

Endoscopy in neutropenic and/or thrombocytopenic patients

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Abstract

AIM: To evaluate the safety of endoscopic procedures in neutropenic and/or thrombocytopenic cancer patients.

METHODS: We performed a literature search for English language studies in which patients with neutropenia and/or thrombocytopenia underwent endoscopy. Studies were included if endoscopic procedures were used as part of the evaluation of neutropenic and/or thrombocytopenic patients, yielding 13 studies. Two studies in which endoscopy was not a primary evaluation tool were excluded. Eleven relevant studies were identified by two independent reviewers on PubMed, Scopus, and Ovid databases.

RESULTS: Most of the studies had high diagnostic yield with relatively low complication rates. Therapeutic endoscopic interventions were performed in more than half the studies, including high-risk procedures, such as sclerotherapy. Platelet transfusion was given if counts were less than 50000/mm³ in four studies and less than 10000/mm³ in one study. Other thrombocytopenic precautions included withholding of biopsy if platelet count was less than 30000/mm³ in one study and less than 20000/mm³ in another study. Two of the ten studies which examined thrombocytopenic patient populations reported bleeding complications related to endoscopy, none of which caused major morbidity or mortality. All febrile neutropenic patients received prophylactic broad-spectrum antibiotics in the studies reviewed. Regarding afebrile neutropenic patients, prophylactic antibiotics were given if absolute neutrophil count was less than 1000/mm³ in one study, if the patient was undergoing colonoscopy and had a high inflammatory condition without clear definition of significance in another study, and if the patient was in an aplastic phase in a third study. Endoscopy was also withheld in one study for severe pancytopenia.

CONCLUSION: Endoscopy can be safely performed in patients with thrombocytopenia/neutropenia. Prophylactic platelet transfusion and/or antibiotic administration prior to endoscopy may be considered in some cases and should be individualized.

Key words: Endoscopy; Neutropenia; Cancer; Bone marrow transplant; Bleeding; Hemorrhage; Infection; Fever; Complication; Thrombocytopenia

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Core tip: Gastroenterologists are often requested to perform endoscopic evaluation in neutropenic and thrombocytopenic patients. Endoscopists may be hesitant to perform these procedures in these situations, due to the fear of possible complications, such as bleeding and infection. In this systematic review, we provide gastroenterologists with the available safety data, preventive measures prior to the procedures, and the diagnostic yield of the procedures in this patient population.

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INTRODUCTION

There are multiple causes for thrombocytopenia and neutropenia, especially in malignant conditions. Both are most commonly seen following chemotherapy for cancer patients or immunosuppression for bone marrow transplant recipients. Additional etiologies include aplastic anemia and hypersplenism. This review will focus on cancer patients with thrombocytopenia as opposed to more acute scenarios, such as idiopathic thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura (TTP). Thrombocytopenia increases the risk of bleeding, in particular from the gastrointestinal (GI) tract, while neutropenia carries the risk of infection with high morbidity and mortality.

Gastroenterologists may be consulted during the course of thrombocytopenia and/or neutropenia for evaluation of GI symptoms. Symptoms, such as GI bleeding, dysphagia, odynophagia, nausea, vomiting, abdominal pain, and alteration of bowel habits, may require evaluation by endoscopy. Clinical suspicion for graft-vs-host disease (GVHD) or an underlying fungal infection may also require endoscopic evaluation. In such clinical situations, one may be hesitant to perform endoscopy.

We performed a systematic review of the literature to help assess the safety of performing endoscopic procedures in thrombocytopenic and/or neutropenic patients. Currently there is very limited data available, but our goal is to increase awareness of this important topic and help further develop evidence-based guidelines.

Current guidelines for endoscopy and thrombocytopenia

The American Society for Gastrointestinal Endoscopy (ASGE) acknowledged that the minimal platelet threshold for endoscopy has not been established^[1]. In 2012, based on limited data^[2-4], ASGE guidelines concluded that a platelet level of 20000/mm³ or greater can be used as a threshold for performing diagnostic upper endoscopies, but a threshold of 50000/mm³ may be considered before performing biopsies^[1]. The ASGE also provided the guidelines shown below, stratifying procedures into high and low risk for bleeding^[5]: (1) Low risk procedures: diagnostic [esophagogastroduodenoscopy (EGD), colonoscopy, flexible sigmoidoscopy], including biopsy, endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy, endoscopic ultrasound (EUS) without fine needle aspiration (FNA), capsule endoscopy, enteroscopy and diagnostic balloon-assisted enteroscopy, and enteral stent deployment without dilation; and (2) High risk procedures: polypectomy, biliary or pancreatic sphincterotomy, pneumatic or bougie dilation, percutaneous endoscopic gastrostomy (PEG) placement, therapeutic balloon-assisted enteroscopy, EUS with FNA, treatment of varices, endoscopic hemostasis, tumor ablation by any technique, and cystogastrostomy.

In a systematic review in 2012, the threshold for platelet transfusion in patients with non-variceal upper GI bleeding was evaluated by analyzing 10 studies, including four randomized controlled trials and six cohort studies^[6]. Due to the paucity of high level evidence, the proper threshold of platelet transfusion specifically in GI bleeding was based on expert opinion, and transfusion of platelets to 50000/mm³ was proposed for GI bleeding^[6].

