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Anaphylaxis to Total Parenteral Nutrition: Developing an Approach to Diagnosis and Management

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Abstract:	Background: A 13-year old male with spina bifida presented with ileus following bladder repair. Total parenteral nutrition (TPN) was infused and he developed urticaria, respiratory distress, and hypotension. Hypersensitivity reactions to TPN are a rare documented phenomenon with the potential to cause serious morbidity among patients. There is no standard detailed protocol for allergy testing of TPN hypersensitivity. The majority of available evidence resides in a limited number of case series and case reports, which have implicated lipid emulsions, vitamin, sulfites, magnesium sulfate and amino acid solutions as allergens. Objective: Our objective is to develop a standard protocol for diagnosing and testing TPN hypersensitivity, as some patients depend on TPN to maintain adequate nutrition. Methods: Through evidence collected in the presented case report and focused review of literature, we suggest an algorithm for TPN allergy testing with considerations including skin prick testing, intradermal testing, test doses, and desensitization. The patient in the presented case was given three different TPN test doses and had increasing severity of hypersensitivity reactions, ranging from mild reaction to anaphylaxis. Results: The patient in the presented case was most likely hypersensitive to the amino acid component of TPN. Conclusion: Hypersensitivity to TPN is rarely documented, and even fewer cases report hypersensitivity to amino acid solutions. Providers can use our suggested protocol on TPN allergy testing when they encounter TPN hypersensitivity, with the hope of reducing the risk of patient morbidity.
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TO THE EDITOR:

The manuscript has been read and approved by all the authors.

The requirements for authorship have been met.

The authors certify that they have (collectively) personally written at least 90 percent of the manuscript.

Authors' contributions:

Camille Vu conceptualized the study, interpreted the data analysis, drafted the manuscript, and approved the final manuscript.

James Quinn interpreted the data analysis, revised the manuscript, and approved the final manuscript.

Patrick Reeves conceptualized the study, oversaw management of the patient, obtained consent, and approved the final manuscript.

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Anaphylaxis to Total Parenteral Nutrition: Developing an Approach to Diagnosis and Management

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Abbreviations/Acronyms:
HSR: hypersensitivity reaction
IDST: Intradermal skin testing
LE: lipid emulsion
MVI: multivitamin
RAST: radioallergosorbent test
TPN: total parenteral nutrition
SPT: skin prick testing
PST: prick skin testing

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Introduction:

A 13-year old male with spina bifida presented with ileus following bladder repair. Total parenteral nutrition (TPN) was infused and he developed urticaria, respiratory distress, and hypotension. This challenging clinical case recommends a standard protocol to diagnose and treat TPN hypersensitivity.

Hypersensitivity reactions (HSR) to total parenteral nutrition (TPN) are a rare documented phenomenon with the potential to cause serious morbidity among patients. Christian *et al* recommended an algorithm for the management of hypersensitivity to parenteral nutrition, but there is no standard detailed protocol for allergy testing.[1] The majority of available evidence resides in a limited number of case series and case reports. Most commonly, varied methods of open challenges have been used to determine a presumptive component or antigen. Less commonly, a small number of case reports have described varied methods of limited skin testing to differing components and possible antigens that are difficult to generalize or determine performance characteristics (Table 1). Several reports described ultimate success in using parenteral nutrition after removing the identified components or antigens. The components most frequently identified were lipids and multivitamins (MVI). Less commonly, individual possible elements or antigens were suggested by skin testing or open challenge; those included amino acid solutions,[1] magnesium sulfate,[2] sulfites,[9, 15] polysorbate 80,[6, 8] hydroxytoluene (BHT), [8] butylated hydroxyanisole (BHA), [8] and individual vitamin components.[4]. This challenging clinical case illustrates an unusual case of progressively worsening HSR to TPN despite successive open challenges eliminating all the commonly identified components associated with

HSR. The accompanying literature review (Table 1) examines the different components associated with TPN HSR and the methods of challenge and testing used. Finally, we use these reports to suggest an approach to the diagnosis and identification of allergens in patients with TPN HSR (Figure 1).

