UiT Norges arktiske universitet

Faculty of Health Sciences

Febrile neutropenia in pediatric cancer patients in Northern Norway

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MED-3950 – Master thesis, Medicine

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Preface

The research conducted in this thesis was conducted as part of the master thesis in medicine at the University of Tromsø. It has been a work lasting one and a half year with a lot of learning, hard work, fun and a little bit of frustration.

I have gotten the opportunity to learn a lot about one specific topic in the otherwise inexhaustible area of both oncology and pediatrics – a rare luxury in the life of a medical student constantly rushing from one topic to the other.

A big thank you to my supervisor Hildegunn Granslo, and my co-supervisors Claus Klingenberg and Trond Flægstad for the ideas, feedback and excellent help throughout the process.

08.05.2022

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1 Summary

Background

Febrile neutropenia in pediatric patients is a feared complication of both cancer and cancer treatment. With low levels of neutrophil granulocytes and toxic chemotherapy, patients are more prone to infections and the spreading of it. With low levels of neutrophils, systemic and local inflammatory symptoms are often weak, and fever may be the only symptom of both a life-threatening bloodstream infection, but also a harmless condition. Empirical antibiotics are the cornerstone of treatment, and information about microbiological trends are important for guiding empiric treatment. No validated prediction systems to differentiate between serious and harmless infections exist to date.

Material and method

All pediatric oncologic patients in Northern Norway presenting with a fever of 38.5°C or higher, and a neutrophil count of less than 500 cells/mm^3 in the period of 2010-2020 were included in the study. Laboratory values, treatment and clinical outcomes such as bacteremia, antibiotic treatment and etiology were obtained.

Results

232 episodes of febrile neutropenia occurred between 2010 and 2020. Blood cultures were only positive in 16.8% of episodes of FN. Gram-positive bacteria were most frequently detected. The most common gram-positive pathogens were viridans group-strepococci (25%). The gram-negative pathogens were E. coli (16.7%) and the moraxella group (4.2%). Antibiotic regimen of choice has shifted from ampicillins in combination with an aminoglycoside to piperacillin/tazobactam. A low white blood count at admission and a high maximum CRP level during an episode have a strong association to having a positive blood culture.

Conclusion

No factors are able to predict the developing of sepsis, but many show associations with a higher risk of it. Microbiological etiology of febrile neutropenia has shifted in Northern

Norway. The empirical antibiotic regimens of choice reflect recommendations in both international and national guidelines.

Abbreviations

ALL: Acute lymphocytic leukemia

AML: Acute myeloid leukemia

ANC – Absolute neutrophil count

CI: Confidence interval

CNS: Central nervous system

CoNS – Coagulase-negative staphylococci

CRP: C-reactive protein

FN – Febrile neutropenia

PEWS – Pediatric early warning signs

UNN – Universitetssykehuset Nord-Norge

MDS: Myelodysplastic syndrome

OR: Odds ratio

PEWS – Pediatric early warning signs

qSOFA – quick sepsis related organ failure assessment

UNN – Universitetssykehuset Nord-Norge

VGS – Viridans group streptococci

WBC: White blood count

2 Introduction

2.1 Background

Febrile neutropenia (FN) is a potential life-threatening condition in pediatric patients undergoing chemotherapy. FN is defined as the occurrence of fever while being neutropenic. Neutropenia is defined as having an absolute neutrophil count (ANC) of less than 500 cells/mm^3, whereas fever is defined by the European Society of Medical Oncology as having an oral temperature of more than 38.5°C or two consecutive readings of more than 38°C for 2 hours (1). Due to low levels of neutrophil granulocytes after chemotherapy, the immune reaction in pediatric oncology patients is weakened. Fever is often the dominant sign of infection, either if the patient is developing sepsis, but also when it is due to a mild, harmless infection.

