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Review article

Recommendations for outpatient parenteral antimicrobial therapy in Brazil



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ABSTRACT

A panel of national experts was convened by the Brazilian Infectious Diseases Society in order to determine the recommendations for outpatient parenteral antimicrobial therapy (OPAT) in Brazil. The following aspects are covered in the document: organization of OPAT programs; patient evaluation and eligibility criteria, including clinical and sociocultural factors; diagnosis of eligibility; venous access and antimicrobial infusion devices; protocols for antimicrobial use and monitoring and cost-effectiveness.

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Introduction

The use of outpatient parenteral antimicrobial therapy (OPAT) as a treatment strategy with the aim of de-hospitalizing patients has been growing since its advent during the 1970s.¹ OPAT has become a safe and standardized practice for patients presenting with various infections who require long-term parenteral antimicrobial therapy. International consensus guidelines have determined that OPAT can be performed in physicians' offices, clinics, specialized infusion centers or in patients' homes.^{2,3}

Patients should be selected for this type of treatment by physicians who are familiar with the infectious conditions that will be treated. They should also be evaluated by nurses who have experience in implementing and managing long-term venous access, and by social workers who will decide whether patients present social, economic and cultural conditions that allow them to be safely treated this way. If patient evaluation and selection are performed adequately, OPAT is acknowledged to be safe, effective, practical and cost-effective.

Its impacts from economic and hospital bed-occupancy points of view are high, as are the undeniable benefits to patients' (and their families') quality of life. By decreasing

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patients' need for and length of hospitalization, OPAT has also shown an impact through reducing healthcare-related infection rates.⁴⁻⁷

Organization of OPAT programs

The organization of OPAT programs should be hierarchical, such that patients are evaluated at an OPAT reference center before being sent to a healthcare unit where they will be treated with either a day-hospital regimen or through home-care. Likewise, every service that receives patients for OPAT needs to rely on a reference center to which patients can be promptly referred in the event of adverse events related to the treatment, along with the transportation logistics for such referrals. In addition to this referral and counter-referral organization, the structure of OPAT programs should always envisage the following:

- Multidisciplinary team trained to make evaluations regarding patients' eligibility for OPAT and to conduct follow-up on this type of therapy. These team should be led by a physician, preferably an infectious disease specialist with experience in using long-term parenteral antimicrobials. In addition, each team needs to include a nurse with experience in manipulating central venous access, and a social worker. A clinical pharmacist may also be included in the team, although this is still an uncommon professional in most Brazilian healthcare services. The functions of each of these professionals are described in Table 1. Other professionals can also be included in the team, according to the patient's profile and availability of the OPAT service provider.¹
- Up-to-date protocols for the rational use of antimicrobials and manipulation of venous access.
- Continuing educational programs to train the professionals involved in patient care within OPAT.

Patient evaluation and eligibility criteria for OPAT

Clinical factors

The main patient eligibility criterion for OPAT programs is the need for long-term parenteral antimicrobial treatment, preferably based on culture and antibiogram results. Oral treatment should always be given preference in cases whenever possible. In addition, only patients who are clinically stable and whose infection and possible comorbidities are under control can be referred for OPAT.

Sociocultural and family-related factors

Patients referred for OPAT should have the social and/or familial support needed for the particular features of this therapy. They need to assume co-responsibility for the treatment, especially in relation to adherence to the therapy and maintenance of venous access. In cases in which drug infusion can be performed at the patient's home, team members should

also certify that the location demonstrates the necessary conditions for safely performing venous infusions.

Patient's and caregiver's inability to comprehend the OPAT program, including catheter care and locomotion difficulties, should be considered an exclusion criterion for OPAT. It is not recommended that patients with histories of active alcoholism or drug addiction be candidates for this therapy practice, especially because of the risk of improper catheter manipulation. Table 2 shows the main characteristics to be evaluated for patient eligibility for OPAT.

