THERAPEUTIC ADVANCES in
Infectious Disease

Review

Taking the route less traveled: on the way to COpAT

Ther Adv Infect Dis

2023, Vol. 10: 1–16

DOI: 10.1177/20499361231192771

© The Author(s), 2023.
Article reuse guidelines: sagepub.com/journals-permissions

Margaret Pertzborn, Christina G. Rivera and Don Bambino Geno Tai

***Abstract*:** Antimicrobial therapy is an essential practice within medicine. Over the last 4 years, complex outpatient antimicrobial therapy (COpAT) with oral antimicrobials has become a rapidly developing area of practice and is non-inferior to outpatient parenteral antimicrobial therapy (OPAT) in certain infectious syndromes. Currently, the available literature does not describe the implementation of oral antimicrobials within the current outpatient antimicrobial therapy process. Throughout this article, the authors present a review of current literature, a proposed definition of COpAT and offer methods readers can utilize to implement an integrated COpAT/OPAT program with oral antimicrobial-specific monitoring within their current practice.

Keywords: antimicrobial therapy, artificial intelligence, bone and joint infections, complex outpatient antimicrobial therapy, COpAT, endocarditis, OPAT, oral antibiotics

Received: 17 March 2023; revised manuscript accepted: 20 July 2023.

Correspondence to:
Margaret Pertzborn
Department of Pharmacy, Mayo Clinic Health System, 1400 Bellinger Street, Eau Claire, WI 54702-1510, USA.
Pertzborn.Margaret@mayo.edu

Christina G. Rivera
Department of Pharmacy, Mayo Clinic, Rochester, MN, USA

Don Bambino Geno Tai
Division of Infectious Diseases and International Medicine, University of Minnesota, Minneapolis, MN, USA

Introduction

Antimicrobial therapy is one of the cornerstones of medical practice. Traditionally, intravenous (IV) antimicrobials are considered more effective than oral antimicrobials and are generally preferred for severe infections. However, the most recent wave sweeping through infectious disease practices involves utilizing oral antimicrobials for severe infections, historically treated with IV antimicrobials almost exclusively, often through outpatient parenteral antimicrobial therapy (OPAT). This is with good reason; no randomized clinical trial has definitively concluded that IV antimicrobials are superior to oral antimicrobials. The prevailing notion of IV antimicrobial superiority is primarily driven by conventional thinking rather than evidence.[1] With this change in practice, a new way of administering and monitoring oral antimicrobials, called complex outpatient antimicrobial therapy (COpAT), has emerged. This article reviews the studies behind the resurgence of oral antimicrobials for the treatment of severe infections. We look back at the history of OPAT/COpAT, propose a formal definition for COpAT and delve into the process of evolving OPAT programs into robust OPAT/COpAT programs.

Methods

A narrative review of COpAT was performed utilizing Medline, and Google Scholar to search for the key terms, 'COpAT', and 'outpatient antimicrobials' to identify PubMed and non-PubMed indexed publications with a citation date through 1 March 2023. Identified articles were then reviewed for relevance; narrative reviews without new data and opinion pieces were allowed. Research limited to the acute care (inpatient) setting was excluded.

History of OPAT

When discussing COpAT, it is essential to distinguish between the multiple acronyms that are utilized in the outpatient antimicrobial workspace. Though the use of the term COpAT was first utilized in the last 5 years, community-based outpatient parenteral antimicrobial/anti-infective

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the Sage and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

therapy (CoPAT) can be found in literature dating back decades.[2–4] OPAT refers to outpatient or community-based infection management *via* IV antimicrobials.[5] Understandably, the difference between COpAT, CoPAT, and OPAT can be challenging to distinguish. In more recent literature, COpAT has more commonly been in reference to oral antimicrobials, and OPAT is most often utilized when referring to parenteral antimicrobials.

The first reported administration of successful OPAT was in 1974 for chronic bronchopulmonary infections in pediatric patients with cystic fibrosis.[6] Since the inception of OPAT, utilization has grown significantly and has become standard of care for many different infections, including osteoarticular infections, bacteremia, and endocarditis.[7–9] Efficacy has been demonstrated among all age groups and in various practice settings, such as the US Veterans Affairs medical centers, long-term care facilities, academic programs, and private practices.[7,10–13]

Multiple studies have demonstrated numerous benefits of OPAT when compared to continued hospitalization, such as shorter hospital stays; prevention of hospital-associated conditions, including nosocomial infections; and decreased cost.[14–16] Additional advantages include the positive social impact from resuming activities of daily living with return to home, work, and school, as well as increased patient satisfaction.[17–19]

Renaissance of oral antimicrobials

The landmark Oral *versus* Intravenous Antibiotics for Bone and Joint Infection (OVIVA) and Partial Oral Treatment of Endocarditis (POET) trials brought about the renaissance of oral antimicrobials.

OVIVA was a randomized, non-inferiority trial that enrolled patients with extra-axial skeleton osteomyelitis, septic arthritis requiring excision arthroplasty, periprosthetic joint infections (PJIs), orthopedic fixation-device infections, and native vertebral osteomyelitis. It concluded that oral antimicrobials are non-inferior to IV antimicrobials for treating bone and joint infections (BJI).[20] Another randomized trial examined 60 patients with PJIs managed with debridement and implant retention and received 12 weeks of therapy, and compared initial 2-week *versus* 6-week IV antimicrobials followed by oral antimicrobials. The study concluded that clinical cure was not statistically different between the two groups (71% *versus* 76%, respectively; $p = 0.77$).[21] A meta-analysis resulted in a similar finding. Although there was moderate to high heterogeneity, analysis of nine studies showed no significant difference in the overall success rate between short *versus* longer duration of IV antimicrobials.[22] Retrospective studies further supported these findings for PJI and native vertebral osteomyelitis.[23,24]

Despite the available evidence, oral antimicrobial regimens for serious infections appear underutilized. Two recent studies in the United States (US) and one in the United Kingdom (UK) explored opportunities for highly bioavailable oral(s) to replace IV antimicrobials for BJI.

