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Chemotherapy-Induced Febrile Neutropenia Managed on an Outpatient Basis at the Pediatric Hematology and Oncology Department of the Ibn Sina Children's Hospital in Rabat

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ABSTRACT

Introduction: Febrile neutropenia (FN) is an important cause of morbidity and mortality in patients with cancer. The general objective of this study was to collect data and analyze the factors influencing management of the febrile neutropenia at the day hospital at the pediatric department of Hematology and Oncology (SHOP) of Rabat.

Patients and Methods: It was a cross-sectional study descriptive and analytical for a period of 3 months (from January 9 to March 31, 2017) which was made at the day hospital at the SHOP. The inclusion criteria were neutropenia (rate of the neutrophil account lower or equal to 500/mm³) and fever following a cure of cancer chemotherapy.

Results: We have registered 43 cases of FN over a period of 3 months. The most affected age group was less than 5 years with a median age of 4 years and ranged from 0 to 15 years. The ALL accounted for 67.4%; 51% of patients lived between 100 and 299 km from the SHOP, and 76.7% of patients have made 1 to 6 hours to reach the SHOP. The median of the neutrophil rate was 100/mm³. Twenty cases (46.5%) had a rate of neutrophil account < 100/mm³. Nine (20.9%) had signs related to infection. Twenty-five (58.1%) have been treated with mono antibiotic therapy, and 16 patients (37.2%) were treated with a bi antibiotic therapy. Fifteen cases (34.9%) were hospitalized for not getting the pyrexia after 72 h of antibiotic therapy. There were no deaths among hospitalized patients. Ninety three percent of the therapeutic education was made by the doctor. Bi-varied analysis showed that evolution depended on the depth of neutropenia.

Conclusion: Outpatients treatment with febrile neutropenia at the day hospital is possible and must take account of the clinical status, isolation of patients and the neutrophil account. Education of patients and parents and stratification of cases are mandatory.

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Introduction

Febrile neutropenia following cancer chemotherapy is the most serious complication of chemotherapy in terms of cytotoxicity [1-4]. It is defined as follows: Neutropenia is defined as a neutrophil count below 500 cells/mm³, or a number of 1000 cells/mm³ with a prediction decrease to 500 cells/mm³ in the following days [5,6]. A febrile state in the neutropenic patient is defined by an axillary or oral temperature $\geq 38.5^{\circ}\text{C}$ at a single intake or $\geq 38.0^{\circ}\text{C}$ on two occasions within an interval of at least one hour [7,8]. Infections are a major cause of morbidity and mortality in children undergoing neutropenia induced by anti-tumor chemotherapy

[9,10]. One third of neutropenic episodes are associated with a febrile episode [10].

The risk of developing febrile neutropenia depends on: the depth of neutropenia (the risk of infection is greatest if PNN are below 100 elements/mm³); - the duration of neutropenia: the risk of infection is high for neutropenia lasting more than 1 week (the duration can be predicted according to the type of chemotherapy and underlying pathology); - and a number of patient-related factors, including age, comorbidities and serum albumin levels [11].

The management of NF is an oncological emergency [12]. hospitalization is not systematic, as it exposes patients to the

risk of nosocomial infections. Prolonged antibiotic therapy also exposes the patient to the risks of emergence of multi-resistant bacteria, drug toxicity and fungal superinfection [13]. According to several studies, patients with febrile neutropenia without signs of severity can be managed on an outpatient basis, with the possibility of daily follow-up to check for signs of severity and response to treatment [14,15]. Daily assessment enables a decision to be taken on whether or not to continue treatment on an outpatient or inpatient basis.

At the Service d'Hématologie et Oncologie Pédiatrique (SHOP) in Rabat, most children with febrile neutropenia are treated on an outpatient basis, initially because of the high number of patients and the limited number of beds available.

The aim of this study was to analyze the factors influencing the management of febrile neutropenia at the SHOP Day Hospital.

