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A novel multi-functional introducer - Safe Easy Endotracheal kit-flexible

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Difficult airways are a common concern for physicians in the department of anesthesiology, emergency medicine, and critical care medicine. SEEK^{flex} (Safe Easy Endotracheal kit-flexible) is a novel multifunctional introducer developed by our team to address difficult airways. It has been registered as a medical device in China (Zhejiang Medical Device Registration Approval No. 20232081322).

The SEEK^{flex} system features a dual-component design, consisting of a primary introducer and a supplementary adapter. With an outer diameter of 4.0 mm and an inner diameter of 2.4 mm, it is compatible with tracheal tubes of an internal diameter exceeding 4.5 mm. The introducer, extending from 43 to 81 cm, is equipped with a flexible steel core for guidance and a smooth polyvinyl chloride (PVC) sheath. This assembly can be securely fastened using a blue locking mechanism, as depicted in **Figure 1A-B** [1].

SEEK^{flex} can be bent at an appropriate angle due to the malleability of its inner core, allowing it to be easily inserted into the trachea just under the epiglottis in cases of unpredicted difficult airway (Cormack-Lehane Grade III). This procedure is facilitated by a video laryngoscope. The endotracheal position of SEEK^{flex} is confirmed by connecting it to an $EtCO_2$ monitor via the adapter after removing the inner core (**Figure 1C**). The endotracheal tube can be eas-

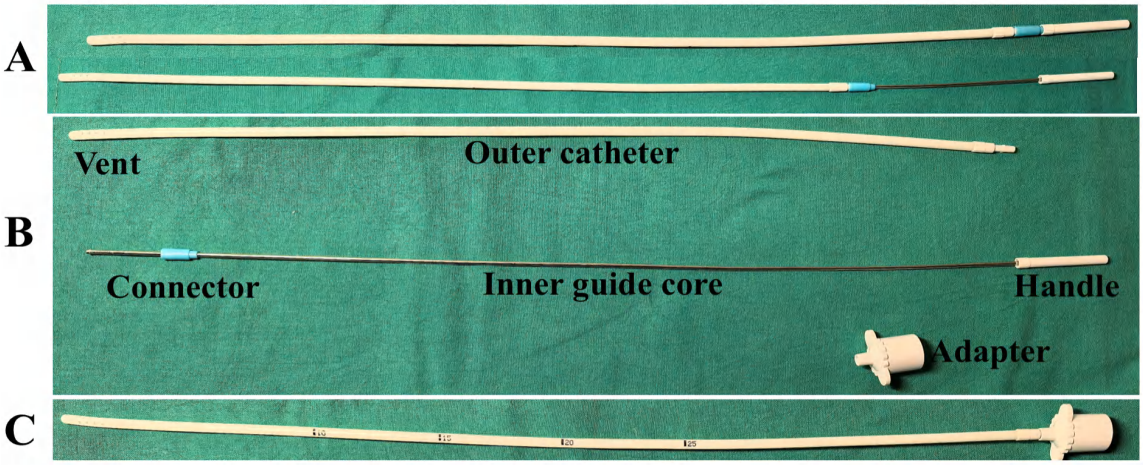

Figure 1. Components of SEEK^{flex}. (A) SEEK^{flex} that is not connected to the adapter; (B) Components of SEEK^{flex}; (C) SEEK^{flex}. SEEK^{flex}, safe easy endotracheal kit-flexible.

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ily advanced into the trachea using the Seldinger technique, with the guidance of reconnected, post-stretching SEEK^{flex}. In addition, we have developed a "12-step" approach for awake tracheal intubation using SEEK^{flex} and a video laryngoscope, which has yielded satisfactory clinical results [2].

At the distal end of the outer catheter, there is one vent at the top and 4 rows of lateral vents. After removing the inner core and attaching the adapter, local anesthetic can be administrated, and oxygenation can be maintained using a ventilator, like a slender tracheal tube. The original version of this introducer was used for reintubation of COVID-19 patients, and the outer catheter could be left in place for subglottic oxygenation after extubation [3]. This feature is also used for oxygenation maintenance and tracheal intubation in emergency situations during bronchoscopic balloon dilation [4].

Several randomized controlled studies, approved by the Ethics Committee of the Naval Medical University and currently in the process of data collection, may further provide robust evidence of its safety and efficacy. We believe that this new multifunctional introducer can be widely adopted by anesthesiologists due to its versatility across multiple clinical scenarios.

Author Contributions:

Zui Zou conceived the original idea and supervised the project. Chenglong Zhu wrote the manuscript. Jianhua Xia helped shape the manuscript. All authors contributed to the article.

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Expert Consensus https://doi.org/10.61189/707615erclry

Abdominal Drainage in Peacetime and Wartime: An Expert Consensus

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Abstract

Abdominal drainage is a key technique in abdominal surgery, primarily aimed at removing fluid, gas, foreign bodies, and necrotic tissue from the peritoneal cavity, reducing the risk of infection, and promoting recovery. The placement and strategy of abdominal drainage should be decided based on individual circumstances to minimize the risk of complications and accelerate the patient's recovery. In wartime, abdominal drainage is mainly used to control intraperitoneal hemorrhage and intraperitoneal infection. This consensus aims to enhance understanding of the application and management of abdominal drainage during both peacetime and wartime, with the goal of improving drainage therapy outcomes and patient safety.

Introduction

Drainage is a fundamental surgical procedure with a long history. The controversy over whether to perform an abdominal drainage persists [1]. Drainage for therapeutic purposes is undoubtedly beneficial, but the placement of prophylactic drainage is fraught with controversy [2-4]. However, peritoneal drainage is of vital importance in both wartime and peacetime, especially for patients with intra-abdominal infections [5]. Additionally, the invention of new technologies and materials has facilitated the continuous development of

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drainage tubes to meet the needs of modern medicine [6]. In peacetime, when healthcare resources are abundant, accelerating recovery is a priority [7]. During wartime, medical resources are extremely limited, and it is crucial to efficiently and safely manage drainage of liver, duodenum, and pancreas injuries. Therefore, there is a need for new types of drainage tubes that are suitable for the wartime medical environment [8]. We analyzed the purpose of abdominal drainage, the different types of drainage tubes, indications for peritoneal drainage, and the use of drainage tubes in the battlefield environment. The purpose of this consensus is to clarify the main uses of peritoneal drainage and provide systematic guidance for healthcare providers to help medical workers implement abdominal drainage properly in different clinical conditions and with limited resources, and to correctly choose and apply drainage tubes to achieve better treatment outcomes.

The objective of abdominal drainage

Abdominal drainage has the basic function of clearing fluid from the abdominal cavity, such as pus, blood, bile, pancreatic juice, and gastrointestinal contents, and preventing them from accumulating again. This helps to reduce the occurrence of infections and damage to organs, promote the resolution of inflammation, and facilitate wound healing [2, 9-13]. In acute pancreatitis, necrotizing pancreatitis, and acute appendicitis with periappendiceal abscess, abdominal drainage can effectively remove necrotic tissue and control infection; alleviate abdominal pain, nausea, and vomiting; reduce the incidence of gastrointestinal obstruction, systemic inflammatory response syndrome, and other complications [14-16]. A abdominal drainage tube can also be used for flushing and, in some cases, used as a delivery channel to administer medication to the patient for treatment [11, 17]. Monitoring and analyzing the drainage also play an important role in preventing postoperative complications such as hemorrhage, anastomotic fistula, biliary fistula, and pancreatic fistula.

Based on the purpose of drainage, peritoneal drainage is divided into prophylactic drainage and therapeutic drainage [18]. These two types of drainage can sometimes be difficult to distinguish in clinical practice. Therapeutic drainage is used for clear intra-abdominal infections or injuries, such as intra-abdominal abscesses, intra-abdominal hematomas and pancreatic necrosis. [11, 15, 19]. Peritoneal drainage allows patients' conditions to improve effectively, therefore therapeutic drainage is necessary and beyond doubt. Prophylactic drainage is mainly used to monitor the presence of postoperative complications such as active bleeding or anastomotic leak. After abdominal surgeries such as pancreaticoduodenectomy, liver resection, splenectomy, and colorectal surgery, placing a peritoneal drainage tube prophylactically enables continuous monitoring and timely evacuation of blood and gastrointestinal contents, and effectively preventing the occurrence of severe complications such as peritonitis [18, 20-22].

Types of abdominal drainage

Passive drainage: Passive drainage does not rely on external power, but relies on gravity, pressure difference or capillary action, such as drainage by a tube or cigarette drains [1]. The Penrose drain is a famous invention of cigarette drainage in history. Passive diversion has a low efficiency and is prone to blockage, increasing the risk of retrograde infection, and it is now used less frequently. Nevertheless, passive drainage tube is facile to manufacture and can be utilized for draining in times of war if necessary.

Active drainage: Active drainage requires an external device to provide negative pressure suction, thereby increasing the suction effect and more effectively removing the suction material. Active drainage devices are typically composed of an outer sump tube and an inner suction tube [23]. Additionally, vacuum sealing drainage (VSD) combines the concepts of "negative pressure, closed, and drainage", using wrapping materials, sealing films, drainage tubes, and external negative pressure suction devices. It has been proven effective in treating severe abdominal infections, preventing wound infections, and promoting healing of burns [7, 24, 25].

Indications of abdominal drainage

Intraperitoneal abscess

An abdominal abscess is formed by a fibrin matrix containing pus. The efficacy of systemic antibiotic therapy diminishes once a peritoneal abscess becomes encapsulated by intraperitoneal tissue and forms cyctic structure. A CT scan is usually the best way to diagnose an abdominal abscess [2]. Appendicitis and diverticulitis are common causes of intestinal perforation and the formation of abscesses in the abdominal cavity.

Whether drainage is performed depends on the size of the abscess [26, 27]. For peritoneal abscesses less than 3cm in size, non-surgical management is effective and safe. Patients with larger peritoneal abscesses (greater than 3 cm) may benefit from percutaneous drainage, which provides a less invasive intervention to to prevent the occurrence of sepsis, stabilizes the patient's condition, reduces the recurrence of abscesses, and provides time to find the cause [2, 27]. Goje et al. conducted a systematic review of the research on minimally invasive treatment of peritoneal abscesses and concluded that compared with conservative treatment with a single antibiotic, minimally invasive techniques (laparoscopic, ultrasound or CT-guided drainage) offer good therapeutic effects; compared with laparoscopy, image-guided puncture drainage has a higher success rate, fewer complications, and shorter hospital stay [28]. However, compared to simply using antibiotics, percutaneous drainage may result in more severe postoperative complications [29]. Therefore, considering the adverse events of peritoneal drainage, surgical treatment should be chosen for difficult percutaneous abdominal drainage insertion and antibiotic failure in patients with intra-abdominal abscesses [27].

