

Systematic Review of Hypersensitivity to Parenteral Nutrition

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Abstract

Hypersensitivity to the components of parenteral nutrition (PN) is a rare but important complication of PN. We performed a systematic review of hypersensitivity to PN to enable us to build an approach to the individual patient who presents with PN hypersensitivity. A systematic literature search was performed in Ovid Medline, CINAHL, Scopus, and Web of Science using terms for “hypersensitivity” AND “parenteral nutrition” and relevant synonyms. A total of 28 articles were analyzed, and 33 hypersensitivities to PN or components of PN were reported in these 28 articles. Reports of hypersensitivity and subsequent conclusions were based on the clinical observations made by each reporting author. These reactions were evenly split between pediatric and adult patients. Hypersensitivity to PN occurred on day of starting PN in 60.6% patients and after that time in 36.3% patients (range: 1–21 days). Of the hypersensitivities that occurred on day 1 of PN, 70% occurred in the first 30 minutes of initiation of PN. Cutaneous manifestations were the most common, followed by anaphylaxis, respiratory symptoms, and hemodynamic instability. The components most frequently identified as allergens were intravenous fat emulsion (48.4%), multivitamin solution (33.3%), and amino acid solution (9%). Based on this review, an algorithm was created to guide the practitioner on management of PN after the occurrence of such a reaction. (*JPEN J Parenter Enteral Nutr.* 2018;00:1–8)

Introduction

Hypersensitivity to the components of parenteral nutrition (PN) is rare. First reported in 1965,¹ hypersensitivity reactions to PN have been known to include minor problems such as pruritus^{2,3} and life-threatening conditions such as anaphylaxis.⁴ While underreporting in the literature is likely, the lack of large studies and even the relative lack of case series suggest that hypersensitivity to components of PN is an uncommon problem.

Food allergies are thought to be increasing.⁵ Components of PN are made from highly allergenic foods such as soy and eggs. New PN components made from allergenic foods such as fish have been introduced in recent years. Given the increasing prevalence of food allergies, the lack of literature, and the potential of anaphylaxis to PN, we performed a systematic review of hypersensitivity to PN to enable us to build an approach to the individual patient with PN hypersensitivity.

This study aimed to systematically review the literature for hypersensitivity to the components of PN currently in use, with the primary goal of characterizing these reactions better. An additional objective of this study was to suggest guidelines on how to manage PN after such a reaction.

Methods

A systematic literature search was performed on November 21, 2017, by a medical librarian (RS) in Ovid Medline, CINAHL, Scopus, and Web of Science using terms for

“hypersensitivity” AND “parenteral nutrition” and relevant synonyms. Search terms included controlled terms from MeSH in Ovid Medline and CINAHL as well as free-text terms in all databases. Search strategies were limited to studies on humans. Complete search strategies are available in Appendix 1. The strategies were adapted for each database as needed. The references of relevant articles were reviewed for additional relevant studies.

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Inclusion Criteria:

- All original articles including human case reports and case series
- Allergy/hypersensitivity to currently available components of PN
- All languages
- Abstracts and full-length articles

Exclusion Criteria:

- Allergy/hypersensitivity to component of PN when not administered as part of PN (e.g., vitamin K, thiamin). We also did not consider iron as a component of PN.

A total of 8165 articles were identified by searching the Ovid Medline, CINAHL, Scopus, and Web of Science databases. After duplicate articles were eliminated, 6130 articles (published from 1912 through 2017) underwent an initial screening process that consisted of a review of article titles and, in some cases, abstracts. Each stage of the review involved applying the inclusion and exclusion criteria. After irrelevant articles were eliminated, full-text articles were obtained and translated when necessary. A total of 69 full-text articles (including 15 articles added from the citations of other articles) were marked for detailed review. This collection included articles dating from 1970–2016, and the articles were in English, Spanish, German, French, Japanese, Russian, and Danish. Forty-one articles were excluded after reviewing full-text versions of each article; 28 of these articles were included in the final analysis. A workgroup was established to critically analyze each relevant article. The findings were summarized, and a conclusion was generated. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is depicted in Figure 1.

