UNIL | Université de Lausanne

Faculté de biologie
et de médecine

Travail de Maîtrise en Médecine No 2506

"Neutropenic enterocolitis in hemato-oncological patients"

Etudiant
Galia Santos, MMéd3 2015-2016

Tuteur
Prof. Oscar Marchetti
Service des Maladies infectieuses, Département de Médecine,
CHUV-UNIL, Lausanne

Co-tuteur
Dr Stefano Giulieri
Service des Maladies infectieuses, Département de Médecine,
CHUV-UNIL, Lausanne

Expert
Prof. Alain Cometta
Service de Médecine interne,
Etablissements hospitaliers du Nord Vaudois, Yverdon-les-Bains

Lausanne, 12 Décembre 2015

TABLE OF CONTENTS

ABSTRACT

Background

Neutropenic enterocolitis (NE) is a life-threatening complication in patients undergoing intensive chemotherapy for hematological malignancies. Aims of this study were to analyze the clinical presentation, diagnostic findings, management and outcome of NE and to explore factors associated with adverse outcome.

Methods

This study describes the presentation and outcome of NE in hemato-oncological patients hospitalized for intensive chemotherapy in the isolation unit of the Infectious Diseases Service at CHUV in 2008 and 2012. Cases were identified from the institutional database and clinical data retrospectively extracted from medical charts.

Results

32 out of 199 hemato-oncological patients (16.1%) presented 35 episodes of NE. According to predefined clinical and radiological/histopathological diagnostic criteria, NE was classified as definite in 14, probable in 19, and possible in 2 cases. Induction or induction-reinduction chemotherapy for acute myeloid leukemia was the most frequent hemato-oncological setting. The triad of neutropenia, fever and digestive symptoms was present in all patients. Bowel wall thickening > 4 mm at CT scan was found in 63.6% of cases. In 34.3% of episodes a bacterial bloodstream infection was documented. Despite a *Candida* gastrointestinal colonization in more than two thirds of cases, invasive candidiasis was documented in only two cases (5.7%). An adverse outcome was observed in 20% of patients: 4 (11.4%) patients had severe sepsis, two (5.7%) septic shock, 6 (17.1%) were admitted to the ICU, one (3%) underwent an endoscopic intervention and recovered, and two patients died (5.7%): in one (3%) death was attributed to NE. High-dose cytarabine resulting in prolonged agranulocytosis and severe mucosal damage was associated with adverse outcome of NE.

Conclusion

This exploratory study reveals the determinant role of intensive chemotherapy for acute myeloid leukemia and especially of high-dose cytarabine in the occurrence of NE. The severe hematological and mucosal toxicity of this regimen are major components in the pathogenesis of NE and are associated with adverse outcome. These findings may help to identify patients at high risk for complications who need prompt management, close follow-up and maybe antimicrobial prophylaxis.

BACKGROUND

Context

Neutropenic enterocolitis (NE) is a severe complication, which is principally observed in patients undergoing intensive chemotherapy for hematological malignancies. NE less frequently occurs in patients with solid tumors or rare hematological conditions such as aplastic anemia, cyclic neutropenia or other diseases associated with absolute or functional neutropenia [1-3].

Incidence

A NE incidence of 5.3 % has been reported in patients hospitalized for treatment of hematological malignancies, high-dose chemotherapy for solid tumors or aplastic anemia [4]. Among acute leukemic patients, incidence ranges from 1 % to 46 %, depending on the clinical settings [2, 3, 5].

Pathophysiology

Although the pathophysiology of NE is not completely elucidated, two major mechanisms contribute to its occurrence. The direct effect of cytotoxic agents on the rapidly dividing cells of the gastrointestinal mucosa is the first step in the pathogenesis of this complication [6]. The toxic damage of the physiological barrier results in the translocation of the bacterial and fungal endogenous flora, which underlies the selective pressure of previous antibacterial and antifungal treatments [2, 3, 5, 7]. As a crucial second step, the neutropenic state induced by the chemotherapy facilitates the microbial invasion of the bowel wall and the secondary hematogenous dissemination [2, 3, 5]. Some authors also consider thrombocytopenia-associated intramural bowel hemorrhage and leukemic or lymphomatous infiltration of the bowel wall as contributing components in the pathophysiology of NE [2, 7]. Although this pathogenetic process is classically reported in the ileocecal region (typhlitis), other segments of the gastrointestinal tract are often simultaneously involved (duodenitis, jejunitis, ileitis, colitis): thus, the use of the term NE is more appropriate [1].

Risk factors

There is few information in the literature about risk factors for developing NE. Cytosine arabinoside (ARA-C) treatment, especially at high dose, has been associated with a higher risk of presenting this complication [2, 3]. Moreover, a patient with NE is at risk for a recurrent episode in a subsequent chemotherapy cycle, which may suggest the role of immunogenetic factors in the pathogenesis [2, 3].

Clinical presentation, laboratory, radiological and pathological findings

The typical clinical presentation of NE consists in fever, abdominal pain (sometimes localized in the right lower quadrant), abdominal distention, bloating, which are frequently associated with nausea,

vomiting, diarrhea, and, sometimes, with bloody stools. The physical examination shows diffuse tenderness, rebound guarding, peritoneal signs and a palpable mass, which can be localized in any abdominal quadrant [1-3, 5, 7, 9, 10]. Specific clinical diagnostic criteria are however lacking [1, 5, 9]. The typical laboratory finding is prolonged profound neutropenia (agranulocytosis, i.e. neutrophil cell blood count < 0.1 G/l during more than 7 days). Neutrophils' recovery is associated with a rapid improvement of the clinical status [3, 9].

The reported rate of positive blood cultures in NE varies largely in the literature [2]. In their study, Gomes et al. reported positive blood cultures in 44 % of definite and 18 % of possible NE episodes [2]. Aerobic and anaerobic Gram-positive and Gram–negative bacteria as well as fungi such as *Candida* and *Aspergillus* have been described in NE, either as monomicrobial or as polymicrobial infections [1, 11].

Signs on conventional X-ray films of the abdomen are nonspecific and not sensitive for the diagnosis of NE. CT scan and ultrasonography of the abdomen are more accurate, in particular for detecting and quantifying bowel wall thickening (BWT) as a characteristic and prognostic radiological finding of NE [1, 9, 12-14].

The pathological findings of NE are characterized by lesions of the bowel wall ranging from mucosal inflammation to transmural necrosis [3, 15].

Morbidity and mortality

The reported mortality of NE is variable [1]: Gomes et al. observed a 22 % mortality rate [2] while Gorschlüter et al. found a 54 % rate [16]. NE with *Clostridium septicum* bloodstream infection has an especially poor outcome (mortality rate up to 50-100 %) [8].

Clinical management

Conservative management of NE is the standard of care which includes broad-spectrum antibacterial and antifungal agents as well as intensive supportive care. Due to the very high mortality of surgical procedures in patients with prolonged bone marrow aplasia, this approach is used very selectively in patients presenting with a refractory septic shock and/or with suspected GI tract perforation.

AIMS OF THIS STUDY

The first aim of this study is to describe the clinical presentation, the diagnostic findings, the treatment and the outcome of NE.

The second aim is to explore factors associated with a poor outcome of NE.

METHODS

Study population

This study describes the presentation and outcome of NE in hemato-oncological patients hospitalized in the isolation unit of the Infectious Diseases Service at CHUV for intensive chemotherapy, i.e. induction, induction-reinduction, or consolidation for acute leukemia or autologous transplantation of hematopoietic stem cells (auto-HSCT) for acute leukemia, lymphoma or myeloma.

