applied sciences

MDPI

Article

Polyamine Content of Enteral Nutrition Formulas: Effect of Daily Intake on the Feeding Tolerance of Patients During the First Week in the Intensive Care Unit

Manuel Sánchez [1,2,3,*,†], Eva Rodríguez-Hernández [1,†], Lorena Suárez [1,2,3], Begoña Cantabrana [1,2,3] and María González-García [4]

[1] Farmacología, Departamento de Medicina, Universidad de Oviedo, 33006 Oviedo, Spain; uo277634@uniovi.es (E.R.-H.); suarezlorena@uniovi.es (L.S.); bego@uniovi.es (B.C.)
[2] Instituto Universitario de Oncología del Principado de Asturias (IUOPA), 33006 Oviedo, Spain
[3] Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), 33011 Oviedo, Spain
[4] Unidad de Cuidados Intensivos, Hospital Universitario Central de Asturias (HUCA), 33011 Oviedo, Spain; gongarmaria@uniovi.es
* Correspondence: sanchezf@uniovi.es; Tel.: +34-985102753
† These authors contributed equally to this work.

Abstract: Enteral nutrition (EN) formulas are necessary for critically ill patients to meet their metabolic requirements. Polyamines (putrescine, spermidine, and spermine) are crucial dietary components, with spermidine being particularly interesting due to its multiple proposed benefits. The requirements for and intake of polyamines have yet to be investigated in adult patients hospitalised in intensive care units (ICUs) who are exclusively fed via commercial EN formulas. The aim of this study was to determine the polyamine content and other biogenic amines of EN formulas and the total intake and gastric residual volume (GRV) in adult ICU patients during their first seven days of hospitalisation. The amines were analysed in 16 EN formulas using high-performance liquid chromatography (HPLC). The clinical data of eight patients of both sexes aged 47 to 77 admitted to the ICU were analysed. Differences existed among the analysed EN formulas. The *N*-acetyl putrescine content was higher than that of the remaining amines. The daily intake of polyamines in the ICU was less than 100 µmol (the dietary intake is above 400 µmol). An inverse correlation existed between total daily polyamine intake and daily GRV, without effects from other biogenic amines being analysed. Polyamine intake in critically ill patients receiving EN is low and could impact these patients' feeding tolerance. These findings underscore the need for further research to explore the clinical implications of increasing the polyamine content of EN formulas.

Keywords: polyamines; putrescine; spermidine; spermine; enteral nutrition formula; polyamine intake; intensive care unit patients

Academic Editor: Małgorzata Ziarno

Received: 4 December 2024
Revised: 3 January 2025
Accepted: 7 January 2025
Published: 11 January 2025

Citation: Sánchez, M.; Rodríguez-Hernández, E.; Suárez, L.; Cantabrana, B.; González-García, M. Polyamine Content of Enteral Nutrition Formulas: Effect of Daily Intake on the Feeding Tolerance of Patients During the First Week in the Intensive Care Unit. *Appl. Sci.* **2025**, *15*, 659. https://doi.org/10.3390/app15020659

1. Introduction

Adequate nutrition is crucial to health at all stages of life [1]. Consequently, when a patient cannot consume food orally, alternatives, such as enteral nutrition (EN) formulas, are necessary, especially for critically ill patients [2]. Parenteral nutrition is only considered when EN is contraindicated, as occurs in certain pathological circumstances [3]. The importance of EN is determined by the fact that the intestinal epithelium does not have blood vessels and mainly relies on nutrients obtained from the intestinal lumen to maintain gastrointestinal homeostasis [4]. Therefore, a prolonged absence of EN can lead to gut

atrophy, luminal starvation, dysbiosis of the microbiota, and impaired immune functions [5]. Several EN formulations are available to provide essential nutrients to hospitalised patients, which are administered via different methods [2,6]. These EN formulas, with their particular characteristics, should meet patients' metabolic requirements and provide them with essential nutrients and trace elements tailored to different clinical situations [7].

EN formulas are expected to contain polyamines (putrescine, spermidine, and spermine), since they are present in all macronutrients [8]. These compounds are essential dietary components, which are also produced by the microbiota. They contribute to the development and growth of the gastrointestinal mucosa and facilitate wound healing [9,10]. Additionally, they serve as a direct energy source for the intestinal cells [11], promote a healthy microbiota (which also produces polyamines as metabolites) [12], stimulate the intestinal immune system [13], and modulate gastrointestinal motility [14,15], thereby facilitating the digestion and absorption of nutrients from birth onwards [16,17].

Intestinal polyamines are absorbed, complementing the endogenous synthesis carried out by the enzyme ornithine decarboxylase. This enzyme converts ornithine into putrescine, which is subsequently transformed into spermidine and then into spermine [18]. The cellular homeostasis of polyamines is tightly regulated, and any disruption in this balance is associated with various pathologies. Polyamines' importance extends to their systemic effects, including DNA replication, RNA transcription, protein synthesis, and post-translational modification. Consequently, polyamines are crucial for regulating cellular proliferation and differentiation [19].

Studies in experimental models [20,21] and epidemiological research [22,23] have found that a higher intake of polyamines is associated with a reduced risk of age-related diseases and a potential increase in longevity. Among the different polyamines, spermidine has garnered particular interest in relation to these effects by eliciting the autophagy [21] and hypusination of the translational regulator eukaryotic initiation factor 5A (eIF5A) [24]. Nonetheless, the requirements for and intake of polyamines remain the subject of debate. Depending on the study, and likely also on the country, the daily intake of total polyamines—the sum of putrescine, spermidine, and spermine—has been found to range from 200 to 410 µmol per person [25–29]. These values may be below the optimal level. Based on an ideal diet, this has been estimated to be 541 µmol from the Swedish Nutrition Recommendations Objectified [30].

Despite their essential biological functions, polyamine intake and its effects in critically ill patients fed with EN formulas have not been previously investigated. These patients may experience acute organ dysfunction and post-intensive care syndrome [31]. Maintaining adequate polyamine homeostasis, particularly spermidine, could produce beneficial effects in these patients, given their protective role on various organs, including the kidney [32], heart [33,34], lungs [35–37], immune system [38], and brain [39], among others.

