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Original Research

Implementing Antimicrobial Stewardship-Oriented Guidelines Using a Change Management Approach: The Example of Febrile Neutropenia

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Background. To reduce unnecessary antimicrobial use in oncology-hematology patients, we developed and implemented a set of facility-specific, antimicrobial stewardship-oriented febrile neutropenia guidelines for leukemia and stem cell transplant patients using a healthcare change management framework.

Methods. The patient setting was a tertiary cancer center in Toronto, Canada. The framework has six core elements: 1) governance and leadership; 2) stakeholder engagement; 3) workflow analysis and integration; 4) communications; 5) training and education; and 6) monitoring and evaluation. We applied elements 1-3 to guidelines design, and 4-6 to guidelines dissemination and implementation.

Results. Element 1) the guidelines were developed by the Antimicrobial Stewardship Program (ASP) and sponsored by the Malignant Hematology Program's senior leadership. They determined the guidelines' scope. Element 2) two ASP team members drafted the guidelines after a literature review. Clinical leaders, content experts, and clinician end-users reviewed the draft. Their feedback was incorporated in the guidelines. Element 3) healthcare human factors engineers conducted a qualitative study with clinicians to optimize guidelines usability, creating a format that is interactive and embedded with hyperlinks for efficient user-interface at point-of-care. Element 4) we informed clinicians that the finalized guidelines are available on our website. Element 5) we demonstrated the guidelines to clinicians at audience-specific venues. Element 6) we continuously report antimicrobial consumption, expenditure, guidelines adherence, and indications of antimicrobials to stakeholders and clinicians.

Conclusion. A healthcare change management framework facilitated the successful development and implementation of new febrile neutropenia guidelines that promote antimicrobial stewardship and standardization of care in malignant hematology patients.

Key words: antimicrobial stewardship; oncology; change management

Chemotherapy-induced febrile neutropenia is associated with considerable morbidity and mortality [1]. Clinicians overseeing the care of these patients are required to perform a thorough assessment and a comprehensive diagnostic workup to determine possible infections and the most appropriate empiric antimicrobials [1]. Given the complexity of this relatively homogeneous patient population, current guidelines recommend an algorithmic approach [1]. The rise of multidrug-resistant organisms and *Clostridium difficile* infections, coupled with limited new antimicrobial agents, have heightened the

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awareness of antimicrobial stewardship among clinicians and administrators, including those responsible for oncology patients [1-3]. Antimicrobial recommendations from international febrile neutropenia guidelines do not account for local characteristics such as susceptibility patterns, healthcare resources, and patient factors [4, 5]. To overcome these limitations, implementation of facility-specific febrile neutropenia guidelines has been encouraged to standardize care and promote antimicrobial stewardship practices, while maintaining focus on the individual patient [1, 6]. Despite available literature on developing and disseminating clinical practice guidelines [7-10], there is limited guidance on local adaptation of published guidelines. We describe the use of a change management framework for the development, implementation, and dissemination of a set of febrile neutropenia guidelines for patients with hematological malignancies at a tertiary cancer center [11]. We review the challenges and lessons learned, aiming to assist others also wishing to use local guidelines to promote antimicrobial stewardship [6].

MATERIALS AND METHODS

Patient setting

Princess Margaret Cancer Centre (PM), a University Health Network (UHN) hospital, is a leading cancer research center in North America with a substantial malignant hematology program, registering 34,380 clinic visits and 24,659 in-patient days in 2015. Leukemia patients undergoing induction chemotherapy and recipients of allogeneic hematopoietic stem cell transplant (HSCT) are expected to experience prolonged and profound neutropenia during their hospital admissions [4]. Patients with febrile neutropenia may also be admitted through ambulatory clinics in PM, from the emergency department of any of 3 nearby acute care hospitals (UHN's Toronto General or Toronto Western Hospitals), or Sinai Health System's (SHS) Mount Sinai Hospital). Mount Sinai Hospital accepts urgent transfers of PM patients requiring admission to critical care. Servicing all of these hospitals is the Sinai Health System-University Health Network Antimicrobial Stewardship Program (SHS-UHN ASP). Established in 2009, the ASP has expertise in immunocompromised patients and has been active in PM's leukemia units since February 2010 [12, 13].

