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Published in:
Clinical Nutrition ESPEN

DOI:
[10.1016/j.clnesp.2020.05.003](https://doi.org/10.1016/j.clnesp.2020.05.003)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van Lieshout, R., Tick, L. W., de Laat, D., Custers, S., Dekker, I. M., Douma, M. D., Kalter, D., Kranenburg, S., van der Lee, D., Rhoon-Bruijnzeel, P., Schlosser, I., Somer, M., van Tilborg, C. J., Visser, W. K., Schouten, H. C., & Beijer, S. (2020). Adherence to guidelines on nutrition support during intensive treatment of acute myeloid leukemia patients: A nationwide comparison. *Clinical Nutrition ESPEN*, 39, 242-250. <https://doi.org/10.1016/j.clnesp.2020.05.003>

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Original article

Adherence to guidelines on nutrition support during intensive treatment of acute myeloid leukemia patients: A nationwide comparison

Rianne van Lieshout^{a,*}, Lidwine W. Tick^b, Daphne de Laat^a, Stephanie Custers^c, Ingeborg M. Dekker^d, Madieke D. Douma^e, Doris Kalter^f, Suzanne Kranenburg^g, Debbie van der Lee^a, Patricia Rhoon-Bruijnzeel^h, Ien Schlösserⁱ, Maaïke Somer^j, Claudia J. van Tilborg^k, Willy K. Visser^l, Harry C. Schouten^m, Sandra Beijerⁿ

^a Department of Dietetics and Nutrition, Maxima MC, De Run 4600, 5504 DB, Veldhoven, the Netherlands

^b Department of Internal Medicine, Maxima MC, De Run 4600, 5504 DB, Veldhoven, the Netherlands

^c Department of Dietetics and Nutrition, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX, Maastricht, the Netherlands

^d Department of Dietetics and Nutrition, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands

^e Department of Dietetics and Nutrition, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, the Netherlands

^f Department of Gastroenterology and Hepatology – Dietetics and Intestinal Failure, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA, Nijmegen, the Netherlands

^g Department of Dietetics and Nutrition, Sint Antonius Hospital, Koekoekslaan 1, 3435 CM, Nieuwegein, the Netherlands

^h Department of Dietetics and Nutrition, Amsterdam UMC, Univ of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

ⁱ Department of Dietetics and Nutrition, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands

^j Department of Dietetics and Nutrition, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands

^k Department of Internal Medicine, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, the Netherlands

^l Department of Dietetics and Nutrition, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands

^m Department of Internal Medicine, Section Hematology, P. Debyelaan 25, 6229 HX, Maastricht University Medical Center, Maastricht, the Netherlands

ⁿ Department of Research and Development, Netherlands Comprehensive Cancer Organization, Godebaldkwartier 419, 3511 DT, Utrecht, the Netherlands

ARTICLE INFO

Article history:

Received 2 April 2020

Accepted 5 May 2020

Keywords:

Acute myeloid leukemia
Intensive chemotherapy
Hematopoietic stem cell transplantation
Nutrition support practices
Parenteral nutrition
Enteral nutrition

SUMMARY

Background & aims: The level of adherence to the updated guidelines of The European Societies for Clinical Nutrition and Metabolism (ESPEN) and for Blood and Marrow Transplantation (EBMT) on nutrition in intensively treated adult acute myeloid leukemia (AML) patients in clinical practice is unknown. The aim of this nationwide survey was to investigate ESPEN/EBMT nutritional guideline adherence during intensive AML treatment, variation in nutrition support practices among hospitals and whether these practices changed after guideline publication.

Methods: All 22 Dutch hospitals providing (aftercare following) high-dose chemotherapy and/or hematopoietic stem cell transplantation for adult AML patients were surveyed on nutrition support practices during these intensive AML treatments. We used an online questionnaire in 2015 and semi-structured telephone interviews in 2018–2019. Both surveys were completed by registered dietitians and addressed the use of enteral (EN) and parenteral (PN) nutrition. The ESPEN/EBMT nutritional guideline adherence was investigated through the telephone interviews.

Results: High-level ESPEN/EBMT guideline adherence and/or uniformity among hospitals regarding nutrition support practices during intensive AML treatment were observed for nutritional screening, -aims, safe food handling and exercise training. Adherence to ESPEN/EBMT recommendations that were not implemented into national guidelines, including nutritional assessment and use of medical nutrition, was poor. All hospitals assessed nutritional intake, -impact symptoms and body weight, but muscle mass, physical performance and degree of systemic inflammation were rarely and variably monitored. Although the number of hospitals using EN as first-choice nutritional intervention increased from 3 hospitals in 2015 to 8 in 2019, PN remained the preferred method of nutrition support. Furthermore, the timing of medical nutrition varied.

* Corresponding author. Maxima MC, De Run 4600, 5504 DB, Veldhoven, the Netherlands.

E-mail address: r.vanlieshout@mmc.nl (R. van Lieshout).

Conclusions: Although the use of EN increased after publication of the updated ESPEN/EBMT nutritional guidelines, adherence to these standards was limited and there was heterogeneity in nutrition support practices during intensive AML treatment among hospitals. Incorporating international nutritional standards into national guidelines by nutrition expert groups immediately upon publication may improve adherence.