In addition to polyamines, other biogenic amines are present in foods, distinguished by their chemical structure and the number of amino groups. These amines are primarily formed through the decarboxylation of specific amino acids in protein-rich or free amino acid-containing foods, and some are endogenously synthesised [40]. Their role and importance in biological systems are different to those of polyamines. They have been reported to cause toxicity [40] and various biological effects [41,42], including some on the gastrointestinal tract through trace amine-associated receptors (TAARs) [43,44]. Although they may be present in EN formulas, they have not been studied.

This study aimed to determine, for the first time, the daily intake of polyamines and other biogenic amines during the first seven days of hospitalisation for critically ill adult patients in intensive care units (ICUs) who were exclusively fed through commercial enteral nutrition (EN) formulas. The research involved analysing the polyamine content

per mL of various EN formulas that are currently administered to these patients using high-performance liquid chromatography (HPLC). Additionally, the study evaluated the impact of polyamine intake on nutrition tolerance by examining its relationship with gastric residual volume (GRV).

2. Materials and Methods

2.1. Determination of the Polyamine Content of Commercial EN Formulas via HPLC

Sixteen commercial EN formulas, all currently being administered to patients in the ICU at the Hospital Universitario Central de Asturias in Spain, were obtained to analyse their polyamine content. Multiple samples from the same batches and from different batches were analysed when available.

The amines were determined by means of HPLC using a pre-column derivatisation method, as previously described [45]. From each EN formula sample, 950 µL was taken and treated with perchloric acid for 10 min at 4 °C to reach a final concentration of 15.8%. The extracts were then centrifuged at 10,000× *g* for 30 min at 4 °C, later 0.2 mL of supernatant was collected and the standard concentration (1.25 µL of a concentration of 1 mM) was added. The sample was neutralised with 0.3 mL of a saturated solution of $NaHCO_3$, and the samples were dansylated overnight (~16 h) with 0.5 mL of a solution containing 5 mg/mL of dansyl chloride in acetone. The next day, 0.1 mL of 100 mg/mL proline was added for 30 min; then, 0.5 mL of toluene was added. Finally, 0.4 mL of the organic phase was removed and dried under a nitrogen atmosphere at 42 °C in a thermoblock (Techne Dri-Block DB3, Cambridge, UK) and then resuspended in 0.2 mL of acetonitrile (VWR, Rosny-sous-Bois-cedex, France).

The HPLC was a Shimadzu Prominence (Shimadzu, Kyoto, Japan) using a C_{18} (2.5 µm, 3.0 × 75 mm) reverse-phase column (XBridge, Waters, Milford, MA, USA) at room temperature between 21 and 23 °C and equipped with two LC-20AD pumps, a fluorescence detector (RF-20A), a SIL-20AD HT autosampler injector at 4 °C, and a DGU-20A3 degasser (all from Shimadzu, Kyoto, Japan). The binary gradient used a flow rate of 0.55 mL/minutes as follows: 0–0.5 min, 0% B; 0.5–10 min, 75% B; 10–11.30 min, 75% B; and 11.3–11.50 min, 0% B. Solvent A was 45% acetonitrile and solvent B was 100% acetonitrile. The injection volume was 5 µL.

The duration of the chromatogram was 14 min. The identification of the compounds was performed using their retention time in minutes (standard: 5.88; *N*-acetyl putrescine: 1.56; *N*-acetyl spermidine: 6.11; β-phenylethylamine: 6.82; isoamylamine: 7.04; putrescine: 7.38; cadaverine: 7.83; *N*-acetyl spermine: 9.41; tyramine: 9.89; spermidine: 10.38; spermine: 12.41) and a wavelength of excitation of 365 nm and emission of 510 nm. All measurements were made using the Shimadzu LCsolution Version 1.25 software. The data analysed were the means of duplicate injections. The quantification of the biogenic amines was performed using 1,3-Diamino-2-hydroxypropane as an internal standard, expressed as nmol/mL of the EN formulas.

2.2. Characteristics of the EN Formulas

The formula characteristics were obtained from the manufacturers, enabling the subsequent EN classification to be analysed (Table 1).

Table 1. Enteral nutrition formulas analysed.

Formula Type	Name	Kcal Per 100 mL	Manufacturer [a]
Complete, polymeric			
Hyperproteic and hypercaloric	Fresubin Thickened	150	Fresenius Kabi
	Isosource Protein Fibre	133	Nestlé Health Science
	Novasource GI Protein	117.4	Nestlé Health Science
	Osmolite Plus	121	Abbott
Normoproteic and hypercaloric	Nutrison Energy	150	Nutricia
	Nutrison Energy Multi Fibre	153	Nutricia
Normoproteic and normocaloric	Fresubin Original Fibre	100	Fresenius Kabi
	Nutrison	100	Nutricia
	Osmolite	101	Abbott
Hyperproteic and normocaloric	Impact Enteral	144	Nestlé Health Science
Complete, special			
Hyperproteic and hypercaloric	Impact	144	Nestlé Health Science
	Nepro HP	180	Abbott
	Nutrison Advanced Diason Energy HP	150	Nutricia
Normoproteic and hypercaloric	Nutricomp Hepa	132	B Braun Sharing Expertise
	Oxepa	152	Abbott
Hypoproteic and hypercaloric	Nepro LP	180	Abbott

[a] Abbott: Zwolle, The Netherlands; B Braun Sharing Expertise: Melsungen, Germany; Fresenius Kabi: Bad Homburg, Germany; Nestlé Health Science: Vitaflo, Germany; Nutricia: Zoetermeer, The Netherlands.

2.3. Chemicals

The following chemicals were used: putrescine (tetramethylenediamine dihydrochloride), spermidine (*N*-(3-aminopropyl)-1,4-butanediamine), spermine (*N*,*N*′-bis (3-aminopropyl)-1,4-butanediamine), *N*-acetyl putrescine (*N*-(4-aminobutyl)acetamide hydrochloride), *N*-acetyl spermidine (N^8-acetylspermidine dihydrochloride), *N*-acetyl spermine (N^1-acetylspermine trihydrochloride), isoamylamine (isopentylamine: 1-amino-3-methylbutane), cadaverine (cadaverine dihydrochloride), tyramine (2-(4-hydroxyphenyl)ethylamine), β-phenylethylamine, and 2-hydroxydiaminopropane. These were purchased from Sigma-Aldrich (St. Louis, MO, USA). The compounds were dissolved in purified water with a 10–15 MΩ·cm resistance.

