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Review

Recent advances in neutropenic enterocolitis: Insights into the role of gut microbiota

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ABSTRACT

Neutropenic enterocolitis (NE) is a life-threatening complication associated with neutropenia and the main cause of acute abdominal syndrome in neutropenic patients, especially those receiving intensive chemotherapy. This review aims to delineate actual insights into this clinical entity, to emphasize diagnostic and therapeutic management, and to generate hypotheses on pathophysiology to identify avenues for research. Diagnosis is based on the association of neutropenia, fever, abdominal symptoms, and radiologic bowel wall thickening. Main complications are sepsis, perforations, and gastrointestinal bleeding. Several mechanisms may be responsible for mucosal injury: treatment-induced necrosis of the intestinal specific infiltrates, spontaneous intramural hemorrhage, or microvascular thrombosis. The prevailing cause is the direct cytotoxicity of chemotherapy. However, the role of gut dysbiosis in NE remains to be fully elucidated. Therapeutic management includes early multidrug antibiotherapy, transfusion support, hematopoietic growth factor treatment, fluid resuscitation, correction of electrolytes imbalance, and bowel rest. Indication and timing for surgical management are still debated.

1. Introduction

Neutropenic enterocolitis (NE) is a life-threatening digestive complication associated with neutropenia. In 1962, Amromin and Solomon reported the first necropsy series of 69 necrotizing enteropathies [1]. Similar descriptions were reported by Prolla et al. in 1964 under the name of agranulocytic lesions – colitis – or necrosis, highlighting the critical role of immunosuppression in the pathogenesis of the disease [2]. The name typhlitis, from the Greek word "typhlon", meaning cecum – or cecitis, in Latin – was coined by Wagner and coworkers in 1970 [3]. The current name of neutropenic enterocolitis was ultimately suggested by Moir et al. in 1976, resulting in a more global definition encompassing severe neutropenia together with either localized or diffused digestive inflammation [4]. We conducted this narrative review to sum up insights into this entity.

2. Research methodology

References for this review were identified through searches of PubMed, Embase and Cochrane databases with the search terms: "NEUTROPENIC ENTEROCOLITIS", "NECROTIZING ENTEROPATHY", "AGRANULOCYTIC LESIONS – COLITIS – NECROSIS", "TYPHLITIS", and "CECITIS" from 1962 until December 2020. Articles were also identified through searches of the authors' own files. The research was restricted to abstracts in English with full-text articles available. The final reference list was generated based on originality and relevance to the broad scope of this review

3. Epidemiology

NE was initially described in pediatric leukemic populations [3]. Adult patients with leukemia, as well as patients presenting other hematological malignancies such as lymphomas, multiple myeloma, and myelodysplastic syndromes, may develop NE, especially when high dose chemotherapy is used as part of autologous hematopoietic stem cell transplantation [5]. From the 2000s onwards, there has been a growing stream of case reports of patients with solid tumors presenting NE, especially small-cell or non-small cell lung carcinomas [6], breast [7], colorectal [8], ovarian [9], and testicular cancers [10]. NE is not only a complication restricted to intensive chemotherapy. It has also been

Abbreviations: NE, neutropenic enterocolitis; ICU, Intensive care unit; NF-κB, Nuclear Factor-κB; aGvHD-GI, acute intestinal graft versus host disease; CMV, cytomegalovirus; PCR, polymerase chain reaction; G-CSF, hematopoietic growth factor.

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described in leukemic patients before the administration of any chemotherapy [11], in aplastic anemia [12], in cyclic neutropenia [13] and in toxic agranulocytosis [14]. Finally, it has been described in other immunosuppressed patients, including patients infected with human immunodeficiency virus [15], solid organ transplant recipients (kidney or heart) [16,17], and patients under immunosuppressive treatment for chronic inflammatory diseases [18].

The prevalence of NE is extremely variable. Indeed, the existing literature consists primarily of case reports and case series, with only a few cohort studies and no published prospective studies. The first necropsy series reported high prevalence of NE, up to 46% in a leukemic pediatric population [4]. The systematic review by Gorschlüter et al., which compiled studies from 1953 to 2004, found a much lower combined prevalence of 5.3% in adults hospitalized with hematological malignancies, solid tumors, and aplastic anemia [19]. Finally, a prevalence ranging from 0.22% to 46% has been reported in recent literature [20,21] (Table 1). As will be further described, these discrepancies may be explained by: (1) the criteria used for diagnosis – whether the final diagnosis is based on clinical suspicion, radiologically or histologically confirmed; (2) the type of radiological imaging used – CT-scan or ultrasonography; and (3) the inclusion or not of patients displaying lesions that do not involve the cecum. NE ranks as the main cause of acute abdominal syndrome in neutropenic patients admitted to the ICU, with a prevalence of 33% in this population [22]. There is little data on the exact percentage of patients presenting NE and admitted to ICUs. NE may require ICU management in case of septic shock, gastrointestinal bleeding, and digestive perforation. In their cohort, Pugliese et al. found that 8% of NE patients required ICU admittance with a 23% mortality rate. Duceau and team focused on 134 critically ill ICU patients over 8 years (2010–2017). Mortality rate in this cohort was 38.8% [23]. This rises to 42.2% when surgical management is required [24].

4. Pathophysiology (Fig. 1)

Although NE was described for the first time almost 60 years ago, its pathophysiology remains unclear. Hypotheses are mostly based on clinical associations and histopathological descriptions. It has been postulated that NE is the result of mucosal injury which, in the context of neutropenia, leads to bacterial invasion of the bowel wall. The resulting consequences sequentially involve: (1) bacterial translocation with subsequent uncontrolled bacteremia in the context of neutropenia; and (2) local production of bacterial endotoxins, creating cytotoxic edema and microvascular thrombosis with mucosal hypoperfusion and necrosis in a self-perpetuating destructive process.