Failure to diagnose and treat FN may lead to the development of sepsis, therefore early risk-assessment and quick initiation of antibiotic treatment before it is confirmed whether this is due to a serious or more harmless infection, is vital. Delay of treatment may lead to longer hospitalization and a greater risk of morbidity (2).

2.2 Definition of sepsis

Sepsis in children is clinically defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (3). It can progress into a septic shock, defined as a severe infection leading to cardiovascular dysfunction – including decrease in blood pressure, the need for vasoactive drugs, oliguria, metabolic acidosis, increased arterial lactate and prolonged capillary refill (4). For children, the sepsis criteria rely on age-specific values for vital parameters.

The Sepsis-3 criteria developed for adults is difficult to apply to pediatric patients due to differences in pathophysiology and clinical manifestations. Children maintain normal blood pressure longer, and they more frequently have viral infections, making the qSOFA (5) unfit for sepsis diagnostics in pediatric patients.

To verify a true bacteremia a pathogen must be detected in a blood culture. If blood cultures show growth with recognized pathogens in ≥ 1 blood culture, or common pathogens (human microbiome) in ≥ 2 blood cultures, bacteremia is verified (6).

2.3 Etiology and epidemiology

Not all episodes of FN derive from bacteremia, but from other bacterial, fungal or viral infections. Therefore, the blood cultures may turn out negative in many cases. A large cohort study in Chicago showed that the presence of pathogens in blood cultures taken at admission after an episode of FN is 21.4% (7). In a multi-center Norwegian study, pathogens were isolated in 17% of the blood cultures obtained from pediatric patients admitted with FN (8).

In the study from Chicago bacterial pathogens were isolated in 176 out of 667 episodes of pediatric FN. The authors suggest that the etiology of pathogens that cause bloodstream infections had shifted over the years. Between 2009 and 2016, the incidence of viridans group-streptococci (VGS) increased, while the Gram-negative pathogens decreased (7). The most common Gram-positive pathogens in this study were VGS (19%), CoNS (14%), and *Staphylococcus aureus* (7%).

In a Norwegian study on pediatric FN (8), they reported more Gram-positive than Gram-negative bacteria isolates in positive blood. Of 39 positive blood cultures, 28 (78%) showed growth of Gram-positive bacterial isolates. Total number of Gram-negative isolates were 11 (28%), and Candida isolates was found in 2 of the blood cultures. The most common Gram-positive pathogens were CoNS (23%), VGS (15%) and *S. aureus* (13%).

The presence of opportunistic pathogens such as CoNS and candida in the positive blood cultures is largely due to the absence of neutrophil granulocytes. These patients are also often hospitalized, and applied with a central venous catheter which may serve as an entry gate for pathogens.

2.4 Empiric treatment

Albeit oncologic conditions in children are treated more and more individually, episodes of FN are still treated almost equally in all patients.

Norwegian guidelines still suggest as empiric treatment of FN a combination of ampicillin and gentamicin. If signs of septicemia, and/or some specific high-risk groups of cancer patients, monotherapy with piperacillin/tazobactam is advised (9). Earlier studies indicate that an empirical regimen with benzylpenicillin or ampicillin in combination with an

aminoglycoside is not inferior to a regimen with third-generation cephalosporin in mono- or combination therapy (8).

If the patient shows signs of clinical decline with affection of hemodynamic stability, guidelines suggest considering switching to meropenem. In patients with FN who are still febrile 96 hours after initiation of antibiotic treatment, guidelines suggest adding empirical candida treatment after additional blood cultures are collected (9).

Guidelines of management of FN suggest cessation of treatment when a patient has had negative blood cultures at 48 hours, been afebrile for at least 24 hours, and have evidence of bone marrow recovery. For low-risk patients, the antibiotic treatment can be discontinued at 72 hours, if the blood cultures turn out negative and the patients have been afebrile for at least 24 hours (10). This, however, can be difficult for a physician to decide on.