Methods:

A 13-year-old Hispanic male with spina bifida and neurogenic bowel and bladder was admitted to the pediatric intensive care unit for bladder rupture and urosepsis requiring emergent surgical repair.

The patient had a known latex allergy causing urticaria. There was no history of asthma or food allergies. Four months prior to this admission, he had a HSR to TPN 1 (Table 2) containing amino acids, dextrose, LE, electrolytes, and MVI. **Thirty minutes into infusion, he developed a neck rash that resolved after discontinuing the infusion; no medications were administered.** TPN 1 was restarted 1.6 hours later, and 30 minutes into infusion, he developed a progressive erythematous rash on his neck, torso, and extremities, temperature to 100.4 F and an elevated heart rate. The patient denied dyspnea, wheezing, abdominal pain, diarrhea or constipation.

During this admission, TPN was initiated for nutritional support due to prolonged intubation. He had central access and close monitoring. Given his history of a prior HSR to TPN, he was initially trialed on TPN 2 (Table 2) without LE, but with amino acids, electrolytes, and multivitamins. **Seventy-five minutes into infusion, he developed diffuse urticaria,**

tachycardia, and increased mean arterial pressure. After discontinuing the infusion and giving diphenhydramine, the heart rate normalized within a few minutes and the rash resolved after two more hours. Epinephrine was not administered, but available at bedside.

Due to the patient's ongoing malnutrition, a further trial of TPN 3 (Table 2) was attempted. TPN 3 was a sulfite-free pre-mixed TPN containing only amino acids, dextrose, and electrolytes; MVI and LE were eliminated. **After five minutes of infusion, he developed hypotension, decreased heart rate and diffuse urticarial rash.** Diphenhydramine was given. Epinephrine was ordered to the bedside, but not administered as symptoms resolved prior to medication arriving.

Results:

No further TPN was infused. On hospital day 8, the patient received methylnaltrexone to reverse opioid-induced constipation, transitioned to gastro-jejunal feeds, then on day 14 started soft mechanical diet and eventually discharged home on day 22 with allergy and immunology follow up. The hypersensitivity to TPN was documented in the medical record and reported to TPN companies as severe reaction to TPN, likely amino acid component.

Discussion:

Drug related HSR are clinical syndromes that vary in presentation and underlying pathophysiology by IgE mediated, complement mediated, and other immunologic mediated mechanisms. They can be associated with varied biomarkers including identification of specific

IgE, tryptase levels, selected HLA types, and shared biosimilarities (i.e. aspirin associated).[19]

The literature suggests that varied presentations and pathophysiology are at work in TPN HSR. Presentations have ranged among immediate anaphylaxis, vasculitic, cutaneous, and delayed and/or prolonged cutaneous reactions.[1] The understanding of TPN HSR pathophysiology has been further confounded in some cases by dose dependency, rate dependency and/or incomplete evaluation.[11, 12] Given this heterogeneity it is not surprising that the cases reported in the literature have used different approaches to attempt to continue TPN use in patients after a reaction. Approaches have varied from full-dose rechallenges, reduced dose challenges, to desensitization and have variably employed skin testing and/or alternative products. These methods have met with varied success in attempts to identify a safe method to support these unique patients with parenteral nutrition.

Based on TPN trials with and without lipids, MVI, and Neotrace-4 elements (Table 2), it appears that our patient was hypersensitive to a component of the amino acid solution. The patient had a latex allergy, but there is no known cross reactivity between latex and TPN. The TPN solutions, bags, and pharmacy equipment and clinical areas were strictly latex-free.