The current general recommendation for platelet transfusion is for a goal of 50000/mm³ prior to any intervention^[7,8]. British guidelines recommend ensuring the availability of platelet support before endoscopic intervention when the platelet count is below 50000-80000/mm³, with no clear established guideline for prophylactic platelet transfusion in thrombocytopenic patients who undergo endoscopy^[9].

Current guidelines for endoscopy and neutropenia

According to the ASGE, there is insufficient evidence to recommend for or against administration of prophylactic antibiotics prior to routine endoscopic procedures in patients with severe neutropenia (absolute neutrophil count or ANC < 500 cells/mL) and that the decision to use antibiotics in these scenarios should be individualized^[10].

The Infectious Diseases Society of America^[11] does not provide any recommendations regarding endoscopy in neutropenic patients. The American Heart Association does not provide guidance regarding

Table 1 Comparison of United States and British guidelines for endoscopy in thrombocytopenic and neutropenic patients

	US guidelines	British guidelines
Thrombocytopenia and endoscopy	ASGE: Acknowledge limited data. Platelet threshold 20000/mm ³ for diagnostic endoscopy; 50000/mm ³ if biopsies performed	BSG: Ensure platelet support is available before endoscopic intervention when platelet count is < 50000-80000/mm ³
Neutropenia and endoscopy	ASGE: Recommend considering antibiotic in immunosuppressed patients undergoing a high-risk procedure	BSG: Recommend antibiotic prophylaxis for ANC < 500/mm ³ and undergoing a high risk procedure (based on risk of bacteremia in immunocompetent patients)

ASGE: American Society for Gastrointestinal Endoscopy; BSG: British Society of Gastroenterology.

prevention of endocarditis in neutropenic patients undergoing endoscopy either^[12].

On the other hand, both the British and European guidelines recommend antibiotics prior to endoscopy if the ANC is less than 500/mm³ and the patient is undergoing a high-risk procedure, such as ERCP with obstructed system, endoscopic dilatation, and sclerotherapy^[9,13,14].

Studies with relevant information are outdated. The studies evaluating the incidence of bacteremia in patients with bone marrow transplant revealed contradictory results^[15,16], with one study reporting clinically relevant bacteremia occurring in 19% of the 47 patients requiring EGD^[15], while the other found no episodes of clinically relevant bacteremia after 67 upper and lower endoscopies in 53 patients^[16].

The British Society of Gastroenterology (BSG) reviewed the risk of bacteremia associated with specific endoscopic procedures in immunocompetent patients. The procedures were categorized as low risk (< 10% risk) and high risk (\geq 10%). Low risk procedures included EUS with FNA, colonoscopy, diagnostic EGD with or without biopsy, rectal digital exam, rigid proctosigmoidoscopy, ERCP without duct occlusion, and variceal band ligation. High risk procedures included sclerotherapy, ERCP with occluded duct, esophageal laser therapy, and esophageal dilation/prosthesis^[14].

Comparisons of United States and British guidelines for endoscopy in neutropenic and thrombocytopenic patients are shown in Table 1.

MATERIALS AND METHODS

To evaluate the safety of the endoscopic procedures in cancer patients with thrombocytopenia and/or neutropenia, two independent reviewers performed an extensive search of the English literature in PubMed, Scopus, and Ovid databases from January 1980 to February 2014 using a combination of keywords, such as "endoscopy", "gastrointestinal", "neutropenia", "thrombocytopenia", "aplastic anemia", and "cancer". Potential studies were identified using the inclusion criteria of evaluation of endoscopic procedure in thrombocytopenic and/or neutropenic patient populations. The search was also limited to human studies. After this initial search, selected articles were screened, and those that were not primarily targeted

at endoscopy or did not use endoscopy as part of patient evaluation were excluded. Once a study of interest was identified, the full text was retrieved and further evaluated, and the references were searched for any additional relevant studies. A net total of 11 studies were identified that discuss endoscopy as the primary target or as a part of the evaluation for GI symptoms in thrombocytopenic and/or neutropenic patients (Figure 1).

The following data were retrieved: type of endoscopic procedures, adverse events, preventive measures when taken, diagnostic yield, and adverse events related to the endoscopic procedures.

The patient populations differed in the included studies. Four studies were done in stem cell transplant patients, two in bone marrow transplant patients, and one in aplastic anemia patients (Figure 2). Also, four studies were performed in the pediatric population while the other seven were performed in adults.

Due to the limited number of relevant studies, both retrospective (8 studies) and prospective (3 studies) studies were included. For the same reason, we did not exclude studies based on study design or number of patients evaluated (Figure 3).

RESULTS

Study design

Please refer to Table 2 for a summary of study design and patient and endoscopic characteristics of the included studies.

Of the 11 studies identified, four studies focused on cancer patients, four on post-stem cell transplant patients, two on patients undergoing bone marrow transplant, and one on patients with aplastic anemia (Figure 2). One of the studies on cancer patients focused exclusively on thrombocytopenic patients^[17].

