Carol Rees Parrish, R.D., M.S., Series Editor

# Cyclic Parenteral Nutrition Infusion: Considerations for the Clinician

Stephen Marc Stout

M. Petrea Cober

**Parenteral nutrition (PN) is typically administered as a 24 hour infusion in acutely ill patients and those requiring only short term PN. Stable patients who require long term or home PN, however, may benefit from a cyclic infusion regimen. Cyclic PN infusion involves daily interruption of PN, allowing patients periodic freedom from infusion equipment. Daily starting and stopping of PN infusion may increase the risk of hyperglycemia and hypoglycemia, respectively. Symptomatic post-infusion hypoglycemia is uncommon in adults, but infusion tapering may be warranted in children <2–3 years old to limit risk. Critically ill, mechanically ventilated patients may not be candidates for cyclic PN infusion based on increases in energy expenditure and carbon dioxide elimination, among other considerations. Metabolic consequences of cyclic PN infusion are reviewed here.**

## BACKGROUND

Parenteral nutrition (PN), the intravenous provision of nutrients, may be indicated in patients exhibiting a wide range of disease states that render enteral nutrition impossible or inadequate. PN is typically initiated as a continuous, 24 hour infusion. However, when PN is indicated long term and/or administered on an outpatient basis, continuous infusion poses some important practical obstacles to patients and their caregivers. Foremost, it requires that patients be continuously connected to infusion equipment that, at best, may interfere with daily activities, and at worst may perpetually immobilize the patient. To address this, PN administration on a cyclic, discontinuous basis has been widely employed to provide patients a "post-infusion" period when infusion equipment may be temporarily disconnected.

Cyclic PN infusion regimens vary widely, but there are some common features. PN is typically administered as a single 10–14 hour infusion, although

Stephen Marc Stout, PharmD, MS, BCPS, Pharmacotherapy Specialist, Metabolism, Interactions, & Genomics Group, Lexicomp, Inc. M. Petrea Cober, PharmD, BCNSP, Clinical Pharmacy Coordinator—Neonatal Intensive Care Unit, Akron Children's Hospital, Assistant Professor of Pharmacy Practice, Northeastern Ohio Medical University.

this duration may range anywhere from 8–23 hours. It is common for PN to run overnight for patient convenience, particularly when administered at home. Numerous infusion initiation and discontinuation formulas exist, and regimens may involve abrupt starting and stopping at the maximum infusion rate, or gradual increases to/tapering from the maximum rate over a given period of time (usually up to 2 hours). The demonstrated effects of these practices are reviewed below. PN components are typically administered simultaneously.

While cyclic PN infusion poses clear practical advantages over continuous infusion for patients receiving PN long-term or at home, the potential metabolic changes that may result from the modified pattern of nutrient provision require consideration. From a metabolic standpoint, there are three key features that may differentiate cyclic PN infusion from continuous infusion. First, it requires daily starting and stopping of infusions, during which time the body must adapt to changes in blood nutrients. Second, it requires higher nutrient infusion rates to supply a similar nutrient load over a shorter period of time. Third, it introduces a post-infusion period when no nutrients are infused. This review was undertaken to synthesize evidence of the metabolic consequences of cyclic PN infusion, for both nutrition support and general practitioners.

## LITERATURE REVIEW

The following is a review of prospective studies describing metabolic consequences of cyclic PN infusion. Major metabolic findings are also summarized in Table 1.

### Infusion Initiation, Discontinuation, and Rate Effects

Infusion of PN in adults and children is associated with a rise in blood glucose concentrations, which return to baseline within 1–2 hours after infusion discontinuation (1–5). Correspondingly, insulin concentrations rise rapidly following infusion initiation and fall rapidly following discontinuation (1–3,5). Insulin and maximum blood glucose concentrations appear to rise in a dose dependent manner with the rate of PN infusion (1,2), and are therefore expected to be greater during cyclic infusion than during continuous infusion. However, when blood glucose elevations occur in stable PN recipients they are generally moderate (<180–200 mg/dL), even with very high dextrose infusion rates (1–5). Greater elevations in patients initiating cyclic PN infusion may signal a need for more gradual shortening of infusion duration and/or administration of exogenous insulin. The risk of persistent hyperglycemia during infusion likely rises with increasing PN infusion rate (1,2), and diabetic patients may be particularly susceptible to PN induced blood glucose elevations (4).

