

American Gastroenterological Association Medical Position Statement: Short Bowel Syndrome and Intestinal Transplantation

This document presents the official recommendations of the American Gastroenterological Association (AGA) on Short Bowel Syndrome. It was approved by the Clinical Practice Committee on August 5, 2002 and by the AGA Governing Board on November 1, 2002.

Short bowel syndrome (SBS) occurs when, after surgery or congenitally, a patient is left with <200 cm of functional small intestine. Absorption is related to the amount of residual intestine; patients at greatest nutritional risk generally have a duodenostomy or a jejunioileal anastomosis with <35 cm of residual small intestine, jejunocolic or ileocolic anastomosis with <60 cm of residual small intestine, or an end jejunostomy with <115 cm of residual small intestine. Patients can be grouped into 2 distinct subgroups: those with colon in continuity and those without colon in continuity. In patients with SBS, the colon becomes an important digestive organ.

Medical Therapy

The most important aspects of medical management of the patient with SBS are provision of adequate macro- and micronutrients and fluid to prevent energy malnutrition, specific nutrient deficiencies and dehydration, and correction and prevention of acid-base disturbances.

Glucose-polymer-based oral rehydration solutions (ORS) with 90–120 mEq/L sodium (Na) should be instituted to decrease dehydration and total parenteral nutrition (TPN) fluid requirements in patients with residual jejunum ending in a jejunostomy. Several commercial ORS are available, or solutions can be formulated by dissolving NaCl (2.5 g), KCl (1.5 g), Na₂CO₂ (2.5 g), and glucose (table sugar, 20 g) in 1 L water. Patients should avoid consumption of plain water and should be encouraged to drink ORS whenever they are thirsty. For patients with residual colon in continuity, ORS may still be of value—provided sufficient Na is present in the diet; the amount of Na in the ORS may not be as critical. For patients with no remaining jejunum, who have residual ileum, the presence of glucose in the ORS is not critical because ileal water absorption is not affected by the presence of glucose.

Magnesium (Mg) deficiency may occur despite a normal serum concentration. It is prudent to measure 24-

hour urine Mg. However, Mg replacement is problematic and often requires intravenous infusion. Oral calcium (Ca) supplementation is recommended routinely (800–1200 mg per day). Iron is absorbed in the duodenum and, in the absence of hemorrhage, is not routinely required as a supplement. Phosphorus deficiency is rare; supplementation is rarely required.

Resection of the ileocecal valve may allow colonic bacteria to populate the small intestine, resulting in bacterial overgrowth. This may negatively impact on digestion and nutrient assimilation, because bacteria compete for nutrients with the enterocytes. Diagnosis of bacterial overgrowth may be more difficult using breath tests because of rapid intestinal transit in SBS. Endoscopically obtained small bowel aspirate for culture may be required. Treatment can be undertaken with oral metronidazole, tetracycline, or other antibiotics.

High-dose H₂ antagonists and proton pump inhibitors reduce gastric fluid secretion, and fluid losses during the first 6 months post-enterectomy. Fluid losses usually require long-term control with anti-motility agents, such as loperamide hydrochloride or diphenoxylate (4–16 mg per day). If these are ineffective, especially in patients without colon in continuity or in patients with minimal residual jejunum or duodenum, use of codeine sulfate (15–60 mg two to three times a day) or tincture of opium may be necessary. Rarely, octreotide (100 µg SQ, three times a day, 30 minutes before meals) is required. It should be used only if fluid intravenous requirements are >3 L daily because post-resection intestinal adaptation may be impaired and the risk for cholelithiasis increased. There is insufficient evidence to recommend the use of bile acid supplements to decrease

Abbreviations used in this paper: CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESLD, end-stage liver disease; IVC, inferior vena cava; ORS, oral rehydration solutions; SBS, short bowel syndrome; SVC, superior vena cava.

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steatorrhea; and they may worsen diarrhea. Cholestyramine is not useful in patients with >100 cm of ileal resection, and it may actually worsen steatorrhea because of the binding of bile salts.

