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MAJOR ARTICLE

Using the Comparing Oral versus Parenteral Antimicrobial Therapy (COPAT) Clinical Trial to Influence Institutional Practice Transformation Towards Earlier Transition to Oral Antibiotics

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(See the Editorial Commentary by Mahoney on pages e682–3.)

Background. Extensive literature has established equivalent efficacy of early intravenous (IV) to oral antibiotic transition. However, there is variability in adoption across practice settings. Unlike Outpatient Parenteral Antimicrobial Therapy (OPAT) programs, Complex Outpatient Antimicrobial Therapy with Oral Agents (COpAT) programs face significant implementation science challenges. We used a clinical trial with broad enrollment criteria to determine the impact of early oral transition in a real-world setting and studied its influence on practice transformation.

Methods. Comparing Oral versus Parenteral Antimicrobial Therapy (COPAT) Trial was a pragmatic, randomized controlled trial at 5 hospitals in 1 rural health system. Patients who required 2 or more weeks of IV antibiotics (for all but central nervous system infections) were randomized 2:1 to experimental (early-oral) group or control (IV-only) group. Two primary outcomes and hypotheses were assessed at 3 months: early-oral group safety superiority and efficacy equivalence. Clinical cases of patients who completed the trial were presented at multiple forums.

Results. The trial was stopped early after two-thirds enrollment for a significant safety benefit. Early-oral group demonstrated a significantly lower adverse event rate (3.2% versus 6.5%, $P = .02$). Lower cumulative hazard for first study-related adverse event in early-oral group (hazard ratio, 0.24; 95% confidence interval, .08–.75; $P = .01$) appeared to emerge by day 10. Therapeutic efficacy was equivalent. Cumulative enrollment in the trial had a significant association with the COpAT:OPAT program consult ratio ($R^2 = 0.54$, $P < .001$).

Conclusions. Early oral antibiotic transition was significantly safer. At our academic health system, implementation of the COPAT Trial accelerated practice transformation.

Clinical Trials Registration. NCT05977868.

Keywords. COpAT program; COPAT Trial; oral antibiotics; practice transformation; implementation science.

The publication of results from landmark clinical trials in 2019 as well as many subsequent studies and reviews firmly established the equivalent efficacy of earlier transition from intravenous (IV) to oral antibiotics for some of the most challenging infectious diseases, including endocarditis and bone/joint infections [1–4]. Complex Outpatient Antimicrobial Therapy with Oral Agents (COpAT) programs have been developed to safely transition and monitor patients on longer-term oral antibiotics. These programs further enhance patient safety by avoiding the need for central venous access and provide cost savings through decreased length of hospital stay [5].

Nationally, COpAT programs have yet to see the same adoption as Outpatient Parenteral Antimicrobial Therapy (OPAT) programs [6]. Some of this is driven by financial incentives. However, since many clinicians were trained during an era when oral antibiotic options generally had poor bioavailability, some have developed an enduring sense that IV antibiotics are inherently more effective than oral antibiotics. Many antibiotics

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in current use have high oral bioavailability, allowing them to achieve serum and tissue concentrations comparable to those for IV antibiotics [7]. Regardless, this pervasive mindset represented a challenge to COpAT program growth at our institution. In addition to outpatient monitoring, our COpAT program focuses on earlier inpatient transition to oral antibiotics and broadly applies the concept that shorter is better [4].

Academic centers are accustomed to participating in clinical trials approved by their institutional review boards (IRB). We sought to use a pragmatic randomized clinical trial, implemented across our rural health system, to study the impact on practice transformation toward earlier transition to oral antibiotics and foster further growth of our nascent COpAT program. Our a priori hypotheses were that, compared with standard of care, earlier transition to oral antibiotics would be associated with fewer adverse events and earlier transition to oral antibiotics would not be associated with a significant difference in treatment efficacy.

METHODS

Trial Design and Oversight

The Comparing Oral versus Parenteral Antimicrobial Therapy (COPAT) Trial was an investigator-initiated, pragmatic, unblinded, randomized controlled trial conducted at 5 Infectious Diseases (ID) faculty-staffed hospitals in the West Virginia University (WVU) Medicine Health System. The trial protocol was approved by the WVU IRB and prospectively registered at ClinicalTrials.gov. The trial was overseen by a data and safety monitoring board (DSMB), and 2 interim analyses were planned: 1 at one-third and 1 at two-thirds target enrollment. All trial participants provided written informed consent.