In the UK study, OVIVA study criteria were used to infer the eligibility of OPAT patients with BJIs for oral antimicrobial regimens and assess possible cost savings using the OPAT database at University College London Hospitals National Health Service Foundation Trust from January 2015 to October 2018. Clinical diagnosis, microbiological data, and allergies were reviewed to ascertain effective oral antimicrobial regimen availability. Daily antimicrobial costs were derived from their hospital pharmacy list pricing. Of 133 OPAT patients treated for BJI, 106 (79.7%) were considered candidates for oral antimicrobial(s); the most common reason for ineligibility was organism non-susceptibility. The authors estimated saving a median of 19.5 IV-antimicrobial days (Interquartile range [IQR] 8.5–37) and UK £1,234 (IQR 569–2594) per patient based on a 6-week oral treatment course.[25]

A retrospective study reproduced the UK study at a single center in the US from January 2018 to April 2020. Of 445 OPAT patients treated for BJI, 281 (73.9%) met the OVIVA inclusion criteria. The most common cause for exclusion was organism non-susceptibility. Of those who met OVIVA criteria but received IV, 69 (25%) patients required an antimicrobial switch, 13 (5%) patients had vascular access complications, and 6 (2%) patients developed *Clostridioides difficile* infection. Oral therapy was estimated to offer an average savings of US$3,270.69 per patient to the US healthcare system.[26]

Applying the OVIVA criteria to 145 randomly selected patients across eight Veterans Affairs centers retrospectively between 1 January 2018 and 31 December 2020, resulted in similar findings. This study allowed for the use of beta-lactams (penicillins), whereas the other two did not include use of oral beta-lactams.[27] Of the 109 (75.2%) patients eligible for oral step-down, 18 (16.5%) of these patients received orals. Two patients had *Staphylococcus aureus* bacteremia concomitant with BJI and were switched to oral therapy after 2 weeks of IV antimicrobials. There was no significant difference in oral use among eligible patients between 2018 at 12.8% (pre-OVIVA) and 2019–2020 (post-OVIVA) at 18.6% ($p = 0.44$); however, this comparison may have been underpowered. As the majority of patients who transitioned to oral antimicrobials were from a single medical center, the authors suggested that the adoption of orals for BJI is strongly dependent on local practice patterns and institutional norms, as seen with general hospital antimicrobial-prescribing practices.[28,29]

A commentary by Seidelman and Sexton[30] cited concerns with the use of orals for BJI, such as patient non-adherence, gastrointestinal intolerance, the emergence of resistance, particularly with *S. aureus*, litigation risk with a high overall treatment failure rate, heterogeneity of syndromes in OVIVA, and risk of low drug exposure in those with high body weight or gastric bypass. Given the controversy, contemporary data is needed to benchmark oral antimicrobial uptake in BJIs. An Emerging Infections Network-sponsored survey is ongoing to assess the current use of oral antimicrobials in the practice of BJIs; results are highly anticipated.

POET enrolled patients with left-sided endocarditis caused by streptococci, *Enterococcus faecalis*, *S. aureus*, or coagulase-negative staphylococci in a randomized non-inferiority trial to continue IV antimicrobials or transition to oral antimicrobials after 10 days of IV therapy. It was concluded that transitioning to oral antimicrobial therapy was non-inferior to continuing IV antimicrobial therapy in these patients.[31] Patients included in the POET trial were also followed for anxiety and depression with the Hospital Anxiety and Depression Scale, at randomization and through 6 months. It was found that throughout treatment, patients in the partial oral group had numerically lower levels of both anxiety and depression when compared to the IV group, though statistical significance was not met.[32] A retrospective study of patients with endocarditis confirmed these findings post-POET. This study compared 46 patients partially treated with oral antimicrobials to 211 patients treated exclusively with IV antimicrobials. There was no statistically significant difference in the recurrence of bacteremia or readmission at 90 days, patients within the oral therapy group also had significantly fewer adverse events.[33]

Enter COpAT

COpAT was first described in the literature, followed by the OVIVA trial in 2019, as oral antimicrobial therapy and monitoring within a comprehensive BJI service that traditionally focused on IV antimicrobial therapy.[2] Though the concept of COpAT as we know it today first emerged in the last 4 years, complex oral antimicrobial regimens have long existed in the realm of other infectious etiologies. Management of nontuberculous mycobacterial disease and tuberculosis involve complex, multi-drug regimens that require long-term treatment and monitoring in the outpatient setting.[34] Furthermore, clinicians caring for patients living with human immunodeficiency virus and acquired immunodeficiency syndrome frequently prescribe and monitor multiple antimicrobial agents simultaneously to treat and prevent opportunistic infections.[35] These are examples of de facto COpAT that clinicians have already deployed in practice over the past few decades. There is no definition for COpAT or specific criteria to define when an oral antimicrobial regimen would be considered complex. The more widely known OPAT is formally defined by an Infectious Disease Society of America (IDSA) panel as the administration of two or more doses of parenteral antimicrobial therapy on different days without intervening hospitalization.[5]

In the landmark trials that brought about COpAT, many patients were treated with a combination of oral antimicrobials and a prolonged duration of therapy. In the OVIVA trial, the median duration of therapy in the oral group was 71 days, and the majority of patients randomized to the oral antimicrobial group received combination therapy. More than half of patients received rifampin and other antimicrobials (beta-lactams, quinolones, tetracyclines, macrolides, and lincosamides). The POET trial included only combination regimens, with a median duration of 34 days.[20,31] Based on

other real-life applications of these trials, the COpAT duration of therapy is at least 30 days, with regimens inclusive of all antimicrobial classes, and can consist of a single antimicrobial or multiple antimicrobials.[2,36]

Redefining outpatient antimicrobial therapy

Adapting from available literature, we define an oral antimicrobial regimen as complex when (1) the anticipated duration of treatment is more than 30 days, or (2) the administration of oral antimicrobial(s) can cause significant adverse drug events (e.g., acute kidney injury, drug-induced liver injury, leukopenia). As the practice of outpatient antimicrobial therapy for severe infections expands to include complex oral antimicrobial regimens, it is important to consider how we can include these patients within our practice. We propose transitioning to an outpatient antimicrobial practice encompassing oral and IV antimicrobials under the same umbrella to provide a full OPAT/COpAT service. Traditional OPAT principles of monitoring and follow-up can be applied to oral antimicrobials to ensure the appropriate clinical response to therapy and monitor for any toxicities from antimicrobials.