2.5 Assessment of children with FN episodes

Patients presenting with FN episodes must as soon as possible be admitted to hospital for further assessment. Blood tests, blood culture and clinical examination should be evaluated immediately when the patients are admitted to hospital, and the patient should start empirical antimicrobial treatment early (6) (9). Pediatric Early Warning Signs (PEWS) is a triage system that are used in Norwegian pediatric wards for early detecting of negative development in pediatric patients' health condition. The patient's respiration, circulation and behavior are given a score, and these are summarized. Maximum possible PEWS score is 13 and the higher score, the stronger indication of a serious development of the disease. PEWS scoring is advised to be done at admission and at a predetermined interval until discontinued by a physician. All PEWS-scores are logged in the patient's medical files (7). PEWS has been used in the Pediatric department in The University Hospital of Northern Norway (UNN) since approximately 2016.

After admission, examination and testing, the patients can be divided into three groups in regards to sepsis; no sepsis, likely sepsis, and verified sepsis. The distinction between a likely sepsis and a verified one lies in the detection of bacteria in a blood culture.

A true sepsis is defined as any infection with a microbiologically or clinically documented bacterial cause. The criteria of microbiologically and clinically documented is met if the

infection was proven by microbiological tests or if the patient showed common clinical signs of infection such as in pneumonia, infections in skin or soft tissue, otitis media/externa, and other infections (10).

FN patients with true sepsis can deteriorate quickly and frequent reassessment of their clinical status should be obtained.

2.6 Prediction of sepsis episodes

Early prediction of sepsis in FN can reduce unnecessary antibiotic treatment, cost and hospitalization, but - no internationally validated prediction model exists to date. A meta-analysis from 2016 looked at associations with sepsis in pediatric patients with FN. Both biomarkers and clinical assessment were included. Interleukin-8 (IL-8) showed a strongly significant association (OR=1.81. 95% CI 1.48-2.28) with microbiologically defined infections. Also, a child presenting as severely unwell had higher likelihood of having sepsis. However, the study also concludes that the latter variable is controversial, because of the question of interrater ability. *Clinical impression* is subject to a physician's experience and level of learning – and implementation of this requires training and experience (12). An absolute neutrophil count (ANC) of < 100/mm^3, duration of neutropenia and a lower level of white blood cell count (WBC) have been associated with the presence of bacteremia in recent studies (13) (8). Also, monocyte count has shown a significantly importance in predicting a verified sepsis, with low levels representing a higher risk of bacteremia (14) and a higher count at admission representing a lower risk (15) (16). The studies speculated if a higher absolute monocyte count were a sign bone marrow recovery and therefore lowered the risk of bacteremia.

2.7 Aim

The main aim of this study is to describe clinical and laboratory characteristics, treatment and outcome among children in Northern-Norway with cancer suffering from chemotherapy-induced FN.

The second aim was to describe the incidence of bacteremia in this population and which species that are most common.

The third aim is to investigate if the patients that have bacteremia, differ from the patients with no detection of bacteria in the blood, in relation to clinical findings when admitted to hospital, biochemical tests, underlying condition, antimicrobial treatment, duration of this treatment and need to change empirical first-line antibiotic regimen.

3 Materials and methods

3.1 Inclusion criteria

All children aged 0-18 years admitted to UNN Tromsø with an oncologic disease and at least one episode of FN occurring between the 1st of January 2010 and the 31st of December 2020. For some relevant analyses, all pediatric oncologic patients were included.

3.2 Setting

The study is based on data from patient medical files, gathered from 2010 through 2020. The cases included are all pediatric oncologic patients in Northern Norway Regional Health Authority (Helse Nord RHF) presenting with an episode of FN while undergoing cancer treatment. This includes episodes of FN in eligible patients admitted to the pediatric department at The University Hospital of North Norway (UNN), Nordland hospital and Finnmark hospital.

