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RESEARCH ARTICLE

HIGH RISK FEBRILE NEUTROPENIA: SUCCESS RATE OF ANTIBIOTIC SCHEMES USED IN HEMATOLOGY DEPARTMENT

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ABSTRACT

Background: Patients receiving chemotherapy (CT) for haematological malignancies usually present febrile neutropenia (FN), defined as fever and neutropenia <0.5 x 10^9/L. The usual treatment is empirical (antibiotics with known action against the usual pathogens in place).
Objective: To compare the success rate of the antibiotics schemes used for management of FN in the hematology department of Centro Médico Nacional"20 de Noviembre".Methods: A randomized, retrospective, longitudinal, descriptive and comparative study of FN cases between 1994 and 2014 was conducted. The results of ceftriaxone/amikacin, ceftazidime/amikacin, imipenem, quinolones and cefepime were compared. The principal outcome was to determine the success (defined as disappearance of fever for 4 straight days, before 15 days of treatment, without changing antibiotics) rate with each scheme.
Results: We studied 493 episodes. Mean age was 38 years (16-92). Fifty-three percent were female. Predominant neoplasia: acute leukemia (59% lymphoid and 32% myeloid). Source of infection was identified in 63% of cases. We eliminated 25 cases. There were thirty-three deaths (7%). There were 402 successful cases (82%). There was no difference (p> 0.26) between the first four schemes. Only cefepime was less effective (p = 0.04), with 68% of success.
Conclusion: No difference in success rate between the several antibiotic scheme was observed, except for cefepime.

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INTRODUCTION

Fever and neutropenia, or febrile neutropenia (FN), is defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours or held for one hour and an absolute neutrophil count <0.5 × 10^9/L, or greater if it is expected to fall below 0.5 × 10^9/L in the coming days (Naurois *et al*., 2010; Freifeld *et al*., 2010). It is expected after chemotherapy in 80% of hematologic malignancies (acute leukemia) (Freifeld *et al*., 2010; Arencibia Núñez *et al*., 2009; Bardossy *et al*., 2011). The mortality exceeds 5% in patients with solid tumors and >11% in hematological malignancies. The prognosis worsens if Gram-negative bacteremia infection is developed (18%). (Experience of the center published in 2015) No infectious source is identified in 20-30% of cases (Freifeld *et al*., 2011). Pathogen prevalence vary among different hospitals and it is generally agreed that, in recent decades, the causative organisms type has changed: Gram-negative were more frequent and now there is a greater association with Gram-positive bacteria.

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Thus, bacteremia, in 10-25% of the events, is caused by Gram-positive, mainly *S. aureus* (20 to 70%) and enterococci (20% and 50%) (Naurois *et al*., 2010; Freifeld *et al*., 2011; Bardossy *et al*., 2011). Prevalence of microorganisms reported in the various departments of hematology in Mexico is heterogeneous. In the INNCMSZ, FN was reported in 95.7% of patients with acute leukemia, with a predominance of *E. coli* as causative pathogen and an overall mortality of 30.6%. In 2011, the Hospital General of Mexico reported gram-positive microorganisms as their mayor cause of bacteremia (43.6%) and *S. epidermidis* as the most prevalent bacteria (Cabrera-García, 2012). There are different ways to classify patients with FN as high or low risk patients. The ESMO (European Society of Medical Oncology) Guidelines include the "Multinational Association for Supportive Care in Cancer Scoring System" prognostic index to assess multiple severity criteria. Another simpler and widely used form, with level of recommendation AII, is to assess risk based on the anticipation of neutropenia, considering as high risk neutropenia when in an evolution of >7 days, profound neutropenia (<0.1 x 10^9/L) is expected or comorbidities are present; otherwise it is considered as low risk neutropenia (Freifeld *et al*., 2011).

In absence of comorbidities estimated mortality is 1.2% - 4.9%; in those patients with > 4 comorbidities mortality increases to 57.4% (Gea-Banacloche, 2013; Lyman *et al*., 2010). Treatment of patients with high-risk FN is based on immediate and empirical antibiotic therapy. There are meta-analysis comparing monotherapy with combination therapies that conclude in asimilar efficacy (with level of evidence IA), although, in cases of prolonged FN and bacteremia, combination of B-lactam with aminoglycoside antibiotics is preferable (Bonilla *et al*., 2012). The IDSA (Infectious Diseases Society of America) guidelines recommend monotherapy with anti-pseudomonal B-lactam, such as cefepime, ceftazidime, carbapenems or piperacillin/tazobactam, with addition of other antimicrobial agents, such as fluoroquinolones or aminoglycosides, in case of complications or suspected antimicrobial resistance (Freifeld *et al*., 2011; Cabrera-García *et al*., 2012). Antibiotics progression with glycopeptides is indicated based on culture results, or empirically if fever persists for > 48 hours (Naurois *et al*., 2010; Freifeld *et al*., 2011; Cherif *et al*., 2004). Empirical antifungal therapy is recommended in cases of persistent fever after 4-7 days of use of broad-spectrum antibiotics (Naurois *et al*., 2010; Freifeld *et al*., 2011; Bardossy *et al*., 2011). Ourhematology department has implemented various schemes of antimicrobial therapy over several years. The objective of this study is to evaluate the global efficacy of these antimicrobial schemes.