Pancreas

For patients with infectious pancreatic necrosis, drainage is recommended [15, 30]. Percutaneous drainage and transwall endoscopic drainage are both treatment options for Walled-off pancreatic necrosis(WON). Percutaneous drainage may result in pancreatic fistulas, but it is a useful supplement to endoscopic drainage for WON patients with severe conditions that cannot be treated by endoscopy or those with deep extensions [15]. For patients diagnosed with necrotizing pancreatitis, no significant difference in complications was observed between early drainage within 24 hours and delayed drainage during the stage of localization formation, and patients assigned to the delayed drainage strategy received fewer invasive interventions [10]. The later drainage intervention for infective necrotizing pancreatitis also aligns with the previous studies' viewpoint [31].

In acute pancreatitis, abdominal drainage is used for the treatment of dysfunction of the gastric outlet resulting from persistent accumulation of pancreatic or peripancreatic fluid, pseudocyst formation, or progression to necrotizing pancreatitis [14]. In rats with acute severe pancreatitis, peritoneal drainage can reduce the severity of pancreatitis and intestinal inflammation [32, 33]. Interestingly, another study found that early peritoneal drainage can promote recovery in severe acute pancreatitis, with the authors explaining that drainage can block the harmful pathophysiological process of pancreatitis-related peritoneal effusion [34].

For pancreaticoduodenectomy, the benefits of postoperative routine drainage are not clear due to the lack of research evidence and the low persuasiveness of the research evidence [35]. Prophylactic peritoneal drainage after pancreaticoduodenectomy may be associated with a higher mortality rate, but has a lower incidence of complications [4]. Distal pancreatectomy with no routine post-operative abdominal drainage is associated with lower rates of major complications, pancreatic fistulas, and readmissions [36]. In general, there is no strong evidence to support the use of prophylactic drainage for pancreatic surgery [22].

Liver and gallbladder

Earlier studies indicated that there was no evidence to support the routine use of drainage tubes after non-complex liver resection [13]. However, a study indicates that peritoneal drainage is helpful in monitoring and treating postoperative complications for patients undergoing elective liver resection [37]. But recent studies have refuted the use of peritoneal drainage after non-complex liver resection, as it increases the risk of wound-related complications but does not reduce the risk of subsequent interventions [38]. Similarly, the use of prophylactic drainage in partial hepatectomy is also uncertain [21].

For patients with liver abscess, ultrasound or CT-guided needle puncture with aspirative drainage is the current standard of care, and bile drainage fluid is an important element in classifying liver abscesses [39].

Acute cholecystitis is not an absolute indication for peritoneal drainage. Placing an abdominal drain after laparoscopic cholecystectomy may not be beneficial for patients, instead, it prolongs the postoperative hospital stay of patients [40]. A randomized controlled study suggests that even with the risk of perforated gallbladder, elective day-case laparoscopic cholecystectomy without drain placement is safe and has fewer complications, such as postoperative fever [41]. These views seem to be consistent with earlier research [42]. When

acute calculous cholecystitis occurs, gallbladder drainage under laparoscopy can avoid open surgery [43]. Additionally, for a cholecystectomy with spilled gallstone, abdominal drainage is an optional treatment [44].

Appendix

For patients with complicated appendicitis, the necessity of performing abdominal drainage after appendectomy has been questioned, as it may increase the overall incidence of complications and hospital stay, thereby prolonging the recovery period [45, 46]. Some scholars even believe that abdominal drainage is a risk factor for postoperative infection in the operative area after appendectomy [47].

Colorectum

Many studies have indicated abdominal drainage after colorectal surgery dose not offer significant benefits compared to no drainage and routine drainage does not significantly affect the incidence of colorectal anastomotic leakage [48-50]. Meanwhile, The placement of a drainage tube in constructing lateral ostomy is often correlated to local necrosis [51]. Additionally, the placement of abdominal drains after elective colorectal surgery is associated with a non-clinically significant longer ostoperative duration of stay, negating the routine use of abdominal drainage in colorectal surgery [52].

Wartime abdominal drainage

Despite some doubts about its effectiveness in certain situations, peritoneal drainage remains an essential treatment in peacetime. Similarly, in wartime conditions, peritoneal drainage plays an important role in medical care.

For intra-abdominal infections such as cholecystitis, acute cholangitis, acute left hemicolon diverticulitis, and postoperative peritonitis, abdominal drainage can be considered as a treatment option [43]. The utilization of abdominal drainage can effectively control the source of infection, facilitating the management of abdominal abscesses or infected abdominal fluid [5, 43]. Percutaneous drainage is a safe and effective procedure in most cases, with an effectiveness rate of around 85% [5]. It allows for minimally invasive removal of abdominal and pelvic abscesses and fluid collections, with a lower rate of mortality and complications [5]. In blunt abdominal injuries, abdominal drainage can remove the collection of blood and fluid, reducing the risk of abdominal fluid accumulation [53]. If no drainage is performed, the accumulation of fluid in the abdominal cavity may lead to or confuse complications such as bleeding, peritonitis, abdominal compartment syndrome, systemic inflammatory response, and respiratory distress [53]. In the event of an open abdominal injury, the placement of a temporary abdominal closure device with a drainage tube as part of an damage control surgical technique facilitates early identification, drainage residual infection and removal of peritoneal fluid, thereby reducing the risk of abdominal compartment syndrome [5]. Surgical debridement should be considered when conservative management or percutaneous drainage fails [54]. Despite many low-quality studies claiming that abdominal drainage should be avoided, scholars generally agree that drainage should be placed in cases of severe peritoneal contamination, high risk of fluid collection, and peritonitis [55].

The liver is the largest solid organ in the abdominal cavity. When liver injury is accompanied by intrahepatic abscess and delayed post-traumatic biliary fistula, drainage of the peritoneal cavity should be performed [56]. The combination of percutaneous drainage and endoscopic techniques may be considered, rather than percutaneous treatment alone [56]. Percutaneous drainage can also serve as the primary treatment option for splenic abscess following non-surgical management of splenic injury [57].

In battlefield conditions, the abdominal drainage tube may face problems such as falling off, blockage, difficulty in automatic drainage, and decreased drainage quality. Consequently, the drainage tube must be designed with a robust fixation mechanism to avert unintended dislodgment during the rescue operation [58]. It should also have a convenient anti-blockage structure and an anti-backflow structure to quickly resolve any blockages in the tube and restore normal functioning of itself [6]. Furthermore, the placement of the peritoneal drainage tube has a negative impact on the patient's mobility and is not conducive to the patient's postoperative recovery. Therefore, the drainage tube should be designed to be lightweight and securely fixed [55]. Additionally, the medical resources and personnel on the battlefield are limited, and it is not possible to provide comprehensive monitoring for every injured person in real time. Therefore, the drainage tube can also be integrated with alarm and monitoring functions to prevent the drainage tube from falling off or

becoming blocked for too long without being treated [58].

Conclusion

In summary, the application of abdominal drainage technology has significant importance and necessity both in peacetime and wartime. In peacetime medical care, abdominal drainage plays an important role in preventing and dealing with postoperative complications in the abdomen, promoting wound healing, and reducing the risk of infection; in wartime situations, the importance of abdominal drainage in monitoring bleeding, removing contaminants, and preventing infection is even more prominent. The difficulties in transportation and the shortage of medical personnel during field rescue operations have prompted the development of more reliable and less prone to blockage drainage tubes, as well as real-time monitoring of drainage conditions, to enhance drainage effectiveness. In the future, abdominal drainage will move towards portability and intelligence to meet the needs of peacetime and wartime.

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Optimal placement of gastrointestinal decompresion catheter in patients with gastric cancer: A randomized and controlled clinical study

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Declaration of conflict of interest: None.

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Highlights

- Gastrointestinal decompression (GID) near the gastric body reduces nausea, vomiting, and discomfort.
- GID near the gastric body is conducive to exposure of the operative space.
- GID near the gastric body improves postoperative recovery of gastrointestinal function.

Abstract

Objective: To investigate the optimal site for intraoperative gastrointestinal decompression (GID). **Methods:** In this prospective study, 62 gastric cancer patients who underwent surgery at Xuzhou Central Hospital from January 2022 to May 2023 were randomly assigned to either a control or experimental group (31 patients/group). For patients in the control group, the conventional method was used for measurement of the gastric tube length, and GID was placed near the cardia. For patients in the experimental group, the gastric tube length was measured using conventional method with an additional 5–10 cm, and GID was placed near the gastric body. Intraoperative gastric tube placement, intraoperative tube adjustments, gastric contents, GID effectiveness, postoperative gastric fluid drainage volume, and gastrointestinal peristalsis recovery were compared between the two groups. **Results:** Intraoperative gastric tube adjustment (x^2=24.952, p<0.001) and volume of gastric fluid drainage (x^2=-14.376, p<0.001) significantly affects GID effectiveness. There were notable differences in GID effectiveness between the two groups (x^2=-4.353, p<0.001). GID near the gastric body reduced postoperative complications (nausea/vomiting: x^2=5.905, p=0.015; aspiration: x^2=4.292, p=0.038) and improved gastrointestinal peristalsis recovery (x^2=3.085, p=0.032). **Conclusion:** GID near the gastric body is safe and effective.

Keywords: Laparoscopy, gastric cancer, gastrointestinal decompression, surgical space exposure, postoperative complications

Introduction

Gastric cancer is a common malignant tumor typically treated by minimally invasive laparoscopic surgery [1]. Successful laparoscopic surgery for gastric cancer requires adequate exposure of the surgical field and sufficient operating space. Using traditional methods to measure the length of the gastric tube, 91.36% of the tube ends are positioned near the cardia, which limits effective release of accumulated gas and liquid from the gastrointestinal tract

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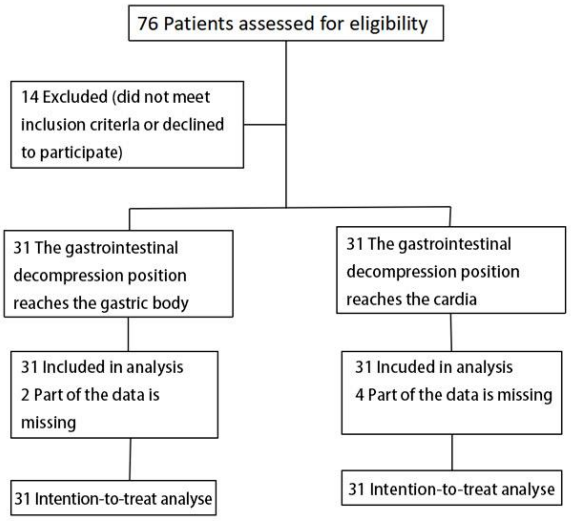

Figure 1. Flowchart of the patient allocation process.

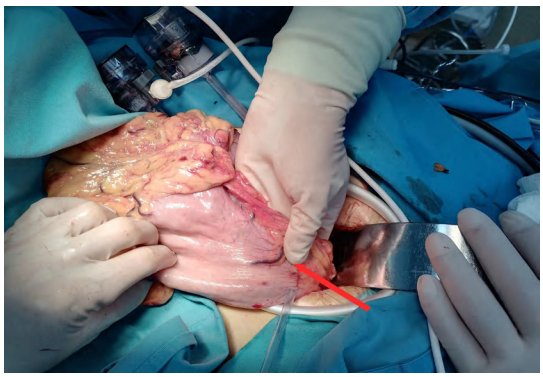

Figure 2. The anterior end of the gastric tube located in the gastric cardia. Photo is from the operating room of Xuzhou Central Hospital.