UNN Tromsø is one of the tertiary pediatric oncology centers in Norway, and although most children with FN in local hospitals are transferred to UNN Tromsø, sometimes weather or special circumstances are reasons for admission and treatment of a patient in local hospital while staying in contact with the Children department at UNN Tromsø. Patients at Nordlandssykehuset Bodø are not routinely transferred to UNN Tromsø, but discharge summaries are sent to UNN Tromsø for cooperation with pediatric oncologists. Information from these patients are gathered from the discharge summaries.

3.3 Study design

The study is a retrospective observational study that aims to describe the patient population, antibiotic use and microbiologic trends, and to retrospectively compare groups of patients with true bacteremia and those with negative blood cultures.

The study was approved as a quality project by the Data Protection Officer (PVO) at UNN in February 2021 and did not require consent from the included patients. All information was analyzed deidentified.

3.4 Database

A complete list of 176 patients aged 0-17 with a cancer diagnosis were retrieved from the study nurse in Pediatric Research Group, and their electronic medical records (DIPS) were the source of all data collection. All patients' medical files were researched by using the search terms «sepsis», «febrile neutropenia» and «neutropenic sepsis» in the medical documents, and searching the laboratory results for both periods of neutropenia, and also logging the date of every blood culture taken. All dates were matched to both an absolute neutrophil count of less than 0,5 $x10^9$/L, and an episode of a registered temperature of either 38.5º Celsius or two episodes of over 38º Celsius. If both criteria were met, an episode of FN was registered.

3.5 Outcomes

Once an episode of FN was identified, laboratory results of the date of admission and throughout the hospital stay, as well as daily notes from both nurses and doctors were the source of information on the following; CRP, leukocytes, hemoglobin, thrombocytes and neutrophil granulocytes.

Data from admission: Initial antibiotic treatment, PEWS-score, oncology diagnosis, age, gender and measured temperature. Both laboratory results and medical notes throughout the stay were used to document the maximum CRP-level, the highest reported temperature, the length of fever and antibiotic treatment, change in antibiotic treatment and reasoning for change, and days until rise in absolute neutrophil granulocyte count.

3.6 Data analysis

All statistics were processed in IBM SPSS Statistics. The patients were split into a bacteremia group and non-bacteremia group for comparisons. The non-parametric Mann-Whitney U was used to compare continuous variables. All data are presented as medians with interquartile range (IQR).

For dichotomous variables a chi-square test was chosen. P-value less than 0.05 was considered to be statistically significant.

4 Results

4.1 Diagnosis

In northern Norway, a total of 176 patients aged 0-17 years were registered with a cancer diagnosis between 2010 and 2020. Of these, 76 patients had ≥ 1 episode of FN. These 76 patients are the study population that met the inclusion criteria of the study. Among these 76 patients I found and included 232 FN episodes.

Most of the episodes were in patients with hematological cancers. Acute lymphocytic leukemia (ALL) accounted for about one in three episodes of FN (36.6%, n=85), while acute myeloid leukemia (AML) together with myelodysplastic syndrome (MDS) in four of episodes (26.3%, n=61). Together, ALL and AML/MDS was the underlying oncologic condition in over half the patients (59.9%) reporting with FN. Lymphomas, CNS tumors and solid tumors accounts for the other 40.1%.

In all 232 episodes of FN, blood cultures were negative in 193 (83.2%) of the episodes, while 39 (16.8 %) of the blood cultures showed bacterial growth. The 39 positive blood cultures were distributed unevenly across the various cancer diagnoses with ALL and AML/MDS accounting for 77% (30/39) of the bacteremia episodes. Adjusted for frequency of the diagnoses, the blood culture showed bacterial growth in one of four patients with AML/MDS (24.6%, 15/61) having an episode of FN. FN in patients with ALL (17.6%, 15/85) and lymphomas (19.0%, 4/21) were proved as bacteremia in under a fifth of the cases, while CNS tumors (3.0%, 1/33) rarely were associated with bacterial blood infections.