From OPAT to COpAT

The IDSA published OPAT guidelines in 2018 and provided recommendations for best practices in managing these patients. The panel recommended that initial patient follow-up be within 1–2 weeks of hospital discharge, the authors provided excellent expert opinion, noting that most of the evidence is either low or very low quality.[5] Monitoring for adverse drug reactions with clinical and laboratory testing was associated with better outcomes. However, the frequency and types of laboratory testing required to monitor safety while on antimicrobial therapy are not well studied. One study showed that weekly monitoring of complete blood count, renal function, and hepatic enzymes rarely showed severe adverse drug reactions or resulted in changes to the antimicrobial regimen, though it remains the standard recommended frequency in IDSA guidelines and is adopted into many clinical OPAT services.[5,37] Multidisciplinary teams have also been noted as essential for appropriate monitoring of an OPAT service and often include an infectious diseases provider, infectious diseases pharmacist, and case management/nursing.[5,38]

While many centers and institutions have protocols developed to guide their OPAT programs and IDSA guidelines for a basis of OPAT practice, there is a lack of professionally endorsed recommendations for COpAT programs. As part of the OVIVA trial protocol patients were seen according to routine policy at local study sites with minimum reviews at 6 weeks (range 21–63 days), 4 months (range 70–180 days), and 1 year (range 250–420 days), within the protocol no description of routine laboratory monitoring was provided.[20] A 'real world' implementation of OVIVA in a UK orthopedic specialty hospital detailed their COpAT approach. Cases underwent multidisciplinary team review. Patients were followed weekly through telemedicine and had in-person visits at 6 and 12 weeks. Serum laboratory monitoring was performed at the discretion of the treating clinician.[36] A practice survey in the US showed that OPAT programs had a median of 43 patients (IQR 10–65) actively enrolled on a given day. Most patients were on IV antimicrobials, and around 10% received orals. Patients on OPAT were usually seen once per month (42.3%) or once weekly (19.2%). In contrast, patients on orals had more variability in visit frequency, the most common intervals being once monthly (33.3%) or nonstandard follow-up (37.5%). Telemedicine was available to over 70% of respondents.[39]

The same principles and best practices that apply to OPAT can also be employed in COpAT. These include program candidate screening, ensuring appropriate antimicrobial regimens (bug-drug match, duration, route), routine review of laboratory results, managing drug interactions and emergent antimicrobial intolerances (e.g., rash), counseling patients, and coordinating care with other clinicians. Pharmacists, physician assistants, and nurse practitioners can, and ideally, should be integrated into all these steps. Additionally, when transitioning between oral antimicrobials or chronic oral suppression, pharmacists can counsel patients, ensure medication access, and ensure appropriate follow-up monitoring is ordered.[40] The operational elements and differences between OPAT and COpAT are highlighted in Table 1.

Table 1. Comparison of operational elements of OPAT and COpAT.

	OPAT	COpAT
Optimal multidisciplinary team	Physician/advance practice provider Nurse Pharmacist Social worker E-health assistant	
Patient care setting	Home Skilled facility Acute care in the home	
	Infusion therapy center	
Vascular access for antimicrobial administration	Central venus catheter Midline Peripheral access	None
Vascular access maintenance	Home health Infusion therapy center	None
Lab monitoring frequency	At least once weekly*	At least every 2–4 weeks**
Infectious diseases provider consult	Required at most institutions	Recommended
During treatment visit(s) for clinical assessment	Varies by infectious syndrome and practice site	Varies by infectious syndrome and practice site
End of treatment visit	Required (clinical assessment and vascular access removal)	Recommended (clinical assessment)
Medication dispensing	Home infusion pharmacy Hospital Pharmacy	Retail pharmacy
Medication quantity dispensed	Up to 1 week dispensed for home infusion Single dose administered at infusion location	Typically entire therapy course
Insurance coverage in the US	Commonly under medical benefit	Pharmacy benefit

*Based on IDSA guidelines.
**Expert opinion.
COpAT, complex outpatient antimicrobial therapy; E-health, electronic-health; IDSA, Infectious Diseases Society of America; OPAT, outpatient parenteral antimicrobial therapy; US, United States.

We have summarized the most common oral antimicrobials used in practice, including recommendations for monitoring (Table 2). These recommendations are specifically to monitor for antimicrobial side effects. Notably, we recommend obtaining specific laboratory results over those within a panel (i.e., ALT *versus* hepatic panel or comprehensive metabolic panel); implementing this targeted approach within practice allows for simplification of laboratory review and empowers nurses and pharmacists to utilize protocols to manage any abnormalities, while limiting the need for unnecessary laboratory testing.

Operationally there are many elements OPAT programs have established that are able to be leveraged when building a COpAT program, while others may need to be uniquely developed. These recommendations for building an OPAT/COpAT program are gleaned from related studies, practice surveys, and expert opinion. The optimal build for a COpAT program will depend on the individual institutional resources, preferences, and local regulations for those utilizing collaborative practice agreements. General considerations with accompanying commentary on steps to starting a COpAT program are discussed in Table 3.