Determining the needs to be fulfilled by the new febrile neutropenia guidelines

In 2011, PM leadership and the ASP team determined that the existing febrile neutropenia guidelines were no longer adequate. Primarily paper-based with limited online availability, the recommendations were outdated and not easily accessible to prescribers. Priority was given to developing a new set of guidelines for the management of febrile neutropenic patients with hematological malignancies due to significant risks of infectious complications, correspondingly high consumption, and expenditure on broad spectrum antimicrobials [4]. Furthermore, there was wide variation in clinical practice from diagnostic workup to antimicrobial prescribing. To accommodate high volumes of patients, frequent turnover of trainees, and clinicians of various disciplines, a new set of guidelines has to be: 1) widely and easily accessible at point of clinical decision-making; 2) user-focused; 3) easily understandable with minimal risk of misinterpretation; 4) tailored to PM patients' microbiology susceptibility patterns and resources; and 5) reflecting current literature and best practices [14]. The guidelines should be founded on antimicrobial stewardship principles that emphasize 6) timely administration of empiric antimicrobials with appropriate spectrum of activity; 7) appropriate diagnostic workup, followed by timely tailoring of antimicrobial therapy when applicable; and 8) use of expertise at point of care [15, 16].

The intervention: healthcare change management framework

The Canada Health Infoway Change Management Framework (Table 1) was designed to support change management leaders, managers, and frontline clinicians who are implementing healthcare solutions in their workflow and practice, particularly solutions related to information and communication technology, therefore applicable to the development and implementation of facility-specific guidelines [11]. There are six core elements: 1) governance and leadership; 2) stakeholder engagement; 3) workflow analysis and integration; 4) communications; 5) training and education; and 6) monitoring and evaluation. We applied the first three to the design process, and the latter three to implementation and maintenance.

RESULTS

Governance and leadership

Governance and leadership are mechanisms to guide, steer, or regulate the course of an initiative [11]. Individuals fulfilling the governance role should have four characteristics related to change management: 1) position power; 2) expertise; 3) credibility, and 4) leadership [12]. These individuals are responsible for resource allocation,

offering advice, keeping the task on course, trouble-shooting barriers, and facilitating solutions to make the project or initiative successful [12]. These roles were fulfilled by members of the Senior Leadership Team at PM: the Malignant Hematology Program's Medical and Senior Clinical Directors, and a Senior Vice President. They have supported the ASP since it implemented academic detailing rounds in leukemia in 2010 [17, 18].

Development of the guidelines occurred under the auspices of the SHS-UHN ASP, the first of its kind for PM. An ASP pharmacist (MSo) and an ASP physician specializing in infectious diseases in immunocompromised hosts (SH) were the co-lead developers of the guidelines. These two ASP team members conduct academic detailing rounds with prescribers to review the antimicrobial needs of all inpatients in malignant hematology [17, 18]. They regularly educate PM's clinicians on antimicrobial stewardship. In consultation with PM's Senior Leadership, it was determined that the scope of the guidelines should include antimicrobial prophylaxis and management (investigations and treatment) of febrile neutropenia to maximize their usefulness. Quarterly meetings were held with Senior Leadership during which the progress of the guidelines was a standing agenda item.

The developmental process (Figure 1) began in 2012 with an environmental scan of current publications and institutional practices. We appraised international and national guidelines on their recommendations and supporting evidence [4, 19-21]. We contacted academic hospitals with comparable expertise in hematological malignancies and HSCT across North America, Britain, Europe, and Australia for their local febrile neutropenia guidelines, which were reviewed in context of their healthcare systems. We formulated a list of clinical questions based on knowledge gaps and clinical controversies, and addressed them with a systematic literature review. Examples are empiric versus pre-emptive antifungal therapy guided by surveillance serum galactomannan assay; use of alternative dosing strategies such as extended infusions of beta-lactam antibiotics; and the risks versus benefits in de-escalating broad-spectrum antibiotics in culture-negative high-risk febrile neutropenia [20-24].

