Artículos originales

Enterocolitis neutropénica: revisión sistemática de casos publicados

Systematic review of case reports concerning adults suffering from neutropenic enterocolitis

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Resumen

Introducción: La enterocolitis neutropénica (ECN) es una entidad clínico patológica bien reconocida que amenaza habitualmente la vida y se asocia con diversas neoplasias sólidas y hematológicas y con la anemia aplásica. *Objetivo:* Evaluar la mortalidad global de la ECN, describir los hallazgos clínicos más frecuentes y las intervenciones terapéuticas reportadas en la literatura médica, con la finalidad de generar hipótesis acerca de los factores que influyen sobre la mortalidad y en la realización de intervenciones quirúrgicas.
Materiales y métodos: Se realizaron búsquedas avanzadas en las bases de datos Medline, Embase, Lilacs y en el motor general Google; además, se utilizaron como estrategias adicionales, búsquedas manuales en diversas revistas. Los reportes fueron considerados según la definición del caso teniendo en cuenta criterios específicos para inclusión y exclusión.
Resultados: Se seleccionaron 228 casos; 109 fueron casos individuales y 40 reportes correspondieron a series de casos. La comparación de los datos obtenidos a partir de los reportes individuales y de las series de casos no reveló diferencias significativas respecto de la mortalidad, intervenciones quirúrgicas, edad y sexo. Se encontró una mortalidad mayor en las mujeres (χ^2=7,51 p=0,006) comparadas con los hombres (50% vs. 28%). No se identificaron diferencias significativas entre las combinaciones de antibióticos respecto de la mortalidad (χ^2=12,85 df 13 p=0,45). La mortalidad (χ^2=3,89 df 1, p=0,049), las intervenciones quirúrgicas (χ^2=7,64 df 1, p=0,006) y la duración de la diarrea (χ^2=4,71 df 1, p=0,043) fueron significativamente diferentes en el 26,4% de los individuos que fueron tratados con antifúngicos; el 81% de los pacientes que no recibieron estos medicamentos murieron, en comparación con el 19% de los sujetos en que se reportó la utilización de antimicóticos.

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Conclusión: La evidencia sugiere que los agentes antifúngicos deben ser usados tempranamente en los pacientes que padecen ECN. Sin embargo, esta hipótesis debe ser evaluada en experimentos clínicos multicentricos con asignación aleatoria.

Palabras clave: Enterocolitis neutropénica, revisión sistemática, colitis, enterocolitis, necrotizante.

Abstract

Introduction: Neutropenic enterocolitis (NEC) is a well recognised clinical-pathological and life-threatening complication in patients suffering from several conditions, including solid and haematological malignancies or aplastic anaemia.
Objective: This review was aimed at evaluating overall NEC mortality rate, describing clinical diagnostic findings and therapeutical interventions reported in the literature and generating a hypothesis regarding factors influencing mortality and surgical intervention.
Materials and methods: An advanced search was made in Medline, Embase, Lilacs and Google. Additional strategies included manual search of specific journals. Reports were considered if they described case definition, inclusion and exclusion criteria.
Results: 275 cases were selected; 109 were from individual data and 40 from grouped data. Comparing data between case reports and case series revealed no significant differences related to mortality, surgical intervention, sex or age. Higher mortality (χ^2=7.51 p=0.006) was found in women (50%) compared to men (28%). No significant difference was found between antibiotic combinations and mortality (χ^2=12.85 df 13 p=0.45).
Mortality (χ^2=3.89 df 1, p=0.049), surgical intervention (χ^2=7.64 df 1, p=0.006) and duration of diarrhoea (χ^2=4.71 df 1, p=0.043) were significantly different in 26.4% of individuals using antifungal agents; death occurred in 81% of patients who did not receive such medication compared to 19% individuals reported as being treated with antifungal agents.
Conclusion: The current evidence suggests that antifungal agents should be used early in patients suffering from NEC. However, this hypothesis must be evaluated in multi-centric, randomised controlled trials.