MATERIALS AND METHODS

This was a randomized, retrospective, observational, comparative and longitudinal study. Records and follow-up sheets of patients treated at the hematology department of Centro MédicoNacional"20 de Noviembre" from January 1994 to December 2014 were analyzed. Patients >15 years old with neutrophils <0.5 x 10^9/L (or less than 1.0 x 10^9/L, if the decline was anticipated to less than 0.5 x 10^9/L in the course of the next seven days, associated to recent use of chemotherapy) with fever higher than 38°C not associated with application of blood products, drugs or leukemia activity were included. Patients with absence of fever but with an obvious source of infection were also included. Patients with intolerance to any scheduled antibiotic, who received antibiotics in the seven days before the start of FN and patients with CNS disturbance contraindicating the use of carbapenems were excluded. Patients who decided to leave the program and secondary deaths to causes other than infection were also excluded. Temperature was measured from armpit. CBC, serum creatinine and liver function tests were measured twice a week. Throat swab, nares culture, otic cultures, urine cultures, peripheral and central blood cultures (if they had indwelling catheter) were performed once a week. All patients received nystatin 500,000 units in mouthwashes every 4 hours and granulocyte colony-stimulating factor (G-CSF) from day 1 of treatment until increase neutrophil count to > 1.0 x 10^9/L.

Schemes randomly selected were: A) Imipenem 50 mg/kg/day intravenously divided into 3 doses administered every 8 hours; B) Amikacin 15 mg/kg/day plus ceftriaxone 30 mg/kg intravenously every 12 hours; C) Amikacin 15 mg/kg/day intravenous plus ceftazidime 30 mg/kg intravenously every 8 hours; D) Cefepime 2 g intravenously every 8 hours; E) Quinolones: moxifloxacin 800 mg daily, levofloxacin 750 mg orally or intravenously daily or gatifloxacin 800 mg daily. Under any scheme selected, if fever persisted for more than three days, vancomycin 30 mg/kg/day IV divided into four doses every 6 hours was added and it was replaced with linezolid in case of shortages. If fever persisted for more than three days, amphotericin 1 mg/kg/day on day 8 of treatment was added. In some cases, the scheme had to be chosen without randomization due shortage of selected antibiotic. The primary outcome was success of treatment, determined as the disappearance of fever for more than 96 hours with the original antibiotic scheme, without evidence of infection. Failure was considered if the fever persisted for more than 14 days or presence of death associated to FN.

Definition of Events

Success: Remission of fever for four days in absence of any infectious manifestation.

Failure: Persistent fever or other infectious manifestation, for more than 14 days from the start of the FN scheme.

Death: Death by infection within 14 days from the onset of FN.

Elimination: Death due to other cause than infection. Removal from the protocol voluntarily by the patient or family.

Toxicity: Any adverse event attributed to antibiotics or antifungals, observed during FN therapy scheme.

Statistical analysis

For data analysis statistical software SPSS Statistics v.220 for Windows was used. Descriptive analysis was performed with measurements of central tendency and dispersion. The comparison was initially made with Kolmogorov–Smirnov test to identify the behavior of the information and, according to the results, comparison with Student's t-test for quantitative variables and Chi2 for nominal variables were performed. To analyze prognostic factors a multivariate analysis with Kruskal-Wallis test for nonparametric ordinal variables was performed and for scalar variables ANOVA test was performed. We consider statistical significance with a $p < 0.05$ value.