Causes for the initial mucosal injury could be multiple: mechanical lesions, treatment-induced necrosis of the intestinal specific infiltrates, spontaneous intramural hemorrhage, or microvascular thrombosis caused by coagulation disorders. However, the prevailing cause is the direct cytotoxicity of chemotherapy. Indeed, NE has been reported mainly after chemotherapy administration, especially during induction chemotherapy for acute leukemia and autologous human stem-cell transplantation for lymphomas. Several drugs have been implicated (Table 2): anthracyclines in the adult leukemic population regardless of the dose [21], platinum-based chemotherapies in lung [6], testis [10], ovarian carcinomas [9]; and taxanes in breast cancers [7].

Gastrointestinal mucositis emerges as a commonly reported risk factor for NE [25]. Gastrointestinal mucositis is an inflammation and/or ulceration of the gastrointestinal tract occurring as a complication of chemotherapy and radiation therapy and thus represents the missing link between chemotherapy and NE. It is mostly associated with aggressive myeloablative chemotherapy. Sonis proposed a five-step model to explain its pathophysiology, including [26]: (1) an initiation phase with the formation of reactive oxygen species (ROS); (2) a primary damage response phase with inflammation and apoptosis largely driven

Table 1
All cohort studies indicating the prevalence and mortality rate of neutropenic enterocolitis in onco-hematologic patients and neutropenic patients.

Article	Inclusion period	Population	Underlying pathology	Diagnostic criteria	Prevalence (%)	Mortality (%)
Onco-hematologic population						
Steinberg et al. 1973 [85]	1969–1971	Adults	Hematology	Histologic	12.0	NA
Moir et al. 1976 [4]	1968–1975	Child	Hematology	Histologic	46.0	NA
Shamberger et al. 1986 [84]	1976–1984	Child	AML	Clinic	32.5	8.00
Mower et al. 1986 [86]	1962–1985	Adults	AL	Histologic	2.60	NA
Katz et al. 1990 [87]	1970–1987	Child	AL	Histologic	24.0	NA
Sloas et al. 1993 [88]	1962–1992	Child	Oncology	Clinico-radiologic	0.35	8.30
Jain et al. 2000 [89]	1990–1995	Child	ALL	Clinic	6.10	4.00
Cartoni et al. 2001 [47]	1995–1998	Adults	Hematology	Clinico-radiologic	2.60	29.5
Pastore et al. 2002 [90]	1999–2000	Adults	AML	Clinic	4.30	28.5
Hogan et al. 2002 [91]	1997–1998	Adults	AML	Clinico-radiologic	15.0	40.0
McCarville et al. 2005 [92]	1990–2001	Child	Oncology	Radiologic	2.60	2.40
Alioglu et al. 2007 [93]	1997–2006	Child	AL and AA	Clinic	9.30	NA
Moran et al. 2009 [25]	1995–2005	Child	Oncology	Clinico-radiologic	5.00	0.00
Mullassery et al. 2009 [94]	2001–2005	Child	Oncology	Clinico-radiologic	6.10	2.50
Rizzatti et al. 2010 [95]	2003–2007	Child	Oncology	Clinico-radiologic	16.2	11.7
El Matary et al. 2011 [20]	1988–2008	Child	Oncology	Clinico-radiologic	0.22	11.0
Li et al. 2011 [96]	2000–2009	Child	Oncology	Clinico-radiologic	2.50	8.30
Altinel et al. 2012 [97]	2006–2009	Child	AL	Clinico-radiologic	13.3	20.0
Sundell et al. 2012 [98]	1995–2006	Child	Oncology	Clinico-radiologic	1.70	0.00
Shafey et al. 2013 [99]	1999–2088	Child	AL	Radiologic	8.50	3.90
Gil et al. 2013 [5]	2006–2010	Adults	HSCT	Clinico-radiologic	12.0	9.60
Pugliese et al. 2017 [50]	2002–2012	Adults	AML	Clinico-radiologic	23.8	23.0
User et al. 2018 [43]	2011–2017	Child	AL	Clinico-radiologic	6.40	30.0
Seddon et al. 2018 [21]	2009–2013	Adults	AML	Clinico-radiologic	37.6	0.00
Neutropenic populations						
Biasoli et al. 1997 [76]	1987–1996	Adults	FN	Clinic	2.00	80.0
Gorschluter et al. 2002 [48]	2001	Adults	Neutropenia	Clinico-radiologic	6.50	50.0
Aksoy et al. 2007 [100]	2001–2003	Adults	Neutropenia	Clinico-radiologic	5.10	18.2
Badgwell et al. 2008 [28]	2000–2006	Adults	Neutropenia Acute Abdomen	Clinico-radiologic	28.0	47.0
Vogel et al. 2010 [51]	2003–2009	Adults	Neutropenia	Clinico-radiologic	7.00	26.0

AML: Acute myeloid leukemia; AL: Acute leukemia; AA: Aplastic anemia; HSCT: Human stem-cell transplantation; FN: Febrile neutropenia; ICU: Intensive care unit; NA: Not available.