Abrupt initiation of PN infusion in adults causes elevations in blood glucose concentrations that reach a steady state after 60–90 minutes (4). Direct comparisons to more gradual introduction have not been made. Abrupt discontinuation of PN infusion in adults causes a decrease in blood glucose, primarily in the first hour after cessation (3,4,6,7). The minimum blood glucose concentration, however, is similar to tapered discontinuation (6,7), as is the pattern of insulin and counterregulatory hormone (epinephrine, norepinephrine, glucagon, growth hormone, and cortisol) concentrations (6). Symptoms of hypoglycemia have not been reported in the cited studies of abrupt PN discontinuation in adults (3,4,6,7).

In contrast to adults, abrupt discontinuation of PN infusion in children has been associated with elevated rates of hypoglycemia compared to tapering of the infusion over 1 hour (8). Notably, this effect was observed in one study of 11 children <3 years old, but not in another study of 15 children 2–11 years old (mean 7.9 years) (5,8). In the study of children <3 years old, abrupt discontinuation was associated with hypoglycemia (defined as blood glucose <40 mg/dL) in 6/11 cases, in children ranging in age from 2.5–36 months, compared to 2/10 cases when infusion was tapered (8). Average glucose concentrations did not decrease below 60 mg/dL at any time point, and no symptoms of hypoglycemia were noted except for two reports of sleepiness.

*(continued on page 15)*

(continued from page 12)

## Macronutrient and Energy Utilization

Several studies have compared patterns of macronutrient utilization between cyclic and continuous PN infusion regimens. Similar nitrogen balance is achieved (1,9–13). Non-protein respiratory quotient (RQ) is approximately 1 during the infusion period of cyclic regimens, similar to continuous infusion, but RQ drops below 1 (0.86 per one study) during the post-infusion period of cyclic regimens (12,13). Estimated daily lipid oxidation is correspondingly lower, and carbohydrate oxidation higher, with cyclic PN infusion. Hepatic triglyceride secretion is similar with continuous and cyclic infusion (14).

Energy expenditure is greater during the infusion period of cyclic PN regimens than the post-infusion period, but total daily expenditure is similar to continuous infusion (11–13). Nighttime oxygen consumption during infusion is similar with continuous and cyclic infusion (15).

## Electrolyte Homeostasis and Urinary Excretory Changes

Urinary volume increases during cyclic PN infusion, as does excretion of urea, creatinine, sodium, chloride, calcium, phosphate, and magnesium (16–18). However, no differences were demonstrated between continuous and cyclic infusion of PN in terms of daily filtered calcium load, fractional calcium excretion, and serum concentrations of calcium, phosphate, and vitamin D.

## Hormones and Circadian Rhythms

As outlined above, circulating insulin concentrations of patients receiving cyclic PN infusion vary with the phase of the regimen, and insulin responses are in general greater than those seen with continuous infusion due to the greater nutrient infusion rate. In contrast, circulating concentrations of counterregulatory hormones (glucagon, cortisol, and growth hormone) are similar in patients receiving cyclic PN infusion and continuous infusion (1).

Circadian rhythms of serum proteins, total cholesterol, low and high density lipoproteins, apolipoproteins A and B, free fatty acids, and triglycerides are detectable in patients receiving cyclic PN infusion (19), but comparisons to continuous PN infusion have not been made.

## PN Associated Hepatobiliary Complications

In adults who experience hepatobiliary dysfunction with continuous PN infusion, switching to cyclic infusion when total bilirubin is between 5 and 20 mg/dL may lead to stabilization of bilirubin and liver function tests (20). Patients maintained on continuous infusion under these circumstances experience continued increases in direct and total bilirubin, and worsening of some liver function tests (alkaline phosphatase or transaminase concentrations, depending on baseline bilirubin). Patients from a general, unselected clinical population receiving PN may exhibit decreases in alkaline phosphatase and lactate dehydrogenase concentrations when switched from continuous infusion to cyclic infusion regimen (9), but there is little evidence of bilirubin change in the absence of substantial baseline elevations.

