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Review Article

The Mortality Rate in Neutopenic Children Population in Oncology an Algerian Study

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Abstract: Febrile neutropenia consecutive to the administration of chemotherapy constitutes the most serious and the most frequent complication of cytotoxic chemotherapies. It is often a sign of infection, being able to quickly turn in septicemia if no treatment is begun; it thus constitutes an emergency for diagnosis and therapeutics. The objective of this work is to study the epidemiological, clinical, biological, etiologic and evolutionary characteristics of the episodes of febrile neutropenia, to evaluate the importance of the infectious risk and the main involved germs, to identify the difficulties of the management and the follow-up of the children having developed a febrile neutropenia and finally. During our retrospective study concerning the episodes of febrile neutropenias diagnosed in the pediatric oncology unit of the pediatric department of the university hospital of Alger over a period of 04 years (from 1 January 2017 to 31 December 2020). 205 patients having solid tumor were collected. Among them 45 cases presented febrile episodes, the average age was 5.75 years with a maximum frequency of them were male, and the main motive for consultation was the fever. The average deadline of occurrence of neutropenia was of 14.6 days. A documentation of the fever is obtained clinically at 20 % of the cases, while in 80 % of the cases, the fever remains unknown origin. The infectious sites found are: a) Skin (6.6%), digestive (4.4%), respiratory (8.8%). b) The average duration of the neutropenia was of 18.8 days. Upon completing this work, we emphasize the need of prompt and appropriate management of the hematological emergency that is febrile neutropenia by an adapted empirical antibiotic therapy after a good bacteriological investigation, without forgetting the importance of prophylaxis based mainly on hygienic mucocutaneous measures and the information/education of parents about the risk of infection and means of prevention.

Keywords: Ferbril neutropenia, pediactric oncology, chemotherapie, traitement complication.

INTRODUCTION

Febrile neutropenia (FPN) is commonly defined by a polynuclear neutrophil count (PNN) less than 500 elements/mm3 or less than 1000 elements/mm3 and whose reduction to levels below 500 elements/mm3 is predictable within 48 hours and a fever ≥ 38.3°C during one dose or ≥ 38°C on 2 occasions 1 hour apart. During these episodes of NPF, the symptoms are poor but the risk of septic shock is high in the absence of early treatment [1, 2].

Epidemiology

Febrile neutropenia is one of the most serious and severe side effects of chemotherapy. Indeed, 10 to 50% of patients with a solid tumor and more than 80% of those with a hematologic malignancy undergoing chemotherapy will develop febrile neutropenia with a respective mortality of around 5 and 11%.

The incidence of fever is 10 to 50% when neutropenia lasts less than 5 to 7 days, whereas it is more than 90% for neutropenia lasting more than 7 to 10 days. In the emergency room, 45% of patients with febrile neutropenia present criteria for severe sepsis or septic shock [3].

Indeed, the frequency of the occurrence of febrile neutropenia remains high according to the results obtained by the different series of patients treated in specialized centers, whether in developed, developing or third world countries.

In France, a study carried out by the Bergogne Institute in Bordeaux, on a population not exclusively infant, involving 504 cases of hematological malignancies and solid tumors, 234 patients had at least one episode of NPF, i.e. an incidence of 46% [4].

In the study conducted by the "Japanese FN Study Group" (JFNSG), among the 201 cases evaluated in Japan, 189 children presented an episode of FN, representing an incidence of 94% [5].

Likewise, in an old study carried out at the hematology and bone marrow transplant department at the Pierre and Marie Curie center (CPMC) in Algeria, the incidence of FN is high. Among the 762 patients evaluated, 759 patients had at least one episode of FN, an incidence of 99.6% [6].

Our study is a retrospective study concerning the episodes of febrile neutropenias diagnosed in the pediatric oncology unit of the pediatric department of the university hospital of Alger over a period of 04 years (from 1 January 2017 to 31 December 2020). 205 patients having solid tumor were collected. Among them 45 cases presented febrile episodes, the average age was 5.75 years with a maximum frequency of them were male, and the main motive for consultation was the fever. The average deadline of occurrence of neutropenia was of 14.6 days.

