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Editorial Comment

Time for paediatric febrile neutropenia guidelines – children are not little adults ☆

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Clinical practice guidelines are important to healthcare professionals and patients to help make decisions related to health, and they may improve the quality of health care.[1–3] In cancer patients, guidelines are important to facilitating management of febrile neutropenia (FN). Several FN guidelines have been rigorously developed by organisations including the Infectious Diseases Society of America and the National Comprehensive Cancer Network, but unfortunately, none are focused on children with cancer and widely applicable. In this commentary, we wish to highlight the rationale for why paediatric FN guidelines are necessary. Important differences are seen between adults and children with cancer which may greatly impact the management of FN and children themselves are not a homogeneous group. The potential areas in which adults and children may differ related to FN may be divided into (1) Host/environment; (2) Risk stratification; (3) Evaluation; (4) Treatment; and (5) Family/psychosocial considerations.

There are several aspects of the host and environment that differ between adults and children. In adults, the most common cancers are lung, colorectal, prostate and breast.[4] In contrast, the most common malignancy of childhood is acute lymphoblastic leukaemia.[4] Consequently, adults and children who present with FN have different underlying cancer diagnoses and different therapeutic treatments.[5] In general, children receive much more intensive treatment with a curative intent compared with adults.[6] Even when focusing on the same cancer type, treatment intensity and both incidence and severity of treatment-related complications are higher in treatment protocols designed for children as compared to adults.[6] Therefore, it is not surprising that regimens used to treat children with cancer are more likely to result in FN.[7] Both of these differences in diagnoses and treatments may impact on the management of FN.

Beside differences in underlying malignancy and treatment, adults and children may have significant differences in immunity, the capacity of immune reconstitution after chemotherapy, and co-morbidities, all of which influence the risk and outcome of FN. The immune system matures throughout the paediatric age range.[8] For example, compared

☆ This manuscript describes the rationale behind the need for paediatric specific febrile neutropenia guidelines.

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to older children and adults, neutrophils in the neonatal period have impaired chemotaxis and bactericidal activity.[9,10] T-cell regeneration following intensive chemotherapy, both in number and T-cell repertoire, critically depends on the age of the patient.[11] Nutrition and lifestyle are different between adults and children, and have an important impact on co-morbidity, which in turn, influence the prognosis of FN. Younger children do not smoke and are less likely to be obese compared with adults.[12] The increase in obesity, along with other age-related illnesses, increases co-morbidities such as type II diabetes, cardiovascular disease, hypertension and pulmonary dysfunction in adults. In addition, important environmental considerations may influence risk and severity of FN. For example, children may attend daycare and school and are more likely to be in contact with other children. Consequently, children typically have greater exposure to viral illnesses.

Together, these differences in host biology, cancer types, treatment and co-morbidity along with environmental considerations result in different epidemiology of infecting organisms for adults and children with FN.[5] This has been shown in one analysis which examined adults and children enrolled onto four randomised trials conducted by the European Organization for Research and Treatment of Cancer (EORTC) published from 1986 to 1994.[5] Among these trials, 75% of participants were adults and 25% were children. Adults were more likely to present with a documented infection during FN as compared to children. Adults were also more likely to experience staphylococcal infections whereas streptococcal infections occurred more often in children.[5] In patients in whom a site of infection was identified, children were more likely to have infections of the upper respiratory tract, consistent with increased viral infections. In addition to differences in the epidemiology of infections for adults and children with FN, there also may be differences in outcomes of FN depending on age.[13] More specifically, in the EORTC analysis previously described, children in comparison to adults had a higher success rate of empiric antibiotics, shorter time to defervescence, fewer adverse events, lower infection-related mortality and better overall survival.[5]

A second major area in which there will be differences between adults and children relates to risk stratification. A widely accepted risk stratification tool is the Multinational Association for Supportive Care in Cancer (MASCC) index.[14] Unfortunately, variables such as chronic obstructive pulmonary disease and age <60 years are used in the calculation of the score, and consequently, children are specifically excluded from this scoring system. In contrast, central venous lines, which are a risk factor in many FN risk prediction rules in adults, are almost ubiquitous in children receiving chemotherapy. Therefore, the well established and prospectively validated risk factors in adult cancer patients cannot be translated in the paediatric setting, and no single risk stratification system has been widely evaluated or clinically adopted in pediatrics.[15] However, several paediatric risk prediction rules have been developed[15] and an important future goal will be for the community to agree upon a common system for use in children.