Hospital admission for management of FN was common for patients with either ALL, AML/MDS and lymphomas. In total 32/37 (86.4%) of patients with ALL and 11/14 (80.0%) of AML/MDS patients had at least one episode of FN. In contrast, only about half of the 23 patients with a lymphoma diagnosis (56.5%) had at least one episode of FN. The AML/MDS subgroup had the highest percentage of more than three FN episodes, with 9/14 (64.3%) patients being admitted to hospital four or more times for management of FN.

4.2 Antibiotic treatment

In the start of the previous decade the antibiotic drug of choice was mainly ampicillin and an aminoglycoside, mainly gentamicin, with over 50% of all administrations in the years 2010-

2016. The other 20-50% was made up of 3rd generation cephalosporins such as ceftazidime, ceftriaxone and cefotaxime, and carbapenems – meropenem exclusively. Of all 154 episodes of febrile neutropenia in the years 2010-2016 piperacillin-tazobactam was not once the therapy of choice. In 2017, the use of piperacillin-tazobactam increased from 0% to 11,5%, and continued to rise to 36,4% in 2018 and onwards to above 80% the following years. The use of carbapenems and 3rd generation cephalosporins fluctuated but seemed to increase until 2017-2018, with a negative trend the following years until it reached 0% in 2020. (Figure 1).

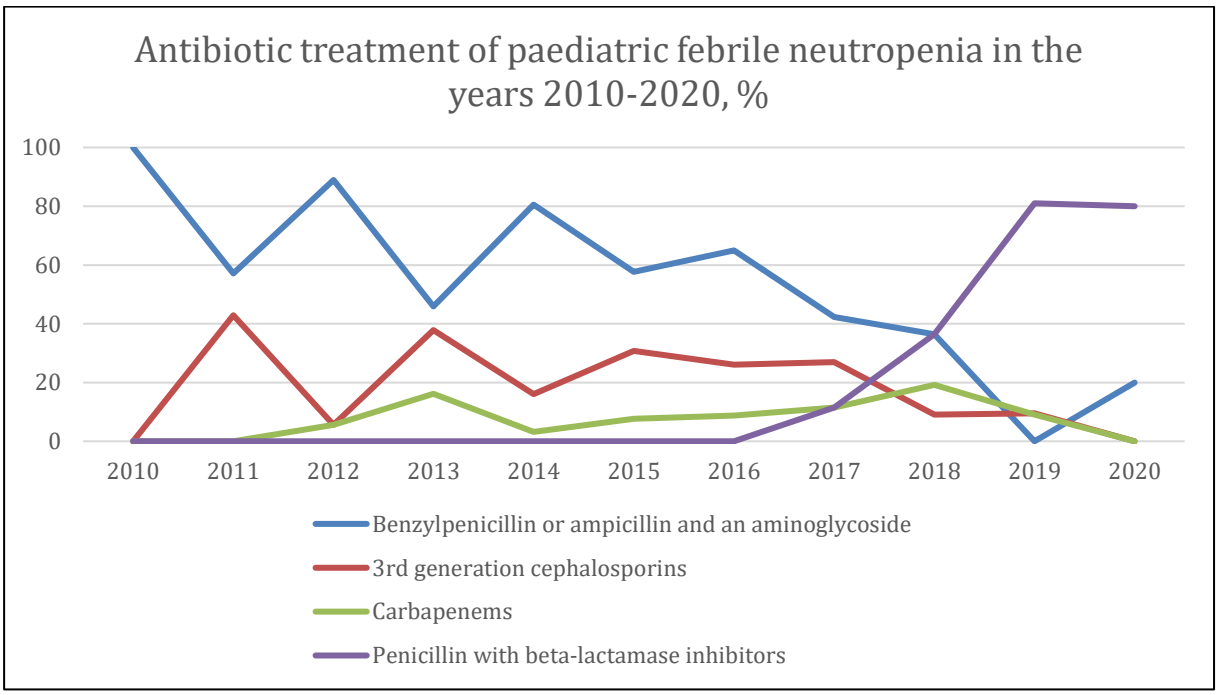

Figure 1: Antibiotic regimen of choice in management of pediatric febrile neutropenia, by year (%).