Two study years (2008 and 2012) were selected, because of a similar case-mix with the highest numbers of chemotherapy cycles according to the institutional database. All discharge letters were screened for standardized key-words associated with NE: "enterocolitis", "colitis" and "typhlitis". Patients who did not undergo one of the above chemotherapy regimens or in whom colitis was associated with an alternative microbiologically documented cause, i.e. *Clostridium difficile* (positive toxin and/or culture) or Cytomegalovirus (multi-level digestive tract injury and detectable viremia) infection, were excluded. Data extracted from medical files and discharge letters were collected in a clinical report form.

*Neutropenic enterocolitis – diagnostic criteria*

NE is difficult to diagnose on a clinical basis. As there is a lack of consensus regarding the appropriate clinical criteria to be fulfilled without confirmatory radiological or pathological examinations, it has been suggested to consider levels of diagnostic certainty. Gomez et al. [2] propose a two-level classification: possible NE with typical clinical presentation and non-conclusive radiology or pathology and certain NE fulfilling clinical and radiological/pathological criteria. In the present study, we used the same principle by adding an intermediate level in the classification: possible, probable, and definite NE. These levels are characterized by an increasing number of criteria fulfilled among a list of five. The first criterion is mandatory: neutropenia defined as a neutrophil count < 0.5 G/l within 48 hours following fever's onset. The additional four criteria are described in Table 1: fever, symptoms associated with abdominal infection, clinical signs at physical examination of the abdomen and radiological or histopathological findings. Two of these four additional criteria were necessary to diagnose possible, three for probable and four for definite NE (Figure 1)

The time of onset of NE was considered as the first day of fever and the time of end as the day of resolution of fever, abdominal pain and clinical signs of abdominal infection (Table 1). When the improvement of NE was complicated by an infection at a different site, the time of resolution of enterocolitis was considered as unknown.

Table 1: Neutropenic enterocolitis - Diagnostic criteria.

Neutropenia (neutrophil count < 0.5G/l)	Mandatory criterion
Fever (body temperature > 38°C, tympanic thermometer) **Abdominal infection - symptoms** (at least one among abdominal pain, diarrhea, bloody stools, vomiting) **Abdominal infection – signs at physical examination** (at least one among abdominal tenderness, abdominal distension, peritoneal signs) **Radiology and/or pathology** (bowel wall thickening)	Additional criteria

Figure 1: Neutropenic enterocolitis - Algorithm of diagnostic probability.
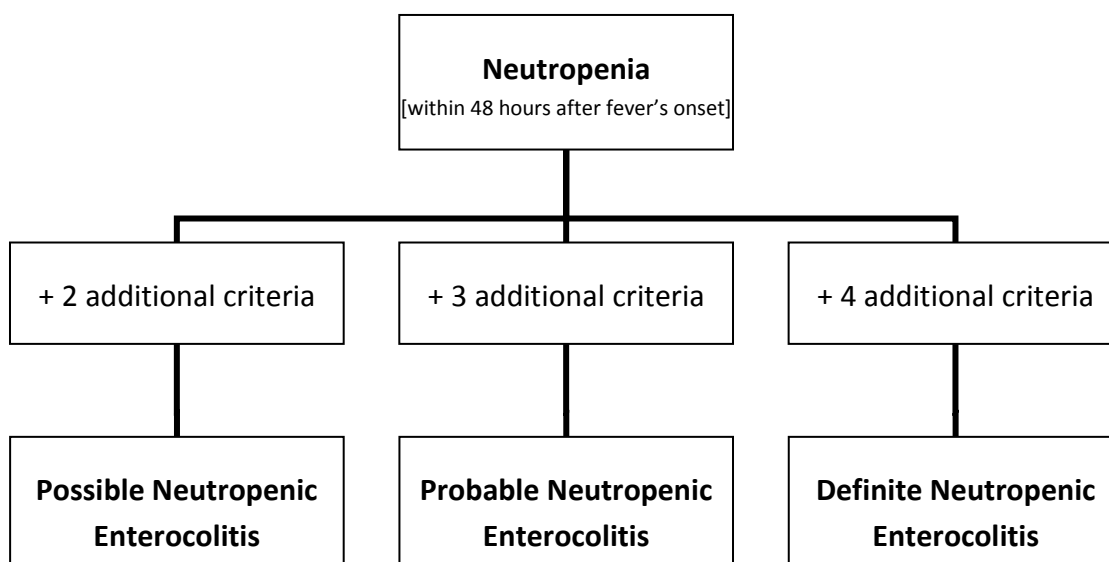
Analysis

Data collected from patients treated in 2008 and 2012 were pooled and analyzed with the StataIC 12 software. A descriptive analysis of the population was performed including demographics, hematological malignancy and chemotherapy, infections other then NE, antimicrobial therapy, fungal markers and colonisation, presentation, laboratory, microbiological findings, therapy and outcome of NE.

A bivariate analysis was performed to investigate the risk factors of adverse outcome in patients with NE by testing its association with variables extracted from the descriptive analysis. Adverse outcome

was defined as at least one of the following five events (Table 2): abdominal surgery, severe sepsis, septic shock, admission to the intensive care unit, and inhospital mortality. These outcomes were considered when they occurred during the course of NE, regardless of a causal relationship with NE. When a patient presented two episodes of NE, the second one was considered in the adverse outcome analysis to keep possible the occurrence of all five events, in particular of mortality. Fisher's exact test was performed for all binary and categorical variables, whereas median's equivalence and Wilcoxon-Mann-Whitney's test were performed for continous variables. A two-tailed $P<0.05$ was set for statistical significance.

Table 2: Adverse outcome definition.

Adverse outcome – at least one of the following criteria
Abdominal surgery
Severe sepsis
Septic shock
Admission to the intensive care unit
Inhospital mortality

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

RESULTS

Among 199 hemato-oncological patients hospitalized for intensive chemotherapy (i.e. induction, induction-reinduction, or consolidation for acute leukemia or autologous transplantation of hematopoietic stem cells (auto-HSCT) for acute leukemia, lymphoma or myeloma), 32 (16.1%) presented a clinical picture of NE (16.0% in 2008 and 16.1% in 2012), see flowchart (Figure 2). Three patients presented two episodes of NE.

Figure 2: Flowchart.

Total, patients

106 (2008)
93 (2012)

Exclusions, patients
No keywords for NE in discharge letter

87 (2008)
74 (2012)

Exclusions, patients
Other reasons

2 (2008)
[chemotherapy (2x)]
4 (2012)
[CMV colitis (1x), Clostridium difficile toxin + (2x), culture + (1x)]

Inclusions, patients

17 (2008 ; 20 episodes)
15 (2012)