Seven of the studies investigated adults, while the other four investigated the pediatric population. Most studies were conducted between 1985 and 2007, with the exception of one that was conducted in the 1970s. Eight studies were retrospective chart reviews, and three were prospective cohort studies. Overt GI bleed was investigated in five studies, while subjects in the remainder of the studies had general GI complaints as the indication for endoscopic procedures. Not all studies looked purely at thrombocytopenic and/or

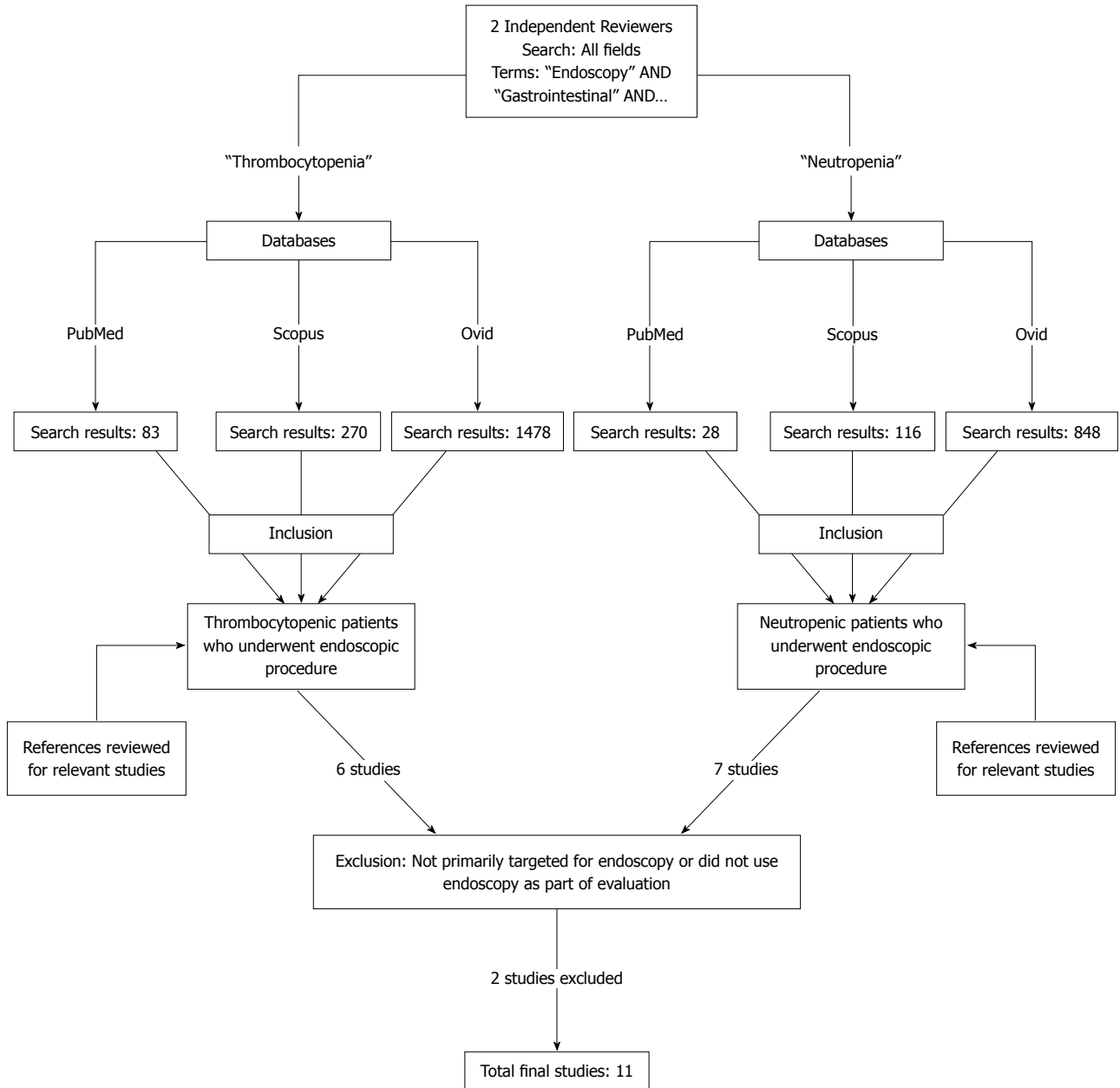


Figure 1 Method of literature search on PubMed, Scopus, and Ovid databases.

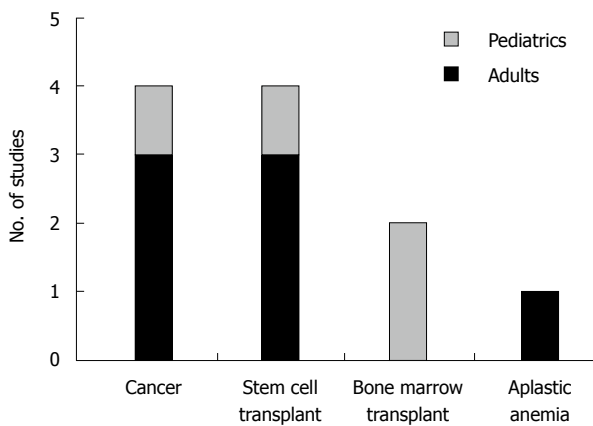


Figure 2 Nature of patients studied and etiologies of neutropenia or thrombocytopenia.