[2, 3]. Moreover, excessive stomach distension leads to poor surgical field exposure and increases the risks of regurgitation/aspiration and postoperative abdominal distension, with reported rates of 10%–70% and 73.3%, respectively [4]. Therefore, traditional methods for measuring gastric tube length fall short in achieving effective gastrointestinal decompression (GID) [5, 6].

Hence, precise gastric tube placement is essential to prevent excessive stomach expansion during surgery, reduce the risk of anastomotic fistula formation, and promote early recovery of gastric function. In our hospital, preoperative GID is routinely performed for patients undergoing laparoscopic gastric cancer surgery. The aim of this study was to assess whether GID near the gastric body offers more advantages over GID near the cardia. The results showed that GID near the gastric body achieved superior outcomes by allowing complete evacuation of gas and gastric juice during surgery, thereby facilitating gastrectomy procedures.

Methods

Study cohort

The study included 62 patients who underwent gastric cancer surgery at Xuzhou Central Hospital from January 2022 to May 2023, meeting the inclusion criteria. The patients were randomly assigned to either a control group (31 patients) or an experimental group (31 patients) using a computer-based block randomization method (block size of 30) with sealed envelopes (**Figure 1**).

Intention-to-treat (ITT) analysis was employed as the primary analytical approach for this study. This method maintains all randomized participants in their originally assigned groups for analysis, regardless of protocol deviations, treatment adherence, or subsequent withdrawal from the study. The ITT approach helps preserve the benefits of randomization and provides a more realistic estimate of treatment effectiveness in clinical practice.

Participants

Inclusion criteria: (1) age>60 years, (2) gastroscopic findings suggestive of gastric cancer, (3) diagnosis of adenocarcinoma confirmed by biopsy, and (4) complete clinical data. Exclusion criteria: (1) mental illness, (2) cervical vertebrae disease, (3) esophageal or gastric variceal hemorrhage, or (4) tumor rupture/bleeding.

Interventions

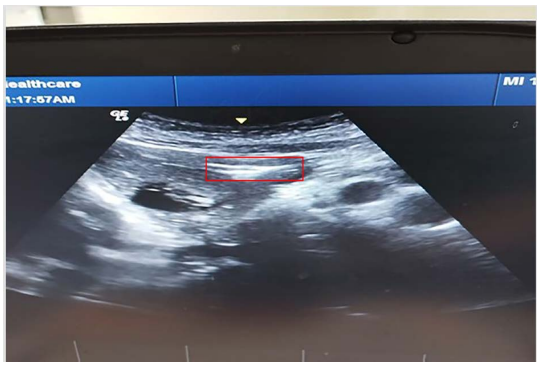

Figure 3. Double-track sign of the gastric tube in the stomach. The photo is from the operating room of Xuzhou Central Hospital.

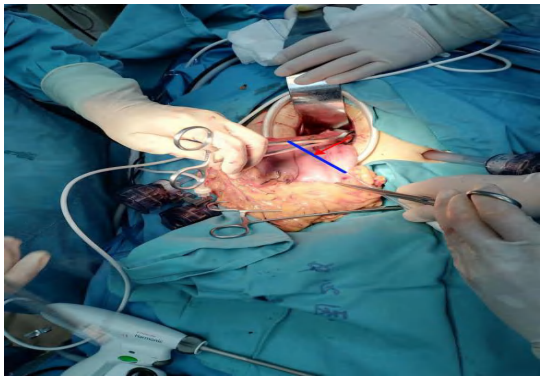

Figure 4. The anterior end of the gastric tube located in the gastric body. The photo is from the operating room of Xuzhou Central Hospital.

For patients in the control group, the conventional method was used to measure gastric tube length, with the GID site placed near the cardia. For patients in the experimental group, the gastric tube length was measured conventionally with an additional 5–10 cm, and the site of GID was near the gastric body.

Patients in the control group were placed in the supine position and the distance from the hairline to the xiphoid process or from the nose tip to the earlobe to the xiphoid process (45–55 cm) was measured [7]. Based on the measured length, the gastric tube was inserted up to the stomach cardia under ultrasound guidance [8]. During the procedure, the gastric tube position of the in the stomach was verified by direct observation of the surgeon (**Figure 2**).

The same procedure was used for patients in the experimental groups; however, the length of the gastric tube was extended by an additional 5–10 cm, allowing the gastric tube to reach the gastric body (**Figure 3** and **Figure 4**).

Evaluation criteria

The primary outcome was the effectiveness in gastric emptying following GID, which was evaluated by the surgeon through direct observation of gastric filling before mobilization of the gastric body. Gastric emptying was scored as follows: 5 points for completely empty, 3 points if partially empty, and 1 point if completely full. Higher scores indicated a better effect of intraoperative GID.

The secondary outcomes included: (1) the gastric tube placement as verified by ultrasonography; (2) intraoperative adjustments due to improper gastric tube placement; (3) gastric juice drainage volume, where higher volumes indicate appropriate placement and a better decompression effect; (4) recovery time of postoperative gastrointestinal peristalsis; and (5) postoperative complications (e.g., nausea, vomiting, and aspiration).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corporation, Armonk, NY, USA). Measurement data were compared using an independent sample t-test and were presented as the mean ± standard deviation, while categorical data were compared using the chi-square test and were presented as numbers and percentages. A probability (p) value<0.05 was considered statistically significant.

In this study, we hypothesized that the effect of intraoperative GID would be inferior in the control group than the experimental group. The primary endpoint of this study was the effectiveness of intraoperative GID.

In the preliminary experiment, the effect of intraoperative GID in the control and experimental groups was 0.0% and 12.3% vs. 1.0% and 11.3%, respectively. At an α value of 0.05 and a power (1-β) of 0.80, a sample size of 30 participants was calculated using the following formula:

$$n_1 = \frac{[u_\alpha \sqrt{p(1-p)(1+c)/c} + u_\beta \sqrt{p_1(1-p_1)+p_2(1-p_2)/c}]^2}{(p_1-p_2)^2}$$

Results

Of the 76 patients initially selected for this study, 14 did not meet the inclusion criteria and were excluded. Finally, 62 patients who met the inclusion criteria were randomly assigned to the control group (gastric tube near

Table 1. Comparison of baseline characteristics between the two groups

		Control group (n=31)	Experimental group (n=31)	X^2	p
Sex (n, %)	Male	17 (54.84)	16 (43.24)	0.065	0.799
	Female	14 (44.16)	15 (56.76)		
Mean age (years)		69.34±8.26	67.89±7.21	0.736	0.464
Mean height (cm)		164±7	166±8	-1.048	0.299
Mean body weight (kg)		67.32±16.66	64.85±18.83	0.547	0.586
Tumor size (n, %)	<4 cm	22 (70.97)	19 (61.29)	0.648	0.421
	≥4 cm	9 (29.03)	12 (38.71)		
Differentiation (n, %)	Well-differentiated	13 (41.94)	14 (45.16)	0.069	0.966
	Moderately differentiated	16 (51.61)	15 (48.39)		
	Poorly differentiated	2 (6.45)	2 (6.45)		
TNM stage (n, %)	I	17 (54.84)	19 (61.29)	0.265	0.607
	II	14 (45.16)	12 (38.71)		

Table 2. Comparison of gastric decompression effectiveness between the two groups (points)

	Effect of intraoperative gastric decompression [example (percentage, %)]			Average
	Completely empty	Partially empty	Full stomach	
Control group (n=31)	5 (16.13)	22 (70.97)	4 (12.90)	3.06
Experimental group (n=31)	27 (87.10)	2 (6.45)	2 (6.45)	4.61
X^2	32.458			-4.353
p	<0.001			<0.001

the cardia) or the experimental group (gastric tube near the gastric body), with 31 patients in each group. As shown in **Table 1**, there were no significant differences in sex, age, height, and weight between the two groups (all p<0.05).

Primary outcome

The primary outcome was the effectiveness of intraoperative GID. As shown in **Table 2**, the experimental group demonstrated significantly better efficacy in intraoperative GID, supported by notably higher proportion of patients achieving completely empty (87.10% vs. 16.13%).

Secondary outcomes

As shown in **Table 3**, after bedside B-ultrasound verification, 2 cases in the test group had the front end of the gastric tube in the cardia, 14 cases in the control group had the front end of the gastric tube in the lower esophagus, and 17 cases had the front end of the gastric tube in the cardia. The frequency of intraoperative tube adjustment was significantly lower, while the gastric fluid drainage volume was significantly higher in the experimental group compared to the control group (all p<0.001).

As shown in **Table 4**, the experimental group showed significantly lower incidence in nausea and vomiting (p=0.015), as well as aspiration (p=0.038) compared to those in the control group. Additionally, the recovery time of gastrointestinal peristalsis in the experimental group was significantly shorter than that in the control group (p=0.032).

Discussion

Gastric cancer, a common malignancy, is typically treated with minimally invasive laparoscopic surgery [9, 10]. Successful laparoscopic surgery for gastric cancer relies on adequate exposure of the surgical field. However, the anatomical structures of the esophagus and stomach can hinder effective removal of accumulated gas and liquid from the gastrointestinal tract. Excessive stomach distension can lead to poor exposure of the surgical field. The reported incidences of reflux/aspiration and abdominal distension are high when a gastric tube is used for GID [11].

Traditional methods for determining tube length often fall short in preventing over-distension

Table 3. Comparison of gastric tube placement, intraoperative tube adjustment, and gastric fluid drainage volume between the two groups

	Placement of gastric tube [example (percentage, %)]			Intraoperative adjustment of the gastric tube (n, %)	Gastric fluid drainage (mL, mean ± standard deviation)
	Lower esophageal segment	Preventriculus	Corpora ventriculi		
Control group (n=31)	14 (45.16)	17 (54.84)	0	21 (67.74)	28.23±11.42
Experimental group (n=31)	0	2 (6.45)	29 (93.55)	2 (6.45)	72.35±12.71
X^2	54.842			24.952	-14.376
p	<0.001			<0.001	<0.001

Table 4. Comparisons of postoperative complications and recovery time of gastrointestinal peristalsis

	Nausea and vomiting (n, %)	Aspiration (n, %)	Postoperative recovery time of gastrointestinal peristalsis (h, mean ± standard deviation)
Control group (n=31)	11 (35.48)	8 (25.81)	46.28±7.17
Experimental group (n=31)	3 (9.68)	2 (6.45)	41.36±5.24
X^2/t	5.905	4.292	3.085
p	0.015	0.038	0.032

during surgery, reducing postoperative anastomotic tension, preventing anastomotic leakage, and promoting early recovery of gastric function [12]. The results of this study indicate that increasing the gastric tube length by 5–10 cm, allowing the tube to reach the gastric body, significantly improves the effectiveness of intraoperative GID.