Results

A total of 28 articles dating from 1976–2016 were analyzed. The vast majority were case reports (24); the rest were case series. Relevant findings of the studies are summarized in Table 1. Thirty-three hypersensitivities to PN or components of PN were reported in these 28 articles. The hypersensitivity reactions were evenly split between pediatric (range: 50 days–17 years) and adult patients (age range: 30–68 years), with 16 reactions (48.4%) reported in each group. In 1 case, the age of the patient was not mentioned.⁶

Hypersensitivity to PN occurred on the day of starting PN in 20 (60.6%) patients and after that time in 12 (36.3%) patients (range: 1–21 days). In cases where only the time of onset of hypersensitivity was specified, day 1 of PN was assumed. In 1 case (3%) neither date nor time of onset of

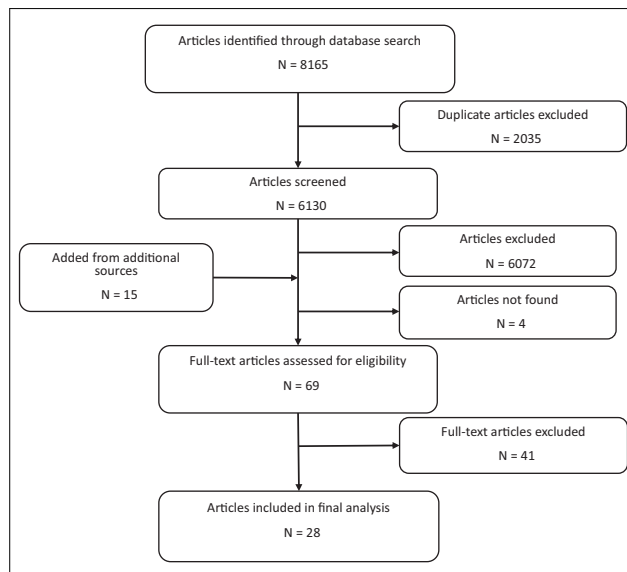


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

hypersensitivity was mentioned.⁶ Of the hypersensitivities that occurred on day 1 of PN, 14 reactions (70%) occurred within the first 30 minutes of initiation of PN.

Cutaneous symptoms/signs (urticarial rash, swelling, erythema, hives, pruritus) were the most common manifestation of hypersensitivity, occurring in 27 (81.8%) cases. Anaphylaxis occurred in 15 (45.4%) patients. Respiratory symptoms (dyspnea, respiratory distress, stridor, bronchospasm, acute respiratory distress syndrome [ARDS]) occurred in 14 (42.4%) cases. Hemodynamic instability (hypotension, shock) was seen in 7 (21.2%) patients. Tachycardia occurred in 6 (18.1%) patients. Other manifestations included back pain (9%), diarrhea (6%), hypoxia (6%), nausea, vomiting, increased body temperature, cyanosis, edema, loss of consciousness, and oral dryness. With the exception of diarrhea, these non-specific symptoms never occurred in isolation, but always along with cutaneous and/or respiratory manifestations.

In the majority of cases, the treating team was able to identify the allergenic component based on the timeline of development of hypersensitivity in relation to introduction of the specific component, or by eliminating the suspected allergenic component and waiting for resolution of hypersensitivity.

Intravenous fat emulsion. The intravenous fat emulsion (IVFE) was implicated in 16 patients (48.4%). In the case of 1 patient (3%), both IVFE and multivitamin solution were implicated.⁷ Among the patients who reacted to IVFE (17 patients: 16 patients plus 1 patient who reacted to both the multivitamin and IVFE), Intralipid® (Baxter Healthcare

Table 1. Overview of Reported Hypersensitivities.