Dietary Management

Typically, patients who have undergone massive enterectomy require TPN, once hemodynamic stability has been achieved, for the first 7–10 days after surgery. Nutritional therapy should be introduced gradually, converting to standard enteral formula as tolerated. The goal is to provide patients with approximately 25–30 kcal/kg per day and 1.0–1.5 g/kg per day of protein. Standard enteral formula is recommended. Nitrogen is the macronutrient least affected by diminished intestinal absorptive surface. Therefore, the utility of peptide-based diets in such patients is generally without merit. Oral intake should be encouraged. There is no value in separating liquids from solids in the diet or with high fat–low carbohydrate or low fat–high carbohydrate diets except for patients with colon in continuity, in whom soluble fiber intake should be encouraged. Soluble fiber is fermented to short-chain fatty acids by colonic bacteria and serve as an additional energy source. Small amounts of medium-chain triglycerides are absorbed by the colon and may be included in the diet as an additional energy source. Lactose-containing foods should not be restricted in the absence of confirmed lactase deficiency or significant proximal jejunal resection. Dietary oxalate should be restricted in the diet in patients with residual colon in continuity. Oral Ca supplements also may be of value for the prevention of Ca-oxalate nephrolithiasis. Randomized, controlled trials have not shown glutamine and/or growth hormone to improve intestinal absorption. Micronutrients, including water-soluble (B1, B2, B3, B6, B12, biotin, folate, C) and fat-soluble (A, D, E, K) vitamins, and trace elements (Zn, Se) often require supplementation (Table 1). Water-soluble vitamin deficiency is rare.

Parenteral Nutrition

Most patients will require TPN, at least initially. For the normally nourished patient, TPN should be supplied at 25–30 kcal/kg per day based on ideal body weight for adults, with greater levels of support for infants and children depending on age. Dextrose is a monohydrate, providing 3.4 kcal/mL. The maximum dextrose infusion rate should be 5–7 mg/kg/min. Blood glucose should be monitored at least daily, optimally qid, and should be <180–200 mg/dL; the addition of regular insulin to the TPN solution may be required. If

Table 1. Vitamin and Mineral Supplements for Patients With Short Bowel Syndrome

Vitamin A	10,000–50,000 units daily ^a
Vitamin B ₁₂	300 µg subcutaneously monthly for those with terminal ileal resections or disease
Vitamin C	200–500 mg
Vitamin D	1600 units DHT daily; may require 25-OH- or 1,23 (OH) ₂ -D ₃
Vitamin E	30 IU daily
Vitamin K	10 mg weekly
Calcium	See text
Magnesium	See text
Iron	As needed
Selenium	60–100 µg daily
Zinc	220–440 mg daily (sulfate form)
Bicarbonate	As needed

NOTE. The table lists rough guidelines only. Vitamin and mineral supplementation must be monitored routinely and tailored to the individual patient, because relative absorption and requirements may vary.

^aUse cautiously in patients with cholestatic liver disease.

insulin is required, it should be added to the TPN bag at an initial dose of 0.1 U/g dextrose; subsequent adjustments should be made as necessary. Intravenous lipids are generally used to provide 20%–30% of infused calories, although a greater percentage of lipid may be used in the patient with significant glucose intolerance or fluid management issues; 20% lipid emulsion is more calorically dense than dextrose. Generally, the percentage of lipid calories should be increased and the percentage of dextrose calories should be decreased if the amount of supplemental insulin required exceeds 0.2 U/g dextrose, although the serum triglyceride concentration should be kept <700–800 mg/dL, and optimally, <400 mg/dL. Protein is supplied in the form of free amino acids and should be supplied at 1.0–1.5 g/kg per day, based on ideal body weight for adults, with greater levels of support for infants and children depending on age.