Positioning GID in the gastric body can alleviate symptoms of nausea and vomiting. Conventionally, the length of the gastric tube is 45–55 cm, only reaching the lower segment of the esophagus or the cardia [13]. At this position, stimulation of the cardiac sphincter often leads to nausea, vomiting, and discomfort. In addition, due to the shallow depth of catheterization, increased abdominal pressure can cause reflux, aspiration, and other complications, aligning with the findings in our study, as the incidences of nausea, vomiting and aspiration were significantly higher in the control group [14]. Positioning the front end of the gastric tube within the gastric body effectively lowers gastrointestinal tract pressure and minimizes discomfort.

Extending the GID position to the gastric body can better expose the surgical space. The conventional method for gastric tube placement is not ideal to achieve satisfactory GID, as gas and liquid retention in the stomach can significantly impact surgical duration and outcomes. Optimal GID is achieved when the gastric tube's tip is placed in the middle - gastric body, facilitating better exposure of the surgical space [15, 16]. When the length of the gastric tube was extended to 50-65 cm, clinical color Doppler ultrasound verified that the front end of the gastric tube reached the gastric body and the surgical space was fully exposed, which is conducive to gastric separation.

In addition, with the gastric body is effectively decompressed, there is no need to further adjust the gastric tube, which reduces the workload and avoids damage to the gastric mucosa caused by repeated extraction and insertion of the gastric tube.

Extending the position of GID to the gastric body is beneficial to postoperative recovery of gastrointestinal function. A study by Zhang et al. reported that the postoperative indwelling time, and incidence of postoperative abdominal distension were reduced while drainage volume was increased, when the depth of gastric tube was extended 45–55 cm to 50–60 cm [17]. Hence, in the present study, the insertion depth of the gastric tube was increased by 5–10 cm to 50–65 cm, allowing the tip of the gastric tube to reach the gastric body. This placement effectively removed gas and liquid from the gastrointestinal tract, reduced intragastric pressure, improve blood circulation in the gastrointestinal wall, accelerated recovery of gastrointestinal peristalsis, and promoted postoperative recovery [18, 19].

Conclusion

The effectiveness of GID is improved by placing the gastric tube in the gastric body. Extending the length of the gastric tube by 5–10 cm to reach the gastric body not only minimizes discomfort caused by gastric tube insertion, but also optimizes surgical field exposure, and promotes postoperative recovery of gastrointestinal function.

However, given that most gastric cancer patients undergoing laparoscopic surgery are elderly, who may suffer from physiological gastroptosis, positioning the gastric tube in the gastric body is ideal. Therefore, Doppler color ultrasound is recommended to assist in accurate gastric tube positioning for GID.

Author contributions: Mingling Wang contributed to the conception of the study, and performed the experiment; Xiaoyan Wang performed the experiment, reviewed and edited the manuscript, and project administration; Kai Wang and Lien Qi contributed significantly to the analysis and manuscript preparation; Mingling Wang and Jing Zhang helped perform the analysis with constructive discussions.

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Impact of intestinal immunologic barrier dysfunction on perioperative complications

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Highlights

- Intestinal barrier dysfunction increases the risk of perioperative complications.
- The immunologic barrier is crucial for maintaining intestinal homeostasis.
- Perioperative factors compromise the intestinal immunologic barrier, increasing infection risk.
- An imbalance between intestinal microbiota and immune cells affects postoperative recovery.
- Clinical intervention studies targeting the intestinal barrier are summarized.

Abstract

Intestinal barrier dysfunction plays a critical role in perioperative complications, especially in the circumstances where immunologic barrier is damaged. This paper reviews the structure of the intestinal immunologic barrier, its interaction with intestinal microbiota, and its effects on intestinal epithelial cells. It emphasizes the key role of the intestinal immunologic barrier in maintaining intestinal homeostasis and explains how its dysfunction increases the risk of infection, anastomotic leakage, gastrointestinal motility disorders, and systemic inflammatory response syndrome during the perioperative period.

Keywords: Intestinal barrier, perioperative complications, immunologic barrie

Introduction

The intestinal barrier is a critical defense system that maintains intestinal microenvironment homeostasis. It comprises the mechanical, chemical, immunologic, and microbial barriers, which collectively preserve intestinal integrity. Among them, the immunologic barrier is crucial in preserving intestinal homeostasis and preventing pathogen invasion [1]. Intestinal immune cells serve as sentinels within the intestinal microecosystem, exhibiting a remarkable capacity to rapidly recognize and clear invading pathogens [2]. In addition to preventing infections, these cells regulate the renewal and repair of intestinal epithelial cells by releasing various cytokines and signaling molecules [3, 4]. This multifaceted immune function reinforces the intestinal barrier, effectively impeding the translocation of harmful substances into the abdominal cavity or systemic circulation [1]. A delicate dynamic equilibrium exists between intestinal immune cells and the intestinal barrier [1]. In a healthy gut microbiome, immune cells remain in a state of vigilant quiescence to avoid overreacting and harming symbiotic microbes. However, disruptions in the intestinal microbiota, particularly an increase in pathogenic bacteria, trigger an immediate activation of immune defense mechanisms. This rapid immune response facilitates pathogen clearance, restores intestinal microecological balance, and preserves intestinal barrier function and stability [3].

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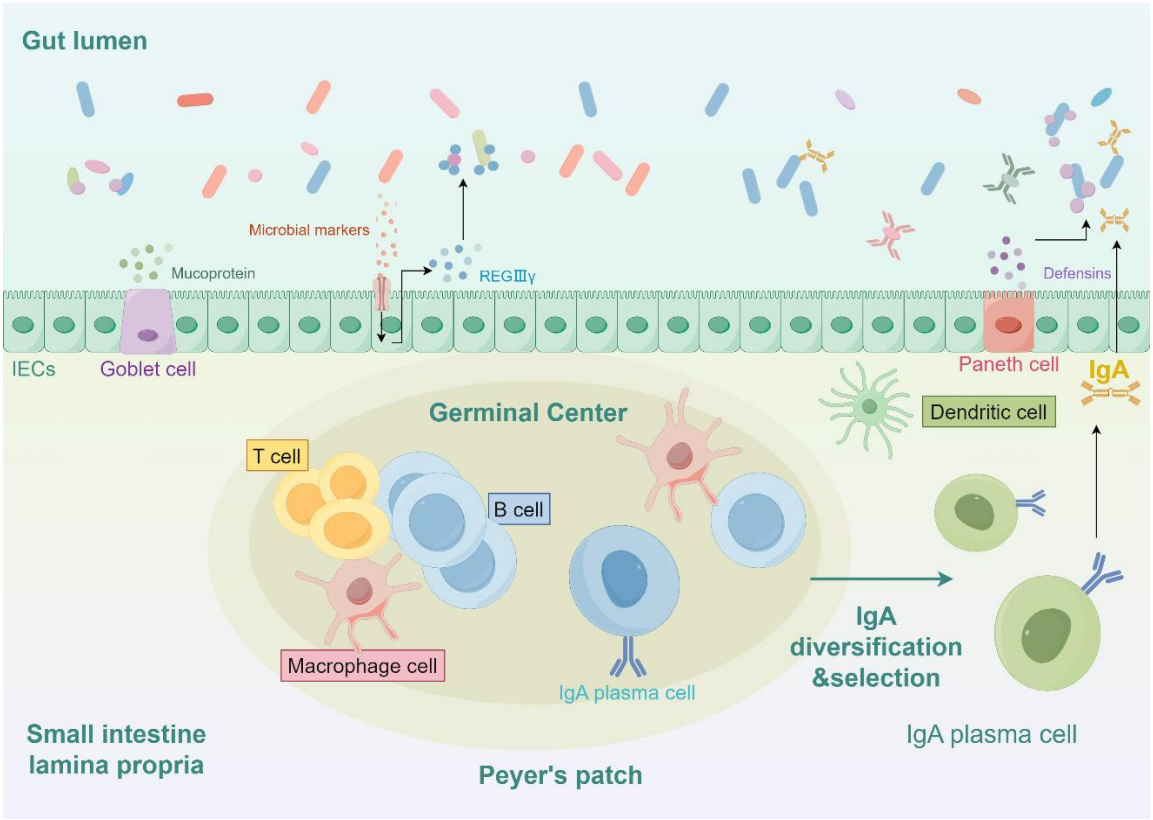

Figure 1. Intestinal barrier composition.

With advances in surgical techniques, and clinical care, surgical outcomes have significantly improved. However, recovery from major surgeries is often disrupted by unpredictable postoperative complications [5]. These complications, including infections, anastomotic leakage, gastrointestinal dysmotility, malabsorption, and cancer recurrence, can substantially impede patient recovery and outcomes [5]. Emerging evidence indicates that disturbances in the balance between the gut microbiome and intestinal immune cells play a crucial role in elevating the risk of postoperative infections [3]. Postoperative infection represents a critical turning point, often leading to severe complications such as anastomotic leakage and systemic inflammatory response syndrome (SIRS) [5]. The intestinal immune cell barrier emerges as a key determinant in this process. This review aims to elucidate the perioperative alterations in the intestinal immune cell barrier and their consequential impact on postoperative recovery following major surgical interventions.

The intestinal immunologic barrier: A complex defense system

Structure of intestinal immunologic barrier

The intestinal barrier represents a sophisticated, multi-layered defense system crucial for maintaining gastrointestinal homeostasis. It consists of three primary components: the biological barrier (gut microbiota), the mechanical barrier (intestinal epithelial cells and their tight junctions), and the immunologic barrier (immune cells within the intestinal mucosa and lamina propria, as well as gut-associated lymphoid tissue (GALT)) [1]. The structure and distribution of the intestinal barrier are shown schematically in **Figure 1**. These interconnected elements work synergistically to facilitate nutrient absorption while preventing pathogen invasion and maintaining mucosal integrity [1].

Within the intestinal epithelium, specialized structures such as Peyer's patches harbor critical immune cells derived from both innate and adaptive immune systems, including thymus-derived T cells, bone marrow or synovium-derived B cells, dendritic cells, and macrophages. Furthermore, antimicrobial peptides secreted by Paneth cells and secretory immunoglobulin A (IgA) produced by plasma cells further fortify the mucosal defense [6]. Paneth cell-derived antimicrobial peptides directly combat bacterial intrusion, while IgA forms a protective layer on the mucosal surface, preventing pathogen adherence and invasion [6]. Peyer's patch is highlighted in **Figure 1**. The intestinal vascular (endothelial) barrier constitutes another protective layer, which effectively limits the translocation of microorganisms and their by-products into the systemic circulation [7]. GALT plays a

pivotal role in immune surveillance, recognizing and responding to foreign antigens within the gut lumen. This lymphoid tissue serves as a primary site for initiating immune responses. The collaboration of various immune cell populations establishes a robust defense mechanism: T cells recognize and eliminate infected or malignant cells; B cells neutralize pathogens through antibody production, particularly IgA; and antigen-presenting cells, such as dendritic cells and macrophages, act as sentinels, engulfing and presenting antigens to activate adaptive immune responses [7]. These details are demonstrated in **Figure 1**.