Our guidelines emphasize a diagnostics-driven, multidisciplinary approach, and application of antimicrobial stewardship principles — specifically timely administration of appropriately selected antimicrobial therapy [15, 16]. We solicited advice from our microbiologist to determine the most appropriate empiric antibiotic regimen based on susceptibility data from PM patients while the diagnostic workup is pending. We aimed to recommend an empiric regimen with the best activity against the most common multidrug-resistant clinical isolates, balanced with minimizing adverse events such as *C. difficile*, toxicity, and selective pressure from widespread use of broad spectrum antibiotics [25]. From 2012 antibiogram, 26% of all gram negative bacteria blood isolates were resistant to piperacillin-tazobactam. Aminoglycosides were 100% susceptible, but prolonged use is limited by nephrotoxicity and cochleovestibular toxicity. To avoid non-discriminant empiric meropenem (96% susceptible in gram negative bacteria), we determined that piperacillin-tazobactam plus a maximum of 72 hours of aminoglycoside while awaiting microbiology results would be the most appropriate empiric regimen. This combination was active against 93% of *E. coli* isolates (accounted for 53% of gram negative bacteria), and 98% of all blood isolates. Empiric therapy is then tailored to colonization history, microbiology results, and clinical status, including discontinuation of aminoglycoside. Empiric vancomycin was added only if skin soft tissue or central line infections are suspected [4].

We reserved antibacterial prophylaxis (ciprofloxacin) for patients undergoing re-induction (elevated bacterial translocation risks from repeated mucosal barrier injuries) or ambulatory consolidation chemotherapy [5]. We stratified antifungal prophylaxis: fluconazole or micafungin with serial serum galactactomanan (pre-emptive approach) for leukemia and posaconazole for post-allogeneic HSCT. Additional recommendations were based on hospital formularies, antimicrobials shortages, and local diagnostic resources, such as using the recently accessible, more sensitive low-dose chest computer tomography for initial imaging, rather than plain film to diagnose pneumonia.

Stakeholder engagement

Stakeholder engagement refers to the process of identifying and managing the perception, issues, and expectations of stakeholders [11]. This step is necessary for any professional behavioral change interventions, including clinical practice guidelines [26]. It helps the developers to understand the needs and objectives of end users and opinion leaders, all of which are essential for maximizing uptake of the guidelines. As our ASP is a joint program between UHN and SHS which share clinical services and patients, we consulted individuals from both institutions. Three drafts of the guidelines were reviewed successively by key stakeholders, including clinical leaders (e.g. Division Head of Malignant Hematology), content experts

Table 1: Summary of the 6 core elements in the healthcare change management framework and their application in our initiative [11]

Core Element	Definition	Application To The Febrile Neutropenia Guidelines Development And Implementation
Design process of the febrile neutropenia guidelines		
Governance and leadership	Mechanisms to guide, steer or regulate the course of a project or initiative	• Identify individuals for governance roles: Malignant Hematology Program's Medical and Senior Clinical Directors and the Senior Vice President of Princess Margaret Cancer Centre • Identify two ASP team members with the most experience with PM's patient population as the co-lead developers of the guidelines
Stakeholder engagement	Process of identifying and managing the perception, issues and expectations of stakeholders	• Review draft guidelines with key stakeholders, clinical leaders, and content experts and clinician end-users • Address questions from reviewers with current literature and clinical data • Incorporate feedback from reviewers into the guidelines
Work flow analysis and integration	Understanding current processes and opportunities for improvement, so that new processes, tools or solutions can be sustainably embedded into the workflow	• Healthcare Human Factors engineers solicit feedback from end-users and design a format that optimizes usability • New interactive format with embedded hyperlinks was re-tested with clinicians to ensure objectives were met
Implementation and dissemination of the febrile neutropenia guidelines		
Communications	Providing stakeholders with what they need to know to prompt appropriate response and/or actions	• Demonstrate finalized guidelines to senior leadership and ASP team • Informed clinician groups of the availability of the guidelines on the SHS-UHN ASP website
Training and education	Imparting knowledge and specific skills among key stakeholders to promote adoption to the new process, tool or solution	• Demonstrate to clinician groups how to use the guidelines in series of training sessions at audience-specific venues to maximize effective communications
Monitoring and evaluation	Reviewing whether the change management activities tool place as planned and the extent to which they are effective	• Quarterly report to stakeholders and clinicians on antimicrobial consumption and expenditure; point prevalence audits on guideline-concordant prescribing; and categories of antimicrobial prescriptions • Ongoing maintenance of guidelines with scheduled updates.