Key words: Enterocolitis, neutropenic, systematic review,colitis, necrotizing enterocolitis.

Introduction

Clinical signs and symptoms of acute abdominal pain are seen in up to 5% of all cancer patients undergoing cytostatic treatment. Neutropenic enterocolitis (NEC) is the most common gastrointestinal infection (up to 50%) related with neutropenia (1).

The association between enteropathy and haematological disturbances was described by Cooke in 1933, who found submucous haemorrhage and appendiceal perforation in children suffering from leukaemia (2) The correlation of necrotising terminal ileum and colon lesions in patients suffering from neutropenia has become more commonly recognised since then.

NEC, also referred to as typhlitis in the early 1970's (from the Greek word *typhlon*, meaning *cecum*), is a clinico-pathological and life-threatening complication in patients suffering from haematological or solid malignancies or who are neutropenic for a variety of other reasons, such as aplastic anaemia or cyclic neutropenia (3,4). Rather than being a specific disease entity, NEC probably represents a syndrome of multiple pathological changes. This may explain the abundance of other terms such as ileocecal syndrome, necrotising enteropathy and necrotising colitis (5-7).

Incidence varies between series and is probably increasing, mainly due to the greater use of multi-agent, aggressive chemotherapeutic regimens for treating neoplastic diseases and the neutropenia which may occur following such treatment (8-14).

Clinical presentation is usually characterised by non-specific symptoms, such as fever, abdominal pain, distension, vomiting and diarrhoea which may be bloody (9,15). Optimal treatment for NEC patients therefore remains controversial. The literature advocates a conservative approach, citing currently high morbidity and mortality rates (10-16).

This review's aim was to evaluate overall NEC mortality rate, describe bacteriological and imaging findings, symptoms and therapeutical interventions reported in the literature and generate some hypothesis concerning the factors influencing mortality and surgical intervention.

Materials and methods

Literature search

Ovid software was used for systematically screening the literature. Medline and Embase were searched from 1966 and 1974 respectively to March 30th 2004, using an advanced strategy including the following Mesh terms and text words: neutropenic colitis, neutropenic enterocolitis, typhlitis, cecitis, necrotising enterocolitis, ileocecal syndrome and acute ileocecal enterocolitis. This model consisted of a method for identifying individual-level patient data from NEC case-series and reports as being a complication of haematological and solid neoplasms or aplastic anaemia, excluding cases involving AIDS patients, those treated with immunosuppressive therapies for rheumatologic diseases, individuals treated with antithyroidal medications, patients undergoing solid organ transplantation or patients without cancer. Additional strategies for Lilacs and Google general search engine were used with the same criteria.

References, lists of review articles, chapters in books related to clinical oncology, haematology and infectious diseases were evaluated; the *Journal of Clinical Oncology*, *Cancer*, the *American Journal of Roentgenlogy*, the *American Journal of Surgery* and *Archives of Surgery* were searched by hand. The process included volumes published between 1970 and 1990. 79 cases found in the Instituto Nacional de Cancerología E.S.E. (Bogotá, D.C., Colombia) between June 1992 and December 2003 was also included. The strategy was limited to reports in English, French, Spanish and Portuguese.

Criteria for article and patient selection

A *priori* selection criteria were determined for limiting articles to reports describing NEC's clinical course in adults (aged over 16) having haematological or solid neoplasms and aplastic anaemia. Case series and individual reports were considered for the review if they described patients having less than 1,000/mm^3 absolute neutrophil count, fever (temperature higher than 38°C) or hypothermia (temperature lower than 36°C), abdominal pain, diarrhoea and (where described) imagenological (i.e. thickening of the bowel wall, mucosal ulceration, loop abnormalities such as distension, ascites, pseudopolypoid changes of the cecal mucosa, pericolic fluid collection or mass, infiltration of the adjacent fascia planes and mural air) or histological findings compatible with enterocolitis. Reports described as pseudomembranous colitis or toxic megacolon in neutropenic patients having haematological or solid neoplasm and aplastic anaemia were considered in the review. If reports described more than one episode of neutropenic colitis in the same patient, then the first was selected.

