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Revisiting Infectious Complications Following Total Parenteral Nutrition Use During Hematopoietic Stem Cell Transplantation

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Abstract

Background: Total parenteral nutrition (TPN) is frequently used to manage caloric needs during hematopoietic stem cell transplantation (HSCT). Previous studies in transplant patients who received TPN have reported widely discordant results with regard to infection and mortality, and risk factors for TPN-related infection remain unclear. **Method:** We conducted a retrospective study of all HSCT recipients treated with TPN between 2005 to 2014 at Northwestern Memorial Hospital to determine the incidence and epidemiology of infections. Electronic records were used to identify patients treated with TPN for at least 2 days who developed infection. **Results:** Among 198 patients treated with TPN, 30% developed documented infection. Total parenteral nutrition treatment duration (13 vs. 7 days; $p < .0001$) and the timing of TPN initiation (> day 9 post HSCT; $p < .0001$) were significantly higher in patients who received TPN and developed infection. Receipt of an allogeneic transplant was associated with increased risk for infection ($p < .0138$), and day 60 mortality was significantly higher in TPN-treated patients with infection ($p < .0001$). **Conclusion:** Stem cell recipients who receive TPN, especially from an allogeneic donor, have high rates of infection and mortality. Minimizing TPN exposure may reduce the chance for infection.

Severe gastrointestinal complications develop frequently during hematopoietic stem cell transplantation (HSCT). Chemotherapy-induced nausea and vomiting (CINV), pain, dysgeusia, fatigue, mucositis, and loss of appetite cause pain and discomfort, and frequently impair oral nutrition. Total parenteral nutrition (TPN) has been shown to improve nutritional status, and guidelines

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recommend starting TPN in HSCT recipients who are unable to maintain 50% of their recommended caloric intake (August, Huhmann, and the American Society for Parenteral and Enteral Nutrition [A.S.P.E.N.] Board of Directors, 2009).

Administration of TPN is not without complications. Results from older studies reported trends toward increased risk for infection associated with TPN use, but with no difference in overall mortality (Lough et al., 1990; Marena et al., 2001; Piñana et al., 2013; Roberts, Miller, Pineiro, & Jennings, 2003; Szeluga, Stuart, Brookmeyer, Utermohlen, & Santos, 1987; Weisdorf et al., 1987). These randomized studies generally administered TPN throughout the entire hospital admission period instead of for shorter periods of time as it is typically used in clinical practice today. Over the past 20 years, new preparative regimens and antimicrobial agents, changes in stem cell donor sources, and emergence of multidrug-resistant organisms likely influence the incidence, spectrum of microorganisms, and clinical outcomes for HSCT recipients treated with TPN, yet new data are lacking. A retrospective study of all HSCT recipients treated with TPN at Northwestern Memorial Hospital between 2005 to 2014 was conducted to determine the prevalence and epidemiology of infections, and identify potential risk factors associated with TPN use.

METHODS

Electronic medical records were used to provide data for all autologous and allogeneic HSCT recipients treated with TPN between January 2005 to December 2014 at Northwestern Memorial Hospital (NMH). Total parenteral nutrition was empirically initiated for severe gastrointestinal adverse events (mucositis, intractable nausea and/or vomiting, gastrointestinal infection, or persistent dysgeusia), with the expectation that patients would not be able to meet at least 50% of their nutritional needs for 5 to 7 days. Patients treated with TPN for graft-vs.-host disease were not included. All patients received at least 48 hours of TPN treatment. Total parenteral nutrition was formulated using standard dextrose, amino acid, and soybean oil fat emulsion and administered through a peripherally inserted central catheter that was generally inserted upon admission to the hospital per stem cell protocol. Serum glucose levels were controlled by the managing service with consultation from the department of endocrinology. Total parenteral nutrition was discontinued when the patient's oral intake exceeded 50% of their nutritional requirements for 2 consecutive days. The study period began upon hospital admission and ended upon initial hospital discharge.

Antimicrobial prophylaxis included acyclovir, fluconazole for autografts, and voriconazole for allografts, and ciprofloxacin. Patients with febrile neutropenia were switched to broad spectrum β-lactam antibiotics. Growth factor support was given routinely for autologous but not allogeneic stem cell recipients. All microbiologically confirmed bacterial and fungal cultures isolated after TPN had been started were included (infection episodes from microorganisms commonly associated with colonization or contamination, such as coagulase-negative staphylococci and others, required two positive cultures from distinct sites drawn peripherally and from the central intravenous line). Viral isolates were excluded. Culture specimens were obtained from urine, blood, and any other appropriate sites, and a chest x-ray was obtained within the first 24 hours. Blood culture specimens were obtained daily while the patient remained febrile. Standard infection precaution measures were maintained throughout the study period.

