

Bundle for the prevention and management of complications of neutropenia in cancer patients

Bundle para prevenção e manejo das complicações de pacientes oncológicos neutropênicos
Bundle de la prevención y manejo de complicaciones de pacientes oncológicos neutropênicos

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ABSTRACT

Objectives: to construct and assess bundle content for the prevention and management of complications in neutropenia in cancer patients. **Methods:** a methodological study developed in four stages: scoping review; bundle construction; material assessment by experts (developed according to Pasquali's psychometry); pilot test in a High Complexity Assistance Unit in Oncology. For content assessment, the Delphi technique was applied in two rounds and those items with Content Validation Coefficient (CVC) > 0.78 and agreement > 80.0% were considered valid. Data were analyzed using descriptive and inferential statistics. **Results:** all bundle requirements reached agreement between judges above 80.0%, in addition to statistically significant levels of assessment. At the end of the Delphi technique, bundle was significantly valid with CVC = 0.92 and CVC = 0.93, respectively. **Conclusions:** bundle content proved to be valid and highly credible.

Descriptors: Neutropenia; Febrile Neutropenia; Drug Therapy, Combination; Nursing Care; Oncology Nursing.

RESUMO

Objetivos: construir e avaliar o conteúdo de um *bundle* para a prevenção e manejo das complicações de pacientes oncológicos neutropênicos. **Métodos:** estudo metodológico, construído em quatro etapas: *scoping review*; construção do *bundle*; avaliação do material por especialistas (desenvolvido segundo a psicometria de Pasquali); teste piloto em uma Unidade de Assistência de Alta Complexidade em Oncologia. Para avaliação de conteúdo, aplicou-se a técnica de *Delphi* em duas rodadas, e considerou-se válidos aqueles itens com Coeficiente de Validação de Conteúdo (CVC) > 0,78 e consenso > 80,0%. Os dados foram analisados por meio da estatística descritiva e inferencial. **Resultados:** todos os requisitos do *bundle* alcançaram concordância entre os juízes superior a 80,0%, além de níveis de avaliação estatisticamente significativos. Ao final da técnica de *Delphi*, o *bundle* se apresentou expressivamente válido com CVC = 0,92 e CVC = 0,93, respectivamente. **Conclusões:** o conteúdo do *bundle* demonstrou ser válido e ter alta credibilidade.

Descritores: Neutropenia; Neutropenia Febril; Quimioterapia Combinada; Cuidados de Enfermagem; Enfermagem Oncológica.

RESUMEN

Objetivos: construir y evaluar el contenido de un *bundle* para la prevención y el manejo de complicaciones en pacientes con cáncer neutropénico. **Métodos:** estudio metodológico, construído en cuatro etapas: revisión del alcance; construcción de *bundle*; evaluación del material por especialistas (desarrollado según la psicometría de Pasquali); prueba piloto en una Unidad Asistencial de Alta Complejidad en Oncología. Para la evaluación de contenido se aplicó la técnica *Delphi* en dos rondas, considerándose válidos aquellos ítems con Coeficiente de Validación de Contenido (CVC) > 0,78 y consenso > 80,0%. Los datos se analizaron mediante estadística descriptiva e inferencial. **Resultados:** todos los requisitos del *bundle* alcanzaron acuerdos entre jueces superiores al 80,0%, además de niveles de evaluación estadísticamente significativos. Al final de la técnica *Delphi*, el *bundle* fue significativamente válido con CVC = 0,92 y CVC = 0,93, respectivamente. **Conclusiones:** el contenido del *bundle* demostró ser válido y tener una alta credibilidad.

Descriptorios: Neutropenia; Neutropenia Febril; Quimioterapia Combinada; Atención de Enfermería; Enfermería Oncológica.

INTRODUCTION

Currently, there are several forms of treatment for malignant neoplasia, such as antineoplastic chemotherapy (CT), biological therapy, external and intraoperative radiation therapy, radioiodotherapy, brachytherapy, surgeries, in addition to hematopoietic stem cell transplantation (HSCT)⁽¹⁻²⁾.

CT consists of using chemical substances, alone or in combination, aiming at treating malignant neoplasms acting at the cellular level, interfering in the process of cell growth and division. However, it constitutes a therapy without specificity; therefore, it does not selectively or exclusively destroy tumor cells, causing toxicities and undesirable effects. CT is an indispensable treatment option in cancer treatment⁽³⁻⁴⁾.

Moreover, this therapy causes myelosuppression, favoring febrile neutropenia (FN) and infections. FN occurs when the absolute neutrophil count is less than 1,000 mm³, usually between 7 to 14 days after CT session, called the NADIR period⁽⁵⁾.

Thus, fever can be the first and only manifestation of infection, particularly during periods of neutropenia induced by CT. Of the patients receiving CT, more than 80% will have at least one febrile episode (body temperature is above 38°C for more than 60 minutes) during the neutropenia period, and from these, 10% to 20% will progress to death, despite the use of broad-spectrum antibiotic therapy⁽⁶⁻⁷⁾.

However, in some patients, instead of fever, hypothermia, hypotension, or mental confusion may occur, since each individual has an immune response. Thus, the possibility of infection must be considered and treated empirically, if there is any sign of clinical deterioration due to neutropenia, regardless of the temperature measured⁽⁷⁾. Generally, recovery takes about one to two weeks and only after this period can a new CT session be submitted⁽⁶⁻⁷⁾.