Publication Year and First Author	Age of Patient	Onset of Reaction After Initiation of PN	Manifestation	Component Implicated	Comments
1976 Hansen ⁸	1 year	Day 3 of PN	Cutaneous manifestations, Increase in temperature	IVFE	Intralipid®
1979 Connon ⁹	Pediatric patient, age not mentioned	Day 11 of PN	Cutaneous manifestations, Respiratory distress/symptoms, Anaphylaxis	IVFE	Intralipid®
1981 Faintuch J ¹⁰	49 years	Within 24 hours	Diarrhea	IVFE	Intralipid®
1981 Kamath ²	58 years	Day 1	Diarrhea	IVFE	Intralipid®
	9 years	Day 20 of PN, 1 hour after initiation of infusion	Cutaneous manifestations	IVFE	Intralipid®
1984 Bass ¹¹	68 years	30 minutes	Cutaneous manifestations, Respiratory distress/symptoms, Anaphylaxis	IVFE	Intralipid®
1987 Pomeranz ¹²	4 years	15 minutes	Respiratory distress/symptoms, Hemodynamic instability, Anaphylaxis, Tachycardia, Cyanosis, Edema of skin	Unknown	Travasol®/Magnesium/MVI-12
1989 Hiyama ¹³	41 years	5 hours	Anaphylaxis, Cutaneous manifestations, Respiratory distress/symptoms	IVFE	Intralipid®
1991 Buchman ³	36 years	Day 2	Cutaneous manifestations	IVFE	Intralipid®
1993 Andersen ¹⁴	48 years	Shortly after	Respiratory distress/symptoms, Hemodynamic instability, Anaphylaxis	IVFE	Lipofundin®
1995 Mounier ¹⁵	30 years	Few minutes	Anaphylaxis, Cutaneous manifestations, Respiratory distress/symptoms	Multivitamin solution	Hydrosol® polyvitamine roche
1997 Weidmann ¹⁶	45 years	15 minutes	Cutaneous manifestations, Respiratory distress/symptoms, Hemodynamic instability, Tachycardia, Anaphylaxis, Back pain	IVFE	Fractionated soybean oil and glycerol-based lipid with soybean lecithin emulsifier
	50 years	15 minutes	Cutaneous manifestations, Respiratory distress/symptoms, Hemodynamic instability, Tachycardia, Anaphylaxis, Back pain	IVFE	Fractionated soybean oil and glycerol-based lipid with egg lecithin emulsifier
	51 years	15 minutes	Cutaneous manifestations, Respiratory distress/symptoms, Hemodynamic instability, Tachycardia, Anaphylaxis, Back pain	IVFE	Fractionated soybean oil and glycerol-based lipid with egg lecithin emulsifier
1998 Market ⁴	4 years	11 days	Cutaneous manifestations, Anaphylaxis	Multivitamin solution	

(continued)

Table 1. (continued)

Publication Year and First Author	Age of Patient	Onset of Reaction After Initiation of PN	Manifestation	Component Implicated	Comments
2002 Wu ¹⁷	8 years	21 days	Cutaneous manifestations	Multivitamin solution	–
2005 Coors ¹⁸	30 years	Few seconds	Respiratory distress/symptoms, Hemodynamic instability, Anaphylaxis, Tachycardia, Oral dryness, Loss of consciousness	Multivitamin solution	–
2005 Crespi Monjo ¹⁹	55 years	After 1 day of infusion	Cutaneous manifestations	Unknown	Multivitamin/trace elements/magnesium sulphate
2005 Gura ²⁰	17 years	Minutes	Anaphylaxis, Cutaneous manifestations, Respiratory distress/symptoms	IVFE	Intralipid [®]
2005 Scolapio ²¹	53 years	Day 16 of PN, 1.5–2 hours into infusion	Cutaneous manifestations	Multivitamin solution	
2009 Huston ²²	50 days	Minutes	Cutaneous manifestations	Amino acid solution	Bisulphite contained in Trophamine [®] solution, Co-administration of PN solution and lipid brought about reaction
2011 Lunn ²³	2 years	14 days	Cutaneous manifestations	IVFE	Intralipid [®]
2012 Bartels ²⁴	15 years	30 minutes	Cutaneous manifestations	Multivitamin solution	
2013 Cragun ⁷	65 years	Immediately	Cutaneous manifestations, Hemodynamic instability, Anaphylaxis, Tachycardia, Hypoxia	Multivitamin solution and IVFE	
2014 Cave ⁶	Not reported	Not reported	Respiratory distress/symptoms	IVFE	Lipid emulsion used as antidote, no other details provided
2014 Darlington ²⁵	5 years	Day 2	Cutaneous manifestations, Nausea and vomiting, Anaphylaxis	Multivitamin solution	
2015 Honda ²⁶	50 years	3 days	Cutaneous manifestations	Amino acid solution	Bisulphite contained in Aminotripa [®] solution
2016 Hernandez ²⁷	1 month	Day 2 of PN, after 60 minutes of infusion	Cutaneous manifestations	Multivitamin solution	
	4 years	Day 3 of PN, after 15 minutes of infusion	Cutaneous manifestations	Amino acid solution	Aminosol [®]
	10 years	2 hours	Cutaneous manifestations	IVFE	Smoflipid [®]

IVFE, intravenous fat emulsion; PN, parenteral nutrition.