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1. Introduction

In The Netherlands, the number of patients with newly diagnosed acute myeloid leukemia (AML) increased from 430 in 1989 to 720 in 2016 [1]. Moreover, AML is the most common type of leukemia among adults [1]. The only available curative treatment for AML consists of intensive (remission induction) chemotherapy followed by a conditioning regimen and hematopoietic stem cell transplantation (HSCT), depending on poor prognostic factors. These high-dose cytotoxic therapies mostly cause substantial gastrointestinal side effects, including anorexia, nausea, vomiting, mucositis and diarrhea, leading to inadequate nutrient intake and -absorption [2–8]. Hence, AML patients are at increased risk of body weight loss and malnutrition, which have been associated with reduced survival- and higher complication rates, and prolonged hospitalization [8–15]. In contrast to other risk factors for poor outcome in AML patients [16], malnutrition is potentially modifiable through adequate nutritional support [8,15].

In 2009, the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism (ESPEN) defined guidelines on nutrition in HSCT [4,17]. A few studies addressed discrepancies between these decade-old guidelines and daily clinical practices [18–22]. Results showed low guideline adherence and wide variation in nutritional support practices during HSCT, especially regarding the use of enteral (EN) and parenteral nutrition (PN) [18–22].

Recently, nutritional guidelines for intensively treated adult hematological patients were updated by ESPEN [2] and the European Society for Blood and Marrow Transplantation (EBMT) [23]. In summary, these guidelines recommend routine malnutrition risk screening, and regular nutritional assessment and -intervention combined with physical exercise in patients at nutritional risk. EN is recommended as the first-choice nutritional intervention in patients who cannot achieve adequate oral food intake whereas PN should be limited to patients with gastrointestinal tract dysfunction. Furthermore, for the prevention of foodborne infections, safe food handling guidelines are preferred to the neutropenic diet.

Information on adherence to these updated ESPEN and EBMT guidelines is lacking. Moreover, to the best of our knowledge, no studies have addressed differences between nutrition support practices in AML patients prior to and after publication of the updated European nutritional standards. Hence, the aim of the present study was to investigate nutritional guideline adherence and current nutrition support practices during intensive treatment of adult AML patients in all Dutch hospitals providing (care following) such treatments. Furthermore, we aimed to investigate changes in nutrition support practices, especially in the use of EN versus PN, after publication of the updated ESPEN and EBMT nutritional guidelines.

We expect to detect and better understand discrepancies between nutritional guidelines and nutrition support practices in intensively treated AML patients, and differences in clinical practices among hospitals. We believe that this knowledge is useful for improving national guidelines on nutrition in these patients and

may contribute to uniformity in nutritional support practices across hospitals.

2. Materials and methods

2.1. Study center selection

In the Netherlands, intensive hematological treatment (after-care) for adult AML patients is centralized in hospitals that meet the criteria for performing clinical trials on high intensive treatment methods in patients with malignant hematological diseases as defined by the Hematology Oncology Foundation for Adults in the Netherlands (HOVON) [24]. Based on these criteria, HOVON recognizes four levels/echelons of intensive hematological care [24].

Hospitals assigned to echelon A are university hospitals and provide the full range of intensive AML treatments, including both autologous- and allogeneic HSCTs. Level B hospitals perform intensive (remission induction) chemotherapy and autologous, but not allogeneic HSCTs. Hospitals assigned to echelon C–HIC (Hematological Intensive Care) and to echelon C–SCT (Stem Cell Transplantation) are limited to perform intensive (remission induction) chemotherapy or to provide care after autologous HSCT, respectively.

Of each of these hospitals, registered dietitians (RDs) who work on the hematology unit were contacted and requested to participate in this study.

2.2. Online survey and semi-structured telephone interviews

Prior to the publication of the ESPEN and EBMT nutritional guidelines for (intensively treated) cancer patients, we evaluated routine nutrition support practices during intensive AML therapy in all Dutch level A to C–HIC/C–SCT hospitals through an online questionnaire (SurveyMonkey®), which was sent to the participating RDs by email in 2015.

After publication of the updated ESPEN and EBMT nutritional guidelines, we surveyed the routine nutrition support practices during intensive AML treatment again and also evaluated the adherence to these revised guidelines. From the end of 2018–2019, we performed semi-structured telephone interviews with the participating RDs. The semi-structured telephone interviews were based on a topic list consisting of the same questions that were included in the online questionnaire survey conducted in 2015. In addition, topics were added to investigate adherence to the updated ESPEN and EBMT recommendations, including general concepts of nutritional treatment relevant to all cancer patients and interventions specifically relevant to patients who receive high-dose chemotherapy and HSCT. The topics that were addressed during the telephone interviews included nutritional risk screening, -assessment and -interventions, the neutropenic diet, methods used to determine patients' energy- and protein requirements, exercise training, the use of pharmaconutrients and pharmacological agents to support nutrition therapy, experiences with the nutrition therapies and implementation of nutrition support in quality care

documents. The topic list, consisting of 40 open- or close-ended questions, is shown in [Appendix 1](#), in which the questions that were used in the online survey in 2015 are highlighted as bold text.