Patients who are most likely to develop FN are those with a history of neutropenia over seven days, recent hospitalizations, use of antibiotics, pneumonia, leukemia or lymphoma in patients after 30 days of hematopoietic stem cell transplantation, lower neutrophil count at 100mm³, bacteremia, Central Venous Catheter (CVC) infection, renal and hepatic failure, other infections^(3,7). FN treatment consists of antibiotic therapy and, normally, patients are hospitalized for hydration and monitoring of signs and symptoms⁽⁶⁾.

Individuals with FN can be classified as low risk, intermediate risk and high risk neutropenic. The risk score is determined using the Multinational Association for Supportive Care of Cancer (MASCC) severity index, which credits points, according to importance, for each variable. The MASCC severity index scores up to a maximum of 26 points (criteria: mild or absent neutropenia intensity - 5 points; absence of hypotension - SBP \geq 90mmHg - 5 points; absence of chronic obstructive disease - 4 points; hematological neoplasia or absence of fungal infection previous - 4 points; absence of dehydration - 3 points; disease intensity: moderate symptoms - 3 points; outpatient fever - 3 points; age <60 years - 2 points) and supports patients' classification as low risk (\geq 21 points) or high risk (<21 points)^(5,7).

Due to the inclusion of interpretation of vital signs, including temperature being part of a Nursing Process (NP), it is necessary to update these professionals on the topic. However, it was found in literature that the scarcity of standardization of the prevention and management of complications can mean fragility of care for patients with FN⁽⁶⁾.

In this regard, a bundle implementation for the prevention and management of complications of neutropenia in cancer patients in healthcare practice is paramount. It is noteworthy that bundle is a structured way to improve the care processes for individuals, i.e., a set of evidence-based practices, which when performed collectively and reliably, provide excellent results to patients⁽⁸⁾. Research indicates that bundles need to be dynamic and put into practice together with health professionals so that, during their use, it is possible to continuously assess the care provided⁽⁹⁾.

In this perspective, Resolution 569 of 2018⁽¹⁰⁾ of the Federal Nursing Council (*Conselho Federal de Enfermagem*) regulates nursing professionals' performance in CT. Among the specific functions of nurses are the development and implementation of therapeutic protocols in the prevention, treatment and minimization of side effects. Thus, bundles have been widely disseminated in hospital institutions, because, when implemented, they are decisive in preventing and reducing complications⁽⁹⁾.

Therefore, the relevance of this study is to provide a bundle with the main measures for the prevention and management of complications in neutropenia in cancer patients. Thus, it contributes substantially to the provision of quality care for people with malignancy undergoing CT treatment.

OBJECTIVES

To construct and assess bundle content for the prevention and management of complications in neutropenia in cancer patients.

METHODS

Ethical aspects

Resolution 466/2012 and 580/2018 of the Brazilian National Health Council (*Conselho Nacional de Saúde*) guided this study, which was approved by a Research Ethics Committee with Human Beings (COEP) of a federal university in Minas Gerais in April 2017 and by the COEP of the co-participating institution in May 2017. All participants received guidance. After reading and accepting, they signed the Informed Consent Term (ICF), guaranteeing their confidentiality and anonymity throughout the research process.

Design, period, place of study

This is a methodological research of a bundle content construction and validation for the prevention and management of neutropenia in cancer patients, based on Pasquali's methodological framework⁽¹¹⁾, with a quantitative approach, guided by the SPIRIT tool. It was developed in four stages: scoping review, bundle construction, assessment of the instrument's content by judges/experts, from May to October 2019, and pilot test in a High Complexity Assistance Unit in Oncology (UNACON) held from November to December 2019.

Inclusion and exclusion criteria; study participants

Bundle assessment, in order to reach the number of judges recommended by Pasquali⁽¹¹⁾, i.e., from six to 20 experts, it was decided to invite a larger number, considering that some might not respond or refuse the invitation.

The selection of judges for validation studies was based on a series of criteria that differ according to the objectives of each research. Time of clinical experience, degree, research experience and publications on the topic addressed were taken into account.

An active search by specialists for advanced research was carried out on the *Curriculum Lattes* platform of the Brazilian National Council for Scientific and Technological Development (CNPq - *Conselho Nacional de Desenvolvimento Científico e Tecnológico*) (<http://lattes.cnpq.br/>) by subject in order to identify health professionals in Brazil able to act as judges of the instrument⁽¹²⁾. For this, the simple search form was used, in the field "search for", in the category "subject", using the terms "oncology" and/or "chemotherapy". Thus, 388 PhD professionals were identified.

To screen the possible judges, the Fehring model⁽¹³⁾ was adapted and used, since it measures a maximum score of 14 points; however, for this selection a minimum score of five points was given for having: master's and PhD degrees in nursing or related fields (mandatory criteria); dissertation addressing cancer care (2 points); thesis with subject in oncology (2 points); certificate or title of specialist in oncology nursing (1 point); research (es) in oncology in the last five years (3 points); authorship of at least two articles in the last three years in the oncology field (3 points); experience in CT and oncology of at least three years (3 points)⁽¹³⁾.

After the search, a total of 60 eligible judges were reached. They received an invitation letter by e-mail, with a period of up to 20 days to return the instrument, in addition to the ICF with the necessary instructions to be able to analyze and assess. The instrument to be filled out for the assessment was built on Google Docs, with initial information for the characterization of the participant and the items of the instrument. Each item had a space where the judges could provide suggestions for change and improvement⁽¹⁴⁾.