2.4. Study Design, Patient Population, and Clinical Data

A retrospective observational study was approved by the Research Ethics Committee of the Principality of Asturias, Spain (reference: CElmPA; No. 2023.089) and was conducted among patients of both sexes aged 18 to 77 who were admitted to the ICU between 1 January 2022 and 31 January 2023.

The study focused on patients who received continuous administration of an EN formula as their sole source of nutrition. The inclusion criteria for the study were a minimum of a seven-day stay in the ICU and the same EN formula administered for at least five days, excluding COVID-19 patients. Eight patients met this criterion. The reasons for admission to the ICU was the need for exhaustive and constant monitoring of the patient's clinical situation. The primary pathologies were abdominal-origin sepsis, liver transplant, sepsis, ketoacidosis, haemodynamic instability, cardiorespiratory arrest, cerebral haemorrhage, and rhombencephalitis. Patients admitted to the ICU during the study period who did not meet the inclusion criteria were excluded.

The daily intake of polyamines in the patients included in the study was estimated based on the volume and polyamine content of the EN formula administered. Clinical information was obtained for each patient, including age, sex, body mass index (BMI), EN formula prescribed, volume of EN and water administered, GRV (considered for the entire day), vomiting, and number and volume of stools.

2.5. Statistical Analyses

The variables analysed in this study are expressed as the mean ± the standard error of the mean. The total amount of polyamines was calculated as the sum of the putrescine, spermidine, and spermine values. The different polyamine intakes were also normalised according to 1000 kcal of the corresponding EN formula administered.

A one-way analysis of variance (ANOVA) was used to determine the potential differences in the polyamine content between the EN formulas.

Bivariate correlation was used to determine the relationship between daily biogenic amine intake and daily GRV. The analyses were performed using IBM SPSS Statistics 27.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Polyamine Content of the EN Formulas

The analysis of the batches showed that the polyamine content in several bottles from the same batch may be similar (e.g., Fresubin Original Fibre, Impact, and Osmolite Plus). However, there may be differences (e.g., Isosource Protein Fibre) or not (e.g., Fresubin Original Fibre and Osmolite Plus) in bottles from different batches (Supplementary Table S1). In all cases, the average value was subsequently calculated as a reference to determine the patients' intake of polyamines.

The analysis showed differences in the polyamine content across the 16 EN formulas included in this study. Significant differences in the total polyamine content (ANOVA, $p < 0.001$) (putrescine, spermidine, and spermine) were observed, being higher in the Impact, Impact Enteral, Nutrison, Nutrison Advanced Diason Energy, Nutrison Energy, and Nutrison Energy Multifibre formulas, ranging from 22.92 to 41.69 nmol/mL. No significant differences existed between them (in those with at least three determinations in different samples) when adjusted for multiple comparisons. The polyamine content of these EN formulas was significantly higher than what was found in Fresubin Original Fibre, Isosource Protein Fibre, Nepro LP, Novasource GI Protein, and Nutricomp Hepa Osmolite Plus, and presumably than what was found in the Nepro and Osmolite formulas, which ranged from 1.05 to 3.38 nmol/mL (Table 2).

Table 2. Polyamine content and total polyamines (considering the sum of putrescine, spermidine, and spermine) in EN formulas in nmol/mL (standard error of mean).

EN Formulas (*n*)	Putrescine	Spermidine	Spermine	*N*-Acetyl Putrescine	*N*-Acetyl Spermidine	*N*-Acetyl Spermine	Total Polyamines
Fresubin Original Fibre (8)	1.87(0.2)	11.46(0.66)	2.55(0.17)	42.39(3.72)	0.58(0.05)	0.28(0.04)	15.88(0.95)
Fresubin Thickened (1)	2.73	1.37	0.52	176.69	3.76	0.67	4.62
Impact (4)	5.81(0.4)	12.48(1.27)	10.82(0.99)	20.81(0.58)	1.45(0.3)	1.47(0.33)	29.1(2.48) ‡
Impact Enteral (1)	10.67	18.24	12.78	29.74	3.75	2.62	41.69
Isosource Protein Fibre (6)	5.88(1.04)	10.04(1.72)	1.52(0.27)	22.71(9.99)	0.66(0.07)	0.2(0.02)	17.43(2.58)
Nepro HP (2)	4.91(1.26)	2.24(0.63)	0.55(0.26)	53.45(7.08)	1.27(0.73)	0.14(0.11)	7.7(2.15)
Nepro LP (5)	1.58(0.43)	1.05(0.2)	0.4(0.1)	29.74(0.9)	1.79(0.93)	0.08(0.01)	3.05(0.54)
Novasource GI Protein (3)	1.18(0.28)	0.81(0.22)	0.14(0.09)	21.2(5.73)	0.48(0.32)	0.02	2.13(0.56)
Nutricomp Hepa (9)	3.28(1.21)	1.09(0.27)	0.55(0.24)	307.99(177.85)	6.93(1.22)	0.32(0.17)	4.92(1.46)
Nutrison (5)	5.13(0.87)	15.99(3.89)	1.8(0.41)	177.59(64.52)	1.63(0.91)	0.26(0.12)	22.92(5.02) ‡
Nutrison Advanced Diason Energy HP (10)	5.75(0.74)	21.42(1.36)	3.2(0.21)	35.15(3.43)	1.49(0.13)	0.54(0.07)	30.37(1.98) ‡
Nutrison Energy (1)	11.13	13.91	1.16	287.73	1.25	0.18	26.19
Nutrison Energy Multifibre (3)	10.8(0.86)	18.69(2.26)	2.12(0.4)	311.19(6.73)	1.12(0.16)	0.29(0.04)	31.61(2.2) ‡
Osmolite (1)	1.7	1.2	0.16	19.82	0.39	0.22	3.06
Osmolite Plus (3)	1.96(0.03)	1.25(0.08)	0.17(0.01)	19.43(0.96)	0.38(0.02)	0.09(0.01)	3.38(0.11)
Oxepa (2)	1.5(0.05)	3.06(0.41)	0.3(0.04)	24.41(0.78)	0.75(0.05)	0.26(0.07)	4.86(0.4)

Values are presented as the mean (standard error of the mean) for a determined number (*n*) of different samples of the nmol/mL content of amines in enteral nutrition (EN) formulas. For total polyamines, ‡ significantly higher (with different values of *p*) regarding Fresubin Original Fibre, Isosource Protein Fibre (except Nutrison), Nepro LP, Novasource GI Protein, Nutricomp Hepa, and Osmolite Plus.