Figure 1: Process of drafting the guidelines

(e.g. Infectious Diseases Specialists), and clinician end-users (e.g. prescribers for leukemia patients). The reviews were conducted in person (individually or in groups), or submitted electronically. We collated, assessed, and incorporated the feedback into the guidelines. We addressed each question and concern with supporting literature and clinical data and provided rationale on why specific suggestions were not included in the final draft.

Workflow analysis and integration

It was imperative that the clinical decision-making processes surrounding febrile neutropenia management was accounted for and sustainably incorporated into the workflow. Although communication usually follows stakeholder engagement, it became apparent that workflow analysis and integration were urgently needed. Reviewers frequently stated that they found the guidelines difficult to follow with "numerous sections and flow diagrams spread over many pages." To overcome this challenge, we consulted Healthcare Human Factors (HHF) [27], a UHN-affiliated program. Human factors engineers apply information about human behavior, abilities, limitations, and other characteristics to the design of tools, systems, tasks, jobs and environments for effective, productive, safe and comfortable human use [28]. Incorporation of human factors in healthcare is recommended to improve patient safety [28, 29].

The HHF team conducted usability testing with a wide spectrum of clinicians using a prototype leukemia patient presenting with febrile neutropenia and infectious complications. Clinicians were asked to use the draft guidelines to facilitate their clinical decisions. The HHF team made observations and conducted a qualitative analysis of the feedback from the clinicians. To enhance