To enable RDs to prepare for the telephone interview, the topic list was sent to them by email timely before the interview. By using telephone interviews, both the questions and provided answers could be clarified, and inconsistencies with regard to the results of the online questionnaire of 2015 could be addressed. The 45–60 minute interviews were recorded after obtaining permission by the RDs. Answers to the questions of the survey from each RD were summarized and subsequently presented to the specific RD. In addition, the RDs were asked to check the reported answers for inconsistencies and to report changes in the nutrition support practices made since the telephone survey, so that we were able to evaluate the most current clinical practices regarding nutrition support during intensive AML treatment. Data are presented in a descriptive way.

3. Results

3.1. Study population

All of the 22 HOVON-affiliated hospitals that perform and/or provide intensive treatment (aftercare) in adult AML patients in The Netherlands were included in this study. Eight of these hospitals were categorized as level A, 4 as level B, 3 as level C–HIC, and 7 as level C–HIC/C–SCT. Of each of these hospitals a RD specialized in the dietary treatment of adult hematological patients participated in this study.

3.2. Documentation of dietary guidelines in medical pathways

In the updated ESPEN nutritional guidelines it is recommended to define standard operating procedures, responsibilities and a quality control process for nutritional risk screening, -assessment and intervention, and for monitoring outcomes. However, the number of hospitals where nutrition support procedures in AML patients were incorporated into clinical pathways had only slightly increased from 8 hospitals in 2015 to 12 hospitals in 2019. Since malnutrition risk screening is mandatory for all Dutch hospitals due to the strong efforts of the Dutch Malnutrition Steering Group (DMSG) [25], the procedure for nutritional screening was well defined, implemented, performed and evaluated in all of our study hospitals.

3.3. Nutritional risk screening and assessment

In both 2015 and 2019, all hospitals determined patients' malnutrition risk score at admission using validated screening tools. In most hospitals (2015: 15 of 22 hospitals; 2019: 16 of 22 hospitals), RDs were routinely consulted immediately upon AML diagnosis irrespective of malnutrition risk scores. The other hospitals consulted a RD in AML patients with abnormal malnutrition screening scores or nutrition impact symptoms. The nutritional assessment strategies in AML patients varied between hospitals ([Table 1](#)). In 2019, all hospitals used body weight and 20 hospitals used nutritional intake and nutrition impact symptoms for assessment of nutritional risk and -status. Eleven hospitals included physical performance and 9 hospitals used body composition or biochemical inflammation measures. In only 5 hospitals, the nutritional assessment covered all domains recommended by ESPEN, including nutritional intake, nutrition impact symptoms, body weight and composition, physical performance and the degree of systemic inflammation.

3.4. Estimation of energy and protein requirements

In 2015, there was wide variety in the equations used to estimate energy requirements in intensively treated AML patients. One RD used the fixed 25–35 Kcal per kilogram body weight per day (kcal/kg/day). Others used the predictive equations of Harris and Benedict [26,27] (HB) (15 hospitals) or the World Health Organization (WHO) [28] (6 hospitals) for estimating resting energy expenditure (REE) with target total energy requirements varying between 1.25 and $1.5 \times$ REE. In 2019, 20 of 22 hospitals uniformly used the WHO equation for estimating energy requirements in accordance with recommendations and study findings of the DMSG ([Table 1](#)) [28–31]. There was, however, low adherence to the updated ESPEN and EBMT guidelines that recommended 25–35 kcal/kg/day and the adjusted HB equation [32], respectively.

In both 2015 and 2019, there was strong uniformity among hospitals regarding the method used for estimating protein needs. In line with the updated ESPEN and EBMT guidelines, the estimated protein requirements were within the range of 1.2–1.5 grams of protein/kg body weight/day in all hospitals. Two RDs reported to use an adjusted body weight based on fat free mass estimations by the Gallagher formula in this equation in overweight patients [29,33].

3.5. Criteria to define inadequate oral intake

There was low guideline adherence and wide variety among hospitals regarding the criteria used to define inadequate oral intake in AML patients. RDs of 18 hospitals used low energy intake (with cut-off thresholds for energy intake ranging between 50 and 80% of estimated total energy requirements) during a certain (anticipated) time period (ranging between 2 and 7 days) to define inadequate oral intake. Four RDs did not use a specific definition. When compared to the definition for inadequate oral intake proposed by ESPEN, 13 RDs used a more stringent definition, while 5 RDs used a similar definition ([Table 1](#)). When compared to the EBMT criteria for inadequate oral intake: 7 RDs applied similar criteria, 5 RDs applied more stringent and 6 RDs applied less stringent criteria.

Since inadequate oral intake was used as an indication for medical nutrition in 20 of 22 hospitals, the timing of medical nutrition also varied widely. One hospital used standard starting- and stopping moments for PN irrespective of oral intake, and one hospital applied EN and PN only in severe and exceptional cases.

3.6. Route of nutrition administration

The number of hospitals using EN as the first-choice nutritional intervention in AML patients with inadequate oral food intake increased from 3 hospitals in 2015 to 8 of 22 hospitals in 2019. In line with the updated ESPEN and EBMT nutritional guidelines, these EN hospitals reserved PN for AML patients with severe oral mucositis, gastrointestinal malfunction, including severe gastrointestinal graft-versus-host disease (GI GVHD), and/or intolerance to the enteral tube (feeding). The arguments for preferring EN to PN included better preservation of bowel integrity (8 hospitals), reduced risk of line infections (6 hospitals) and serum liver test abnormalities (2 hospitals), and earlier improvement of oral food intake (2 hospitals) with EN when compared to PN.