Statistical analyses were performed by using t-test for difference in group means of continuous variables. Nonparametric test (Wilcoxon rank-sum test) was used when comparing groups with data that were not normally distributed. Chi-squared or Fisher's exact test was used for difference in frequency counts of categorical variables.

RESULTS

One hundred and ninety-eight of 1,369 patients (14%) who underwent HSCT during the study period received TPN. Most patients (92%) received a myeloablative conditioning regimen. Table 1 shows patient demographics for stem cell recipients who did or did not receive TPN during the same time period. There was no significant difference in age, gender, diagnoses, or donor source.

Figure 1 shows the distribution of days when patients were started on TPN. Median day to start

TPN was day +8 after stem cell infusion (range: 0–48 days). Median TPN treatment duration was 8 days.

Table 2 compares microbiologically confirmed infections in autologous and allogeneic stem cell recipients who received TPN. Among 198 TPN-treated patients, a total of 103 isolates were documented in 58 (30%) patients. Overall, allogeneic stem cell recipients had significantly higher rates of infection compared to autologous patients ($p < .0013$). Gram-positive infections were the most frequently identified organisms and were more prevalent in allogeneic stem cell recipients. Among 26 patients previously colonized with vancomycin-resistant *Enterococcus* (VRE), 7 (27%) developed VRE infection. Gram-negative infections (GNI) were seen in 12 (10%) and 12 (15%) of autologous and allogeneic SCT recipients, respectively ($p < .3759$). Six of these GNI cases (25%) were caused by extended spectrum β-lactamase–producing organisms, 3 (38%) of which came from a pool of 8 patients who were colonized before TPN was started. Of the 10 proven fungal infections, 7 were caused by organisms that were resistant to fluconazole and voriconazole prophylaxis, including 6 cases of *Candida glabrata*, of which 4 were isolated from the bloodstream and 2 from bronchoalveolar lavage (BAL) specimens and 1 case of Mucor isolated from a BAL specimen. Overall, polymicrobial infection was seen in 22 patients (11%) and occurred in 38% of all patients with infection. The rate of *Clostridium difficile* infection was higher in allogeneic SCT recipients; however, the rate did not reach statistical significance ($p < .0709$). The bloodstream was the major source for all documented sources of infection and occurred significantly higher in allogeneic recipients ($p < .0301$). Pulmonary infections also occurred more often in allogeneic SCT recipients ($p < .0022$).

Figure 2 shows time to infection after TPN was started. The median time to infection was 6 days after TPN started, with more than 80% of infections occurring within 9 days of TPN initiation. More than 85% of patients were neutropenic at the time of infection.

Table 3 compares TPN-treated patients who did or did not develop infection. There was no difference in age or gender between groups. Most patients from both groups were neutropenic (> 87%) when TPN was initiated. Compared to autografts, receipt from either a matched sibling or unrelated allogeneic stem cell donor was identified as a risk factor for infection ($p < .0138$). Total parenteral nutrition treatment duration was significantly longer in patients who developed infection (13 vs. 7 days; $p < .0001$), and TPN-treated patients with infection were found to have initiated TPN at a later day post-stem cell infusion compared with TPN-treated patients without infection (day 10 vs. day 7; $p < .0004$). Day 60 mortality was significantly higher in allografts ($p < .0011$, overall response rate: 2.89, 95% confidence interval = 1.54–5.43).

Table 1. Patient Characteristics

	TPN (%)	No TPN (%)	*p* value
Autologous SCT			
Number	118	867	
Age, median (range)	58 (19–78)	59 (21–76)	.21
Female gender	52 (44)	315 (36)	.2455
Diagnosis			
Multiple myeloma	77 (65)	644 (74)	.11
Non-Hodgkin lymphoma	26 (22)	160 (18)	.313
Hodgkin disease	8 (7)	36 (4)	.224
Other	8 (7)	54 (8)	.33321
Allogeneic SCT			
Number	80	303	
Age, median (range)	52 (19–76)	52 (18–72)	.1428
Female gender	40 (50)	139 (45)	.4516
Diagnosis			
Acute myeloid leukemia	45 (58)	146 (47)	.1075
Non-Hodgkin lymphoma	11 (14)	52 (17)	.6114
Acute lymphocytic leukemia	6 (8)	28 (9)	.8253
Myelodysplastic syndrome	5 (6)	16 (5)	.558
Other	13 (13)	69 (22)	.0827
Donor source			
Matched sibling	52 (64)	211 (68)	.5006
Unrelated donor	28 (36)	98 (32)	

Note. TPN = total parenteral nutrition; SCT = stem cell transplant.