Our patient developed immediate mild to severe HSR, with increased severity on repeat exposure to different TPN compositions, which highlights the need for providers to recognize and manage HSR. Despite repeated open challenges after elimination of the most common identified components and sources for HSR, he did not tolerate parenteral nutrition and non-enteral support was elected to mitigate further risk of reaction. Our challenging clinical case is similar to many

discussed in the literature in which a culprit agent was not identified as having caused the TPN HSR. By extension, our case demonstrates the need for further research to better consolidate the inconsistencies of clinical approaches to TPN HSR. In doing so, a standardized approach could be formulated which would facilitate appropriate TPN selection for a patient following a HSR event. Christian *et al* recommended an algorithm for the management of hypersensitivity to parenteral nutrition. Our evaluation of this TPN HSR case and the available literature has yielded a detailed protocol for allergy testing and rechallenges, especially in cases of severe HSR

Diagnostic capabilities to evaluate TPN HSR are limited. Review of the literature provides inconsistent evidence as to whether skin prick testing (SPT) reliably predicts future reactors vs. non-reactors. Analyzing the literature reveals discrepancies in concentrations tested non-standardized or incompletely described testing agents; inconsistent or incomplete description of criteria for positive testing; and lack of control subjects. Of note, the individual components of TPN were not always available for use during the diagnostic phase.[10, 12, 14, 20] Few studies used a human control to decrease false negative results for SPT.[2, 3, 4, 6] . Review of the literature demonstrates that SPT, intradermal injections, basophil activation (single case), and/or patch testing (single case) were considered positive by the authors to components of TPN HSR in 53% (8/15, Table 1) where testing was done. The small number and limited use of controls and limited use of confirmatory challenges prevent any valid estimation of positive or negative predictive values of the testing. However, there were no serious adverse events described to the testing including intradermal testing to full strength and super-concentrations above full strength.[2, 3, 4, 12] In three cases, positive skin tests were used to select alternative agents or to direct the elimination of a component of the TPN allowing the other components to continue

116 successfully.[9] Additionally, food testing for egg, soy, legume led to the elimination or successful
117 substitution of lipid products based on differing food based sources of the lipid emulsion in three
118 cases.[5, 7, 21]
119
120 We believe that SPT should be performed in severe HSR and/or when the allergen is unable to
121 be identified, such as with our patient. In patients experiencing a severe HSR and when the
122 allergen is unable to be identified, it seems reasonable and safe to consider skin testing in the
123 evaluation. In keeping with the identified cases and the Allergy Diagnostic Testing Practice
124 Parameter, SPT could be performed undiluted, starting with all individual components in the
125 patient's TPN, such as amino acid solution, LE, and MVI (Figure 1).[22] If there is a positive test,
126 then individual ingredients can be tested, and might be obtained from the manufacturer. If the
127 SPT results are negative, the next step is intradermal testing with 1:1,000 – 1:100 dilutions.
128 Three studies used super-concentrated, undiluted, and/or 1:10 dilutions safely but lack of
129 controls limits the ability to assess possible irritating concentrations.[3, 4, 12]
130
131 If the testing was positive for LE sensitivity, then different LE made from soybean and safflower
132 oil can be skin tested. If LE triggered a HSR, they should be tested for egg, soy, or peanut
133 protein allergies, as manufacturers state these are contraindications to LE use.[23] If Intralipid
134 caused HSR, Liposyn II was found to be tolerable (Table 1).[11]
135
136 In further exploring the role of skin testing, there is debate on the influence of soy or food allergy
137 and TPN HSR, particularly to lipid emulsion.[1, 20, 23] Some samples of soybean oil were found to
138 contain very low but measurable quantities of soy proteins but immunoblotting with sera from

patients with soy allergy did not show any IgE binding.[24] Several studies performed radioallergosorbent testing (RAST), which was positive for egg white, egg yolk, and soybean in cases of suspected LE HSR. Manufacturers state egg, soy, or peanut protein allergies are contraindications to LE use.[24]