Table 2. Recommendations for oral antimicrobial dosing and monitoring.*

Common COpAT antimicrobials (treatment for > 30 days or high toxicity risk)						
Oral antimicrobial	**Standard oral dosing**	**Bioavailability**	**Adverse drug events**	**Monitoring**	**Monitoring frequency**	**Drug interactions**
Amoxicillin	500–1000 mg TID	74–92%	GI, rash, hepatotoxicity	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	None clinically relevant
Amoxicillin/ clavulanate	875/125 mg BID	60%	GI, rash, hepatotoxicity	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	None clinically relevant
Azithromycin	250–500 mg daily 500 mg TIW (NTM)	38%	GI, QTc prolongation, hearing changes	ALT, Audiogram, ECG TDM in select circumstances	ALT: Baseline, then once every 2-4 weeks Audiogram: Baseline, then if symptomatic** ECG: Baseline, then at least monthly	QTc prolonging medications, magnesium, and aluminum containing products
Bedaquiline	400 mg daily for 2 weeks, then 200 mg TIW thereafter	Unknown	GI, QTc prolongation, hepatotoxicity, arthralgia	Alk phos, ALT, AST, Bilirubin, ECG TDM in select circumstances	Labs: Baseline, then monthly ECG: Baseline, after 2 weeks, then at least monthly	QTc prolonging medications, CYP3A4 Inducers, CYP3A4 inhibitors
Cefadroxil	500–1000 mg BID	90%	Hypersensitivity, hepatotoxicity, serum sickness	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	None clinically relevant
Cefdinir	300 mg BID	16–21%	GI, hypersensitivity, hepatotoxicity	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	Iron, antacids
Cefpodoxime	200–400 mg BID	50%	GI, hypersensitivity, hepatotoxicity	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	Acid reducing medications, cation containing products
Cephalexin	500–1000 mg q6H	90–100%	GI, hypersensitivity, hepatotoxicity	ALT, CBC, SCr	Baseline, then once every 2–4 weeks	Zinc
Ciprofloxacin	500–750 mg BID	70–80%	GI, QTc prolongation, tendinitis, AAA, retinal detachment, dysglycemia, psychiatric/CNS disturbances	ALT, SCr, ECG TDM in select circumstances	Labs: Baseline, then once every 1–2 weeks ECG: Baseline, then at least monthly	QTc prolonging medications, cation containing products, CYP1A2 substrates, CYP3A4 substrates

(Continued)

Table 2. (Continued)

Common COpAT antimicrobials (treatment for > 30 days or high toxicity risk)						
Oral antimicrobial	**Standard oral dosing**	**Bioavailability**	**Adverse drug events**	**Monitoring**	**Monitoring frequency**	**Drug interactions**
Clindamycin hydrochloride	150–450 mg q6H	90%	GI, hypersensitivity, hepatotoxicity	Not routinely indicated	N/A	CYP3A4 inducers, CYP3A4 inhibitors, neuromuscular-blocking agents
Clarithromycin	500 mg BID 500 mg TIW (NTM)	50–55%	GI, QTc prolongation, hearing changes	ALT, SCr, Audiogram, ECG TDM in select circumstances	Labs: Baseline, then once every 2–4 weeks Audiogram: Baseline, then if symptomatic** ECG: Baseline, then at least monthly	QTc prolonging medications, CYP3A4 substrates, CYP3A4 inducers, P-gp substrates
Clofazimine	50–100 mg daily	68–95%	Body fluid discoloration, skin changes, GI, QTc prolongation, hepatotoxicity	ALT, ECG TDM in select circumstances	ALT: Baseline, then once every 2–4 weeks ECG: Baseline, after 2 weeks, then at least monthly	QTc prolonging medications, cation containing products, CYP3A4 substrates, CYP2D6 substrates, CYP2C8 substrates
Dapsone	100 mg daily	86%	Hemolytic anemia, dapsone syndrome, eosinophilic pneumonitis	ALT, CBC, G6PD, SCr	ALT, SCr: Baseline, then periodically CBC: Weekly for 1 month, then once monthly G6PD: Baseline	CYP3A4 inducers
Delafloxacin	450 mg BID	58%	GI, QTc prolongation, tendon, joint and muscle pathologies, peripheral neuropathy, CNS disturbances, exacerbation of myasthenia gravis or psychiatric disorders	ALT, SCr, ECG	Labs: Baseline, then every 1–2 weeks ECG: Baseline, then periodically	Cation containing products
Doxycycline	100 mg BID	95%	GI, photosensitivity, esophageal ulceration	ALT, CBC	Baseline, then periodically	Cation containing products, rifampin, phenytoin, phenobarbital, carbamazepine

(Continued)

Table 2. (Continued)

Common COpAT antimicrobials (treatment for > 30 days or high toxicity risk)						
Oral antimicrobial	**Standard oral dosing**	**Bioavailability**	**Adverse drug events**	**Monitoring**	**Monitoring frequency**	**Drug interactions**
Ethambutol	15–20 mg/kg daily (max 1600 mg)	80%	Optic neuritis, peripheral neuropathy, hepatotoxicity	ALT, Ishihara color test, visual acuity testing TDM in select circumstances	ALT: Baseline, then monthly Ishihara: Baseline, monthly self-assessment Vision: Baseline, then every 1–3 months	Aluminum containing products
Fluconazole	100–800 mg BID	⩾90%	Hair loss, hepatotoxicity, GI, QTc prolongation	ALT, Scr, ECG TDM in select circumstances	ALT, SCr: Baseline, in 2 weeks, then at least monthly ECG: Baseline, then at least monthly	CYP2C9 substrates, CYP2C19 substrates CYP3A4 substrates, QTc prolonging agents
Isoniazid	5 mg/kg daily (max 300 mg) Administer with pyridoxine 50-100 mg daily	90% (decreased with food)	Peripheral neuropathy, hepatotoxicity, neurotoxicity, cytopenias, MAO inhibition	Alk phos, ALT TDM in select circumstances	Baseline, then at least monthly	CYP2C9 substrates, CYP2C19 substrates CYP3A4 substrates, CYP2A6 substrates, CYP2E1 substrates Avoid with tyramine and histamine containing foods
Itraconazole	100–300 mg daily to BID (capsule, solution) 130–260 mg daily to BID (SUBA® formulation) Formulations are not interchangeable	55% (capsule-increased with food) 85% (solution-decreased with food) 90% (SUBA® formulation)	Heart failure, hypertension, hepatotoxicity, QTc prolongation	ALT, potassium, sodium, ECG TDM	ALT: Baseline, in 2 weeks, then monthly Potassium, Sodium: Baseline, then periodically ECG: Baseline, then at least monthly	QTc prolonging medications, CYP3A4 substrates, P-gp substrates, CYP3A4 inducers, CYP3A4 inhibitors, acid-reducing medications (itraconazole capsule only)
Isavuconazonium sulfate	372 mg TID for six doses, then 372 mg daily	98%	Hepatotoxicity, QTc shortening, peripheral edema	ALT TDM in select circumstances	ALT: Baseline, in 2 weeks, then at least monthly	CYP3A4 substrates, P-gp substrates, CYP3A4 inducers, CYP3A4 inhibitors