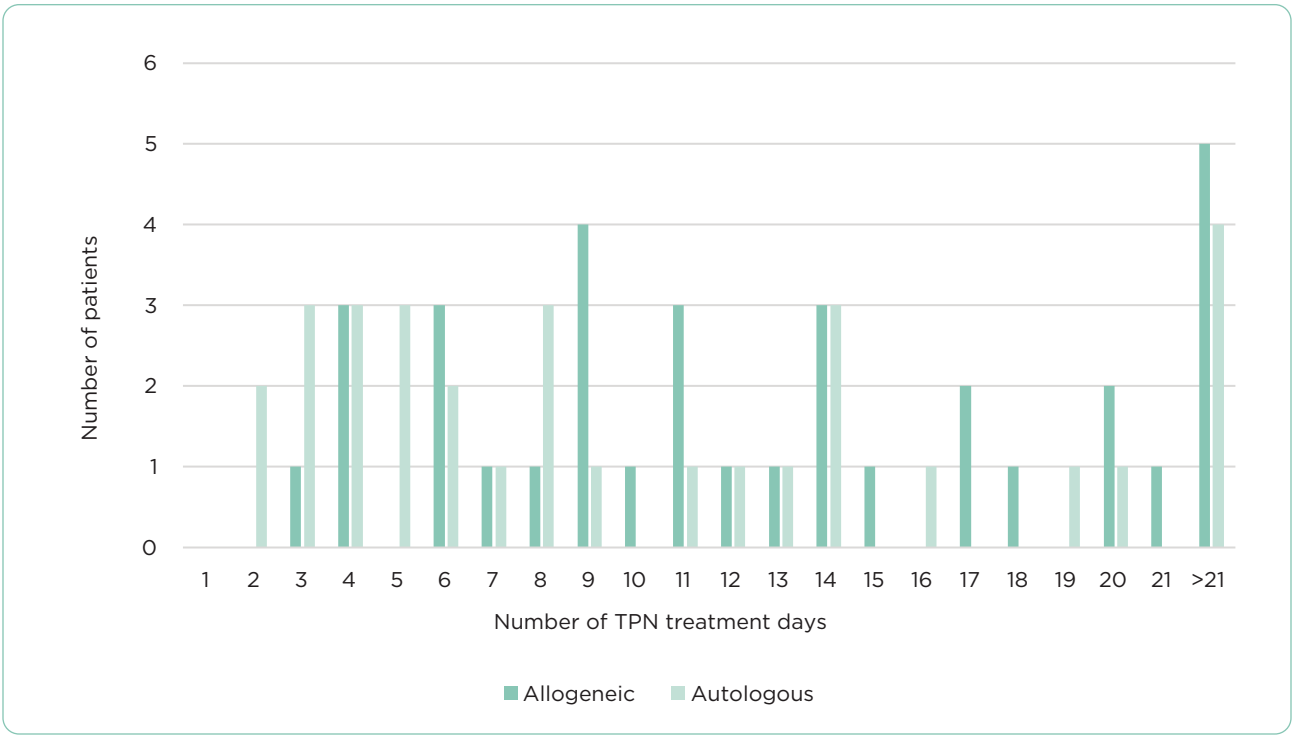

Figure 1. Number of total parenteral nutrition treatment days in patients with infection.

DISCUSSION

Gastrointestinal toxicities are common during hematopoietic stem cell transplantation and are a source of morbidity and mortality. Deciding when to initiate TPN is challenging. Guidelines recommend that patients with significant reductions in caloric intake for more than 5 to 7 days should trigger consideration for initiating TPN (August et al., 2009); however, a lack of a clear association between improved nutritional parameters and survival, and the potential toxicities associated with TPN use, have led some investigators to question the advisability of these recommendations (Arfons & Lazarus, 2005; Baumgartner et al., 2017). The current study shows autologous and allogeneic stem cell recipients who receive TPN have high rates of infection, and the risk for infection is related to donor source, TPN treatment duration, and time of initiation. Overall mortality, especially in patients who undergo allogeneic stem cell transplantation, is significant.

The epidemiology of infection in the current study is similar to results reported from other transplant centers (Piñana et al., 2013; Roberts et al., 2003) and from studies in cancer patients (Dimick et al., 2003; Marena et al., 2001; Nucci et al., 1998). Gram-positive microorganisms, primarily from the bloodstream, were the most frequent cause of infection. Infections caused by gram-negative microorganisms occurred less frequently; however, a significant number were multidrug resistant and polymicrobic, which are known risk factors for poor outcomes (Trifilio et al., 2015). Somewhat surprisingly, auto- and allograft patients had equal rates of fungal infection.