Initially, TPN is infused continuously while postoperative complications are addressed and metabolic issues stabilized. Attempts should be made, when appropriate, to wean patients who have sufficient absorptive capacity; maximal adaptation may take as long as 1–2 years. For patients who will require TPN at home, the infusion should be compressed to overnight. Typically, this would be during a 10-hour period with an additional 30–60-minute taper period; some patients with fluid management issues will be unable to tolerate this infusion rate. Cycling to overnight infusion should be a gradual process. Once goal infusion volume has been determined (e.g., 1.5, 2.0, 2.5, or 3.0 L for adults; with less volume for infants and children), the total volume should be infused over gradually decreasing time periods (e.g., compress by increments of 2–4 hours). TPN should be

infused ideally via a single lumen catheter with its tip positioned in either the superior vena cava (SVC) or inferior vena cava (IVC) to decrease the risk of infection and thrombosis. Tunneled catheters, implantable ports, or percutaneously inserted central catheters (PICCs) should be used at home, although the experience with PICCs for >1 year at home is minimal. To qualify for Medicare reimbursement, home TPN must be required for at least 3 months, fat malabsorption must be documented, and enteral feeding must have failed.

The patient's home environment should be evaluated. A room, preferably the bedroom—definitely not a “dirty” room, such as the kitchen or bathroom—should be identified for TPN to be set up prior to use. The patient should be instructed to purchase a small refrigerator to be used solely for TPN storage. A local support group under the umbrella of the Oley Foundation (1-800-776-OLEY) should be contacted. Transition from hospital to home may be smoother if the patient has another patient contact who previously has undergone the same process. The patient should undergo some education about TPN prior to hospital discharge, including the indications for TPN, basic instruction on getting their solutions ready for use (they will need to add their vitamins, insulin, and H₂ blockers if prescribed, and flush catheter), catheter care, dressing changes, and information on their intravenous pump. It is often useful for the patient to meet their home care nurse (who will continue the education process at home until the patient or caregiver is self-sufficient) prior to discharge. The treating physician should have some familiarity with appropriate catheter care and the identification of complications associated with long-term TPN, including catheter-related infections, occlusions, and metabolic complications.

Patients should not be discharged home until their fluid and electrolyte requirements have stabilized. Once home, office visits and laboratory monitoring should initially be more frequent, although the stable patient who has minimal difficulty generally can visit the office and have routine laboratory testing done as infrequently as 3 times a year.

Patients in whom TPN is being weaned, and who acquire <75% of the nutritional needs parenterally, should have vitamin (usually fat-soluble vitamins) and trace metal (Zn, Cu, Se) analyses performed 2–3 times yearly, and whenever possible deficiencies are clinically recognized. Vitamin K is not a constituent of all parenteral multivitamin solutions, although vitamin K is present in the intravenous lipid emulsion. Therefore, the prothrombin time should be regularly monitored, espe-

cially in those patients who lack residual colon. During clinic visits, the catheter exit site or skin overlying an implanted infusion port should be examined for warmth, erythema, and tenderness, and the catheter dressing should be examined for purulent exudate, which may signal infection. A properly maintained catheter may remain in place for many years.

Medication Absorption

Oral medication absorption is often impaired and larger doses, intravenous, or sublingual delivery may be required; significant interpatient variability may be observed.

Role of Surgery

Nontransplant Surgery

Restoration of intestinal continuity, such as reanastomosis of small intestine with colon, should be performed whenever possible, because it can be performed with relatively low morbidity and mortality (often with discontinuation of TPN). Other forms of bowel lengthening surgery have significant associated morbidity and mortality, and therefore should be considered only in select patients.

Intestinal Transplantation

Indications for Transplantation

Thus far, intestinal transplants have been performed only in patients who have developed life-threatening complications attributable to their intestinal failure and/or long-term TPN therapy. Medicare has approved payment for intestinal transplants in patients who fail TPN therapy for one of the following reasons:

1. Impending or overt liver failure (increased serum bilirubin and/or liver enzyme levels, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding, hepatic fibrosis, or cirrhosis).
2. Thrombosis of major central venous channels (2 thromboses in subclavian, jugular, or femoral veins). Evidence supporting this indication is weak.
3. Frequent central line-related sepsis (2 episodes of systemic sepsis secondary to line infection per year, 1 episode of line-related fungemia, septic shock, or acute respiratory distress syndrome). Evidence supporting this indication is weak.
4. Frequent severe dehydration.