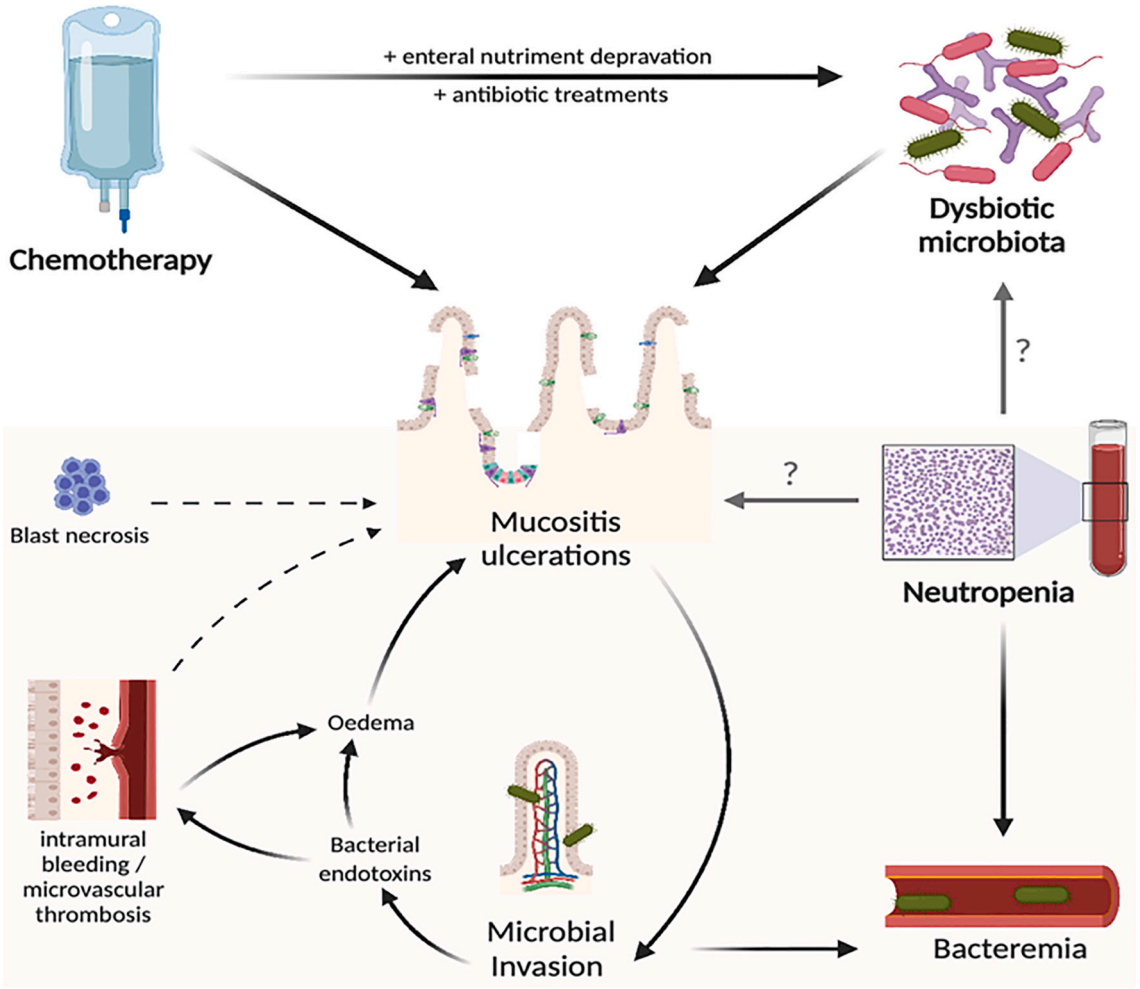

Fig. 1. Suspected pathophysiology for neutropenic enterocolitis.

Table 2
Chemotherapeutic agents that have been associated with neutropenic enterocolitis.

Topoisomerase inhibitors	Anthracyclines (daunorubicin, doxorubicin, idarubicin, epirubicin and mitoxantrone)
	Irinotecan
	Etoposide
Microtubule inhibitors	Taxanes
	Vinca alkaloids
	Pemetrexed
Antimetabolite agents	Cytarabine
	Gemcitabine
	5-fluorouracil and capecitabine its pro-drug
Alkylants	Cyclophosphamide
	Ifosfamide
	Platinum-based chemotherapy

by the activation of Nuclear Factor-κB (NF-κB); (3) a signal amplification phase promoted by key pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6) amplifying the inflammation response and apoptosis; (4) a phase of ulcer formation promoting bacterial translocation; and (5) a healing phase, with cell proliferation. We therefore hypothesize that NE could be the uncontrolled step 4 in the proposal by Sonis. The two factors that could hamper the healing process may reside in a deep and/or prolonged neutropenia and severe gut microbiota dysbiosis.

Indeed, prolonged neutropenia is the most robust risk factor of NE identified in the literature [27], and has been repeatedly associated with mortality [28]. It may be responsible for the perpetuation of bacterial sub-mucosal proliferation and intra-vascular translocation. Profound neutropenia is also thought to be directly involved in mucosal lesions although the underpinning mechanism remains to be clarified [29].

Gut microbiota play a critical role in the maintenance of mucosal trophicity, immune homeostasis, and the clearance of invading pathogens. Low-diversity dysbiosis has been observed in cancer patients [30]. In allogeneic hematopoietic stem cell transplantation profound dysbiosis is associated with infectious complications [31], acute gastrointestinal graft versus host disease (aGvHD-GI) [32], and overall mortality [33]. The main factors that may alter gut microbiota in cancer patients are conditional chemotherapy [34], antibiotherapy [35], and diet modifications. This reduced diversity in the gut microbiota is associated with a reduced proportion of anaerobes and an increased proportion of facultative anaerobes from the Proteobacteria and Bacilli phyla [30]. In 1970, Wagner et al. suggested the potential role of digestive flora changes in the pathophysiology of NE [3]. Reyna-Figueroa and colleagues also approached this issue when they described the association between the development of NE and the use of antimicrobials [27], but no study has ever focused on the modifications of gut microbiota within the course of NE. However, recent findings on the interaction of host-microbiota, especially in stem cell transplant patients, may generate hypotheses to identify avenues for research. First, within the Firmicutes phyla, the increased abundance of pro-inflammatory bacteria from the Lactobacillales can compromise epithelial barrier integrity [36] and stimulate local inflammation [37]. Concurrently, the reduced abundance of anti-inflammatory short chain fatty acids producing bacteria

from the Clostridiales order can lead to increased permeability and inflammation [38]. Third, the injury of Paneth cells that has been observed after total body irradiation or during aGvHD-GI may contribute to increased intestinal permeability and bacterial translocation [39] [40]. Indeed, Paneth cells are epithelial cells located in intestinal crypts which secrete antimicrobial peptides (defensins) that can regulate the composition of the gut microbiome [40]. Moreover, they serve as multifunctional guardians of stem cells, by providing essential niche signals involved in epithelial regeneration [41]. Finally, Shono et al. have shown that mucus degradation induced by mucinolytic bacteria such as *Akkermansia muciniphila* exacerbate aGvHD-GI and favor bacterial translocation [42].