Patients

Eligible patients were hospitalized adults (aged ≥18 years) being planned for discharge with at least 2 additional weeks of IV antibacterial therapy for any of the following infection types: endovascular including endocarditis, bone/joint, skin/soft tissue, pulmonary, gastrointestinal, or genitourinary. Patients had to be able to participate in routine OPAT/COpAT program follow-up that included telephone check-ins, laboratory monitoring, and ID clinic follow-up visits. Patients were excluded if they were determined inappropriate for monitoring through OPAT (eg, active injection drug use, lack of infusion resources, or unstable outpatient environment) and/or COpAT program(s) (eg, unable to take oral medication or lack of an effective oral antibiotic option based on susceptibility testing). A complete list of inclusion and exclusion criteria is included in the Supplementary Appendix.

Patients were enrolled between 4 August 2023 and 14 February 2025. Once enrolled, patients were randomized 2:1 to an experimental (early-oral) group that received COpAT program services or a control (IV-only) group that received OPAT program services at hospital discharge. All patients had ID clinic follow-up visits at 2, 6, and 12 weeks after discharge. A patient satisfaction survey, reproduced in the Supplementary Appendix, was administered at the 6-week visit.

Choice of Antibiotics

For patients randomized to the early-oral group, antibiotic regimens with high bioavailability (Supplementary Table 1) were chosen following collaboration by at least 2 ID physicians on the research team. Transition to oral antibiotics occurred at randomization or, if bacteremic, once blood cultures were negative for 48 to 72 hours. For patients randomized to the IV-only group, antibiotic regimens were chosen based on consulting ID physician preference.

Outcomes and Study Hypotheses

Two primary study outcomes were assessed: (1) therapeutic safety based on (a) adverse events related to antibiotic therapy/vascular access that required intervention and/or (b) readmission for any cause in 3 months and (2) therapeutic efficacy determined by clinical cure/control of infection at 3 months as independently adjudicated by the same 2 ID physicians (J. A. G., C. L. S.) blinded to study arm (using clinical and laboratory parameters). A secondary outcome was patient satisfaction at 6 weeks.

Our a priori hypotheses were 2-fold: therapeutic safety would be superior in the early-oral group compared with the IV-only group and therapeutic efficacy would be equivalent between the early-oral and IV-only groups.

Additional Trial Procedures

All 5 study sites conducted regular assessments of enrollment and patient safety through weekly data reporting sheets. Recorded safety events included readmissions, antibiotic side effects/toxicities, and line-related adverse events. Principal investigators (J. J. J., A. R. S.) chaired monthly meetings with staff at all sites to ensure data entry was up to date and all recorded safety data were reviewed in a timely fashion. Sites shared interesting clinical trial case reports from patients in the early-oral group who had completed the trial to help build confidence in systemwide practice transformation.

Implementation Science

During the planning and implementation phases of the COPAT Trial, investigators built support for the trial across the WVU Medicine Health System through a series of educational sessions. A Jeopardy teaching tool, found in the Supplementary Appendix, consisting of 6 COPAT Trial cases from the early-oral group was administered at Medicine Grand Rounds (an earlier tool with 15 cases had been shared with ID and Hospital Medicine Divisions). For each case, providers recorded their response to the question, "What is your

comfort with early IV to oral antibiotic transition for this patient (at time of trial randomization)?" After the outcomes were shared, Final Jeopardy questions were used to determine whether the clinical case presentations helped improve provider comfort (Table 1).

Statistical Considerations and Interim Analysis

Statistical design and sample size justification were based on superiority in patient safety—patients in the early-oral group would experience a lower adverse event rate versus those in the IV-only group. Power analysis was conducted to determine the number needed for a 2:1 assignment to early-oral versus IV-only group, assuming adverse event proportions of 0.04 and 0.22, respectively [1, 2, 5]. A sample size of 135 patients (early-oral, 90; IV-only, 45) achieved greater than 80% statistical power with a significance of 0.05. A Bayesian statistical model was used to assess adverse events and efficacy outcomes. The stopping rule for therapeutic safety and efficacy, included in the Supplementary Appendix, was applied at the second interim analysis. The trial could stop early if the probability of the early-oral group being better than the IV-only group was greater than 0.9.