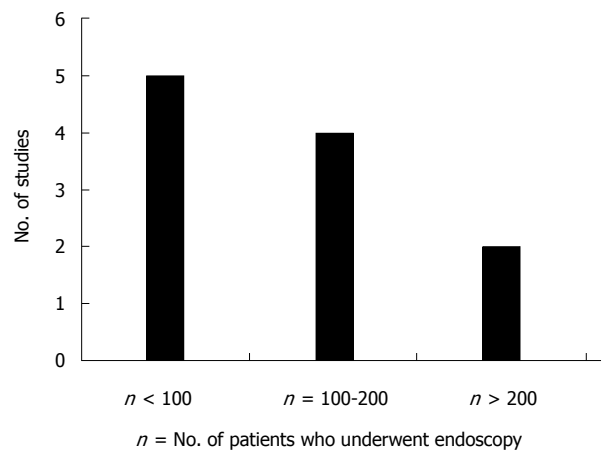


Figure 3 Size of study.

Table 2 Study design and characteristics of patients and endoscopies

Study	Design	Patient and endoscopic characteristics
Buderus <i>et al</i> ^[19] (2012)	Retrospective 1995-2004	38 pediatric cancer patients with various GI complaints 40 diagnostic endoscopies, 7 follow-up endoscopies, 10 therapeutic endoscopies Diagnostic yield 82.5%: Gastritis, esophagitis, duodenitis, colitis, Mallory-Weiss tears, ulcer
Chu <i>et al</i> ^[17] (1983)	Retrospective 1978-1979	133 cancer patients with thrombocytopenia and overt GI bleed 187 diagnostic endoscopies, no therapeutic endoscopies Diagnostic yield 92% for upper, 60% for lower exam: Unifocal and multifocal lesions in majority; rare diffuse bleeding
Gorschlüter <i>et al</i> ^[20] (2008)	Retrospective 1993-2005	104 acute leukemia patients after myelosuppressive chemotherapy 131 primary endoscopies, 40 follow-up endoscopies; includes 16 therapeutic interventions and 5 ERCPs (2 for jaundice, 2 for suspicion of cholecystitis, 1 for suspicion of cholangitis) Diagnostic yield 91% for upper, 70% for lower exam: esophagitis, gastric erosions, hiatal hernia, gastritis
Kaur <i>et al</i> ^[22] (1996)	Retrospective 1986-1993	43 post-bone marrow transplant patients with overt GI bleed 31 endoscopies total: 26 EGD, 5 colonoscopy; 2 endoscopies required hemostasis Diagnostic yield 100% for upper, 80% for lower exam: Diffuse esophagitis, gastritis, or duodenitis in upper exam; 2 ulcers, 1 colitis, 1 tumor recurrence in lower exam
Kaur <i>et al</i> ^[23] (2013)	Retrospective 2007-2010	11 pediatric patient requiring PEG placement in anticipation of BMT (BMT group) compared with 30 patients requiring PEG placement for other indications (comparison group)
Khan <i>et al</i> ^[24] (2006)	Retrospective 1995-2002	191 pediatric patients who underwent hematopoietic stem cell transplantation 198 EGDs, 220 lower endoscopies. All diagnostic endoscopies for GI complaints, mostly for nausea, vomiting, and non-bloody diarrhea. Diagnostic yield 32% for upper, 16% for lower exam: Mucosal abnormalities most common Acute GVHD in 14% on histological exam Non-GVHD histological evidence of inflammation in 24%
Park <i>et al</i> ^[21] (2010)	Retrospective 2002-2007	32 patients with aplastic anemia and overt GI bleed, each evaluated by endoscopy, 3 of which required therapeutic intervention Diagnostic yield 66%: bleeding sites in esophagus, stomach, duodenum, small intestine, large intestine
Ross <i>et al</i> ^[25] (2008)	Retrospective 2002-2006	112 patients with simultaneous upper and lower endoscopic procedures following hematopoietic stem cell transplant. All diagnostic endoscopies for GI symptoms Diagnostic yield: GVHD diagnosed in 81% of patients
Schulenburg <i>et al</i> ^[26] (2004)	Prospective cohort 1996-2001	42 post-allogeneic stem cell transplant patients admitted for GI complaints 22 upper, 12 lower, and 13 upper and lower endoscopies performed, unclear distinction between primary and follow-up endoscopies Diagnostic yield 100%: Majority GVHD, gastritis, CMV, bacterial enteritis
Schwartz <i>et al</i> ^[18] (2001)	Prospective cohort 1985-1987 and 1996-1997	1102 patients with hematopoietic cell transplantation followed prospectively, of whom 75 developed severe GI bleed. Endoscopic evaluation included diagnostic and therapeutic procedures, however, number of procedures was unclear Diagnostic yield: Majority had multiple sites of bleed, caused by GVHD and peptic acid esophageal ulcers
Soylu <i>et al</i> ^[27] (2005)	Prospective cohort 1999-2005	451 patients with hematological malignancies, of which 32 developed overt GIB 25 upper GI bleeding episodes, of which 8 EGDs were performed, remainder managed by supportive care. The other 7 patients had lower GI bleed episodes caused by neutropenic enterocolitis excluding the need for endoscopic procedures. Diagnostic yield 100% (8 endoscopies): Erosive gastritis (5/8), duodenal ulcers (3/8) in upper GI bleed

GI: Gastrointestinal; ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophagogastroduodenoscopy; PEG: Percutaneous endoscopic gastrostomy; GVHD: Graft-*vs*-host disease.

neutropenic patients.