The Delphi technique was performed. In this way, the specialists answered, through rounds, an evaluative questionnaire. Of the 60 possible judges first selected, 16 agreed to participate in bundle assessment, corresponding to the first round (Delphi I)^(8,15), when there were suggestions for changes in the instrument for improvement. The changes considered pertinent and, after adjustments, the feedback of the responses was sent together with the bundle, configuring the second round (Delphi II), a stage in which there was the participation of 14 judges (it stands out that these 14 judges participated in the two rounds), with loss of two due to the non-return of the instrument within the established period.

In the fourth stage (pilot test), 12 nurses participated and 30 neutropenic patients of intermediate risk and high risk of FN were assessed. Nurses working in the oncology outpatient department of CT were included. Nurses who were on vacation, on sick leave for health treatment, on maternity leave or on leave for professional training were excluded⁽¹⁶⁾.

The selection of patients was carried out for convenience at an oncology outpatient clinic of CT on the days of collection, meeting the following inclusion criteria: a score of 15 on the Glasgow scale and being under CT treatment for hematological malignancy. This last criterion was based on the result of a study that inferred that hematological cancer patients had more FN^(5,7). The Glasgow scale was applied to ensure that patients had an adequate level of temporal, personal and spatial orientation, as noted in the item "verbal response" on the scale, as well as an adequate motor response

- another item on the scale - in order to comply with some of the guidelines provided for neutropenia control. It is noteworthy that these items, added to the ocular opening, consistently indicate the degree of integration of the central nervous system. Exclusion criteria were established: presenting some solid neoplasm associated with hematology, in order to homogenize the sample.

The sample was designed based on the records of patients registered at a CT outpatient clinic, considering a 95% confidence level and 5% sampling error, which resulted in 250 service users. Bearing in mind that it is a pilot study and, for that, a percentage of approximately 10% is suggested⁽¹⁷⁾.

Study protocol

Initially, the results derived from the literature review were used, in order to identify the scientific evidence on nursing care for neutropenia in cancer patients through scoping review⁽¹⁸⁾ (according to the PRISMA-ScR recommendations⁽¹⁹⁾ and the method proposed by the Joanna Briggs Institute, Reviewers Manual 2017⁽²⁰⁾, based on national and international scientific evidence (Chart 1)).

The scoping review protocol⁽¹⁸⁾ was registered in the Open Science Framework (<https://osf.io/axwm7>), Participants, Concept and Context (PCC) strategy⁽¹⁸⁻¹⁹⁾ was used to construct the research question : P (participants) - Neutropenic cancer patient, C (concept) - FN after CT and C (context) - Health services that care for cancer patients after CT in FN. Thus, the research questions were: which nursing care are relevant, in the context after CT, in relation to FN prevention? Which nursing practices are important in the management of FN complications?

The search strategy was adapted according to the specificities of each database and the analogous combination of descriptors was kept: (Antineoplastic Agents OR Drug Therapy OR Chemotherapy, Adjuvant OR Induction Chemotherapy OR Consolidation Chemotherapy OR Maintenance Chemotherapy OR Medication Therapy Management OR Antineoplastic Combined Chemotherapy Protocols) AND (Chemotherapy-Induced Febrile Neutropenia OR Febrile Neutropenia) AND (Nursing OR Oncologic Nursing).

Articles published with full texts, in Brazilian Portuguese, Spanish and/or English, with no time limit, that addressed nursing care for neutropenia in cancer patients were included. Articles that did not include the guiding questions, editorials, experience reports, scientific communication, reviews, letters, theoretical essays, single case studies were excluded, as well as reviews that only addressed the prevention and management of FN-related complications of cancer patients performed by physicians, dentists, and pharmacists.

The search was carried out from October 2018 to June 2019, in the National Library of Medicine and National Institutes of Health (PUBMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, SCOPUS, Latin American & Caribbean Literature in Health Sciences (LILACS) and Cochrane library databases. The articles were selected by two independent reviewers in order to confirm the relevance of the review questions and, if so, to extract the data of interest. All doubts or inconsistencies were resolved by agreement among the authors. For the stage of separation, synthesis and report of the essential information discovered in each study, a structured instrument was used to collect this data, which allowed extent synthesis, interpretation, and analysis, nature and distribution of the studies incorporated in the review⁽¹⁸⁾.

Chart 1 - References used as a basis for bundle construction, Minas Gerais, Brazil, 2020

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To be continued

Chart 1 (concluded)

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The critical assessment of sources of evidence is optional in the scope of the scoping review⁽¹⁹⁻²⁰⁾. In this study, we opted to perform it in order to meet one of the objectives of the review, which was to be a reference for constructing the bundle. In accordance with evidence-based practice, the conduct described in the bundle was analyzed and classified according to Melnyk and Fineout-Overholt's proposal⁽⁴⁶⁾, which systematizes the levels of evidence in: level I - arising from systematic review or meta-analysis of trials randomized, controlled clinical trials or clinical guidelines based on systematic reviews of randomized controlled clinical trials; level II - from at least one well-designed randomized controlled clinical trial; level III - from well-designed clinical trials without randomization; level IV - derived from a cohort and case-control study, both well-designed; level V - proceeding from a systematic review of descriptive and qualitative studies; level VI - arising from a single descriptive or qualitative study; level VII - from the opinion of authorities and/or expert committee reports⁽⁴⁶⁾.