Figure 2a: Draft guidelines before Healthcare Human Factors Engineer involvement

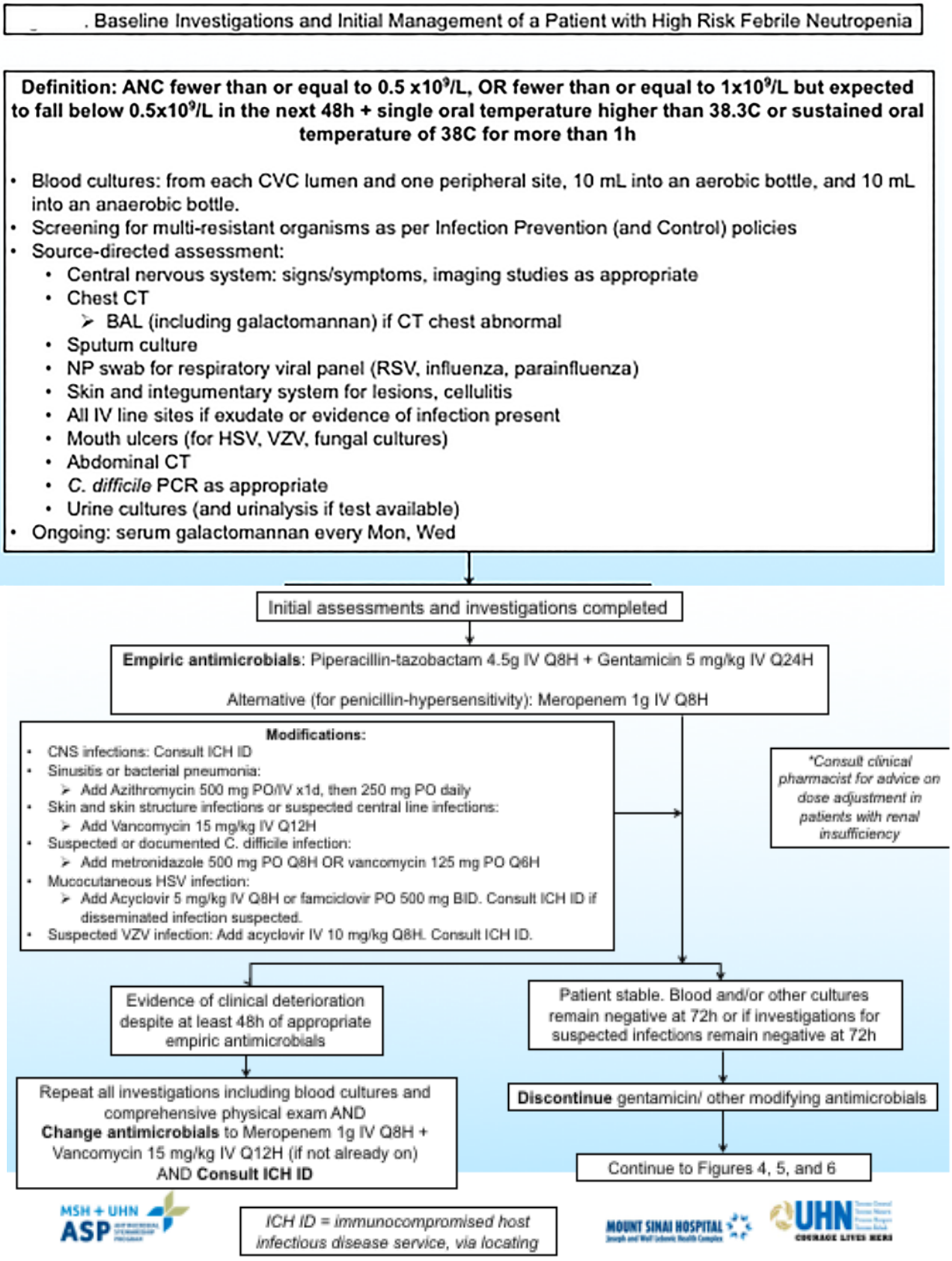
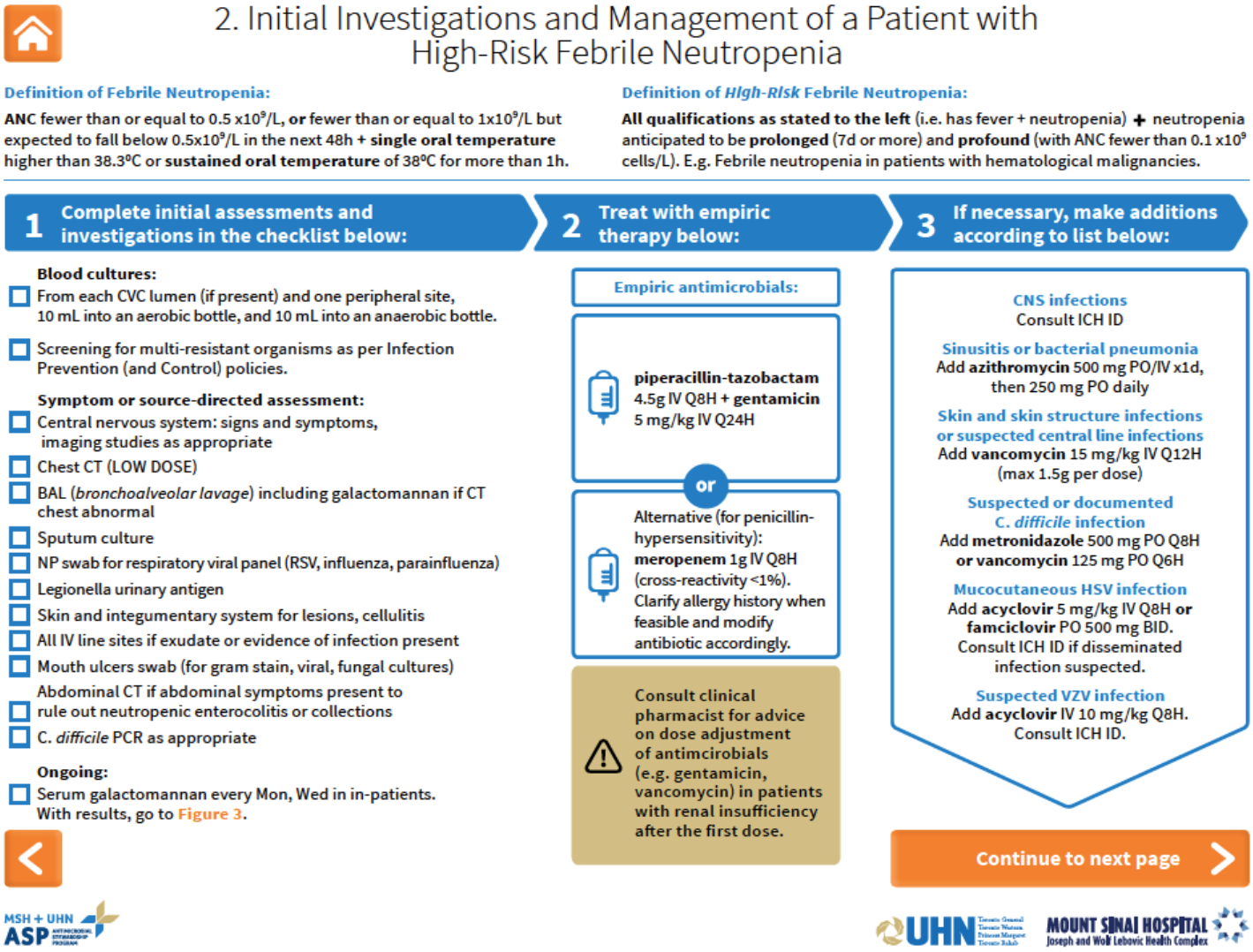


