MSH + UHN ASP ANTIMICROBIAL STEWARDSHIP PROGRAM

FEBRILE NEUTROPENIA PROTOCOL FOR SOLID TUMOR AND LYMPHOMA VERSION OCTOBER 2014

FREQUENTLY ASKED QUESTIONS

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1. How is this protocol different from the High-Risk Protocol? What steps did you take to avoid confusion between the two?

The target population in the "High Risk" Protocol is patients whose neutropenia is anticipated to be prolonged (absolute neutrophil count or ANC lower than or equal to $0.1x10^9$/L at nadir) and profound (longer than 7 days). Examples of high risk neutropenia would be those with malignant haematological diseases or patients undergoing hematopoietic stem cell transplant. In comparison, the target population in the solid tumor and lymphoma febrile neutropenia (FN) protocol are patients whose neutropenic period is anticipated to be shorter than or equal to 7 days and with ANC nadir higher than $0.1x10^9$/L. Such patients are anticipated to have lower risk of infectious complications as a result of faster recovery of neutrophils and less profound immunosuppression, compared to their high-risk counterparts. To make the two protocols more distinguishable from each other, yet maintain their relatedness, we reversed the colour scheme in the solid tumor FN protocol. We have clearly stated criteria for eligibility for the solid tumor FN protocol, and cross referencing was made where applicable.

References:

- Flowers CR, Seidenfeld J, Bow E, et al. Antimicrobial Prophylaxis And Outpatient Management Of Fever And Neutropenia In Adults Treated For Malignancy: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2013;31:794-810.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52(4):e56–e93.

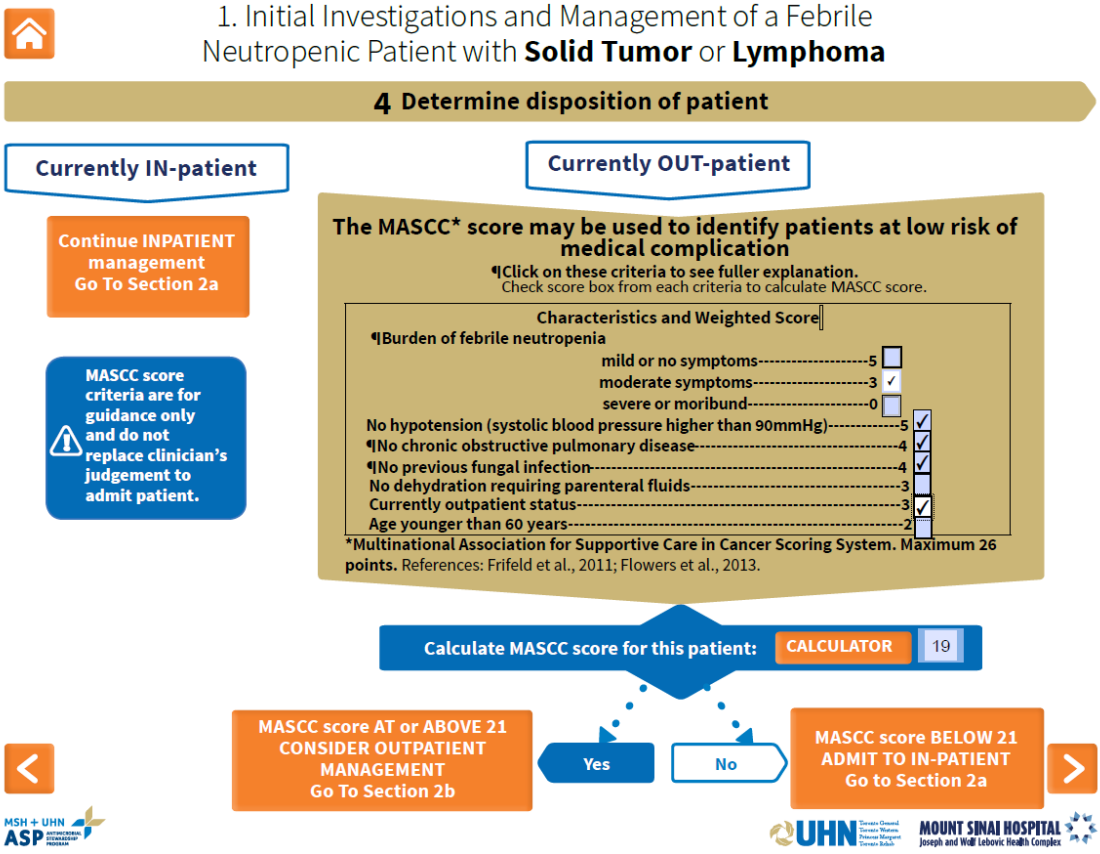
2. What about certain high-risk lymphomas? Those patients may have neutropenia similar to that of patients with malignant haematological diseases.