The integrity of this multi-faceted barrier system is paramount for maintaining health. Intestinal mucosal barrier dysfunction and increased permeability enable bacteria or toxins to enter the blood or lymphatic channels in the circulatory system, leading to SIRS. When treatment is inappropriate or not timely, the condition may progress to multiple organ dysfunction syndrome [8]. In this pathophysiological cascade, the immunologic barrier plays a critical role in modulating the inflammatory response and preventing systemic complications.

The microbial barrier is the outermost barrier of the intestinal tract. The chemical barrier is close to the microbial barrier and is a layer of mucous membrane. Physical barrier, also known as mechanical barrier, includes the mucosal epithelium, lamina propria, and muscularis mucosae. Mucosal epithelium has an inherent epithelium, including immune cells and enterocytes, and is reinforced by tight junctions. Beneath the lamina propria, the immunologic barrier is composed of immune cells located within the mucosa and lamina propria, as well as the GALT. The gut vascular barrier is the deepest protective layer of the intestinal tract. The intestinal immunologic barrier, depicted in detail, reveals a sophisticated network of immune components. Peyer's Patches, crucial immune structures within the intestinal epithelium, serve as aggregation sites for key innate and adaptive immune cells, including T and B lymphocytes. Paneth cells contribute to the barrier function through the secretion of antimicrobial peptides, while plasma cells produce secretory IgA, both playing pivotal roles in mucosal immunity. The GALT houses Foxp3+ regulatory T cells, dendritic cells, and macrophages, all of which synergistically maintain intestinal immune homeostasis. The right panel elucidates the diversity and selection process of IgA, highlighting its role in recognizing and responding to a broad spectrum of antigens and pathogens, thereby serving as a critical component of the intestinal immune defense system.

Intestinal immunologic barrier and intestinal microbiota

The human gut microbiome comprises a diverse community of microorganisms, including bacteria, fungi, and viruses [9]. Most of these microbes are commensal bacteria that benefit the host by aiding digestion and competing with pathogens for colonization sites [10]. To distinguish between commensals and pathogens, intestinal epithelial cells (IECs) and innate immune cells, including dendritic cells and macrophages, utilize specialized mechanisms known as pathogen-recognition receptors [11]. These receptors include toll-like receptors, nucleotide-binding and oligomerization domain (NOD)-like receptors, and RIG-I-like receptors, which recognize microbial markers, such as bacterial DNA, flagellin, and components of bacterial cell wall [12, 13]. These microbial markers persistently stimulate IECs to produce antimicrobial agents, including regenerating islet-derived protein III-γ, angiogenin-4, and cytokines such as IL-33 and IL-25 [14]. These molecules play crucial roles in maintaining intestinal homeostasis and promoting the development of tolerogenic immune cells [15]. Consequently, this intricate interplay between the microbiome and host immune system preserves symbiotic relationships and maintains microbial equilibrium within the gut ecosystem.

Patients with inflammatory bowel disease exhibit impaired pathogen recognition due to aberrant expression of pattern recognition receptors. Frameshift mutations in the NOD2 gene, a member of the NOD-like receptor family expressed in the cytosol of IECs, have been identified in patients with Crohn's disease (CD) [16]. Studies in NOD2-deficient mice revealed compromised goblet cell function and elevated interferon-gamma production by intraepithelial lymphocytes. Furthermore, these mice displayed an enrichment of commensal Bacteroides species, potentially contributing to mucosal inflammation [17]. Thymic stromal lymphopoietin (TSLP), produced by IECs in response to commensal microorganisms such as Gram-negative Escherichia coli or Gram-positive *Lactobacillus rhamnosus*, represents another critical regulator of intestinal immunity [18]. TSLP upregulates CD40, CD80, and CD86 expression on dendritic cells via the signal transducer and activator of transcription signaling pathway, promoting the differentiation of non-inflammatory TH2 cells or regulatory T cells [19]. Study by Taylor et al. demonstrated increased production of IL-12/23p40 and interferon-gamma in TSLP

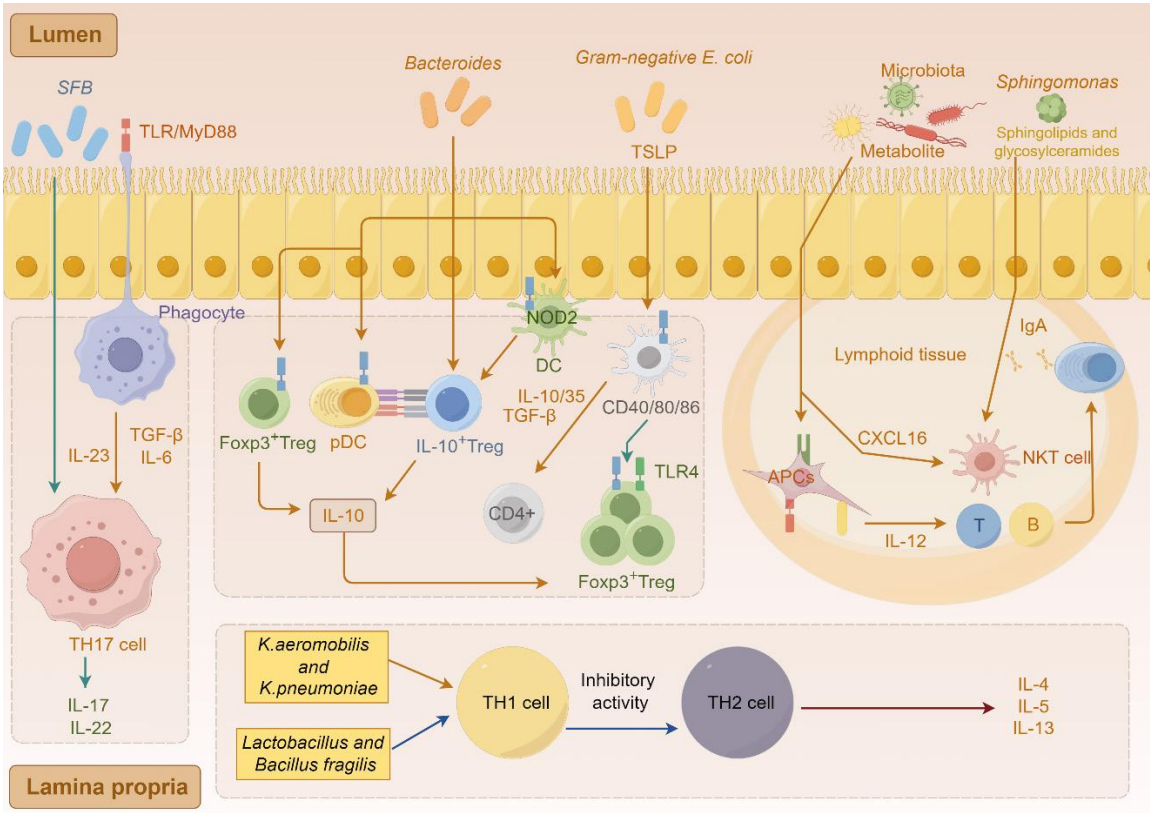

Figure 2. The influence of intestinal microorganisms on the development of intestinal immune cells.

receptor-deficient mice during acute intestinal inflammation induced by dextran sodium sulfate [20]. This finding suggests that excessive IL-12 production by dendritic cells can inhibit TH2 cell development. Notably, in CD patients, IECs often fail to produce TSLP, leading to uncontrolled IL-12 release and subsequent disruption of intestinal homeostasis.

The gut microbiota profoundly influences the function and activity of diverse T cell subpopulations, including Th1, Th2, Th17, and regulatory T cells [3]. Specific bacterial genera have been shown to modulate distinct T cell responses. For instance, colonization of germ-free mice with *Klebsiella* species (*K. aeromobilis* and *K. pneumoniae*) induces Th1 cell proliferation and expansion in the gut [21]. Conversely, certain strains of Lactobacillus and Bacillus fragilis inhibit Th2 activity by enhancing Th1 responses [22]. Th2 cells, which produce interleukins IL-4, IL-5, and IL-13, play crucial roles in humoral immunity, defense against helminth, and chronic inflammatory conditions such as allergies and asthma [23]. Th17 cells, in contrast, are potent pro-inflammatory immune cells implicated in autoimmune and inflammatory disorders [23]. Th17 cell differentiation is predominantly initiated by the cytokines transforming growth factor (TGF)-β and IL-6 and sustained by IL-23 [24]. Research has shown that Gram-positive segmented filamentous bacteria, also known as *Candidatus arthromitus*, promote Th17 cell development and the secretion of various cytokines such as IL-17 and IL-22 [25]. Conversely, Treg cells facilitate immune tolerance through contact-dependent mechanisms and the production of immunomodulatory cytokines such as IL-10, TGF-β, and IL-35 [26]. Regulatory T cells are broadly categorized into induced regulatory T (iTreg) cells and natural regulatory T cells [27]. Recent studies have identified five *Bacteroides* species (*B. intestinalis*, *B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, and *B. massiliensis*) capable of effectively inducing colonic Treg cell development [28]. These findings underscore the complex interplay between the gut microbiota and T cell subpopulations in maintaining intestinal homeostasis and modulating immune responses.

Metabolites produced by the gut microbiota play a crucial role in modulating T cell development and function, facilitating rapid responses to intestinal stimuli and promoting adaptive immune responses [3]. Recent studies have elucidated specific mechanisms by which microbial metabolites influence various T cell subsets. For instance, Luu et al. demonstrated that valerate, a short-chain fatty acid produced by *Megasphaera massiliensis*, regulates IL-12 synthesis in antigen-presenting cells, thereby modulating CD8+ T lymphocyte activation [29]. Natural killer T (NKT) cells, another important component

of the intestinal immune system, are activated by microbial antigens such as sphingolipids and glycosylceramides [30]. Furthermore, microbial-derived bile acids have been shown to influence NKT cell accumulation in the liver by mediating CXCL16 expression. Notably, *Clostridium species* can alter bile acid composition, leading to elevated CXCL16 levels in hepatic sinusoidal endothelial cells [31]. In contrast, *Fusobacterium varium* significantly suppresses a broad spectrum of genes associated with bile acid metabolism, resulting in a marked reduction of both CD4+ and CD8+ T cell populations [32]. These findings underscore the complex interplay between gut microbial metabolites and the host immune system. Various gut microbiota can respectively enhance the growth and differentiation of Th1, Th2, Th17, Treg, T, and NKT cells. The connection between the flora and cells is clearly depicted in **Figure 2**.