RESULTS

493 FN episodes were studied. Mean age was 38 years old (16 - 92 years); gender distribution was slightly higher for females. The most frequent pathology was acute leukemia in 445 (90%); 59% of lymphoid lineage and 31% myeloid. Almost half of patients (48%) received chemotherapy during the protocol inclusion; 13% were on days 1-5 after the last dose of chemotherapy, 26% on days 6 - 10 and 12% were on days >10 after the last chemotherapy dose. No difference was found in the distribution among the schemes ($p > 0.08$) (Table 1). No source of infection was identified in 211 cases (43%). The most frequent sites of infection were: upper respiratory tract 82 (17%), lower respiratory tract 67 (12%), cutaneous abscess 32 (7%), sepsis 28 (6%), colitis 27 (6%), anorectal abscess 27 (6%), urinary tract 12 (2%) and intravenous access 11 (2%). Blood cultures were positive in only 43 patients (0.9%). The most common bacteria were *S. aureus* and *S. epidermidis* with 9 and 8 cases, respectively. The distribution of bacteria in the blood cultures was irregular across schemes ($p = 0.03$) (Table 2).

Table 1. Baseline data of patients included by antibiotic therapy schemes used (p> 0.08)

	A (157)	B (126)	C (92)	D (62)	E (56)	Total (493)
Age (years)	40	34	40	40	36	38
Female (%)	53	51	47	55	53	52
ALL (N=)	93	74	52	36	35	290
AML (N=)	55	35	33	13	19	155
Others (N=)	9	17	7	13	2	48
Previous FN (mean)	1.5	1.4	1.4	1.4	1.7	1.5
Fever (days, mean)	1.1	1.2	1.1	1.2	1.1	1.1
Maximum fever (mean)	38.6	38.7	38.6	38.5	38.5	38.6
Neutrophils*	0.14	0.18	0.15	0.12	0.15	0.15

Other: severe aplastic anemia, myelodysplastic syndrome, multiple myeloma or lymphoma.
FN: Febrile neutropenia. A: Imipenem. B: Amikacin/Ceftriaxone C: Amikacin/ceftazidime D: Quinolones E: Cefepime. ALL: acute lymphoblastic leukemia. AM; Acute myelogenous leukemia. * Mean X 10^9/L.

Table 2. Isolated microorganisms (N = 43) in blood cultures by antibiotic scheme (p = 0.003)

MICROORGANISM	A	B	C	D	E	Total
Included	157	126	92	62	56	493
S aureus	2	6	0	1	0	9
S epidermidis	1	1	1	0	5	8
S maltophilia	4	0	0	1	2	7
E coli	0	2	1	1	0	4
P aeruginosa	0	0	0	1	2	3
Acinetobacter Sp	1	1	0	0	1	3
S viridans	0	0	0	2	0	2
S B hemolítico	1	1	0	0	0	2
K pneumoniae	1	0	0	0	0	1
E cloacae	0	0	0	0	1	1
Enterobacter Sp	0	1	0	0	0	1
Acinetobacter inofii	0	1	0	0	0	1
Kocuriarosea	0	0	1	0	0	1

A: Imipenem. B: Amikacin/Ceftriaxone C: Amikacin/ceftazidime D: Quinolones E: Cefepime

Table 3. Outcome each antibiotic scheme (p = 0.04)

Scheme	Success	Failure	Death*	Eliminated
A (n=, %)	141 (89.8)	6 (3.8)	6 (3.8)	4 (2.5)
B (n=, %)	103 (61.7	7 (5.6)	8 (6.3)	8 (6.3)
C (n=, %)	69 (75)	10 (10.9)	7 (7.6)	6 (6.5)
D (n=, %)	51 (82.3)	4 (6.5)	3 (4.8)	4 (6.5)
E (n=, %)	38 (67.9)	6 (10.7)	9 (16.1)	3 (5.4)
Total	402 (81.5)	33 (6.7)	33 (6.7)	25 (5.1)

A: Imipenem. B: Amikacin/Ceftriaxone C: Amikacin/ceftazidime
D: Quinolones E: Cefepime*: death by febrile neutropenia

Overall results in the cultures of the upper respiratory tract were positive in 177 cases. The five most common bacteria (75%) were gram-positive bacteria: coagulase-negative staphylococci (CoNS) 76 (46%); *S. aureus* 20 (11.3%); *E. viridans* 16 (9%); beta-hemolytic streptococci 13 (7%); *S epidermidis* 8 (5%).

Table 4. Removal reasons (n = 25)

REASON	N= (%)
Death*	13 (52)
Breach	6 (24)
Withdrawal	4 (16)
Hypersensibility	2 (1)

* Causes other than febrile neutropenia.