Please refer to Figures 2 and 3 for study characteristics.

Endoscopic therapeutic interventions

Of the 11 studies, six described therapeutic interventions^[18-23] (Table 3). Endoscopic hemostasis was discussed in six studies, which included sclerotherapy for varices, epinephrine and/or fibrin glue injections, electrocautery with or without injection, clip placement, and argon plasma coagulation (APC)^[18-22,24]. All were successful with the exception of one study,

which had a very small sample size^[18].

Two studies described successful placement of duodenal and naso-jejunal feeding tubes^[19,20]. One study described five patients who underwent ERCP with and without sphincterotomy, three of which had true pathology in the biliary tree while the remaining two patients had no abnormality detected^[20]. Successful PEG tube placements were described in two studies; however, both studies reported infectious adverse events in neutropenic patients (see "Infectious Adverse Events" below)^[19,23].

Table 3 Thrombocytopenic precautions, therapeutic interventions, and bleeding adverse events

Study	Thrombocytopenic precautions <i>n</i> = No. thrombocytopenic patients	Therapeutic intervention	Bleeding Adverse events
Buderus <i>et al</i> ^[19]	Platelets < 30000/mm ³ : Biopsies not taken <i>n</i> = 12 (Platelets < 50000/mm ³ ; 3 of 12 had platelets < 30000/mm ³)	4 PEG tube placements 1 PEG tube removal 2 sclerotherapies for varices 6 NJ tubes placement	None
Chu <i>et al</i> ^[17]	Platelets < 20000/mm ³ : Biopsies not performed Platelet transfusion not a prerequisite, but made available <i>n</i> = 44 (Platelets < 40000/mm ³ ; 25 of 44 had platelets < 20000/mm ³)	None	None
Gorschlüter <i>et al</i> ^[20]	Platelets < 10000/mm ³ : Prophylactic platelet transfusion <i>n</i> = unknown Median platelets 23000/mm ³	8 endoscopic hemostasis in upper exam, including: 5 used fibrin glue 2 used fibrin glue plus epinephrine 1 used epinephrine alone ERCP in 5 patients	2 of 106 (1.9%) primary upper EGD had proven adverse events: hemorrhage induced by EGD (one stopped bleeding spontaneously and the other one required injection)
Kaur <i>et al</i> ^[22]	Platelets < 50000/mm ³ : Prophylactic platelet transfusion No target platelet count sought For all patients: Prophylaxis with H ₂ blockers or sucralfate or both Hematopoietic cell progenitor support <i>n</i> = 27 (Platelets < 50000/mm ³)	Duodenal tube placement in 8 patients 2 patients underwent successful electrocautery for bleeding ulcers	No ERCP-related adverse events 10 of the 31 patients in which endoscopies were performed had recurrent bleed at median of 7 d after index bleed (range 2-27 d), none readmitted No adverse events as a result of endoscopy
Kaur <i>et al</i> ^[23]	None <i>n</i> = unknown	11 PEG tube placements	None reported
Khan <i>et al</i> ^[24]	For platelets < 50000/mm ³ : Platelets transfused during procedure <i>n</i> = 111 (Platelets < 50000/mm ³)	None	GI bleeding adverse events occurred in 12 procedures out of 418 total procedures (2.9%). Thrombocytopenia was significantly associated (<i>P</i> < 0.01) with bleeding, occurring in 10 of the 12 procedures with bleeding adverse events 8 cases of bleeding events following EGD, of which there were: 4 cases of duodenal hematomas that resolved with conservative management 1 case requiring repeat endoscopy with electrocautery 3 cases of acute GVHD managed conservatively 4 cases of bleeding events following lower endoscopy [†] All due to acute GVHD Appear to have been managed conservatively
Park <i>et al</i> ^[21]	For platelets < 5000/mm ³ or unstable (fever, hemorrhagic signs) patients with a platelet < 10000/mm ³ : Prophylactic platelet transfusion <i>n</i> = unknown	3 patients successfully treated with argon plasma coagulation for gastric angiodysplasia, hemoclips on colon ulcer, hemoclips on duodenal Dieulafoy's lesion	1 death from massive GI bleed Re-bleed of Dieulafoy lesion, successfully treated by re-clipping No adverse events attributable to endoscopy
Ross <i>et al</i> ^[25]	For platelets < 25-50000/mm ³ : Prophylactic platelet transfusion at discretion of endoscopist 44 patients received prophylactic platelet transfusion <i>n</i> = at least 44 (Platelets < 25000-50000)	None	None reported
Schulenburg <i>et al</i> ^[26]	For platelets < 50000/mm ³ : Prophylactic platelet transfusion Platelet support to maintain count > 20000/mm ³ <i>n</i> = unknown	None	None
Schwartz <i>et al</i> ^[18]	For platelets < 50000/mm ³ : No endoscopy if 50000/mm ³ not reached <i>n</i> = unknown	2 attempted endoscopic hemostasis 1 injection successful 1 bipolar cautery plus injection that was unsuccessful and required surgery	No adverse events attributable to endoscopy reported

Soylu <i>et al</i> ^[27]	For platelets < 20000/mm ³ : Prophylactic platelet transfusion Active bleeding with higher platelet count also received prophylactic transfusion Severe thrombocytopenia (level not defined): EGD withheld in 17 of 25 upper GI bleeding episodes Colonoscopy withheld in 7 lower GI bleeding episodes <i>n</i> = unknown	None	No deaths or adverse events attributable to endoscopy
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GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; PEG: Percutaneous endoscopic gastrostomy; GVHD: Graft-*vs*-host disease.

