

## Updates in Paediatric Fever and Neutropenia

Fever and neutropenia (F&N) in children with cancer is a common reason for presenting to medical attention and is a medical emergency. Neutropenic patients are at increased risk of bacterial, viral and fungal infections. F&N has historically been a significant cause of morbidity and mortality, but outcomes have improved significantly over time due to rapid assessment at time of fever and early initiation of empiric antibiotic therapy. Gram-negative bacterial infections were initially the most common, but the incidence of gram-positive bacterial infections has increased over time. In many cases, an infectious organism or focus is never identified.



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The Antimicrobial Stewardship Committee at British Columbia Children's Hospital (BCCH) is made up of representatives from infectious diseases, microbiology, pharmacy and various other specialties from the hospital (oncology, NICU, PICU and others). The committee recently spent several months reviewing the most recent evidence and guidelines on management of paediatric fever and neutropenia. An important source for this discussion was the international paediatric guidelines published in the *Journal of Clinical Oncology* in 2012. From these discussions, an updated version of the BCCH fever and neutropenia guidelines was developed. The new guidelines apply to all oncology patients with known or suspected malignancy, patients receiving antineoplastic agents, patients who are less than six months post-

allogeneic stem cell transplant or still on immunosuppressive agents post-transplant and patients who have completed cancer therapy but still have a central venous catheter in place. **These guidelines currently apply to patients seen at BC Children's Hospital only.**

Many of the key principles of fever and neutropenia management remain the same. Fever definitions are unchanged, with temperature at or above 38.5C by mouth (38.0 axillary). Parents are still instructed to call oncologist on-call at BCCH if this occurs, at which time the patient needs to be seen at BCCH oncology clinic or emergency department. Rapid presentation and assessment remain key points with obtaining of lab results and initiation of empiric antibiotics promptly.

Several important changes to the previous algorithm include:

- 1) Recommendation to obtain peripheral blood culture in addition to central line cultures at time of initial presentation with F&N. The best available pediatric F&N evidence is that the rate of obtaining a true positive culture is increased by approximately 13% if a peripheral culture is added at the time of first fever spike. An additional component of the initial workup that has been re-emphasized is collection of a clean-catch midstream urine for analysis and culture (though this should never delay antibiotic administration). Chest x-ray continues to be recommended only for patients with respiratory symptoms.
- 2) Adoption of a risk-stratification system to divide neutropenic patients (neutrophil count below 0.5) into high vs. low-risk groups. The detailed criteria for risk stratification are included in the updated guideline. High-risk criteria include disease-related factors (e.g. infant ALL, Down syndrome), components of the clinical presentation (e.g. severe mucositis, evidence of a significant local infection, recent sepsis) and certain laboratory results (e.g. ANC <0.1). High-risk patients will continue to be admitted for IV antibiotics, but the low-risk group (defined as the absence of any high-risk features) will be treated with outpatient levofloxacin if tolerated and if follow-up is reliable. An example of a low-risk patient who could be considered for oral levofloxacin is a stable patient receiving maintenance chemotherapy for ALL who presents with a fever and URTI symptoms and is found to have an ANC of 0.4. Multiple studies show this or similar approaches to be safe and well-tolerated.
- 3) Recommendation of piperacillin/tazobactam as the single antibiotic for all stable high-risk F&N patients, regardless of diagnosis. Patients often received combination therapy with gentamicin in the past. In addition, patients with some high-risk diagnoses (particularly AML) previously received vancomycin in addition to the piperacillin/tazobactam. However, studies suggest that combination therapy adds toxicity but does not add any benefit for stable patients. Unwell patients will continue to receive multiple broad-spectrum antibiotics.

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# Clinical Trials in Pediatric Oncology

Outcomes in Pediatric Oncology have improved dramatically over the past three decades, with more than 80% of children diagnosed with cancer today likely to be cured of their disease. There are many factors contributing to this success, with one of the most important being the high participation rate of pediatric patients in well-organized, multi-center clinical trials; approximately 50% of children aged 0 to 14 years are enrolled on clinical trials, while a significantly lower percentage of adult patients participate.

Clinical trials are undertaken to determine the most effective and safest treatment for a disease. Each trial is aimed at improving survival rates or reducing side-effects of treatment. Enrolment of patients on clinical trials whenever possible should be considered the standard of care in cancer treatment for children, adolescents and young adults.