Similar to adults, infants receiving continuous PN infusion may experience stabilization of bilirubin concentrations following a change to a cyclic infusion regimen, although prospective evidence of such an effect is anecdotal (21).

## Use in Critical Illness and Mechanical Ventilation

In critically ill mechanically-ventilated patients, cyclic PN infusion increases energy expenditure to a greater extent than continuous, accompanied by increases in oxygen uptake and carbon dioxide elimination (22). Nitrogen balance is unaffected, as are excretion of counterregulatory hormones (norepinephrine, epinephrine, and cortisol) and serum responses of insulin, glucagon, glucose, and triglycerides; serum cortisol decreases may be greater in response to cyclic PN infusion compared to continuous infusion. Heart rate and blood pressure do not differ substantially between cyclic and continuous infusion, or between the infusion and post-infusion periods of cyclic regimens.

**Table 1.**
**Characteristics and Major Findings of Prospective Studies of Cyclic PN Infusion**

| *Study* | *N* | *Age** | *Design* |
|---|---|---|---|
| **Macronutrient and Energy Utilization** | | | |
| Byrne 1982 (1) | 5 | 19–61 y | Before-after |
| Maini 1976 (9) | 14 | 23–74 y | Before-after, some patients received one intervention only |
| Messing 1983 (10) | 14 | 16–68 y | Before-after |
| Lerebours 1988 (11) | 12 | 18–70 y | RCT, crossover |
| Just 1990 (12) | 5 | 45 ±9 y | RCT, crossover |
| Pullicino 1991 (13) | 8 | 23–46 y | Parallel group non-RCT, with some repeat studies and crossover patients. |
| Isabel-Martinez 1989 (14) | 13 | 58 ± 6 y (24 h infusion), 60 ± 3 y (16 h infusion) | RCT, parallel group |
| Fagioli 1991 (15) | 8 | 5–12 y | Parallel group non-RCT |
| **Electrolyte Homeostasis and Urinary Excretory Changes** | | | |
| Wood 1995 (16) | 5 | 19–72 y | Parallel group non-RCT with historical control |
| Boncompain-Gérard 2000 (17) | 16 | 28–63 y | Before-after |

*(continued on page 20)*

| *Parameter evaluated* | *Outcome* |
|---|---|
| Nitrogen balance (PN nitrogen minus measured urine and gastrointestinal losses) | Similar with 24, 17, and 12 h daily infusion |
| Nitrogen balance (precise assay and calculation details unclear) | Similar with 24 h and 14–16 h daily infusion.<br>Patients allowed various dextrose-free solutions (some containing amino acids) or oral feeding during non-infusion period. |
| Nitrogen balance (PN nitrogen minus measured urine and stool losses, and estimated "miscellaneous" losses) | Similar with 24 h infusion and cyclic regimens (average 9 h non-infusion period).<br>Possible greater nitrogen balance with continuous infusion in 4 patients with steroid induced hypercatabolism. |
| Nitrogen balance (PN nitrogen minus measured urine and gastrointestinal losses) | Similar with 24 h and 16 h daily infusion |
| Energy expenditure (indirect calorimetry) | Similar with 24 h and 16 h daily infusion<br>Greater during infusion period than non-infusion period of cyclic regimen |
| Nitrogen balance (precise assay and calculation details unclear) | Similar with 24 h and 15 h daily infusion |
| Energy expenditure (indirect calorimetry) | Similar with 24 h and 15 h daily infusion |
| Non-protein RQ (indirect calorimetry) | >1 during infusion of 24 h and 15 h daily infusion regimens, significantly lower (RQ 0.86–0.95, depending on time of measurement) during non-infusion period of cyclic regimen. |
| Nitrogen balance (PN nitrogen minus measured urine and gastrointestinal losses) | Similar with 24 h and 12 h daily infusion |
| Energy expenditure (indirect calorimetry) | Similar with 24 h and 12 h daily infusion |
| Non-protein, non-glycerol RQ (indirect calorimetry) | >1 during infusion of 12 h daily regimen, significantly lower (RQ 0.86) during non-infusion period. Statistical comparison to values during 24 hr infusion (RQ 0.92) not made. |
| Plasma trigylceride secretion (radiolabeled plasma triglyceride measurement following intravenous bolus of tritiated glycerol) | Similar with 24 h and 16 h daily infusion |
| Oxygen consumption (indirect calorimetry during sleep) | Similar with 24 h and 12 h daily infusion, during infusion |
| Urine electrolyte content and volume, serum electrolyte and 25-hydroxy vitamin D concentrations | Urinary calcium greater with 12 h or 18 h infusion compared to 24 h. Similar daily urinary filtered calcium load and fractional calcium excretion, and similar serum calcium, phosphorus, magnesium, 25-hydroxy vitamin D concentrations. |
| Urine electrolyte content and volume. | Urine volume and excretion of calcium, magnesium, and phosphate greater during infusion period than non-infusion period of a 12 h daily infusion regimen. |