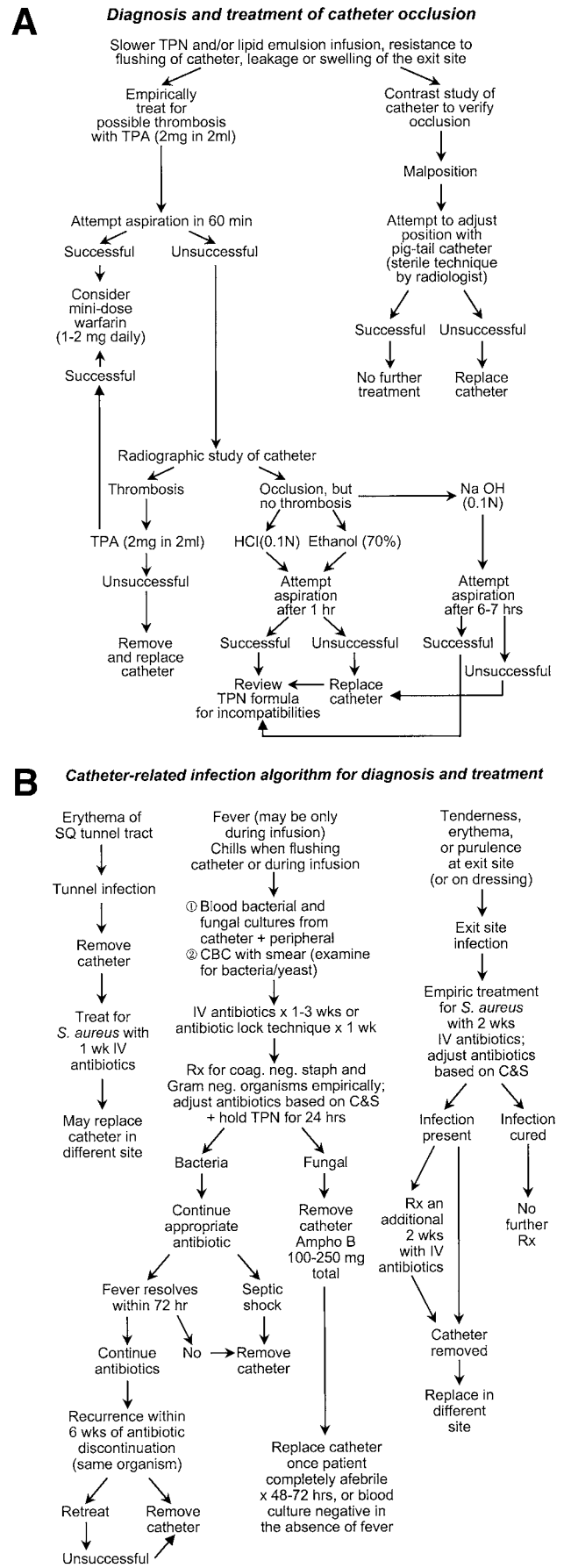
Until better data become available, these parameters are likely to be widely recognized as the indications for intestinal transplantation.

Complications of Long-term TPN That Could Lead to the Need for Intestinal Transplantation