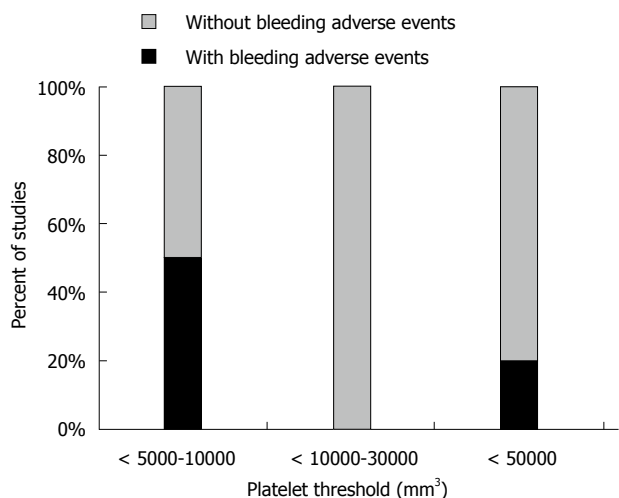


Figure 4 Proportional distribution of studies with and without bleeding adverse events for platelet threshold level used for taking precautions (*i.e.*, withhold biopsy, transfuse platelets).

Thrombocytopenic patient populations

Ten of the 11 studies investigated thrombocytopenic patient populations and commented on precautions used. In five studies, transfusions were given if the platelet count was less than 50000/mm³^[18,22,24-26]. In patients with an overt GI bleed, different approaches were undertaken, including platelet transfusion if the count was < 10000^[21], < 20000^[27], or < 50000/mm³^[22], avoiding endoscopy if the platelet count of 50000/mm³ was not achieved^[18], or making the platelets available as needed without requiring transfusion as a prerequisite indication prior to endoscopic procedures^[17].

In the study by Buderus *et al*^[19], prophylactic transfusions were not given but no biopsies were taken if the platelet count was < 30000/mm³. In the study by Gorschlüter *et al*^[20], prophylactic platelets were given if the platelet count was < 10000/mm³.

Three studies discussed thrombocytopenic precautions for biopsies^[17,19,24]. These precautions included withholding biopsies if the count was less than 20000/mm³^[17], withholding biopsies if the count was less than 30000/mm³^[19], or avoiding duodenal biopsies if the risk of bleeding was estimated to be high,

although a specific platelet count was not mentioned and four cases of duodenal hematoma (one associated with pancreatitis) were reported in that study^[24] (Table 3).

Bleeding adverse events

Out of the four studies with records of bleeding adverse events, two studies reported bleeding adverse events related to endoscopy^[20,24]. The total number of bleeding adverse events was very small, ranging from 2/106 to 12/418 (1.9%-2.9%) endoscopic procedures, and most of them were managed conservatively with the exception of three patients who needed repeat endoscopy. One of these three patients stopped bleeding spontaneously^[20], another required injection^[20], and the last one required electrocautery^[24]. Four additional patients developed duodenal hematomas, which were managed conservatively^[24]. None of the above adverse events caused major morbidities.

Bleeding adverse events were found to be relatively low among thrombocytopenic patients. Figure 4 summarizes the proportion of studies with and without bleeding adverse events for each given platelet cutoff.

Neutropenic patient populations

Neutropenia was generally defined as an absolute neutrophilic count of less than 500 cells/mm³, although two studies defined it as ANC < 1000/mm³^[17,22] while another study used a cut off of 1500/mm³^[23]. Eight studies involved neutropenic patients undergoing endoscopy^[17-23] (Table 4). Broad-spectrum antibiotics were given to all patients with neutropenia and fever. Precautions for afebrile neutropenic patients varied among the studies. One study gave all patients antibiotics during the aplastic phase^[26]. In a second study, endoscopy was not performed if pancytopenia was severe, defined as very low values in two or more cell lines, including ANC < 500/mm³, platelet count < 20000/mm³, and absolute reticulocyte count < 60000/mm³^[21]. In the study by Khan *et al*^[24], broad-spectrum antibiotics were given if the absolute neutrophilic count was < 1000/mm³. In Buderus' study, antibiotics were given to the patients undergoing colonoscopy who had high inflammatory conditions without clear definition