Diagnosis of eligibility for OPAT

Patients with diagnoses of the infections described below are considered eligible for treatment under an OPAT regimen:

- Complicated upper respiratory tract infections, including malignant external otitis, necrotizing external otitis and rhinosinusitis⁸⁻¹¹;
- Respiratory infections, including complicated pneumonias, empyemas, lung abscesses, cystic fibrosis, exacerbations of the conditions of chronic obstructive pulmonary disease (COPD), infected bronchiectasis, community-acquired pneumonia, and nosocomial pneumonia¹²;
- **Microbiologically-proven** endocarditis due to *Streptococcus viridians*^{13,14} in patients who do not present signs of possible complications of infectious endocarditis or predictors of poor prognosis. Patients with conditions related to other agents or without microbiological proof are not considered eligible for OPAT in Brazil;
- Complicated infections of the urinary tract^{15,16};
- Intra-abdominal infections, including secondary peritonitis, abscess, sepsis, cholecystitis with perforation or abscess, intra-abdominal abscess, appendicitis with perforation or abscess, stomach or intestinal perforation, peritonitis, diverticulitis with perforation, peritonitis or abscess.^{17,18} Patients are considered eligible for OPAT when they have stabilized and do not require new surgical interventions;
- Skin and soft-tissue infections, including cellulitis, large abscesses, surgical wound infections, infected burns, infected ulcers, infected bites and pyomyositis.^{19,20} Patients are considered eligible for OPAT when they have stabilized and do not require surgical interventions;
- Osteoarticular infections, including pyoarthritis, acute and chronic osteomyelitis, and orthopedic implant-related infections.^{5,21}

Venous access and antimicrobial infusion devices

The type of medication, duration of therapy, frequency of antimicrobial administration, and condition of the patient's venous network should be taken into account when determining venous access mechanisms allowed for OPAT, either using peripheral or central devices. Central catheters are indicated in cases of parenteral antimicrobial treatment with an estimated duration longer than 14 days and when the prescribed antibiotics have a pH lower than five or higher than nine.

Table 1 – Professionals required for an OPAT program and their attributes.

Professional	Main attributes within the team
Physician (preferably an infectious disease specialist)	<ul style="list-style-type: none"> - Team leadership; - Clinical evaluation of patient's infectious conditions and their comorbidities; - Determination of whether clinical stability allowing OPAT exists; - Prescription of the antimicrobial to be used; - Participation in the decision of what type of catheter should be used by patients; - Participation in assessments on patient's and caregiver's capacity for comprehension; - Initial evaluation on patients who are recommended for OPAT^a; - Clinical and laboratory monitoring of patients undergoing OPAT^a; - Clinical evaluation of possible events presented during treatment and decision on the need for transferring to the reference center for OPAT^a.
Nurse (with experience in manipulation of central catheters)	<ul style="list-style-type: none"> - Prescription of drug infusion procedures for OPAT^a (reconstitution and dilution of antimicrobials and duration of infusion) in accordance with the protocol; - Participation in the decision regarding what type of catheter should be used by patients; - Participation in assessments of patient's and caregiver's capacity for comprehension; - Supervision of antimicrobial infusion; - Daily inspection of the catheter insertion site and communication with the doctor in the event of abnormalities; - Minimum of once-weekly changing of dressings at catheter insertion site; - Patient guidance regarding catheter care; - Patient guidance regarding drug storage precautions; - Evaluation of patient's home sanitary conditions, in the event of referral for homecare OPAT^a.
Social worker	<ul style="list-style-type: none"> - Participation in assessments of patient's and caregiver's capacity for comprehension; - Documentation of patient's and their caregiver's consent to OPAT; - Evaluation of patient's social conditions for OPAT (especially transportation); - Establishment of contact between patient's hospitalization service or reference center for OPAT and the healthcare service where the therapy will take place.
Clinical pharmacist	<ul style="list-style-type: none"> - Participation in assessments of patient's and caregiver's capacity for comprehension; - Participation in prescription of drug infusion procedures for OPAT (antimicrobial reconstitution and dilution, and duration of infusion), in accordance with the protocol; - Patient guidance about drug storage precautions; - Participation in clinical and laboratory monitoring of patients undergoing OPAT.

OPAT, outpatient parenteral antimicrobial therapy.

Table 2 – Main characteristics for patient eligibility for OPAT.