We identified the duration of TPN use as a risk factor for infection. Intuitively this makes sense, yet other study results have shown variable and even paradoxical results with regard to length of TPN treatment and rates of infection. One study reported the duration of total parenteral nutrition was longer in cases that did not develop infection (Snydman, Murray, Kornfeld, Majka, & Ellis, 1982). Within the transplantation setting, the connection between TPN duration and risk for infection is largely unknown. As previously mentioned, bloodstream infections were found to be the major source of infection in TPN-treated patients. It is well established that central line catheter–related infections increase with duration of catheter use (Dimick et al., 2003). In the same vein, in neutropenic patients, the chance for developing an infec-

tion increases with the duration of neutropenia (Li, Shih, Klippel, Reiner, & Page, 2014; Piñana et al., 2014). Collectively, the effects of these two risks factors appear to coincide well with the time to infection (Figure 2) seen in our study.

It is unclear why TPN-treated patients who develop infection were found to have started TPN at a later day post-transplantation compared to TPN-treated patients without infection (day +10 vs. day +7). This has not been previously reported. Neutropenia and mucositis normally develop around day +5 and lasts for 7 to 14 days. One can only speculate that the cumulative effect of additional days of prolonged and profound neutropenia and mucositis somehow places patients at a higher risk for developing infection. Further study is needed to validate this surmise.

The study design and primary objectives of this study differ significantly from earlier randomized trials. Older studies treated patients with TPN throughout the neutropenic and non-neutropenic periods, usually lasting 3 to 4 weeks. In contrast, we believe the current study, albeit retrospective, more clearly reflects TPN use and infection as seen in clinical practice today, during short periods of time when patients are profoundly neutropenic and experiencing high levels of gastrointestinal toxicities.

Whether TPN causes infection or infection is caused by other conditions that exist during transplantation which prompts TPN use is difficult to discern. A recent observational study that included 22 stem cell recipients treated with TPN reported an increased risk for infection in patients colonized with multidrug-resistant organisms (Ferreira et al., 2018). The current study also observed a relatively high percentage of gram-negative (38%) and vancomycin-resistant *Enterococcus faecium* (27%) infections that came from the pool of patients previously colonized with multidrug-resistant organisms.

One could also reasonably argue that TPN-treated patients have increased risk for infection because they experience more severe mucositis, a known risk factor for gut-related infections (McCann et al., 2009; Ohbayashi et al., 2008; Sonis et al., 2004; Vera-Llonch, Oster, Ford, Lu, & Sonis, 2007). Assessing mucosal injury is difficult, as most of the gastrointestinal tract cannot be directly visualized during clinical examination. In the current study, infection rates caused by organisms typically associated with mucosal translocation through damaged epithelium (*Enterobacteriaceae* species and viridans streptococci) were 10% and 5%, respectively. By way of comparison, in a well-matched population of SCT recipients treated at Northwestern Memorial Hospital during the same time period who did not receive TPN, gut-related infections from GNI were 3% ($p < .005$) and viridans strep-

Table 2. Documented Infections in Total Parenteral Nutrition–Treated Patients (Total Isolates = 103)

Infection	No. (%)	*p* value
Patients with infection	58 (30)	$p < .0013$
Autologous	24 (20)	
Allogeneic	34 (43)	
Polymicrobic	25 (11)	$p < .01412$
Autologous	10 (10)	
Allogeneic	15 (19)	
Gram-positive species	56 (28)	$p < .0013$
Autologous	22 (19)	
Allogeneic	34 (43)	
Gram-negative species	24 (12)	$p < .3759$
Autologous	12 (10)	
Allogeneic	12 (15)	
C.difficile	12 (6)	$p < .0708$
Autologous	4 (3)	
Allogeneic	8 (10)	
Fungal	10 (5)	$p < .9900$
Autologous	6 (5)	
Allogeneic	4 (5)	
Infection source		$p < .0301$
Blood	50 (25)	
Autologous	23 (19)	
Allogeneic	27 (34)	
Urinary	19 (10)	$p < .1394$
Autologous	8 (10)	
Allogeneic	11 (9)	
Pulmonary	22 (11)	$p < .0022$
Autologous	8 (7)	
Allogeneic	14 (18)	