Corporation, Deerfield, Illinois, USA) was the brand of IVFE used in 10 cases (58.8%). Smoflipid® (Fresenius Kabi, Uppsala, Sweden) and Lipofundin® (B Braun Medical Inc., Melsungen, Germany) were implicated in 1 case each (5.8% each). The brand of IVFE was not specified in 5 cases (29.4%).

Multivitamin solution. The multivitamin solution was implicated in 11 patients (33.3%). In 1 patient (3%), both IVFE and multivitamin solution were implicated.⁷

Amino acid solution. The amino acid solution was implicated in 3 patients (9%). Aminosol® (Vitrum, Stockholm, Sweden) was the brand of amino acid solution used in 1 case.²⁷ The bisulphite additive, which is commonly added to medications as an antioxidant and preservative and is present in some amino acid solutions,²⁸ was implicated in the other 2 patients.^{22,26} In 1 of the 2 cases, bisulphite was an additive in the PN solution Aminotripa®²⁶ (Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan), while in the other, bisulphite was part of the Trophamine® (B. Braun Medical Inc. Irvine, California, USA) solution.²²

Unknown allergen. The allergen was unknown or narrowed down to a few components (but not to a single component) in 2 patients (6%). In 1 of these cases the authors were able to narrow down the allergenic component to the amino acid solution (Travasol®, Baxter Healthcare Corporation, Deerfield, Illinois, USA), magnesium, and the multivitamin solution.¹² In the other case the allergenic component was narrowed to the multivitamin solution, magnesium, and the trace element mixture.¹⁹

In 1 case report, co-administration of the PN solution (containing Trophamine®) and the IVFE brought about a reaction (rash). Administration of either the PN solution by itself or the IVFE alone did not cause a hypersensitivity reaction.²²

Fourteen of the reported reactions were considered severe. Of these reactions, the IVFE was the allergenic component in 9 cases (64.2%), and the multivitamin solution was implicated in 3 cases (21.4%). Eleven (78.5%) of these 14 hypersensitivities occurred on day 1 of PN administration. Of these severe reactions occurring on day 1 of PN, 10 (90.9%) reactions occurred within the first hour of PN administration.

Many allergenic foods are potential ingredients of PN. The presence of the allergenic protein component in predominantly the lipid portion of PN is controversial. Three patients with a prior history of food allergy had a documented reaction to the PN component related to his/her allergenic food. One patient reacted to a component of PN to which he had a documented previous allergy, i.e., the patient who had a history of fish allergy and reacted to Smoflipid®.²⁷ Two other patients had reactions to

Intralipid®, which contains egg phospholipid and soybean oil, and they had previous allergies to egg²³ and legumes.¹³ Almost one-third of the patients (9/33) had positive immunologic or skin tests to various foods or components of PN. A summary of the atopic history and allergy testing of the patients reported has been included in Table 2.

Discussion

Hypersensitivity to PN is a rare event. Making some very general assumptions, we speculate that the rate of PN hypersensitivity in the U.S. may be around 1.5 per million patients who are provided PN. Hypersensitivity to PN can occur in patients of all ages, irrespective of atopic history. The majority of hypersensitivity reactions occur on the first day of exposure to PN, although reactions can occur days after initiation of PN. Although cutaneous manifestations are frequently reported, a wide range of hypersensitivity reactions can occur, including some that would be considered serious or life threatening. Severe reactions were more likely to occur within the first hour of PN initiation. The most frequently implicated allergenic agents are IVFE and the multivitamin solution.

Our study has gathered all the available data on a rare and potentially underreported complication. We have used these data to suggest an algorithm to manage the patient who presents with a potential hypersensitivity to PN. The strengths of our study include an analysis of all available medical literature in all languages. We excluded components of PN that are no longer in use, such as casein hydrolysates, to make our recommendations more practical.