The bundle construction stage, initially had 37 items, distributed in five modules: 1) concerning risk factors; 2) concerning prevention; 3) concerning management; 4) concerning specific management for pediatrics; 5) concerning the nursing team. Each of these modules was analyzed according to the assessment criteria instituted by Pasquali⁽¹¹⁾: behavior, objectivity, simplicity, clarity, relevance, precision, variety, modality, typicality, credibility, breadth, and balance. It should be noted that there was a chart clarifying each of these 12 criteria, and they were assessed using a Likert-type scale, being: "1 - inadequate (I)"; "2 - partially adequate (PA)"; "3 - adequate (A)".

The fourth stage referred to a pilot test performed at a UNACON for 30 consecutive days in November and December 2019. Initially, its implementation in the chemotherapy outpatient clinic and in the oncology inpatient unit was carried out to train nursing professionals to use it.

Two workshops were held in a private room in the study setting, with an average duration of 40 minutes, with nurses and the researcher in charge of the research, with a view to training for the use of the prevention and management of complications bundles for neutropenia in cancer patients. Validation of available material and human resources was included, in addition to viable care according to cost, ease of implementation and adherence to these measures. It should be noted that the workshops were organized, according to participants' preference and availability.

Data analysis

The assessments performed by judges on the bundle were inserted in Microsoft Excel 14.0®. After analyzed, the scores attributed to each item were verified. The relevance of all items was obtained by applying Content Validity Coefficient (CVC)⁽¹¹⁾. The item with more than 80% agreement between the judges (assessed as adequate) and a CVC > 0.78 was considered valid⁽¹¹⁾.

Furthermore, descriptive and inferential analysis (binomial test) was performed. Agreement among judges and CVC scores acquired in the Delphi rounds. For this, p value ≤ 0.05 was chosen as a parameter for statistical significance.

RESULTS

When constructing the bundle, it became evident that, in the initial format, one item was joined to another previously listed. The changes made consisted essentially of simplicity (aims only at an idea for a given item and allows for proper understanding), clarity (content has simple and unambiguous expressions), precision (each item of the instrument occupies a defined and distinct position from the others) and in the modality (phrases with extreme expressions were avoided), resulting in increased agreement. The finished bundle had 36 items (Chart 2).

Chart 2 - Bundle for the prevention and management of complications of neutropenia in cancer patients, Minas Gerais, Brazil, 2020

Chart 2

BUNDLE FOR THE PREVENTION AND MANAGEMENT OF COMPLICATIONS OF NEUTROPENIA IN CANCER PATIENTS		
Conduct	Actions/Measures	Level of evidence
Concerning risk factor	d) To pay attention to the handling of catheters properly, especially semi-implantable catheters (more susceptible to infection than fully implantable catheters).	VI
	e) To pay attention to hand and equipment hygiene, which can be channels of transmission of pathogens to cancer patients.	II
	f) To guide patients to avoid closed places with clusters of people and individuals with contagious diseases.	VI
Concerning prevention	a) To observe the use of G-CSFs, especially in the first cycle of CT, since it decreases the incidence, duration and severity of hospitalizations for FN or other neutropenic complications, in addition to minimizing reductions in CT doses and possible delays. Recommended for patients over 65 years of age; spinal cord infiltration; open wounds; active infections or other serious comorbidities; received extensive previous treatment or CT and combined radiation therapy, and received a CT regimen with a documented rate of FN greater than 20%.	II
	b) To pay attention to the proper administration of G-CSFs subcutaneously. The drug should be started 24 hours after CT and repeated every 24 hours. When G-CSF is used in patients treated with weekly CT regimens, it should be stopped 24 hours before next treatment, once G-CSF has been used in 1 cycle, it must be used in all subsequent cycles of the same form.	VI
	c) To continuously assess the risk factors for post-chemotherapy FN.	IV
	d) To guide patients and family members about the importance of hand hygiene and disinfection of materials.	II
	e) To carry out an outpatient nursing consultation (offer patients a tangible education, to reinforce post-CT care to prevent FN, risk of sepsis and clarify patients' doubts).	IV
	f) To periodically schedule laboratory tests for patients after CT to assess the immune system, explaining the need for it to continue with CT treatment.	IV
	g) To advise patients to use Telenursing whenever necessary (use technology to provide guidance to patients, especially those from distant regions/use appropriate communication to avoid generating errors). This feature allows professional and patient proximity, provides integration, protection and security.	IV

BUNDLE FOR THE PREVENTION AND MANAGEMENT OF COMPLICATIONS OF NEUTROPENIA IN CANCER PATIENTS		
Conduct	Actions/Measures	Level of evidence
Concerning risk factor	a) To determine patients' lack of knowledge and information about the disease, treatment and care to be used.	II
	b) To assess the risk factors for FN such as advanced age, previous FN, radiation therapy and/or previous CT, associated comorbidities, previous hospitalizations, aggressive or metastatic cancer, catheter manipulation, weakened immune system, low levels of albumin, hematological diseases (leukemias, lymphomas or other bone marrow diseases).	II
	c) To assess issues such as psychosocial well-being, lifestyle, organic functions (kidney, liver, heart function); recovery of spinal cord activity, people recently submitted to HSCT, SIRS and hemodynamic instability.	II