The number of hospitals using PN as the preferred route of nutrition administration irrespective of gastrointestinal function (PN hospitals) decreased from 17 hospitals in 2015 to 12 of 22 hospitals in 2019. Reasons for these PN hospitals to favor PN included the frequent occurrence of severe oral mucositis (11 hospitals), gastrointestinal nutrient malabsorption and/or severe diarrhea (11

Table 1

Adherence to the 'ESPEN guidelines on nutrition in cancer patients' and to the 'EBMT recommendations on nutritional support following HSCT' during intensive AML treatment in Dutch hospitals.

	ESPEN recommendations [2]	EBMT recommendations [23]	Current nutritional support practices in the Dutch hospitals that provide intensive AML treatment (aftercare) (n = 22)
(Nutritional) screening and assessment			
Malnutrition risk screening	<ul style="list-style-type: none"> Regularly (weekly) from diagnosis. BMI, weight loss, food intake. Validated tool 	<ul style="list-style-type: none"> All patients NRS 2002 	<ul style="list-style-type: none"> 22/22 all patients ≤ 24 hours after hospital admission. 15/22 SNAQ 7/22 MUST 22/22 by RD
Nutritional assessment	<ul style="list-style-type: none"> In patients with abnormal nutritional screening. Nutritional intake, nutrition impact symptoms, muscle mass, physical performance, degree of systemic inflammation. 	<ul style="list-style-type: none"> In patients with abnormal nutritional screening and/or BMI < 18. Early involvement RD, standardized monitoring of nutritional intake. Nutritional reassessment every 3 days with NRS 2002. 	<p>Consultation RD/nutritional counseling:</p> <ul style="list-style-type: none"> 21/22 in patients with abnormal nutritional screening and/or nutrition impact symptoms. 16/22 upon AML diagnosis. 1/22 in severe and exceptional cases only. <p>Strategies used:</p> <ul style="list-style-type: none"> 22/22 body weight (change). 20/22 nutritional intake, nutrition impact symptoms. 9/22 body composition (9/9 handgrip strength, 8/9 BI(V)A, 4/9 triceps skinfold thickness, and upper arm-, abdomen- and calf circumference). 4/22 PG-SGA 9/22 degree of inflammation/fever/other diseases. 1/22 ventilated hood 11/22 physical activity
Energy and substrate requirements			
Energy requirements	<ul style="list-style-type: none"> 25–30 kcal/kg/day 	<ul style="list-style-type: none"> Adjusted HB equation or BASA-ROT table [32] (25–30 kcal/kg/day). 	<ul style="list-style-type: none"> For estimating REE: <ul style="list-style-type: none"> 20/22 WHO equation 1985 [28], 10/20 HB equation 1918 [26] in patients with BMI > 30 kg/m² 2/22 HB 1984 equation [27] For estimating total energy requirements: <ul style="list-style-type: none"> 17/22: 1.3 xREE 2/22: 1.4 xREE 1/22: 1.5 xREE 2/22: 1.3–1.5 xREE 20/22 1.2–1.5 <ul style="list-style-type: none"> 2/20 used estimated kg FFM (by Gallagher formula [29,33]) instead of kg body weight in overweight patients. 1/22 1.2 1/22 ≥ 1.5
Protein requirements (in g/kg body weight/day)	<ul style="list-style-type: none"> 1.0, if possible up to 1.5 	<ul style="list-style-type: none"> 1.2–1.5 In severe enteral GVHD: 1.5–2.0 	<ul style="list-style-type: none"> 20/22 1.2–1.5 <ul style="list-style-type: none"> 2/20 used estimated kg FFM (by Gallagher formula [29,33]) instead of kg body weight in overweight patients. 1/22 1.2 1/22 ≥ 1.5
Weight-losing patients with insulin resistance	<ul style="list-style-type: none"> ↑ energy density of diet and ↓ glycemic load by ↑ ratio of energy from fat to energy from carbohydrates. 		<ul style="list-style-type: none"> In nutritional interventions: management glucose levels subordinate to maintenance nutritional status. Combined dietary and pharmacological measures. 11/22 ↓ energy intake from carbohydrates (especially products with high amounts of additional sugar), carbohydrates regularly spread over meals. 8/22 no dietary interventions. 3/22 no experience with these problems yet. 22/22 reference intake set at Dutch recommended daily allowance. Supplementation only on indication: <ul style="list-style-type: none"> (risk for) refeeding syndrome (22/22), increased nutrient losses or (risk for) deficiencies (17/22), higher age/prednisone use (vitamin D) (6/22), (risk for) prolonged coagulation time (vitamin K) (7/22).
Vitamins and minerals	<ul style="list-style-type: none"> Supplementation in amounts equal to RDA. Discourage high dose micronutrients in absence of deficiencies. 	<ul style="list-style-type: none"> Multivitamins during HSCT. Supplementation vitamin D: 4000 IU at admission; maintenance therapy: 1500 IU/day. Vitamin K: 1×/week during EN. Higher dose only if overt deficiency. 	