Parametric and nonparametric tests (χ^2, Fisher exact, and Mann–Whitney U) were used to examine differences in demographics and organism type, proportion of total antibiotics administered IV or orally, and cumulative adverse events. Incidence of adverse events was calculated by dividing the observed number of events by the total number of person-weeks. Time-to-event variables were summarized using survival and cumulative hazard plots; the Cox proportional hazard ratio was used to evaluate the difference between early-oral and IV-only groups. A linear regression model was used to examine the strength of association between ratio of COpAT:OPAT program consults and number of enrolled patients.

Table 1. Results From Jeopardy Teaching Tool Administered at Department of Medicine Grand Rounds

Comfort with Early IV to PO Antibiotic Transition: Comparing Oral versus Parenteral Antimicrobial Therapy Trial Cases in Early-Oral Arm

Infectious Diseases Categories	Uncomfortable Very uncomfortable	Neutral	Comfortable Very comfortable
Endovascular	39%	27%	35%
Bone and joint	23%	21%	55%
Miscellaneous	19%	24%	56%
Yes, I feel more comfortable transitioning from IV to PO antibiotics after reviewing the cases (N = 48)			90%
Yes, if I needed prolonged antibiotics (and had good PO options), I will still prefer to get a peripherally inserted central catheter and start with IV (N = 49)			14%

Abbreviations: IV, intravenous; PO, oral.

RESULTS

Early Termination for Safety Benefit

Application of the stopping rule after enrolling 90 patients (early-oral, 62; IV-only, 28) led to the conclusion that continuation of the trial would add no important statistical information. The probability that continuing the trial to full enrollment would conclude in favor of the IV-only group for the therapeutic safety outcome was less than 1%, and the probability that the trial would conclude in favor of the early-oral group was greater than 99%. The DSMB recommended early trial termination.

Patient Enrollment

Across the 5 study sites, 862 patients were reviewed, and 471 (55%) were found to be eligible for the study. Reasons for ineligibility included substance use disorder in 20% (varied across sites from 3% to 62%), physician preference for IV or oral antibiotics (12% each), and other factors such as homelessness

Table 2. Demographics and Infection Type Characteristics Among 90 Patients Enrolled in the Comparing Oral versus Parenteral Antimicrobial Therapy Trial

Demographics and Infection Type Characteristics	Total N = 90	Early-Oral n = 62	Intravenous-Only n = 28
Age, median (IQR), y	60 (20)	57.5 (20)	61.5 (18.5)
Male, n (%)	57 (63)	37 (60)	20 (71)
Length of stay, median (IQR), d	9 (5)	8 (5)	10 (4)
Comorbidities, n (%)			
Obesity	56 (62)	39 (63)	17 (61)
Diabetes	44 (49)	33 (53)	11 (39)
Cardiac	31 (34)	18 (29)	13 (46)
Pulmonary	15 (17)	10 (16)	5 (18)
Renal	6 (7)	6 (10)	0 (0)
Intensive care unit admission, n (%)	17 (19)	11 (18)	6 (21)
Infection type, n (%)[a]			
Endovascular	13 (14)	8 (13)	5 (18)
Bone/joint	66 (73)	46 (74)	20 (71)
Other[b]	11 (12)	8 (13)	3 (11)
Bacteremia,[c] n (%)	43 (48)	30 (48)	13 (46)
Staphylococcus aureus, n (%)	25 (58)	16 (53)	9 (69)
Surgery/Drainage,[d] n (%)	74 (82)	55 (89)	19 (68)
Organism isolated[a]			
S. aureus, n (%)	55 (61)	38 (61)	17 (61)
Methicillin-resistant *S. aureus*, n (%)	18 (33)	15 (39)	3 (18)
Methicillin-susceptible *S. aureus*, n (%)	37 (67)	23 (61)	14 (82)
Streptococcus species, n (%)	20 (22)	13 (21)	7 (25)
Enterobacterales, n (%)	11 (12)	8 (13)	3 (11)

Abbreviation: IQR, interquartile range.