Clinical factors	<ul style="list-style-type: none"> ● Need for long-term parenteral antimicrobial treatment; ● Clinical stability; ● No histories of active alcoholism or drug addiction.
Sociocultural and family-related factors	<ul style="list-style-type: none"> ● Comprehension of OPAT and ability to collaborate; ● Ability to transport the patient to the infusion center, in cases of treatment under a day hospital regimen; ● Sanitary conditions of drug infusion at home, in cases of homecare.

OPAT, outpatient parenteral antimicrobial therapy.

Valved catheters of the PICC type (peripherally inserted central catheter) should be the device of choice for performing OPAT. Semi-implantable or totally-implantable catheters can be used, especially if the patient is already using one of these devices. Use of short-term central venous catheters (double or mono-lumen) for OPAT is contra-indicated.

Use of peripheral venous access for OPAT is possible, but it requires certainty that the patient has a good-quality peripheral venous network.²² Table 3 shows the types of central catheters indicated for OPAT in Brazil and their indications, duration, advantages and disadvantages.

Depending on the patient's clinical conditions and comorbidities, larger or smaller dilution volumes may be required. In these cases, participation of a physician, nurse, and clinical pharmacist is important for prescribing and guiding drug dilution. Table 4 shows the general recommendations

for reconstitution, dilution and infusion of antimicrobials used in OPAT, along with doses and posology of each drug envisaged. These recommendations can be modified according to the patient's clinical condition. Administration of antimicrobials in bolus form is not recommended.² Antimicrobial infusion should preferentially be performed under supervision of a nurse with experience in manipulating central catheters, in accordance with the following recommendations⁵:

- Prepare all materials to be used for antimicrobial infusion in advance;
- Sanitize hands before and after manipulating the catheter. Procedure gloves must be used;
- Before antimicrobial infusion, a flush using 0.9% saline solution should always be performed using 10 mL syringes

Table 3 – Types of central lines indicated for OPAT in Brazil.

Type of central line	Indication	Duration	Characteristics
Valved peripherally inserted central catheter (valved PICC)	Antimicrobial treatment with estimated duration longer than 14 days	Up to 6 months	<ul style="list-style-type: none"> - Cost-effective - Easy insertion - Lower incidence of infection - Lower risk of air embolism and reflux - Higher safety for homecare therapy
Tunneled semi-implanted central catheter	Antimicrobial treatment with estimated duration longer than 14 days	Up to 6 months	<ul style="list-style-type: none"> - Surgical implantation - Open extremity - Blockage using heparin solution is needed - Low risk of infection - 2nd choice for treatment, when insertion of PICC is not possible
Totally implanted central catheter	Antimicrobial treatment with estimated duration longer than 14 days	Up to 5 years	<ul style="list-style-type: none"> - High cost - Surgical implantation - Blockage using heparin solution is needed - Access through Huber needle, replaced every seven days - High risk of infection with daily manipulation (generally indicated for chemotherapy against cancer, which requires less manipulation) - Indication only for OPAT should be avoided

OPAT, outpatient parenteral antimicrobial therapy.

Table 4 – Recommendations and instructions for antimicrobial use in OPAT in Brazil.

