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Review / Revisão

Screening for the outpatient treatment of febrile neutropenia

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Febrile neutropenia is a frequent and potentially fatal adverse event of chemotherapy. Nowadays, febrile neutropenia is considered an emergency and it is known that prompt infusion of antibiotics decreases mortality. Several studies demonstrated that febrile neutropenia is a heterogeneous group of diseases and that factors such as outpatient status, no hypotension, no dehydration, no chronic obstructive pulmonary disease, no symptoms, no previous fungal infection and age < 60 years are protective factors against serious complications as demonstrated by the Multinational Association for Supportive Care in Cancer (MASCC). These data show that outpatient treatment and early discharge is safer and much research has shown lower costs for outpatient treatment in low-risk patients with febrile neutropenia. The aim of this work is to review and discuss tools (in particular the MASCC index) for safe screening of febrile neutropenia for outpatient treatment in addition to demonstrate results of research.

Keywords: *Neutropenia/drug therapy; Fever; Anti-bacterial agents/therapeutic use; Ambulatory care; Outcome assessment (health care); Sensivity and specificity; Risk factors; Triage; Review*

Introduction

Febrile neutropenia (FN) is a frequent complication of chemotherapy and, depending on the intensity of chemotherapy protocols, is potentially fatal.[1,2] It is well known since the study of Bodey et al. was published in 1966, that the risk of fungal and bacterial infection is inversely proportional to the neutrophil count and that this risk increases as the period of neutropenia draws out.[3,4] In the early 1970s, it was common to wait for the microbial agent to be isolated or to better define the focus of infection before beginning treatment. In 1971 Schimpff et al., on observing a 50% to 80% mortality rate for FN patients and realizing that in most cases the focus could not be clearly identified and that cultures were usually negative, recommended the immediate and empirical use of broad-spectrum antibiotics.[5] This aggressive approach reduced mortality to between 10% and 40%.[5-7]

After these studies, FN, considered a medical emergency, was treated with intravenous broad-spectrum antibiotics in-hospital. However, it was evident that FN involved extremely varied characteristics involving multiple variables that directly influence the outcome of cases. Thus in 1988, Talcott et al. examined protective factors against serious complications and showed that factors such as fever at home, absence of other clinical comorbidities and evidence of response to chemotherapy were associated to low complication and death rates.[8] The safety of outpatient management based on intense, early and continued treatment for patients with the three aforementioned protective factors was confirmed in 1992[9] suggesting that FN, if there were instruments to assess risk, could be treated on an outpatient basis. Although several studies have demonstrated safety in respect to protective factors in FN, these studies used different criteria to classify conditions that were low risk for complications. They could not

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therefore be considered safe and efficient in the clinical management of FN.[2] In 2000, with the aim of standardizing the definition of low-risk FN, a prospective multicenter study involving cancer units that treat FN was carried out with the purpose of validating an international score to identify patients at low risk for serious complications or death.

The index of the Multinational Association for Supportive Care of Cancer (MASCC) was established using numerous clinical and laboratory variables in a prospective analysis of 756 patients. This index standardized criteria for low-risk FN.[2] Other prospective studies have been performed and the MASCC index,[10] which is now widely accepted, was validated.[11] Although there is consensus regarding the MASCC index in the classification of low and high risk FN, it is not widely accepted that patients with low-risk FN can be treated as outpatients using oral antibiotics. Recently, however, research demonstrated the safety of the outpatient management of patients with low risk FN.

Pharmacoeconomic studies estimate a cost variation for each FN event of between US$ 2,000 and US$ 11,000. According to Canadian and British studies, 25.8% of the cost is related to antibiotics and 16.4% to exams. It is estimated that about US$ 5,000 can be saved per episode of FN when the patient is discharged early and referred to outpatient services. The use of oral rather than intravenous antibiotics can reduce the cost by 80%.[12]

The importance of studying the possibility of outpatient management of FN and to define risk groups can help us treat patients safely in Day Hospitals, as well as reduce costs and improve indication for hospitalization. The aim of this study was to review articles that studied risk analysis instruments and evaluate results of outpatient management of FN.