(Continued)

Table 2. (Continued)

Common COpAT antimicrobials (treatment for > 30 days or high toxicity risk)						
Oral antimicrobial	**Standard oral dosing**	**Bioavailability**	**Adverse drug events**	**Monitoring**	**Monitoring frequency**	**Drug interactions**
Levofloxacin	500–750 mg daily	99%	GI, QTc prolongation, tendinitis, AAA, retinal detachment, dysglycemia, psychiatric/CNS disturbances	ALT, SCr, ECG TDM in select circumstances	Labs: Baseline, then every 1–2 weeks ECG: Baseline, then at least monthly	QTc prolonging medications, cation containing products
Linezolid	600 mg BID 600 mg once daily has been used for NTM	100%	GI, myelosuppression, neuropathy, serotonin syndrome, optic neuropathy, lactic acidosis	CBC TDM in select circumstances	Baseline, weekly for 2 weeks, then twice weekly thereafter	Serotonergic agents
Metronidazole	500 mg BID or TID	99%	GI, CNS toxicity, peripheral toxicity Use beyond 6 weeks not recommended due to increased toxicities	ALT, CBC, SCr	Baseline, then every 2–4 weeks	CYP2C9 substrates, warfarin, QTc prolonging agents, ethanol
Minocycline	100 mg BID	95%	GI, photosensitivity, esophageal ulceration, dizziness	ALT, CBC	Baseline, then periodically	Cation containing products, rifampin, phenytoin, phenobarbital, carbamazepine
Moxifloxacin	400 mg daily	90%	GI, QTc prolongation, Tendinitis, AAA	ALT, SCr, ECG TDM in select circumstances	Labs: Baseline, then every 1–2 weeks ECG: Baseline, then at least monthly	QTc prolonging medications, cation containing products
Omadacycline	300 mg daily	34.5%	GI, hepatotoxicity	ALT	Baseline, then periodically	Cation containing products, anticoagulants
Penicillin V potassium	250–500 mg TID or q6H	50%	GI, hypersensitivity, black hairy tongue	ALT, CBC, SCr	Baseline, then every 2–4 weeks	None clinically relevant
Posaconazole	300 mg BID (DR tablets) 100–300 mg daily to TID (suspension)	54%	Hypertension, hypokalemia, hepatotoxicity, pseudohyperaldosteronism, QTc prolongation	ALT, potassium, sodium TDM	ALT: Baseline, every 2 weeks, then at least monthly Potassium, Sodium: Baseline, then periodically ECG: Baseline, then at least monthly	QTc prolonging medications, CYP3A4 substrates, acid-reducing medications (suspension only)

(Continued)

Table 2. (Continued)

Common COpAT antimicrobials (treatment for > 30 days or high toxicity risk)						
Oral antimicrobial	**Standard oral dosing**	**Bioavailability**	**Adverse drug events**	**Monitoring**	**Monitoring frequency**	**Drug interactions**
Pyrazinamide	25–40 mg/kg daily (max 2000 mg)	>90%	GI, arthralgia, myalgia, hepatotoxicity	Alk phos, ALT, Uric acid TDM in select circumstances	Alk phos, ALT: Baseline, then at least monthly Uric acid: Periodically	Cyclosporine
Rifabutin	5 mg/kg daily (max 300 mg)	85%	Discoloration of body fluids, GI, uveitis, myelosuppression, arthralgias, hepatotoxicity	Alk phos, ALT TDM in select circumstances	Baseline, in 2 weeks, then monthly	CYP3A4 substrates, CYP3A4 inducers, CYP3A4 inhibitors, oral hormonal contraceptives
Rifampin	10 mg/kg daily (max 600 mg)	86%	Discoloration of body fluids, GI, myelosuppression, arthralgias, hepatotoxicity	Alk phos, ALT TDM in select circumstances	Baseline, in 2 weeks, then monthly	Substrates of CYP3A4, 2D6, 1A2, 2B6, 2C8/9, and P-gp, oral hormonal contraceptives
Sulfamethoxazole/trimethoprim	10–20 mg/kg/day (TMP component) in divided doses OR 1–2 DS (800/160 mg) tablet(s) BID	~90%	GI, rash, nephrotoxicity, myelosuppression	ALT, CBC, potassium, SCr TDM in select circumstances	High dose (TMP 10–20 mg/kg/day): Baseline, then weekly For prolonged oral standard dosing (1–2 DS tablet(s) BID): Baseline, then every 2–4 weeks	Methotrexate, CYP2C8/9 substrates, CYP2C9 inhibitors, CYP2C9 inducers, P-gp inhibitors
Tedizolid	200 mg daily	91%	GI, myelosuppression, neuropathy	CBC	Baseline, weekly for 2 weeks, twice weekly thereafter	None clinically relevant
Voriconazole	200 mg BID	96%	Visual changes, fluoride toxicity, photosensitivity, squamous cell carcinomas, QTc prolongation	ALT, ECG TDM	ALT: Baseline, in 2 weeks, then monthly ECG: Baseline, then at least monthly	Substrates, inducers, and inhibitors of CYP3A4, CYP2C9 and CYP2C19

*See supplementary for main sources of data.
**Consider routine audiograms every 1–3 months when used long term (i.e., NTM) or in combination with ototoxic drugs (aminoglycosides, etc.)
AAA, abdominal aortic aneurysm; Alk phos, alkaline phosphatase; ALT, alanine aminotransaminase; AST, aspartate aminotransferase; BID, twice daily; CBC, complete blood count; CNS, central nervous system; COpAT, complex outpatient antimicrobial therapy; CYP, cytochrome P450; DS, double strength; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; IND, investigational new drug; MAO, monoamine oxidase; max, maximum; N/A, not applicable; NTM, nontuberculous mycobacteria; q6H, every 6 h; SCr, serum creatinine; TDM, therapeutic drug monitoring; TID, three times daily; TIW, thrice weekly; TMP, trimethoprim.