Th1 cells: *Klebsiella* species, specifically *K. aeromobilis* and *K. pneumoniae*, promote the proliferation and expansion of Th1 cells within the gut. Th2 cells: *Lactobacillus* and *Bacillus fragilis* have been shown to suppress Th2 activity by enhancing Th1 responses. Th2 cells are primarily responsible for the production of interleukins such as IL-4, IL-5, and IL-13. Th17 cells: The differentiation of Th17 cells is primarily initiated by cytokines TGF-β and IL-6, with IL-23 playing a crucial role in sustaining this process. Segmented Filamentous Bacteria play a crucial role in the development of Th17 cells and the secretion of various cytokines, including IL-17 and IL-22. Treg cells: Treg cells help maintain immune tolerance through both contact-dependent mechanisms and the production of immunomodulatory cytokines such as IL-10, TGF-β, and IL-35. Species within the *Bacteroides* genus, including *Bacteroides intestinalis*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, and *Bacteroides massiliensis*, are known to induce colonic Treg cells. CD4+ T cells: TSLP produced by Gram-negative Escherichia coli influences CD4+ T cells through the signal transducer and activator of transcription signaling pathway. CD8+ T cells: The metabolite valerate controls the synthesis of IL-12 by antigen-presenting cells and affects the activity of CD8+T cells. NKT cells: Sphingolipids and glycosylceramides produced by *Sphingosinomonas* activate NKT cells. Microbial bile acids mediate the expression of CXCL16 and affect the accumulation of NKT cells.

Intestinal immunologic barrier and intestinal epithelial cells

The gastrointestinal tract is perpetually exposed to a diverse array of dietary and bacterial antigens, necessitating a robust immune defense against potential external threats. The intestinal epithelium plays a pivotal role in limiting antigen exposure to immune cells, thereby preventing hyperactive immune responses [33]. Serving as the primary defense mechanism of the intestine, epithelium is characterized by a sophisticated structure that forms a meticulously regulated barrier. This barrier comprises a monolayer of tightly packed columnar epithelial cells, interconnected by tight junctions [33]. While tight junctions contribute to the physical barrier, specialized IECs, such as goblet cells and Paneth cells, play crucial roles in antimicrobial defense and are integral to the innate immune system [2]. **Figure 3** provides an overview of the intestinal mucus barrier and its related cellular activities.

Secretory IECs, including goblet cells and Paneth cells, establish the intestinal mucus barrier by secreting mucus and antibacterial proteins. This barrier primarily consists of gel-like mucins, such as mucin-2 and mucin-6, secreted by goblet cells. These mucins are glycoproteins that form an intricate network, effectively impeding pathogen penetration [34]. The mucosal architecture of the small intestine and large intestine exhibits distinct structural differences. The mucus layer in the small intestine is relatively loose and thin, whereas the mucus layer in the colon is notably thicker and stratified into inner and outer layers. While the outer mucus layer of the small intestine allows bacterial penetration, the inner colonic mucus layer adheres firmly to the epithelial surface, preventing bacterial invasion [35]. Additionally, goblet cells produce molecules such as clover factor 3, which support mucosal recovery and repair [36]. Another product of goblet cells, the Resistin-like molecule β, is upregulated in response to Th2 cytokines during nematode infections [37]. Paneth cells contribute to this defense by producing antimicrobial peptides, with defensins being the most abundant [38]. Human α-defensins 5 (HD5) and 6 (HD6) are particularly significant. HD5 disrupts bacterial plasma membranes and is effective against both Gram-positive and Gram-negative bacteria, while HD6 encapsulates bacteria in a “straitjacket,” thereby restricting their activity until they lose viability [39]. Chu et al. demonstrated that HD6 can bind to bacteria and self-assemble into a nanonet, effectively countering *Salmonella typhimurium* [40]. In CD patients, the expression levels of both HD5 and HD6 are notably down-regulated [41]. Paneth cells also secrete lysozyme, a potent glycosidase that hydrolyzes peptidoglycan in bacterial

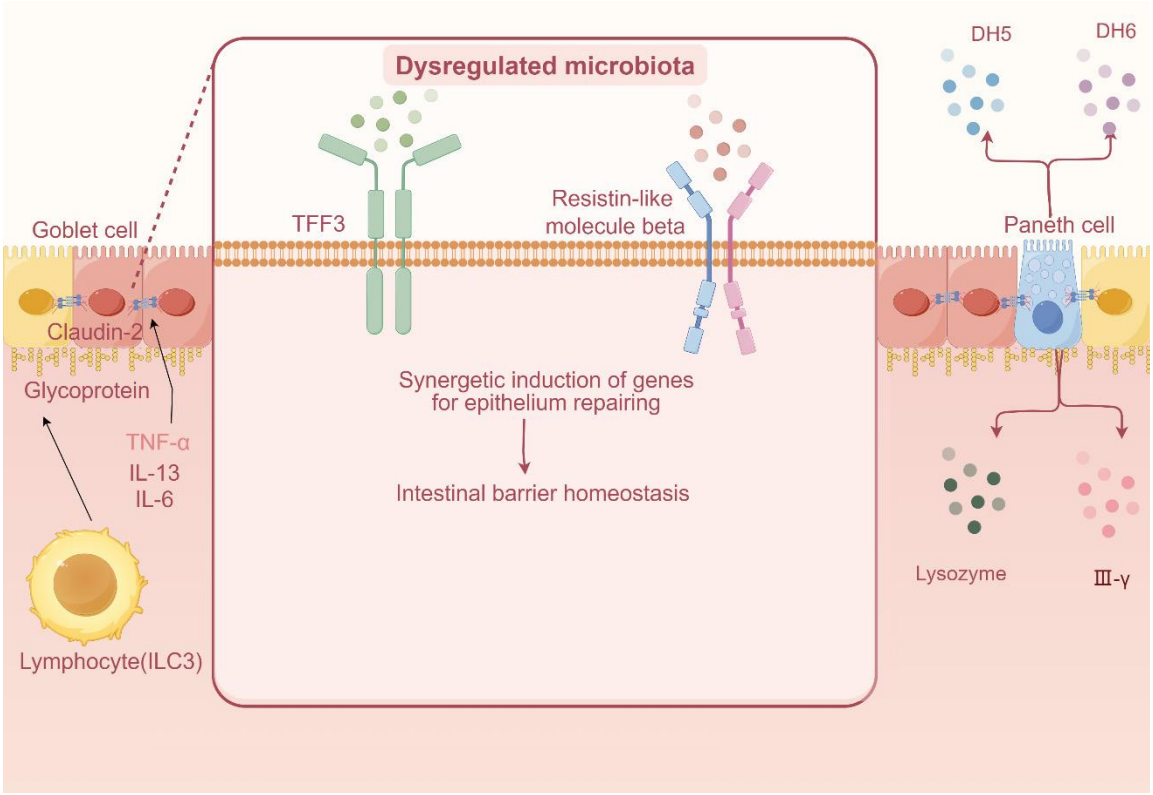

Figure 3. Immune function of the intestinal epithelium.

cell walls, thereby exerting potent antibacterial effect [42]. Additionally, Paneth cells produce regenerating islet-derived protein III-γ, which similarly targets bacterial cell wall [42]. Research has demonstrated that mice deficient in regenerating islet-derived protein III-γ exhibit persistent inflammatory responses [43]. Moreover, the intestinal epithelium also contributes to intestinal immune system maturation by delivering antigens to immune cells in a regulated manner. Microfold (M) cells, located in the follicle-associated epithelium and distributed from crypts to villi, internalize microbes and antigens from the gut lumen and transport them to immune cells in GALT. This process is crucial for the development and regulation of intestinal immune system [44].

Pro-inflammatory cytokines play a significant role in modulating intestinal tight junction function and maintaining barrier integrity [45-48]. IL-13 has been strongly correlated with the upregulation of Claudin-2, a protein involved in forming pore-like channels between IECs [45, 46]. In Caco-2 cells, a widely utilized model of IECs, stimulation with IL-1β induces a redistribution of occludin, another TJ protein, and increases the expression of myosin light chain kinase [47]. Innate lymphoid cells type 3 (ILC3) induce glycosylation of IECs, facilitate their normal differentiation, and enhance interactions with symbiotic bacteria. A deficiency in ILC3 results in differentiation defects and impaired barrier function [48].

Disruption of homeostasis significantly elevates the risk of autoimmune diseases and chronic inflammation [49]. Deficiencies in proteins such as FADD, which regulates cell death, can result in programmed necrosis of IECs, potentially leading to chronic enteritis [50]. Additionally, imbalances in IEC renewal and replacement mechanisms can result in excessive antigen invasion, triggering intestinal inflammation, as observed in ulcerative colitis and CD [49].

Goblet cells are responsible for secreting glycoproteins that play a crucial role in preventing pathogen penetration. Additionally, they produce trefoil factor 3, which plays a crucial role in epithelial cell repair. Additionally, goblet cells secrete Resistin-like molecule beta, contributing to immune function. Paneth cells, on the other hand, secrete anti-microbial peptides, with defensins being the most abundant. The two significant defensins in humans are HD5 and HD6. Furthermore, Paneth cells release lysozyme and lectins, which facilitate the production of regenerating islet-derived protein III-gamma, an enzyme that hydrolyzes peptidoglycans in bacterial cell walls. IL-6, IL-13, and tumor necrosis factor (TNF)-α have been shown to upregulate Claudin-2 expression. ILC3 are capable of inducing glycosylation of intestinal

epithelial cells and facilitating their normal differentiation. A deficiency in ILC3 results in abnormalities in epithelial cell differentiation.

Potential harm to the intestinal immunologic barrier during the perioperative period

The perioperative period encompasses the crucial stages before and after surgical procedures, during which patients' physiological states undergo significant fluctuations, making it a high-risk interval susceptible to various complications. Recent advancements in medical research have increasingly demonstrated a significant association between dysfunction of the intestinal immunologic barrier and perioperative complications.

Preoperative period

Malnutrition

Preoperative malnutrition has been identified as a factor that compromises the intestinal immunologic barrier, thereby elevating the risk of postoperative complications [51]. A study by Mingwei indicated that the concentrations of diamine oxidase, D-lactic acid, and endotoxin on postoperative days 3 and 7 were significantly reduced in patients receiving enteral immunonutrition, compared to the control group, which did not receive immunonutrition [51]. Additionally, on day 7 post-surgery, patients in the study group exhibited lower peripheral blood white blood cell counts and neutrophil to lymphocyte ratio, alongside elevated albumin levels. These findings suggest that enteral immunonutrition may help mitigate systemic inflammatory responses. [51]. One month after surgery, the study group also showed a significant increase in CD4+T and CD8+T cell counts, indicating a long-term positive effect of enteral immunonutrition on cellular immune function [51].

Stress reaction

Psychological and physiological stressors have a substantial influence on intestinal barrier function, particularly in pigs, which are considered an ideal model for investigating diseases linked to early life adversity. The pig model provides a deeper understanding of how psychological stressors affect gut barrier function and their long-term consequences during ontogenesis. By employing the pig early weaning stress (EWS) model, studies have explored its impact on intestinal health and function from different perspectives [52–55]. In the study of Medland et al., female EWS pigs at 60 and 170 days of age exhibited a significantly heightened response to veratridine-induced short-circuit current when compared to a late-weaning control group [55]. This response was inhibited by specific neurotoxins, suggesting an enhancement in secretomotor neuron function. Additionally, the number of choline acetyltransferase-positive intestinal neurons in the ileum was higher in EWS pigs, along with enhanced cholinergic signaling. This was accompanied by a downregulation of mucosal muscarinic receptor 3 gene expression, which may be associated with the regulation of intestinal function. Pohl et al. demonstrated that, in comparison to the late-weaning control group, EWS pigs exhibited a higher incidence of chronic functional diarrhea, increased intestinal permeability, and elevated mast cell counts during both juvenile and adult stages [54]. These findings underscore the long-term detrimental effects of EWS on porcine intestinal health.