5. Diagnostic

5.1. Clinical presentation

Clinical presentation includes a broad range of non-specific symptoms: fever, abdominal pain and tenderness, diarrhea or constipation, nausea, and vomiting [43]. NE-induced complications can also be present at diagnosis, including: (1) infectious complications, ie., bacteremia, or fungemia, and septic shock; (2) local complications, ie., intestinal perforations, peritonitis, abscesses, and fistulation [44]; and (3) gastrointestinal bleeding [45]. Finally, occlusive syndrome [23], and abdominal compartment syndrome have also been reported [46]. In patients who have received chemotherapy, symptomatology appears after a median delay of 14 days after chemotherapy initiation [23]. Laboratory findings mostly include pancytopenia and electrolyte imbalances with hyponatremia, hypophosphatemia, hypokalemia, and hypoalbuminemia [43].

5.2. Radiological presentation (Fig. 2)

Cartoni and colleagues [47] and Gorschlüter et al. [48], were the first to use ultrasound as part of the diagnostic criteria. They observed that bowel wall thickening (1) could properly be evaluated by ultrasonography; (2) was correlated with NE when higher than 4 mm; and (3) was correlated with mortality when greater than 10 mm. Concurrently, Kirkpatrick and Greenberg were the first to present an extensive CT-scan assessment of gastrointestinal complications of neutropenic patients [49]. The study compared 53 patients with clinical diagnosis of NE, 14 with *Clostridium difficile*-associated colitis and 7 with GvHD. In their study, bowel wall thickening greater than 4 mm was present in all patients regardless of the diagnosis. The thickening proved to be greater than in *Clostridium difficile* colitis but located exclusively in the colon. Characteristics of NE were patchy damage of the entire digestive tract with bowel wall thickening greater than 4 mm associated with pneumatosis in 21% of the cases, mesenteric stranding in 51%, and ascites in 43% of patients. Nowadays, imaging evaluation represents a key step in the diagnostic process. Recent studies have gone so far as to suggest that an early radiological diagnosis either by ultrasound [50], or CT-scan [51] is associated with survival. It provides multiple crucial points: (1) confirming the pathologic bowel wall thickening according to the standardized criteria; (2) excluding differential diagnoses of acute abdominal syndrome: appendicitis, acute cholecystitis, mesenteric ischemia, acute pancreatitis, intussusception; (3) assessing factors associated with a severe course: bowel wall thickening greater than 10 mm, pneumatosis, extensive damage; and (4) searching for complications: perforation, abscess, peritonitis, fistula, active bleeding. Either abdominal CT-scan or ultrasound have been recommended. CT-scan should be performed with contrast injection. Conversely, oral contrast administration is not only useless but could be harmful in this context.

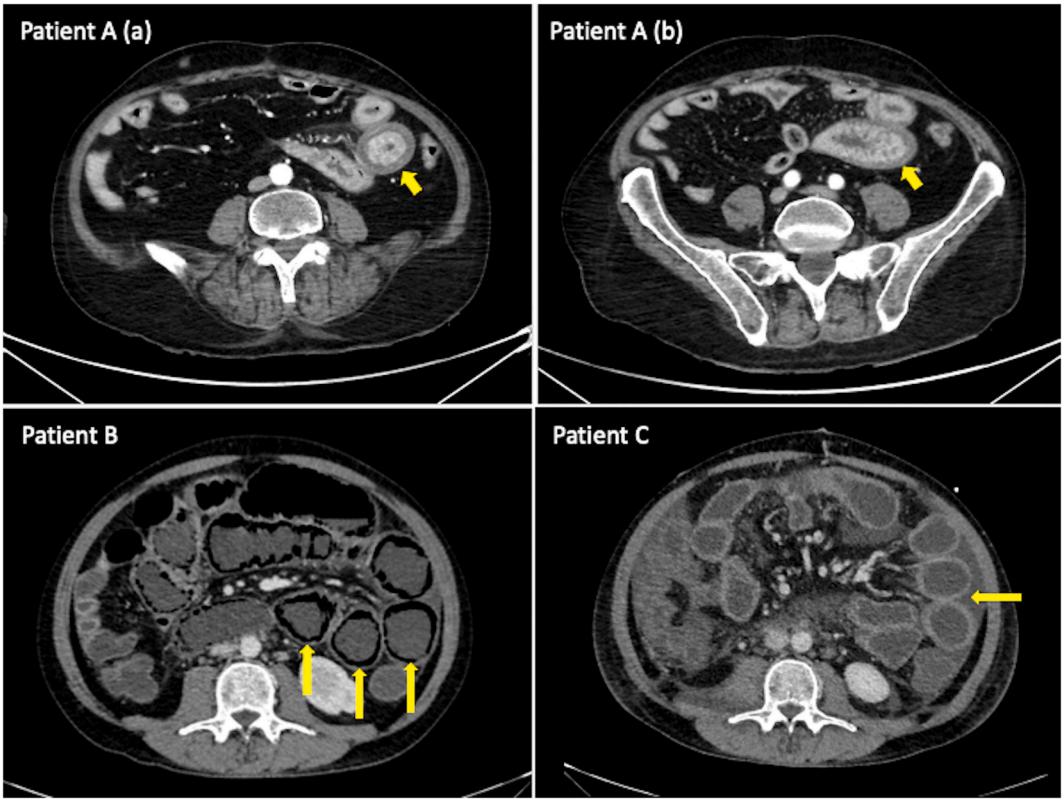

Fig. 2. Contrast enhanced abdominal CT-scans of neutropenic enterocolitis.
A: Segmental bowel wall thickening (→) with mucosal enhancement of the duodenum and the jejunum. a) Cross section (> 4 mm) b) Longitudinal section (>30 mm).
B: Parietal pneumatosis (→) with mucosal enhancement involving the entire digestive tract and no arterial thrombosis.
C: Peritoneal effusion (→) with bowel wall thickening and mucosal enhancement.