Keywords for NE in discharge letter :
« enterocolitis », « colitis », « typhlitis »
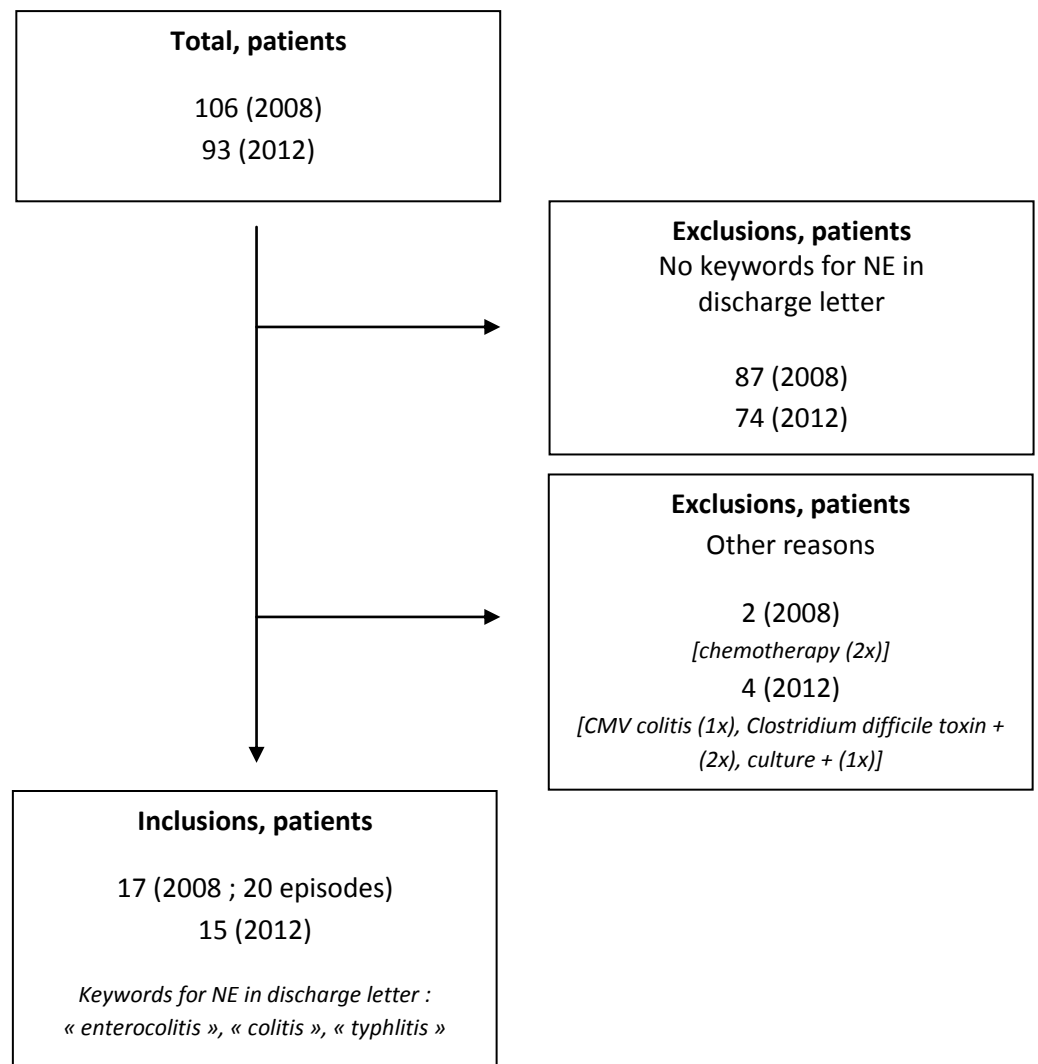
Population's demographic characteristics (Table 3)

Median age was 57 years (range 21 to 69). Men and women were equally represented.

Most patients underwent intensive chemotherapy for acute myeloid leukemia (AML, 59.4%). At admission, 51.4% of patients were in remission of their disease (partial or complete). 37.4% of patients were hospitalized after first diagnosis for induction chemotherapy. Refractory (induction-reinduction) and recurrence of disease were less frequent.

Median duration of stay in the isolation ward was 31 days (range 19 to 76). Stays exceeding 31 days were only found in patients undergoing induction's chemotherapy.

Table 3: Population's demographics and hemato-oncological disease characteristics.

31 Patients	
Age [years] Median; min - max	57; 21 - 69
Sex Male n/ N (%)	15/32 (46.9)
Underlying hematological disease **AML** (including MDS, CML) n/N (%) **NHL, HL, MM** n/N (%) **ALL, NK** n/N (%) **AML and NHL** n/N (%)	 18/32 (56.3) 11/32 (34.4) 2/32 (6.3) 1/32 (3.1)
35 Hospitalizations for intensive chemotherapy = Neutropenic episodes	
Hematological disease - status **First diagnosis (Induction)** n/N (%) **Refractory disease (Induction-reinduction)** n/N (%) **Remission (partial, complete)** n/N (%) **Recurrence** n/N (%)	 13/35 (37.1) 2/35 (5.7) 18/35 (51.4) 2/35 (5.7)
Duration of stay [days] Median; min - max	31; 19 - 76

AML: acute myeloid leukemia, **MDS**: myelodysplasic syndrome with blastic transformation, **CML**: chronic myeloid leukemia with blastic crisis, **NHL**: non-Hodgkin Lymphoma, **HL**: Hodgkin lymphoma, **MM**: multiple myeloma, **ALL**: acute lymphoblastic leukemia, **NK**: blastic plasmacytoid dendritic cells neoplasia.

Chemotherapy (Table 4)

Considering all episodes of NE (N=35), induction for acute leukemia (induction1, induction 2, or induction followed by reinduction) was the most frequent type of chemotherapy (23/35, 65.7%). Cytosine arabinoside (cytarabine) was administered in 31/35 (88.6%) chemotherapy cycles. Cytosine arabinoside was not administered in 4 chemotherapy cycles, which included auto-HSCT for multiple myeloma (n=3) and another regimen for blastic plasmacytoid dendritic cells neoplasia (n=1). The dose of cytarabine varied from 1'260 to 13'400 mg/m^2 depending on the underlying hematological disease

and the type of chemotherapy (example of induction 1 therapy: cytarabine + idarubicine (low-dose cytarabine), example of induction 2 therapy: cytarabine + amsacrine (high-dose cytarabine), example of induction-reinduction therapy: cytarabine + idarubicine, directly followed, without recovery from medullar aplasia, by cytarabine + amsacrine (high-dose cytarabine)). Among patients treated with cytarabine containing regimens, 16.1% developed a severe rash (cutaneous toxicity) requiring systemic corticosteroids. The median onset of rash was on day 12 after onset of chemotherapy and its duration was between 3 and 14 days. Patients receiving high-dose cytarabine were more likely to develop a rash (P=0.042).

All patients received multi-drug regimens except three patients undergoing auto-HSCT for MM (melphalan).

Table 4: Chemotherapy.

Type of chemotherapy	
Induction 1 n/N (%)	11/35 (31.4)
Induction 2 n/N (%)	10/35 (28.6)
Induction + reinduction n/N (%)	2/35 (5.7)
Auto-HSCT n/N (%)	12/35 (34.3)
Cytotoxic drugs	
Cytarabine n/N (%)	31/35 (88.6)
Clofarabine n/N (%)	2/35 (5.7)
Anthracycline (idarabucine, amsacrine, daunorubicine) n/N (%)	24/35 (68.6)
Alkylating agent (melphalan, carmustine, cyclophosphamide) n/N (%)	12/35 (34.3)
Topoisomerase inhibitor (etoposide) n/N (%)	9/35 (25.7)
Other (**vincristine, tretinoid**) n/N (%)	2/35 (5.7)
Cytarabine	
Dose [mg/m^2] Median; min - max	1600; 1260 - 13'400 *(N=31)*
Cytarabine Rash (requiring systemic corticosteroids)	
Rash n/N (%)	5/31 (16.1)
ARAC dose if rash present [mg/m^2] Median; min-max	12'000; 1400 – 13'400 *(N=5)*
Onset [days post chemo] Median; min - max	12; 2 – 25 *(N=5)*
Duration of rash [days] Median; min - max	8; 3 – 14 *(N=5)*

Auto-HSCT: Autologous hematopoietic stem cells transplantation

Infections, antibacterial and antifungal drugs prior to NE (Table 5)

Prior to NE, 34.3% of patients had presented an episode of infection: fever with intestinal mucositis was one of the most frequent infections preceding NE (40.0% of all infectious episodes previous NE,

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

N=16). Antibacterial and antifungal drugs had been administered to 34.3% and 37.1% of patients, respectively. Antibacterial agents were only administered for therapy of infections, while no antibacterial prophylaxis was used. Fluconazole was the most prescribed antifungal drug, principally as prophylaxis in selected high-risk patients with AML (e.g. induction chemotherapy).

63.6% and 97.0% of patients had oral and/or intestinal mucositis, respectively. The onset of intestinal mucositis was very close to the onset of NE (median delay 2 days, range -14 to 15). Its median duration was 11 days (range 4 to 34).