Case series were included if it was possible to obtain all the information required for performing overall mortality and risk-factor analysis.

Article assessment

Two of the authors (AFC and LR) independently reviewed each article to determine report eligibility; disagreements relating to inclusion or exclusion of some cases were resolved by consensus.

Statistical analysis

Data was independently collected by two reviewers using a standard form and analysed by using SPSS 11.0 software. Descriptive statistics were used for characterising patients. Differences between the groups were analysed by using χ^2 test, Fisher's exact test or the Mann-Whitney U test. A 5% level was considered significant.

Results

275 cases were selected from the results of an extensive literature search (see references 17 to 108) yielding 578 references, 109 were from individual data and 40 from grouped data; 38% of the references could not be found due to restricted access to biomedical information on paper or in electronic format.

The reports had been published fairly evenly over the time period with 50% of them being published

between 2000 and 2004, 28.5% in the 1990´s, 13% in the 1980´s and 8.5% during the 1970´s. Mortality differed in each decade, being higher for patients treated during the last 5 years (41%) and the 1970´s (78%).

Overall NEC mortality was 38%. Median age was 43.5 in the 148 (53.7%) women and 38.5 (46.3%) in the 127 men; overall median age was 40.

Patients were compared from the four largest case series (n>30) and individual reports regarding differences in mortality (p=0.47), distribution of gender (p=0.22), type of treatment (surgical or medical; p=0.27) and age (p=0.9 using Mann-Whitney U test) for evaluating similarity between single data reports and grouped data reports.

Individual data analysis

Patient characteristics

Almost 80% of patients having NEC had haematological conditions; **table 1** presented distribution of neoplasm in patients with NEC. Higher mortality (χ^2=7.51 p=0.006) was found in women (50%) compared to men (28%), even after excluding women suffering from breast cancer (χ^2=6.51 p=0.011). NEC was presented in 29% of the 69 patients where it was reported in the first cycle and 35% in the second cycle of chemotherapy. Mean duration for diarrhoea was 7.8 days (SD +/- 5.8), median interval debut for this symptom following chemotherapy was 9 days and median duration of neutropenia was 11 days (beginning at the moment of colitis diagnosis).

Median neutrophil count at diagnosis was 200 and mean fever duration before presenting gastrointestinal symptoms was 5.47 days (SD +/- 3.44). Level and duration of neutropenia when disease was diagnosed did not influence mortality rate, number of days with diarrhoea and the need for surgical intervention.

Fifty percent of patients received just cytosine arabinoside or in combination with other cytotoxic medications, 40.2% anthracyclines and 10.7% taxanes (mainly docetaxel, given as a single agent or in combination with vinorelbin). Mortality and surgical intervention did not differ with the use of these medications.

Table 1. Distribution of neoplasm in patients with NEC.

Pathological diagnosis	Frequency	%
Acute myeloid leukemia	119	43.6
Acute lymphoblastic leukemia	48	17.5
Breast cancer	26	9.5
Aplastic anemia	20	7.3
Lymphomas	17	6.4
Chronic myeloid leukemia	12	4.4
Non-small cell lung cancer	9	3.3
Multiple myeloma	7	2.7
Colon cancer	4	1.7
Gastric cancer	2	0.7
Small cell lung cancer	2	0.7
Tongue cancer	1	0.4
Osteogenic sarcoma	1	0.4
Thyroid cancer	1	0.4
Hairy cell leukemia	1	0.4
Pontine glioma	1	0.4
Germ cell tumor	1	0.4
Adenocarcinoma of unknown primary site	1	0.4
Ovarian cancer	1	0.4
Soft tissue sarcoma	1	0.4
Total	275	100.0

Vomiting, intestinal bleeding and mucositis were reported in 47%, 25% and 16% respectively; mucositis was statistically related to mortality (χ^2=4.14 df=1; p=0.042). Nutritional status before onset of NEC was given in 52% of reports; 71% of them had a poor subjective evaluation.