To be continued

To be continued

Chart 2

BUNDLE FOR THE PREVENTION AND MANAGEMENT OF COMPLICATIONS OF NEUTROPENIA IN CANCER PATIENTS		
Conduct	Actions/Measures	Level of evidence
Concerning prevention	h) To observe the occurrence and start immediate treatment for vomiting, mucositis, diarrhea, which are predisposing factors to the onset of infection, which may contribute to FN.	IV
Concerning management	a) To request the start of antibiotic therapy within 1 hour to guarantee positive effects in the treatment, avoid possible organizational problems, such as delays in filling out the prescription, problems with the system with a specific form, delays in transferring the emergency service to the inpatient unit, problems with the pharmacy process, or delay in medication administration.	VII
	b) To perform exam collection, if neutrophils are less than 500mm ³ , temperature higher than 38.0°C and patients received CT in the last 14 days. Collect blood culture and urine samples (according to the institutional protocol) and send them to the laboratory on an urgent basis and start the antibiotic. To perform exams for kidney, liver, urine culture (IN) colproculture (IN) imaging exams radiology, ultrasound, tomography. Perform culture of other sites, such as catheters.	VI
	c) To assess the antibiotic used, in cases of low risk (oral antibiotic therapy). In high-risk cases, patients must be hospitalized and use intravenous antibiotics.	IV
	d) To perform early sepsis screening, source assessment, timely administration of appropriate antibiotics and management of infusion. Fever should be recognized as an emergency and antibiotics should be used promptly to prevent sepsis, septic shock and death.	V
	e) To pay attention to the recombinant human G-CSF that stimulates the proliferation of bone marrow progenitor cells and their differentiation into functional blood cells, which helps in the recovery of patients with neutropenia. G-CSF can be administered to patients who are experiencing an episode of FN ("secondary prophylaxis"). Recommendations include starting treatment with CSFs 24 hours after CT administration.	VI
	f) To monitor nutritional status and advise patients not to eat raw foods if their neutrophil is less than 500mm ³ (neutropenic patients should avoid raw foods due to the presence of bacteria in food, should avoid raw dairy products, herbs, honey, fruits and fresh vegetables, cold meats and cheeses and water from wells (so include well-cooked foods in meals).	VI

To be continued

Chart 2

BUNDLE FOR THE PREVENTION AND MANAGEMENT OF COMPLICATIONS OF NEUTROPENIA IN CANCER PATIENTS		
Conduct	Actions/Measures	Level of evidence
Concerning management	g) To assess signs and symptoms, grade of FN patients is in (grade zero - 2,000mm ³ or higher, grade 1 - 1,500 to 1,999mm ³ , grade 2 - 1,000 to 1,499mm ³ , grade 3 - 500 to 999mm ³ and grade 4 - less than 500mm ³) and monitor vital signs for 4/4 hours or whenever necessary according to patients' clinical picture using devices exclusively for patients with FN or performing disinfection of the devices to avoid cross contamination.	VI
	h) To perform hand hygiene, prepare the necessary materials for the procedure, rub the catheter hub with antiseptics (alcoholic chlorhexidine 0.5% or alcohol 70%). Access catheters with sterile devices only. To perform the dressing change of the fully implantable catheter every 7 days in case of transparent film and replace the dressings in cases of dirt, damp or loose.	VI
Concerning specific management for pediatrics	a) To pay attention to the dosage of antibiotics, since most are fractionated. They must be equipped with a graduated chamber and/ or use of the infusion pump, which allows the infusion of medicines at the appropriate dosage and time.	VII
	b) To assess the child's psychosocial issues and family support (the presence of parents helps during treatment). To provide a pleasant, creative, quiet place for recovery.	VII
	c) To establish dialogue with children, using a language that is easy to understand and adapted to their age. Knowing how to listen to questions carefully.	VII
	d) To carry out the selection of appropriate equipment for children, such as equipment and extenders, micropores, splints.	VII
Concerning the recommendations to the nursing team	a) To promote the continuing professional qualification to prevent and recognize possible complications related to FN such as sepsis, pneumonia, cellulite.	IV
	b) To emphasize the importance of hand hygiene before the preparation and administration of medications, punctures, catheter handling.	II
	c) To educate patients about the disease, FN and post-CT care.	IV
	d) To instruct patients and family members to take care at home, when checking the temperature, signs and symptoms that should be reported to a health professional (such as: fever, chills, bleeding, persistent pain even with the use of prescription drugs).	IV

To be continued

Chart 2 (concluded)

BUNDLE FOR THE PREVENTION AND MANAGEMENT OF COMPLICATIONS OF NEUTROPENIA IN CANCER PATIENTS		
Conduct	Actions/Measures	Level of evidence
Concerning the recommendations to the nursing team	e) To assess patients before CT treatment (investigation and nursing diagnoses), in order to elaborate relevant interventions (perform nursing consultation periodically).	IV
	f) To encourage nurses to discuss the need for hematopoietic support with other members of the health team.	V
	g) To assess the risk of FN in order to design supportive care plans, considering the myelosuppressive potential of the treatment regimen.	IV
	h) To use an evidence-based approach to nursing care.	IV
	i) To document the results and response to treatment before the next CT cycle to be administered.	IV
	j) To monitor possible complications of patients, especially elderly people, children and individuals most likely to become myelosuppressed.	IV