PN Management in the Case of PN Hypersensitivity

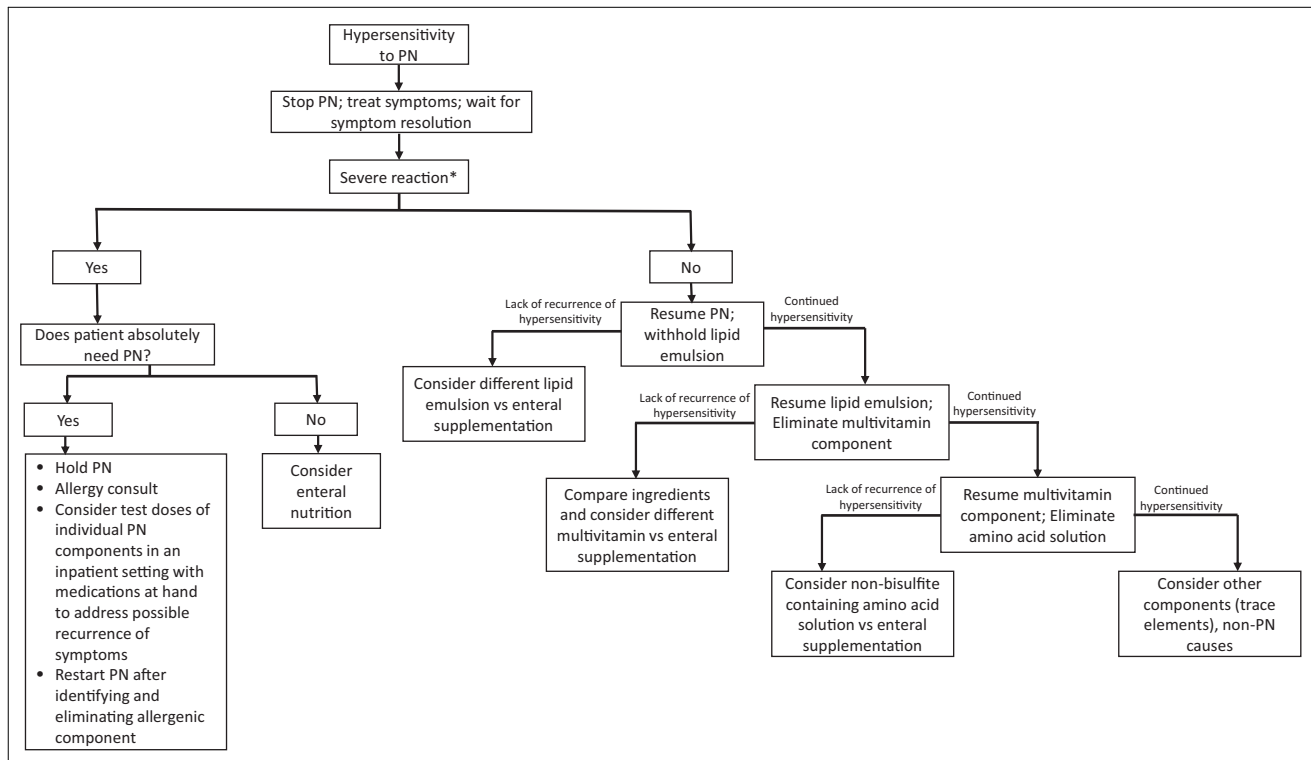
In case of a severe reaction or anaphylaxis, PN must be discontinued, and the patient must be treated emergently. No further nutrition interventions are recommended until resolution of the hypersensitivity symptoms. After the symptoms resolve, consultation with an allergist and administration of test doses of each PN component is recommended to attempt to identify the allergenic component. When a component is identified, PN with an alternative to the allergic component or without the allergic component can be attempted. Both the test doses and the reintroduction of the modified PN solution should be done in an inpatient setting and with antihistamines and epinephrine available in case of a reaction.

We have also designed an algorithm to guide the practitioner on PN management after the occurrence of PN hypersensitivity (Figure 2). Removal of the suspected agent and re-challenge are recommended based on this review. We recommend that this process, too, be initiated in the inpatient setting with antihistamines and epinephrine available

Table 2. Overview of Atopic History and Allergy Testing of Reported Patients.