Table 3. Establishing a COpAT program.

Steps	Considerations	Commentary	Key stakeholders
Step 1. COpAT resources: Assess available resources within the institution to establish a new program	Is there an existing OPAT program that can be leveraged to incorporate patients on orals? Are new positions needed and justified, or can current staff be leveraged to include COpAT in their role?	In most instances, an existing OPAT program can incorporate oral antimicrobial monitoring. If no OPAT program exists, the need for COpAT could be incorporated into a new program proposal	Physicians, pharmacists, APPs, nursing, E-health, hospital management
Step 2. Patient selection: Determine the patients on oral antimicrobials that will be entered into the program or patients on IV antimicrobials that can be transitioned to oral therapy	Are there drug-based criteria for selection? Are there patient-based criteria for selection?	Drug-based criteria could include factors related to drug duration and certain 'high-risk' drugs (linezolid, SMX-TMP, etc.), as per Table 2. Patient-based criteria could include PWID, those with other social determinants of health concerns (lack of insurance, etc.), and other patients for whom oral therapy is clinically appropriate, compared to IV antimicrobials	Physicians, pharmacists, APPs
Step 3. Patient identification: How will the patients that qualify for COpAT be identified for enrollment?	Are patients identified by ID providers? Can stewardship or TOC programs assist in patient identification?	Most OPAT programs require ID involvement; thus, providers are already reviewing patients that may be suitable for COpAT. Stewardship led initiatives can be implemented to identify appropriate COpAT patient upon discharge utilizing patient-specific criteria and review of discharge prescriptions. If TOC programs are already in place, they can also utilize these teams to identify appropriate patients.	Physicians, pharmacists, APPs
Step 4. Patient enrollment: How will the identified patients be enrolled?	Is there an existing OPAT program enrollment process in place that can be leveraged to incorporate COpAT patients?	Often, the process utilized to enroll OPAT patients can be applied to the enrollment of COpAT patients. If a previously established process for OPAT is not in place, methods to enroll patients can include sending notification of eligibility *via* EHR	Physicians, pharmacists, APPs, nursing, E-health
Step 5. Patient monitoring: What are the monitoring requirements, and how are those requirements enacted?	Are there drug-specific parameters that can drive monitoring criteria?	Drug monitoring criteria can be based on drug-specific factors, as per Table 2. The development of department-specific protocols can allow for streamlined patient monitoring.	Physicians, pharmacists, APPs, nursing
Step 6: Patient management: Who will provide oversight and continue management of patient on discharge?	Who will be responsible for monitoring patients?	Guidelines for nursing-led monitoring, implementation of pharmacist collaborative practice agreements, and leverage of APPs may be reasonable based on available resources within a program.	Physicians, pharmacists, APPs, nursing

(Continued)

Table 3. (Continued)

Steps	Considerations	Commentary	Key stakeholders
Step 7: Patient follow-up: What frequency will patients be seen to ensure appropriate response to treatment?	Will the patient be seen at the end of therapy?	End-of-therapy follow-up may be necessary depending on the infectious syndrome, this may be able to be done *via* telehealth or in person as appropriate.	Physicians, pharmacists, APPs, nursing, E-health
	Will there be a patient follow-up between discharge and the end of therapy?	Patients may benefit from additional counseling from a COpAT team member on their medications after discharge, or when changes are made to a regimen, this can often be done utilizing telehealth by a pharmacist or nursing staff.	

APP, advance practice provider; COpAT, complex outpatient antimicrobial therapy; E-health, electronic-health; EHR, electronic health record; ID, infectious diseases; IV, intravenous; OPAT, outpatient parenteral antimicrobial therapy; PWID, person who injects drugs; SMX-TMP, sulfamethoxazole-trimethoprim; TOC, transitions of care.

For established COpAT programs looking to advance, develop metrics, optimizing multidisciplinary team member roles, quality improvement projects, and research are suggested efforts to mature the practice, described further in Table 4.

The future

The utilization of oral antimicrobials is expected to expand to further indications and patients as additional studies on bacteremia, endocarditis, and intra-abdominal infections are published. However, antimicrobial resistance is worsening, making it unlikely that oral antimicrobials will completely replace IV antimicrobials in the near future. We believe the best way forward for outpatient antimicrobial utilization is for OPAT programs to be upgraded into OPAT/COpAT programs, including both IV and complex oral antimicrobial regimens.

A potential paradox could be widespread, unfettered real-world use of long-term oral antimicrobials causing resistance that limits treatment options to only IV, making it essential that the new and improved model for an OPAT/COpAT program fully integrate with antimicrobial stewardship efforts. This would include utilization of the shortest duration of antimicrobial therapy for efficacy, optimization of antimicrobial regimens based on antimicrobial susceptibility testing, and utilizing pharmacokinetics to ensure the optimal antimicrobial regimen is selected.[41] One way this can be implemented is by incorporation of antimicrobial stewardship at discharge. A program at an academic medical center implemented a process within discharge where an ID pharmacist was notified of discharge antimicrobial prescriptions by the outpatient pharmacist and reviewed prescriptions for any drug-related problems, such as suboptimal dose or unnecessarily long duration. Over a 6-month time period 803 prescriptions were reviewed and 43.1% of these prescriptions had a drug related problem, with the most common problems being treatment duration (35.9%), drug selection (35.2%), and dose selection (20.1%).[42] Another study utilized transitions of care pharmacists at a community teaching hospital to review discharge medication lists utilizing a scoring tool identifying patients at highest risk for mortality within 30 days. Over a 1-year period 1100 patients were reviewed on discharge, with 298 antimicrobial interventions made, the most common being, incorrect dose (29.9%) and incorrect duration (24.8%).[43]

Additionally, research on diagnostic stewardship is sorely lacking, and the optimal frequency and type of monitoring for antimicrobials are unknown. Currently, quality improvement audits, reporting, and metrics are not mandated by any professional or governmental organization within the US for OPAT/COpAT programs. However, they are necessary to ensure optimal patient care. Lastly, artificial intelligence will be a crucial tool for COpAT programs in the future. Programs that could harness its full potential can potentially reduce the need for manual review of data, predict

Table 4. Advancing an existing COpAT program.