If the testing was positive for the amino acid solution, then different amino acid solutions can be skin tested first, such as vegetable oil-based amino acid solution (ClinOleic) and the lower sulfite containing Neoparen 2 (Table 1).[9, 14] Our patient has reacted negatively to TPN containing sulfite-free 10% FreeAmin II,[I6] 15% Aminosyn II,[17] and Clinimix E,[18] amino acid solutions. Clinimix E is premixed TPN with manufacturer-reported anaphylaxis.[18] Therefore, different TPN admixtures with electrolytes can be skin tested: Nutriflex[25] (amino acids and dextrose), or Kabiven and Perikabiven (lipid, amino acids and dextrose).[26] Perikabiven has manufacturer-reported allergic and anaphylaxis reactions during post-approval use.[26] TrophAmine and Travasol are amino acid solutions that contain bisulfite, causing HSR in two case reports.[9, 15]

If the testing was positive for vitamin sensitivity, then testing for polysorbate,[6] individual vitamins such as B complex,[4] or different vitamin solutions can be performed.[2]

If all testing is negative, then magnesium, aluminum, and trace elements can be considered. Decreasing the osmolality of TPN to below 1391-1928 mOsmol/kg was found to resolve HSR in one study.[27] One study found that Intralipid caused HSR, but later on was tolerated, so contaminant with egg was hypothesized.[11] Oral challenges can be considered, and have been performed with MVI, ingesting intravenous MVI,[12] and metabisulfite with negative results.[3]

If skin testing is negative – or if it is not performed due to lack of availability, contraindication, or provider/patient choice and TPN remains indicated despite the risk – then challenge dosing may be indicated. Most of the cases that pursued challenges after the initial reaction, simply rechallenged with full strength components. Pre-medications were generally not used or not commented upon with few exceptions. One case report under pharmacist recommendation used 30 mL IV infusion trials, with pre-treatment of diphenhydramine and hydrocortisone, but patient still had immediate reactions attributed to multivitamin after passing the 30 mL test dose.[23] Our patient developed reactions after 13-96 mL solutions containing different amino acids (Table 2). Concerningly, on several occasions, full strength challenge resulted in severe HSRs; however, no fatalities were reported. We recommend a more conservative approach to challenge, outlined in three studies where there where milder or no reactions occurred. The initial challenge dose could begin with either 1% the daily dose or 1 mL (whichever is less) of the individual component.[5, 10] If those results are negative, then the patient could be challenged with the individual component starting at 25 mL/hr IV of 180 mL total for an adult.[11] We recommend that rechallenges could be performed in mild to moderate HSR, but each challenge should involve single components for easy identification of triggers. For severe HSR, graded challenge possibly guided by skin testing may be an option, but if the risk versus benefit indicated that a positive element was needed, then desensitization could be considered over challenge dosing. A single successful report of desensitization using the method described by Castells provides another alternative.[28]

Our patient is at increased risk for future surgeries and nutritional need for TPN. Based on TPN trials with and without lipids, MVI, and Neotrace-4 elements (Table 2), it appears the patient was

hypersensitive to the amino acids solution, although the full allergy testing discussed above was not initially performed. He was able to tolerate IV fluids of dextrose 15% with electrolytes, no MVI, no trace elements, and no amino acids. Until he undergoes TPN allergy testing, if he requires protein for nutritional support, 25% albumin can be considered instead of amino acids. Future studies can examine how amino acid formulations are derived and its impact on hypersensitivity. Desensitization for prolonged TPN can be further explored. In scenarios involving prolonged TPN and withholding certain components due to HSR, we recommend consulting dietitians and pharmacists to ensure adequate nutrition.

Hypersensitivity to TPN is rarely documented, and even fewer cases report hypersensitivity to amino acid solutions. Based on our case results and review of literature, we suggest a protocol to approach the diagnosis and management of TPN HSR with considerations including skin prick testing, intradermal testing, test doses, and desensitization. Providers should be aware that LE, vitamin, sulfites, magnesium sulfate and amino acid solutions have been implicated as allergens.