[a]Numbers too small for detailed subgroup analysis.

[b]Skin and soft tissue, pulmonary, gastrointestinal, genitourinary.

[c]Endocarditis, 9; line-associated/primary bacteremia, 3; secondary bacteremia, 31.

[d]$P = .04$.

and/or lack of capacity to give informed consent. Of the eligible patients, 80% declined participation, with 54% declining randomization due to oral antibiotic preference. A total of 94 patients enrolled, but 4 withdrew early prior to hospital discharge: 2 preferred oral antibiotics, 1 preferred IV antibiotics, and 1 transitioned to comfort care. Thus, 90 patients remained enrolled, followed up in ID clinic, and completed the trial (Supplementary Figure 1).

Patient Characteristics

The study population's demographic and infection type characteristics are shown in Table 2. The early-oral and IV-only groups were similar in age (median, 60 years), sex (63% male), comorbid conditions, and infection type. Bone/joint infections were most common (73%) followed by endovascular infections (14%). Forty-eight percent of all patients had bacteremia—10% with endocarditis. A surgical or drainage procedure was performed more often in the early-oral versus IV-only group (89% versus 68%, $P = .04$). *Staphylococcus aureus* was the most common organism isolated and accounted for 25 of the 43 patients (58%) with bacteremia.

Antibiotic Proportion and Duration

Figure 1 shows the proportion of oral versus IV antibiotics in the study groups. Both groups had similar total antibiotic duration (nearly 6 weeks), with almost 90% of the course completed with oral antibiotics in the early-oral group. Transition from IV to oral antibiotics occurred at a median 4 days in this group. Even in the IV-only group, 39% of the antibiotic course was completed with oral agents, reflecting our standard practice of transitioning from IV to oral for the last 2 to 3 weeks of treatment. The top 5 oral antibiotics used were cefadroxil, linezolid, levofloxacin, amoxicillin-clavulanate, and metronidazole. The top 5 IV antibiotics used were cefazolin, ceftriaxone, ertapenem, daptomycin, and ampicillin-sulbactam.

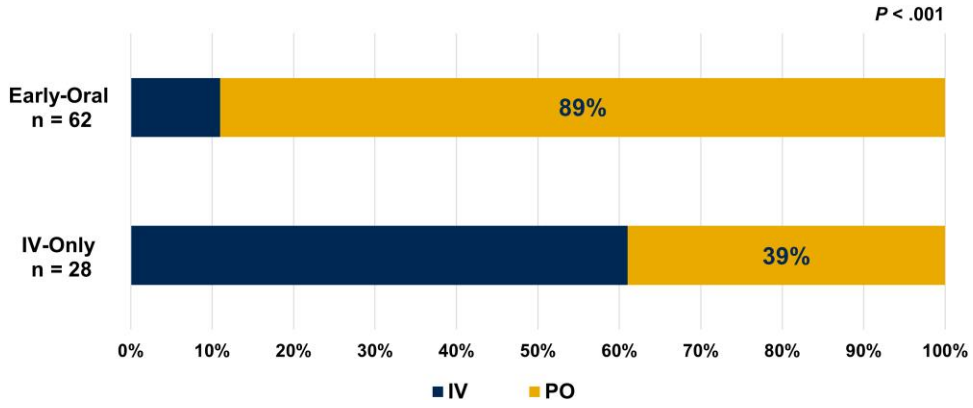

Figure 1. Proportion of total antibiotic days administered intravenously or orally in the Comparing Oral versus Parenteral Antimicrobial Therapy Trial. Comparison of the proportion of IV and oral antibiotic days in the experimental (early-oral) and control (IV-only) groups with both groups averaging similar total duration of therapy: early-oral versus IV-only group = 38 days versus 40 days ($P = .52$). The proportion of total therapy by oral antibiotics was significantly higher in the early-oral group (89% versus 39%, $P < .001$). Abbreviations: IV, intravenous; PO, oral.