Antimicrobial	Dose and posology for normal renal and hepatic functions	Reconstitution	Dilution	Duration of infusion
Amikacin	15 mg/kg once a day	Not required	100–200 mL of 0.9% SS, 5% GS or Ringer's lactate solution	30–60 min
×				
Gentamicin	5 mg/kg once a day	Not required	50–200 mL of 5% GS	30–120 min
Cefepime	2 g twice a day	10 mL of sterile distilled water	50–100 mL of 0.9% SS, 5% GS or Ringer's lactate solution	30 min
Ceftaroline	600 mg twice a day	20 mL of sterile distilled water	50–250 mL of 0.9% SS, 5% GS or Ringer's lactate solution	30 min
Ceftazidime	2 g twice a day	5–10 mL of sterile distilled water	50–100 mL of 0.9% SS, 5% GS or Ringer's lactate solution	30–60 min
Ceftriaxone	2 g once a day	10 mL of sterile distilled water	50–100 mL of 0.9% SS, 5% GS or Ringer's lactate solution	15–30 min
Ertapenem	1 g once a day	10 mL of sterile distilled water	50 mL of 0.9% SS	30 min
Meropenem	2 g twice a day	20 mL of sterile distilled water	250 mL of 0.9% SS or 5% GS	60 min
Vancomycin	15 mg/kg twice a day	10 mL of sterile distilled water	200 mL of 0.9% SS or 5% GS	60 min
Teicoplanin	6 mg/kg once a day	10 mL of sterile distilled water	50–100 mL of 0.9% SS, 5% GS or Ringer's lactate solution	60 min
Daptomycin	4–6 mg/kg once a day	10 mL of 0.9% SS	50 mL of 0.9% SS	30 min
Linezolid	600 mg twice a day	Not required	50–100 mL of 0.9% SS, 5% GS or Ringer's lactate solution	30–120 min
Tigecycline	50 mg twice a day	Not required	50 mL of 5% GS	30–60 min
Anidulafungin	100 mg once a day	30 mL of its own diluent	100 mL of 0.9% SS or 5% GS	90 min
Caspofungin	50 mg once a day	10 mL of sterile distilled water	100 mL of 0.9% SS	60 min
Micafungin	100 mg once a day	5 mL of 0.9% SS	50 mL of 0.9% SS or 5% GS	60 min
Voriconazole	3–4 mg/kg twice a day	19 mL of sterile distilled water	200–250 mL of 0.9% SS, 5% GS or Ringer's lactate solution	60–120v
Amphotericin B (lipid complex)	5 mg/kg once a day	20 mL of sterile distilled water	200–500 mL of 5% GS	120 min
Amphotericin B (liposomal)	3–5 mg/kg once a day	10 mL of sterile distilled water	200–500 mL of 5% GS	120 min

0.9% SS, 0.9% saline solution; 5% GS, 5% glucose solution. OPAT, outpatient parenteral antimicrobial therapy.

Table 5 – Recommendations of antimicrobials for pediatric patients in OPAT in Brazil.^a

Antimicrobial	Dose and posology for normal renal and hepatic functions
Amikacin	15 mg/kg once a day
Gentamicin	7 mg/kg once a day
Cefepime	50 mg/kg/dose twice a day
Ceftaroline	35–45 mg/kg in 3 doses
	Maximum dose 1200 mg/day
Ceftazidime	50 mg/kg/dose twice a day
Ceftriaxone	50 mg/kg once a day
	For meningitis, 50 mg/kg/dose twice a day
Ertapenem	15 mg/kg/dose twice a day
Meropenem	40 mg/kg/dose twice a day
Vancomycin	15 mg/kg/dose twice a day
Teicoplanin	6 mg/kg once a day
Daptomycin	There is no standardization
Linezolid	10 mg/kg/dose twice a day
Tigecycline	There is no standardization
Anidulafungin	There is no standardization
Caspofungin	50 mg/m ² once a day
Micafungin	There is no standardization
Voriconazole	4 mg/kg/dose twice a day
Amphotericin B (lipid complex)	5 mg/kg once a day
Amphotericin B (liposomal)	3–5 mg/kg once a day

OPAT, outpatient parenteral antimicrobial therapy.
^a For children over 28 days old.

(never use syringes with smaller or larger volumes, because of the pressure difference and risk of catheter rupture). In the case of patients with semi-implanted catheters (Hickman, Broviac or Leonard type) or totally implanted catheters (port-a-cath), 5 mL of blood should be aspirated before flushing, to remove the previously infused heparin solution;

- During preparation for antimicrobial infusion, the recommendations for reconstitution, dilution and duration of administration of the antibiotics should be carefully followed;
- At the end of the infusion, a new flush of 0.9% saline solution should be performed using a 10 mL syringe;
- For patients with semi-implanted catheters (Hickman, Broviac or Leonard type) or totally implanted catheters (port-a-cath), a seal should also be placed using 3–5 mL of heparin solution (100 IU/mL) after the last flush of saline solution. The catheter manufacturer's recommendations should be reviewed;
- The dressing and catheter stabilizer (if present) should be changed every seven days. Use transparent film to observe the insertion site;
- Communication between patients and their referral nurses is important in cases of possible accidents, such as catheter perforation, obstruction and exudation in the insertion area, or signs of bacteremia, phlebitis or thrombosis;
- Do not use the catheter if there are signs of infection during its insertion (hyperemia or exudation in the skin around the catheter) or bacteremia. Immediately send the patient to the team that performed the insertion or that has been designated for dealing with adverse event occurrences;
- In the event of obstruction, do not attempt to clear the catheter; in such cases, a peripheral venous puncture should be performed and the team that performed the insertion or that has been designated for dealing with adverse

event occurrences should be contacted in order to schedule a new catheter insertion;

- If the PICC has a caliber smaller than 3.8 Fr, blood must not be collected and blood byproducts must not be transfused.