The remaining cultures were 16 different microorganisms, with a frequency less than 7 each. Overall results in stool cultures: positive in 130 cases; the most frequent bacteria (92%) were *E. coli* 61 (47%); *E. hystolitica* 39 (30%); *K. pneumoniae* 9 (7%); *Enterobacter sp.*7 (5.3%); *P. aeruginosa* 4 (3%). The remaining cultures (8%) were 6 different microorganisms, with a frequency less than 3 each. In anorectal abscesses cultures: 19 positive cultures; the most common microorganisms (79%) were *E. coli 5* (26%); *E. hystolitica* 4 (21%); *S. epidermidis* and *K. pneumoniae*, with 3 (15.7%) each. In 11 positive results from skin abscesses cultures the predominant bacteria was *E. coli* 5 (45.4%). The remaining were: *E. viridans*, *Citrobactersp*, *E. cloacae*, *Proteus sp*, *Pseudomonas sp* and Coagneg staph. Eight urine cultures were positive: *E. coli* 3 (37.5%); *K.pneumonie* 2 (25%); the rest were *E. viridans*, *E. cloacae* and *Klebsiella sp.*No patient showed elevated creatinine levels at the end of the protocol. Mean days with fever at the end of the program was 4.88 with no difference among the groups (p = 0.058). Amikacin/ceftriaxone was the scheme with most days with fever (5.44 days) and imipenem withfewer days observed (4.29 days).

Glycopeptides use for persistent fever was observed in 51.1% of patients. The rate of progression to vancomycin was 47%, 59%, 37%, 52% and 48% and linezolid 9%, 1%, 21%, 5% and 2% for A, B, C, D and E schemes, respectively. Antifungal use, for fungal infection or persistent fever, was observed in 26% of patients. The two schemes with greater progression were cefepime and imipenem schemes with 26.8% and 26.7% (p = NS), respectively.Fungal infection was confirmed in 42 patients (0.9%). Scheme A had the highest frequency, with 21 cases (p = 0.0001). The most frequently isolated agent was *Candida sp*40 (95%). One case of aspergillus and one case of mucormycosis were observed. The used antifungals were: Amphotericin 93 (19%), voriconazole 31 (6%), caspofungin 3 (1%) and posaconazole 1 (0.2%). Success was observed in 402 patients, failure in 66 patients (faults in 33 patients and death by infection in 33 patients). When comparing between the antibiotic schemes, imipenem was the most successful with almost 90% and had the lowest mortality observed. The scheme with the lowest success rate (70%) and the highest mortality (16.1%) was cefepime (Table 3). Twenty-five patients were eliminated (Table 4). Two cases of hypersensitivity were observed in scheme B. There was no need to stop treatment due to toxicity. Before starting the febrile neutropenia protocol, all baseline data were analyzed. Adverse prognostic factors ($p < 0.05$) were starting antibiotics before day 6 of chemotherapy, creatinine >1.0 mg/dL as anorectal abscess, severe sepsis and colitis presence. Adverse prognostic variables during the evolution of FN were mean creatinine 1.2 mg/dL (SD 0.8), neutropenia 1.3 X 10^9/L (SD 2.7) and duration of fever for 10 days (SD 5). We evaluated the prognostic implications in terms of death and vancomycin or other glycopeptide use and the relative risk was 1.0 (CI 0.5-2.1). In case of use of any antifungal the relative risk was 2.37 (CI 1.16-4.85).

DISCUSSION

In this protocol, all schemes had a statistically comparable efficacy, except the cefepime scheme. There seems no advantage in using initial monotherapy, although the imipenem scheme, without statistical processing, seems to be the most effective. Taking into account failures alone, as herein defined, amikacin/ceftazidime scheme and cefepime scheme are equally ineffective; however, after including deaths into failures, as herein defined, cefepime scheme is clearly the least effective. Cefepime or ceftazidime monotherapy recommendation, as described by the last IDSA, ESMO and ASCO guidelines (Naurois *et al*., 2010; Freifeld *et al*., 2010; Gea-Banacloche, 2013) is not applicable in our context. Empirical therapy with cefepime as first line antibiotic has motivated controversies in recent years. Reports from various experimental studies of success as monotherapy were 40 to 82%, and 93.2% as initial therapy with potential escalation to other antibiotics (Montalar *et al*., 2002; Cherif *et al*., 2004; Ghalaut *et al*., 2007). Also, several meta-analyzes coincide with our experience where cefepime is associated with increased mortality and a RR 1.44 compared to ceftazidime, carbapenems or piperacillin-tazobactam, and an average mortality up to 26%. This is associated to their lack of activity against *Enterococcus sp* (Paul *et al*., 2006; Towne *et al*., 2009; Paul *et al*., 2010; Zowalaty *et al*., 2015; Lynch, 2012). Although not statistically significant, the difference between amikacin/ceftriaxone and amikacin/ceftazidime schemes is noticeable. One would expect similar or better effectiveness of last scheme given its action against *P. aeruginosa*.