Methods

The SHOP day hospital served as the setting for this study. This was a descriptive and analytical cross-sectional study lasting 3 months (January 9 to March 31, 2017). The study population was children followed up for febrile neutropenia at the SHOP day hospital during the aforementioned period. We included all children presenting with 3 criteria: - neutropenia (PNN rate less than or equal to 500/mm3) - fever - following a course of cancer chemotherapy. We did not include Children seen in consultation for fever and with PNN above 500/mm3. Children with PNN less than or equal to 500/mm3 but without fever. Patients with neutropenia not induced by chemotherapy. Children in low-risk NF were managed in HDJ: hemodynamically stable, no signs of severe sepsis.

All children with a temperature $\geq 39^{\circ}\text{C}$ and or who had an infectious focus were treated with Ceftriaxone- and Amikacin-based bi-antibiotherapy. The others were treated with Ceftriaxone or Amoxicillin-clavulanic acid-based mono-antibiotics. Children with mucositis were treated with Fluconazole injection. Children were monitored during their stay in HDJ, with daily clinical evaluation to monitor the evolution of febrile neutropenia and decide whether to continue antibiotic therapy on an outpatient basis or hospitalize the patient. Children whose clinical condition worsened (appearance of signs of severe sepsis, hemodynamic instability) were hospitalized. Children whose fever persisted after 72 h of HDJ antibiotic therapy were also hospitalized.

Children with apyrexia after 72 h of injectable antibiotic therapy were started on oral antibiotics. Data were collected over a successive 3-month period. Data were collected on the basis of a pre-established and validated survey form. Data were collected

by consulting SHOP emergency room consultation registers, patients' files, their personal follow-up notebooks, and any other document that could provide information on the follow-up of the children. Some data were collected by interviewing the parents and/or the child. Data were entered using epi data® (3.1) and analyzed using SPSS® (version 20). Quantitative variables were analyzed by calculating the mean and median. The Fischer exact and Pearson tests were calculated, and a value of $p<0.05$ was considered statistically significant. A value of $p>0.05$ was considered statistically insignificant.

Informed consent was obtained from parents and children (for older children aged ≥ 15 years) prior to data collection. Confidentiality of questioning, assessments and all medical record data was respected.

Result

We recorded 43 patients admitted for neutropenia in the day hospital. The age group most affected was 0-(years with 19 cases or 44. 2%. Among the 43 patients, there were 29 cases of ALL, 6 ALL, 2 cases of brain tumor, 2 cases of neuroblastoma, 2 cases of nephroblastoma. 1 case of Ewing's sarcoma and 1 case of non-Hodgkin's lymphoma. 2 patients (4.7%) had a central line. 19 patients (44.2%) lived less than 100km from the SHOP. 22 patients lived between 100 and 299 km from the SHOP, i.e. 51.2% AND 2 patients lived more than 500 km away, i.e. 4.7%. The majority of patients, i.e. 76.7%, travelled between 1 and 6 hours before arriving at the SHOP.

Table 1: Distribution of NF Cases According to CBC Results on Admission

NFS elements	Number (N=43)	%
PNN in intervals (/mm³)		
< 100	20	46.5
100 - 299	16	37.2
300 - 500	7	16.3
Hemoglobin (g/dl)		
≤ 7	10	23.3
>7	33	76.7
Interval platelets (/mm³)		
<50.000	15	34.9
50-99.000	5	11.6
≥ 100.000	23	53.5

PNN : =145 Average,58|Median=100,00/mm³
Hemoglobin : Average =8.38|Median:8,10 g/dl
Platelets : Average: 131.125,58|Median :110.000/mm³

Table 2: Distribution of the Time Taken to Present NF Cases to the Shop Doctor, According to the Agent who Provided Therapeutic Education

Therapeutic educator	Presentation deadline (hours)				Total
	< 1	1 to minus 2	2 to minus 3	3 or more	
Doctor	8	19	9	6	40
Doctor and nurse	2	0	0	0	2
Total	6	19	9	6	42
Fischer exact : p=0,53(p> 0,05)					

Table 3: Distribution of NF Cases According to Follow-Up Diagnosis

Follow-up diagnosis	Evolution after 72 h of treatment		Total
	Apyrexia	Failure to achieve apyrexia	
Cérébral tumor	1	1	2
Acute lymphoblastic leukemia	18	11	29
Acute myeloblastic leukemia	3	3	6
Non hodgkin lymphoma	1	0	1
Wilms tumor	2	0	2
Neuroblastoma	2	0	2
Ewing Sorcoma	1	0	1
Total	28	15	43