Protocols for antimicrobial use and monitoring

Antimicrobial use within an OPAT regimen

Referral of patients for OPAT requires use of antimicrobial protocols adapted to this reality, especially regarding drug posology: the drugs need to be administered once or twice a day. The choice of antimicrobials should be based on culture and antibiogram results, if possible, and patient's comorbidities and possible drug interactions should be considered.^{5,23–26}

In Brazil, the following antimicrobials are considered acceptable for use in OPAT: amikacin, gentamicin, ceftriaxone, cefepime, ceftazidime, ceftaroline, ertapenem, linezolid (when formulation for oral use is not available), tigecycline, daptomycin, teicoplanin, vancomycin, amphotericin B (lipid formulations), caspofungin, anidulafungin, micafungin and voriconazole (when formulation for oral use is not available). Meropenem was also included, considering this drug could safely be administered twice a day in patients with stable clinical condition.^{5,27} Table 4 shows the dose and posology recommendations for using antimicrobials in OPAT in Brazil for patients with normal renal function, as well as recommendations for reconstitution, dilution and infusion of these drugs. Table 5 shows dose and posology recommendations for children outside of the neonatal period. In these cases, care regarding reconstitution, dilution and duration of infu-

Table 6 – Recommendations for routine monitoring in patients undergoing OPAT.

Antimicrobial	Minimum frequency of examinations to be performed					Observations
	Complete blood cell analysis	Renal evaluation (urea and creatinine)	Hepatic evaluation (ALT, AST, alkaline phosphatase and, gamma GT)	Potassium	CPK	
Amikacin	Every 14 days	Every 7 days	Every 14 days	Every 7 days	–	Ototoxicity may occur: monitor hearing and vestibular functions
Gentamicin	Every 14 days	Every 7 days	Every 14 days	Every 7 days	–	
Cefepime	Every 14 days	Every 14 days	Every 14 days	–	–	A decrease in the convulsive threshold may occur A decrease in the convulsive threshold may occur Serum level control (vancomycin) can be performed every 7 days
Ceftaroline	Every 14 days	Every 14 days	Every 14 days	–	–	
Ceftazidime	Every 14 days	Every 14 days	Every 14 days	–	–	
Ceftriaxone	Every 14 days	Every 14 days	Every 7 days	–	–	
Ertapenem	Every 14 days	Every 14 days	Every 14 days	–	–	
Meropenem	Every 14 days	Every 14 days	Every 14 days	–	–	
Vancomycin	Every 7 days	Every 7 days	Every 7 days	Every 7 days	–	
Teicoplanin	Every 14 days	Every 14 days	Every 14 days	–	–	Optical neuropathy may occur: monitor visual acuity
Daptomycin	Every 14 days	Every 14 days	Every 14 days	–	Every 7 days	
Linezolid	Every 7 days	Every 14 days	Every 14 days	–	–	
Tigecycline	Every 14 days	Every 14 days	Every 7 days	–	–	Nausea may occur even in the absence of hepatic enzyme alterations; consider concomitant administration of antiemetics
Anidulafungin	Every 14 days	Every 14 days	Every 14 days	–	–	Weekly dose of magnesium may be necessary
Caspofungin	Every 14 days	Every 14 days	Every 14 days	–	–	
Micafungin	Every 14 days	Every 14 days	Every 14 days	–	–	
Voriconazole	Every 14 days	Every 14 days	Every 14 days	–	–	
Amphotericin B (lipid complex)	Every 7 days	Every 3 days	Every 7 days	Every 3 days	–	
Amphotericin B (liposomal)	Every 7 days	Every 3 days	Every 7 days	Every 3 days	–	

OPAT, outpatient parenteral antimicrobial therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Gamma GT, gamma glutamyl-transferase; CPK, creatine phosphokinase.

sion need to be specified in accordance with the instructions from the physician responsible for the case.