An immediate explanation is the low frequency of this agent in patients reviewed here. Another is the sensitivity of the agent to amikacin (Freifeld *et al*., 2010; Zowalaty *et al*., 2015; Lynch 2012). It is possible that lower efficacy of cefepime improves if combined with amikacin. In an open randomized study in 40 patients with FN and hematologic malignancies, cefepime against ceftazidime (both 2 g IV every 12 hours) monotherapieswere compared and a success rate of 60% for cefepime and 55% for ceftazidime ($p \geq 0.05$) was observed.[15] Still, the cost-benefit of these combinations is highly debatable. According to drug costs in our hospital in March 2016, a day of amikacin/ceftriaxone therapy is three times cheaper than a day of amikacin/cefepime therapy (http://isssteapache.issste.gob.mx/transparenciaproactiva/Fichero.php. Actualizado 31/marzo/2016. Accesado 11/abril/2016). The overall success rate of our FN schemes was 81.5%. Compared to international reports, our overall death rate of 6.69% is comparable to that reported in developed countries and in Latin America (7 to 11%) (Arencibia Núñez, 2009; Madrid *et al*., 2013; Rabagliati *et al*., 2009; Viscoli *et al*., 2005) and lower compared with other developing countries. It is also lower than other Mexican hospitals which report 13.5% to 39% (Ugarte Torres, 2006; Karanwal *et al*., 2013; Lakshmaiah *et al*., 2015).

Antimicrobial scaling to some antifungal recommendation is based on the frequency of fungal infection as a FN complication due long-term persistent neutropenia. We foundno relationship to the antimicrobial class employed at the beginning of the FN episode (Naurois *et al*., 2010; Arencibia Núñez, 2009; Lynch, 2012). Is particularly striking that*S. maltophilia*was the third in frequency in blood cultures, species previously considered rare, enhancing the importance in monitoring this germ, and if the trend continues or increases, consider the empirical inclusion of trimethoprim sulfamethoxazole (Cho *et al*., 2015; Álvarez-Vera *et al*., 2015). In 2005 a study in our medical center comparing gatifloxacin against ceftriaxone/amikacin combination for febrile neutropenia therapy in patients with acute leukemia, with success rates for both schemes of 90%, was published (López-Hernández *et al*., 2005). Ten years after this study we can assert that the success rate of FN therapy schemes decreased, being imipenem the only antibiotic with a success rate close to that 90% previously reported, which implies an increase in bacterial resistance and/or inadequate hygiene or isolation. While scaling and rotation of antibiotics is mentioned among the strategies to avoid the increase in resistance, once both strategies have been implemented in our department, limited to the availability of antibiotics, it is necessary to insist on optimizing hygiene measures. Rotary schemes have shown reduction of resistant gram-negative bacteria from 8.5 to 0.9% (Chong *et al*., 2013). Our plan is to maintain a rotary plan for the antibiotic schemes that resulted more effectively. Adverse prognostic factors reported here include those that predict longer duration of neutropenia (FN at start of chemotherapy or within first days post-chemotherapy) and severity of infection (site of infection and severe sepsis, particularly with increased creatinine). During the FN episode single most important adverse prognostic factor is lack of neutrophils promotion. They are logical findings. Literature refers multiple prognostic markers on sepsis evolution in patients with neutropenia in intensive care unit. Currently one of the main trends is the initial and follow upmeasurements of serum procalcitonin and its depuration, with greater evidence than others acute phase reactants such as erythrocyte sedimentation rate or C-reactive protein (Arencibia Núñez, 2009; Bonilla *et al*., 2012).

Therefore, it is important to note that, even though none of these markers were contemplated as a variable in this study, we included clinical variables capable of predict a complication in the evolution of patients. In addition, there are other studies in patients with severe sepsis where cytopenias and source of sepsis had greater value in mortality prediction that procalcitonin. Our opinion is to keep in use clinical prognostic indicators in force and avoid increased costs with test that may result superfluous.

Conclusion

There is no significant difference in success rate among imipenem, amikacin/ceftriaxone, amikacin/ceftazidime and quinolones schemes in patients with febrile neutropenia. The cefepime scheme showed the lowest efficacy, with statistical significance. We do not recommend it in these patients. Adverse prognostic factors may be obtained by unsophisticated clinical and laboratory methods. We consider the use of other prognosis factors that may increase the economic cost of care unnecessary.

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