*(continued from page 17)*

**Table 1 (continued).**
**Characteristics and Major Findings of Prospective Studies of Cyclic PN Infusion**

| *Study* | *N* | *Age** | *Design* |
|---|---|---|---|
| Lipkin 1988 (18) | 17 | 27–69 y | Crossover non-RCT |
| **Hormones and Circadian Rhythms** | | | |
| Byrne 1982 (1) | 5 | 19–61 y | Before-after |
| Matuchansky 1985 (19) | 6 | 51–69 y | No comparator (modeling/regression, single group) |
| **PN Associated Hepatobiliary Complications** | | | |
| Hwang 1976 (20) | 65 | 15–72 y | RCT, parallel group |
| Maini 1976 (9) | 14 | 23–74 y | Before-after, some patients received one intervention only |
| Collier 1994 (21) | 10 | 33–53 wk gestational age when cyclic infusion begun | Before-after |
| **Use in Critical Illness and Mechanical Ventilation** | | | |
| Forsberg 1994 (22) | 16 | 25–79 y | RCT, parallel group |

*Ages stated as either range or mean ± standard deviation, per study reporting.

| *Parameter evaluated* | *Outcome* |
|---|---|
| Urine electrolyte content and volume. | Similar daily urine calcium and magnesium, and fractional excretion, with 12 h and 24 h infusion. Greater daily urine volume with 12 h infusion. |
| Serum insulin and counterregulatory hormone (glucagon, cortisol, growth hormone) concentrations | Insulin concentration during infusion greater with 12 h and 17 h infusion compared to 24 h. Counterregulatory hormone concentrations similar with 24, 17, and 12 h daily infusion. |
| Serum concentration patterns of serum proteins, total cholesterol, low and high density lipoproteins, apolipoproteins A and B, free fatty acids, and triglycerides. | Circadian rhythms detectable in patients receiving 12 h daily infusion. |
| Liver function tests (transaminases, direct and total bilirubin, alkaline phosphatase). | No significant changes in patients with total bilirubin between 5 and 20 mg/dL during 24 h infusion who were switched to 12 h infusion. Increases in direct and total bilirubin, and some liver function tests, in patients maintained on 24 h infusion. Advantages of cyclic infusion not apparent in patients with baseline total bilirubin >20 mg/dL. |
| Total bilirubin, transaminase, alkaline phosphatase, and lactate dehydrogenase concentrations. | Significantly lower alkaline phosphatase and lactate dehydrogenase concentrations with 14–16 h daily infusion compared to 24 h. Other measures similar.<br>Patients allowed various dextrose-free solutions (some containing amino acids) or oral feeding during non-infusion period. |
| Serum direct bilirubin | Direct bilirubin increased an average of 2.2 mg/dL during 24 h infusion, in the 2 weeks prior to initiation of cyclic infusion, then decreased an average of 1 mg/dL in the 2 weeks following initiation of cyclic infusion. Statistical comparisons not made. |
| Oxygen uptake, carbon dioxide elimination, energy expenditure (indirect calorimetry) | Greater with 12 h daily infusion compared to 24 h infusion |
| Nitrogen balance (PN nitrogen minus measured urine losses and other assumed losses) | Similar with 24 h and 12 h daily infusion. |
| Urinary excretion of counterregulatory hormones (norepinephrine, epinephrine, and cortisol) and serum responses of insulin, glucagon, glucose, and triglycerides. | Similar with 24 h and 12 h daily infusion. |
| Heart rate, blood pressure. | Similar with 24 h and 12 h daily infusion.<br>Similar during infusion and non-infusion period of cyclic regimen. |

## DISCUSSION

Cyclic PN infusion is widely employed in patients who receive PN long term. Prospective clinical data to date have described some important similarities to continuous infusion in terms of achievable nitrogen balance, energy expenditure, nighttime oxygen consumption during infusion, hepatic triglyceride secretion, circulating counterregulatory hormone concentrations, and systemic concentrations of calcium, phosphate, magnesium and 25-hydroxy vitamin D.