Factors	Considerations	Commentary	Key Stakeholders
COpAT metrics	Is there a method to track COpAT metrics manually or automatically?	Utilization of metrics and reports within an EHR or external metric software can be beneficial to monitor COpAT-specific metrics. If these resources are not available, utilization of spreadsheets to track patient visits and interventions is also possible.	Physicians, pharmacists, APPs, hospital quality and leadership
COpAT roles	Is there an opportunity to divest COpAT work from physicians to other team members? Are there certain patients that could be followed entirely by APPs or Pharmacists?	Through utilization of collaborative practice agreements, pharmacists can manage many COpAT patients. Nurses can be given autonomy through guidelines allowing for patient monitoring and escalation based off practice-specific criteria. Utilizing protocols to identify uncomplicated patient populations may allow for patient management followed completely by pharmacists and/or APPs.	Physicians, pharmacists, APPs, nurses
COpAT quality assurance projects	What opportunities exist to evaluate programs and identify possible areas for improvement?	Available tools to ensure program quality and evaluate areas for improvement include FMEA, lean methodology, etc.	Physicians, pharmacists, APPs, nurses
COpAT research and publications	Is there scholarly work that can be done in your program?	Given the recent development of COpAT within practice there remains large gaps for additional research and publications. Scholarly output allows for further advancement of all COpAT practices.	Physicians, pharmacists, APPs, nurses
COpAT artificial intelligence	What is the potential role of artificial intelligence in COpAT?	AI may be able to assist in predicting adverse drug reactions and identify patients at higher risk. AI can adjust the frequency and type of laboratory monitoring tailored to specific patients.	IT specialists, hospital quality and leadership, physicians, pharmacists, APPs, nurses

AI, artificial intelligence; APP, advance practice provider; COpAT, complex outpatient antimicrobial therapy; E-health, electronic-health; EHR, electronic health record; FMEA, failure mode and effects analysis; IT, information technology; OPAT, outpatient parenteral antimicrobial therapy.

adverse drug reactions before they occur, and even guide laboratory monitoring.

Conclusion

The use of oral antimicrobials for serious infections is a growing trend in infectious disease practices due to recent high-level evidence showing that oral antimicrobials are non-inferior to IV antimicrobials in treating certain severe infections, with additional benefits of decreased cost and potential improvements within anxiety and depression on therapy, leading to the emergence of COpAT to complement this change in practice. Integration of both oral and IV outpatient antimicrobials within a dual OPAT/COpAT program with utilization of the current OPAT best practices and addition of antimicrobial and diagnostic stewardship efforts will be essential as clinical practice continues to advance with evolving literature.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Margaret Pertzborn: Conceptualization; Project administration; Writing – original draft; Writing – review & editing.

Christina G. Rivera: Conceptualization; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

Don Bambino Geno Tai: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iDs
Margaret Pertzborn https://orcid.org/0000-0002-9898-7266

Don Bambino Geno Tai https://orcid.org/0000-0003-0581-8015

Supplemental material
Supplemental material for this article is available online.

References

1. Davar K, Clark D, Centor RM, *et al.* Can the future of ID escape the inertial dogma of its past? The exemplars of shorter is better and oral is the new IV. *Open Forum Infect Dis* 2022; 10: ofac706.
2. Seaton RA, Ritchie ND, Robb F, *et al.* From 'OPAT' to 'COpAT': implications of the OVIVA study for ambulatory management of bone and joint infection. *J Antimicrob Chemother* 2019; 74: 2119–2121.
3. Williams DN and Raymond JL. Community-based parenteral anti-infective therapy (CoPAT). Pharmacokinetic and monitoring issues. *Clin Pharmacokinet* 1998; 35: 65–77.
4. Rehm S, Campion M, Katz DE, *et al.* Community-based outpatient parenteral antimicrobial therapy (CoPAT) for *Staphylococcus aureus* bacteraemia with or without infective endocarditis: analysis of the randomized trial comparing daptomycin with standard therapy. *J Antimicrob Chemother* 2009; 63: 1034–1042.
5. Norris AH, Shrestha NK, Allison GM, *et al.* 2018 Infectious diseases society of America Clinical Practice Guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis* 2019; 68: e1–e35. 2018/11/14. DOI: 10.1093/cid/ciy745.
6. Rucker RW and Harrison GM. Outpatient intravenous medications in the management of cystic fibrosis. *Pediatrics* 1974; 54: 358–360.
7. Cox AM, Malani PN, Wiseman SW, *et al.* Home intravenous antimicrobial infusion therapy: a viable option in older adults. *J Am Geriatr Soc* 2007; 55: 645–650.
8. Pajarón M, Fernández-Miera MF, Allende I, *et al.* Self-administered outpatient parenteral antimicrobial therapy (S-OPAT) for infective endocarditis: a safe and effective model. *Eur J Intern Med* 2015; 26: 131–136.
9. Rentala M, Andrews S, Tiberio A, *et al.* Intravenous home infusion therapy instituted from a 24-hour clinical decision unit for patients with cellulitis. *Am J Emerg Med* 2016; 34: 1273–1275.
10. Bryant PA and Katz NT. Inpatient versus outpatient parenteral antibiotic therapy at home for acute infections in children: a systematic review. *Lancet Infect Dis* 2018; 18: e45–e54.
11. Petrak RM. Outpatient antibiotic therapy in long-term care facilities. *Infect Dis Clin North Am* 1998; 12: 995–1008.
12. Muldoon EG, Switkowski K, Tice A, *et al.* A national survey of infectious disease practitioners on their use of outpatient parenteral antimicrobial therapy (OPAT). *Infect Dis (Lond)* 2015; 47: 39–45.
13. Nguyen HH. Hospitalist to home: outpatient parenteral antimicrobial therapy at an academic center. *Clin Infect Dis* 2010; 51: S220–S223.
14. Petrak RM, Skorodin NC, Fliegelman RM, *et al.* Value and clinical impact of an infectious disease-supervised outpatient parenteral antibiotic therapy program. *Open Forum Infect Dis* 2016; 3.
15. Wolter JM, Cagney RA and McCormack JG. A randomized trial of home vs hospital intravenous antibiotic therapy in adults with infectious diseases. *J Infect* 2004; 48: 263–268.
16. Dalovisio JR, Juneau J, Baumgarten K, *et al.* Financial impact of a home intravenous antibiotic

program on a medicare managed care program. *Clin Infect Dis* 2000; 30: 639–642.