Fischer exact : p=0,23(p > 0,05)

Table 4: Evolution of NF Cases According to Treatment Received in HDJ

Treatment received	Evolution after 72 h of treatment		Total
	Apyrexia	Failure to achieve apyrexia	
Mono antibiotherapy	19	6	25
Bi antibiotherapy	8	8	16
Antibiotics and others	1	1	2
Total	28	15	43

Fischer exact : p=0,11(p > 0,05)

Table 5: Evolution of NF Cases According to PNN Count on Admission

PNN count on admission	Evolution after 72 h of treatment		Total
	Apyrexia	Failure to achieve apyrexia	
< 100 /mm ³	9	11	20
100 – 299 /mm ³	14	2	16
300 – 500 /mm ³	5	2	7
Total	28	15	43

Fischer exact :p=0,013(p< 0,05)

Discussion

During the course of our study, 43 cases of NF were recorded. The age group most affected was under 5 years. The median age was 4 years, with extremes ranging from 0 to 15 years. Mullen CA, et al. of the University of Texas Department of Pediatrics, over a period of 2 years, reported 73 episodes of fever and neutropenia in 41 outpatients. Malk SA et al. in their study at the Rabat Pediatric Hemato-Oncology Department (SHOP), 51 children presented 76 episodes of febrile neutropenia following chemotherapy [16]. Badr M et al. at the Zagazig pediatric oncology unit in Egypt, between June 2013 and June 2014, recorded 50 patients who presented with 113 episodes of febrile neutropenia [17]. Mullen CA et al. found in the Department of Pediatrics at M. D. Anderson University in Texas over a 2-year period, 73 episodes of NF in 41 patients who were treated as outpatients [18]. Gupta A, et al. in a randomized trial of oral and intravenous antibiotic therapy at Institute Rotary Cancer Hospital, All India Institute of Médical Sciences, the median age of patients recruited were 8.25 and 7.75 years [19]. Hiroto Inaba et al. in a retrospective study which included all patients enrolled for AML02 at St. Jude between October 2002 and October 2008, found in 103 registered children a median age at diagnosis of 8.7 years [20]. Twenty-nine NF cases were ALL, or 67.4% followed by AML, 6 cases or 14.3%.Aquino et al found in a study

at Children's Medical Center in Dallas from June 2004 to May 2007, 67% ALL and 4% AML [21]. Gupta A et al. found 51% ALL in a randomized study of oral or intravenous outpatient treatment of NF at the Institute Rotary Cancer Hospital, New Delhi, from January 2006 to December 2007 [19]. Of the 43 NF cases recorded, none had received growth factors after the chemotherapy treatment preceding the NF episode. 2 patients (4.7%) had a central venous line. -The greatest number of cases lived far from the department, between 100 and 299 km from the SHOP, i.e. 51.2%, with extremes of 5 to 688 km. The majority of patients, 33 (76.7%), took a long time to reach the SHOP, between 1 and 6 hours. The average was 3.19 hours, with extremes ranging from 30 minutes to 24 hours. We looked for a correlation between the distance separating the patient's place of residence from the SHOP and the number of hours on the road. The Pearson test was carried out: $p=0$ (<0.05), showing a correlation between distance and number of hours on the road. In the case of a child living in a remote village 288km from SHOP, we found that it took him 24 hours to get to SHOP (questioning showed that he had to make 2 Taxi-Bus changes before reaching SHOP). SHOP is a referral service for pediatric oncology in Morocco, receiving children from all over the country. Chemotherapy is administered at intervals of 1 to 3 weeks, depending on the protocol, and patients return home until the next treatment.

In Rabat, the house of parents association l'AVENIR provides accommodation for children and their carers during outpatient treatments (NF treated on an outpatient basis, chemotherapy treatments and check-ups). However, the capacity of the Maison de l'AVENIR cannot accommodate the children and their parents continuously, which explains why the children are obliged to return home after chemotherapy treatments.