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Table

Table 1. Literature Review of Allergy Testing Results

First Author	Patient Age (years)	Parenteral nutrition component implicated in hypersensitivity	Atopic/allergic history	Skin Prick Testing (SPT), Intradermal testing, or Patch test Result and Protocol if available	Other Tests	Timing of test after HSR	Volume tested or that provoked reaction	Tolerated Alternative Treatment
Positive Skin Testing Cases								
1987 Pomeranz[2]	4	Travasol /Magnesium/MVI-12	NA	Skin prick test equivocol to MgSO4 (2/7 wheal and flare). Intradermal test positive to undiluted Travasol, magnesium, and MVI-12; negative for 1:1000 dilution. Tested Viaflex tubing, Travasol bisulfite amino acid solution, magnesium sulfate 50%, zinc chloride, Calcium (Sandoz), two different MVI solutions, saline, histamine control.		10 weeks		
1998 Market[3]	4	Multivitamin and Aminosyn	NA	Positive 1:10 diluted MVI skin prick testing. Positive intradermal injections of 1:10 and 1:100 fresh TPN and 1:10 Aminosyn 10%. Tested original solutions with newly opened solutions, starting with an initial 1:10 dilution skin-prick test that, if results were negative, was followed by intradermal injection of 1:10 and 1:100 dilutions of the same substance. After testing original and fresh TPN, lipid emulsion, and undiluted Aminosyn 10% and pediatric MVI.	Negative metabisulfite oral challenge	4 days		
2002 Wu[4]	8	Multivitamin	NA	Intradermal test positive to vitamin B complex solution (B1, B2, B6, nicotinamide, sodium pantothenate, calcium pantothenate) in 1:1, 1:10, and 1:100 dilution.		1 year		
2005 Gura[5]	17	Intralipid	Peanut (anaphylaxis), soy	Skin test positive for several foods including soy, peanut			Rechallenge: 1% of the daily dose (0.2 ml, 40 mg) intravenously, caused HSR	Omegaven, soy-free and fish-oil based lipid emulsion, required US FDA permission

2005 Coors[6]	30	Multivitamin	Oral allergy syndrome (apple, pear, peach, cherry, hazelnut-containing cross-reactive allergens homologous to birch pollen allergens), seasonal allergies	Skin prick positive to Multibointa and its component polysorbate 80. SPT on Multibionta, latex fluids, extracts from pollen and molds (eg, Alternaria, Cladosporium, and Aspergillus species), and preservatives following Dreborg methods. SPT separately performed on ingredients of the multivitamin preparation.	Enzyme-linked immunosorbent assay, IgE immunoblotting, and flow cytometric detection of basophil activation	4 months after delivery		Stop infusion, resume enteral feeds
2011 Lunn[7]	2	Intralipid	Egg (emesis)	Skin prick positive to egg (negative to peanut and soy).	Immunocap serum testing positive to egg yolk and egg white, total IgE 10.7IU/mL		After 14 days of 3 g/kg/day of Intralipid. No testing volumes given	Stop infusion, resume enteral feeds
2014 Ghatak[8]	19	Intralipid	No known allergies	Skin testing positive to soy, Intralipid, propofol. Negative to penacillin				
2015 Honda[9]	50	Bisulphite component of Aminotripa	NA	Patch test positive to Aminotripa (0.04% sodium bisulphite) and sodium bisulphite (0.1% and 1%). Negative patch test to Neoparen 2 (infusion with 0.002% sodium bisulifite).			1800 mL, reacted on day 3	Neoparen 2, with lower concentration of sodium bisulite (0.002%)
Negative Skin Testing Cases								
1981 Kamath[10]	9	Intralipid		Skin tests negative to normal saline and intralipid. Positive histamine.		2 days	Rechallenge on day 3: 1 ml of Intralipid was given intravenously, causing reaction	
1991 Buchman[11]	36	Intralipid	NA	Negative skin prick to soy oil, safflower oil or samples of Intralipid or Liposyn II.	RAST positive to egg white, egg yolk, soy bean.			Liposyn II (prepared from equal quantities of safflower and soybean oil)
2005 Scolapio[12]	53	Multivitamin	Sulfa drugs, skin reaction to fabric softener Snuggle, dust, mites, seasonal allergies	Skin test negative to MVI and MVI + TPN mixed in a 0.9% saline solution at 1:10 dilution, full strength (10 mL in 2.0 L normal saline, 0.005%), twice full strength (0.001%), and 4 times full strength (0.02%).	Serum tryptase and 12-hour urinary histamine level during PN infusion containing the multivitamin was unchanged from baselin. Oral MVI		PN+MVI reaction at 2 hours. Continuous 90 mL/hr infusion, reacted on day 16. Also, her symptoms were not observed until 2 hours into the cyclic infusion, when the rate of the PN reached 182 mL/h.	Oral MVI