Table 5: Infections, antibacterial and antifungal drugs prior to NE.

Antibacterial and/or antifungal drugs prior to NE	
n/N (%)	18/35 (51.4)
Antibacterial drugs prior to NE	
n/N (%)	12/35 (34.3)
Antifungal drugs prior to NE	
n/N (%)	13/35 (37.1)
Antifungal prophylaxis n/N (%)	10/35 (28.6)
Fluconazole n/N (%)	11/35 (31.4)
Voriconazole n/N (%)	2/35 (5.7)
Liposomal amphotericin B n/N (%)	1/35 (2.9)
Infections prior to NE	
MDI-B n/N (%)	2/35 (5.7)
MDI-nB n/N (%)	5/35 (14.3)
CDI n/N (%)	6/35 (17.1)
FUO n/N (%)	4/35 (11.4)
Mucositis	
Oral n/N (%)	21/33 (63.6) *(2 missing)*
Intestinal n/N (%)	32/33 (97.0) *(2 missing)*
Oral and Intestinal n/N (%)	21/33 (63.6) *(2 missing)*
Intestinal mucositis	
Onset [days post onset of chemo] Median; min - max	7; -3 – 26 *(N=32)*
Duration [days] Median; min – max	11; 4 – 34 *(N=32)*
Delay between onset and onset of NE Median; min – max	2; -14 – 15

MDI-B: microbiologically documented infection with bacteremia, **MDI-nB**: microbiologically documented infection without bacteremia, **CDI**: clinically documented infection, **FUO**: fever of unknown origin

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Immunosuppression, fungal colonization and fungal markers (Table 6)

51.4% of patients received corticosteroids before the onset of NE, most frequently (66.7%) as part of intensive chemotherapy before auto-HSCT (other indications: cytarabine rash, trans-retinoic acid syndrome).

73.5% and 70.4% of patients have positive oropharynx and/or stool cultures for yeasts, respectively. *Candida albicans* was the most frequent colonizer: 92.0% and 94.7% of positive oropharynx and stool cultures, respectively. Other yeasts and molds were also isolated: *Candida glabrata* (oropharynx (O), stools (S)), *Candida guillermondii* (O), *Candida dubliniensis* (O), *Candida krusei* (S), *Candida tropicalis* (S), *Geotrichum* spp (S), *Saccharomyces cerevisiae* (S) and *Aspergillus niger* (S). Cultures were reported positive for the first time after the onset of NE in 96.0% patients.

Only one patient showed positive fungal markers (positive galactomannane, then positive mannane and anti-mannane antibodies): in this patient a probable invasive pulmonary aspergillosis and a possible hepatosplenic candidiasis was diagnosed. Anti-mannane antibodies were positive at admission in two patients and remained positive: these results represented a previous seroconversion and were not correlated with a diagnosis of invasive mycosis during the hospital stay.

Table 6: Immunosuppression, fungal colonization and fungal markers.

Corticosteroids	
Administration n/N (%)	18/35 (51.4)
Dose (prednisone equivalent) [mg/day] Median; min - max	156; 14 – 156 *(N=18)*
Yeast colonization	
Oropharynx	
Yeast colonization n/N (%)	25/34 (73.5)
Time between colonization and onset NE Median; min – max	0; -14 - 17
Colonization prior NE n/N (%)	12/25 (48.0)
Candida albicans n/N (%)	23/25 (92.0)
Stools	
Yeast colonization n/N (%)	19/27 (70.4)
Time between colonization and onset NE Median; min – max	0; -9 - 24
Colonization prior NE n/N (%)	6/19 (31.6)
Candida albicans n/N (%)	18/19 (94.7)
Yeasts other than *Candida* spp	
Stools culture species	
***Geotrichum* spp** n/N (%)	3/35 (8.6)
Aspergillus niger n/N (%)	2/35 (5.7)

Saccharomyces cerevisiae n/N (%)	3/35 (8.6)
Fungal markers	
Galactomannane positive n/N (%)	1/28 (3.6) *(7 missing)*
Mannane positive n/N (%)	1/28 (3.6) *(7 missing)*
Anti-mannane positive n/N (%)	3/28 (10.7) *(7 missing)*

Positivity cut-offs

Galactomannane:	0.25 – 0.5 [index]
Mannane: 2008	0.25 – 0.5 [ng/ml]
2012	62.5 – 125 [pg/ml]
Anti-mannane antibodies:	0 – 5 [UA/ml]

Clinical presentation of NE (Table 7)

The median onset of NE was on day 9 after onset of chemotherapy (for patients undergoing auto-HSCT, median onset was on day 3 post transplantation) and on day 1 of neutropenia. The median duration of NE was 12.5 days (range 3 to 59).

All patients presented the following triad: neutropenia, fever and digestive symptoms. Diarrhea was observed in all patients. 88.6% of patients presented with abdominal signs at physical examination: 82.9% abdominal tenderness, 60% peritoneal signs, 40.0% at the classical localization in the right lower quadrant. 45.7% of patients had positive radiology and/or pathology findings. According to the diagnostic classification used in the present study (Figure 1), 54.3% of patients had probable, 40% definite, and 5.7% possible NE. Among probable cases, most presented the previously described triad with abdominal signs at physical examination.

Table 7: Clinical presentation of NE

Inclusion criteria	
Neutropenia n/N (%)	35/35 (100.0)
Fever n/N (%)	35/35 (100.0)
Digestive symptoms n/N (%)	35/35 (100.0)
Abdominal signs n/N (%)	31/35 (88.6)
Positive radiology and/or histopathology n/N (%)	16/35 (45.7)
Positive radiology n/N (%)	16/35 (45.7)
Positive pathology n/N (%)	1/35 (2.9)
Possible NE[b] n/N (%)	2/35 (5.7)
Probable NE[b] n/N (%)	19/35 (54.3)

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Definite NE[b] n/N (%)	14/35 (40.0)
Neutropenic enterocolitis chronology	
Onset [days post chemo] Median; min - max	9; 1 – 29
Onset [days post auto-HSCT] Median; min - max	3; 1 – 8 *(23 missing)*
Onset [days post neutropenia] Median; min - max	1; -2 - 31
Duration [days] Median; min – max	12.5; 3 – 59 *(3 missing [a])*
Symptoms / signs	
Fever n/N (%)	35/35 (100.0)
Abdominal pain n/N (%)	30/35 (85.7)
Diarrhea n/N (%)	35/35 (100.0)
Vomiting n/N (%)	19/35 (54.3)
Bloody stools n/N (%)	6/35 (17.1)
Abdominal tenderness n/N (%)	29/35 (82.9)
Peritoneal signs n/N (%)	21/35 (60.0)
Localization in right lower quadrant n/N (%)	14/35 (40.0)

[a]: end of NE unknown

[b]: definition: see figure 1

Laboratory and radiological findings in NE (Table 8)

All patients were in agranulocytosis at the time of NE diagnosis (median duration 10 days, range 0 to 34 days). C-reactive protein was elevated (median: 214.5 [mg/l], range 23 – 472 [mg/l]). Two patients presented with an elevated lactatemia (> 2 mmol/l) and both died.

62.9% patients had a CT scan. The most frequent radiological sign of NE was bowel wall thickening (BWT, more than 4mm): in 64.3% patients BWT was more than 10 mm. BWT was more frequently located in the right colon or ileocecal region (42.9%), followed by small bowel (35.7%), right and left colon (14.3%) and small bowel plus colon (7.1%). Infiltration of adipose tissue (50.0%) and ascites (45.5%) were also observed. In six patients with clinical diagnosis of probable NE (neutropenia, fever, abdominal symptoms and signs), no radiological BWT or other indirect sign of NE was found.

Table 8: Laboratory and radiological findings in NE.