17. Cochrane S. A mark of approval. Patient satisfaction with an i.v. Self-infusion teaching programme. *Prof Nurse* 1994; 10: 106–111.
18. Fine MJ, Pratt HM, Obrosky DS, *et al*. Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. *Am J Med* 2000; 109: 378–385.
19. Eron LJ and Passos S. Early discharge of infected patients through appropriate antibiotic use. *Arch Intern Med* 2001; 161: 61–65.
20. Li H-K, Rombach I, Zambellas R, *et al*. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med* 2019; 380: 425–436.
21. Manning L, Metcalf S, Dymock M, *et al*. Short-versus standard-course intravenous antibiotics for peri-prosthetic joint infections managed with debridement and implant retention: a randomised pilot trial using a desirability of outcome ranking (DOOR) endpoint. *Int J Antimicrob Agents* 2022; 60: 106598.
22. Bouji N, Wen S and Dietz MJ. Intravenous antibiotic duration in the treatment of prosthetic joint infection: systematic review and meta-analysis. *J Bone Jt Infect* 2022; 7: 191–202.
23. Tai DBG, Berbari EF, Suh GA, *et al*. Truth in DAIR: duration of therapy and the use of quinolone/rifampin-based regimens after debridement and implant retention for periprosthetic joint infections. *Open Forum Infect Dis* 2022; 9: ofac363.
24. Marconi L, Tedeschi S, Zamparini E, *et al*. Oral versus standard antimicrobial treatment for pyogenic native vertebral osteomyelitis: a single-center, retrospective, propensity score-balanced analysis. *Open Forum Infect Dis* 2022; 9: ofac366.
25. Marks M, Bell LCK, Jones I, *et al*. Clinical and economic impact of implementing OVIVA criteria on patients with bone and joint infections in outpatient parenteral antimicrobial therapy. *Clin Infect Dis* 2020; 71: 207–210.
26. Bhagat H, Sikka MK, Sukerman ES, *et al*. Evaluation of opportunities for oral antibiotic therapy in bone and joint infections. *Ann Pharmacother* 2023; 57: 156–162.
27. Mareau J, Alexander B, Egge J, *et al*. Eligibility for and use of oral antimicrobial therapy among veterans with osteoarticular infections: a retrospective study across 8 medical centers. *Open Forum Infect Dis* 2022; 9: ofac450.
28. Livorsi D, Comer A, Matthias MS, *et al*. Factors influencing antibiotic-prescribing decisions among inpatient physicians: a qualitative investigation. *Infect Control Hosp Epidemiol* 2015; 36: 1065–1072.
29. Broom J, Broom A, Plage S, *et al*. Barriers to uptake of antimicrobial advice in a UK hospital: a qualitative study. *J Hosp Infect* 2016; 93: 418–422.
30. Seidelman J and Sexton DJ. Is long-term oral therapy for treatment of bone and joint infections ready for prime time? *Clin Infect Dis* 2021; 73: e2589–e2591.
31. Iversen K, Ihlemann N, Gill SU, *et al*. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med* 2019; 380: 415–424.
32. Bundgaard JS, Iversen K, Pries-Heje M, *et al*. The impact of partial-oral endocarditis treatment on anxiety and depression in the POET trial. *J Psychosom Res* 2022; 154: 110718.
33. Freling S, Wald-Dickler N, Banerjee J, *et al*. Real-world application of oral therapy for infective endocarditis: a multicenter retrospective, cohort study. *Clin Infect Dis* 2023: ciad119.
34. Daley CL, Iaccarino JM, Lange C, *et al*. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Clin Infect Dis* 2020; 71: e1–e36.
35. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America, https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection (accessed 9 March 2023).
36. Azamgarhi T, Shah A and Warren S. Clinical experience of implementing oral versus intravenous antibiotics (OVIVA) in a specialist orthopedic hospital. *Clin Infect Dis* 2020; 73: e2582–e2588.
37. Zukauckas K, Benefield RJ, Newman M, *et al*. Why bother? Lab monitoring in beta-lactam outpatient parenteral antimicrobial therapy. *Antimicrob Agents Chemother* 2022; 66: e0057922.
38. Heintz BH, Halilovic J and Christensen CL. Impact of a multidisciplinary team review of potential outpatient parenteral antimicrobial therapy prior to discharge from an academic

medical center. *Ann Pharmacother* 2011; 45: 1329–1337.

39. Rivera CG, Mara KC, Mahoney MV, *et al.* Survey of pharmacists on their roles and perceptions of outpatient parenteral antimicrobial therapy in the United States. *Antimicrob Steward Healthc Epidemiol* 2022; 2: e69.

40. Ortonobes S, Mujal-Martínez A, de Castro Julve M, *et al.* Successful integration of clinical pharmacists in an OPAT program: a real-life multidisciplinary circuit. *Antibiotics* 2022; 11: 1124.

41. Mahoney MV, Childs-Kean LM, Khan P, *et al.* Recent updates in antimicrobial stewardship in outpatient parenteral antimicrobial therapy. *Curr Infect Dis Rep* 2021; 23: 24.

42. Parsels KA, Kufel WD, Burgess J, *et al.* Hospital discharge: an opportune time for antimicrobial stewardship. *Ann Pharmacother* 2022; 56: 869–877.

43. Leja N, Collins CD and Duker J. Antimicrobial stewardship by transitions of care pharmacists at hospital discharge. *Hosp Pharm* 2021; 56: 714–717.

Visit Sage journals online journals.sagepub.com/home/tai

Sage journals