitis
Role of antibiotics: clinical pharmacological considerations
Sedation and analgesia
Role of nutrition in recovery

In tertiary peritonitis, the surgical strategy does not appear to be the pivotal factor. Relaparotomy reveals no evident infectious foci; in fact, only serosanguinous fluid is found in which selected microorganisms are cultured. [29] Mechanosurgical solutions are likely to have reached their limit once tertiary peritonitis has developed. Intraoperative peritoneal lavage was previously used as an attempt to reduce bacterial contamination and debris.[33] Its efficacy, however, has never been proved. Repeated handling of the bowel may endanger their integrity and promote translocation. Some authors therefore recommend limiting the use of peritoneal toilet to vacuum drainage of purulent exudates and fecal debris along with controlled debridement.[34]

Use of temporary closure devices in open abdomen management has many advantageous physiological effects that are relevant to the surgeon and intensivist. However, complications include inability to achieve primary fascial closure leading to a large abdominal wall defect and enterocutaneous fistula (ECF) formation.[28]

Table 7: Systemic approach to management of Multi-Organ failure

Organ System	*Treatment*
Renal	Alkalanisation of urine Fluid resuscitation/ restriction Dialysis
Respiratory	Chest physiotherapy Nebulization Oxygen Support Ventilatory Support
Hepatic	Remove / Avoid hepatotoxic drug Replenish glucose storage Nutritional support and replenish albumin N-acetyl cysteine
Cardiac	Vasopressor support Anti-arrythmics Rule out occult / pre-existing heart conditions
Hematological	Replenish blood and blood products based upon hemogram and thromboelastography Correction of coagulopathy
Endocrine dysfunction	Hypo/hyperglycemia Steroid therapy for relative adrenal insufficiency

Postoperative Care

Most patients with TP will benefit from ICU management after surgery given their needs for concomitant organ failure management and hemodynamic monitoring or support. Communication between the peri-operative team and ICU team about intra-operative events including status of new or pre-existing devices, airway or pulmonary concerns, and interventions cannot be over emphasized. Such hand-offs should better be in written and may serve as best practice to ensure information fidelity.[30]

Organ Failure in Tertiary Peritonitis

Regular monitoring of organ system is required for early diagnosis of failing organ systems (Table 7).

Role of Antibiotics Clinical Pharmacological Considerations[35]

Underlying chronic illnesses as well as organ dysfunction may influence the pharmacokinetics and pharmacodynamics of the drugs especially antibiotics. The cornerstone of appropriate antimicrobial therapy is the timing, spectrum and dosing of antibiotics (Table 8).

Dosing recommendations in these patients are frequently extrapolated from studies in healthy volunteers and other non-critically ill patient populations. These extrapolations may result in unintended toxicities or therapeutic failures because of differences in bioavailability, volume of distribution, and clearance. Given the uncertainties that may impact the therapeutic effect of antimicrobials, use of therapeutic drug monitoring in certain cases may ensure adequate therapeutic targets while monitoring for potential toxicities.

Table 8: Guidelines for treatment of tertiary peritonitis (University of Michigen).