Table 3. Safety and Adverse Events Among 90 Patients Enrolled in the Comparing Oral versus Parenteral Antimicrobial Therapy Trial

Safety and Adverse Events	Total N = 90	Early-Oral n = 62	Intravenous-Only n = 28	*P* Value
Total event rate	4.3%	3.2%	6.5%	.02
Events per enrolled patient-week	46/1080	24/744	22/336	
Readmissions	30 in 24 patients	20 in 17 patients	10 in 7 patients	.99
Antibiotic side effects[a]	8 in 8 patients	4 in 4 patients	4 in 4 patients	.25
Line-related adverse events[b]	8 in 7 patients	0	8 in 7 patients	< .001
Total[c]	46 in 33 patients	24 in 20 patients	22 in 13 patients	.29

Abbreviation: IV, intravenous.

[a]Side effects needing intervention included thrombocytopenia in 2, yeast infection in 2, myalgias/arthralgias in 2, drug-induced lung injury in 1, and nausea in 1 patient(s).

[b]Of the 28 patients in the *IV-only* group, 19 had a peripherally inserted central catheter (PICC), 8 had a midline, and 1 had no line (was on long-acting lipoglycopeptide). Of the 8 adverse events, 6 involved a PICC. Adverse events included line malfunction in 6 (required removal in 3) and inadvertent removal by 2 patients—2 patients needed line reinsertion.

[c]Eight patients had 2 events, 1 patient had 3 events, and 1 patient had 4 events.