Ultrasound is helpful for patient follow-up, and has the benefit of being a low cost, no contrast injection without ionizing radiation, a major issue in the pediatric population. It may also be a useful tool for imaging patients who are too unstable for transport to the CT-scanner. However, because of its superior accuracy compared to ultrasound to diagnose NE, to exclude differential diagnoses and to identify complications, a CT-scan remains the standard reference and should be privileged in severe NE patients, when feasible. Colonoscopy is contraindicated because of the high-risk of associated perforation.

5.3. Definition (Fig. 3)

The diagnostic for NE remains a challenge for every clinician as no specific criteria exists to date. Nesher and Rolston formalized the last bundle of criteria in 2013 [52] with major criteria including neutropenia under 500.10^9 neutrophils/L, fever exceeding 38.3 °C (oral or rectal), and bowel wall thickening (CT-scan or ultrasound) greater than 4 mm in cross-section and 30 mm in longitudinal section. Minor criteria include abdominal pain, distension or cramping, diarrhea, and lower gastrointestinal bleeding. Several differential diagnoses must be ruled out, including aGvHD-GI, radiation-induced enteritis, an exacerbation of inflammatory bowel diseases or an infectious colitis. Microbiological investigations are necessary to exclude all known gastrointestinal pathogens including *Clostridium difficile* and *Cytomegalovirus* (CMV) gastrointestinal disease, as well as other viruses (*Norovirus, Rotavirus, Adenovirus, human Astrovirus*, and *Sapovirus*), bacteria (*Salmonella* spp., *Yersinia enterocolitica, Shigella* spp. *Enterotoxigenic and Shiga-toxin producing Escherichia coli*, *Campylobacter* spp., *Plesiomonas shigelloides,* and *Vibrio* spp.), *Mucormycosis*, *Aspergillosis, Microsporidia* and parasites (*Cryptosporidium* spp., *Giardia* spp., and *Strongyloides stercoralis*). Stool culture, detection of toxigenic *Clostridium Difficile* and a parasitological stool examination should be performed [53]. If available, enteropathogen multiplex nucleic acid amplification tests may be helpful with a good sensitivity and specificity in symptomatic patients [53–56].