The study by Ziegler et al., which examined the impact of environmental adaptation on intestinal barrier function in pigs subjected to transport stress, revealed that adapted pigs showed significantly enhanced permeability of intestinal macromolecules within one hour of initial in vitro incubation, suggesting that environmental adaptation may exacerbate intestinal permeability [52]. However, unacclimated pigs displayed superior wound-healing capabilities and more consistent recovery of transepithelial resistance, indicating that stress may facilitate the effective repair of the intestinal barrier. Subsequent analyses revealed that acclimated pigs demonstrated diminished expression of the tight junction protein claudin-4 during the recovery phase, whereas unacclimated pigs exhibited enhanced localization of this protein in the apical membrane. These findings further support the hypothesis that acute stress may expedite the repair of the intestinal barrier. Xia's research elucidated the impact of EWS on the formation of intestinal mucin O-glycans and the composition of intestinal microbiota, revealing that EWS led to the development of aberrant mucin O-glycans, characterized by truncated glycans, reduced acidic glycans, and elevated fucosyl glycans, which may contribute to intestinal inflammation and disease [53]. Additionally, EWS modified the gut microbial composition by increasing the prevalence of pathogenic bacteria, including E. coli and Shigella, further exacerbating risks to intestinal health.

Preoperative gut preparation

Preoperative gut preparation can significantly influence the diversity and functionality of the microbiota, which in turn affects postopera-

tive recovery. In a study by Wang et al. using 6-week-old MRL/lpr mice (a model for systemic lupus erythematosus), a notable reduction in the Firmicutes to Bacteroidetes ratio was observed [56]. This alteration in microbial composition was characterized by a decrease in the Peptostreptococcaceae family and an increase in the Rikenellaceae family, which were strongly correlated with heightened intestinal permeability in MRL/lpr mice, as indicated by elevated fecal levels of albumin and IgA, alongside reduced expression of the intestinal tight junction protein ZO-2. By 18 weeks of age, these mice exhibited signs of intestinal inflammation, including elevated levels of phosphorylated NF-κB, IL-6, and IgG in the colon, signifying an active inflammatory response in the gastrointestinal tract. Furthermore, a substantial increase in eubacterial populations was observed in the liver, suggesting that gut microbiota may have translocated to the liver via a compromised intestinal barrier, potentially initiating or exacerbating the hepatic immune response.

Immunosuppression

Preoperative immune status significantly impacts postoperative recovery. A study by Fragiadakis et al. highlighted the pivotal role of CD14+ monocytes in this process, demonstrating that their signaling responses, including pSTAT3, pCREB, and pNFκB, are closely linked with postoperative fatigue, hip function recovery, and pain alleviation [57]. Furthermore, the responses of classical and plasmacytoid dendritic cells to LPS and IL-2/GM-CSF stimulation were also correlated with postoperative recovery metrics. The study also highlighted that the Toll-like receptor 4 signaling pathway in monocytes is crucial for clinical recovery and emphasized that damage-associated molecular patterns (DAMPs), including high mobility group protein B1 (HMGB1) and heat shock proteins, activate innate immune cells via Toll-like receptor 4 receptors, significantly impacting postoperative recovery.

In addition, the preoperative immune status is closely linked to the risk of postoperative infection. The study by Zhang et al. demonstrated that patients who received transfusions exhibited significantly lower levels of TNF and IL-17A compared to those who did not receive transfusions, indicating a possible connection between the preoperative immune response and postoperative infection risk [58]. There was also a direct correlation between the robustness of the postoperative immune response and susceptibility to postoperative infection, as evidenced by postoperative immunosuppression. Torrance's study demonstrated a four-fold increase in IL-10 mRNA and protein levels following surgery, peaking within two hours post-surgery [59]. This was accompanied by a reduced expression of mHLA-DR on the cell surface, indicating postoperative immunosuppression. Elevated postoperative IL-10 levels are correlated with an increased risk of infection, suggesting that monocyte dysfunction and immunosuppression are common after major surgical procedures. Fortunately, clinically available immune stimulants, such as GM-CSF and interferon-gamma, have been shown to restore mHLA-DR levels, which may help reverse postoperative immunosuppression [59].

Period of operation

Surgical wound

Blunt abdominal trauma can result in early morphological damage to the intestines, particularly affecting the intestinal epithelial cells [60]. The extent of injury is directly proportional to the trauma's intensity; more severe trauma correlates with more pronounced intestinal damage, including manifestations such as intestinal bleeding and tissue rupture. Furthermore, the functionality of the intestinal immunologic barrier may be significantly compromised, facilitating to the translocation of intracellular molecules, such as intestinal fatty acid-binding protein, into the bloodstream. This translocation serves as a biomarker for intestinal barrier dysfunction, with its concentration being indicative of the trauma's severity.

Following trauma, the gastrointestinal tract triggers both local and systemic immune responses [61]. Neutrophils, serving as the primary line of defense, rapidly accumulate and become activated at the site of injury. This is accompanied by elevated plasma levels of inflammatory cytokines. These neutrophils migrate to the site of injury via chemotaxis, a process modulated by pro-inflammatory cytokines like IL-6 [61]. DAMPs released post-surgery, such as HMGB1, stimulate the formation of neutrophil extracellular traps through specific signaling pathways, thereby intensifying the inflammatory response [62]. Furthermore, systemic immune responses are characterized by increased plasma concentrations of inflammatory cytokines, such as macrophage inflammatory protein 2 and TNF [62]. While these immune responses help clear dead tissue and promote repair, they can also result in excessive inflammation, contributing to further tissue damage [60].

Traumatic injury can simultaneously trigger

both the SIRS and Compensatory Anti-inflammatory Response Syndrome [63]. These syndromes are induced by tissue damage and hemorrhagic shock, leading to the release of DAMPs from necrotic and injured cells. DAMPs activate immune cells and complement pathways through the engagement of pattern recognition receptors, initiating the release of cytokines involved in systemic inflammation [62]. HMGB1, a critical DAMP, is markedly elevated in the bloodstream following trauma and is correlated with injury severity, the onset of sepsis, and the development of MODS [63, 64]. Furthermore, HMGB1 exerts a direct influence on the vascular endothelium by facilitating neutrophil adhesion, enhancing endothelial permeability, and enhancing the production of adhesion molecules and cytokines [64].

Following trauma, the concentrations of pro-inflammatory cytokines and chemokines, including IL-1B, IL-6, IL-8, granulocyte-colony stimulating factor, and TNF-α, rise rapidly and remain elevated over hours and days [65]. Concurrently, the levels of various anti-inflammatory mediators, such as TGF-β1 and IL-10, also increase in circulation [66]. Patients with MODS show elevated levels of both pro-inflammatory and anti-inflammatory cytokines upon admission, in contrast to patients without MODS [66]. Furthermore, traumatic injury can alter neutrophil function and phenotype, alongside variations in lymphocyte counts, potentially increasing the risk of infections in trauma patients [67, 68]. Severely injured individuals often exhibit low levels of CD62L and high levels of CD11b on their cell surfaces, indicating neutrophil activation [67]. Furthermore, lymphocyte counts increases during the hyperacute phase (less than 2 hours) following injury, but significant lymphocytopenia can occur as early as 4 hours post-injury [68].

Anesthetic drug

Anesthetic agents have been shown to modulate innate immune responses by diminishing the cytotoxic activity of natural killer (NK) cells [69]. The underlying mechanism is likely multifactorial, with substantial evidence indicating the involvement of interferons [70]. Combined in vivo and in vitro studies in mice have demonstrated that anesthetic exposure inhibits interferon's ability to enhance NK cell toxicity, and this inhibitory effect can persist for several days post-anesthesia [70]. Clinical investigations further support these findings, showing a reduction in basal NK cell activity within the peripheral blood mononuclear cells of patients subjected to general anesthesia [71]. However, this diminished NK cell activity can be restored by interferon treatment [71]. Recent research indicates that sevoflurane and isoflurane cause a dose-dependent decrease in NK cell cytotoxicity, likely through inhibition of lymphocyte function-associated antigen 1, an adhesion molecule essential for NK cell functionality [72]. These findings may hold significant implications for oncological surgeries, considering the critical role of NK cells in cancer immune surveillance and immunoediting [73].

Anesthetic agents such as isoflurane and sevoflurane are known to suppress T lymphocyte function [74-76]. These anesthetics exert their inhibitory effects on T lymphocytes by impeding the transcription factor activating protein 1 and its downstream target gene IL-3 [74]. Additionally, isoflurane and sevoflurane induce apoptosis in T lymphocytes in a dose-dependent manner, and also influence production of B lymphocytes and cytokines [75]. Specifically, isoflurane and sevoflurane inhibit the secretion of pro-inflammatory cytokines, including IL-1β and TNF-α, from human peripheral monocytes in response to tumor cells, which may potentially facilitate tumorigenesis [76].

Hypoxia

Hypoxia is a crucial physiological phenomenon within the intestine, exerting significant effects on both physiological and pathological states of the body [77]. Within intestinal tissue, a pronounced vertical oxygen gradient is established between the submucosa, which is abundant in blood vessels, and the nearly anoxic intestinal lumen [78]. In the colonic region, the partial pressure of oxygen progressively declines from approximately 145 mmHg (around 21% O_2) to markedly low levels within the intestinal lumen [79]. A similar gradient exists in the small intestine, albeit with differing specific values [79].

The adaptation of intestinal cells to hypoxic conditions is primarily governed by hypoxia-inducible factors [80]. Under hypoxic conditions, hypoxia-inducible factors become stabilized and facilitates the expression of a series of genes that enable cellular adaptation to low-oxygen environments. These genes predominantly include erythropoietin (regulating erythropoiesis), vascular endothelial growth factor (promoting angiogenesis), and glycolytic enzymes (modulating cellular metabolism) [81, 82]. Furthermore, research has demonstrated that acute hypoxia, such as that induced by surgical procedures, can compromise the integrity of the intestinal barrier [83]. Brief exposure to hypoxia leads to elevated secretion of IgA

and pro-inflammatory cytokines, alongside enhanced expression of pro-inflammatory markers like Toll-like receptor 4 and inducible nitric oxide synthase (iNOS) [83]. Prolonged hypoxia leads to a marked increase in the populations of IL-17-producing cells, NK cells, and dendritic cells within the gut, while significantly reducing the number of naive T cells in Peyer's patches [83]. These findings underscore the complex influence of hypoxia on intestinal immune function.