We were concerned that various definitions of "high-risk" may cause confusion, particularly amongst clinicians whose areas of expertise are outside the specialty of Oncology. Therefore we made reference only to the anticipated duration and nadir of the neutropenia in determining risk of infectious complications. *Patients with lymphomas receiving chemotherapy that results in prolonged and profound neutropenia should be managed following the High-Risk Protocol.*

3. The Multinational Association for Supportive Care in Cancer (MASCC) scoring system is complex and challenging to follow. How am I supposed to apply this in the clinical setting?

Inpatient management is considered the standard approach to oncology patients presenting with neutropenic fever. However, carefully selected patients may be managed as outpatients following systematic risk assessment, such as the MASCC index which has been well validated. It was endorsed by the American Society of Clinical Oncology and the Infectious Diseases Society of America in their respective guidelines, as a means to identify patients at low risk of medical complications.

We made an effort to improve the usability and visual appeal of the tool with an online calculator and pop-up boxes with more details to avoid overcrowding the screen.



- To get a fuller explanation of burden of symptoms, chronic obstructive disease or previous fungal infection, click on the wording next to ¶ to see a pop-up box with details, then re-click to close.

- As the list of criteria are selected (or unselected), MASCC score is automatically calculated and will be shown in the box next to "calculator".

We have emphasized that MASCC score does not replace clinician's judgement to admit patient but serves as guidance only. We chose not to arbitrarily modify this score without prospective validation, and therefore have retained its original contents. Lastly, we strongly encourage the clinician to contact the primary oncologist (or delegate) to discuss disposition of the patient, and to arrange follow-up assessment. Patient would therefore only be managed as outpatient when it is deemed appropriate by the clinicians involved.

References:

- Klastersky J and Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer. 2013 May;21(5):1487-95. Doi: 10.1007/s00520-013-1758-y. Epub 2013 Feb 27.
- Flowers CR, Seidenfeld J, Bow E, et al. Antimicrobial Prophylaxis And Outpatient Management Of Fever And Neutropenia In Adults Treated For Malignancy: American Society of Clinical Oncology Clinical Practice Guidelines. J Clin Oncol 2013;31:794-810.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52(4):e56–e93.

4. Why does the protocol recommend gentamicin and cefazolin as empiric regimen? This deviates from our long-standing use of piperacillin-tazobactam, plus I would be concerned about using lots of aminoglycoside.

The most recent and complete PMH in-patient antibiogram was supplied by Microbiology based on isolates collected in Jan to Dec 2011. Amongst blood isolates, the prevalence of extended-spectrum beta-lactamase producing *E. coli* (most common) was estimated to be about 30% using resistance to 3rd generation cephalosporins as a surrogate marker, which makes piperacillin-tazobactam less reliable as an empiric agent. Since then, the continued rise of ESBL-producing gram negative bacilli (GNB) has been widely reported in Toronto, in Ontario and the rest of Canada. Aminoglycosides are more reliable than fluoroquinolones in their activity against ESBL-producing organisms, while maintaining anti-pseudomonal activity. Importantly, aminoglycosides are meant to be used for no longer than 72h. As soon as the absence of an ESBL-GNB is established, aminoglycoside should be stopped. In patients with renal insufficiency (CrCL under 50 mL/min), usually only the first dose is required while investigations are underway. Cefazolin at 2g Q8H provides empiric coverage against susceptible *Enterobacteriaceae* as well as methicillin-susceptible *S. aureus*. Should the need for IV antibiotics continue, in the absence of an identified source, we do recommend switching to piperacillin-tazobactam, and to consider consultation from Infectious Diseases.

References:

- Lowe C, McGeer A, Muller MP, Katz K for the Toronto ESBL Working Group. Antimcirob Agents Chemother 2012;56:3977.
- Denisuik AJ, Lagace-Wiens PRS, Pitout JD et al. Molecular epidemiology of extended-spectrum beta-lactamase, AmpC beta-lactamase and carbapenemase producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from Canadian hospitals over a 5-year period: CANWARD 2007-2011.
- Babinchak T, Badal R, Hoban D, et al. Trends in susceptibility of selected gram-negative bacilli isolated from intra-abdominal infections in North America: SMART 2005–2010. Diagn Microbiol Infect Dis 2013;76: 379-81.
- McGeer A and Fleming CCA. Antimicrobial Resistance In Common Hospital Pathogens In Ontario Report 2012. Quality-Management Program-Laboratory Services Department of The Ontario Medical Association.
- PMH antigiobram hyperlink: http://www.antimicrobialstewardship.com/antibiograms

5. This protocol seems to suggest that antibiotics are tailored to a specific infection (i.e. narrowed) if one identified, even during the neutropenic period? I always thought we kept broad until recovered then tailored based on source?

We followed the antimicrobial stewardship framework in developing this protocol, i.e. 1) start with broad empirical coverage; 2) perform and request necessary and appropriate investigations; and 3) tailor therapy based on results from the investigations. The period of neutropenia associated with solid tumor and most lymphomas is anticipated to be short, 5-7 days, and the nadir is usually not as low as those with malignant haematological diseases (see also Question 1.) In addition, it usually takes 1-2 days for a pathogen to be identified with susceptibility results. The period of not keeping broad coverage while ANC counts are low is therefore relatively short, practically speaking.