The distance of patients' homes from the ward can influence the time it takes to administer antibiotics. The literature reports that the vast majority of centers respect a delay of less than 60 minutes for the administration of antibiotics in NF [22]. It is therefore essential to create networks to enable the nearest center to be consulted in the event of a fever, even for the most remote patients. Twenty NF cases had $PNN < 100/mm^3$, i.e. 46.5%, and 16 cases had PNN between 100 and $299/mm^3$, i.e. 37.2%. The mean PNN count was $145.58/mm^3$ and the median $100/mm^3$, with extremes of 0 and $500/mm^3$. Ten cases had $Hb \leq 7$ g/dl and 33 cases had $Hb > 7$ g/dl. The mean Hb was 8.38 and the median 8.10. Children with Hb levels <7 g/dl were all transfused in HDJ with packed red blood cells. More than half the patients had a platelet count $>100,000/mm^3$; five cases, or 11.6%, had platelets between 50 and $100,000/mm^3$ and a median of $110,000/mm^3$. All children with a platelet count $<50,000/mm^3$ and who had signs of bleeding were transfused with platelet concentrates in the hospital HDJ. Of the 43 NF cases, 9 (20.9%) had infection-related signs, and 34 (79.1%) had no infection-related signs. The signs found were: 1 case of bilateral purulent otorrhea (a CT scan was performed, and given the persistence of the fever, which showed bilateral mastoiditis), the patient was hospitalized; another case of erythematopulmonary angina was hospitalized for failure to achieve apyrexia. A cough with rales on pulmonary auscultation in one patient, who was hospitalized for failure to achieve apyrexia. There was a case of urinary burning (ECBU done after the start of antibiotic therapy came back negative) in a patient hospitalized for failure to achieve apyrexia after 72 hours of antibiotics. This highlights the need for a full clinical examination on admission to look for an infectious focus, in order to determine whether the patient should be managed as an outpatient or not. Among the 43 NF cases, there was 1 case of grade II mucositis (2.3%).

Twenty-five cases (58.1%) were treated with a single course of antibiotics. Sixteen cases (37.2%) were treated with dual antibiotic therapy. Two cases were treated with antibiotics and other drugs (notably Fluconazole).

A correlation was sought between distance from place of residence and time to presentation to the SHOP doctor. The Pearson test was calculated and showed $p=0.182$, indicating a non-significant correlation between distance from home and time to SHOP. Solutions include setting up a number where parents and children can call for advice. All children's cancer centers and pediatric oncology units in the UK have open access for patients and/or carers to call for advice 24 hours a day, as recommended by NICE (2005) [7]. Setting up a network of local hospitals in liaison with SHOP may also be another solution.

Forty-two out of 43 NF cases received therapeutic education. Only one case did not know whether or not therapeutic education had been provided (it was not the same person who usually accompanied the child on chemotherapy courses). In the majority of cases (40), i.e. 93%, therapeutic education was provided by the doctor. In two cases (4.7%), it was carried out by both the doctor and the nurse.

Twenty-eight patients achieved apyrexia after 72 hours of antibiotic therapy, while 15 cases (34.9%) did not achieve apyrexia within this timeframe, and were therefore hospitalized.

A relationship was sought between the health worker who provided the therapeutic education and the delay in presentation to SHOP. The Fischer exact test was carried out with $p=0.53$ ($p>0.05$), i.e. statistically insignificant. So therapeutic education by the doctor or doctor and nurse had no impact on the time to SHOP. In this department, there is a nurse who is responsible for therapeutic education.

This may be due to the fact that the therapeutic education provided did not cover all NF-related issues, including therapeutic urgency. This study showed that 93% of therapeutic education was carried out by the doctor. The doctors who prescribe chemotherapy in the consultation cubicles do not have enough time to address all the questions and concerns of parents and children. And do nurses have enough time to talk to parents and children during chemotherapy treatments?

Perhaps a standardized therapeutic education module should be offered to all patients: Meetings, brochures, audio and video cassettes.

Firstly, we looked for a correlation between the follow-up diagnosis and the evolution of NF: the Fischer exact test gave $p=0.23$ ($p>0.05$), which shows that there was no statistically significant relationship between the follow-up diagnosis and the evolution (the evolution did not depend on the follow-up diagnosis).

Secondly, we looked for a relationship between the treatment received and the evolution by performing the Fischer exact test, which gave $p=0.11$ ($p>0.05$), showing that there was no statistically significant relationship between the treatment received at the day hospital and the evolution of NF (the evolution did not depend on the treatment received).