The EN formulas with the highest putrescine content were Nutrison Energy Multifibre, Isosource Protein Fibre, and Nutrison Advanced Diason Energy HP. For spermidine, the highest contents were found in Nutrison Advanced Diason Energy HP, Nutrison Energy Multifibre, Nutrison, Impact, and Isosource Protein Fibre. The Impact formula had a significantly higher spermine content than the other formulas, followed by Nutrison Advanced Diason, Fresubin Original Fibre, and Nutrison Energy Multifibre. In all the analysed EN formulas, the polyamine with the highest content was *N*-acetyl putrescine, without significant differences among the formulas studied. Nutricomp Hepa had the highest content of *N*-acetyl spermidine and Impact had the highest content of *N*-acetyl spermine (Table 2; *p* values in Supplementary Table S2).

The ANOVA conducted on the remaining biogenic amines present in the EN formulas revealed significant differences in the levels of cadaverine and β-phenylethylamine ($p < 0.001$), while no significant differences were found for isoamylamine and tyramine. The post hoc analysis indicated that the β-phenylethylamine content was significantly higher in the Nutricomp Hepa formula compared to the other formulas. Additionally, cadaverine levels were significantly higher in the Nutrison Advanced Diason Energy HP formula than in all other EN formulas, except for Nutrison Energy Multifibre, which had a significantly higher cadaverine content than Nepro LP, Novasource GI Protein, Nutricomp Hepa, and Nutrison (Table 3). The protein content, caloric density, osmolarity, and chemistry of the nutrients of the EN formulas were not associated with the differences in polyamine composition.

Table 3. Average biogenic amine content in EN formulas in nmol/mL (standard error of mean).

EN Formulas (*n*)	Cadaverine	Tyramine	*β*-Phenyl-Ethylamine	Isoamylamine
Fresubin Original Fibre (8)	1.21(0.1) ***	0.97(0.08)	0.26(0.03) ***	7.78(2.94)
Fresubin Thickened (1)	1.66	4.01	0	8.43
Impact (4) (Nestle Health Science)	1.32(0.1) *	1.59(0.08)	0.55(0.02) ***	1.71(0.25)
Impact Enteral (1)	2.88	3.03	0.54	7.26
Isosource Protein Fibre (6)	1.4(0.32) *	2.25(0.5)	0.34(0.03) ***	5.22(1.43)
Nepro HP (2)	1.72(0.67)	4(0.41)	1.42(0.48)	14.27(7.14)
Nepro LP (5)	0.58(0.19) ***,ΦΦ	2.57(1.74)	1.57(0.77) ***	6.04(1.06)
Novasource GI Protein (3)	0.6(0.14) ***,Φ	0.78(0.26)	0.05	4.32(0.31)
Nutricomp Hepa (9)	1.62(0.35) *	2.44(0.51)	6.87(1.01) ***	63.33(29.49)
Nutrison (5)	0.81(0.18) ***,Φ	1.82(0.39)	0.6(0.33) ***	7.08(1.36)
Nutrison Advanced Diason Energy HP (10)	2.67(0.22)	1.5(0.15)	0.65(0.09) ***	5.23(1.12)
Nutrison Energy (1)	1.04	3.47	0.34	8
Nutrison Energy Multifibre (3)	2.47(0.13)	1.32(0.21)	0.56(0.08) ***	4.13(1.98)
Osmolite (1)	0.62	0.71	0.46	2.32
Osmolite Plus (3)	0.68(0.02)	0.79(0.07)	0.39(0.01) ***	2.07(0.62)
Oxepa (2)	0.53(0.05)	0.71	0.6(0.07)	1.42(0.08)

Values are presented as the mean (standard error of the mean) for a determined number (*n*) of different samples of the nmol/mL content of amines in enteral nutrition (EN) formulas. For cadaverine, * $p < 0.05$ and *** $p < 0.001$ by comparison with Nutrison Advanced Diason Energy HP; $^{\Phi}$ $p < 0.05$; and $^{\Phi\Phi}$ $p < 0.01$ by comparison with Nutrison Energy Multifibre. For β-phenylethylamine, *** $p < 0.001$ by comparison with Nutricomp Hepa.

3.2. Patients and Daily Polyamine Intake via EN Formulas

The study included eight patients—six males and two females—with an average age of 64.1 ± 3.6 years and an average BMI of 27.12 ± 1.81 kg/m^2. The average daily intake of EN formula varied between 185.2 mL and 1085 mL, with an average of 1034.03 ± 181.4 kcal/person/day, ranging from 244.46 to 1642.91.

By considering the daily volume administered and the polyamine content of the EN formula given to each patient, we calculated the total daily intake of polyamines (Figure 1a), putrescine (Figure 1b), spermidine (Figure 1c), and spermine (Figure 1d) for each patient.