There may be an advantage to cyclic PN infusion in reducing PN associated hepatobiliary dysfunction. There is a well described benefit of cyclic infusion in stabilizing total and direct bilirubin concentrations in adult patients receiving continuous PN infusion with bilirubin between 5 and 20 mg/dL. Additionally, it has been speculated that the observed insulin and metabolic shifts from the infusion to post-infusion period could potentially reduce the risk of hepatic impairment due to excessive glycogen and fat deposition (9), although clear documentation of such an effect is lacking.

Daily starting and stopping of PN infusion may lead to hyperglycemia and hypoglycemia, respectively. Additionally, increased nutrient infusion rates necessitated by cyclic PN infusion lead to dose-dependent increases in the insulin and blood glucose responses. Hyperglycemia may be transient or persistent. While symptomatic post-infusion hypoglycemia appears to be uncommon in adults, even with abrupt termination of PN infusion, children less than 2–3 years old may benefit from an infusion taper to minimize this risk.

Critically ill, mechanically ventilated patients may be better candidates for continuous PN infusion than cyclic due to increased carbon dioxide production and reduced apparent metabolic efficiency with the latter. Other theoretical concerns in these patients include the potential for disruption of hemodynamic stability, and interference with intensive insulin therapy.

While published literature to date has not comprehensively characterized all metabolic effects of cyclic PN infusion in adults and children, the existing data, combined with the obvious practical advantages of cyclic infusion, have established cyclic PN infusion as a preferred modality in stable patients requiring long term and/or home PN. In addition to the data reviewed here, there are myriad reports describing clinical experiences with cyclic PN infusion programs which, while generally providing only very weak objective evidence of any particular metabolic effect, may be seen as lending additional evidence of long-term safety. See Table 2 for considerations for the clinician.

**Table 2.**
**Practical Considerations for the Clinician**

**Consider cyclic PN infusion in:**
- Stable inpatients
- Patients involved in daytime acute care therapy or transferring to rehabilitative services/facilities
- Otherwise ambulatory patients whose mobility is hindered by infusion equipment
- Patients anticipated to receive PN long term at home
  - Some may prefer daytime infusion due to frequent nocturnal urination
  - Portable pumps can help increase mobility for patients receiving daytime infusion or longer infusion duration.

**Additional caution/monitoring may be warranted in:**
- Patients <3 years of age
- Patients with presumed low glycogen stores (e.g. severe malnourishment, neonates)
- Patients with sensitive fluid status (e.g. congestive heart failure)
- Patients receiving long-acting insulin or insulin drips

**Avoid in:**
- Hemodynamic instability
- Critical illness/mechanical ventilation

## CONCLUSION

Several metabolic consequences of cyclic PN infusion have been described in prospective clinical studies. Overall, the data support the widespread implementation of cyclic PN for stable patients who require long term and/or home treatment, with a few important caveats. Most notably, tapered infusion discontinuation is preferable in children less than 2–3 years old due to a possible elevated risk of hypoglycemia.

*(continued on page 24)*

*(continued from page 22)*

Hyperglycemia during infusion, while often transient, may require adjustment in some patients. ■