Intervention

Reports showed that 56% of patients treated surgically died compared to 34.9% of those treated medically (χ^2=6.12; df 1, p=0.013).

The most frequent antibiotic treatments used in the 179 individual reports were beta-lactam combined with a betalactamase inhibitor having antipseudomonal activity (25.2%), followed by beta-lactam combined with betalactamase inhibitor having anti-pseudomonal activity and aminoglycoside (13.2%), just carbapenem (7%) and a combination of beta-lactam with no anti-pseudomonal activity plus

an aminoglycoside (5%). 30% of the reports had insufficient information. No significant difference was found between antibiotic combination and mortality (χ^2=12.85 df 13, p=0.45). Mean time for antibiotic treatment was 12.56 (SD +/- 10), directly correlated with duration of neutropenia (Pearson correlation R=0.58, p=0.000).

Reported patients who used metronidazol (45%) as complementary therapy did not reveal any significant difference in mortality (χ^2=1.53 df 1, p=0.21) including surgically treated individuals. No differences were found when duration of diarrhoea (more or less than 6 days) was compared with using this antibiotic in the subgroup of patients who survived (p=0.20). The same results were obtained for vancomycin used in 31% of patients.

Mortality (χ^2=3.89 df 1, p=0.049) and surgical intervention (χ^2=7.64 df 1, p=0.006) were significantly different in 26.4% of patients using antifungal agents. Death occurred in 81% of patients who did not receive such medication, compared to 19% of individuals reported as being treated with antifungal agents. However, no statistical differences were found between amphotericin B and fluconazole or when used in combination. Moreover, mortality rate was significantly lower in surgically treated patients that received antimicotics (Fisher's exact test p=0.05). Survival also appeared to be increased in patients having negative blood cultures (χ^2=4.66 df 1, p=0.031).

Additionally, antifungal agents significantly reduced the duration of diarrhoea (χ^2=4.71 df 1, p=0.043) but not the frequency of bloody stools. Significance related to mortality was maintained for the group of patients treated during the last decade (χ^2=6.0 df 1, p=0.05).

Growth stimulant factors did not influence mortality or the duration of diarrhoea in patients suffering from NEC. Mortality rates did not differ in the 22% of patients treated with total parenteral nutrition.

Microbiological findings

51.4% of the 111 blood cultures reported were negative, 31.5% Gram negative, 9% Gram positive, 7.2% anaerobes and 0.9% *Candida sp.* No statistical differences were found between isolated pathogens from blood or stool cultures compared to mortality. Table 2 presents microbiological isolations from blood cultures.

Table 2. Microbiological isolations from blood cultures

	Frequency	%
Negative	57	51.4
Escherichia coli	14	12.6
Klebsiella pneumoniae	9	8.1
Staphylococcus aureus	7	6.3
Clostridium septicum	4	3.6
Pseudomonas aeruginosa	4	3.6
Clostridium perfringens	2	1.8
Clostridium sp.	2	1.8
Proteus mirabilis	1	0.9
Serratia ficaria	1	0.9
Enterococcus faecium	1	0.9
Enterobacter cloacae	1	0.9
Stenotrophomona maltophilia	1	0.9
Bergellela zoohelcum	1	0.9
Alcaligenes xilosoxidans	1	0.9
Serratia marcesens	1	0.9
Streptococcus sp.	2	1.8
Pseudomonas fluorescens putida	1	0.9
Candida sp.	1	0.9
Total	111	100.0

Ninety-four stool cultures were reported; 59.6% were negative, 18.8% Gram negative, 11.7% anaerobes, 7.4% several *Candida* species and 3.2% Gram positive. **Table 3** presented microbiological isolations from stool cultures.