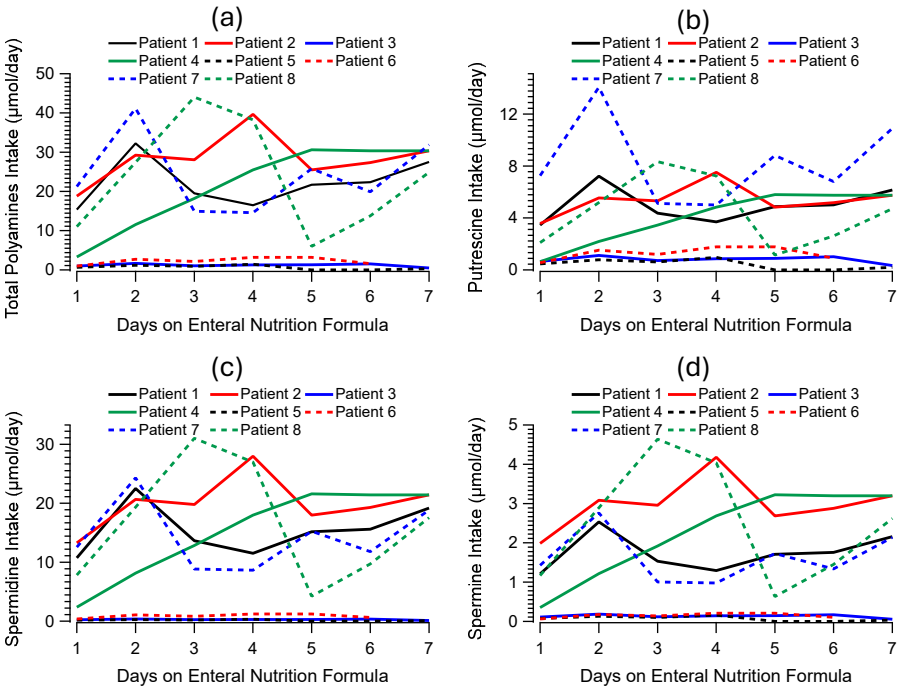

Figure 1. Daily total polyamine intake (sum of putrescine, spermidine, and spermine) (**a**); putrescine (**b**); spermidine (**c**); and spermine (**d**) in µmol/day, determined in each of the eight patients. The EN formula administered and the pathologies of the patients were as follows: Patient 1—Nutrison (abdominal origin sepsis); Patient 2—Nutrison Advanced Diason Energy HP (liver transplant); Patient 3—Nutricomp Hepa (sepsis); Patient 4—Nutrison Advanced Diason Energy HP (ketoacidosis); Patient 5—Nutricomp Hepa (haemodynamic instability); Patient 6—Novasource GI Protein (cardiorespiratory arrest); Patient 7—Nutrison Energy Multifibre (cerebral haemorrhage); and Patient 8—Nutrison Advanced Diason Energy HP (rhombencephalitis).

The patients' average total polyamine intake was 17.18 ± 4.79 µmol/day. The intake of putrescine was 4.04 ± 1.01 µmol/day, the intake of spermidine was 11.53 ± 3.42 µmol/day, and the intake of spermine was 1.62 ± 0.49 µmol/day. These intakes, in µmol/day, correspond to 2.36 ± 0.67 mg/day for total polyamines, 0.36 ± 0.09 mg/day for putrescine, 1.67 ± 0.49 mg/day for spermidine, and 0.33 ± 0.1 mg/day for spermine. The intake expressed in mg per 1000 kcal was as follows: total polyamines: 1.93 ± 0.46 mg/1000 kcal/day; putrescine: 0.333 ± 0.06 mg/1000 kcal/day; spermidine: 1.33 ± 0.36 mg/1000 kcal/day; and spermine: 0.27 ± 0.06 mg/1000 kcal/day.

Among the main polyamines, spermidine was the most important, although the intake of *N*-acetyl putrescine was the highest. Regarding the remaining amines, isoamylamine intake was higher than the others (Table 4).

Table 4. Average daily (standard error) intake of biogenic amines via enteral nutrition (EN) in µmol/day.

Biogenic Amines	Daily Intake via EN (Standard Error) (µmol)	Range of Daily Intake via EN (µmol)
Putrescine	4.04 (1.01)	0.21–14.06
Spermidine	11.53 (3.42)	0.07–32.39
Spermine	1.62 (0.49)	0.03–4.84
Total Polyamines	17.18 (4.79)	0.31–45.92
N-Acetyl putrescine	81.59 (27.35)	3.87–405.17
N-Acetyl spermidine	1.26 (0.14)	0.16–2.36
N-Acetyl spermine	0.27 (0.08)	0.01–0.82
Cadaverine	1.47 (0.38)	0.1–4.04
Tyramine	1.11 (0.16)	0.15–2.56
β-Phenyletylamine	0.73 (0.18)	0.02–2.34
Isoamylamine	7.05 (1.49)	0.58–21.53

The bivariate correlation analysis of the patients' daily GRV regarding the total quantity of polyamines provided by the EN formulas showed a significant negative correlation ($r = 0.003$; $p = -0.437$; $n = 45$), as well as for the polyamines putrescine ($r = -0.407$; $p = 0.006$; $n = 45$), spermidine ($r = -0.434$; $p = 0.003$; $n = 45$), spermine ($r = -0.409$; $p = 0.005$; $n = 45$), and *N*-acetyl spermine ($r = -0.359$; $p = 0.015$; $n = 45$). No significant correlation was found between *N*-acetyl putrescine and *N*-acetyl spermidine. Tyramine also showed an inverse correlation ($r = -0.386$; $p = 0.009$; $n = 45$) and was positive for β-phenylethylamine ($r = 0.513$; $p < 0.001$; $n = 45$) and isoamylamine ($r = 0.525$; $p < 0.001$; $n = 45$).

4. Discussion

This study found that commercially available EN formulas may not meet the daily polyamine requirements of critically ill patients, compared with a similar population's average dietary intake [8]. Daily intake may be associated with gastrointestinal effects. To the best of our knowledge, this is the first study to determine the composition of polyamines in EN formulas.

Significant differences in polyamine composition were found among the 16 EN formulas analysed in this study. These differences were not associated with the nutritional characteristics of the formulas, such as the protein content, caloric density, osmolarity, or chemistry of the nutrients. Commercial preparation processes may be responsible for the variations in the polyamine content in the tested EN formulas. The polyamine content of the EN formulas was notably lower than that found in most foods of equivalent weight [8].

The analysis of eight patients admitted to the ICU for diverse pathologies revealed that the average daily polyamine intake from the EN formulas administered to the patients during their first seven days in the ICU was only 12–25 µmol/day (considering the sum of putrescine, spermidine, and spermine). Even if patients were to ingest higher EN infusion rates—up to 63 mL/minute, supplying 1512 mL/day—the estimated polyamine intake would still be only 6–63 µmol per day, depending on the EN formula administered. These values are considerably lower than the estimated daily dietary intake in the same population (around 400 µmol/day) [8] and also for the polyamines considered individually. The average daily intake of putrescine (4.04 µmol/day), spermidine (11.53 µmol/day), and spermine (1.62 µmol/day) were much lower than the average content in a regular diet, which was 273.05 µmol/day, 87.71 µmol/day, and 49.82 µmol/day, respectively [8]. The reduced intake is not associated with the low-calorie consumption observed in the patients, which is approximately 1000 kcal/day, compared to 2200 kcal/day in individuals from the same population following a regular diet [8]. Adjusting the intake per 1000 kcal highlights that the EN formulas have a low polyamine content [8].