Laboratory	
Agranulocytosis n/N (%)	35/35 (100.0)
Duration [since admission] [days] Median; min - max	10; 0 - 34
Neutropenia n/N (%)	35/35 (100.0)
Duration [since admission] [days] Median; min - max	14; 6 – 41 *(3 missing [a])*
CRP maximal value [mg/l] Median; min - max	214.5; 23 – 472 *(9 missing)*

PCT maximal value [µg/l] Median; min - max	0.62; 0.12 - 24.3 *(20 missing)*
Lactate more than 2 mmol/l n/N (%)	2/35 (5.7)

Radiology	
CT n/N (%)	22/35 (62.9)
Abdominal CT	
Bowel wall thickening (> 4 mm) n/N (%)	14/22 (63.6) *(N=22)*
Infiltration of adipose tissue n/N (%)	11/22 (50.0) *(N=22)*
Ascites n/N (%)	10/22 (45.5) *(N=22)*
Mesenteric/retroperitoneal adenopathies n/N (%)	8/22 (36.4) *(N=22)*
Periportal oedema n/N (%)	6/22 (27.3) *(N=22)*
Gall bladder hydrops/distention n/N (%)	3/22 (13.6) *(N=22)*
Intestinal dilatation n/N (%)	2/22 (9.1) *(N=22)*
Parietal contrast enhancement n/N (%)	2/22 (9.1) *(N=22)*
No signs for NE n/N (%)	6/22 (27.3)
Thoracic CT	
Pulmonary infiltrate/lesion n/N (%)	7/22 (31.8) *(N=22)*
Pleural effusion n/N (%)	3/22 (13.6) *(N=22)*

[a] : 1 case : neutropenia at admission, 2 cases : neutropenia at discharge (including one death)

Reference ranges

Agranulocytosis: neutrophile count < 0.1G/l

Neutropenia: neutrophile count < 0.5 G/l

C reactive protein (CRP):   < 10 [mg/l]

Procalcitonine (PCT):   0.25 – 0.5 [µg/l]   localized bacterial infection

0.5 – 2 [µg/l]   systemic bacterial infection

> 2 [µg/l]   association with septic state

Lactate: < 2 [mmol/l]

Microbiological documentation of NE (Table 9)

Blood cultures from central venous catheter and peripheral venipuncture were performed at the onset of all episodes of NE. Bacteremia was detected in 34.3% patients: Gram negative rods, Gram positive cocci and fungi were isolated. In several cases a concomitant central venous catheter infection was present (bacteremia with *Staphylococcus epidermidis*). One patient presented a mixed polymicrobial infection: peripheral blood cultures were positive for *Candida albicans* (1/4 bottles, 1/2 sets, i.e. proven invasive fungal infection according to EORTC/MSG) and central catheter blood cultures were positive for *Klebsiella* (oxytoca group) (1/4 bottles, 1/2 pairs).

In one case, *Enterococcus faecalis* was detected in the bile culture. This patient presented a

neutropenic duodenitis with stenosis of Vater's papilla (sample of bile collected during sphincterotomy and stenting of biliary duct).

Table 9: Microbiological documentation of NE.

Microbiology	
Blood cultures	
Blood culture sampled n/N (%)	35/35 (100.0)
Blood culture positive n/N (%)	12/35 (34.3)
FUNGI	
Candida albicans n/N (%)	1/35 (2.9)
GRAM-NEGATIVES	
Enterobacter cloacae n/N (%)	1/35 (2.9)
Escherichia coli n/N (%)	4/35 (11.4)
Klebsiella **(oxytoca group)** n/N (%)	1/35 (2.9)
GRAM-POSITIVES	
Enterococcus faecalis n/N (%)	2/35 (5.7)
Enterococcus faecium n/N (%)	2/35 (5.7)
Staphylococcus aureus n/N (%)	1/35 (2.9)
Staphylococcus epidermidis n/N (%)	2/35 (5.7)
Staphylococcus haemolyticus n/N (%)	1/35 (2.9)
Streptococcus mitis n/N (%)	1/35 (2.9)
Streptococcus pneumoniae n/N (%)	1/35 (2.9)
Streptococcus vestibularis n/N (%)	1/35 (2.9)
Peptostreptococcus n/N (%)	1/35 (2.9)
Other cultures (bile)	
Enterococcus faecalis n/N (%)	1/ 35(2.9)

Medical and surgical management of NE (Table 10)

All patients received broad-spectrum antibacterial drugs from the onset of symptoms for a median duration of 19.5 days. 82.9% of patients were treated with antifungal drugs (in a majority fluconazole

was switched to broad-spectrum agents: caspofungin, amphotericin B or voriconazole), sometimes with a delay from the beginning of symptoms because of clinical deterioration or lack of improvement despite appropriate antibiotics.

Opiates were prescribed as symptomatic treatment of abdominal pain. Medical therapy was completed by hemodynamic support, nutritional support (nasogastric tube) and bowel rest (parenteral nutrition).

Only two patients underwent surgical therapy during hospitalization: in one NE was the indication for surgery (duodenitis requiring sphincterotomy of Vater's papilla and stenting of biliary duct).

Table 10: Medical therapy of NE.

Medical therapy	
Antimicrobial drugs	
Delay between onset NE and antimicrobial drugs [days] Median; min - max	0; 0-0
Antibacterial drugs	
n/N (%)	35/35 (100.0)
Duration [days] Median; min – max	19.5; 8 – 54 (N=34, 1 missing [a])
Delay between onset NE and antibiotics [days] Median; min - max	0; 0 - 1
Antifungal drugs	
n/N (%)	29/35 (82.86)
Duration [days] Median; min – max	15.5; 4 – 65 (N=26, 3 missing [a])
Delay between onset NE and antifungal drugs [days] Median; min – max	1; 0 – 13 (N=29)
Fluconazole n/N (%)	23/29 (79.3)
Voriconazole n/N (%)	10/29 (34.5)
Liposomal amphotericin B n/N (%)	7/29 (24.1)
Caspofungine n/N (%)	20/29 (69.0)
Other medications	
Opiates n/N (%)	26/35 (74.3)

[a]: end of treatment unknown

Outcome of NE (Table 11)

Seven of 35 patients (20%) showed an adverse outcome (23.5% in 2008, 20.0% in 2012): one fulfilled the criteria for possible, three for probable, and three for definite NE.

One patient developed an ileus. None presented an intestinal perforation. One patient presented both a possible invasive candidiasis and a probable invasive aspergillosis and one a proven invasive candidiasis (positive blood cultures for *Candida albicans* and hepatosplenic lesions on CT). Three

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

patients presented a second episode of NE during a subsequent chemotherapy cycle.

Six of 35 patients (17.1%) were transferred to the intensive care unit for sepsis associated with NE or for other reasons than NE (bleeding, sepsis associated with another infection).

Two patients died during hospitalization (inhospital mortality: 5.7%) due to septic complications: one death was attributed to NE and one to pulmonary legionellosis.

Table 11: Outcome of NE.

Outcome	
Severe sepsis n/N (%)	4/35 (11.4)
Septic shock n/N (%)	2/35 (5.7)
Multiple organ failure n/N (%)	2/35 (5.7)
ICU transfer n/N (%)	6/35 (17.1)
Duration of ICU stay [days] Median; min - max	4.5; 1 – 16, *(N=6, 29 missing)*
Ileus n/N (%)	1/35 (2.9)
Intestinal perforation n/N (%)	0/35 (0.0)
Surgery n/N (%)	1/35 (2.9)
	Sphincterotomy and stenting of biliary duct
Recurrence of NE (3 months, during following cure) n/N (%)	6/35 (17.1)
Proven invasive candidiasis with hepatosplenic lesions (3 months) n/N (%)	1/35 (2.9)
Possible hepatosplenic candidiasis and probable pulmonary aspergillosis (3 months) n/N (%)	1/35 (2.9)
Mortality [30 days and inhospital] n/N (%)	2/35 (5.7)

Factors associated with adverse outcome of NE (Tables 12, 13, 14)

By bivariate analysis, several factors were statistically associated with adverse outcome of NE (Table 12). Patients with NE and acute leukemia, in particular those undergoing induction-reinduction chemotherapy, those receiving high-dose cytarabine (third tertile of the dose distribution) and presenting a severe cytarabine rash (requiring a treatment with systemic corticosteroids), and those with a longer duration of agranulocytosis, had more frequently an adverse outcome.