Radiological findings

Abdominal plain radiography was only done in 18% of reported cases. Ultrasound of the abdomen was done in 32% cases, 75% of them were described as abnormal and main combined findings were the presence of bowel wall thickness plus distension and ascites in 44%, followed by bowel wall thickness plus dilatation in 16% of individuals. Ultrasound revealed intestinal wall thickening in 79% of evaluated patients.

Table 3. Microbiological isolations from stool cultures

	Frequency	%
Negative	57	59,6
Clostridium difficile	8	8,5
Escherichia coli	7	7,4
Pseudomonas aeruginosa	6	6,3
Candida albicans	5	5,3
Staphylococcus aureus	2	2,1
Clostridium sp.	2	2,1
Enterobacter cloacae	2	2,1
Bacteroides clostridiform	1	1,0
Serratia marcesens	1	1,0
Candida cruzei	1	1,0
Candida glabrata	1	1,0
Proteus mirabilis	1	1,0
Enterococcus sp.	1	1,0
Klebsiella oxytoca	1	1,0
Total	94	100,0

Abdominal scan was reported as abnormal in 39% of cases and revealed unusual wall thickness of the large or small intestine in 81% of them. Mean bowel wall thickness was 11.67 mm (SD +/- 3.44; range 5 to 20).

The degree of mural thickening measured by abdominal scan was related to mortality. Death occurred in 80% of patients having wall thickness of more than 10 mm, compared to 20% of patients with bowel wall thickness less than 10 mm (χ^2=4.18; df 1 p=0.013). The presence of wall thickness was associated with the need for a major abdominal surgical intervention (Fisher's exact test p=0.043) and correlated with the duration of diarrhoea (Pearson correlation R=0.45, p=0.048). However, patients with mural thickening had not used antibiotics for a significantly longer period (p=0.061) or had a higher frequency of bloody stools (p=0.21).

Reported CT scans described bowel distension in 42% of patients; the mean for this imaging finding was 8.31 cm (SD +/- 2.72); this abnormal condition was not associated with surgical intervention or higher mortality rates. Computed tomography scan also showed ascites and pneumatosis intestinalis in 21% and 14% of evaluated patients, respectively.

Pathological findings

Reports concerning pathological specimens were available in 58 cases, 45 obtained from surgically treated cases and 13 from autopsies. Macroscopically, the affected bowel was oedematous, hemorrhagic and thickened. Histopathological analysis revealed that 69.2% of patients had diffuse ischemic colitis, 17.3% cecal inflammation with transmural pneumatosis, 3.8% leukaemic infiltration, 3.8% diffuse ileitis, 1.9% were normal and 4% related to other conditions. Greater mortality was found among reports that described diffuse ischemic colitis (χ^2=12.34 df=5, p=0.03).

Discussion

Case reports document unusual medical occurrences and can represent early evidence in identifying diseases, adverse effects and formulating hypotheses concerning possible risk factors. They are one of the most common studies published in medical journals (109). Systematic reviews of case reports cover a large number of subjects and are sensitive for detecting novelty, but they might have lesser specificity for medical decision-making (110,111).

This study' strength lay in a clearly defined comprehensive search and case definition using clear selection and exclusion criteria. This may have led to reduced misclassification of cases. This review included cases from many countries treated in several conditions. Particular comparison was used if individual reports differed from larger case series to evaluate whether authors of those cases reported severe symptoms, surgical intervention or death more frequently without finding any differences.

Main findings

NEC management is controversial. Treatment approaches have ranged from small case studies and recommendations have ranged from conservative management with supportive care to immediate surgical intervention, suggested in previous reports as being potentially advantageous treatment (3,10,25). Our study did not find evidence in favour of premature laparotomy; however, clear indications for surgery have been described, including bowel perforation, generalised peritonitis, continued bleeding

(despite corrected coagulopathy) and the presence of mass (3). Higher mortality in surgical patients may be explained by more severe compromise at the time of intervention.