Note: HSCT - hematopoietic stem cell transplantation; SIRS - systemic inflammatory response syndrome; FN - febrile neutropenia. CT - antineoplastic chemotherapy; G-CSFs - granulocyte colony stimulating factors; IN - if necessary

PhD professionals with practical experience in oncology (mean = 23.10 and standard deviation = 9.87 in Delphi I; mean = 22.39 and standard deviation = 10.34 in Delphi II) participated in teaching. The minimum age of specialists was 30 years old and maximum of 62 years old (mean = 46.18 and standard deviation = 10.79 in Delphi I; mean = 46.0 and standard deviation = 11.44 in Delphi II), whose mean length of training was 24.10 years and standard deviation = 7.63 in Delphi I; mean = 23.28 and standard deviation = 8.72 in Delphi II. Most currently work in oncology and in teaching, 56.3% and 50%, respectively (Table 1). They practiced in northeastern, southeastern, and southern Brazil.

Table 1 - Characterization of judges participating in Delphi I and II phases, Minas Gerais, Brazil, 2020, (n = 16 and n = 14)

Characterization of judges	Delphi I (n=16) n(%)	Delphi II (n=14) n(%)
Sex		
Female	14 (87.5)	12 (85.7)
Male	2 (12.5)	2 (14.3)
Age		
From 30 to 40 years	5 (31.3)	5 (35.7)
41 to 50 years	5 (31.3)	5 (35.7)
51 to 60 years	4 (25.0)	3 (21.4)
Over 60 years	2 (12.4)	1 (7.2)
Time passed since graduation in nursing		
More than 10 years	14 (87.5)	12 (85.7)
Less than 10 years	2 (12.5)	2 (14.3)
Currently operating area		
Teaching and assistance and/or management in oncology	9 (56.3)	7 (50.0)
Teaching	4 (25.0)	4 (28.5)
Teaching and management in oncology	2 (12.5)	2 (14.3)
Assistance and/or management in oncology	1 (6.2)	1 (7.2)

Table 2 describes the final agreement among the judges regarding the analyzed items of bundle content for the prevention and management of complications of neutropenia in cancer patients, who obtained agreement (“adequate”), according to Pasquali’s assessment criteria.

According to what was shown in Table 2, it was observed that none of the items were below what is recommended in the actions/measures for the prevention and management of complications of neutropenia in cancer patients so that such bundle would be considered valid in Delphi I. It was possible to reach an agreement index for all analyzed items regarding the bundle content, in which relevance/pertinence and balance were the best assessed (CVC = 0.96 and CVC = 0.94, respectively). Concerning the general estimate, the instrument had CVC = 0.92 in this stage.

It should be noted that the suggestions of the judges in Delphi I for the items that needed to be revised were regarding their form of presentation and reallocation. In the bundle, requests were made to change the title of the bundle, adding complications after handling, given the importance of including adverse situations that may affect cancer patients. In “concerning management” conducts, the time for changing the fully implanted central venous catheter dressing (FICVC) was made, i.e., changing it every seven days, in the case of a transparent film, and replace dressings if dirt, moisture or loosened. Also included, the friction of the catheter hub with antiseptics (alcoholic chlorhexidine 0.5% or alcohol 70%).

Another request was withdrawn from the collection of two blood culture samples, if the temperature is higher than 38.0°C or if patients received CT in the last 14 days; however, this item was not fulfilled, since FN represents a serious complication with high mortality. In “pediatric-specific” actions, the first item on CVC burrows was condensed into one of the “regarding management” items, due to not being specific to the pediatric population.

In the Delphi II round, it was feasible to reach an agreement index for all analyzed items related to the bundle content, in which credibility and accuracy were the most satisfactorily assessed (CVC = 0.95 and CVC = 0.94, respectively). Regarding the general estimate, the instrument had CVC = 0.93 at this stage.

It is noteworthy that in Delphi I and II, none of the items had a CVC below 80.0%, all the items analyzed were statistically significant (p ≤ 0.05) regarding agreement among experts.

Concerning pilot test, nurses with practical experience in the oncology outpatient clinic of CT (mean = 4.16 and standard deviation = 3.24), mean age of 32.16 and standard deviation of 5.90, whose average training time was 5.12 and standard deviation of 4.36 participated. These nurses considered that the bundle met the objectives for which it was proposed and recommended its use/application in sectors that assist cancer patients. They only suggested word reduction without losing meaning in some items. The instrument had CVC = 1.0 in this phase.

DISCUSSION

The construction and assessment of a bundle content for the prevention and management of complications of neutropenia in cancer patients was developed with methodological rigor in order to allow scientific knowledge to be accessible to nursing professionals working in oncology.

Table 2 - Agreement among judges in Delphi I and II stages for the assessed items of bundle content for the prevention and management of complications in neutropenia in cancer patients, Minas Gerais, Brazil, 2020, (n=16 e n=14)