Patients presenting fever and intestinal mucositis (CDI) before the onset of NE developed more frequently septic complication. Patients with documented bacteremia during NE had more frequently an adverse outcome. By contrast, patients presenting adipose tissue infiltration on CT scan had a better outcome than those who did not. Moreover, BWT was not significantly associated with the outcome. Using more sensitive statistical tests for continous variables (Table 14), other factors appeared to be of significance. A low body mass index and a long duration of NE increased the risk of adverse outcome.

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Other factors showed non-significant trends for an association with adverse outcome (Table 13): female sex, old age, infection prior to NE (without distinction of site and etiology), antibiotics and/or antifungal drugs prior to NE, prolonged antibacterial and broad-spectrum antifungal therapy for NE, patients admitted to or discharged from the isolation unit with neutropenia. Antifungal prophylaxis did not seem to protect from adverse outcome.

Table 12: Adverse outcome - statistically significant associations.

	Overall	Poor outcome (line %)		Exact Fisher's test p-value
		n	**%**	
Hematological disease (N=32)				0.034
Double diagnosis [LMA, LNH]	1	1	100.0	
LLA, NK	2	1	50.0	
LMA [included LMC, SMD]	18	4	22.2	
LH, LNH, MM	11	0	0.0	
Type of chemotherapy (N=32)				0.007
Induction 1	8	1	12.5	
Induction 2	10	3	30.0	
Induction-reinduction	2	2	100.0	
Auto-HSCT	12	0	0.0	
CDI prior NE (N=32)				0.034
Yes	5	3	60.0	
No	27	3	11.1	
Severe cytarabine rash (requiring systemic corticosteroids) (N=28)				0.002
Yes	5	4	80.0	
No	23	1	4.4	
Cytarabine dose [tertiles of distribution] (N=32)				0.007
1 [1260 - 1520 mg/m^2]	8	0	0.0	
2 [1521 - 1600 mg/m^2]	9	0	0.0	
3 [1601 - 13'4000 mg/m^2]	11	5	45.4	
Bacteremia during NE (N=32)				0.018
Yes	12	5	41.7	
No	20	1	5.0	
Duration agranulocytosis [tertiles of distribution] (N=32)				0.050
1 [0 – 5 days]	9	0	0.0	
2 [6 – 11 days]	11	1	9.1	
3 [12 -34 days]	12	5	41.7	
CT - Infiltration of adipose tissue (N=19)				0.011
Yes	9	0	0.0	
No	10	6	60.0	

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Table 13: Adverse outcome - not statistically significant trends.

	Overall	Poor outcome (line %)		Exact Fisher's test p-value
		n	%	
BMI (N=32)				0.147
<18.5 kg/m^2	2	1	50.0	
>=18.5 & <=25 kg/m^2	12	4	33.3	
>25 & <=30 kg/m^2	13	1	7.7	
>30 kg/m^2	5	0	0.0	
Sex (N=32)				0.178
Female	17	5	29.4	
Male	15	1	6.7	
Age related to median [Halves of distribution] (N=32)				0.196
1 (<57 years)	14	1	7.1	
2 (>=57 years)	18	5	27.8	
Infections (MDIB, MDInB, CDI, FUO) prior to NE (N=32)				0.060
Yes	10	4	40.0	
No	22	2	10.0	
Antibacterial or antifungal drugs prior to NE (N=32)				0.076
Yes	15	5	33.3	
No	17	1	5.9	
Antibacterial drugs prior to NE (N=32)				0.060
Yes	10	4	40.0	
No	22	2	9.1	
Antifungal drugs prior to NE (N=32)				0.148
Yes	11	4	36.4	
No	21	2	9.5	
Duration of neutropenia (N=32)				0.053
Tertiles of distribution				
1 [6 – 8 days]	8	0	0.0	
2 [9 – 18 days]	11	1	9.1	
3 [19 – 41 days]	10	3	30.0	
Neutropenia at admission or discharge	3	2	66.7	
Abdominal CT-scan (N=32)				0.059
Yes	19	6	31.6	
No	13	0	0.0	
Duration of NE [tertiles of distribution] (N=30)				0.149
1 [3 – 8 days]	9	0	0.0	
2 [9 – 15 days]	9	1	11.1	
3 [16 – 59 days]	12	4	33.3	
Antifungal drugs NE (N=32)				0.564
Yes	26	6	23.1	
No	6	0	0.0	

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Broad-spectrum antifungal drugs NE (N=26)				0.628
Yes	18	5	27.8	
No	8	1	12.5	
Duration antifungal drugs NE [tertiles of distribution] (N=23)				0.498
1 [4 – 9 days]	10	1	10.0	
2 [10 – 30 days]	10	3	30.0	
3 [31 – 65 days]	3	1	33.3	
Duration antibacterial drugs NE [tertiles of distribution] (N=31)				0.588
1 [8 – 13 days]	7	0	0.0	
2 [14 – 26 days]	13	3	23.1	
3 [27 – 54 days]	11	2	18.2	

Table 14: Adverse outcome – continous variables analysis.

	Exact Fisher's test p-value	Median equivalence's test (exact) p-value	Mann-Whitney's test p-value
BMI	0.147	0.172	**0.0263**
Age	0.196	0.194	0.1532
Cytarabine dose	**0.007**	**0.005**	**0.0025**
Duration of neutropenia	0.053	0.279	0.0569
Duration of agranulocytosis	**0.050**	0.172	**0.0050**
Onset of NE post chemotherapy	0.497	0.383	0.1578
Duration of NE	0.149	**0.042**	**0.0165**
Duration antibacterial drugs prior to NE	0.229	0.524	0.1087
Duration antifungal drugs prior to NE	0.200	1.000	0.8501
Duration antibacterial drugs NE	0.588	0.654	0.5013
Duration antifungal drugs NE	0.498	0.618	0.2470

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

DISCUSSION

Incidence - Population characteristics

In the present study, 32/199 (16.0%) of hemato-oncological patients hospitalized in the isolation unit for intensive chemotherapy developed a clinical picture of NE.

This incidence is higher than that expected according to recent reviews. Gorschlüter et al. reported an incidence of 5.6% in patients treated for acute leukemia [4]. This can be explained by differences in the diagnostic definition of NE. Our study did not require radiological or pathological criteria for inclusion: clinical criteria were meant to cover a broader spectrum of the presentation of NE which might contribute to the identification of factors associated with severe forms and adverse outcome.

Acute myeloid leukemia was the most frequent underlying hematological disease in our population. According to the literature, the subgroup of patients suffering from acute leukemia is at higher risk to develop NE [4] due to aggressive chemotherapy regimens resulting in toxic mucositis, profound and long-duration neutropenia, and, prolonged use of antibiotics. Patients undergoing induction or induction-reinduction chemotherapy (refractory disease) for acute leukemia followed by prolonged neutropenia represented also the majority of the cases of NE in the present study.

Clinical presentation

The classical triad fever-abdominal pain-diarrhea was observed in 85.7% of our patients with NE [2]. Other authors reported similar data [17] in patients with solid tumors or hemato-oncological cancers who were neutropenic on admission or during therapy. In the present study, 82.9% patients presented abdominal tenderness, 60.0% peritoneal signs and 40.0% pain localized in the right lower quadrant, as classical clinical signs of NE. NE is difficult to diagnose based on clinical presentation, which can be confounded by concomitant infections at different sites or non-infectious conditions associated with the underlying disease or the chemotherapy.