In our series, our results are superimposable with those of the literature. Among the 205 cases evaluated, 45 children presented at least one episode of FN, an incidence of 21.9%.

Table 01: Incidences and frequencies of FN episodes in the different series of studies

The studies	Number of cases	Number of cases of FN	Incidence of FN	Number of episodes
Institut Bergonié - Bordeaux	504	234	46%	315
CHOP-CHU Nancy	-	41	-	69
JFNSG-Japon	201	189	94%	189
CPMC-Algérie (old study)	762	759	99,6%	1431
CHOP Tunisie	-	128	-	200
COHP-Rabat	-	51	-	76
Our study	205	45	21,95%	69

Risk factors for febrile neutropenia:

Infection is a significant cause of mortality in cancer patients. Indeed, these patients present several infectious risk factors (general and specific) very often associated. These factors are linked to the cancer pathology and its treatments on the one hand, and to the patient (individual factors) on the other hand. These factors can be summarized as:

- The depth and duration of neutropenia.
- Bacterial environmental ecology.
- Alteration of anatomical barriers.
- The underlying pathology.
- The type of chemotherapy administered.
- The presence of foreign material (central catheters, implantable chambers, etc.).
- Intensity of previous cytotoxic treatments.
- General condition and presence of associated pathology….

A- General Factors:

The incidence and severity of infections are correlated with the depth and duration of neutropenia [7]. The number of PNNs is inversely proportional to the infectious risk, so the lower the number of PNNs, the greater the infectious risk and vice versa [8]. The absolute neutrophil count (ANC) during chemotherapy-induced myelosuppression is lower between 5 and 10 days (Figure 01) [9]. The risk of infection is high if neutropenia lasts more than a week, in addition there is an increase in fungal and viral risk [10]. The depth and duration of neutropenia are themselves linked to the underlying pathology (hematological or not), its duration, immunosuppression and chemotherapy.

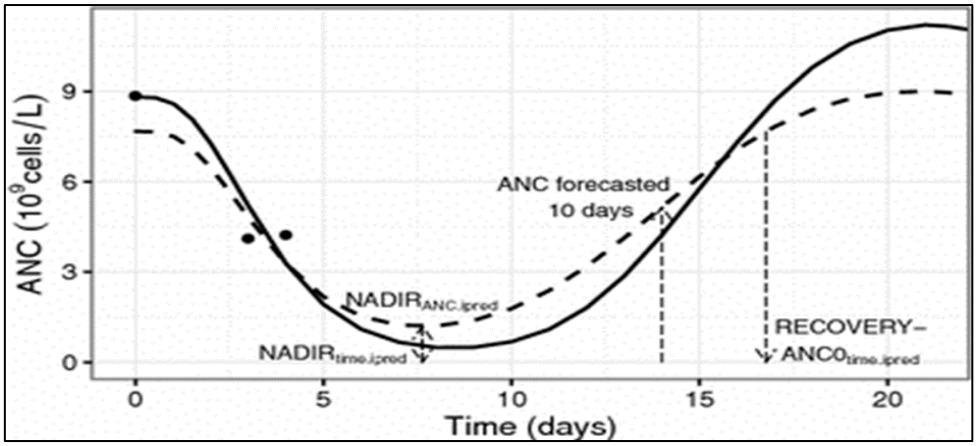


Figure 1 [9]: The absolute neutrophil count (ANC) versus time during chemotherapy-induced myelosuppression

Chemotherapy for solid tumors causes neutropenia of short duration (3-7 days), most often between the 8th and 16th day after chemotherapy. The incidence and severity of FN increases during treatment of ALL or lymphoma or during autologous marrow transplantation [11]. The risk is greatest in cases of acute leukemia and allogeneic marrow transplantation, which can be accompanied by deeper neutropenia sometimes lasting two to three weeks; the risk of infections, particularly of fungal origin, is then greater. There is a well-established correlation between the dose of cytotoxic administered and the hematological toxicity of chemotherapy. This has been documented in particular in prospective randomized studies comparing doses of anthracyclines or alkylating agents. However, there are only a few protocols for which the risk of febrile grade IV neutropenia exceeds 75% [12, 13]. These are essentially chemotherapy protocols used in pediatric oncology and possibly adapted for adults (for example COPADM in lymphomas, VIDE in Ewing sarcomas, etc.).