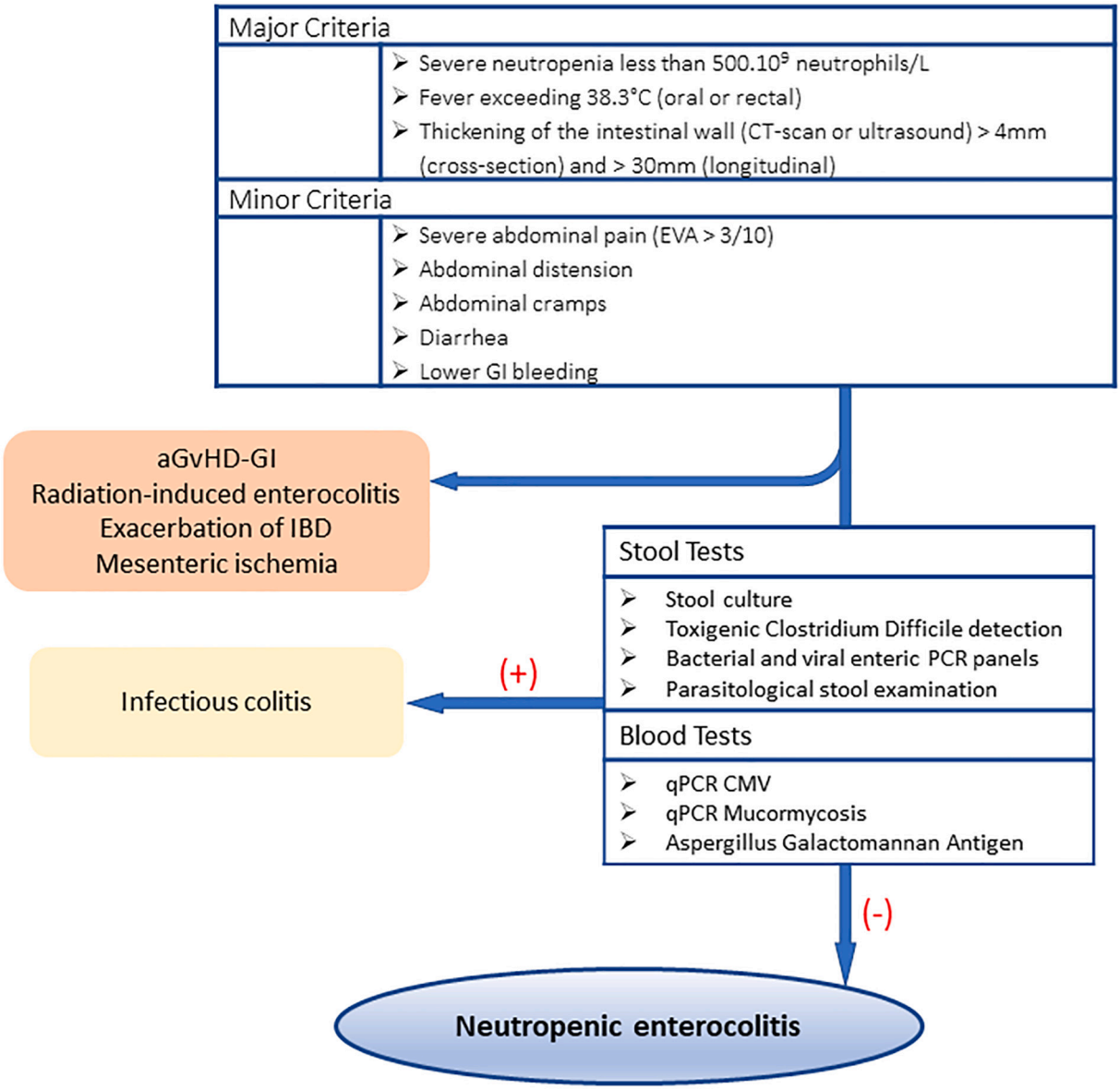

Fig. 3. Nesher and Rolston diagnostic criteria [52] and suggested microbiologic tests to exclude differential diagnosis.
Enteric PCR panels should include *Norovirus, Rotavirus, Adenovirus, human Astrovirus, Sapovirus, Salmonella* spp., *Yersinia enterocolitica, Shigella* spp. *Enterotoxigenic* and *Shiga toxin-producing Escherichia coli*, *Campylobacter* spp., *Plesiomonas shigelloides*, and *Vibrio* spp. aGvHD-GI: Gastrointestinal acute graft versus host disease. EVA: verbal rating scale. CMV: Cytomegalovirus. GI: gastrointestinal. IBD: Inflammatory Bowel Diseases. PCR: polymerase chain reaction. qPCR: quantitative polymerase chain reaction.

Regarding gastrointestinal CMV disease, proven disease requires macroscopic mucosal lesions and viral documentation in tissue. However, because of the high risk of colic perforation during NE, colonoscopy and gut biopsy are often contraindicated. We suggest a kinetic analysis of plasma CMV DNA load to search for a possible CMV disease [57,58]. Similarly, microscopy observations and culture of tissue specimens allow definitive diagnoses of gastrointestinal *Mucormycosis* and *Aspergillosis* [59]. However, a molecular based diagnostic from blood and serum may be helpful for the diagnosis of *Mucormycosis* or *Aspergillosis* [60]. Therefore, blood Aspergillus and Mucorales PCR testing and *Aspergillus* Galactomannan antigen detection should be performed in the initial work-up of NE patients. In case of persisting symptoms after hematological recovery, colonoscopy may be discussed to rule out these differential diagnoses.

5.4. Histopathological description (Fig. 4)

Histopathological descriptions came from initial autopsy studies [4] and pathological study of surgical specimens [61]. Macroscopically, gross pathological findings include variable wall thickness, luminal dilatation, and extensive ulcerations covered by necrotic and hemorrhagic debris. NE can affect the entire digestive tract albeit with a patchy lesional pattern [61]. The cecum and the right colon are the most frequently affected areas. Hypotheses accounting for this specific location include the terminal nature of the cecum vascularization, its distensibility with relative stasis and bacterial overgrowth, and its relative scarcity in lymphoid organs [62]. Microscopical examinations disclose transmural edema, mucosal and submucosal hemorrhage, necrosis varying from superficial ulcerations to full thickness, and perivascular and submucosal microorganism proliferation [4,61]. The absence of granulocytes is a salient histopathological feature, but moderate mononuclear inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes have been reported. Specific leukemic infiltration was described in case reports when NE occurred before administration of chemotherapy but is seldom reported in more recent series [61].

5.5. Microbiology

In the latest studies, bacteremia accounts for 50% of patients [5,23,43]. Bacterial identification yielded 60% *Enterobacteriaceae* (*Escherichia coli, Klebsiella* spp., *Enterobacter cloacae),* 25% Gram-positive cocci (*Enterococcus* spp., *Staphylococcus* spp., *Streptococcus* spp.), 5% anaerobes and 6% *Pseudomonas* spp. [23]. Bacteriemia due to *Clostridium* species: *Clostridium septicum* but also *Clostridium Tertium* and *Clostridium Chauvoei* have been reported [63]. As *Clostridiaceae* are gas forming Gram-variable bacillus, *Clostridiaceae* infections should be suspected whenever NE symptomatology is associated with cutaneous necrotic lesions indicating myonecrosis. Fungemia accounts for around 6% of patients. *Candida* spp. are the most represented species (76–94%). Radiologically assessed enteritis is associated with the occurrence of fungemia [23]. A hypothesis for this observation could be a higher fungi inoculum in the proximal digestive tract. Enteral damages and fungemia could also be surrogates of NE severity. Indeed, NE severity involves severe mucosal damage, neutropenia and dysbiosis of gut microbiota, which are known risk factors for bloodstream Candida infection [64,65].

6. Therapeutic management (Fig. 5)

Therapeutic management has not been standardized to date due to the dearth of high-level evidence studies. NE is often associated with major complications such as septic shock, gut perforation, and major gastrointestinal bleeding. Several studies suggest early ICU admission policy in neutropenic patients as delayed ICU admission is associated with lower survival in these cases [66–69]. Therefore, we strongly suggest early ICU admission of patients with NE especially in the case of hemodynamic instability, suspected gastrointestinal bleeding, or acute abdominal syndrome. Medical management should focus on infectious, hematologic, and metabolic disorders.

6.1. Infectious management (Table 3)

Sepsis is the main complication of NE. Akin to febrile neutropenia the empirical antibiotherapy is a medical emergency and must be initiated within the first hour [70]. Empirical antibiotherapy should include an anti-pseudomonal beta-lactam (ceftazidime, cefepime, piperacillin-tazobactam or carbapenem) associated with nitroimidazole if a cephalosporin is selected. The choice should be tailored according to prior patient-specific culture data and institutional epidemiology. Due to the high prevalence of associated mucositis and gram-positive cocci (mainly *Enterococcus faecium)* bacteriemia in NE patients (up to 27% of patients in the study by Duceau and coworkers [23]), we suggest that a glycopeptide should be initiated, especially in patients with hemodynamic instability as recommended by the Infectious Diseases Society of America guidelines [70]. The association of an aminoglycoside should be considered in the case of hemodynamic instability or multi-drug resistant colonization to broaden the spectrum of antibacterial coverage.