Items	Complication Prevention and Management Actions/Measures									
	Concerning risk factors		Concerning prevention		Concerning management		Concerning specific management for pediatrics		Concerning nursing team	
	Delphi I (ρ value*)	Delphi II (ρ value*)	Delphi I (ρ value*)	Delphi II (ρ value*)	Delphi I (ρ value*)	Delphi II (ρ value*)	Delphi I (ρ value*)	Delphi II (ρ value*)	Delphi I (ρ value*)	Delphi II (ρ value*)
Behavior	85.41% (0.003)**	87.5% (0.03)**	87.5% (0.03)**	87.5% (0.03)**	85.41% (0.003)**	83.3% (0.03)**	93.7% (0.03)**	100 % (0.00)	91.6% (0.03)**	100 % (0.00)
Objectivity	85.41% (0.003)**	87.5% (0.03)**	91.6% (0.03)**	85.41% (0.003)**	85.41% (0.003)**	83.3% (0.03)**	93.7% (0.03)**	97.7% (0.03)**	93.7% (0.03)**	100 % (0.00)
Simplicity	81.25% (0.002)**	85.41% (0.03)**	87.5% (0.03)**	83.3% (0.03)**	85.41% (0.003)**	85.41% (0.03)**	95.8% (0.03)**	100 % (0.00)	91.6% (0.03)**	100 % (0.00)
Clarity	87.5% (0.03)**	85.41% (0.03)**	87.5% (0.03)**	87.5% (0.03)**	83.3% (0.03)**	85.41% (0.03)**	93.7% (0.03)**	100 % (0.00)	95.8% (0.03)**	100 % (0.00)
Relevance/pertinence	97.9% (0.03)**	85.41% (0.03)**	97.9% (0.03)**	87.5% (0.03)**	91.6% (0.03)**	87.5% (0.03)**	93.7% (0.03)**	100 % (0.00)	97.7% (0.03)**	100 % (0.00)
Precision	91.6% (0.03)**	87.5% (0.03)**	97.3% (0.03)**	85.41% (0.003)**	89.5% (0.03)**	97.7% (0.03)**	89.5% (0.03)**	100 % (0.00)	95.8% (0.03)**	100 % (0.00)
Variety	95.8% (0.03)**	83.3% (0.02)**	89.5% (0.03)**	85.41% (0.003)**	83.3% (0.02)**	97.7% (0.03)**	97.7% (0.03)**	97.7% (0.03)**	91.6% (0.03)**	100 % (0.00)
Modality	91.6% (0.03)**	85.41% (0.03)**	89.5% (0.03)**	85.41% (0.003)**	89.5% (0.03)**	97.7% (0.03)**	97.7% (0.03)**	100 % (0.00)	93.7% (0.03)**	100 % (0.00)
Typicality	91.6% (0.03)**	87.5% (0.03)**	85.41% (0.03)**	83.3% (0.03)**	83.3% (0.02)**	97.7% (0.03)**	97.7% (0.03)**	100 % (0.00)	93.7% (0.03)**	100 % (0.00)
Credibility	93.7% (0.03)**	87.5% (0.03)**	93.7% (0.03)**	85.41% (0.003)**	95.8% (0.03)**	100 % (0.00)	89.5% (0.03)**	100 % (0.00)	95.8% (0.03)**	100 % (0.00)
Breadth	93.7% (0.03)**	87.5% (0.03)**	97.3% (0.03)**	85.41% (0.003)**	89.5% (0.03)**	100 % (0.00)	93.7% (0.03)**	100 % (0.00)	95.8% (0.03)**	95.3% (0.03)**
Balance	95.8% (0.03)**	87.5% (0.03)**	93.7% (0.03)**	83.3% (0.03)**	93.7% (0.03)**	97.7% (0.03)**	93.7% (0.03)**	100 % (0.00)	93.7% (0.03)**	93.7% (0.03)**

Note: *Binomial test; ** $p \leq 0.05$.

Patients who are undergoing CT are likely to develop FN. About 10% to 20% of these are likely to be affected by adverse situations that can lead to death, if not diagnosed and treated early^(5,7).

High-risk neutropenic patients, according to the MASCC severity index⁽⁵⁾, need to receive broad-spectrum intravenous antibiotic therapy (ATB), with an indication for hospitalization. Individuals with low risk and intermediate risk of complications can be considered candidates for oral or intravenous ATB, most of the time, without the need for hospitalization⁽⁵⁾. Thus, delays in detecting the risk of neutropenia can lead to severe damage to the person's health and, in their assessment, nurses must identify the risk factors for FN as early as possible, in addition to the design and implementation of preventive actions and management of complications^(3,47).

A bundle assists in the process, as it is an instrument that guides professionals in their conduct, since it has appropriate formal quality, easy to read, content based on scientific evidence^(8,48).

During the bundle research and construction, the following stood out: the effectiveness of education on self-care; Telenursing use; periodic nursing consultation; hand hygiene before any access to CVC; preferably use a closed infusion system; implement assistance protocols linked to permanent education, in addition to the guidance of patients and family members; assess the risk factors for infection; be prepared to recognize the indicators of sepsis, severe sepsis, and septic shock; monitor the use of G-CSF and/or antibiotics to reduce FN in patients who received QT, according to organizational protocol^(5-7,18).

Many studies have shown that nurses, who work in the oncology field, play a fundamental role in the design, development and

development of a formal risk assessment tool with international guidelines related to FN, while working together with the entire multidisciplinary team^(6-7,18).

To the initial format of the bundle, no items were added to those initially listed. This implies that specialists considered the verification items related to the conduct regarding risk factors, prevention, management, specific management for pediatrics and the nursing team to prevent and manage complications of neutropenia in cancer patients sufficient. The recommendations allowed the achievement of the desired objective, in addition to the increase in the instrument's agreement and reliability.

It should be noted that of the 37 items of the instrument, the changes made consisted of clarity and typicality (in the item "regarding management") and precision (in the item "regarding specific management of pediatrics"). In the second module it was only necessary to spell check the entire bundle.