					chewable no rxn, IV liquid MVI from TPN taken orally no reaction.			
2011 Babakissa[13]	4 days		NA	Skin prick tests negative to histamine, Travasol, Intralipid, MVI, egg yolk extract, and egg white extract.	Day of reaction: normal CBC, eosinophils, total immunoglobulin E (IgE), and C-reactive protein. RAST negative for white and yellow egg, soy, and latex.	7 days, 3 months, and 22 months	Not performed	Discontinued TPN, breast fed, discharged at 11 days old
2016 Hernandez case 1[14]	1 month	Multivitamin	NA	Negative skin prick tests				Excluded MVI and trace elements from infusion
2016 Hernandez case 2[14]	4	Amino acid solution (Aminosol)	NA	Negative skin prick tests				Aminovent infant
2016 Hernandez Case 3[14]	10	Smoflipid	Fish	Negative skin prick tests				Vegetable oil-based amino acid solution (ClinOleic)

Table 2. Three Total Parenteral Nutrition (TPN) Characteristics. TPN 1 was given 4 months prior to this pediatric intensive care unit admission. TPN 2 and 3 were given on hospital day 9 and 10 respectively.

	TPN 1	TPN 2	TPN 3
TPN Component			
Amino Acid Type	FreAmine III 10%[16]	Aminosyn ll 15% Sulfite free[17]	Sulfite Free Clinimix E[18]
Unusual components of amino acid	Sodium bisulfite (antioxidant), Aluminum	Aluminum	
Total Volume Prepared (without lipids) (mL)	2040	1920	2000
Amino Acid Concentration	3.4%	3.4%	5.0%
Dextrose Concentration (%)	12.5%	12.5%	15.0%
Energy from Carb (%)	54.1	75.8	71.8
Energy from Protein (%)	17.2	24.2	28.2
Energy from Fat (%)	28.7	0	0
Amino Acid (g)	69	65	100
Nitrogen (g/L)	0	1	16.52
Intralipid (g)	46	0	0
Sodium (mEq)	92	141	70
Potassium (mEq)	59	60	60
Magnesium (mEq)	11.5	20	10
Calcium (mEq)	5	25	9
Acetate (mEq)	0	47	160
Chloride (mEq)	121	144	78
Phosphate (as HPO4) (mmol)	30	10	30
Gluconate	5	25	0
Sulfate	11.5	20	0
Infuvite Adult MVI (mL)	10	10	0
Neotrace-4 elements (mL). Each mL contains: 6.6 mg zinc sulfate heptahydrate. 0.39 mg cupric sulfate pentahydrate. 77 mcg manganese sulfate monohydrate . 4.36 mcg chromic chloride hexahydrate	3	3	0
Famotidine (mg)	20	0	0
Osmolarity (mOsmol/L)	1125.65	1154.16	1350
Kcal/day	1603	1076	1420
Volume Infused (mL)	43	96	13.3
Dose Amino Acid Administered (g)	1.4	3.3	0.7
Rate (mL/hour)	85	80	80
Time from infusion start until reaction (min)	30	75	5
Grade of Hypersensitivity	1 (mild, cutaneous only)	2 (moderate, anaphylaxis)	3 (severe, anaphylaxis with cardiac or pulmonary symptoms)