In the short term, the daily intake of polyamines may influence tolerance to EN formulas. This is suggested by the observed inverse correlation between total and individual polyamines—such as putrescine, spermidine, and *N*-acetyl spermine—and daily GRV [6]. The total polyamine and spermidine contents in the EN formulas were associated with contributing close to 20% of the variations in GRV in these patients. Additionally, tyramine also showed an inverse correlation, while β-phenylethylamine and isoamylamine were associated with worse EN tolerance. The association between polyamines and gastrointestinal tolerance aligns with their reported effects of modulating gastrointestinal motility [14,15] and maintaining gastrointestinal homeostasis, as described in experimental models [46,47]. Some of these gastrointestinal effects have been attributed to spermidine [48].

This study focused on determining the content of polyamines in EN formulas and their local effect on the gastrointestinal tract. It cannot be ruled out that additional clinical effects could arise if there is a prolonged reduction in the administration of polyamines due to their role as an energy source for the epithelium [11], their involvement in epithelial

growth [49], their stimulation of the gut immune system [50], and their contribution to microbiota homeostasis [51]. Moreover, such a reduced intake could have a broader impact on cellular polyamine homeostasis, potentially influencing the protective roles attributed to polyamines, especially spermidine, in vital organs such as the kidneys [32], lungs [35–37], heart [33,34], brain [39], and immune system [38]. These changes may be particularly significant for critically ill patients who are on mechanical ventilation and may experience persistent organ dysfunction after intensive care [31]. Therefore, investigating the effects of polyamine supplementation in these patients would be worthwhile.

Variations were also observed in the amounts of other biogenic amines, considered trace amines, which produce biological effects [41,42], including effects on the gastrointestinal tract via trace amine-associated receptors (TAARs) [43,44]. However, the administered quantities may be below the levels required to activate receptors [44] and induce effects [40], as they were less than 1 mg per day.

The study has some limitations due to its retrospective design (the polyamine content estimated by the EN formulas was not the one they administered) and it involved a small number of patients. Therefore, it should be considered preliminary. However, the significantly low intake of polyamines highlights the necessity for further research to investigate the clinical implications of increasing the polyamine content in EN formulas and its administration among critically ill patients in ICUs.

5. Conclusions

The findings of this study confirm that critically ill patients who receive EN formulas have a low polyamine intake, which may result in polyamine deprivation. If this continues for a long period, it could adversely impact the patient's health and recovery due to the multiple effects of polyamines on the gastrointestinal system, immunity, and protein synthesis. To help address this issue, future studies should examine the clinical implications of increasing the polyamine content of EN formulas on organ protection and reducing the health decline in critically ill patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app15020659/s1, Table S1: Biogenic amine content in enteral nutrition (EN) formulas (nmol/mL), expressed as a range when the number of data points (n) is $\geq$2, or as a single value when n = 1, for each batch; Table S2: Bonferroni multiple comparisons regarding the polyamine content in the enteral nutrition (EN) formulas analyzed (significative when p-value $\leq$ 0.05).

Author Contributions: All authors were involved in the conception and design of the study. E.R.-H., L.S., M.S. and B.C. analysed polyamines in EN formulas. M.G.-G. and E.R.-H. consulted the clinical data of the patients. B.C., M.G.-G. and M.S. wrote the article and all authors provided comments on previous manuscript versions. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by a Grant from Instituto de Investigación Sanitaria del Principado de Asturias (ISPA) (Convocatoria Intramural para el Fomento de Proyectos de Investigación 2018).

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the Principality of Asturias, Spain (reference: CElmPA; No. 2023.089).

Informed Consent Statement: Informed consent was not applicable since this was a retrospective study.