(continued on next page)

Table 1 (continued)

	ESPEN recommendations [2]	EBMT recommendations [23]	Current nutritional support practices in the Dutch hospitals that provide intensive AML treatment (aftercare) (n = 22)
Nutritional interventions			
Patients with or at risk of malnutrition who are able to eat	<ul style="list-style-type: none"> • Treatment of nutrition impact symptoms. • Dietary advice. • ONS. • No dietary provisions restricting energy intake. 	<ul style="list-style-type: none"> • Additional energy and protein rich snacks. • Protein and calorie enrichment main courses. • ONS 	<ul style="list-style-type: none"> • 22/22 treatment of nutrition impact symptoms, energy/protein rich meals/snacks, dietary advice by RD, ONS. • 22/22 discourage/advice against energy restricting dietary provisions by counseling/unbiased discussion, recognizing/acknowledging patients' wish to commit to these diets. Patients have final choice whether or not to proceed with diet. • 4/22 no criteria
Criteria for inadequate food intake	<ul style="list-style-type: none"> • >1 week no oral intake or oral intake <60% of daily energy needs for >1–2 weeks. 	<ul style="list-style-type: none"> • Oral intake <60% of daily energy needs for 3 consecutive days. 	<ul style="list-style-type: none"> • Compared to ESPEN: <ul style="list-style-type: none"> ◦ 5/22 similar criteria ◦ 13/22 more stringent criteria • Compared to EBMT: <ul style="list-style-type: none"> ◦ 7/22 similar criteria ◦ 5/22 more stringent criteria ◦ 6/22 less stringent criteria
Preferred route of nutrition administration in patients requiring medical nutrition	<ul style="list-style-type: none"> • EN (PN only in patients with severe gastrointestinal dysfunction). 	<ul style="list-style-type: none"> • EN (PN only in patients with severe gastrointestinal dysfunction). 	<ul style="list-style-type: none"> • 8/22 EN (PN only in patients with severe gastrointestinal dysfunction). • 12/22 PN (6/12 never apply EN, 6/12 only if PN is not possible). • 1/22 no clear policy, (EN or PN depending on opinion hematologist). • 1/22 no PN/EN • 22/22 risk screening, prevention and treatment of the refeeding syndrome according to 'The Dutch consensus statement on Refeeding syndrome' [29,48], closely resembling the ESPEN recommendations.
(Risk for) refeeding syndrome	<ul style="list-style-type: none"> • Gradual ↑ oral nutrition, EN/PN over several days. • Supplementation vitamins, monitoring/supplementation electrolytes, monitoring fluid balance, volume circulation, heart rate/rhythm, clinical status. 	—	
Home artificial nutrition (EN or PN)	<ul style="list-style-type: none"> • Patients with chronic insufficient dietary intake and/or uncontrollable malabsorption. 	—	<ul style="list-style-type: none"> • 15/22 only in the few AML patients with inadequate intake at hospital discharge, mostly EN. • 7/22 no home EN or PN.
Neutropenic/low bacterial diet	<ul style="list-style-type: none"> • Safe food handling recommended over neutropenic diet. • No low bacterial diet >30 days after allo-HSCT. 	<ul style="list-style-type: none"> • Safe food handling recommended over neutropenic diet. 	<ul style="list-style-type: none"> • 22/22 apply to national GFHS. • Safe food handling guidelines, dietary advice on which products put immunocompromised patients at increased risk of foodborne infections. • 22/22 during use of immunosuppressive drugs, and/or from initiation until the end of treatment, antimicrobial prophylaxis or neutropenic phase.
Pharmaconutrients and pharmacological agents to improve nutritional status/clinical outcome	<ul style="list-style-type: none"> • Besides corticosteroids, progestins/prokinetics, N-3 fatty acids/fish oil in anorectic patients with advanced disease, other pharmaconutrients or agents are not recommended. 	<ul style="list-style-type: none"> • No routine use of immunonutrients. 	<ul style="list-style-type: none"> • 12/22 occasionally corticosteroids to ↑ appetite. • 5/22 prokinetic agents to ↓ satiety. • 1/22 glutamine in PN to ↑ clinical outcome. • 22/22 no progestins, cannabinoids, androgenic steroids, (branched-chain) amino acids/metabolites, non-steroidal anti-inflammatory drugs, N-3 fatty acids/fish oil to ↑ appetite, taste disorders, intake, body weight, FFM.

Allo = allogeneic, AML = acute myeloid leukemia, BI(V)A = bio-electrical impedance (vector) analysis, BMI = body mass index, EBMT = European Society for Blood and Marrow Transplantation, EN = enteral nutrition, ESPEN = European Society for Clinical Nutrition and Metabolism, FFM = fat free mass, g = gram, GFHS = Guidelines for Food Hygiene and Safety, GVHD = graft-versus-host disease, HSCT = hematopoietic stem cell transplantation, HB = Harris and Benedict, INR = international normalized ratio, IU = international units, kg = kilogram body weight, MUST = Malnutrition Universal Screening Tool, NRS 2002 = Nutrition Risk Screening 2002, ONS = oral nutritional supplements, PG-SGA = Patient-Generated Subjective Global Assessment, PN = parenteral nutrition, RD = registered and accredited dietician, RDA = recommended daily allowance, RI = remission induction, SNAQ = Short Nutritional Assessment Questionnaire, WHO = World Health Organization.

hospitals), a sore mouth and/or throat (9 hospitals), the risk of hemorrhages in thrombocytopenic patients following feeding tube placement (7 hospitals), higher level of comfort for patients (5 hospitals), severe GI GVHD (4 hospitals), an already accessible intravenous route for nutrition administration (4 hospitals) and enteral tube feeding intolerance (3 hospitals).