Clinical research in pediatric oncology may be undertaken by a single institution, but because childhood cancers are rare diseases with limited patient numbers, few centers have enough patients to adequately answer important clinical questions. Multi-institutional clinical trials are therefore essential for clinical cancer research to achieve its primary goal of improving future treatment. One of the largest pediatric clinical trial cooperative groups is the Children's Oncology Group (COG). COG is devoted exclusively to childhood and adolescent cancer research, and is supported by the National Cancer Institute (NCI). COG unites more than 8000 experts in childhood cancer in more than 250 leading children's hospitals across the world, including the pediatric cancer centers of all major universities and teaching hospitals throughout Canada and the United States. COG is ultimately responsible for the development and coordination of cancer clinical trials conducted at its member institutions. BC Children's Hospital has been a member of COG since its inception in 2000, and a member of the Children's Cancer Group (CCG) before that. CCG, the first pediatric oncology clinical trial group in North America, was formed in 1955. Other



Back row: Fatima Dharsee, Jessica Davis, Dr. David Dix, Alana Nemetchuk, Colleen Jantzen, Colleen Fitzgerald  
Mid row: Stephanie Badour, Lauren Bailey, Octavia Choi, Jo-Anne Shinde  
Front row: Alicia Lim, Martina Barbour  
Missing: Nita Takeuchi, Nicole Kelly

groups formed later, including the Pediatric Oncology Group (POG), the National Wilms' Tumor Study Group (NWTG) and the Intergroup Rhabdomyosarcoma Study Group (IRSG). In the year 2000, these four cooperative groups merged together to form the Children's Oncology Group (COG).

Many individuals and organizations are involved in developing a clinical trial. For each new trial a group of healthcare professionals and other experts propose a treatment and determine how it should be administered. It is important to appreciate that each new trial is extensively reviewed by experts in and outside of COG before the study is approved. There is also a Research Ethics Board (REB) associated with every hospital participating in the trial, to ensure the full protection of the rights of the patients enrolled. A clear understanding of the goals of the trial, as well as the risks and benefits of participation on the trial, are essential to the ethical conduct of a trial. It is also important for patients and families to understand that participation on a clinical trial is always voluntary and never a prerequisite to receiving the best possible care.

There are two types of clinical trials, therapeutic and non-therapeutic trials.

Therapeutic trials enroll patients that provide a specific treatment to study its impact on cancer. Non-therapeutic trials do not provide treatment to patients, but instead study factors which may advance the understanding of cancer. For example, a non-therapeutic study may involve the collection of tissue specimens to study the biology of specific cancer cells. The results of non-therapeutic studies are often used in the development of new therapeutic studies.

Within therapeutic trials there are three different phases to evaluate new treatments:

- 1) Phase 1 trials are designed to evaluate the dosage of new treatments. The maximum tolerated dosage of a drug is determined; this is the maximum dose at which there are no unacceptable side effects.
- 2) Phase 2 studies are designed to demonstrate the response of an agent to a specific tumor, in a dose and schedule previously determined in a phase 1 trial. Importantly, tumor response does not necessarily result in improved long-term outcome for patients.

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- 3) Phase 3 studies are the studies usually offered to new patients at the time of diagnosis. The aim of these studies is to evaluate a new drug or drug combination, often in a randomized fashion, by comparing two or more study arms. Usually one treatment arm is the standard or best current treatment. New treatment arms have been shown to be effective in other studies but have not yet been directly compared to the current best treatment.

Randomization is a process like flipping a coin to ensure that each patient has an equal chance of being assigned to any of the treatment arms. In most studies, we do not know which treatment is better until all children taking part in the trial have completed treatment and have been followed for a few years. However, if during the course of a trial one of the treatments is found to be a superior option, the trial is stopped and all children will be given the better treatment. The best treatment

for each individual patient is always of paramount importance, and if for any reason the study treatment is not working for an individual patient, the plan will be changed.

Of note, if a clinical trial is not available at the time that a specific patient is diagnosed, the best known standard treatment will be offered.

Investigational new drug studies can also be conducted in pediatric hospitals. In these studies, the laboratory results and results from the use of the drug are closely monitored and made available to the drug manufacturers.

Within the Division of Oncology at BC Children's Hospital, we are committed to providing the highest quality of clinical care for all patients, whether they are enrolled on clinical trials or not. The benefit of having access to clinical trials includes being able to provide our patients with the latest treatments and new agents, as well as allowing us to contribute to the knowledge necessary to improve treatments in the future. At BCCH we have a highly motivated and committed team, across all disciplines,

to support our efforts. While the individual contributors to this team are too many to mention, special thanks needs to be given to our Clinical Research Assistants (CRAs): Martina Barbour, Colleen Jantzen, Jess Davis, Alecia Lim, Octavia Choi, Nicole Kelly, Alana Nemetchuk, Lauren Bailey, Joanne Shinde and Nita Takeuchi. We depend on the tireless efforts of our CRAs every single day. An extra-special thank you also needs to go to Fatima Dharsee (CRA Manager), Stephanie Badour (COG Lead CRA), and Colleen Fitzgerald (Clinical Research Manager) whose invaluable insight, commitment and leadership make this important work possible.

In January 2016, I was appointed Principal Investigator for COG at BCCH. I am honored to assume this role. Please feel free to contact me or any member of our team if you have questions regarding COG clinical trials in the Division of Hematology/Oncology/BMT.