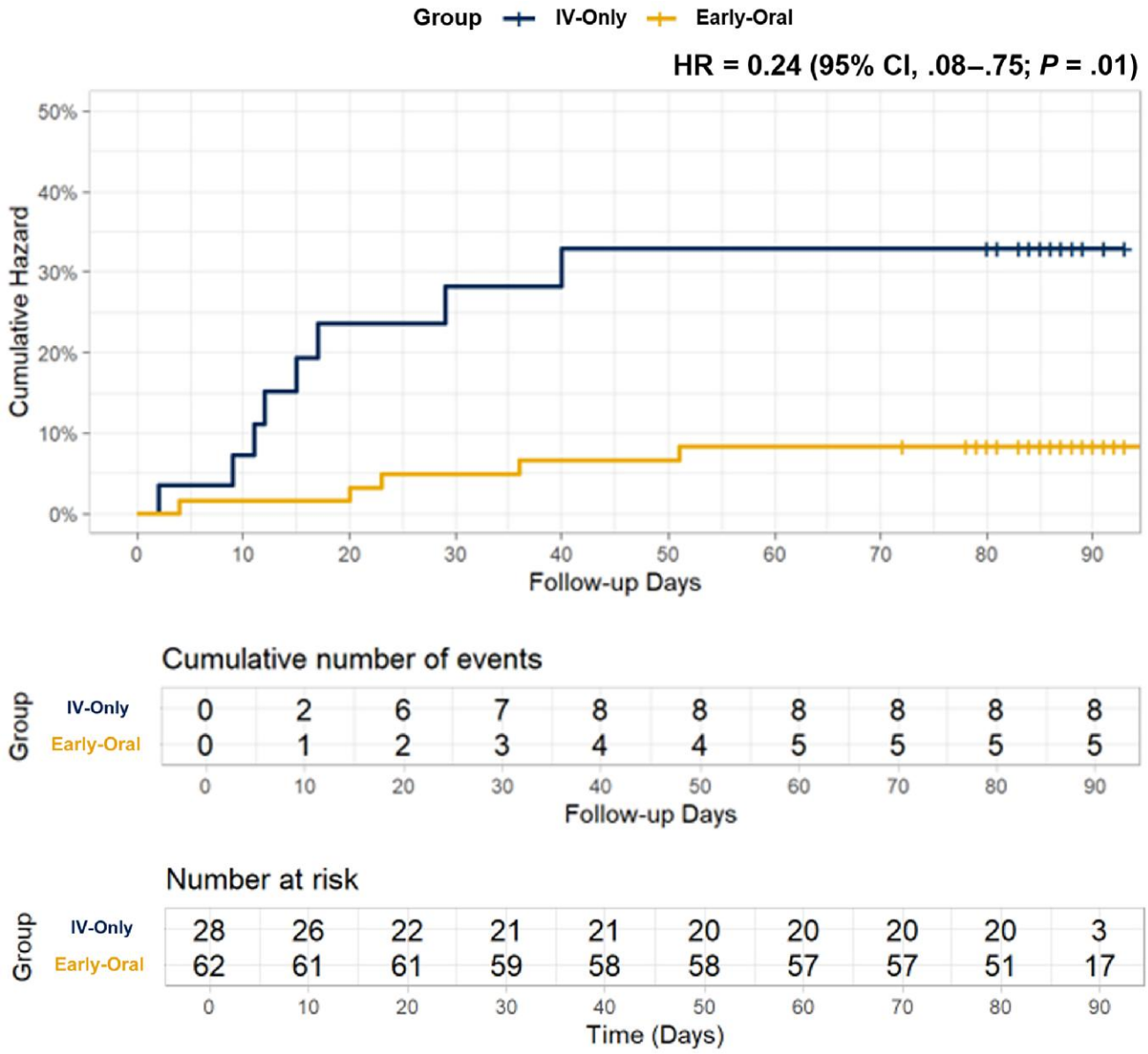

Figure 2. Cumulative hazard for first study-related adverse event in the Comparing Oral versus Parenteral Antimicrobial Therapy Trial. Cumulative hazard with curves appearing to separate by day 10. The tables show the accumulation of events and patients still at risk (until the final follow-up visit at 12 weeks). Rate of events in the experimental (early-oral) group was less than that in the control (IV-only) group (HR, 0.24; 95% CI, .08–.75; $P = .01$). Abbreviations: CI, confidence interval; HR, hazard ratio; IV, intravenous.

Primary Outcomes

The COPAT Trial was stopped early at two-thirds enrollment because of a significantly lower adverse event rate in the early-oral group (early-oral group versus IV-only group: 3.2% versus 6.5%, $P = .02$), as shown in Table 3. This composite outcome was driven by line-related adverse events (8 adverse events among 7 of 28 or 25% of patients in the IV-only group). Cumulative hazard for first study-related adverse event was lower in the early-oral group (hazard ratio, 0.24; 95% confidence interval, .08–.75; $P = .01$), with curves separating at around day 10, as shown in Figure 2 and Supplementary Figure 2.

The coprimary outcome of equivalent therapeutic efficacy in both groups was also met as independently adjudicated by the same 2 ID physicians blinded to randomization arm. All patients, except 1, achieved clinical cure/control of infection. One patient in the early-oral group required additional surgical source control with an amputation procedure.

Secondary Outcome

The patient satisfaction survey completed by 89 of 90 patients at 6 weeks showed very strong preference for oral antibiotics overall (91%) and in each group (early-oral versus IV-only