In both 2015 and 2019, one hospital had no clear policy regarding the preferred route of nutrition administration, but PN was most frequently applied. Moreover, one hospital had a wait-and-see approach towards both EN and PN, applying PN in exceptional and severe cases only because of the potential complications, including line infections, hepatic dysfunction, intolerance, risk of hemorrhages, and because of the expected natural recovery of nutritional status.

Remarkably, PN remained a commonly applied nutritional intervention in intensively treated AML patients in all EN hospitals, due to frequent gastrointestinal symptoms, including severe oral mucositis and GI GVHD, and other problems related to either the feeding tube or EN. RDs reported complaints of pain or wounds in the nose, throat and/or mouth (oral mucositis) (15 hospitals), a feeling of irritation (11 hospitals) and early satiety (10 hospitals), nausea (9 hospitals), diarrhea and/or malabsorption (7 hospitals), vomiting (6 hospitals), abdominal complaints or pain (2 hospitals), hemorrhages (1 hospitals) and delayed gastric emptying (1 hospitals). Other reasons for the common use of PN were the reluctance and lack of confidence or experience of caregivers regarding the use of EN in AML patients. Many feared intolerance, hemorrhages and patient discomfort associated with EN or the feeding tube.

However, RDs reported PN-associated complications too, including serum liver test abnormalities (19 hospitals), line infections (16 hospitals), hyperglycemia (13 hospitals), fluid overload (1 hospitals) and patients' limited freedom of movement (1 hospitals).

Hospitals used general indications for initiating PN in enterally fed AML patients, including ileus, intractable vomiting, severe oral mucositis, and severe diarrhea, malabsorption and/or GI GVHD. None of the hospitals used well-defined quantitative criteria or clear cutoff points to indicate the need for transition from EN to PN. In patients with severe acute GI GVHD, the allogeneic HSCT centers initiated partial or complete PN when volume of watery diarrhea exceeded 500–1000 ml/day, in line with the literature on this issue [5,22,34–36], and reserved EN for patients with a stool volume

below this threshold and an inadequate oral nutrient intake and/or for the post-acute/recovery phase.

3.7. Guidelines for Food Hygiene and Safety

For the prevention of foodborne infections, specific nutritional hygiene advice is provided to intensively treated AML patients [2,23]. Results from our surveys showed that 21 hospitals in 2015 and all hospitals in 2019 uniformly complied to the national Guidelines for Food Hygiene and Safety (GFHS) of the Dutch Hematology Dietitians expert group [37]. In line with the updated ESPEN and EBMT nutritional guidelines and current literature showing no evidence to support the use of neutropenic diets in immunocompromised patients [38–40], the GFHS preferred safe food handling guidelines endorsed by national authorities on food safety to the more strict neutropenic diets.

3.8. Exercise training

In line with ESPEN recommending maintenance of physical activity during intensive chemotherapy and HSCT, 21 of 22 hospitals consulted a physiotherapist in most AML patients. However, many RDs were initially unknown with the content of physiotherapeutic therapy (Table 2). One hospital provided physiotherapeutic counseling in severe and exceptional cases only.

4. Discussion

Results of this nationwide survey on nutrition support practices in AML patients receiving high-dose chemotherapy and HSCT showed that there was strong adherence to the updated ESPEN and EBMT nutritional guidelines and/or uniformity among hospitals regarding nutritional screening, methods used to estimate patients' protein and energy requirements, safe food handling and physical exercise support. There was both poor guideline adherence and little uniformity among hospitals regarding the incorporation of nutrition support procedures into clinical pathways, nutritional assessment, the definition of inadequate oral intake and the use of medical nutrition. Although the number of hospitals using EN as the first-choice nutritional intervention had increased from 3 to 8 hospitals after publication of the updated ESPEN and EBMT

Table 2

Adherence to the 'ESPEN guidelines on nutrition in cancer patients' regarding exercise training during intensive AML treatment in Dutch hospitals.

	ESPEN recommendations [2]	Current physical exercise support practices in the Dutch hospitals that provide intensive AML treatment (aftercare) (n = 22)
Physical exercise training (during intensive chemotherapy/HSCT)	<ul style="list-style-type: none"> Goals of nutritional/metabolic therapy must place considerable emphasis on maintenance/↑ muscle mass. Combined nutrition and physical therapy aiming for maintenance (or ↑) physical activity to support muscle mass/strength, physical function, metabolic pattern. 	<ul style="list-style-type: none"> 22/22 maintenance/↑ muscle mass main goal of nutritional therapy. 22/22 consultation of physiotherapist: <ul style="list-style-type: none"> 18/22 upon AML diagnosis. 1/22 on indication. 2/22 upon AML diagnosis/on indication. 1/22 in exceptional and severe cases only. Aims physical therapy: maintain/↑ muscle mass/strength, endurance, physical functioning, and mobility, and ensure safe transfers. Many RDs initially unknown with content of physiotherapeutic therapy. 14/22 resistance and aerobic exercise. 6/22 cycling and other unknown individualized and exercise. 2/22 unknown Variety of training devices: hometrainer, crosstrainer, dumbbells, treadmill, step, dynabands, bedside cycles.
Type of physical exercise	<ul style="list-style-type: none"> Individualized resistance and aerobic exercise. 	