Figure 2b: Draft guidelines after Healthcare Human Factors Engineer involvement



usability, an interactive, hyperlinked format with a clear, functional layout that follows the clinician's decision-making workflow was created as the best solution to meet the needs of the end-user (Figures 2a and 2b). By selecting embedded links within the protocol installed at appropriate junctures, the clinician is efficiently self-guided to the most relevant section at point of clinical decision-making. The guidelines were re-tested in the new format with a small group of clinicians to ensure the changes met the desired objectives.

Communication

The guidelines can be accessed through this link from the publically accessible SHS-UHN ASP website and its mobile version. We demonstrated the finalized version of this HHF-engineered guidelines to PM Senior Leadership team and the ASP team, acknowledged their support, and communicated our preliminary plan for dissemination and implementation. We announced the guidelines' availability through electronic communications to all stakeholders, content experts, and clinician end-users to raise awareness, and recognize their contributions. We asked each group to suggest the most appropriate venue to disseminate the guidelines, (e.g. business meetings, educational rounds, ASP rounds, or electronic communications-only). We used this feedback to determine when, how, and with whom to demonstrate the guidelines. Communication and demonstration of the guidelines occurred at all sites with the relevant clinical groups that care for patients with hematological malignancies. By tailoring our communication strategies, we efficiently highlighted the most relevant components of the guidelines to clinicians.

Training, education, and implementation

We began our febrile neutropenia guidelines "training roadshow" with clinicians in malignant hematology, HSCT, and intensive care units, as they are the core care providers for the target patient population. We educated clinicians on the functionality and rationale for implementing the guidelines in venues per the audience's requests: small group sessions in the intensive care units; grand rounds and small groups in malignant hematology; and each program's business meetings. We then targeted clinicians in General Internal Medicine and the Emergency Department. We disseminated the guidelines to PM's affiliated community hospitals and provided training to local clinicians through Cancer Care Ontario, a government agency responsible for standardizing cancer services in the province of Ontario. We periodically repeat the education to maximize end-users' exposure to the guidelines – especially trainees and new staff. We continuously reference them as standard of care during academic detailing rounds.

Monitoring and evaluation

Guidelines should be evaluated regularly for their validity to ensure they reflect current literature and best practices [6, 14]. The Appraisal of Guidelines for Research & Evaluation II (AGREE II) is a twenty three-item instrument developed and validated for this task [30]. There are six domains: 1) scope and purpose; 2) stakeholder involvement; 3) rigor of development; 4) clarity of presentation; 5) applicability; and 6) editorial independence followed by overall guideline assessment [30]. We did not formally appraise the new guidelines, but strived to ensure that the guidelines meet all the criteria.