Monitoring

Patients undergoing OPAT should be monitored from the clinical and laboratory points of view. Adverse events include catheter-related issues (insertion site infection, bacteremia, blood stream infection and air embolism), drug infusion-related problems, and side effects relating to the antimicrobial

used. The entire multidisciplinary team needs to be alert to the occurrences of these events and be trained to take the necessary actions. The team should also be trained to detect possible hypersensitivity reactions (allergies) to antimicrobials, which may appear at any time during the treatment.

Laboratory drug monitoring should be conducted every two weeks for the majority of the drugs used. Because of the higher reported occurrence of renal side effects, patients using amikacin, gentamicin, vancomycin and amphotericin

B (lipid formulations) should have weekly doses of urea and creatinine.^{5,2} When necessary, monitoring of serum levels of vancomycin can also be performed weekly.² Table 6 shows the monitoring recommendations for patients undergoing OPAT according to the antimicrobial used. These recommendations can be adapted according to the presence of comorbidities or particular situations of each patient.

Cost-effectiveness

Implementation of an OPAT system has been shown to impact the number and duration of hospitalizations of patients with infections that require long-term parenteral treatments. It also ensures favorable clinical outcomes and improves the patient's quality of life. In addition to individual benefits, OPAT enables better allocation of hospital beds and resources if implemented as a healthcare policy because it demonstrates high cost-effectiveness.

Studies conducted in other countries have shown that the cost of a patient treated with an OPAT regimen is between 40 and 75% lower than the cost of a patient who is treated with a hospital regimen. This resource saving can reach 40,000 dollars per patient.^{28–32} In Brazil, implementation of an OPAT program in a public orthopedics and trauma hospital was shown to enable reallocation of over 11,000 hospital beds for patients who required hospitalization.⁵

Therefore, it can be concluded that, in addition to the advantages mentioned above, implementation of OPAT strategies in Brazil can lead to better allocation of healthcare resources, both within the public National Health System and in the private (supplementary) system.

Conflicts of interest

- Priscila R. Oliveira: Declares participation in educational activities for MSD, Sanofi-Aventis, Bayer Schering Pharma, Pfizer and Abbott and has developed clinical research activities for MSD and Pfizer.
- Vladimir C. Carvalho: Declares participation in educational activities for MSD and Pfizer and has developed clinical research activities for MSD and Pfizer.
- Sergio Cimmerman: Declares participation in educational activities for Abbvie, BMS, Farnocimica, Gilead, Janseen, MSD, United Medical.
- Ana Lucia M. Lima: Member of advisory board for Sanofi-Aventis. Declares participation in educational activities for MSD, Sanofi-Aventis, Bayer Schering Pharma, Pfizer and Abbott and has developed clinical research activities for MSD and Pfizer.

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Appendix A.

Diretrizes Brasileiras para Terapia Antimicrobiana Parenteral Ambulatorial group: Ana Cristina Gales, Universidade Federal de São Paulo; Bil Randerson Bassetti, Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória; Carla Sakuma de Oliveira, Universidade Estadual do Oeste do Paraná; Cassia da Silva Felix, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; César Leite, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; Eitan Naaman Berezin, Faculdade de Ciências Médicas da Santa Casa de São Paulo; Eliana Lima Bicudo dos Santos, Secretaria da Saúde do Distrito Federal; Guillermo S. Pinheiro de Lemos, Hospital de Urgências de Goiânia; Ivan Silva Marinho, Hospital e Maternidade São Camilo; Mariangela Ribeiro Resende, Universidade Estadual de Campinas; Marcos Cyrillo, Secretaria Municipal de Saúde de São Paulo; Mário Sérgio Lei Munhoz, Universidade Federal de São Paulo; Sylvia Maria de Lemos Hinrichsen, Universidade Federal de Pernambuco; Tania Mara Varejão Strabelli, Universidade de São Paulo.

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