Figure

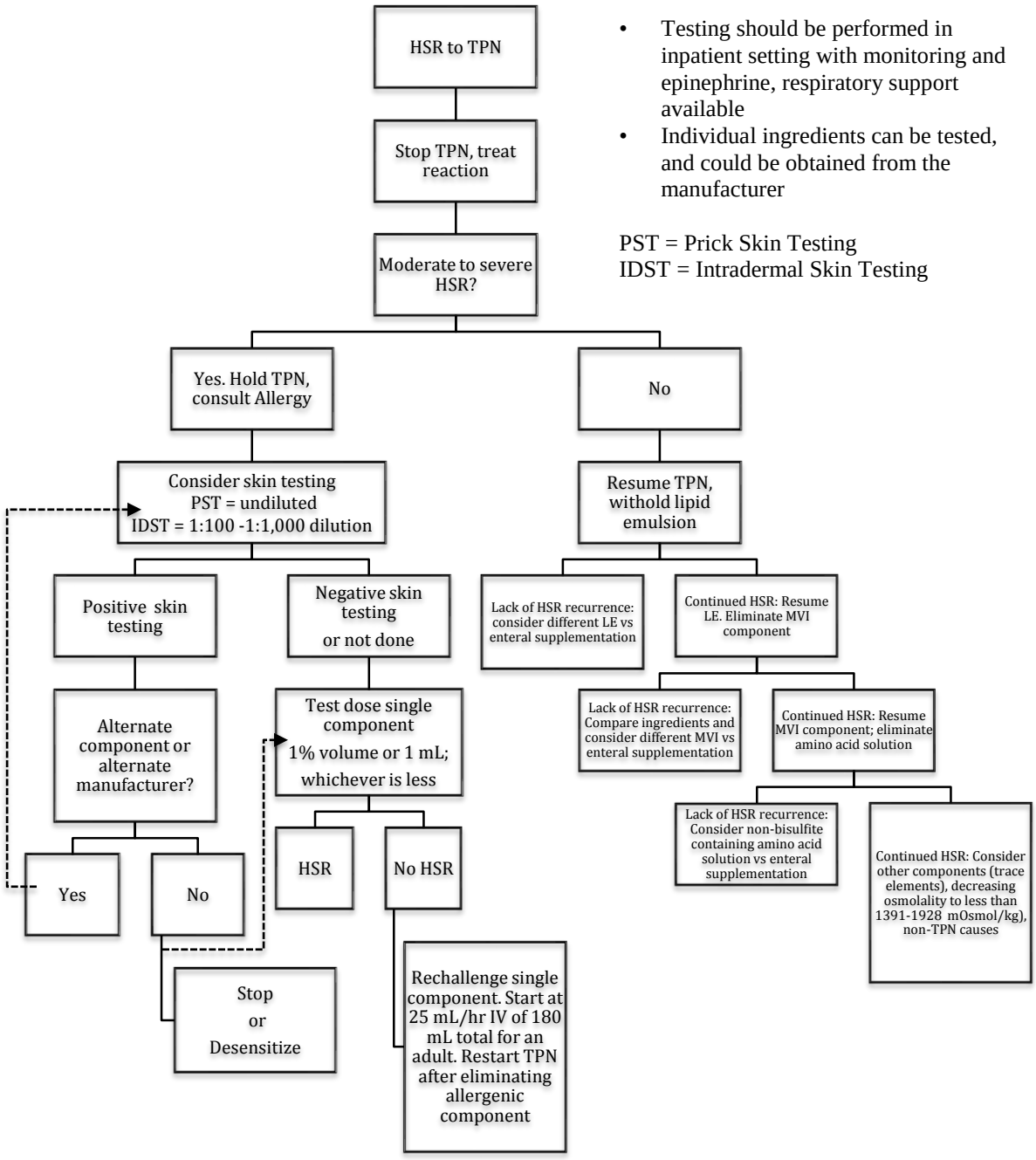

Figure 1. Our suggested diagnostic algorithm for skin testing and challenging total parenteral nutrition (TPN) hypersensitivity reactions (HSR). Adapted with permission from Christian *et al.*[1]

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