We determined that an annual review for potential updates would be adequate. Modifications, if warranted, would be based on local data, practice-changing literature, and feedback that we actively solicit from guidelines end-users [6]. We continuously report antimicrobial use data to understand the impact of the guidelines [6]. Our ASP Quarterly Report is distributed to all stakeholders and frontline clinicians. For each program in which the ASP intervenes we report: antimicrobial consumption and expenditure; nosocomial *C. difficile* infection rate; number of multidrug-resistant *E. coli* blood isolates; and number of *Candida spp.* blood isolates. Specific to the new guidelines, we report the proportion of antimicrobial prescription indicated as prophylaxis, empiric, pre-emptive, or targeted therapy as process measures to reflect the diagnostic-driven approach central to the guidelines (Figure 3).

In 2014, we updated the guidelines by adding management of pulmonary infiltrates, based on recommendations from a multisite, interdisciplinary working group led by members of the ASP team (SH and MSo). We added a Frequently Asked Questions document on the ASP website addressing common questions from end-users.

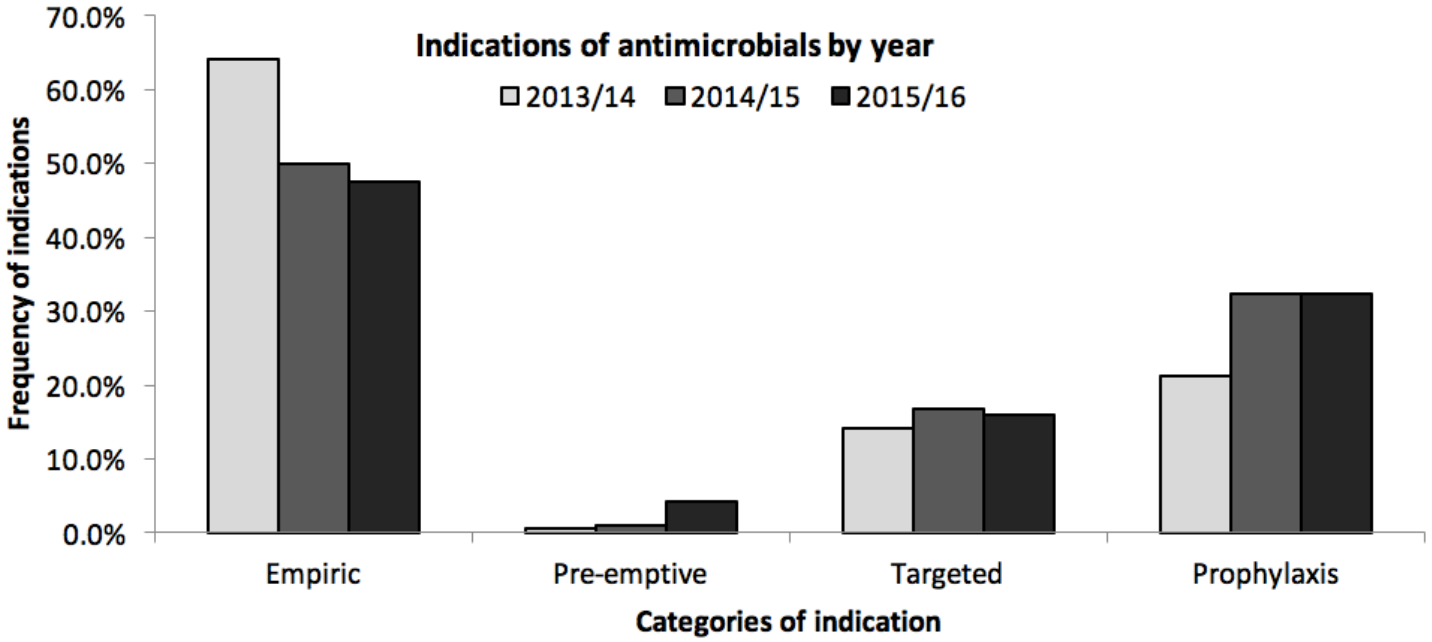
Between 2014 and 2015, we conducted four point-prevalence audits (in total 147 patients) on guideline-concordant prescribing on these parameters: selection of empiric antibiotic regimen; antimicrobial prophylaxis; routine surveillance serum galactomannan; and de-escalation of aminoglycoside after 48-72h according to microbiology results. The results were not intended as an evaluation of prescriber performance but to help us understand the reasons for deviation from guidelines, identify opportunities to improve the guidelines, and modify our communication strategies. Audits results indicated that the recommended empiric regimen consisting of piperacillin-tazobactam and up to 72 hours of aminoglycoside was prescribed on average in 50% of the 67 eligible patients with febrile neutropenia. This rate did not change significantly over time. One patient was inadequately treated empirically due to discordance from guideline recommendations: the patient received piperacillin-tazobactam without an aminoglycoside (susceptible) for the first 72 hours, but piperacillin-tazobactam-resistant *Enterobacter cloacae* was recovered from blood, i.e. appropriate therapy was delayed.

