## Introduction
Neutropenia and febrile neutropenia (FN) are among the most important toxicities associated with myelosuppressive chemotherapy.

Clinical implications: decreased total chemotherapy dose, delayed chemotherapy treatment schedule, hospitalization, broad spectrum antimicrobial exposure, treatment failure.

Hematopoietic granulocytes colony-stimulating factors (G-CSF) have been shown to:
- Reduce the duration and severity of neutropenia and the risk of FN
- Enable delivery of more intensive or dose-dense chemotherapy when indicated

Remaining concerns with respect to adverse events and costs have led the American Society of Clinical Oncology (ASCO) to develop clinical practice guidelines for the use of G-CSF.

Filgrastim use in primary prophylaxis (PP) of FN in children is generally guided by specific research protocols. Its use in FN treatment for this population is also common. As part of a descriptive analysis of filgrastim conducted by the PGT in 2016, an assessment of its use was performed in the pediatric population in four university teaching hospitals (UTh) in Québec.

## Methods
The complete protocol is available at: [www.pgtn.qc.ca](http://www.pgtn.qc.ca)

### Objectives
- Determine real life use of filgrastim in hospitalized patients (indication, dose, number of doses received, absolute neutrophil counts (ANC) at the start and end of treatment when appropriate: ex: treatment of FN);
- Identify additional FN risk factors presented by patients receiving filgrastim in PP or secondary prophylaxis;
- Identify additional risk factors associated with a poor clinical outcome in patients treated for FN who received filgrastim.

### Participants
With the support of participating hospital-based pharmacy computer systems, pediatric patients receiving filgrastim during their hospital stay between August 1st 2014 and July 31st 2015 were identified;
- Through the medical records of participating centers, patients diagnosed with FN during the same timeframe were identified. FN patients were cross-matched with those receiving G-CSF (filgrastim, pegfilgrastim);
- Based on these criteria: analyses included a maximum of 50 randomly selected FN patients receiving filgrastim and 50 patients receiving filgrastim for other indications per UTh.

*Since pegfilgrastim is not on hospital formularies, all patients received filgrastim.

### Methods
- Study design: retrospective descriptive analysis;
- Clinical data information sources: medical files (paper or electronic), pharmacy and oncology nursing notes, laboratory results and any other useful documentation;
- Data management: Information was collected on a standardized data collection sheet and entered into an ACCESS database;
- Statistical analyses: Descriptive data are presented as mean ± SD, median (range) or %.

## Results
A total of 175 episodes of care (EC) in 148 patients were identified where patients received filgrastim during the study period.

### General population

<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics</th>
<th>NUMBER OF PATIENTS (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>Male (%) / Female (%)</td>
<td>90 / 58</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>7.95 years (Range: 0.01 to 17.5)</td>
</tr>
<tr>
<td>Weight (mean)</td>
<td>31.3 kg</td>
</tr>
<tr>
<td>Mean length of stay per EC (median length)</td>
<td>21.6 days (8 days)</td>
</tr>
</tbody>
</table>

*23 patients had 2 EC and 2 patients had 3 EC.

### Filgrastim indications during the study period (N = 175)

- **Primary prophylaxis** (45.1%)
- **Secondary prophylaxis** (34.4%)
- **FN treatment** (20.4%)
- **Bone marrow stimulation (for transplant)** (4.6%)
- **Post transplant** (12.5%)
- **Chronic congenital neutropenia** (3.4%)
- **Part of an AML treatment protocol** (0.6%)
- **Before chemotherapy** (2.9%)
- **Other** (4.0%)

### FN risk of chemotherapy for patient receiving PP filgrastim (n = 79)

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>PATIENTS (n)</th>
<th>ESTIMATED FN RISK FACTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumor</td>
<td>15</td>
<td>High</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>14</td>
<td>High</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>11</td>
<td>High</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>5</td>
<td>High</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>1</td>
<td>Moderate</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>1</td>
<td>Moderate</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>1</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hodgkins lymphoma</td>
<td>13</td>
<td>Moderate</td>
</tr>
<tr>
<td>Non-hodgkins lymphoma</td>
<td>9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3</td>
<td>High</td>
</tr>
</tbody>
</table>

In 57 EC (72.2%) filgrastim was continued after hospital discharge.

### Discussion
Most of the time, the use of filgrastim for PP in pediatrics will be guided by research protocols. As with adults, the use of filgrastim is reasonable in PP for pediatric patients with a high probability of FN. PP in patients at moderate risk of FN should also be considered if patients present at least one other FN risk factor.

Compared with the adult population, there is no officially published pediatric FN management guide available to clinicians. The decision to use filgrastim in FN is usually determined within each individual protocol or the protocol leaves the decision-making to the clinician, based on a case-by-case clinical evaluation.

In adults, ASCO, NCCN, and IDSA suggest that hematopoietic colony-stimulating factors may be considered for the treatment of patients at risk for significant complications related to infections or with poor prognostic factors such as when patients are at risk for severe neutropenia (neutrophils less than 0.1 x 10^9/L) and prolonged (more than 10 days), have uncontrolled primary disease, pneumonia, hypotension, failure of multiple organs (septic shock), an invasive fungal infection, or if they were hospitalized at the time the fever developed.

In the pediatric setting, neither the Children Oncology Group (COG) nor the SickKids in Ontario mention the use of filgrastim in its recommendations for the management of FN. In contrast, the clinician may initiate treatment with filgrastim, based on his or her clinical judgment, if the patient's condition is rapidly deteriorating.

If one of the objectives of using filgrastim is to shorten the duration of FN, it is important to monitor the ANC results closely. In the adult population, ASCO recommends continuing filgrastim administration until ANC is at least 2 x 10^9/L, whereas the product monograph advises stopping the treatment if the ANC exceeds 10 x 10^9/L after the nadir. The latter also specifies that the daily administration should be spread out over a maximum of two weeks after the anticipated nadir of the chemotherapy regimen but the duration of the treatment necessary for the attenuation of neutropenia may depend on the myelosuppressive potential of the selected chemotherapeutic regimen. In some pediatric protocols, the COG recommends stopping the use of filgrastim after having an ANC greater than 0.5 x 1.5 x 10^9/L for 2 days, while in other protocols, no value is specified.

## Conclusion
Tools to help clinicians with filgrastim prescription outside of clinical research protocols (preprinted orders, FN guidelines, standardized ANC for filgrastim discontinuation) should be developed and shared to optimize its use.

### Limitations
- Retrospective study
- Identification of patients prior to release of ASCO and COG guidelines for G-CSF use
- Completeness of notes in patient files may vary between clinicians
- Limited number of patients selected

We would like to thank all pharmacy students who help collect patient information.

### References
- The Hospital for Sick Children (SickKids) (Ontario) web site: Consulted online on May 10th, 2018 at: www.sickkids.ca/HematologyOncology/IPFNG/index.htm

### Contact Information
For any question or additional information, contact: ghislain.berard.riussse-chus@ssss.gouv.qc.ca