1st line: Piperacillin-tazobactam*4.5 g IV q6h Low/medium-risk allergy to penicillins: Cefepime* 2 g IV q8h + Metronidazole 500 mg PO/IV q8h Consider the addition of vancomycin to cefepime for enterococcus coverage in critically ill patients with risk factors defined in comments. High-risk allergy / contraindication to beta-lactams: Vancomycin* + Aztreonam* 2 g IV q8h + Metronidazole 500 mg PO/IV q8h Notes: • Empiric therapy should take into account prior cultures and severity of presentation (especially presence of severe sepsis/shock). Both factors may dictate alternative empiric therapies from the above. • Pre-existing drains are often colonized and should not be cultured. Step-down oral therapy if tolerating orals and susceptibilities (if available) do not demonstrate resistance Amoxicillin-clavulanic acid* 875 mg PO BID OR Cefuroxime* 500 mg PO BID + Metronidazole 500mg PO TID
General: 4 days after adequate source control - Extended with inadequate source control or persistent clinical symptoms or signs of infection. Patients with bacteremia: 7–14 days - GNR bacteremia:7-day duration of IV therapy (or oral quinolone at discharge) may be appropriate o Rapid clinical improvement within 72 hours o Not polymicrobial or bacteremic with Pseudomonas o Not neutropenic, o HIV with CD4 >200 o Remains hemodynamically stable at day 7 o Been afebrile ≥48 hours (at day 7)
▪ Enterococcus coverage: Risk factors in ICU patients include septic shock, repeated abdominal surgery, prosthetic valve, and recent cephalosporin or quinolone use. ▪ Empirical MRSA coverage: if known to be colonized with MRSA and discontinued if MRSA is not recovered in culture. ▪ Candida coverage: Fluconazole* 800 mg X 1, then 400 mg IV/PO q24h (or Micafungin 100 mg IV q24h if candidemic or in shock) considered empirically but should be discontinued if Candida is not identified on culture. Notes: • Empiric therapy should take into account prior cultures and severity of presentation (especially presence of severe sepsis/shock). Both factors may dictate alternative empiric therapies from the above. • Pre-existing drains are often colonized and should not be cultured.

Source: Guidelines for treatment of intra-abdominal infections in adults, Michigen Medicine, University of Michigen. https://www.med.umich.edu/asp/pdf/adult_guidelines/Intra-ab_ADULT.pdf

Analgesics and Sedation

Adequate pain control and judicious use of sedatives can decrease the duration of mechanical ventilation, allows early mobilization and reduces length of ICU and hospital stay. WHO Analgesic ladder is always preferable as it decreases the adversities of drug and combinations may help to optimize the analgesic response.[36]

Nutrition: Role in Recovery

Nutrition evidence-base ICU guidelines recommend early enteral nutrition progressively implemented within 48 hours of admission. Use of high-protein formulation and if feasible, a progressive resistance-based exercise program is recommended. Protein administration at greater than 2 g/kg body weight per day is essential to combat hypercatabolic state of illness. Several studies have attempted to define an "average" protein loss across the open abdomen and have suggested an addition of 1.5 g protein/dL of effluent in the nutritional prescription.[30]

Enteral nutrition (EN) is preferred over parenteral nutrition (PN) in hemodynamically stable patients because of their potential physiologic advantages. Inflammatory response modulation, reduction of insulin resistance, maintenance of gut integrity and prevention of translocation of gut flora are well established advantages of EN when started within first 7 days of ICU admission. However, PN may be added to EN in order to provide patient with the recommended caloric and protein intake (1.2 and 3 g/kg/day to improve nitrogen balance).[37]

No current recommendation to use hormonal agonists in those with chronic critical illness including tertiary peritonitis. There are no evidence supporting the use of omega 3 fatty acids, arginine, glutamine etc as supplements in critically ill patients with peritonitis.[30]

As discussed in etiopathogenesis, anabolic steroids is useful in addressing the state of hypercatabolism. Similarly, use of corticosteroids to address relative adrenal insufficiency and Immune stimulatory therapy with IFN gamma to manage the state of immune paralysis and to enhance recovery, need clinical trials to define their indications and dosage before recommending them in routine practice and is something worth pursuing.

CONCLUSION

Tertiary peritonitis represents a unique challenge to the surgeon and ICU multi-professional team. This bio-altered host, often in multiorgan failure, represents a subset of patient where failed source-control transitions into chronic critical illness. Targeted nutritional support, antimicrobial stewardship, well structured anesthesia and sedation strategy, and timely intervention in cases of organ failures may fast track patient recovery. The true nature and exact characterization of this disease is still somewhat obscure. Is it a true entity, if yes the what are clinical, microbiological and biochemical markers that will stamp a clinical entity as TP. Isn't the defined time limit of 48 hours too early to establish the diagnosis of tertiary peritonitis. Once this is elucidated, perhaps more relevant guidelines for the diagnosis and management can then be drawn.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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