Mullen A et al. in a randomized trial to determine whether pediatric cancer patients with low-risk NF could be safely treated on an outpatient basis: this was a prospective study and included 41

patients over a 2-year period. Patients were assessed and given a dose of ceftazidime. They were observed for 12 hours and randomized. One arm received oral Ciprofloxacin and the second arm received outpatient ceftazidime. Of the 73 episodes treated as outpatients: 31/33 episodes in the ceftazidime arm progressed well and remained as outpatients; 32/40 episodes in the Ciprofloxacin group also progressed well and remained as outpatients. The difference was not significant. In conclusion, low-risk NF patients can be safely treated on an outpatient basis, either orally or by injection [16].

Gupta A et al. demonstrated similar success rates in their randomized study of oral antibiotic therapy (Amoxicillin-clavulanic acid and Ciprofloxacin combination) versus IV (Ceftriaxone and Amikacin). In the per-protocol analysis, treatment was successful in 55/61 episodes in the oral arm and 54/58 in the IV arm. Interestingly, treatment was also successful in patients with $PNN \leq 100/mm^3$. In both arms Fluconazole and Aciclovir were used in 7 episodes (5 cases in the oral arm and 2 cases in the IV arm). Success was achieved in 50/61 episodes in the oral arm and 52/58 episodes in the IV arm. In conclusion, the results were similar and the analysis showed no difference [19].

Manji A et al. in a systematic review of outpatient management of NF showed that there was no statistically significant difference between oral and intravenous antibiotic therapy. Sixteen articles were included in the meta-analysis. There were fewer treatment failures or antibiotic modifications in the outpatient setting than in the hospital (15% versus 28%, $P=0.04$), but the difference was not significant between oral and parenteral antibiotic therapy (20% versus 22%, $p=0.68$). Of the 953 episodes treated in the outpatient setting and 676 episodes treated with oral antibiotics, no case was associated with infection-related mortality [23].

3rdly, we looked for a relationship between the depth of neutropenia and the outcome after 72 h of treatment using the Fischer exact test, which gave $p=0.013$ ($p<0.05$), showing that the outcome depended on the number of PNN on admission. The higher the PNN, the more patients achieved apyrexia after 72 hours of antibiotic therapy. Cases with PNN between 100 and 500 elements/mm³ achieved apyrexia more than those with $PNN < 100$ elements/mm³. According to the literature, the risk of infection increases when $PNN < 100/mm^3$ [5].

What is highly relevant in our study is that all 15 cases hospitalized for failure to achieve apyrexia in HDJ continued with IV antibiotic therapy adapted to the clinical course and context, and improved. There were no deaths among them. Therefore, the fact that they were first treated on an outpatient basis prior to hospitalization was not a detrimental factor.

Conclusion

Chemotherapy-induced febrile neutropenia is the most frequent and dreaded complication of cancer chemotherapy. The initiation of antibiotic therapy remains an emergency. In the African context, given the lack of hospital space and the high cost of in-patient treatment (families are confronted with costly management of the underlying cancer), the need for antibiotic therapy is a major concern.

References

1. Mueller EL, Walkovich KJ, Mody R, Achamyeleh Gebremariam, Matthew MD (2015) Hospital discharges for fever and neutropenia in pediatric cancer patients: United