There is no recommendation about the proper time to initiate empiric antifungal therapy in NE. In febrile neutropenia it is recommended after five to seven days of appropriate antibacterial therapy and persistent fever or in case of hemodynamic instability [71,72]. However, the last study by Duceau et al. supported an earlier treatment in case of radiologically assessed enteritis [23]. Echinocandins should be favored for empirical treatment, especially in the case of hemodynamic

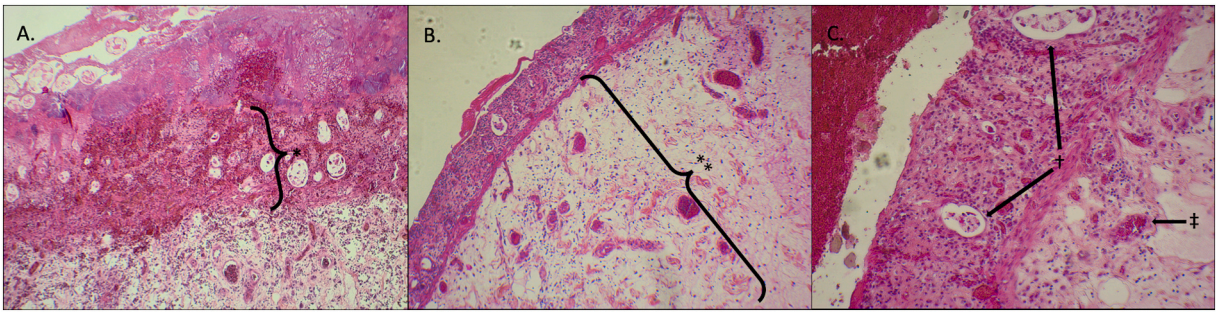

Fig. 4. Histopathological observations.
Hematoxylin and eosin stain.
X5 scanning magnification (Fig. 4A and B), and X10 scanning magnification (Fig. 4C).
A: Extensive coagulative mucosal necrosis with intramural hemorrhage (*).
B: Extensive coagulative mucosal necrosis with submucosal edema (**). Paucity of inflammatory cells infiltrate.
C: Necrotic colonic glands (†) and congestive vessels (‡).

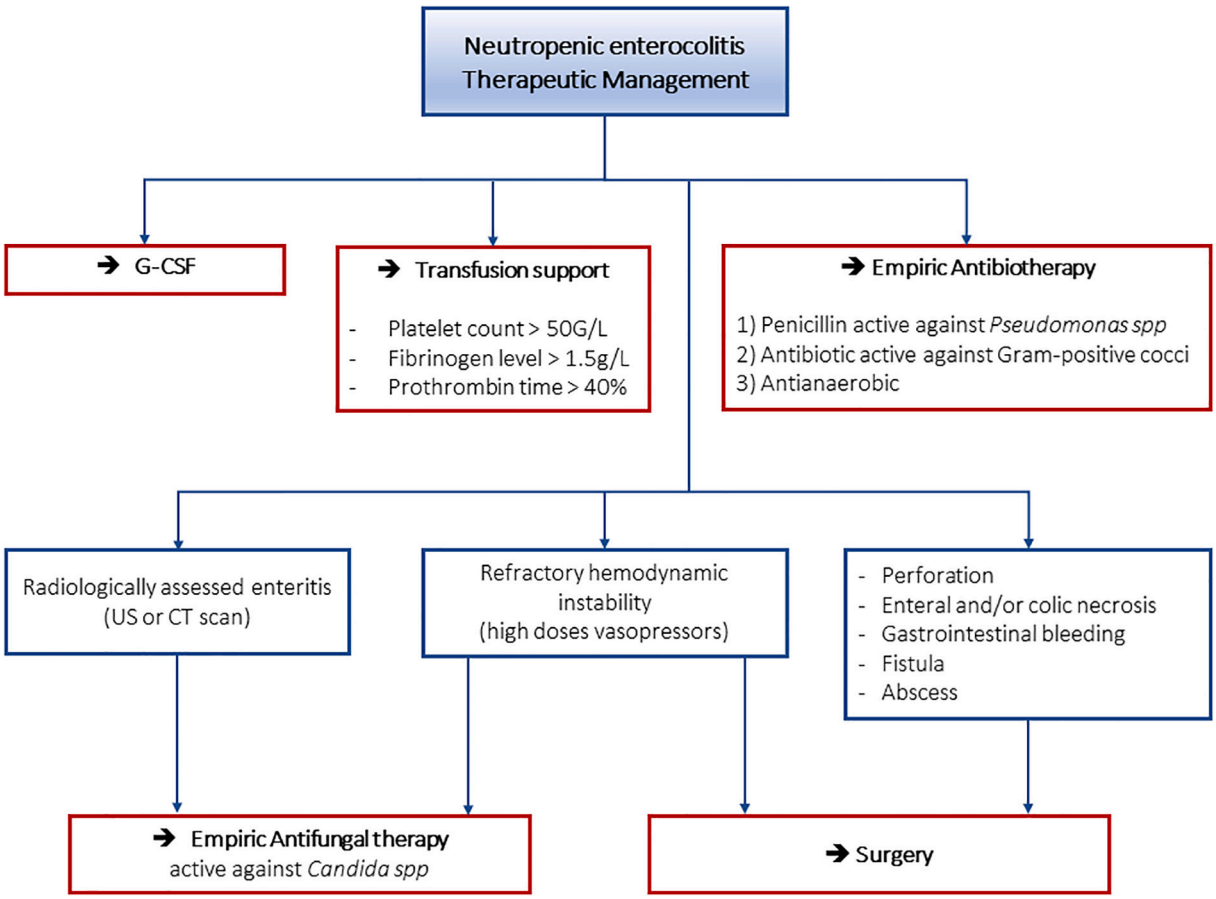

Fig. 5. Proposed therapeutic management for neutropenic enterocolitis.
G-CSF: hematopoietic growth factor. US: ultrasound.