A recently published guide has suggested that patients suffering from NEC should be treated with systematic antibiotics started immediately after cultures have been taken, considering the expected pathogens. Empirical treatment should consist of an acylureidopenicillin in combination with a beta-lactamase inhibitor or a third- or fourth-generation cephalosporin in combination with an aminoglycoside and metronidazol or monotherapy with a carbapenem (1). However, previous meta-analysis designed to evaluate beta-lactam or beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia suggested an advantage for broad-spectrum beta-lactam monotherapy over beta-lactam-aminoglycoside combination therapy for febrile neutropaenia (112).

This review did not find any differences associated with mortality rates between antibiotic combinations or in favour of using metronidazol or vancomicyn. However, empirical use of these medications must be considered on an individual basis, according to prevailing symptoms, signs and bacteriological findings.

Fungal isolates (including *Candida* and *Aspergillus* sp.) were only found in 14% of NEC cases before death, compared to 53% of post-mortem cases (14). McCullough and MacDonald recently suggested that antifungal coverage must be added to initial antibiotic coverage if an NEC patient remains febrile after 72 hours. They recommended that earlier administration of antifungal drugs should be considered if risk factors for visceral infection are present (prolonged duration of neutropenia, prior evidence of fungemia and fungal colonisation) (113). Although more evidence is needed, antifungal agents appear to be beneficial for reducing mortality in 62%, surgical intervention in 33% and diarrhoea in 28% of cases and must therefore be considered by clinicians. We propose that antifungal treatment should be started earlier, even in patients having negative blood or stool cultures, with no prior evidence of systemic fungal infection and without considering the duration of neutropenia.

Additional measures (such as bowel rest and using gastric decompression) have been uniformly used in managing NEC patients during the last few decades. Such procedures are not evidence-based but are generally recommended when considering intolerance to feeding and gastrointestinal symptoms. No randomised controlled trial has evaluated the effectiveness of growth stimulant factors in treating NEC; our review shows no difference in selected outcomes.

We are not able to explain the higher mortality rates in women. After excluding breast cancer patients, this difference was still maintained. Future studies should evaluate this finding. As previously suggested, wall thickening evaluated by CT scan could predict mortality; however, this study only evaluated abnormal tomography.

Study limitations

Cases of NEC reported in the literature may have special characteristics that differentiate them from unpublished cases; it is difficult to ensure that published cases represent the study population. Case series represent the largest and most complete percentage of patients over a defined period of time which we believe to be similar to the study population. Our study has evaluated potential bias by comparing four large series with individual case reports, no significant differences being found.

Not all the information from the cases was available for analysis, thus leading to bias being reported. Misclassification of the exposure or intervention may have occurred and some reports may have omitted publishing the use of several medications or complementary interventions. Several authors may not have reported the administration of antifungal agents leading to changing the association in the suggested effect of such medication. However, the results show that this group of medications has a potential effect on controlling mortality rate.

The use of hypothesis test may be controversial in this type of studies. Furthermore, many variables were collected and several types of statistical analysis were performed which may have led to random error. Nevertheless, positive associations (such as higher mortality in surgically treated patients, individuals with wall thickening greater than 10 mm or

the usefulness of antifungal agents) are sustained by biological plausibility.

Implications for practice and research

Current evidence suggests the early use of antifungal agents for reducing mortality, surgical intervention rates and duration of diarrhoea; however, different classes of antifungal medications must be evaluated for effectiveness and safety in multicentric randomised controlled trials. Other medications (such as metronidazol) used empirically in such patients, growth stimulant factors and different combinations of antibiotics or complementary interventions (such as parenteral nutrition) should also be evaluated.

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