The third area relates to evaluation of FN. In terms of history and physical examination, elicitation of symptoms and reliability of signs may be altered in children who are too young to communicate and who may not be co-operative with physical evaluation. Blood cultures are also potentially problematic since much greater volumes are typically obtained from adults with FN and volume of blood is an important factor in successful isolation of an organism during low-grade bacteremia.[16] Consequently, a single blood culture in a child with FN may miss as much as 10% of true episodes of bacteremia.[17] In terms of diagnosing urinary tract infection, the value of dipstick urine testing and reliance on nitrite positivity has been shown to vary greatly between neonates, pre-school children and adolescents.[18] The need for urine cultures in asymptomatic neutropenic children may therefore be different compared to adults. In addition, there are several surrogate markers of infection that are well established in adult patients, whereas the test characteristics are often unknown or uncertain in children, such as the use of galactomannin testing for early diagnosis of invasive fungal infections.[19]

The fourth area of consideration includes treatment issues. Many of these relate to availability of pharmaceutical agents in children, in particular regarding paediatric approval and dosing. For example, piperacillin-tazobactam is a common antibacterial agent in the treatment of FN, but not licensed in children younger than 2-years of age. Ciprofloxacin which plays an important role in adults for antibacterial prophylaxis,[20] is licensed for paediatric sub-groups only (e.g. children with cystic fibrosis), but is not approved for children with FN. Similarly posaconazole, which has no paediatric label and for which phase I/II studies are in progress to define a paediatric dosage, is recommended as prophylaxis for high risk patients according to at least one guideline.[20] Notably, even for drugs in which dosing information is available for children, very often, dosing information is not available for neonates. Another issue in terms of drug administration is whether children are able or willing to tolerate oral formulations. Also, children may be too young to swallow tablets or capsules and thus, availability of a suspension formulation is an important practical consideration.

Finally, there are a tremendous number of family/psychosocial issues that will differ between adults and children. This is exemplified by the fact that most children do not make decisions on their own behalf but rather, the decision-makers are parents or other caregivers. The nature of the decision-maker is likely to fundamentally change the psychology of decision-making and reporting of quality of life and treatment preferences.[21] For example, adults are primarily responsible for their own monitoring of FN and drug administration if treated as an outpatient while for children, parents become responsible for these tasks. Caring for a child with cancer results in worse physical and psychosocial quality of life for parents[22] and consequently, healthcare providers must consider parental abilities and needs in recommending a management strategy in paediatric FN. This aspect has not been considered in previous FN guidelines.

All these differences between adults and children with FN clearly merit guidelines focused on paediatric patients of all different age groups. Such guidelines should be developed by an international collaborative group which will ensure that the guidelines are acceptable to a wide audience and hope-

fully, will promote appropriate consistency in FN management across different countries. Although we recognise that there are considerable differences in environment and health care systems between different countries, the adaptation of any guideline to the local context will improve any guideline's utility.[23] There are many aspects of care related to paediatric FN that could be included in a guideline, but we believe that two issues should drive the focus. First, guidelines should examine areas in which there is uncertainty in best practice. Second, paediatric guidelines also should concentrate on areas that are known to be, or may be different in children as compared to adults. The development of these guidelines will facilitate and hopefully bring more uniformity to the treatment of children with FN.

Conflict of interest statement

None declared.

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