Data Availability Statement: Data are available on request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Mozaffarian, D.; Rosenberg, I.; Uauy, R. History of modern nutrition science-implications for current research, dietary guidelines, and food policy. *Bmj* **2018**, *361*, k2392. [CrossRef] [PubMed]
2. Mohamed Elfadil, O.; Velapati, S.R.; Patel, J.; Hurt, R.T.; Mundi, M.S. Enteral Nutrition Therapy: Historical Perspective, Utilization, and Complications. *Curr. Gastroenterol. Rep.* **2024**, *26*, 200–210. [CrossRef] [PubMed]
3. Wischmeyer, P.E.; Klek, S.; Berger, M.M.; Berlana, D.; Gray, B.; Ybarra, J.; Ayers, P. Parenteral nutrition in clinical practice: International challenges and strategies. *Am. J. Health Syst. Pharm.* **2024**, *81*, S89–S101. [CrossRef] [PubMed]
4. Kong, S.; Zhang, Y.H.; Zhang, W. Regulation of Intestinal Epithelial Cells Properties and Functions by Amino Acids. *Biomed. Res. Int.* **2018**, *2018*, 2819154. [CrossRef] [PubMed]
5. Demehri, F.R.; Barrett, M.; Ralls, M.W.; Miyasaka, E.A.; Feng, Y.; Teitelbaum, D.H. Intestinal epithelial cell apoptosis and loss of barrier function in the setting of altered microbiota with enteral nutrient deprivation. *Front. Cell. Infect. Microbiol.* **2013**, *3*, 105. [CrossRef]
6. Doyle, D.J.; Hendrix, J.M.; Garmon, E.H. American Society of Anesthesiologists Classification. [Updated 17 August 2023]; In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: https://www.ncbi.nlm.nih.gov/books/NBK441940/ (accessed on 3 December 2024).
7. Yang, H.; Hou, L.; Sun, H.M.; Ye, S.H. Comparison of micronutrients in adult enteral formulas widely used in clinical practice. *Food Sci. Nutr.* **2023**, *11*, 6096–6105. [CrossRef] [PubMed]
8. Cantabrana, B.; Peña-Iglesias, P.; Castro-Estrada, P.; Suárez, L.; Bordallo, J.; Barreiro-Alonso, E.; Sánchez, M. Dietary intake of polyamines in a Spanish adult population: Age-dependent correlation with Healthy Eating Index and Dietary Inflammatory Index scores. *Nutrition* **2024**, *130*, 112608. [CrossRef]
9. Liu, B.; Jiang, X.; Cai, L.; Zhao, X.; Dai, Z.; Wu, G.; Li, X. Putrescine mitigates intestinal atrophy through suppressing inflammatory response in weanling piglets. *J. Anim. Sci. Biotechnol.* **2019**, *10*, 69. [CrossRef]
10. Minetti, A.; Omrani, O.; Brenner, C.; Allies, G.; Imada, S.; Rösler, J.; Khawaled, S.; Cansiz, F.; Meckelmann, S.W.; Gebert, N.; et al. Polyamines sustain epithelial regeneration in aged intestines by modulating protein homeostasis. *bioRxiv* **2024**. [CrossRef]
11. Bardócz, S.; Grant, G.; Brown, D.S.; Pusztai, A. Putrescine as a source of instant energy in the small intestine of the rat. *Gut* **1998**, *42*, 24–28. [CrossRef] [PubMed]
12. Tofalo, R.; Cocchi, S.; Suzzi, G. Polyamines and Gut Microbiota. *Front. Nutr.* **2019**, *6*, 16. [CrossRef]
13. Hesterberg, R.S.; Cleveland, J.L.; Epling-Burnette, P.K. Role of Polyamines in Immune Cell Functions. *Med. Sci.* **2018**, *6*, 22. [CrossRef] [PubMed]
14. Sánchez, M.; Suárez, L.; Andrés, M.T.; Flórez, B.H.; Bordallo, J.; Riestra, S.; Cantabrana, B. Modulatory effect of intestinal polyamines and trace amines on the spontaneous phasic contractions of the isolated ileum and colon rings of mice. *Food Nutr. Res.* **2017**, *61*, 1321948. [CrossRef] [PubMed]
15. Kim, Y.C.; Sim, J.H.; Kim, Y.H.; Kwon, S.C.; Lee, S.J.; Kim, S.R.; Kim, D.W.; Park, S.M.; Youn, S.J.; Lee, S.J.; et al. Effects of polyamines on contractility of guinea-pig gastric smooth muscle. *J. Korean Med. Sci.* **2007**, *22*, 48–56. [CrossRef] [PubMed]
16. ter Steege, J.C.; Buurman, W.A.; Forget, P.P. Spermine induces maturation of the immature intestinal immune system in neonatal mice. *J. Pediatr. Gastroenterol. Nutr.* **1997**, *25*, 332–340. [CrossRef]
17. van Wettere, W.H.; Willson, N.L.; Pain, S.J.; Forder, R.E. Effect of oral polyamine supplementation pre-weaning on piglet growth and intestinal characteristics. *Animal* **2016**, *10*, 1655–1659. [CrossRef] [PubMed]
18. Schibalski, R.S.; Shulha, A.S.; Tsao, B.P.; Palygin, O.; Ilatovskaya, D.V. The role of polyamine metabolism in cellular function and physiology. American journal of physiology. *Cell Physiol.* **2024**, *327*, C341–C356. [CrossRef] [PubMed]
19. Xuan, M.; Gu, X.; Li, J.; Huang, D.; Xue, C.; He, Y. Polyamines: Their significance for maintaining health and contributing to diseases. *Cell Commun. Signal.* **2023**, *21*, 348. [CrossRef] [PubMed]
20. Soda, K.; Dobashi, Y.; Kano, Y.; Tsujinaka, S.; Konishi, F. Polyamine-rich food decreases age-associated pathology and mortality in aged mice. *Exp. Gerontol.* **2009**, *44*, 727–732. [CrossRef] [PubMed]
21. Eisenberg, T.; Knauer, H.; Schauer, A.; Büttner, S.; Ruckenstuhl, C.; Carmona-Gutierrez, D.; Ring, J.; Schroeder, S.; Magnes, C.; Antonacci, L.; et al. Induction of autophagy by spermidine promotes longevity. *Nat. Cell Biol.* **2009**, *11*, 1305–1314. [CrossRef] [PubMed]
22. Kim, J.; Baek, Y.; Lee, S. Dietary polyamine intake lowers the risk of all-cause and cardiovascular disease-related mortality: Follow-up of the Korean National health and nutrition Examination survey 2007–2015. *J. Funct. Foods* **2024**, *119*, 106268. [CrossRef]
23. Soda, K.; Kano, Y.; Chiba, F. Food polyamine and cardiovascular disease--an epidemiological study. *Glob. J. Health Sci.* **2012**, *4*, 170–178. [CrossRef]
24. Madeo, F.; Hofer, S.J.; Pendl, T.; Bauer, M.A.; Eisenberg, T.; Carmona-Gutierrez, D.; Kroemer, G. Nutritional Aspects of Spermidine. *Annu. Rev. Nutr.* **2020**, *40*, 135–159. [CrossRef] [PubMed]