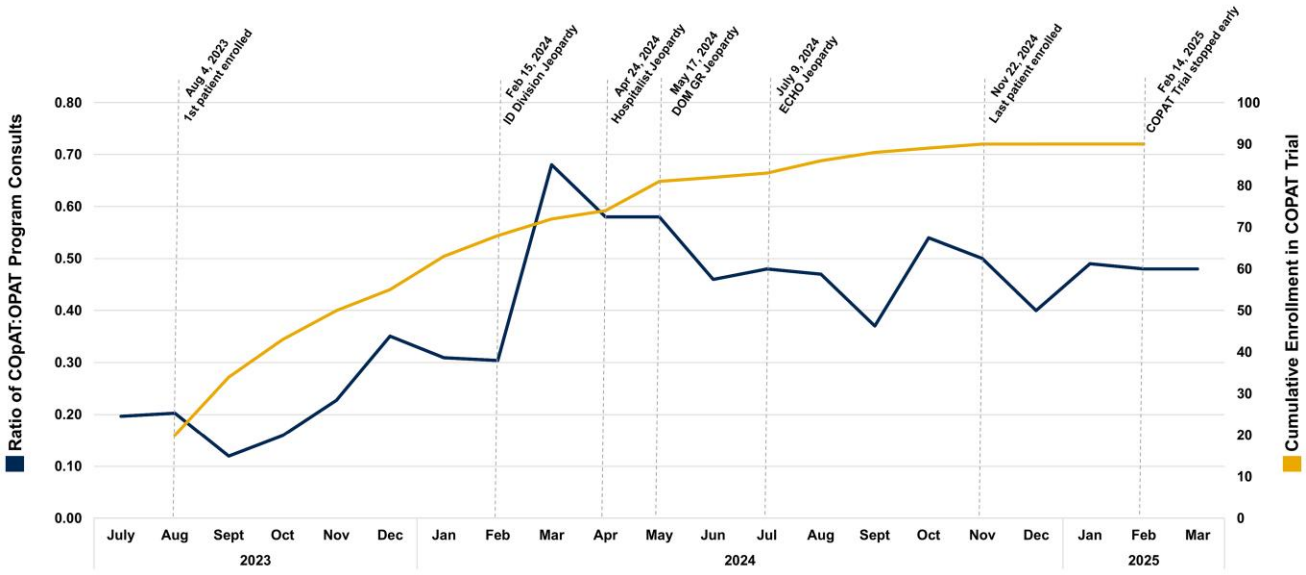

Figure 3. Ratio of COpAT:OPAT program consults and COPAT Trial cumulative enrollment. Cumulative enrollment in the COPAT Trial plotted alongside the COpAT:OPAT program consult ratio. COPAT Trial enrollment dates of first and last patients are denoted as well as early termination date. Similarly, Jeopardy teaching session dates to ID and Hospitalist Divisions as well as to the Department of Medicine Grand Rounds are marked. A final presentation was also made to our Statewide OPAT and COpAT Programs Extensions for Community Healthcare Outcomes (ECHO) session. Cumulative enrollment in the COPAT Trial had a significant association with the ratio of COpAT:OPAT program consults (R^2= 0.54, P < .001). For each additional 10 patients enrolled, the COpAT:OPAT program ratio increased by 0.06. Abbreviations: COPAT, Comparing Oral versus Parenteral Antimicrobial Therapy; COpAT, Complex Outpatient Antimicrobial Therapy with Oral Agents; DOM, Department of Medicine; GR, Grand Rounds; ID, Infectious Diseases; OPAT, Outpatient Parenteral Antimicrobial Therapy.

group: 98% versus 75%, P = .001). While only 1 of 61 patients (2%) in the early-oral group preferred to be in the alternate study arm, 21 of 28 patients (75%) in the IV-only group would have preferred the oral antibiotic arm. Almost all patients in both groups (90%) felt their treatment was successful (1 undecided), with patients reporting an overall trial satisfaction of 98% (Supplementary Table 2).

Practice Transformation

Consults placed to our nascent COpAT program and well-established OPAT program were tracked. Cumulative enrollment in the trial had a significant association with the COpAT:OPAT program consult ratio (R^2= 0.54, P < .001), with the ratio increasing by 0.06 for each additional 10 patients enrolled, as shown in Figure 3. As provider comfort levels with earlier IV to oral antibiotic transition improved, rates of COPAT Trial enrollment decreased (eg, 43 patients enrolled in the first 3 months, 20 patients in the next 3 months, 1 patient in the last 3 months).

DISCUSSION

At onset of the coronavirus disease 2019 (COVID-19) pandemic, our quaternary care university medical center had a well-established OPAT program. Our COpAT program was first developed and implemented in January 2021 for an inpatient service that catered to patients with substance use disorder (SUD)/injection drug use (IDU) associated infections that required prolonged antibiotics, as outlined in the Supplementary Appendix. The COVID-19 pandemic's impact on inpatient bed scarcity triggered our COpAT program's accelerated development. Our standard of care for serious infections such as endocarditis and bone/joint infections transitioned from 4 to 6 weeks of all IV antibiotics to oral antibiotics for the last 2 to 3 weeks [8]. Over time, the spectrum of patients enrolled in our COpAT program broadened, with non-SUD patients transitioning to oral antibiotics earlier. However, compared with OPAT, inpatient referrals to our COpAT program lagged far behind.