We shared the audit results with the clinical team and Senior Leadership. It was identified that there may be knowledge gaps among prescribers who are less familiar with malignant hematology patients, (e.g. on-call trainees). To address this, we are creating an electronic order set covering the initial investigations and prescribing of antimicrobials. Within the order set, we will include a direct link to the SHS-UHN ASP website to ensure the full guidelines are easily accessible during computerized prescriber order entry.

DISCUSSION

Application of the healthcare change management framework resulted in a new set of febrile neutropenia guidelines aligned with the "principles for responsible standardization in healthcare" [6]. We explained to frontline clinicians that the goal of standardizing febrile neutropenia management is to improve care, and ensured that they were provided with the opportunities and resources to participate in the developmental process [6].

Figure 3: Indications of all antimicrobials by fiscal year following implementation of the new febrile neutropenia guidelines for hematological malignancies



Definitions of indications:

Empiric: Patient has risk factors and signs and symptoms of infection but causative pathogen and its susceptibility are not identified or available. Pre-emptive: Patient has risk factors and presence of biomarkers (serum galactomannan). Targeted: Patient has signs and symptoms of infection, plus the causative pathogen has been identified, and the antimicrobial therapy is tailored for it. Prophylaxis: Patient has risk factors for infection.

We learned from the reasons behind deviations from the guidelines and continue to share the impact of the guidelines in our quarterly report [6]. The guidelines are maintained to ensure they reflect current evidence [14].

Successes

Senior Leadership and the ASP team considered the guidelines to be successfully implemented. Endorsed by hematologists, the guidelines are widely disseminated. The online link is provided to patients in a wallet card to ensure the same standards are followed if they present it to their local hospitals. The engineered format is a key feature of enhanced usability and has become our template for complex guidelines and algorithms (see SHS-UHN ASP website)

Lessons learned

We learned several important lessons relevant to future guideline development.

Lesson 1: Budgeting

We did not consider the need for a budget. We found, unexpectedly, that Healthcare Human Factors consultation can be expensive, even though we deemed it to be an essential element of our success. We turned to Senior Leadership for funding support. While our initial request was quickly approved, it soon became apparent that the Human Factors team's involvement was extensive, and we had to request additional funding. Understandably, approval for the second request was less forthcoming. Our lack of anticipation caused some delay in the project.

Lesson 2: Managing resistance from front-line clinicians

Despite a formalized process to engage end-users, we were met with resistance from some clinicians during our training roadshow. For example, a hematologist was concerned about the myelosuppressive effect of routine antiviral prophylaxis hampering bone marrow recovery. We used literature (appropriate dosing and role of acyclovir prophylaxis), and local data (cases of mucocutaneous Herpes Simplex Virus infections attributed to suboptimal prophylaxis) to allay his

apprehensions and gained endorsement. We learned to tailor our approach to ensure individuals' perceived barriers and concerns are addressed promptly.

Lesson 3: Project timeline

We struggled to meet the milestones of the project timeline because it could not accommodate any delays, such as consultation with Healthcare Human Factors. To meet the deadline, we obtained expedited approval from our institution's Pharmacy and Therapeutics Committee, given the guidelines had undergone extensive reviews. We should have first assessed the risk of delay, and mitigated it accordingly.

CONCLUSION

Using the healthcare change management framework, we effectively developed, implemented, and maintained a new set of facility-specific, antimicrobial stewardship-oriented guidelines for febrile neutropenia in hematology-oncology patients. ♦

Notes

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