- States, 2009. BMC Cancer <http://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1413-8>.
2. Teuffel O, Amir E, Alibhai SMH, Joseph Beyene, Lillian Sung (2011) Cost-effectiveness of Outpatient Management for Febrile Neutropenia in Children with Cancer. *PEDIATRICS* 127: 279 286.
3. Mueller EL, Walkovich KJ, Yanik GA, Sarah JC (2015) Variation in management of fever and neutropenia among pediatric patients with cancer: a survey of providers in michigan. *Pediatr Hematol Oncol* 32: 331 340.
4. Cheng S, Teuffel O, Ethier MC, Wing R, Alibhai SMH, et al. (2011) Health-related quality of life anticipated with different management strategies for paediatric febrile neutropaenia. *Br J Cancer* 105: 606 611.
5. Hughes WT, Armstrong D, Bodey GP, Jerry LS, Lowell SY, et al. (2002) guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 34: 730 751.
6. Mendes AVA, Sapolnik R, Mendonça N (2007) New guidelines for the clinical management of febrile neutropenia and sepsis in pediatric oncology patients. *J Pediatr Rio J* 83: 54 63.
7. Hawkins J (2009) Supportive care: managing febrile neutropenia: Fever in a child receiving cancer therapy requires prompt action because it could indicate a life-threatening infection. Jeanette Hawkins summarises the issues and practice implications. *Paediatr Care* 21: 33 37.
8. Ahmed N, El Mahallawy HA, Ahmed IA, Shima Nassif, Aamal El Beshlawy, et al. (2007) Early hospital discharge versus continued hospitalization in febrile pediatric cancer patients with prolonged neutropenia: A randomized, prospective study. *Pediatr Blood Cancer* 49: 786 792.
9. Saini S, Rosoff PM (2007) Are we finally ready for outpatient management of febrile neutropenia? *Pediatr. Blood Cancer* 49: 765 766.
10. Teuffel O, Sung L (2012) Advances in management of low-risk febrile neutropenia: *Curr Opin Pediatr* 24: 40 45.
11. Cameron D (2009) Management of chemotherapy-associated febrile neutropenia. *Br. J. Cancer* 101: 18-22.
12. Ozdemir N, Tuysuz G, Celik N, Leman Yantri, Ethem Erginöz, et al. (2016) febrile neutropenia in children with acute lymphoblastic leukemia: single center experience. *Türk Pediatri Arş* 51: 79-86.
13. Leverger G (2004) Antibiothérapie ambulatoire chez les enfants neutropéniques fébriles: Analyse de la littérature : Prise en charge ambulatoire des neuropénies fébriles en onco-hématologie - 1/2 Les principes. *Presse Médicale* 33: 330-337.
14. Ziino O, Tucci F, Rossi MR (2011) Outpatient management of febrile neutropenia in children with cancer. *Pediatr Rep* 2011 févr 3: 8.
15. Morgan JE, Stewart L, Phillips RS (1999) Protocol for a systematic review of reductions in therapy for children with low-risk febrile neutropenia. *Syst Rev* 3: 119.
16. Mullen CA, Petropoulos D, Roberts WM, Rytting M, Zipf T, et al. (1999) Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer* 86: 126-134.
17. Malk SA, Kili A, El Kababri M, Hessissen L, Khorassani M El, et al. (2013) Neutropénie fébrile chimio-induite : expérience d'un centre d'hématologie et d'oncologie pédiatrique. *Afr J Cancer* 5: 68-72.
18. Badr M, Hassan T, Sakr H, Nehad Karam, Doaa Abdel Rahman, et al. (2016) Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. *Mol Clin Oncol* 5: 300-306.

19. Gupta A, Swaroop C, Agarwala S, Ravindra Mohan Pandey, Sameer Bakhshi (2009) Randomized Control Trial Comparing Oral Amoxicillin-clavulanate and Ofloxacin With Intravenous Ceftriaxone and Amikacin as Outpatient Therapy in Pediatric Low-risk Febrile Neutropenia. *J Pediatr Hematol Oncol* 31: 635-641.
20. Inaba H, Gaur AH, Cao X, Patricia M Flynn, Stanley B Pounds, et al. (2014) Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia: Antibiotic Prophylaxis in Pediatric AML. *Cancer* 120: 1985-1992.
21. Aquino VM, Cost C, Gomez A, Daniel C Bowers, Octavio Ramilo, et al. (2012) Predictive Value of Interleukin-5 and Monocyte Chemotactic Protein-1 for Bacteremia in Children With Febrile Neutropenia. *J Pediatr Hematol Oncol* 34: 241-245.
22. McCavit TL, Winick N (2012) Time-to-antibiotic administration as a quality of care measure in children with febrile neutropenia: A survey of pediatric oncology centers. *Pediatr Blood Cancer* 58: 303-305.
23. Manji A, Beyene J, Dupuis LL, Phillips R, Lehnbecher T, et al. (2012) Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children-a systematic review of prospective trials. *Support. Care Cancer* 20: 1135-1145.