AML = acute myeloid leukemia, HSCT = hematopoietic stem cell transplantation, RDs = registered dietitians.

guidelines, PN remained the preferred method for nutritional support.

Nutrition support guidelines are considered to be valuable tools for improving quality of nutritional care and for reducing unwanted variability in clinical practices [41,42]. Moreover, evidence from a recent large randomized controlled trial [43] and systematic review with meta-analysis [44] showed that adherence to nutritional standards can improve important clinical outcomes, including survival. However, the frequent disregard of guidelines is a well-known problem [41,42]. Although our results are encouraging, showing high adherence to several recommendations of the ESPEN/EBMT nutritional standards, some guideline recommendations were still poorly followed. In line with our study findings, limited nutritional guideline adherence and variability in nutrition support practices during intensive hematological treatment was observed in the few earlier surveys performed in other countries [18–22].

Remarkably in our study was that RDs especially adhered to national guidelines, and consequently only to ESPEN/EBMT recommendations which were incorporated into national guidelines. This is in line with the literature about improving guideline adherence [41,42,45]. The current study showed that the highest level of ESPEN/EBMT guideline adherence and uniformity in nutrition support practices among hospitals was observed for recommendations that had sufficient scientific evidence and were translated into national guidelines drawn and implemented by influent national nutrition expert platforms.

An example is nutritional screening which was routine practice at hospital admission in all hospitals as recommended by ESPEN and the EBMT. In contrast to our study, surveys in other countries observed malnutrition risk screening in only 36–60% of hospitals [20–22].

The strong commitment to nutritional screening in the current study may be explained by the strong efforts of the DMSG to enhance awareness, prevention, identification and treatment of malnutrition [25]. These efforts resulted in the incorporation of the Performance Indicator Screening and Treatment of Malnutrition (PISTM) into the basic set of quality criteria for hospitals of the Dutch Health Care Inspectorate, and made malnutrition risk screening mandatory for all Dutch hospitals [25,46].

Furthermore, the PISTM requires a protein intake of 1.2–1.5 g/kg/day on the fourth day of hospital admission [25,46]. This may explain the high adherence to the ESPEN/EBMT nutritional guidelines and high uniformity among participating hospitals regarding the target protein intake in AML patients.

The strong adherence to the ESPEN/EBMT recommendation to apply safe food handling guidelines rather than neutropenic diets observed in our study may be due to their incorporation into the firmly established GFHS [37] which were applied in all hospitals. These findings were in contrast to other surveys where 60–93% of hospitals applied a neutropenic diet [18,20–22].

Other ESPEN/EBMT recommendations that were well and uniformly followed (see Table 1), were also incorporated into influent national nutritional guidelines [29,37,47,48].

The high uniformity among hospitals but nonadherence to the updated ESPEN/EBMT guidelines regarding the methods for estimating AML patients' energy requirements may be explained by the conflicting DMSG's recommendations based on studies suggesting that the WHO/HB equations were superior to the fixed 25–30 kcal/kg/day [26,28–31].

Similar to our study, nutritional intake was an element of nutritional assessment in previous surveys [18–20,22]. However, other elements recommended by ESPEN, i.e. body composition, physical activity and the degree of inflammation, were not routinely and uniformly monitored in both the current and

previous surveys [19,20,22]. Noteworthy, although all RDs agreed that physical exercise and nutrition should be combined as one intervention to improve muscle mass, the latter was rarely assessed. These results may be explained by a lack of time, equipment, education [18,41] and consensus on which measurements and threshold values to use [2,49,50]. Moreover, guidelines provide no recommendations on how to optimize nutritional intervention upon abnormal assessment outcomes [51].

The DMSG's promotion of timely EN/PN when oral intake provides below 75% of daily needs [25,51] and the PISTM may explain why most hospitals used more stringent criteria to define inadequate oral intake and start medical nutrition when compared to the criteria proposed by ESPEN. The heterogeneity in the timing of medical nutrition observed in our and a Swiss survey may be due to lack of evidence-based consensus on which variables best define the indication for EN/PN in AML patients [17,21,22,50].

In line with other surveys, the current study showed that PN was the preferred method for nutritional support in intensively treated AML patients in most hospitals due to frequent gastrointestinal disorders, including severe oral mucositis and GI GVHD, enteral feeding (tube) intolerance and caregivers' reluctance to apply EN [18–22,36,52–54]. A possible barrier to implement EN as the first-choice nutritional intervention as recommended by ESPEN/EBMT may be that the use of PN is a rigid and deeply-rooted practice with long tradition in this patient group. The improved post-HSCT survival rates associated with PN in the randomized controlled trial of Weisdorf [55] may have contributed to the common use of PN. Moreover, until recently, ESPEN advised against routine EN during intensive hematological treatment, preferring PN in certain situations because of possible complications associated with enteral tube placement [56] and/or EN. Furthermore, EN during intensive AML treatment is not supported by high-level scientific evidence [2,8,36,52,53,57] and national recommendations promoting EN during intensive AML treatment are lacking [37].