Table 3
Proposition for empirical antibiotherapy in neutropenic enterocolitis.

	Penicillin:
	- Piperacillin-tazobactam
Gram-negative bacilli:	Cephalosporin:
	- Ceftazidime
- Pseudomonas spp.	- Cefepime
- Enterobacteria	Carbapenem:
	- Meropenem
	- Imipenem
	Nitroimidazoles (if cephalosporin is selected)
Anaerobes	- Metronidazole
	- Ornidazole
Gram-positive Cocci:	Glycopeptides:
	- Vancomycin
- Streptococcus spp.	- Teicoplanin
- Enterococcus spp.	Daptomycin
- Staphylococcus spp.	Linezolid
Fungi:	
	Echinocandins
	Fluconazole
- Candida spp.	

instability or known colonization with an azole-resistant strain because of their fungicide activity on all *Candida* species except *Candida Parapsilosis* [73,74]. Azole antifungal agents should not be used empirically in patients receiving fluconazole or posaconazole long-term prophylaxis because of the risk of selection of *Candida Krusei* and acquired resistance in the case of *Candida Glabrata*.

6.2. Hematological management

Prophylactic platelet transfusion is recommended to prevent severe hemorrhagic complications. Platelet transfusion threshold should be 10 g/L [75], but we advise raising the threshold to 50 g/L when gastrointestinal bleeding is observed. Similarly, coagulopathy should be corrected. We suggest targeting a prothrombin time international normalized ratio of more than 40% and a rate of fibrinogen of more than 1.5 g/L.

Finally, as reported earlier, prolonged neutropenia is associated with NE [76], and NE-related mortality [28]. Therefore, hematopoietic growth factor (G-CSF) treatment [77] and granulocyte transfusion have been proposed [78]. However, there is no randomized control trial regarding the use of G-CSF in NE. The use of G-CSF is nonetheless aligned with the guidelines of the European Organization for Research and treatment of Cancer (EORTC) which recommend G-CSF treatment in febrile neutropenic patients who are “at a higher risk of infection-related complications” [79]. Those recommendations are based on the meta-analysis by Clark et al. which observed a decrease of time to neutrophil recovery, length of hospitalization, and infection-related mortality with G-CSF treatment [80].

6.3. Metabolic management

First, metabolic support must include intravenous fluid resuscitation and correction of electrolytes imbalance [52]. Second, bowel rest and sometimes bowel decompression with nasogastric suction are necessary.

Total parenteral nutrition is then needed to prevent malnutrition in these patients. Simultaneously, treatments that may aggravate ileus (antidiarrheal and opioid agents) should be avoided.

Some authors consider the possibility of minimal enteral feeding in selected patients [19]. Pending clinical trials, this approach derives from a sound pathophysiological and experimental perspective, including: (1) the association of enteral fasting with significant mucosal atrophy and abnormal gut permeability in critically ill patients [81]; (2) the major local inflammation, epithelial apoptosis and gut microbiota anomalies observed under total parenteral nutrition [82]; and (3) the efficiency of minimal enteral feeding to shorten recovery of methotrexate-induced mucositis in rat models [83].

6.4. *Surgical management*

Due to the potential risks associated with abdominal surgery during neutropenia and thrombopenia, physicians are often reluctant to perform surgery in NE patients. However, in 2018, Saillard and team [24] found that abdominal surgery during NE was not associated with increased mortality as long as it was combined with intensive resuscitation. Shamberger and coworkers were the first to issue objective criteria for surgical treatment: (1) the persistence of gastrointestinal bleeding despite the medical treatment of thrombocytopenia and clotting abnormalities; (2) the presence of free intraperitoneal gas revealing perforation or of parietal pneumatosis revealing necrosis; (3) the clinical deterioration despite optimal medical management; and (4) the development of other indications for surgery (appendicitis etc.) [84]. The optimal timing of surgery in NE patients remains to be defined [29].

7. Conclusion and future considerations

NE is a frequent and underestimated complication of neutropenia in onco-hematological patients who often require ICU admission. The pathophysiology of NE needs to be reconsidered in the light of recent discoveries on gut microbiota and its role in maintaining the integrity of the intestinal barrier and inflammatory response. A better understanding of NE mechanisms may improve specific management of these patients.

8. Practice points

1. Diagnosis of neutropenic enterocolitis is based on the association of neutropenia under 500.10^9 neutrophils/L with fever exceeding 38.3 °C, and bowel wall thickening.
2. It is the main cause of acute abdominal syndrome in neutropenic patients, with a prevalence of 33% in this population.
3. Sepsis is the main complication with bacteremia in 50% of patients (Enterobacteriaceae but also Gram-positive cocci, Anaerobes, and Pseudomonas spp.) and fungemia in 6% of patients.
4. Therapeutic management combines broad spectrum empiric antibiotherapy, potential antifungal therapy, hematopoietic growth factors, transfusion support, and sometimes surgical management.
5. Early antifungal therapy should be discussed in case of radiologically assessed enteritis.

9. Research agenda

1. Studies focusing on the involvement of gut microbiota in the pathophysiology of neutropenic enterocolitis may pave the way for identifying new microbiota-based therapeutic interventions.
2. Indications and timing of surgery should be further evaluated in larger studies.
3. Indications of minimal enteral feeding should be further evaluated in larger studies.

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Authors' contributions

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- Literature search and data selection process
- Data analysis.
- Figure drawing.
- Original draft writing.

Pr Elie Azoulay.

- Verification of underlying data.
- Validation.

Pr Lara Zafrani:

- Literature search and data selection process.
- Supervision.
- Verification of underlying data.
- Validation.

Declaration of Competing Interest

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