## References


1. Byrne WJ, Lippe BM, Strobel CT, Levin SR, Ament ME, Kaplan SA: Adaptation to increasing loads of total parenteral nutrition: Metabolic, endocrine, and insulin receptor responses. *Gastroenterology*. 1981;80(5 pt 1):947-956.
2. Wood RJ, Bengoa JM, Rosenberg IH: Urinary C-peptide measurements in patients receiving continuous and cyclic total parenteral nutrition. *J Lab Clin Med*. 1985;105(2):259-264.
3. Wagman LD, Newsome HH, Miller KB, Thomas RB, Weir GC: The effect of acute discontinuation of total parenteral nutrition. *Ann Surg*. 1986;204(5):524-529.
4. Krzywda EA, Andris DA, Whipple JK, et al: Glucose response to abrupt initiation and discontinuation of total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1993;17(1):64-67.
5. Werlin SL, Wyatt D, Camitta B: Effect of abrupt discontinuation of high glucose infusion rates during parenteral nutrition. *J Pediatr*. 1994;124(3):441-444.
6. Eisenberg PG, Gianino S, Clutter WE, Fleshman JW: Abrupt discontinuation of cycled parenteral nutrition is safe. *Dis Colon Rectum*. 1995;38(9):933-939.
7. Nirula R, Yamada K, Waxman K: The effect of abrupt cessation of total parenteral nutrition on serum glucose: a randomized trial. *Am Surg*. 2000;66(9):866-869.
8. Bendorf K, Friesen CA, Roberts CC: Glucose response to discontinuation of parenteral nutrition in patients less than 3 years of age. *JPEN J Parenter Enteral Nutr*. 1996;20(2):120-122.
9. Maini B, Blackburn GL, Bistrian BR, et al: Cyclic hyperalimentation: an optimal technique for preservation of visceral protein. *J Surg Res*. 1976;20(6):515-525.
10. Messing B, Pontal PJ, Bernier JJ: Metabolic study during cyclic total parenteral nutrition in adult patients with and without corticosteroid-induced hypercatabolism: Comparison with standard total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1983; 7(1):21-25.
11. Lerebours E, Rimbert A, Hecketsweiler B, Hellot MF, Denis P, Colin R: Comparison of the effects of continuous and cyclic nocturnal parenteral nutrition on energy expenditure and protein metabolism. *JPEN J Parenter Enteral Nutr*. 1988;12(4):360-364.
12. Just B, Messing B, Darmaun D, Rongier M, Camillo E: Comparison of substrate utilization by indirect calorimetry during cyclic and continuous total parenteral nutrition. *Am J Clin Nutr*. 1990;51(1):107-111.
13. Pullicino E, Goldberg GR, Elia M: Energy expenditure and substrate metabolism measured by 24 h whole-body calorimetry in patients receiving cyclic and continuous total parenteral nutrition. *Clin Sci (Lond)*. 1991;80(6):571-582.
14. Isabel-Martinez L, Skinner C, Parkin A, Hall RI: Comparison of the effects of enteral feeding with continuous and intermittent parenteral nutrition on hepatic triglyceride secretion in human beings. *Surgery*. 1989;105(3):415-420.
15. Fagioli I, Bes F, Franc B, Putet G, Ricour C, Salzarulo P: Oxygen consumption during sleep in children under continuous and cyclic nutrition. *Physiol Behav*. 1991;49(6):1159-1162.
16. Wood RJ, Bengoa JM, Sitrin MD, Rosenberg IH: Calciuretic effect of cyclic versus continuous total parenteral nutrition. *Am J Clin Nutr*. 1985;41(3):614-619.
17. Boncompain-Gérard M, Robert D, Fouque D, Hadj-Aïssa A: Renal function and urinary excretion of electrolytes in patients receiving cyclic parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2000;24(4):234-239.
18. Lipkin EW, Ott SM, Chesnut CH 3rd, Chait A: Mineral loss in the parenteral nutrition patient. *Am J Clin Nutr*. 1988;47(3):515-523.
19. Matuchansky C, Fabre J, Guillard O, Morichau-Beauchant M, Reinberg A: Effects of cyclic (nocturnal) total parenteral nutrition and continuous enteral nutrition on circadian rhythms of blood lipids, lipoproteins, and apolipoproteins in humans. *Am J Clin Nutr*. 1985;41(4):727-734.
20. Hwang TL, Lue MC, Chen LL: Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function. *Hepatogastroenterology*. 2000;47(35): 1347-1350.
21. Collier S, Crough J, Hendricks K, Caballero B: Use of cyclic parenteral nutrition in infants less than 6 months of age. *Nutr Clin Pract*. 1994;9(2):65-68.
22. Forsberg E, Soop M, Lepapea A, Thörne A: Metabolic and thermogenic response to continuous and cyclic total parenteral nutrition in traumatised and infected patients. *Clin Nutr*. 1994; 13(5):291-301.