For the vast majority of chemotherapies in current practice, the incidence of FN varies between 5 and 40% [14]. [15] Indeed, in a recent survey concerning most of the randomized trials published in the management of breast cancer or lymphoma, Lyman *et al.*, report that, on the one hand,

Hematological toxicity and its complications are not always described and, on the other hand, they vary greatly depending on the studies while chemotherapy programs seem identical [16]. In any case, the risk of neutropenia also seems linked to the treatment phase with a greater risk during the first courses. Indeed, a recent follow-up study showed that 65% of hospitalizations for febrile aplasia occurred during the first two cycles of chemotherapy [17].

It should be noted that 5% of patients receiving standard conventional chemotherapy will actually experience an episode of FN, while 40% of patients receiving intense chemotherapy will actually experience FN. Added to this is individual susceptibility to the risk of FN.

The parameters conditioning this individual susceptibility are still only partially known: the site of the tumor, the coexistence of an active infection, a deterioration in general condition (assessed by performance status), malnutrition, bone marrow invasion, age and probably the intensity of previous treatments [18].

In most studies, only some of these parameters are studied, most of the published models do not take into account the same factors, they take into account pretreated patients (secondary prophylaxis) whereas the information would be all the more necessary as the benefit that must be estimated must be estimated before any treatment [19].

B- Specific Factors:

For certain infections, more specific risk factors have been identified [20]:

- For Streptococcus viridans septicemia:
- Major neutropenia.
- Severe oropharyngeal mucositis.
- Antibiotic prophylaxis with fluoroquinolone or cotrimoxazole.
- Chemotherapy with hight dose of cytarabine

Treatment with gastric anti-secretory or antacid.

- Colonization marked by oral streptococci:
- For invasive candidiasis:
- Intense and prolonged neutropenia.

- The presence of a central venous line.
- Broad-spectrum antibiotic prophylaxis.
- Corticosteroid therapy.
- Recent history of abdominal surgery.
- For aspergillosis (21):
- Profound and prolonged neutropenia,
- The duration and intensity of corticosteroid therapy without a very precise threshold having been set,
- The existence of work in the immediate vicinity (emission of dust).

C- Biological Factors:

- Absolute neutrophil count greater than 100/mm3.
- Absolute monocyte count greater than 100/mm3.
- Expected duration of neutropenia less than 7 days.
- Normal or subnormal liver tests and kidney function.

Furthermore, Kern *et al.,* and Freifeld *et al.,* proposed a series of criteria to classify the patient in the high-risk neutropenia category. These criteria are: the existence of an allogeneic transplant, the presence of renal or hepatic or respiratory insufficiency, a state of shock, intravenous administration of treatment, HIV infection, catheter infection or central nervous system, abdominal pain, nausea and/or vomiting, diarrhea, and neurological or mental disorders [22, 23].

In order to develop easy-to-use tools, Talcott *et al.,* defined, in 1992, four groups of patients through a prospective study conducted in two centers including a total of 444 patients:

- Group 1: patients already hospitalized.
- Group 2: patients not hospitalized but immediately presenting with comorbidity: hemodynamic instability, hemorrhage, respiratory failure, neurological disorders, etc.
- Group 3: non-hospitalized patients whose underlying condition is not controlled.
- Group 4: non-hospitalized patients without comorbidity and whose underlying condition is controlled.

Talcott *et al.,* estimated that patients already hospitalized had the most frequent complications and non-hospitalized patients, whose cancer was progressive, had the highest mortality rates [24].