Table 4 Neutropenic precautions and infectious adverse events

Study	Neutropenic precautions <i>n</i> = No. of afebrile neutropenic patients	Infectious adverse events
Buderus <i>et al</i> ^[19]	ANC < 1000/mm ³ threshold: Upper endoscopies performed under “aseptic conditions” (not defined), appears that this did not include antibiotic prophylaxis Colonoscopies performed under antibiotic prophylaxis <i>n</i> = 10 (ANC < 1000/mm ³)	One (2.1%) procedure-related adverse event: Fever and abdominal tenderness after colonoscopy Patient had not received antibiotic prophylaxis despite neutropenia (ANC 490/mm ³); no explanation given in article Symptoms resolved in 2 d under IV antibiotics
Chu <i>et al</i> ^[17]	None <i>n</i> = unknown	None
Gorschlüter <i>et al</i> ^[20]	Neutropenia not defined <i>n</i> = unknown Median WBC 1.5 G/l	16 of 106 (15%) primary upper EGD: Fever within 48 h 3 of 20 (15%) primary colonoscopies: Fever within 48 h Total # patients with fever following endoscopy: 19. 5 of these died within 10 d. Not significantly different from # patients who died without having a fever following endoscopy.
Kaur <i>et al</i> ^[22]	Neutropenia not defined <i>n</i> = unknown	No ERCP-related adverse events 2 deaths due to sepsis
Kaur <i>et al</i> ^[23]	No neutropenic precautions taken <i>n</i> = 4 (ANC < 1500/mm ³)	No adverse events attributed to endoscopy 4 (36%) infectious adverse events total (both neutropenic and non-neutropenic) 2 patients neutropenic at time of PEG placement. First patient had cellulitis and small abscess at PEG site, treated by removal of PEG Second patient had cellulitis at PEG site, treated by IV antibiotics 2 patients non-neutropenic at time of PEG placement, but had neutropenia at the time of infection
Khan <i>et al</i> ^[24]	For ANC < 1000/mm ³ : Broad-spectrum antibiotics prophylaxis <i>n</i> = 148 (WBC < 4000/mm ³)	No infectious adverse events related to endoscopy. 1 colonic perforation resulting in death
Park <i>et al</i> ^[21]	“Severe aplastic anemia” defined as bone marrow cellularity less than 25% and very low values for at least 2 of 3 hematopoietic lineages (including ANC < 500/mm ³) No precautions (no patients with fever) <i>n</i> = 28 (Severe aplastic anemia)	No adverse events attributable to endoscopy
Ross <i>et al</i> ^[25]	None <i>n</i> = 0	None reported
Schulenburg <i>et al</i> ^[26]	Antibiotic prophylaxis during aplasia for all patients No extra prophylaxis for endoscopy	None
Schwartz <i>et al</i> ^[18]	None <i>n</i> = unknown	No adverse events attributable to endoscopy
Soylu <i>et al</i> ^[27]	Severe neutropenia (level not defined): Withhold endoscopy in 17 upper and 7 lower GI bleed episodes <i>n</i> = unknown	No adverse events attributable to endoscopy

EGD: Esophagogastroduodenoscopy; PEG: Percutaneous endoscopic gastrostomy; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal.

of this state, and upper endoscopies were performed under aseptic conditions if the absolute neutrophil count was < 1000/mm³; however, these conditions were not defined^[19].

Infectious adverse events

Infectious adverse events were discussed in three of the seven studies^[19,20,23]. One study reported fever and abdominal tenderness in a neutropenic patient who did not receive prophylactic antibiotics prior to colonoscopy^[19]. In the second study, 15% of patients undergoing upper and lower endoscopy developed

fever within 48 h after the procedure, of whom 26% (five patients) died thereafter^[20]. No patients died as a direct result of endoscopy, and the death rate was not significantly different in patients who did or did not have a fever following endoscopy.

ANC at the time of PEG tube placement appeared to have a major influence on outcome, with a high infection rate in neutropenic patients. Infection can also occur when the patient becomes neutropenic after the PEG tube placement^[23]. PEG placement should be avoided if possible during significant neutropenic episodes^[23].

Benefits of endoscopic procedures

The diagnostic yield varied among the studies, ranging from 30% to 100% among patients who underwent upper endoscopy. The yield for colonoscopy or sigmoidoscopy was lower. The majority of the findings were esophagitis, gastritis, duodenitis, erosions, ulcers, cytomegalovirus (CMV) infection, fungal infection, GVHD, hiatal hernia, colitis, proctitis, and tumors.

Chu *et al.*^[17] showed in patients who have thrombocytopenia and GI bleed that unifocal or multifocal source of bleeding was the most common finding rather than diffuse mucosal oozing, which accounted for only 12% of patients with platelet counts < 40000/mm³ in this study.

Although the treatment plan was changed for more than 55% of patients undergoing upper endoscopy, this was mostly comprised of the addition or modification of acid suppression therapy^[20].

DISCUSSION

Based on our literature review, it appears that endoscopy can be safely performed in most thrombocytopenic and neutropenic patients. Thrombocytopenia and neutropenia should not be viewed as absolute contraindications for endoscopy. In fact, endoscopy can provide a high diagnostic utility, helping to discern peptic ulcer disease, GVHD, and viral and fungal infections, among other diagnoses. Additionally, we learned that diffuse mucosal oozing is unlikely to be the etiology for a GI bleed in this group of patients^[17]. It is also clear that endoscopic interventions, including hemostasis, feeding tube placement, and even ERCP, can be accomplished successfully. One interesting finding is that peptic ulcer disease was a common finding. Hence, one may consider attempting empiric acid suppression therapy before endoscopic evaluation in high risk patients.