Parenteral nutrition component implicated in hypersensitivity	Atopic/allergic history	Positive allergy testing
Patients With Prior Atopic History		
Smoflipid®	Fish	—
Intralipid®	Legumes	RAST positive to soy
Multivitamin	Sulfa drugs	—
Intralipid®	Egg (emesis)	Skin prick positive to egg, Immunocap serum testing positive to egg yolk and egg white
Multivitamin	Sulfa drugs, nuts, mites, seasonal allergies	—
Intralipid®	Peanut (anaphylaxis)	Skin test positive for several foods including soy, peanut
Multivitamin	Oral allergy syndrome, seasonal allergies	Skin prick positive to Multibonta® and its component polysorbate 80
IVFE, unknown type	Paclitaxel	—
Patients With No Prior Atopic History But Positive Allergy Testing		
Bisulphite component of Aminotripa®	Not applicable	Patch test positive to Aminotripa® and bisulphite
Multivitamin	Not applicable	Skin prick and intradermal injection showed positive reaction to Aminosyn®
Travasol®/Magnesium/MVI-12	Not applicable	Dermal skin testing positive to Travasol®, magnesium, and MVI-12
Multivitamin	Not applicable	Dermal allergy testing positive to vitamin B complex
Intralipid®	Not applicable	RAST positive to egg white, egg yolk, soy bean

IVFE, intravenous fat emulsion; RAST, radioallergosorbent test; —, no information available about allergy testing.

**Figure 2.** Suggested Algorithm for the Management of Hypersensitivity to Parenteral Nutrition.

*Severe reaction is anaphylaxis or any reaction associated with cardiorespiratory compromise; PN, Parenteral Nutrition.

in case of a reaction. Pharmacist input regarding stability of PN solution following removal of individual components is necessary.

Based on the frequency with which each component has been implicated in our review, we recommend the following order of elimination:

1. Intravenous fat emulsion
2. Multivitamin solution
3. Amino acid solution
4. Other components (such as trace elements)

During the process of PN administration, a perceived allergy to PN may be to components that are not truly part of the PN, but to other chemicals or devices that the patient is exposed to. Such reactions have been described in response to chlorhexidine gluconate (when used as a skin disinfectant),²⁹ nickel (from an eyelet in an intravenous needle),³⁰ and latex (from the rubber stopper of the PN solution).³¹ It is critical to consider these and other exposures when encountering a patient with possible hypersensitivity to PN.

One important limitation of this study is that our data rely on observations and conclusions of individual authors. Also, an intense area of interest to the individual practitioner is whether a patient with a known food allergy (that is also a component of PN) should receive that component of PN. We specifically are unable to address this important concern. The PN components implicated in hypersensitivity are frequently known to cause non-immunoglobulin (Ig)E-mediated reactions. Despite this, allergy consultation can be considered on a case-by-case basis. The provision of IVFE (Intralipid® or Smoflipid®) is the most likely PN component to be a cause for concern in patients with pre-existing food allergies. These products contain oils and lecithins from soybean, egg, fish, and olive. Intralipid® does not list allergy to egg or soybean as a contraindication, whereas Smoflipid® lists allergies to egg, soybean, fish, and peanut as contraindications. The primary concern is that, although Ig-mediated reactions are typically not directed toward lipid molecules, there could be protein contamination from the listed sources. Of note, one study documented the lack of allergenic soy in Intralipid®.³² However, at least 3 of the patients described in our review with a prior history of food allergy then had a documented reaction to the related PN component. Finally, the American Academy of Asthma, Allergy, and Immunology advised that Propofol, a general anesthetic which contains soybean oil and egg lecithin, is not contraindicated in patients with egg or soy allergy.³³ Also, in our study, there were fewer reactions to IVFE after the year 2000, which may be due to improvements in the creation of these emulsions.

We have summarized the hypersensitivity reactions to PN that have been described in the literature and have generated an algorithm that can be used to manage PN in patients with

a hypersensitivity reaction. Given the relatively rare nature of this complication, it is unlikely that the management algorithm will ever be sufficiently tested. However, our study identifies the need for a global database to help improve diagnosis, characterization, and management of PN hypersensitivity.