Groups 1, 2 and 3 correspond to high risk groups with 33% secondary complications and 10% mortality, group 4 corresponding to a low risk group with 5% secondary complications and no deaths ($p < 0.000\ 001$) [61], The score that seems most suited to clinical practice is that developed by the MASCC (Multinational Association for Supportive Care in Cancer), the objective of which is to simply identify patients at low risk of complications.

A prospective study on a cohort of 756 patients thus considered 43 clinico-biological variables making it possible to isolate seven weighted parameters. The maximum score is 26, and a score greater than 21 predicts low risk, with no serious complications. Its positive predictive value evaluated on a validation group ($n = 383$) is 91%, its specificity of 68% and its sensitivity of 71% [69]. However, the MASCC score does not seem to be widely used in daily practice, although several recent American, European and Asian studies show that it is feasible and reliable [25, 26].

The reason for the current under-use of this score merits investigations to identify possible obstacles to the dissemination of this tool.

Even if an infection is only proven in approximately 30% of patients arriving at the emergency room in FN (27), some will develop severe sepsis and die quickly. The patients most at risk of febrile neutropenia are those who have hematological cancer (lymphoma, acute leukemia), who have received a bone marrow transplant (allograft is more risky than autograft), who have had a relapse of their cancer, who have concomitant diseases (chronic obstructive pulmonary disease, etc.), who are of advanced age and whose neutropenia is profound (PNN<100 elements/mm3).

In our series, the PNN rate was less than 100 elements/mm3 in 04 children, or 8.9% of cases.

Evaluation of the febrile episode:

Febrile neutropenia is often a sign of infection, which can quickly progress to sepsis if no treatment is undertaken. It therefore constitutes a medical emergency. Febrile neutropenic patients do not represent a homogeneous population, the risk of complications not being the same for everyone. To stratify these patients according to the risk of infectious complications, clinical or biological selection criteria were evaluated.

A- Clinical evaluation:

Clinically, neutropenic patients present some particularities that are important to be aware of. Inflammatory reactions are often less significant, or even absent, making the identification of an infectious point of origin uncertain. Monitoring the temperature is sometimes difficult: hypothermia is possible as well as an absence of fever despite signs of infection, while on the contrary, fever can be linked to the underlying neoplasia or induced by certain treatments. In all cases, the possible speed of progression of infections must be taken into account. The clinical assessment of the febrile neutropenic patient is an important element of risk assessment. The diagnostic approach must be exhaustive and be based more particularly on:

- As immunosuppression is a reduction of the normal inflammatory response to invasive microorganisms, neutropenic children often present with atypical or minimally symptomatic clinical signs. Sometimes, the clinical picture can be serious from the outset with hypotension and shock requiring immediate resuscitation measures.
- The clinical examination is essential in the search for an infectious source likely to point towards the origin of the fever and to start probabilistic antibiotic therapy guided by the infectious agents according to the clinical presentation.
- The clinical examination must be complete and detailed: examination of the ENT area (ears, mouth, throat, nose), skin lesions, nails, fingers and toes. Particular attention will be paid to the catheter and its route, from the gastrotomy or any other foreign body likely to induce inflammation, to the oral cavity (mucositis), to the perineum (anal ulcerations), and to the existence of digestive and/or pulmonary signs. Additionally, according to the Infectious Disease Society of America (IDSA), if the patient has a central line, a catheter culture as well as a peripheral blood culture should be performed [28]. In the event of pulmonary symptoms, it is essential that the child be treated near a pediatric intensive care unit and particularly if there are signs, even minimal, of pulmonary distress (oxygen dependence, slight fluttering of the wings of the nose, etc.), because it is often necessary to perform bronchoalveolar washing for diagnostic purposes.
- Finally, the patient's digestive symptoms, such as diarrhea, should be taken into account in order to detect bacterial translocation at the gastrointestinal level [29]. It should be noted that, despite all these examinations, only 20 to 30% of patients receive a clear diagnosis of infection associated with NPF, according to the IDSA (28). Which is compatible with what we found in our series.

Infectious localization

In the literature, the most frequently found clinical foci are mainly cutaneous, digestive, respiratory, but their distribution varies from one center to another. In our series, clinical documentation of fever was obtained in 20% of cases.