In 66 of 232 episodes (28.4%), antibiotic regimen was modified at least once throughout the treatment period (Table 1). In 59/66 (89.4%) of the changes a broader spectrum antibiotic were chosen, leaving 7 (10.6%) of the changes to a more narrow-spectrum antibiotic. Meropenem and vancomycin were the most frequent second line antibiotic agents. The two most frequent causes of changing antibiotic regimen was persistent fever after initiation of antibiotic treatment, and after microbiological susceptibility testing (Table 1).

Reason of change	Frequency, n=66	Percentage
Increased CRP level	11	15.2 %
Persistent fever	29	42.4 %
Drug reaction	5	7.5 %
Kidney failure	2	3.0 %
Prehospital decision	1	1.5 %
Susceptibility testing	20	28.8 %

Table 1: Reasons of antibiotic regimen modification, n=66.

Modifying of initial regimen occurred in 30 of the 39 positive blood cultures, with either adding an antimicrobial agent or changing regimen. The median (interquartile range) length of intravenous antibiotic treatment in all 232 episodes of FN was 6 (4-9) days.

When blood cultures were positive, 90% (27/30) of regimen changes was to a broad-spectrum antibiotic such as meropenem, vancomycin and linezolid.

4.3 Pathogens

A total of 48 pathogens were identified in this study. 70.8% of these were Gram-positive, and 29.2% were Gram-negative. The most common Gram-positive pathogens were VGS (n=12, 25%), S. aureus (n=7, 14.6%) and CoNS (n=5, 6.3%). The Gram-negative pathogens were E. coli (n=8, 16.7%) and moraxella group (n=2, 4.2%). In total, Gram-positive species were found in 34 of the 39 (87.2%) positive blood cultures. Gram-negative species were found in 14 of the 39 (35.9%) positive blood cultures. Nine blood cultures showed growth of more than one species (Table 2).

Pathogen	Frequency	Gram stain
Viridans streptococci group (VGS)	12	Positive
Staphylococcus aureus	7	Positive
Coagulase-negative staphylococci (CoNS)	5	Positive
Enterococcus	4	Positive
Group A beta-hemolytic streptococci (GAS)	3	Positive
Micrococcus	2	Positive
Clostridium tertium	1	Positive
	34	
Escherichia coli	8	Negative
Klebsiella	3	Negative
Moraxella	2	Negative
Pantoea	1	Negative
	14	

Table 2: Frequency of pathogens in positive blood cultures between 2010-2020, n=48.

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Gram+	75%	50%	66.6%	90.9%	50%	75%	66.6%	62.5%	0%	0%	75%
Gram-	25%	50%	33.3%	9.1%	50%	25%	33.3%	37.5%	0%	100%	25%
Gram+	3	1	2	10	2	3	2	5	0	0	6
Gram-	1	1	1	1	2	1	1	3	0	1	2
Total	4	2	3	11	4	4	3	8	0	1	8

Table 3: Distribution of species found in blood cultures in FN patients 2010-2020 by year, n=48 and in %.

The positive blood cultures in the previous decade has mainly shown a predominance of Gram-positive bacteria with only one year presenting with less than half of the distribution. The frequency of detected species has ranged from 0 to a maximum of 8 per year (Table 3).

Maximum CRP levels were significantly higher in the bacteremia group compared to those without bacteremia. In contrast, there were no significant differences in CRP levels between the groups at time of admission. Median leukocyte count, platelet count and ANC were all significantly lower in the bacteremia group. Having a longer period of neutropenia and fever were also significantly associated with a higher risk of bacteremia with a p-level of <.001, as

well as a PEWS-score at admission of more than 2 represented a significant association of bacteremia (Table 4).