Regarding the level of scientific evidence for bundle items, most publications were derived from well-designed cohort and case-control studies (level IV - 38.8%) and at least one single descriptive or qualitative study (level VI - 22.2%).

This may suggest that FN management is based on cohort, case-control and descriptive studies; however, the lack of clinical trials can be clarified by the entanglement in guaranteeing reliability and legitimacy, by the diversity of variables and, mainly, by the ethical judgments that make the existence of a control group unenforceable⁽⁴⁹⁾.

The assessment process involved the participation of 16 judges in Delphi I (1st round) and 14 of these judges in Delphi II (2nd round).

Reliability and validity are essential criteria for assessing the quality of an instrument. In this perspective, validity is related to the fact that an instrument measures exactly what it is suggested to measure. Reliability is the ability to stress a result properly. They are essential criteria for the quality of an instrument⁽¹¹⁾.

In this study, we highlight the significant experience of the judges participating in assessment stages, who were PhD with high experience in teaching and practicing in oncology, both in care and management. Literature shows that master's degree and PhD degree holders are largely responsible for enabling repercussions in practices and, therefore, in the advancement of nursing⁽¹⁵⁾.

In this logic, authors point out in a previous study that Brazilian nurses with some type of *stricto sensu* graduate education (specialization) fit into a reality that is guided by policies that materialize and cause innovations in their acts to achieve significant educational, scientific and technological impacts for nursing and health⁽⁵⁰⁾.

Therefore, it is understood that the participation of experienced judges and involved in assistance, management and research is relevant for the assessment of instruments to be applied in practice, as this study proposed when assessing a bundle for prevention and management complications of neutropenia in cancer patients.

Concerning the Delphi technique used to consult a group of expert judges on the topic, the objective was not to deduce a simple answer or just reach agreement, but quality opinions and responses were obtained for a given investigation presented to a panel of experts, as recommended by the methodological framework⁽¹¹⁾.

After the bundle assessment, the judges presented a significant coefficient of agreement in all the items assessed, in order to make the instrument valid in relation to behavior, objectivity, simplicity, clarity, relevance, precision, variety, modality, typicality, credibility, breadth, and balance^(11,51).

Judges' suggestions regarding FN management were to remove two blood culture samples, if patients' temperature is above 38.0°C and he received CT in the last 14 days; however, this item did not was fulfilled, since FN is a serious complication with mortality that can reach levels above 50%^(5,7,18).

The measurement of axillary temperature greater than 38.0°C, being a single episode or several, is already an alert for a picture of FN. Laboratory tests are carried out in the presence of fever, including blood culture, and if the neutrophil count is less than 500mm³ in the next 48 hours, FN diagnosis is confirmed⁽⁷⁾.

Other items suggested in these conducts were the adequacy of the time for changing the fully implanted CVC dressing and including rubbing the catheter hub with antiseptics (0.5% alcoholic chlorhexidine or 70% alcohol). Literature points out that if a patient is sweating or if the site of insertion of the CVC is bleeding, a gauze dressing should be used until this is resolved, and replace the dressing at the catheter site whenever it becomes damp, loose or visibly dirty. If transparent dressings are used, replace every seven days⁽⁵²⁾.

Disinfection on surfaces of needle-free connectors and intravascular access devices (catheter hub) needs to be carried out before any manipulation, using appropriate antiseptic agent in mechanical friction, whose recommended solutions are 0.5% alcoholic chlorhexidine or 70% alcohol, in order to decrease the number of microorganisms on its surface. Such measures involve training, use of a sterile barrier and establishment of care routines for handling CVC⁽⁵³⁾.

Literature points out that the acceptable coefficient of agreement among the members of the expert committee must be at least 0.80 and, preferably, greater than 0.90⁽⁵¹⁾, as shown in this study (CVC = 0.93). Such variations proved to be statistically significant ($p \leq 0.05$), which demonstrates the achievement of the best agreement associated with improvements in the instrument between Delphi rounds, in addition to the instrument being shown to be reliably applicable in practice.

Finally, a pilot test carried out in an UNACON, in order to verify its adequacy and efficiency. It was well assessed by all participating nurses. They only suggested word reduction without losing meaning in some items, and the beginning of follow-up implementation via Telenursing was considered a success with great return both for the professional and for patients followed up in the initial period of 30 days.

Study limitations

One of the limitations of this study is related to not conducting a more robust research than a pilot test, another point to be highlighted is the definition of judges, which is not always easy to achieve. In this study, we chose to use the criteria proposed by Fehring⁽¹³⁾, which considers aspects based on clinical experience, but it cannot be guaranteed, in fact, that all items become a guarantee of clinical expertise.

Contributions to nursing and health

The study's contribution to nursing and health is the possibility of bundle subsidizing the health care of people with malignant neoplasia, directing the use of good health practices in order to prevent and manage the complications of neutropenia in cancer patients, being an essential context for NP.

CONCLUSIONS

The results obtained in the study of bundle construction and assessment for the prevention and management of complications of neutropenia in cancer patients pointed out psychometric properties permissible for its use in oncology health services. Agreement among judges provided evidence for bundle reliability, with changes to the items they advised. The instrument assessment was measured with a significant outcome, following the methodological rigor of the Delphi technique. After pilot test, the participating nurses recommended using bundle in sectors that care for cancer patients.

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