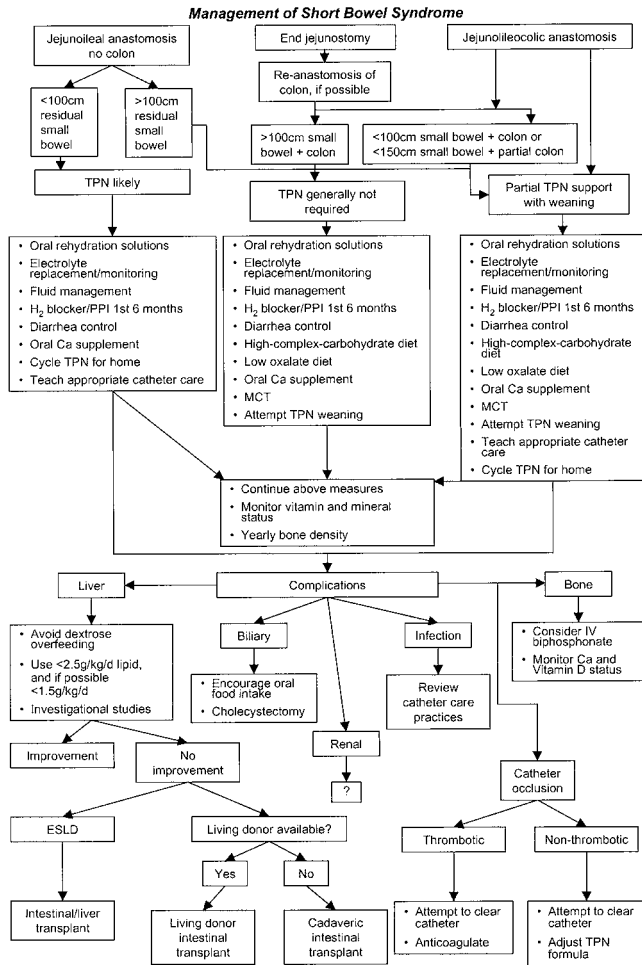
For patients who develop TPN-associated liver disease, investigational studies using metronidazole, oral lecithin, ursodeoxycholic acid, or intravenous choline to treat or prevent the development of TPN-associated liver disease should be considered. Otherwise, no specific therapy is available. Care should be taken to avoid dextrose overfeeding fatty acid deficiency from insufficient intravenous lipid emulsion (minimum of 2%–4% or 4%–8% of nonprotein calories as linoleic acid or lipid emulsion, respectively) and to limit intravenous lipid intake to <2.5 g/kg per day, possibly even to <1 g/kg per day. There is no role for carnitine supplementation.

In patients with end-stage liver disease (ESLD) related to SBS, combined intestine-liver transplant may be the only option; isolated liver transplantation is not recommended. However, carefully selected ESLD patients with significant residual intestine, who are very likely to be weaned from TPN soon after transplant, can achieve successful isolated liver transplantation. Isolated intestine transplantation is not recommended in the setting of ESLD, although outcome data stratifying intestine-only transplant recipients based on their pretransplant liver abnormalities do not exist. It is not yet clear when the TPN-associated hepatic pathological process progresses to the point of irreversibility. Patients with SBS who progress to ESLD are placed on the waiting list for a combined intestine-liver transplant, but have an extremely high mortality rate exceeding all other solid organ transplant waiting lists, including isolated liver transplants.

With proper catheter care techniques, the rate of catheter-related infections and thrombosis can be minimized. Calcium phosphate compatibility should be monitored in the TPN solution to prevent non-thrombotic catheter occlusion. Prior catheter thrombosis is a risk factor for development of SVC/IVC syndrome in the future; therefore, warfarin anticoagulation should be undertaken in patients with prior catheter thrombosis in the absence of catheter malposition as the cause. Typically, TPN catheters are first placed in the SVC by accessing either the internal jugular, brachial, or subclavian veins. If these veins are no longer accessible, the catheters are usually placed in the IVC via the femoral or saphenous veins. True loss of catheter insertion sites is



Algorithm 1. (A) Diagnosis and treatment of catheter occlusion. (B) Catheter-related infection algorithm for diagnosis and treatment.



Algorithm 2. Management of short bowel syndrome.

extremely rare; clinicians often prematurely determine that a patient has no suitable venous access. When all the usual central veins have been exhausted, alternatives include translumbar or transhepatic access to the IVC, and thoracotomy with direct placement of an intra-atrial catheter, among others.

Current Management of the Intestinal Transplant Patient

Standards of care for intestinal transplantation are still evolving and will continue to evolve until outcomes are comparable to those seen with other solid organ transplants. All patients should have a complete cardiopulmonary evaluation. If intestinal failure resulted from mesenteric thrombosis, the etiology should be sought. Metastatic malignancies and active or uncontrolled systemic infections, including human immunodeficiency virus, exclude transplantation.