Most studies used a threshold of 50000/mm³ for prophylactic platelet transfusion prior to endoscopic procedures, although some performed uneventful endoscopies with lower counts. Therefore, based on this review and general practice guidelines, we recommend using 50000/mm³ as the threshold to perform endoscopy. However, if clinically required, lower platelet counts may be considered by the endoscopist. Platelet transfusion during the procedure for patients who could not maintain this threshold is an option especially if a high risk procedure is planned. Although patients with lower platelet levels have undergone endoscopic procedures or endoscopic biopsies, duodenal biopsies, in particular, should be avoided if the platelet count is < 20000/mm³, as they can be a high risk factor for bleeding and hematoma development.

In terms of the clinical application of platelet threshold, it is worth considering the risk and benefit of platelet transfusion to achieve a platelet goal. Transfusion is not without risks. Alloimmunization to

platelets is especially a problem in the cancer or bone marrow transplant patient population, as they are likely to require multiple transfusions over time. Transfusion reactions and infection are also risks that still should be taken into account. In addition, unlike other blood products, such as red blood cells, platelets can be quickly transfused immediately before or during the procedure.

As for neutropenia, it is more challenging to develop guidelines, as fewer studies are available. For those who are afebrile, antibiotics should be given prior to high risk procedures, such as ERCP with obstruction of the biliary tree, endoscopic dilatation, or variceal endoscopic treatment. For neutropenic patients requiring low risk endoscopic procedures, the endoscopist may consider antibiotics. Notably, patients who had fevers following endoscopy did not receive antibiotics in the reviewed studies. One may argue that if the ANC is less than 500/mm³, then antibiotics should be given regardless of the presence of fever. When administered, the antibiotics should cover gram-negative rods and anaerobes^[20].

Authors of several studies have emphasized the effectiveness and importance of endoscopy when evaluating patients with GI symptoms, in spite of low platelet and neutrophil counts, considering the high diagnostic yield and low adverse event rate^[21,22,26]. In one study that involved only eight endoscopies in 25 episodes of overt GI bleed, the authors expressed that endoscopy may not be necessary because GI bleeding was not the cause of death in these patients^[27].

Limitations of this systematic review include the small number of available relevant studies, which required the use of older and/or small size studies. There was also a lack of consistency in study design among the included studies. Due to the nature of the search method, the data used may also reflect publication bias; most of the data were obtained through retrospective reviews.

Endoscopy can be safely performed in the settings of thrombocytopenia and neutropenia. Prophylactic platelet transfusion prior to endoscopy may be considered for platelet counts < 50000/mm³, although platelet counts below this threshold are not an absolute contraindication to endoscopy. We recommend prophylactic antibiotics in afebrile patients with neutropenia prior to high-risk endoscopic procedures. For low risk procedures in afebrile neutropenic patients, prophylactic antibiotics may be considered. Risks and benefits should be weighed in each individual scenario with thrombocytopenic and/or neutropenic patients who require endoscopic evaluation.

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COMMENTS

Background

There is limited data available regarding the safety and preventive measures prior to endoscopic procedures in cancer patients with thrombocytopenia and neutropenia. American Society for Gastrointestinal Endoscopy (ASGE) guidelines acknowledge that there is limited pertinent data, but recommend a platelet threshold of 20000/mm³ for diagnostic endoscopy and 50000/mm³ if biopsies are performed. British guidelines recommend ensuring platelet support is available before endoscopic intervention when platelet counts are below 50000-80000/mm³. Regarding neutropenia, the ASGE recommends that the decision to use antibiotics in patients with ANC < 500 should be individualized. British guidelines recommend antibiotic prophylaxis if ANC < 500/mm³ and a patient is undergoing a high-risk procedure. In this systematic review, a summary of the relevant studies is being presented. This article will help treating physicians consider diagnostic yield and safety of endoscopic procedures when facing these difficult cases, in addition to applying preventive measures when necessary.

Research frontiers

The majority of the relevant studies were retrospective. Future large prospective studies are needed. Currently, the data in the field is relatively limited, and any additional studies would help to solidify the recommendations regarding the safety of endoscopy in thrombocytopenic and neutropenic patients.

Innovations and breakthroughs

Investigating the safety of endoscopy in neutropenic and thrombocytopenic settings is an ever evolving process, to which new data will contribute to a better understanding and help us provide better care to our patients. The approach to advancing knowledge on this topic will likely be a gradual amalgamation of data.

Applications

Based on this systematic review, if endoscopic evaluation of a patient with thrombocytopenia is indicated, the procedure should not be withheld solely based on their platelet level. Platelet transfusion may be considered in some cases depending on the platelet count and the type of the procedure being performed. In afebrile neutropenic patients, we recommend prophylactic antibiotics prior to high-risk endoscopic procedures and consideration of antibiotics prior to low-risk procedures. Febrile neutropenic patients are mostly on antibiotic treatments that should be continued.

Peer-review

The topic investigated in this article is interesting. Nevertheless, studies included in this "systematic review" are very different in design and endpoints. The quality of the available data is poor, and it is very difficult (or impossible) to analyze them in a rigid framework, such as a meta-analysis, or even a systematic review.

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