Clinical symptoms and signs of NE are largely variable: some forms of NE have been diagnosed by CT scan imaging despite a very mild clinical picture, emphasizing the lack of sensitivity of the classical clinical presentation [18].

Abdominal symptoms/signs of infection suggest NE or intestinal mucositis: one might question whether these two clinical entities can be differentiated. In our study population, 97% of NE patients did present intestinal mucositis. Interestingly, the median delay between the onset of intestinal mucositis and NE was 2 days. This shows that intestinal mucositis is the first step of NE as a continuum of a common pathogenesis. Considering the wide range of severity, the clinical

presentation and other factors might help the physician to identify patients at particular risk to develop an adverse outcome.

Figure 4 A common pathological pathway of intestinal mucositis and NE.
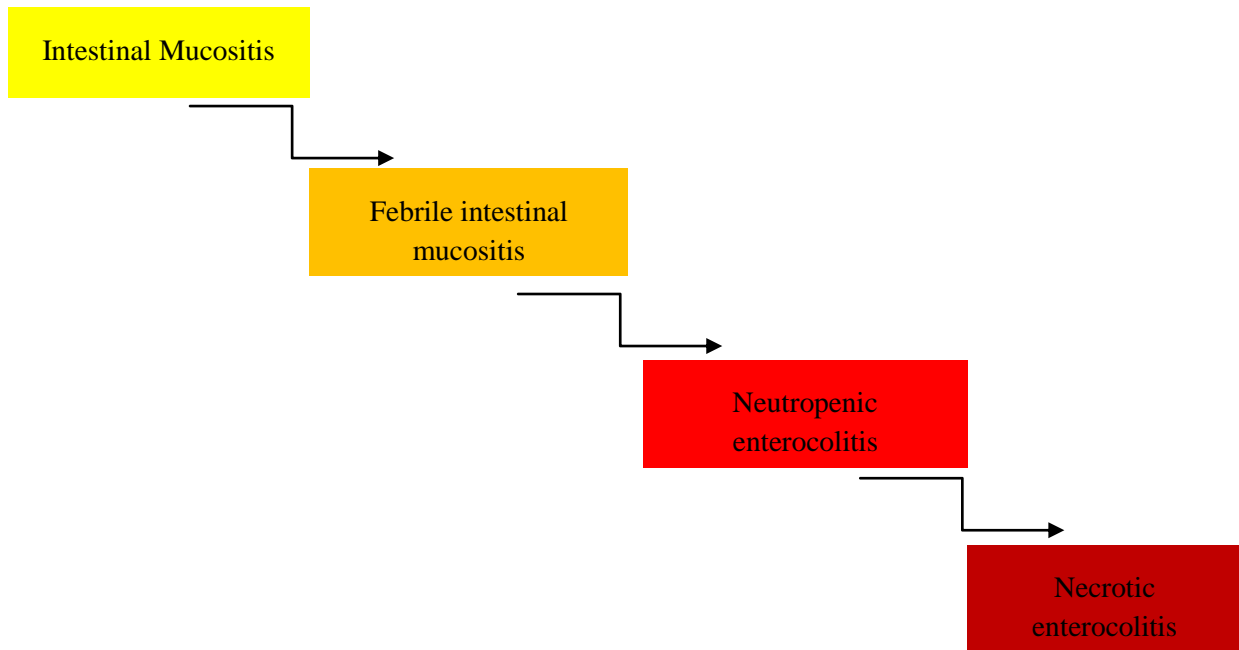
Microbiological findings

In one third of NE patients, blood cultures were positive for bacteria (Gram-negative rods or Gram-positive cocci). In several cases infection was polymicrobial and in one patient concomitant bacteremia and fungemia were documented. These microbiological data are similar to those described in the literature [11] and confirm the role of the intestinal flora in the pathogenesis of NE.

In more than two thirds of patients gastrointestinal tract colonization by yeasts (*Candida albicans* was the most frequent colonizer) or rarely molds *(Aspergillus* spp) was documented. Their role in the pathogenesis has been demonstrated in the literature by the documentation of fungal and mixed bacterial-fungal invasion involving *Candida* spp and *Aspergillus* spp in rare cases of NE [16]. However, the majority of the reported episodes of NE are of bacterial etiology. This is consistent with the findings in our study: two episodes of invasive candidiasis (5.7% of all NE) have been documented. In addition, fungal markers might fail to detect localized forms of fungal NE because of their lack of sensitivity in the absence of hematogenous dissemination.

Laboratory findings

Neutropenia was present in all patients. Its duration was variable depending on the chemotherapy regimen (shorter in auto-HSCT than in acute leukemia).

Inflammatory markers such as C-reactive protein and procalcitonine were not measured in all patients, but were found significantly elevated in patients with severe forms of NE and adverse outcome.

Two critically ill patients presented a high lactate level in the context of septic shock: both died.

Radiological findings

Some authors consider that CT scan is needed for confirmation of NE [19]. Gorschlüter et al. reported bowel wall thickening, a typical sign of NE, in a patient with the clinical diagnosis of intestinal mucositis [13], highlighting the continuum in the pathogenesis between these two entities. Less than two thirds of patients underwent an abdominal CT scan in the present study. This reflects the indications applied in our practice for CT imaging in febrile neutropenic patients with abdominal symptoms/signs: lack of clinical improvement after appropriate antibacterial and antifungal therapy, suspected local complications such as perforation or persistent fever with suspected invasive fungal infection. Two thirds of patients examined by abdominal CT scan presented bowel wall thickening more than 4 mm (BWT): in two thirds BWT exceeded 10 mm (cf. illustrations in Appendix 1). Cartoni et al. associated a BWT of more than 10 mm with adverse outcome of NE [12]. Other frequent CT signs associated with NE in our study and previously described in the literature were infiltration of adipose tissue, ascites and mesenteric/retroperitoneal adenopathies. In the remaining third of patients CT scan imaging did not reveal bowel wall thickening (BWT). These patients presented very suggestive clinical findings (fever, abdominal tenderness and peritoneal signs), which were classified as probable NE: these cases might represent non-severe forms of NE. On the other hand, these negative CT finding were issued from routine interpretation and imaging have not been read at second look by senior radiologists.

Medical and surgical therapy

All but one patient were treated conservatively. The management of NE included broad-spectrum antibacterial agents, hemodynamic support, and symptomatic treatment (mainly opioids). The majority of patients also received antifungal agents: therapy was started during the course of NE or ongoing prophylaxis was either modified for a broad-spectrum agent or continued unchanged. Parenteral or naso-gastric tube nutrition was administered in some patients.

No surgical bowel resection or exploratory laparotomy was performed.

A patient with duodenitis and mechanical cholestasis underwent an interventional endoscopic drainage

and recovered.

These management practices reflected the recent recommendations for an intensive conservative management with strict indications for surgical interventions in presence of local complications or bleeding [19, 20].

Morbidity / Mortality

In our study, the inhospital mortality was very low (5.7%) compared to the literature (up to 50.0-100.0% [1]). This ten- to twentyfold difference might be explained by the inclusion of milder forms of NE in our study and/or reflect differences in type and timing of conservative and antimicrobial management. 10% of patients developed a severe sepsis during the course of NE and two (5.7%) presented a septic shock and died: in one patient death was attributed to the complications of NE and in the second to a microbiologically documented lung legionellosis.