Definition of febrile neutropenia – initial evaluation

The main references define the term neutropenia as a neutrophil count < 500 cells/mm^3 [2,11,13,14] or < 1000 cells/mm^3 with a tendency to drop according to the FN treatment guidelines of the American Society of Infectious Diseases.[11] The concept of fever in Brazil is distinct from that published due to the method of measuring body temperature. In Brazil it is not normal to take the oral or tympanic temperature. Most publications define fever as oral or tympanic temperature exceeding 38.3°C or duration of a temperature of 38ºC for more than one hour.[11,13,14] In Brazil we measure axillary temperature which is lower than the oral temperature. Souza Viana et al. on analyzing FN in adult Brazilian patients, defined fever as an axillary temperature ≥ 38°C.[15]

A study conducted in Japan defined fever as an axillary temperature ≥ 37.5°C.[16] On reviewing the literature, no consensus was found on the definition of fever using the axillary temperature. We believe that fever is an axillary temperature of between 37.5ºC and 38ºC, which is why so many physicians use 37.8°C.

It is important that FN is always suspected whenever a patient has fever or signs and symptoms of infection while being submitted to chemotherapy. The patient in these circumstances should be considered neutropenic until a blood test confirms or discards this complication. Thus, in the initial assessment it is necessary to analyze the current cancer status, previous chemotherapy, to do a detailed physical examination and to request the laboratory tests that are described in Table 1. The initial administration of antibiotics should be seen as emergency use. There are numerous protocols for FN and so the emergency room physician should evaluate the severity of the patient's illness (to decide on hospital or outpatient management) and the risk of infection with gram-positive cocci and/or fungi and to initiate supportive therapy as quick as possible.

Table 1. Initial topics in the evaluation of febrile neutropenia

Medical history, physical examination and laboratory exams
1. Intensity of symptoms. How sick is the patient?
2. Fever at home / in-hospital?
3. Status of cancer: is it in Remission? Stable? In progression?
4. Evaluation of recently administered chemotherapy: the risk of prolonged neutropenia? Other toxicities expected?
5. Prior invasive fungal disease?
6. Use of prophylactic antibiotics?
7. Comorbidities: chronic obstructive pulmonary disease? Heart failure? Chronic renal failure?
8. Signs of dehydration?
9. Presence of mucositis?
10. Signs of severe sepsis?
11. Patient has implanted catheters? Signs of infection?
12. Hemogram
13. Renal function, liver enzymes
14. Chest x-ray
15. Blood cultures (peripheral one pair)
16. Blood culture (one pair for each access route of catheter)
17. Urine culture

Guidelines from the MASCC study [2] and of NCCN [32]

In the 1980s it became evident that FN evolved in different ways. Talcott et al. carried out a retrospective study of 184 FN patients and identified four risk groups: Group I: patients hospitalized with FN; Group II: patients with neutropenia and fever at home, who due to comorbidities require hospitalization; Group III: patients with neutropenia and fever at home without comorbidities, but with uncontrolled cancer; Group IV: patients with neutropenia and fever at home without comorbidities and with controlled cancer. It was demonstrated that patients belonging to group IV (n = 112) had a complication rate of 2% and no deaths;

the results suggested that it is possible to identify low-risk FN using the clinical characteristics.[8] In 1992, Talcott et al. carried out a prospective study in two hospitals. A total of 444 FN patients were studied and classified according to these risk groups. For groups I to III combined, the complication and death rates were 17% and 10% respectively, while in group IV the complication rate was 5% and no deaths occurred. It was thus suggested that less invasive therapeutic strategies should be devised for these low-risk patients.[9]

Similar to Talcott et al., other authors began to publish and in the 1990s several studies involving low-risk FN patients, including children[17,18] and adults[19-21], demonstrated the feasibility of outpatient management using oral or intravenous antibiotics after early discharge.