- Cutaneous manifestations, found in 6.6% of cases.
- Digestive outbreaks represented 4.4% of documented infections, most often diarrhea and abdominal pain (Table 2).

Table 2: Comparison of the frequencies of infectious clinical outbreaks in the different series of studies [30-31]

Infectious localization	CPMC-Algérie (old study)	CHOP-Tunisia	COHP-Rabat	Our study
Cutaneous	45 %	5,7 %	56 %	6.6%
Digestive	35 %	12 %	12 %	4.4%
Pulmonary	14 %	-	24 %	8.8%
otolaryngology	-	47 %	4 %	-
Urinary tract	-	-	-	-
Bones	-	-	4 %	-
Other	6 %	32,3 %	-	-

Biological Evaluation:

Table 03: Classification of neutropenia according to their absolute values [32].

Classification	PNN values
Discreet Neutropenia	> 1000 elements/mm3
Moderate Neutropenia	Between 500 and 1000 elements/mm3
Serious Neutropenia	Between 200 and 500 elements/mm3
Very serious Neutropenia	< 200 elements/mm3

In all children with MPN, infection is always suspected, and testing should be initiated to detect the site of infection.

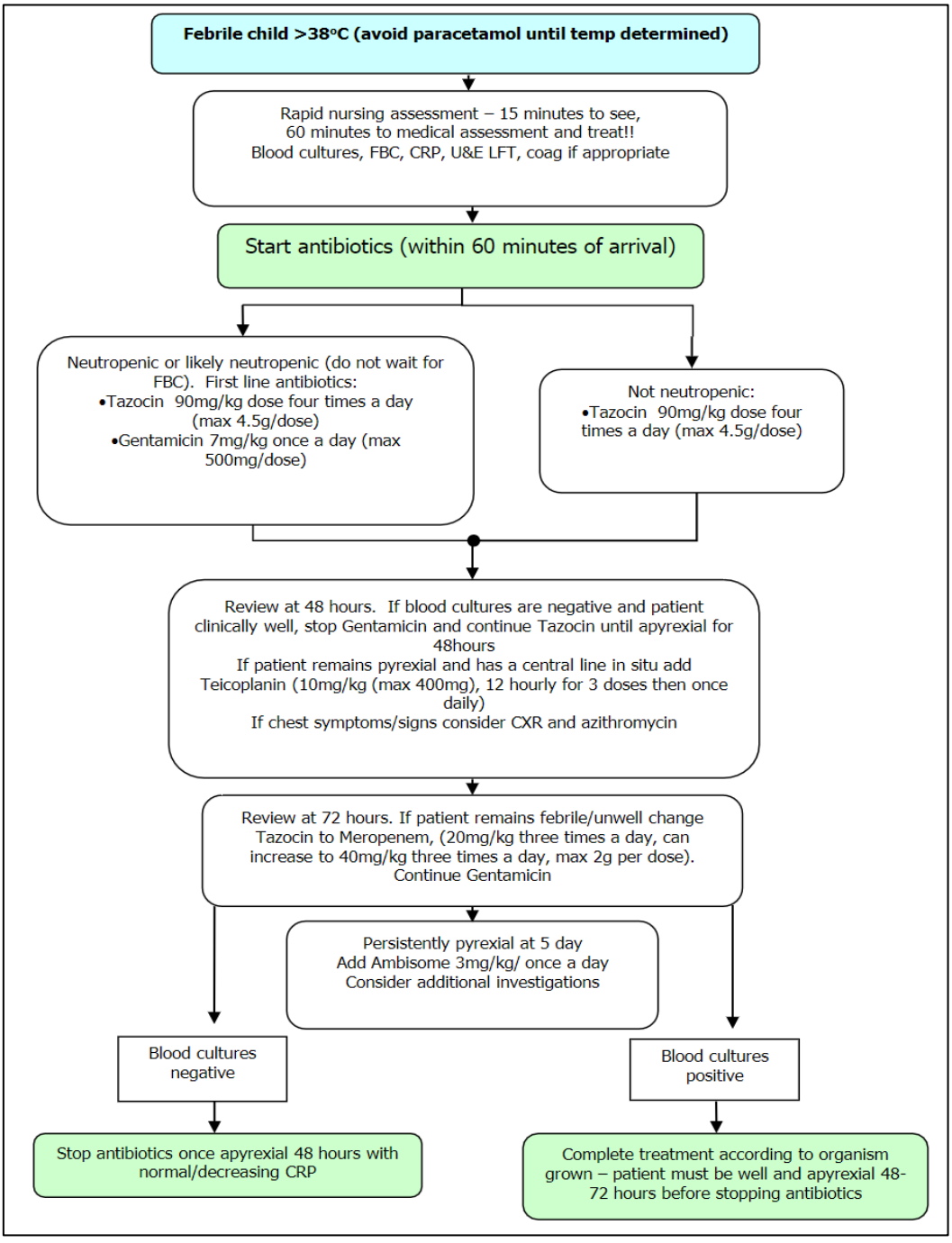
Blood Count: CBC

The diagnosis of neutropenia is essentially based on the blood count which also makes it possible to objectify the neutropenia and its depth, and to specify whether it is isolated, which is rather rare, or is associated with other possible cytopenias.

Several variables related to neutropenia have a direct impact on the risk of developing infection and its recovery, the main ones being its depth and duration [33]. Neutropenia is classified according to its importance linked to the absolute number of PNN [34] (table 03);

Combined Antibiotic Therapy:

The standard antibiotic therapy in febrile neutropenic patients is the combination of a beta-lactam with an aminoglycoside. Several combinations of equivalent effectiveness have been described in the literature; the choice of one or the other depends on the bacterial ecology of each department and the therapeutic habits of the medical teams. As an alternative to cephalosporins, the use of a piperacillin-tazobactam or imipenem combination can be proposed. The prescription of glycopeptides is only justified in certain clinical situations such as septic shock, suspected catheter infection, skin infection, severe mucositis, known previous colonization with pneumococcus resistant to penicillin and cephalosporins. Their first-line use is highly debated but can be combined with aminoglycosides or cephalosporins in cases suggestive of CGP infection [26, 35].