25. Ralph, A.; Englyst, K.; Bardocz, S. Polyamine content of the human diet. In *Polyamines in Health and Nutrition*; Bardócz, S., White, A., Eds.; Kluwer Academic Publishers: London, UK, 1999.
26. Atiya Ali, M.; Poortvliet, E.; Strömberg, R.; Yngve, A. Polyamines in foods: Development of a food database. *Food Nutr. Res.* **2011**, *55*, 5572. [CrossRef] [PubMed]
27. Zoumas-Morse, C.; Rock, C.L.; Quintana, E.L.; Neuhouser, M.L.; Gerner, E.W.; Meyskens, F.L., Jr. Development of a polyamine database for assessing dietary intake. *J. Am. Diet. Assoc.* **2007**, *107*, 1024–1027. [CrossRef]
28. Nishibori, N.; Fujihara, S.; Akatuki, T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem.* **2007**, *100*, 491–497. [CrossRef]
29. Buyukuslu, N.; Hizli, H.; Esin, K.; Garipagaoglu, M. A Cross-Sectional Study: Nutritional Polyamines in Frequently Consumed Foods of the Turkish Population. *Foods* **2014**, *3*, 541–557. [CrossRef]
30. Atiya Ali, M.; Poortvliet, E.; Strömberg, R.; Yngve, A. Polyamines: Total daily intake in adolescents compared to the intake estimated from the Swedish Nutrition Recommendations Objectified (SNO). *Food Nutr. Res.* **2011**, *55*, 5455. [CrossRef]
31. Martín-Vicente, P.; López-Martínez, C.; Rioseras, B.; Albaiceta, G.M. Activation of senescence in critically ill patients: Mechanisms, consequences and therapeutic opportunities. *Ann. Intensive Care* **2024**, *14*, 2. [CrossRef] [PubMed]
32. Luo, D.; Lu, X.; Li, Y.; Xu, Y.; Zhou, Y.; Mao, H. Metabolism of Polyamines and Kidney Disease: A Promising Therapeutic Target. *Kidney Dis.* **2023**, *9*, 469–484. [CrossRef] [PubMed]
33. Eisenberg, T.; Abdellatif, M.; Schroeder, S.; Primessnig, U.; Stekovic, S.; Pendl, T.; Harger, A.; Schipke, J.; Zimmermann, A.; Schmidt, A.; et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat. Med.* **2016**, *22*, 1428–1438. [CrossRef] [PubMed]
34. Wang, T.; Li, N.; Zeng, Y. Protective effects of spermidine levels against cardiovascular risk factors: An exploration of causality based on a bi-directional Mendelian randomization analysis. *Nutrition* **2024**, *127*, 112549. [CrossRef] [PubMed]
35. Yarova, P.; Al-Zadjali, R.B.A.; Scott, J.; Josiah, E.; Turnbull, E.; Ebbern, C.E.; Telezhkin, V.S.; Rostron, A.; Riccardi, D.; Simpson, A.J. Polyamines as regulators of pulmonary inflammation. *Eur. Respir. J.* **2024**, *64*, PA5327. [CrossRef]
36. Luo, J.; Kim, Y.J.; An, X.; Fan, L.; Erb, C.; Lou, D.; Yao, Y.; Ferguson, A.A.; Pan, Y.; Chen, K. Spermidine dampens inflammation by directly inhibiting Th17 cytokine production through a PRDX1 associated antioxidant pathway. *bioRxiv* **2021**. [CrossRef]
37. Baek, A.R.; Hong, J.; Song, K.S.; Jang, A.S.; Kim, D.J.; Chin, S.S.; Park, S.W. Spermidine attenuates bleomycin-induced lung fibrosis by inducing autophagy and inhibiting endoplasmic reticulum stress (ERS)-induced cell death in mice. *Exp. Mol. Med.* **2020**, *52*, 2034–2045. [CrossRef] [PubMed]
38. Chia, T.Y.; Zolp, A.; Miska, J. Polyamine Immunometabolism: Central Regulators of Inflammation, Cancer and Autoimmunity. *Cells* **2022**, *11*, 896. [CrossRef]
39. Arthur, R.; Jamwal, S.; Kumar, P. A review on polyamines as promising next-generation neuroprotective and anti-aging therapy. *Eur. J. Pharmacol.* **2024**, *978*, 176804. [CrossRef]
40. Del Rio, B.; Fernandez, M.; Redruello, B.; Ladero, V.; Alvarez, M.A. New insights into the toxicological effects of dietary biogenic amines. *Food Chem.* **2024**, *435*, 137558. [CrossRef]
41. Kovács, T.; Mikó, E.; Vida, A.; Sebő, É.; Toth, J.; Csonka, T.; Boratkó, A.; Ujlaki, G.; Lente, G.; Kovács, P.; et al. Cadaverine, a metabolite of the microbiome, reduces breast cancer aggressiveness through trace amino acid receptors. *Sci. Rep.* **2019**, *9*, 1300. [CrossRef]
42. Teng, Y.; Mu, J.; Xu, F.; Zhang, X.; Sriwastva, M.K.; Liu, Q.M.; Li, X.; Lei, C.; Sundaram, K.; Hu, X.; et al. Gut bacterial isoamylamine promotes age-related cognitive dysfunction by promoting microglial cell death. *Cell Host Microbe* **2022**, *30*, 944–960.e948. [CrossRef] [PubMed]
43. Moiseenko, V.I.; Apryatina, V.A.; Gainetdinov, R.R.; Apryatin, S.A. Trace Amine-Associated Receptors' Role in Immune System Functions. *Biomedicines* **2024**, *12*, 893. [CrossRef] [PubMed]
44. Berry, M.D.; Gainetdinov, R.R.; Hoener, M.C.; Shahid, M. Pharmacology of human trace amine-associated receptors: Therapeutic opportunities and challenges. *Pharmacol. Ther.* **2017**, *180*, 161–180. [CrossRef]
45. Escribano, M.I.; Legaz, M.E. High performance liquid chromatography of the dansyl derivatives of putrescine, spermidine, and spermine. *Plant Physiol.* **1988**, *87*, 519–522. [CrossRef] [PubMed]
46. Kasahara, N.; Teratani, T.; Yokota, S.; Sakuma, Y.; Sasanuma, H.; Fujimoto, Y.; Ijichi, T.; Urahashi, T.; Yoshitomi, H.; Kitayama, J.; et al. Dietary polyamines promote intestinal adaptation in an experimental model of short bowel syndrome. *Sci. Rep.* **2024**, *14*, 4605. [CrossRef]
47. Tan, B.; Xiao, D.; Wang, J.; Tan, B. The Roles of Polyamines in Intestinal Development and Function in Piglets. *Animals* **2024**, *14*, 1228. [CrossRef] [PubMed]
48. Wang, Z.; Jiang, D.; Wang, X.; Jiang, Y.; Sun, Q.; Ling, W.; An, X.; Ji, C.; Li, S.; Qi, Y.; et al. Spermidine improves the antioxidant capacity and morphology of intestinal tissues and regulates intestinal microorganisms in Sichuan white geese. *Front. Microbiol.* **2023**, *14*, 1292984. [CrossRef] [PubMed]

49. Rao, J.N.; Xiao, L.; Wang, J.Y. Polyamines in Gut Epithelial Renewal and Barrier Function. *Physiology* **2020**, *35*, 328–337. [CrossRef] [PubMed]
50. Chamoto, K.; Zhang, B.; Tajima, M.; Honjo, T.; Fagarasan, S. Spermidine-an old molecule with a new age-defying immune function. *Trends Cell Biol.* **2024**, *34*, 363–370. [CrossRef] [PubMed]
51. Yu, L.; Zhang, C.; Zhai, Q. Gut Microbes Participate in Host Polyamine Metabolism. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2419368121. [CrossRef]