	Bacteremia. n=39	Non-bacteremia, n=193	p-value[1,2]
Median age at time of diagnosis	4	3	.960
Median age at onset of FN	5	5	.901
Female/male (%)	13/26 (33/66)	73/120 (38/62)	.717
Diagnosis			
ALL	15/39 (38.5%)	85/193 (44.0%)	.856
AML	15/39 (38.5%)	61/193 (31.6%)	.073
Lymphoma	4/39 (10.3%)	21/193 (10.9%)	.761
CNS tumor	1/39 (2.6%)	33/193 (17.1%)	**.022**
Solid tumor	4/39 (10.3%)	28/193 (14.5%)	.615
Laboratory values			
Median CRP at admission (IQR)	27 (12-90)	29 (12-52)	.613
Median leukocyte count (IQR)	0.2 (0.1-0.5)	0.6 (0.3-1.3)	**<.001**
Median hemoglobin (IQR)	8.7 (7.2-9.7)	8.8 (7.8-9.8)	.208
Median platelets (IQR)	39 (27-55)	53 (30-97.5)	**.022**
Median ANC (IQR)	0.0 (0.0-0.025)	0.0 (0.0-0.2)	**.005**
Median maximum CRP during treatment (IQR)	168 (118-291)	66 (30-112)	**<.001**
Median d of neutropenia	13 (7-18)	8 (5-12)	**<.001**
Outcome			
Median d of fever (IQR)	4 (2-9)	2 (1-4)	**<.001**
Median d of antibiotics (IQR)	10 (7-15)	5 (4-8)	**<.001**
Change of therapy	30/39 (76.9 %)	36/157 (22.9 %)	**<.001**
Median PEWS-score (IQR)	2 (1-3.75)	1 (0-2)	**.043**
Median maximum temperature (IQR)	39.4 (39.0-39.9)	38.9 (38.5-39.3)	**<.001**

Table 4: Comparison of laboratory values and outcomes in patients in bacteremia and non-bacteremia group, n=232. [1]: Mann-Whitney U test (continuous variables). [2]: Fishers chi-square test (dichotomous variables).

5 Discussion

In this retrospective observation study, I have detected 232 episodes of FN. In 17 % of the cases, blood cultures were positive, with a dominance of Gram-positive bacteria. During the 11 years, empiric antibiotic treatment has changed from ampicillin in combination with an aminoglycoside to piperacillin-tazobactam. Median counts of leukocytes, platelets and neutrophils at admission were significantly lower in patients with verified bacteremia.

The chosen antibiotic regimen was modified in 66 out of 232 cases, with persistent fever as the reason of change in just under half of the cases. Guideline recommendations state that persistent fever in an otherwise stable patient should not automatically trigger a change in antibiotic regimen (17). In this study, most cases where the treatment regime was modified there was a change to meropenem or vancomycin. A randomized study has shown that adding vancomycin to a regimen of piperacillin-tazobactam after persisting fever of three days showed no difference in time to defervescence compared to the placebo group (18). In this study, patients were not registered as stable or unstable, and therefore it is difficult to evaluate whether the changes were based on febrile unstable patients or other reasons for change to a broader spectrum in those with persisting fever as reason of change.

After the International Pediatric Fever and Neutropenia Guideline Panel (IPFNP) in 2017 stated a strong recommendation for choosing antipseudomonal beta-lactams as monotherapy in high-risk patients (7), piperacillin/tazobactam have become the main antibiotic regimen of choice in this group. A regimen of ampicillin in combination with an aminoglycoside was the regimen of choice from 2010-2016, with a steady decrease to 20% in 2020 although Norwegian guidelines still suggest penicillin or ampicillin in combination with gentamicin as the empiric regimen. 3rd generation cephalosporins and carbapenems have decreased to under 10% as first line choices in the latter parts of the century. In the summer of 2015 there was global restrictions of the supply of carbapenems. At UNN they limited the use by having doctors consult with infection specialists before administering carbapenems. This lead to a reduced use of carbapenems in the hospital as a whole, and therefore restrictions were continued from 2016. There restrictions may also have contributed to the reduced use in FN episodes in the pediatric department (19).