In 1999, Kern et al. studied 353 FN patients in 25 European hospitals. Patients considered low risk had duration of neutropenia (< 1000 cells/mm^3) of less than ten days, clinical stability and no specific focus of infection. Patients were randomly assigned for oral (ciprofloxacin and amoxicillin-clavulanate) or intravenous (cephtriaxone and amikacin) treatment. All patients were hospitalized during the entire study even though one group used oral therapy. The success rates for intravenous and oral treatments were 86% and 84%, respectively. During the study, three patients in the oral treatment group died, compared to five in the intravenous group. Hence, it was concluded that there was no significant difference in the treatment of low risk FN cases by intravenous and oral drugs.[22]

In 1999 in the USA, Freifeld et al. studied 232 low risk FN episodes of 163 patients.[23] The criteria for low risk were: neutropenia lasting less than ten days, hemodynamic stability, no abdominal pain, nausea, vomiting, diarrhea, altered mental status, infection of catheters, or new episode of pulmonary infiltration at radiologic examination and prophylactic antibiotic therapy was not employed. Patients were randomly allocated to two groups and treated in hospital. A ciprofloxacin and amoxicillin-clavulanate combination was used in the oral group and intravenous ceftazidime in the other. Both arms also used placebos: oral and intravenous preparations. Treatment was considered successful in 71% and 67% of the cases taking oral and intravenous antibiotics, respectively. No deaths occurred in either group.[23] Kern et al. also concluded that treating hospitalized low-risk NF patients with a combination of ciprofloxacin and amoxicillin-clavulanate was safe and effective.[22,23]

While these studies proved to be safe, the classification criteria of low-risk FN were varied. They can not therefore be considered safe and efficient in the clinical management of FN.[2]

With the aim of standardizing the definition of low-risk FN, a prospective multicenter study was performed in 2000 which involved cancer units that treat FN in order to validate an international score able to identify patients at low risk for serious complications or death. This study was conducted by the Infection Study Section of the Multinational Association of Supportive Care in Cancer (MASCC). The outcomes of this study included hypotension (SBP < 90 mmHg), respiratory failure, admission to the intensive care unit, disseminated intravascular coagulation, altered mental status, heart failure, severe bleeding requiring transfusion, arrhythmia and renal failure as serious complications. Numerous clinical and laboratory variables of 756 patients were analyzed. The study found that the main factors that predict low risk were: no other symptoms except for fever or mild to moderate symptoms, no hypotension, no dehydration, no chronic obstructive pulmonary disease (COPD), no previous fungal infection in oncohematological patients, fever at home, patients without oncohematological disease and age less than 60 years old (Table 2). Thus, a scoring system was designed using multivariate analysis; patients with a score of less than 21 points were defined as low-risk FN cases. The positive predictive value for low risk was 91%, specificity 68% and sensitivity 71% for an outcome without serious complications.[2]

One of the first studies that demonstrated the reliability of the MASCC index in the Brazilian population was published by Souza Viana et al. in 2008. Of 53 FN episodes the MASCC index had sensitivity, specificity, and positive and negative predictive values of 87.9%, 85%, 90.6% and 80.9%, respectively. There were no deaths in the Brazilian

Table 2. Points system of the Multinational Association for Supportive Care in Cancer (MASCC)

Criteria for protection	Points
1. Disease intensity: absent or mild[1]	5
2. No hypotension (systolic blood pressure ≥ 90mmHg)	5
3. No chronic obstructive pulmonary disease[2]	4
4. Hematologic neoplasia or no previous fungal infection	4
5. No dehydration[3]	3
6. Disease intensity: moderate symptoms[1]	3
7. Fever as outpatient	3
8. Age < 60 years	2

Total points: 26 points. Low risk ≥ 21 points; High risk < 21 points

1. Intensity of disease: subjective assessment of patient's general condition: can not add item 1 to item 6 - if the clinical condition is serious this criterion can not be scored
2. SBP: Systolic Blood Pressure
3. Chronic obstructive pulmonary disease - characterized by acute bronchial asthma or emphysema or need for oxygen therapy or steroids and/or bronchodilators
4. Dehydration = the need for intravenous hydration

patients classified as low risk however four cases evolved with complications due to FN.[15]

It is worth remembering the advantages and disadvantages of the MASCC Index as an instrument to define risk. The advantages are linked to the extremely clinical form of evaluation without costs related to laboratory tests. The facts that prove the power of the risk assessment of the MASCC index compared to inflammatory biochemical markers were tested by Uys et al.[24] This study analyzed 78 events of 63 FN patients. Risk was assessed by measuring the procalcitonin, C-reactive protein, and interleukins (IL): IL-1 beta, IL-6, IL-8, IL-10 and by the MASCC score. Although procalcitonin was strongly associated to the MASCC score, multivariate analysis demonstrated that the MASCC score was the only independent variable able to predict whether FN would result in serious complications and death or not.[24] Another important advantage is the time required to define disease status; there is no need to wait hours or days for a laboratory result.