Management of neutropenia and fever

Evolution:

In the literature, mortality varies from 0 to 40% (3% for Klastersky [36] and 2.1% for Sigurdardottir *et al.*, [37], returning to the results of the different studies, the mortality rate seems higher, it is most often acts of septic shock following serious infections Thus, in the study carried out by the Bergonié institute, the mortality percentage was 10.7%, i.e. deaths and which all occur in a context of septic shock in BGN.

While in our study mortality was 11.1%, which is similar to the study by the CHOP-RABAT institute.

The following table shows the mortality rate reported by studies carried out at the different centers

Table 04: comparison of mortality rates in the different studies

	CHU Annaba- Al	CHU FH-Tunisia	Institut bérgonié-France	CHU Ibn-Rochd-Casablanca	COHP – Rabat	Our study
Mortality Rate	38 %	22 %	10,7 %	35%	11,1 %	11.1%

CONCLUSION

The use of intensive cytotoxic treatment in oncology settings has led to an increase in the number of patients with febrile neutropenia treated.

In these patients, the main risk is the occurrence of infectious episodes whose severity is directly proportional to the depth of neutropenia and its duration.

Fever is often the first symptom of infection, requiring the urgent initiation of broad-spectrum antibiotic therapy, described as empirical, without waiting for the results of infectious assessments and also most often Re-hospitalization of the patient due to the risk of death from infection.

The clinical examination is most often of little help and the germ is rarely isolated, but the outcome under antibiotic therapy is generally favorable.

Detection of neutropenia and early empirical initiation of broad-spectrum antibiotic therapy constitute the cornerstone of the management of patients with febrile neutropenia, and makes it possible to drastically reduce infection-related mortality.

Conflicts of Interest: The authors declare no conflicts of interest

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