Two landmark clinical trials, Partial Oral Treatment of Endocarditis (POET) and Oral versus Intravenous Antibiotics for Bone and Joint Infections (OVIVA), had shown that early transition from IV to oral antibiotics at 7 to 10 days was non-inferior to continued IV antibiotics nearly 5 years prior to implementation of our COPAT Trial [1, 2]. Subsequent multiple additional studies and reviews, including WikiGuidelines, have highlighted the benefits of early oral antibiotic transition [3, 4, 9, 10]. Despite extensive clinical evidence, COpAT programs had not yet been widely incorporated into clinical practice. Our COPAT Trial was designed to highlight the improved safety of oral antibiotics and was conducted with the goal of accelerating practice transformation to earlier oral antibiotic transition across our rural health system. The trial also extended the

concept of earlier IV to oral antibiotic transition to 4 days for all patients except those with central nervous system infections.

The COPAT Trial found that earlier IV to oral antibiotic transition was significantly safer and, like POET and OVIVA, did not compromise clinical outcomes. The total adverse event rate in the IV-only group was more than 2-fold higher than that in the early-oral group, largely driven by differences in line-related events. These differences in safety appeared to emerge by day 10. Moreover, patients expressed a strong preference for oral antibiotics.

Clinician discomfort with earlier IV to oral antibiotic transition falls into the realm of implementation science rather than lack of clinical data. This can be overcome by educational strategies such as our monthly case discussions and Jeopardy teaching tool. Over the study period as provider comfort level with earlier IV to oral antibiotic transition improved, the COpAT: OPAT program consult ratio increased. As more patients were referred to our COpAT program, there was a corresponding decrease in trial enrollment. Providers got more comfortable with transitioning patients to oral antibiotics without going through the randomization process.

In the COPAT Trial, patients in the early-oral group transitioned from IV to oral antibiotics at a median 4 days. This was earlier than had occurred in POET and OVIVA. *Staphylococcus aureus* was the most commonly isolated organism. Of the 43 patients with bacteremia, 25 (early-oral, 16; IV-only, 9) had *S. aureus* bacteremia (SAB). All except 1 patient in the IV-only group had complicated SAB. The subset of patients in the early-oral group with SAB also transitioned from IV to oral antibiotics at median 4 days, with all achieving clinical cure/control of infection at 3 months. This allowed our ID providers to become increasingly comfortable with earlier transition to oral therapy for complicated SAB. As there are recognized data gaps in establishing optimal SAB treatment, further research is needed (ClinicalTrials.gov, NCT07148960).

Our trial had important limitations including a low enrollment rate (and potential selection bias) driven primarily by 54% of eligible patients declining participation due to a strong preference for oral antibiotics. Also, the trial was not blinded. This was for pragmatic reasons, as a major focus was on practice transformation. Assessment of clinical cure/control by the same 2 ID physicians blinded to study arm minimized potential bias from the open-label design. More patients in the early-oral group had source control, and this could certainly have contributed to the equivalent therapeutic efficacy in both groups. Also, transition from IV to oral antibiotics in the IV-only group for the last 2 weeks may not be considered a standard IV course. However, a full IV course would likely have further increased the number of line issues in the IV-only group. Oral regimens were selected through expertise of at least 2 ID physicians to optimize safety for individual participants. This trial was deliberately inclusive without selection according to infecting organism or infection site, with the exception of exclusion of central nervous system (ie, brain) infections. Patients with active SUD/IDU were excluded as they did not meet criteria to be discharged with OPAT program. However, these patients may be among those who benefit most from early oral antibiotic transition [11]. In addition, all patients were followed through established OPAT and COpAT programs for safety monitoring. Our study results may not be generalizable to institutions or practices that do not have these programs in place.

In conclusion, early IV to oral transition significantly improves antibiotic treatment safety without compromising effectiveness across many serious infectious diseases. At our academic institution and health system, implementation of the COPAT Trial with case-based education accelerated practice transformation among skeptical providers to earlier oral antibiotic transition.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. All authors contributed to the trial and development of this article.

Disclaimer. Outcome data are available at ClinicalTrials.gov. Data from the trial are otherwise not publicly available.

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