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- 4) Advice against altering empiric therapy purely for persistent fever in stable patients. Practice has often been to add additional antibiotics if patients have persistent fever (e.g. vancomycin), but this has not shown to have a consistent benefit and so is no longer recommended. If a new focus of infection becomes apparent that would require alternative antibiotics, changes to therapy are still being made.
- 5) Suggestion to discontinue empiric antibiotics in low-risk patients who have become afebrile and have negative cultures, regardless of whether they have yet count recovery. Studies have shown no increase in adverse outcomes with this approach.
- 6) Recommendation that antibiotic therapy is not required for febrile non-neutropenic patients who are well and have reliable follow-up, unless required to treat a focal infection. Well, non-neutropenic patients with fever previously received ceftriaxone

for 48 hours. However, rates of serious infection in the absence of any concerning clinical features are exceptionally low, so empiric antibiotics are no longer recommended in this situation.

These new guidelines have now been in use at BCCH since September 2015, but have not yet been launched provincially. The department is currently working to evaluate the first several months' experiences with the new protocol. After this review is complete, we will be evaluating whether any additional changes need to be made to the protocol and whether it is ready to be launched provincially. In the interim, the previous F&N protocol remains in place for the communities outside of BCCH. To locate these guidelines, please visit Oncology section of the BCCH website.

<http://www.bcchildrens.ca/health-professionals/clinical-resources/oncology> and then click resource tab.

Fever & Neutropenia guidelines  
<http://www.bcchildrens.ca/Oncology-Site/Documents/FeverandNeutropenia.pdf>

Fever without Neutropenia guidelines  
<http://www.bcchildrens.ca/Oncology-Site/Documents/FeverwithoutNeutropenia.pdf>

The screenshot shows the BC Children's Hospital website. At the top is the logo and a search bar. Below is a navigation menu with 'Search' and 'Menu'. The 'Oncology' section is highlighted. Below the 'Oncology' header, it says 'BC Children's Hospital works collaboratively with the BC Cancer Agency and the Children's Oncology Group to provide recommendations for investigation, treatment and follow-up for children with cancer.' Below this is a table with three columns: 'Guidelines', 'Resources', and 'Health-care teams'. The 'Resources' column is active. The table lists several resources with expandable icons (+):

Guidelines	Resources	Health-care teams
	Fever & neutropenia	+
	Chemotherapy administration	+
	Procedures	+
	Immunization	+
	Websites	+
	Past lectures	+

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Subspecialty Resident (PGY-7),  
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## Announcements



### Welcome

We welcome Dr. Caron Strahlendorf to the Pediatric Oncology Hematology Network as the new medical consultant. She is also the Head of the Division of Pediatric Oncology/Hematology/BMT at BC Children's Hospital.

### Pediatric Oncology Hematology Education Day: Innovation, Inspiration and Engagement

Place: BC Children's Hospital

<http://ubccpd.ca/course/pediatric-oncology-hematology-education-day>



**BALDING FOR DOLLARS**

### Balding for Dollars

Balding for Dollars main event

Sign up to shave your heads or cut-off your locks in support of kids with cancer

Date: Saturday, May 14, 2016

Place: Child and Family Research Institute at BC Children's Hospital

[http://baldingfordollars.com/event/balding-for-dollars-main-events-2016/?instance\\_id=20](http://baldingfordollars.com/event/balding-for-dollars-main-events-2016/?instance_id=20)

### Pediatric Oncology Group of Ontario (POGO) 2016 AfterCare Education Day

Date: June 13, 2016

Place: Toronto, Ontario

[www.pogo.ca/education/2016-pogo-aftercare-education-day/](http://www.pogo.ca/education/2016-pogo-aftercare-education-day/)

### Association of Pediatric Hematology/Oncology Nurses (APHON) Annual Conference

Date: September 29-October 1, 2016

Place: Indianapolis, IN

[www.aphon.org/meetings/futuredates.cfm](http://www.aphon.org/meetings/futuredates.cfm)

### SIOP (International Society of Pediatric Oncology) Annual Conference

Date: October 19-22, 2016

Place: Dublin, Ireland

[www.siop2016.kenes.com/congress-information/general-information#VwQ4RZRdWS0](http://www.siop2016.kenes.com/congress-information/general-information#VwQ4RZRdWS0)

### THE PROVINCIAL PEDIATRIC ONCOLOGY/HEMATOLOGY NETWORK

The Network is an interdisciplinary organization whose goal is to ensure appropriate diagnosis, management, follow-up, and end-of-life care for pediatric patients with malignancies and blood disorders.

The Network supports community hospitals and practitioners, and develops partnerships with other healthcare facilities to enable seamless and integrated care for patients and families on treatment and off treatment.

It will further develop and enhance the research programs of basic, translational, and clinical research to better childhood cancer control and improve outcomes for these patients and their families.

#### FOR MORE INFORMATION

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Our mission is to improve the health and welfare of children in BC with cancer and blood disorders through research, education, and care.