Ischemia reperfusion

Ischemia-reperfusion (I/R) injury is a common pathological condition that triggers a systemic inflammatory response, resulting in damage to multiple organs and potential functional failure. Research has demonstrated that miR-185-5p is upregulated in I/R conditions, exacerbating intestinal barrier damage by inhibiting the autophagy pathway [84]; ATG101 has been identified as a target gene of miR-185-5p, and its overexpression can enhance autophagy, thereby mitigating the intestinal barrier damage induced by I/R [84]. Intestinal I/R injury can induce stress and damage to IECs, potentially leading to their death and mitochondrial dysfunction. This dysfunction results in elevated levels of mitochondrial DNA (mtDNA), with plasma mtDNA serving as a predictor for SIRS risk following trauma [84, 85]. The release of mtDNA due to intestinal I/R injury can activate resident immune cells, thereby enhancing the production of inflammatory cytokines within the gut [84]. Zhang et al. have demonstrated that mtDNA can cause neutrophil-mediated organ damage, which is associated with increased secretion of TNF-α and IL-6 [85]. Numerous studies have indicated that the Toll-like receptor 9-MyD88 signaling pathway plays a role in intestinal I/R injury [86]. For instance, Victoni et al. demonstrated that the absence of MyD88 resulted in reduced intestinal inflammation and injury, which is linked to diminished neutrophil recruitment and decreased production of pro-inflammatory cytokines [86]. Furthermore, prior study has shown that the administration of oxidized mtDNA via tail vein injection enhance the levels of inflammatory mediators and chemokines [87].

Perioperative complications and intestinal immunologic barrier

Infection

Dysfunction of the intestinal immunologic barrier constitutes a significant contributor to postoperative infections [59]. Surgical site infections, in particular, represent the predominant cause of hospital readmissions, thereby escalating healthcare expenditures [5].

Despite efforts to target environmental and skin-derived microorganisms, approximately 10% of patients still experience postoperative infections [88]. A clinical analysis of 3,515 patients who developed infections after general surgical procedures revealed that the primary pathogens were common intestinal microorganisms, such as *Escherichia coli*, and *Clostridium sp.*, suggesting that these pathogens may have breached the intestinal barrier and entered the systemic circulation [88]. Furthermore, numerous studies have demonstrated that perioperative probiotic therapy for patients undergoing colorectal cancer surgery can improve intestinal microecology and enhance immune responses, resulting in a significant reduction in superficial incisional infection rates postoperatively [89-92].

Anastomotic leakage

Infection and other factors contribute to impaired anastomotic healing and the formation of fistulas. Anastomotic leakage represents one of the most potentially severe complications that can arise during the reconstruction of the digestive tract following major surgical procedures, posing a significant challenge for surgeons [5]. A critical aspect of normal wound healing is the development of granulation tissue, which includes fibroblasts, collagen, and blood vessels, signaling a healing response [93]. Postoperative bacterial infection at the anastomotic site can exacerbate inflammation and hinder this healing process [5].

Dysbiosis of the intestinal microbiota has been recognized as contributor to anastomotic leakage [94]. Several clinical studies have shown that perioperative oral antibiotic therapy (or local decontamination) in patients undergoing gastrointestinal surgery can significantly reduce the incidence of anastomotic leakage [95-98]. Some intestinal bacteria are known to produce collagenases that degrade collagen in the intestinal wall and stimulate intestinal epithelial cells to secrete matrix metalloproteinases 9, exacerbating tissue damage and local inflammation. This mechanism may explain how intestinal pathogens promote anastomotic leakage. The microbial composition in biological samples (such as feces, mucosa, the resected specimen, or drain fluid) from patients with and without anastomotic leakage after colorectal surgery were compared, and the findings indicated that collagenase-producing bacteria are more

common in patients with anastomotic leakage, such as *Fusobacterium nucleatum* [99-100]. Serial animal experiments have also confirmed that local colonization with collagenase-producing bacteria (such as *Enterococcus faecalis* and *Pseudomonas aeruginosa*) can increase the incidence of postoperative anastomotic leakage, while administration of plasminogen inhibitors to mice postoperatively can effectively alleviate collagen degradation and colonic perforation [101-102].

SIRS

The translocation of bacteria and endotoxins resulting from compromised intestinal barrier integrity can trigger systemic inflammatory responses. Infections, characterized by the invasion of pathogens such as bacteria, viruses, and fungi, represent a primary cause of SIRS [5]. These pathogens activate the host's immune system, eliciting an inflammatory response [2]. Aberrant secretion of inflammatory mediators can weaken the tight junctions between intestinal epithelial cells, increasing intestinal permeability and facilitating the translocation of intestinal bacteria and endotoxins into the systemic circulation [33]. This impairment of the intestinal immunologic barrier exacerbates the systemic inflammatory response, creating a deleterious cycle. Once bacteria and endotoxins enter the systemic circulation, they elicit an amplified immune response and inflammatory cascade, potentially resulting in tissue and organ damage. Furthermore, impairment of the intestinal immunologic barrier may initiate inflammation and contribute to the development of autoimmune diseases within the gastrointestinal tract.

In a study comprising 85 patients diagnosed with SIRS, a positive correlation was identified between gut bacterial load and blood levels of IL-6 [103]. This observation suggests that compromised intestinal barrier integrity may facilitate bacterial translocation into the bloodstream, thereby initiating systemic inflammatory responses. Additionally, elevated levels of intestinal fatty acid-binding protein were significantly associated with hypotension, increased respiratory rate, hyperglycemia, and elevated Sequential Organ Failure Assessment scores. These findings further substantiate the direct relationship between intestinal epithelial damage and the severity of SIRS.

Conversely, pediatric multi-system inflammatory syndrome, characterized by systemic inflammation and multiple-organ involvement, may be linked to disruptions in the IL-6 signaling pathway induced by the SARS-CoV-2 virus [104]. Recent research has identified an intrinsic connection between intestinal barrier integrity and IL-6 levels, suggesting that the bacteriophage-like properties of SARS-CoV-2 might enhance interactions between the virus and gut microbiota [104]. This interaction could lead to increased translocation of viral components and bacterial toxins, thereby exacerbating systemic inflammation [104].

Gastrointestinal motility disorder

Gastrointestinal dyskinesia is a common consequence of significant gastrointestinal remodeling, encompassing conditions ranging from malabsorption (linked to increased gastrointestinal motility) to postoperative intestinal obstruction (POI) [105]. Intestinal immune cells are crucial in regulating gastrointestinal physiology, particularly in terms of motility. POI refers to the temporary cessation of coordinated gastrointestinal motility following abdominal surgery, which adversely affects quality of life, extends hospital stays, and escalates socioeconomic costs [105].

Alterations in the gut microbiota following gastrointestinal surgery largely contribute to changes in gastrointestinal motility [106]. In the POI model, notable alterations in the microbial community were observed, including a reduction in the abundance of *Lactobacillus* (including both *Bifidobacterium* and *Lactobacillus*) and an increase in *Bacteroides* and *Blautia* [107]. Another clinical study showed that patients with colorectal cancer who have a lower abundance of Faecalibacterium are at a higher risk of developing postoperative intestinal obstruction [108]. A meta-analysis involving 1,773 subjects confirmed that perioperative supplementation with probiotics or synbiotics can effectively promote gastrointestinal function recovery after gastrointestinal cancer surgery [109]. These microbial shifts were also associated with decreased fecal butyrate levels [107]. Butyrate, a crucial short-chain fatty acids (SCFAs), serves as the primary energy source for intestinal epithelial cells and is critical for enhancing intestinal barrier function [107].

Additionally, butyrate plays a central role in immune regulation, notably by promoting the differentiation of colonic regulatory T cells to help suppress inflammatory responses [107]. Further research by Parada Venegas et al. demonstrated a significant reduction in butyrate-producing bacteria, which is closely linked to a decrease in fecal SCFAs [110]. While the precise mechanism linking reduced SCFAs to

heightened immune activation and increased permeability is yet to be fully elucidated, probiotic treatment has demonstrated efficacy in restoring SCFAs levels, particularly in malnourished individuals. Probiotics also enhance the expression of G-protein-coupled receptors, including GPR41, GPR43, and GPR109A, on macrophages [110]. The interaction of SCFAs with these receptors facilitates the repair of epithelial barrier function and the activation of anti-inflammatory signaling pathways.

Improving gut barrier may reduce postoperative complications

Liver transplantation is the only effective treatment for end-stage liver diseases, yet postoperative infections significantly reduce the surgery's success rate. Gut barrier dysfunction is a primary cause of early postoperative infectious complications following liver transplantation. Bacterial translocation disrupts the intestinal barrier, enabling pathogens to enter the bloodstream and trigger infections [111]. Clinical trials have shown that the combination therapy of probiotics/prebiotics can significantly reduce the incidence of postoperative bacterial infections, thus leading to shorter hospital stay or antibiotic therapy [112]. For postoperative colorectal cancer patients, probiotics had been proven to effectively reduce infectious complications by improving the integrity of the gut mucosal barrier [113]. In the case of anastomotic leak, animal experiments have demonstrated that exogenous butyrate administration enhanced the healing and strength of colonic anastomoses in rats [114]. Furthermore, supplementation with probiotics or synbiotics during the peri-operative period may improve gastrointestinal motility recovery following gastrointestinal surgery. A recent meta-analysis by Tang et al. indicated that peri-operative probiotics or synbiotics supplementation effectively shortened the time to first flatus and first defecation, while also reducing POI [115].

Conclusion

This review provides a comprehensive summary of the role of intestinal barrier dysfunction in perioperative complications, emphasizing the significant impact of immunologic barrier damage on postoperative outcomes. A close interaction exists between the intestinal immunologic barrier and the intestinal microbiome, wherein intestinal epithelial cells and immune cells detect microorganisms via pathogen recognition receptors. Concurrently, microbial metabolites, such as short-chain fatty acids, exert regulatory effects on intestinal immune cells. Under healthy conditions, a homeostatic balance is maintained between microbial populations and immune cells. Disruption of this equilibrium triggers an immune response. The intestinal epithelium serves as the primary defense mechanism, forming a barrier through the tight junctions and secretory cells, including goblet cells and Paneth cells. Concurrently, pro-inflammatory cytokines, such as TNF-α, IL-13, and IL-6, play key roles in modulating intestinal tight junctions and maintaining barrier integrity.

Preoperative factors, including malnutrition, stress response, intestinal readiness, and immunosuppressive status, alongside operative factors such as surgical trauma, anesthetic agents, hypoxia, and ischemia-reperfusion, can undermine the integrity of the intestinal immunologic barrier. This, in turn, increases the risk of postoperative complications, such as infection, anastomotic leakage, systemic inflammatory response syndrome, and gastrointestinal motility disorders.

The innovation of this review lies in its comprehensive analysis of the specific mechanisms through which the intestinal immunologic barrier contributes to perioperative complications. It highlights the necessity for further investigation into the interaction between the intestinal microbiota and the immunologic barrier to enhance perioperative management strategies.

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