The disadvantages are mainly related to the subjectivity of the definition of the intensity of the disease; it is extremely difficult to delineate the boundaries between mild and moderate and between moderate and severe symptoms.

Another important fact relates to the small percentage of oncohematological cases compared to the total cases in published articles. There are few studies that only tested oncohematological patients (Table 3)

Table 3. Characteristics of published articles that studied febrile neutropenia in respect to percentages of oncohematological cases, the MASCC index and mortality

References	Episodes of FN (n)	Oncohematological cases (%)	Mortality MASCC Low-risk (%)	Mortality MASCC High-risk (%)
Klastersky et al.[2]	756	16	6	39
Souza Viana et al.[15]	53	64.2	0	21.8
Cherif et al.[13]	105	100	2	5.2
Girmenia et al.[14]	90	100	3	40
Baskaran et al.[25]	116	100	7	29

FN = febrile neutropenia

Table 4. Published studies reporting positive blood culture rates associated to febrile neutropenia

References	Episodes of FN (n)	Oncohematological cases (%)	Positive blood culture rate (%)
Feld et al.[27]	471	90	13
Girmenia et al.[14]	90	100	12
Klastersky et al.[2]	756	16	27
Klastersky et al.[28]	2142	57	23.3

FN = febrile neutropenia

Positive blood cultures - a risk factor

Bacteremia is a relatively common complication in FN patients. Mortality appears to be high in FN patients complicated by bacteremia, especially when the clinical focus of infection has been identified (complex bacteremia).[26]

According to the literature, positive blood culture rates in oncohematological FN cases vary between 12% and 24% as illustrated in Table 4.

The largest sample size was in a study published by Klastersky et al. in 2007, who studied 2142 episodes of FN. The association between bacteremia and mortality was statistically significant: 10% of patients with bacteremia died versus 3% of cases without this risk factor.[28]

Procalcitonin - a new risk marker

Recently, other risk factors for FN have been studied. Procalcitonin is a marker widely studied. Von Lilienfeld-Toal et al. carried out a prospective study involving 35 oncohematological patients with 94 episodes of FN. Higher levels of procalcitonin were seen in FN episodes with documented infection (microbial isolation) compared to episodes with unknown infection foci. In episodes where the procalcitonin levels dropped by 70% after the second day without fever, the sensitivity, specificity, and positive and negative predictive values for the absence of fever during a period of five days or more were 100%, 75%, 50% and 100%, respectively.[29]

It is important to mention the study of Massaro et al., who analyzed procalcitonin and C-reactive protein levels in 52 hospitalized patients with onco-hematological-related FN. The average serum procalcitonin concentration was significantly higher in patients with severe infection (6.7 ng/mL versus 0.6 ng/mL) compared to C-reactive protein. As a marker, a serum procalcitonin concentration of more than 0.245 ng/mL had a sensitivity of 100% and specificity of 69.2%.

This study suggests that in this population, procalcitonin may be a diagnostic marker for severe systemic infection and is probably better than C-reactive protein.[30]

Outpatient management and use of oral drugs

Although the MASCC index appears to be a useful instrument to screen the risk of FN patients, until now there is no consensus on how to treat low-risk patients. Most articles that mention outpatient treatment for low-risk patients

Table 5. Studies that evaluated the safety of in-hospital oral antibiotic use for low risk febrile neutropenia patients

References	Episodes of FN (n)	Oncohematological cases (%)	Cases treated as outpatients (%)	Oral drug utilized	Success rate (%)
Chamilos et al.[31]	55	22	100	Moxifloxacin	91
Cherif et al.[13]	279	100	64	Ciproflaxacin + amoxicillin with clavulanate	99
Girmenia et al.[14]	90	100	76	Cefixime	72
Klastersky et al.[33]	178	7	44	Ciproflaxacin + amoxicillin with clavulanate	96