The lack of well-defined quantitative criteria to indicate the need for transition to PN in enterally fed AML patients in current clinical practice may result from the paucity of data on this issue in literature [2,23]. Quantitative threshold values for the general indications for PN currently provided by nutritional standards (i.e. ileus, intractable vomiting, and severe (grade 3–4) diarrhea, mucositis and GI GVHD) could be defined according to severity grading systems, including the Common Terminology Criteria for Adverse Events, World Health Organization Grading of Mucositis, and/or according to frequency, volume and consistency of fecal output or citrulline levels [7,34,58,59].

Two other ESPEN guideline recommendations that were poorly followed included the recommendations to increase the ratio of energy from fat to energy from carbohydrates in weight-losing cancer patients with insulin resistance, and to consider corticosteroids, progestins and N-3 fatty acids/fish oil in patients with advanced disease, and prokinetics to reduce nutrition impact symptoms (including early satiety, lack of appetite and/or reduced food intake), and/or to improve lean body mass and body weight [2]. The low-level adherence to these recommendations for cancer patients in general may be that they were less applicable to AML patients receiving intensive treatment regimens. In this patient group, nutrient intake is often strongly compromised, leaving only little or no room for optimizing the fat-to-carbohydrate ratio of the oral dietary intake. Furthermore, AML patients receiving high-dose chemotherapy and HSCT are treated with curative intent, and several pharmaconutrients or pharmacological agents are already part of routine medical care.

The poor incorporation of nutrition support procedures into clinical pathways may have contributed to the limited European guideline adherence. This is in line with previous literature

reporting that clinical pathways can improve guideline adherence [54,60,61].

Identifying differences in nutrition support practices during intensive AML treatment among hospitals is the first step toward more uniformity in clinical practices. The latter is of the utmost importance, because most AML patients have to change hospitals during treatment and are confronted with differences in nutrition support. Uncertainty may arise among these vulnerable patients, and caregivers may lose credibility [8]. To the best of our knowledge, this is the first study addressing adherence to the updated ESPEN/EBMT nutritional guidelines during intensive AML treatment. Moreover, with 100% response rates in both surveys of 2015 and 2018–2019, this study is the first to provide insight into nationwide nutrition support practices prior to and after publication of the European nutritional guidelines.

A limitation of our study is that we did not assess and analyze the barriers to guideline adherence [41], which is essential for the development of tailored strategies for successful implementation of nutrition support guidelines [41]. Another limitation is that we used different survey methods in 2015 compared to 2019. To overcome this limitation, we incorporated the survey questions of 2015 into the survey of 2018–2019.

In conclusion, the current study shows high-level adherence to the updated ESPEN and EBMT nutritional guidelines and/or uniformity among hospitals regarding nutritional screening, aims for protein and energy intake, the use of GFHS and physical exercise support during intensive AML treatment. We observed non-adherence and heterogeneity in nutritional assessment strategies and the use of medical nutrition. In order to improve guideline adherence and uniformity in this field, barriers to guideline adherence should be assessed and analyzed. Our results showed high ESPEN/EBMT guideline adherence only if recommendations were translated into national guidelines of influential nutrition expert groups. Therefore, international nutritional standards should be implemented into national guidelines by expert platforms and into clinical pathways immediately upon publication. The next step is an assessment of the barriers to nutritional guideline adherence and the development of a position paper, including a decision tree, authored by the Dutch Hematology Dietitians expert group. Since our national survey on nutritional guideline adherence during intensive AML treatment provided valuable information that can help improving (uniformity among hospitals regarding) nutrition support in this field, we would encourage other countries to apply a similar approach.

Statement of authorship

Rianne van Lieshout contributed to the conception of the study. Rianne van Lieshout and Sandra Beijer contributed to the design of the study. Rianne van Lieshout, Daphne de Laat, Stephanie Custers, Ingeborg M. Dekker, Suzanne Kranenburg, Doris Kalter, Patricia Rhoon-Bruijnzeel, Ien Schlösser and Maaïke Somer contributed to acquisition of the data. Analysis of the data was performed by Rianne van Lieshout. Rianne van Lieshout, Sandra Beijer, Lidwine W. Tick, Harry C. Schouten, Daphne de Laat and Claudia J. van Tilborg contributed to the interpretation of the data. Rianne van Lieshout drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved of the final version to be submitted.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

We declare no conflicts of interest.

Acknowledgements

We thank the Departments Nutrition and Dietetics of all the Dutch hospitals providing intensive AML treatment (after)care for their participation in the online survey and telephone survey of this study: Albert Schweitzer Hospital, Dordrecht; Amphia Hospital, Breda; Amsterdam University Medical Centers, locations VU University Medical Center and Academic Medical Center, Amsterdam; Canisius Wilhelmina Hospital, Nijmegen; Erasmus University Medical Center, Rotterdam; Haga Hospital, The Hague; Isala Hospital, Zwolle; Jeroen Bosch Hospital, Den Bosch; Leids University Medical Center, Leiden; Maastricht University Medical Center, Maastricht; Maxima MC, Veldhoven; Meander Medical Center, Amersfoort; Medical Center Leeuwarden, Leeuwarden; Medical Spectrum Twente, Enschede; Onze Lieve Vrouwe Gasthuis, Amsterdam; Radboud University Medical Center, Nijmegen; Reinier de Graaf Gasthuis, Delft; Rijnstate Hospital, Arnhem; Sint Antonius Hospital, Nieuwegein; University Medical Center Groningen, Groningen; University Medical Center Utrecht, Utrecht.

Appendix I. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2020.05.003>.

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