The local microbial etiology of FN is important for guiding empiric antibiotic treatment. In this study, 70.8% of the identified pathogens were Gram-positive and 29.2% was Gram-negative. Compared to a Norwegian national multicenter study identifying pathogens from 2002 to 2004, the situation is the same, with 72% versus 28% (8). However, the frequency of VGS have increased from 15.4% in 2002-2004, to 25% both in 2010-2020, while CoNS have decreased from 23.1% to 6.3% in the same time period (8). The increase of VGS in blood cultures have also been recognized internationally from 2009-2016 (7), and our findings describe a possible ongoing trend in the etiology of pediatric FN. A total of nine blood

cultures showed polymicrobial growth, and could therefore represent contaminated blood cultures. This has not been followed up on in this study.

There seems to be few significant differences in the underlying diagnoses of the patients with a positive and a negative blood culture, except from the CNS tumors – who seems to rarely have positive blood cultures. ALL and AML/MDS are the diagnoses that have the highest risk of FN, while patients with AML/MDS are more likely than patients with ALL to be admitted to hospital more than three times due to FN. With a median length of intravenous antibiotic treatment of 8 days, pediatric patients with AML/MDS spent far more days in hospital than any other diagnoses due to FN.

Blood samples are frequently obtained during a hospital stay with febrile neutropenia, and some values seems to be associated with a greater risk of having bacteremia. Median leukocyte count at admission and median maximum CRP during treatment period both have a significant association to having a bacteremia, with having leukocyte counts < 0.5 indicating a higher chance of bacteremia, and having CRP levels above 118 during treatment period also indicating a higher chance of a positive blood culture. The impact of a low WBC complies with the international consensus.

The study population contains all pediatric oncologic patients treated at UNN over an 11-year period and to the best of our knowledge the results are therefore representing the occurrence of FN, treatment and outcomes of the studied population. Laboratory values and most clinical outcomes are validated. However, the study has limitations. Fever onset was registered as the reported temperature measured by parents at home. Treatment was started irrelevant of temperature at hospital admission. Inter-rater ability in this group is low. As in all retrospective studies there may be missing data and/or wrong interpretation of data from a medical file. The inclusion process is somewhat dependent on information in exported electronic discharge summaries from local hospitals if patients were not transferred to UNN for treatment of FN, and if this was lacking, cases of FN would not have been picked up.

6 Conclusion

There were 232 episodes of FN among 76 patients age 0-17 years with malignant disease admitted to the UNN or other hospitals in the region in the period of 2010-2020.

Patients with ALL and AML/MDS are more prone to episodes of FN, with AML/MDS being the diagnosis that result in the highest number of repeated hospital admissions with FN.

Blood cultures were positive in 16.8% of all episodes with FN. This number complies with both national and international studies. Many laboratory values and clinical outcomes are associated with a higher risk of having a verified sepsis with a microbiologically proven bacteremia, but none of the factors seems to be able to strongly predict whether patients presenting with FN are having a bacteremia or not. Validated predictive scores still remain to be made.

Although the relative proportion of gram-positive versus gram-negative pathogens has stayed the same, the VGS have increased its incidence in blood cultures, similar to recent international trials.

Ampicillin in combination with an aminoglycoside was the most frequent antibiotic regimen of choice until 2017, when guideline recommendation changed. Since then, most pediatric patients presenting with FN have been treated with a regimen of piperacillin/tazobactam. Alternative regimens of carbapenems and 3rd generation cephalosporins started decreasing in 2017.

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