20% of patients presented an adverse outcome, i.e. at least one of the following events: abdominal surgery, severe sepsis, septic shock, admission to the intensive care unit, or inhospital mortality. Several factors were found to be associated with adverse outcome in a bivariate analysis. The majority of them reflect a common denominator in patients with the hematological diagnosis of acute myeloid leukemia. Induction or induction-reinduction chemotherapy with high-dose cytarabine results in intestinal mucositis and prolonged agranulocytosis, which are associated with severe infection and bloodstream dissemination. In addition, the association found between low BMI and adverse outcome of NE might reflect an increased individual vulnerability to severe complications or simply be the consequence of a prolonged critically ill status due to such a severe condition. These findings are confirmed in the literature: hematological and mucosal toxicity associated with high-dose cytarabine has been described as a major risk factor for NE in hemato-oncological patients [2-3]. While these factors associated with adverse outcome are not modifiable, they help to identify high-risk patients who need a very close follow-up in presence of symptoms/signs of abdominal infection and who might benefit of primary antibacterial and antifungal prophylaxis.

Due to the low number of patients, the retrospective and observational design, and the heterogeneity of the sample, we were unable to draw conclusions on the impact of treatment strategies on the outcome of NE, for example, the role of broad-spectrum antifungal drugs. Although proven or probable IFI are rare in the setting of NE, as confirmed by our findings, antifungal therapy is often administered empirically. This approach is based on the recommendation that an IFI should be suspected in patients with persistent neutropenic fever and symptoms/signs of infection despite broad-spectrum antibiotics. Thus, in the presence of severe NE, the administration of an antifungal therapy with a fungicidal affect

on *Candida* (echinocandin or amphotericin B) is consistent with these recommendations [21, 22]

Critical analysis of methods and results

This study is characterized by numerous limitations.

The first limitation is the definition of NE. We included all patients with a clinical diagnosis of NE in the discharge letter based on standardized key words. In some patients CT scan imaging had not been not performed or failed to confirm a BWT as major criterion of NE: a merely clinical diagnosis might have overestimated the incidence of NE or resulted in the inclusion of less severe cases of NE. Conversely, a systematic review of CT imaging by senior radiologists for improving the accuracy of the radiological findings was not performed: a more careful reading might have detected additional cases with BWT which might have been missed in the routine interpretation by less experimented radiologists. Further, the used selection key words might have missed cases of NE, e.g. those reported in the discharge letter with a diagnosis of intestinal mucositis with fever. Moreover, the different diagnostic criteria used in the literature make comparisons of findings and outcomes very difficult. The decision to study two years over a discontinued period was based on the similar case-mix with a high number of chemotherapy cycles at risk of NE: this might have been a source of selection bias resulting in data not reliably reflecting the epidemiology, e.g. with an overestimation of the incidence and severity of NE. However, the potential of bias is probably limited because the hemato-oncological population hospitalized in the isolation ward, the chemotherapy regimens, and the management of infections remained unchanged over the years. The similar incidence rates of NE (16%) and of adverse outcomes (20%) observed in 2008 and 2012 confirm that these data are probably representative of the five-year period.

The small number of patients resulting in a limited power of statistical analyses is an important limitation. In addition, the multiplicity of statistical tests was not taken into account, which might have overestimated the significance of some results. This study is thus merely exploratory and results of statistical analyses need to be carefully interpreted. Finally the findings on factors associated with adverse outcome were derived from a bivariate analysis, because the multivariate approach was not applicable in such a limited sample size.

Strengths of the present study in patients with NE are: i) the findings on a rare life-threatening medical condition for which few data are available in adult patients receiving intensive chemotherapy, ii) the identification of factors associated with adverse outcome which might have practical consequences on prevention and management of NE in high-risk patients.

CONCLUSION

In conclusion, this exploratory study points to the determinant role of intensive chemotherapy for acute myeloid leukemia and especially of high-dose cytarabine in the occurrence of NE. The hematological and mucosal toxicity resulting in prolonged agranulocytosis and severe intestinal mucositis are major components in the pathogenesis of NE and are associated with severe forms and adverse outcome. These findings may help the physician to identify the patients at high risk to develop complications who need a prompt management with close follow-up and maybe antimicrobial prophylaxis.

ACKNOWLEDGEMENTS

BIBLIOGRAPHY

1. Cloutier, R.L., *Neutropenic enterocolitis.* Hematol Oncol Clin North Am, 2010. **24**(3): p. 577-84.
2. Gomez, L., R. Martino, and K.V. Rolston, *Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases.* Clin Infect Dis, 1998. **27**(4): p. 695-9.
3. Wade, D.S., H.R. Nava, and H.O. Douglass, Jr., *Neutropenic enterocolitis. Clinical diagnosis and treatment.* Cancer, 1992. **69**(1): p. 17-23.
4. Gorschluter, M., et al., *Neutropenic enterocolitis in adults: systematic analysis of evidence quality.* Eur J Haematol, 2005. **75**(1): p. 1-13.
5. Cunningham, S.C., et al., *Neutropenic enterocolitis in adults: case series and review of the literature.* Dig Dis Sci, 2005. **50**(2): p. 215-20.
6. Blijlevens, N.M., J.P. Donnelly, and B.E. De Pauw, *Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview.* Bone Marrow Transplant, 2000. **25**(12): p. 1269-78.
7. Wach, M., et al., *Neutropenic enterocolitis: a serious complication during the treatment of acute leukemias.* Ann Hematol, 2004. **83**(8): p. 522-6.
8. Gorbach, S.L., *Neutropenic enterocolitis.* Clin Infect Dis, 1998. **27**(4): p. 700-1.
9. Song, H.K., et al., *Changing presentation and management of neutropenic enterocolitis.* Arch Surg, 1998. **133**(9): p. 979-82.

10. Gil, L., et al., *Neutropenic enterocolitis after high-dose chemotherapy and autologous stem cell transplantation: incidence, risk factors, and outcome.* Transpl Infect Dis, 2013. **15**(1): p. 1-7.

11. Kontoyiannis, D.P., et al., *Case records of the Massachusetts General Hospital. Case 13-2014. A 41-year-old man with fever and abdominal pain after stem-cell transplantation.* N Engl J Med, 2014. **370**(17): p. 1637-46.

12. Cartoni, C., et al., *Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography.* J Clin Oncol, 2001. **19**(3): p. 756-61.

13. Gorschluter, M., et al., *Abdominal infections in patients with acute leukaemia: a prospective study applying ultrasonography and microbiology.* Br J Haematol, 2002. **117**(2): p. 351-8.

14. Hoeffel, C., et al., *Multi-detector row CT: spectrum of diseases involving the ileocecal area.* Radiographics, 2006. **26**(5): p. 1373-90.

15. Katz, J.A., et al., *Typhlitis. An 18-year experience and postmortem review.* Cancer, 1990. **65**(4): p. 1041-7.

16. Gorschluter, M., et al., *Severe abdominal infections in neutropenic patients.* Cancer Invest, 2001. **19**(7): p. 669-77.

17. Aksoy, D.Y., et al., *Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis.* Ann Oncol, 2007. **18**(1): p. 183-9.

18. Bodey, G.P., *Unusual presentations of infection in neutropenic patients.* Int J Antimicrob Agents, 2000. **16**(2): p. 93-5.

19. Nesher, L. and K.V. Rolston, *Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy.* Clin Infect Dis, 2013. **56**(5): p. 711-7.

20. Davila, M.L., *Neutropenic enterocolitis.* Curr Opin Gastroenterol, 2006. **22**(1): p. 44-7.

21. Aguilar-Guisado, M., et al., *Universal antifungal therapy is not needed in persistent febrile neutropenia: a tailored diagnostic and therapeutic approach.* Haematologica, 2012. **97**(3): p. 464-71.

22. Giulieri S., D.D.J., Marchetti O., *Prévention, Diagnostic et Traitement des Infections chez les Patients Hémato-Oncologiques*, S.d.M.I. Unité d'Isolement, Département de Médecine, CHUV, Editor. 2013, CHUV: Lausanne. p. 19.

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

APPENDIX 1- CT scan imaging in two patients with NE.