It is essential to determine if associated liver pathology exists in patients being evaluated for potential intestinal

transplantation; etiologies other than TPN or malabsorption should be considered. Hepatic aminotransferases, total bilirubin, albumin, international normalized ratio, and platelet count should be determined, and liver biopsy should be performed. Portal venous pressure should be measured to exclude portal hypertension, although normal results may be deceiving in patients who have had major intestinal resections, since most portal inflow will be missing. Patients and their families should meet with a social worker, psychiatrist, and a financial/insurance counselor who understand the complex medical, psychologic, and social issues involved with organ transplantation. Living donation should be considered to eliminate waiting time, optimize HLA matching, and simplify coordination of donor-recipient procedures.

After the transplant, intestinal recipients require life-long immunosuppression. While immunosuppressive regimens vary between individual centers, tacrolimus and prednisone are generally included. Other agents may include mycophenolate mofetil, azathioprine, cyclosporine, rapamycin, cyclophosphamide, prostaglandin E1, OKT3, ATG, and daclizumab. In the early post-transplant period, blood tacrolimus concentrations should be 20–30 ng/mL. Simultaneous transplantation of donor bone marrow has been performed in an attempt to induce recipient hyporesponsiveness to donor tissues. This approach has not clearly altered outcomes in intestinal transplant patients, although long-term effects remain to be seen.

Following transplantation, multi-visceral recipients require monitoring in an intensive care unit, while isolated intestine recipients can usually go directly to a non-intensive care unit bed. Within the first week post transplant, if a gastrointestinal contrast study has excluded an anastomotic leak, enteric feeding should be initiated. If the patient is not ready or willing to eat, tube feedings should be started. Once initiated, enteral nutrition is gradually increased until nutritional goals are met, at which time TPN can be discontinued. Some patients may require only fluid supplements. Many infants with congenital SBS may require tube feeding because of reluctance to eat. Thought to be due to these infants never having learned to eat, this phenomenon requires long-term re-education and psychologic counseling.

Rejection is the most common cause of graft loss in intestinal transplant recipients. While clinical signs are frequently unreliable, fever and gastrointestinal symptoms (bloating, cramping, diarrhea, increased stomal output) are often present. There are no reliable biochemical markers of rejection. Small intestinal endoscopy with

multiple biopsies (6 total biopsies) initially should be performed biweekly; because early rejection may not be endoscopically apparent, biopsy specimens should be obtained even from normal appearing mucosa. Increased intestinal permeability (diethylenetriaminepentaacetic acid nuclear medicine scan) also has a high correlation with acute rejection. Cytomegalovirus (CMV) enteritis can resemble rejection clinically and histologically; therefore, intestinal allograft biopsy specimens should be reviewed by a pathologist experienced with intestinal transplantation. When rejection is diagnosed, high-dose intravenous corticosteroids should be administered for 3 days (methylprednisolone 500 mg daily or equivalent). In severe or corticosteroid-resistant rejection, antibody therapy (OKT3, thymoglobulin) for this agent may be used for up to 14 days. Because of the theoretical potential for bacterial translocation from injured bowel, broad-spectrum antibiotics should be administered during rejection. After rejection is reversed, the adequacy of maintenance immunosuppression should be reassessed.

The high level of immunosuppression necessary to prevent intestinal rejection contributes to many post-transplant complications, including sepsis. Unless intestinal rejection underlies sepsis, immunosuppression

should be reduced. In progressive or persistent sepsis, immunosuppression withdrawal and removal of the intestinal graft should be considered before sepsis is irreversible. CMV enteritis can also lead to graft loss; CMV-positive donors are avoided in CMV-negative recipients, and CMV prophylaxis with ganciclovir should be continued for a prolonged period after transplant. If CMV infection is suspected (fever, flu-like symptoms, diarrhea, headache, leucopenia), confirmation should be obtained by an antigenemia assay, and ganciclovir and/or CMV-specific hyperimmune globulin should be initiated. Post-transplant lymphoproliferative disorders are responsible for 14% of post-transplant deaths. Because the Epstein-Barr virus (EBV), the causative agent in post-transplant lymphoproliferative disorders, is ubiquitous in the adult population, use of EBV negative donors is impractical. However, ongoing surveillance of peripheral blood EBV load can provide guidance for preemptive therapy with acyclovir and/or hyperimmune globulin.

Address requests for reprints to: Chair, Clinical Practice Committee, AGA National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

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