Table 3. TPN-Treated Patients With or Without Infection

	TPN with infection (%)	TPN without infection %)	*p* value
Number	58	140	
Age, mean (range)	53 (19–77)	54 (21–76)	.5300
Female gender	32 (55)	67 (48)	.4187
Transplant type			
Autologous	24 (20)		.0013
Allogeneic	34 (42)		
Donor source			
Matched sibling	23 (68)		.2644
Unrelated donor	11 (32)		
TPN starting date post-SCT, mean (range)	10.3 (0–48)	7.4 (-6–27)	.0014
Patients neutropenic when TPN started	55 (95)	115 (89)	.6653
Number of TPN treatment days (range)	13.8 (2–43)	7.3 (2–20)	.0001
Day 60 mortality	23 (28)	12 (9)	.0011

Note. TPN = total parenteral nutrition.

tococci 5%, respectively ($p < .557$). Acknowledging the limitations of comparing two retrospective studies, these results suggest most infections did not originate from the gastrointestinal tract.

To confound issues, most often, mucositis is accompanied by other gastrointestinal toxicities that prompt TPN use. Nausea and vomiting, dysgeusia, lack of appetite, diarrhea, and fatigue occur frequently (50%–100%, 40%–80%, and 30%–80%, respectively), yet generally are not associated with increased infections (Bevans, Mitchell, & Marden, 2008; Einhorn, Rapoport, Navari, Herrstedt, &

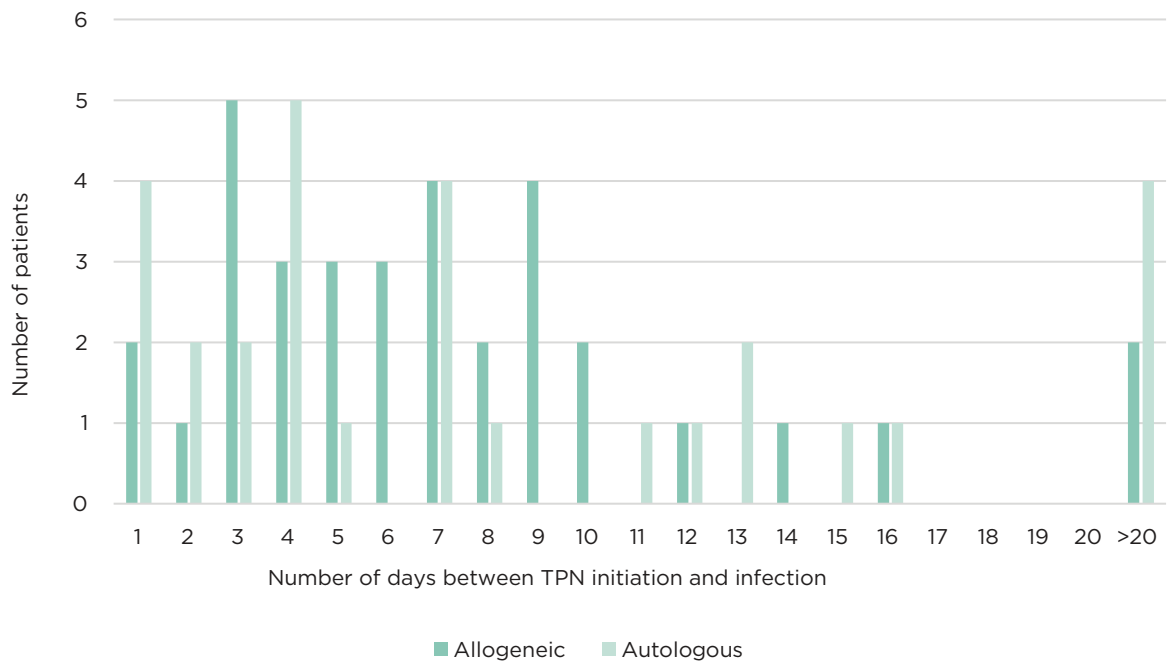

Figure 2. Time to infection.

Brames, 2016; Frödin, Lotfi, Fomichov, Juliusson, & Börjeson, 2015; Okada et al., 2016; Shah et al., 2016; Trigg & Inverso, 2008).

Whatever the cause, the current study may provide assistance to advanced practitioners and other health-care workers who play a pivotal role in initiating and maintaining patients on TPN during stem cell transplantation. The results suggest stem cell recipients who receive TPN are at high risk for infection and day 60 mortality. Bearing in mind the risk factors that were identified (allogeneic stem cell recipients, treatment duration, and time of TPN initiation) may lower the risk for infection. The relatively small sample size of our study could confound the results, and a prospective study is needed to pinpoint which cofactors contribute most to the development of infection during TPN use. Total parenteral nutrition should be used judiciously and discontinued as soon as possible to decrease the risk for infection.

Disclosure

The authors have no conflicts of interest to disclose.

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