Table 6. Eligibility criteria for treatment of febrile neutropenia with oral antibiotics

1st Rating: Clinical and laboratory indications for outpatient treatment
1A) MASCC score ≥ 21 points or
1B.1) Fever at home and
1B.2) Absence of comorbidities and
1B.3) Duration of neutropenia < 7 days and
1B.4) Performance status (ECOG: 0-1) and
1B.5) Serum creatinine < 2 mg/dL and
Liver enzymes < 3 x above the normal level
2nd Assessment: Social for outpatient treatment
2A) Consent for home treatment
2B) Possibility of returns to outpatient clinic every 24 hours
2C) Home telephone number
2D) Able to go to the emergency service
2E) Maximum distance to hospital of 1h transport
3rd Rating: treatment with oral antibiotic
3A) No nausea or vomiting
3B) Capacity to comprehend use of oral antibiotic
3C) Absence of prophylaxis quinone
4th Assessment: Observation and Tracking – Start of treatment between 2-12 h
4A) Confirmation of low-risk, observation of clinical stability
4B) Observe reactions to antibiotics
4C) Planning for early discharge and early return
4D) Instructing the patient to return if signs become severe
4E) Revaluation face-to-face or by telephone between 12-24 h

According to the National Comprehensive Cancer Network Practice Guidelines in Oncology - v.1.2007

and prescribed orally administered drugs (were designed as follows: all patients are initially hospitalized and 24 to 72 hours later are reassessed for early discharge and outpatient management on oral antibiotics.[13,14,31,32] Thus, for patients assessed as low risk, the success rates are very high (Table 5). This does not mean that discharging FN patients considered low-risk at diagnosis and prescribing oral antibiotics is so safe, as was demonstrated in these studies.

The National Comprehensive Cancer Network (NCCN) in its guidelines V.I.2007, defines the following parameters for the outpatient treatment of FN: evaluation to identify low-risk, social assessment for outpatient treatment, evaluation for suitability to treat by orally administered drugs and short-term observation of treatment (Table 6). After careful evaluation, these patients should be monitored daily in respect to identification of cultures, new signs and symptoms, persistence of fever beyond the third day of treatment, lack of adherence to oral drug therapy and clinical examination for the first 72 hours. The NCCN suggests that, when there are no complications, the follow up can be by daily telephone conversations until the end of treatment. Currently, more and more studies analyze safety parameters for early discharge with outpatient management and, until now, the MASCC index is the safest and best standardized risk assessment instrument.[32]

Conclusions

It should be stressed that to design protocols for the outpatient management of febrile neutropenia, it is essential to perform: careful clinical and laboratory evaluations, a social assessment and to have a nursing structure to monitor the returns and evolution of patients. Without an organized outpatient clinic structure this approach and form of treatment is highly risky.

Resumo

A neutropenia febril (NF) é uma complicação frequente e potencialmente fatal nos pacientes em tratamento quimioterápico. Entendemos hoje que a neutropenia febril é considerada uma emergência clínica e que a administração de antibióticos de amplo espectro diminui drasticamente a mortalidade. Estudos sugerem que a neutropenia febril compreende um grupo extremamente heterogêneo e que dados clínicos como febre domiciliar, ausência de hipotensão, ausência de desidratação, ausência de doença pulmonar obstrutiva crônica, ausência de outros sintomas, ausência de infecção fúngica prévia e idade < 60 anos são fatores de proteção para complicações clínicas graves segundo o estudo da Multinational Association for Supportive Care of Cancer (MASCC). Estes dados permitem maior segurança para o tratamento ambulatorial e alta precoce, uma vez que estudos fármaco-econômicos demonstram importante redução de custos no tratamento ambulatorial da neutropenia febril . O objetivo desta revisão é discutir instrumentos de segurança da triagem de um paciente neutropênico febril (principalmente pela utilização do índice MASCC), como também demonstrar as formas descritas na literatura do tratamento ambulatorial e seus resultados.

Descritores: *Neutropenia/quimioterapia; Febre; Agentes antibacterianos/uso terapêutico; Assistência ambulatorial; Avaliação de resultados (cuidados de saúde); Sensibilidade e especificidade; Fatores de risco; Triagem; Revisão*

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