Statement of Authorship

P. S. Goday contributed to the conception of the research; P. S. Goday, R. Sieracki, and V. J. Christian contributed to the design of the research; R. Sieracki and V. J. Christian contributed to the acquisition of the data; P. S. Goday, M. Tallar, C. L. S. Walia, and V. J. Christian contributed to the analysis and interpretation of the data; V. J. Christian drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix I: Search Strategy

Database: OVID MEDLINE

#	Search strategy
1	exp hypersensitivity
2	(hypersensitiv* or allerg*).mp.
3	(rash or exanthema*).mp. or exp exanthema
4	exp cross reactions/ or cross react*.mp.
5	(sensitiz* or intoleran*).mp.
6	exp anaphylaxis/ or anaphyla*.mp.
7	exp urticaria/ or urticaria*.mp.
8	exp angioedema/ or angioedema*.mp.
9	exp Dermatitis, Atopic
10	atopic dermatit*.mp.
11	atopic eczema*.mp.
12	exp dermatitis/ or exp eczema
13	(dermatiti* or eczema*).mp.
14	exp pruritis/ or pruriti*.mp.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp Parenteral Nutrition
17	(parenteral* and nutrition*).mp.
18	(parenteral* and feed*).mp.
19	(intravenous* and feed*).np. or (intravenous* and nutrition*).mp.
20	16 or 17 or 18 or 19
21	15 and 20
22	21 not (Animals/ not (Animals/ and Humans/))
23	remove duplicates from 22

Database: CINAHL

#	Search Strategy
1	(MH "Hypersensitivity+")
2	Hypersensitiv* OR allerg*
3	(MH "Exanthema")
4	Rash* OR exanthema
5	"cross react*" OR sensitiz* OR intoleran*
6	(MH "Anaphylaxis")
7	Anaphyla* OR urticaria* OR angioedema*
8	(MH "Urticaria+")
9	(MH "Angioedema")
10	(MH "Dermatitis, Atopic")
11	"atopic dermatit*" OR "atopic eczema"

12	MH eczema OR MH dermatitis OR (dermatit* OR eczema*)
13	MH pruritus OR pruritic*
14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
15	(MH "Parenteral Nutrition+") OR (MH "Parenteral Nutrition Solutions")
16	Parenteral* AND ((nutrition* OR feed*)
17	Intravenous* AND ((nutrition* OR feed*)
18	S15 OR S16 OR S17
19	S14 AND S18

Database: SCOPUS

#	Search Strategy
1	((TITLE-ABS- KEY (human* OR man OR men OR woman OR women OR child OR children OR pediatri* OR paediatric* OR patient OR patients OR adult OR adults OR adulthood* OR person OR persons OR people OR youth OR youths OR teenager* OR teen OR teens OR adolescen* OR infant* OR infanc* OR baby OR babies OR neonat* OR perinat* OR boy OR boys OR girl OR girls OR newborn* OR toddler* OR kid OR kids OR minor OR minors OR schoolchild* OR juvenile*))) AND ((TITLE-ABS- KEY (hypersensitiv* OR allerg* OR rash OR exanthema* OR sensitiz* OR intoleran* OR "cross react*" OR anaphyla* OR urticaria* OR angioedema* OR "atopic dermatitis" OR "atopic eczema*" OR dermatiti* OR eczema* OR pruriti*)) AND (TITLE-ABS- KEY ((parenteral* AND nutrition*) OR (parenteral* AND feed*) OR (intravenous* AND feed*) OR (intravenous* AND nutrition*))))

Database: Web of Science

#	Search Strategy
1	TS=(hypersensitiv* OR allerg* OR rash OR exanthema* OR sensitiz* OR intoleran* OR "cross react*" OR anaphyla* OR urticaria* OR angioedema* OR "atopic dermatitis" OR "atopic eczema*" OR dermatiti* OR eczema* OR pruriti*) AND TS=((parenteral* AND nutrition*) OR (parenteral* AND feed*) OR (intravenous* AND feed*) OR (intravenous* AND nutrition*)) AND TS=(human* OR man OR men OR woman OR women OR child OR children OR pediatri* OR paediatric* OR patient OR patients OR adult OR adults OR adulthood* OR person OR persons OR people OR youth OR youths OR teenager* OR teen OR teens OR adolescen* OR infant* OR infanc* OR baby OR babies OR neonat* OR perinat* OR boy OR boys OR girl OR girls OR newborn* OR toddler* OR kid OR kids OR minor OR minors OR schoolchild* OR juvenile*)