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Partial oral antibiotic treatment of endocarditis in patients who inject drugs: a case series

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Background: Recent literature has demonstrated that partial oral antibiotic treatment of infectious endocarditis is non-inferior to IV therapy in select patients. Despite the rising incidence of injection drug use-related endocarditis, partial oral therapy has not been well studied in persons who inject drugs.

Objectives: To evaluate the rate of relapsed infection and 90 day mortality in patients with infectious endocarditis treated with partial oral antibiotic therapy.

Methods: Consecutive patients with infectious endocarditis treated with partial oral antibiotic therapy were identified by study investigators and reviewed by independent clinicians. The decision to use partial oral antibiotic therapy was made by the institution's multidisciplinary endocarditis team.

Results: In 11 cases of infective endocarditis treated with partial oral antibiotic therapy, 9 of which were complicated by injection drug use, there were no relapsed infections with the primary organism. Five patients underwent surgical valve replacement, and the median duration of oral antibiotic therapy was 23 days. All patients survived to in-hospital discharge and 90 days post-discharge. Ten patients followed up with an infectious diseases provider after discharge.

Conclusions: These data add to existing literature demonstrating non-inferior outcomes with partial oral antibiotic treatment when compared with IV antibiotic treatment alone in patients with endocarditis, including persons who inject drugs.

Introduction

Infective endocarditis (IE) is associated with significant morbidity and mortality and has an increasing incidence in the USA. Management decisions are often complex regarding optimal duration and selection of antibiotic therapy and consideration of valve surgery. Both the American Heart Association and European Society of Cardiology have published consensus treatment guidelines that include antibiotic recommendations.[1] While these guidelines make brief mention of potential oral antibiotic regimens, the standard of care for treating IE is currently IV antibiotic therapy, typically for a period of 4–6 weeks.[1] While IV therapy can often be successfully completed in the outpatient setting, this typically necessitates the placement of a peripherally inserted central catheter (PICC). This carries risk of infection and thromboembolism and often requires the patient to have stable housing or disposition to a medical facility capable of administering IV medications. Arranging reliable transportation and home health nursing for post-discharge follow-up can be challenging as well.

Historically, there have been concerns that oral antibiotics would not sufficiently sterilize a valvular vegetation and consequently providers have been reluctant to use oral therapy for IE patients. However, evidence suggests partial oral antibiotic treatment may be an appropriate alternative to long term IV antibiotics in certain patients.[2,3] In 2020, Iversen *et al.*[2] demonstrated that de-escalating patients with left-sided endocarditis to oral antibiotics after at least 10 days of IV treatment was

non-inferior to completion of a full course of IV therapy. Notably, only five patients in this study had a history of IVDU, which is an increasing cause of IE in the USA.[2,4,5] Persons who inject drugs (PWIDs) have a substantial potential benefit from partial oral treatment as they may have challenges with the follow-up required with outpatient parenteral therapy and are often refused admission to nursing facilities. As a result, these patients may remain hospitalized for several weeks to receive antibiotics, incurring substantial costs.[4–6] PWIDs are also noted to have higher rates of patient-directed discharges. Despite this, a study of 293 PWIDs with patient-directed discharges observed a reduction in 90 day all-cause readmission in patients who were prescribed oral antibiotics.[3] We report our experience treating 11 cases of IE with partial oral antibiotic therapy.

Methods

Oral antibiotic protocol

The cardiovascular infectious diseases consultation service, in conjunction with the hospital's antimicrobial stewardship team, developed an evidence-based protocol outlining potential oral antibiotic regimens for patients with IE caused by MSSA, CoNS, viridans streptococci and *Enterococcus faecalis* (Appendix S1, available as Supplementary data at *JAC-AMR* Online). Notably IE caused by MRSA was not included in the protocol given the paucity of existing literature supporting the use of oral therapy in these cases.[2]

Patient cases

Institutional review board exemption was obtained from the University of Pittsburgh and consent was not required. Patients with IE treated with partial oral antibiotics were selected by the hospital's multidisciplinary endocarditis team based on the pathogen, patient preference or desire to leave the hospital, and eligibility of the patient for outpatient parenteral treatment as determined by the health system's infusion company. Patients were not offered oral therapy if MRSA was the aetiologic pathogen, they had other medical needs that required prolonged hospitalization beyond the completion of the IV antibiotic course or if the decision to treat with IV antibiotic therapy did not impact their disposition from the hospital. This last exclusion criterion was designed to exclude patients who could receive IV antibiotic treatment in the outpatient setting as this therapy is considered the 'standard of care' treatment by the American Heart Association endocarditis guidelines.[1] However, many individuals in the studied population who were medically stable for discharge could not complete IV antibiotics at home solely because they would not be accepted by a home health care agency or infusion company. Rather than confine these otherwise functional individuals to hospitals or nursing facilities to complete IV therapy the investigators offered oral antibiotics as an alternative treatment that, while not currently 'standard of care' has been shown to be non-inferior in a randomized controlled trial.[2] Patients with MRSA endocarditis were excluded, as highlighted above, due to the limited existing data for partial oral antibiotic treatment of IE secondary to this pathogen.[2] Oral therapy was offered to all remaining patients, including those in whom the decision to use IV antibiotics necessitated that the patients remain in the hospital or at a skilled nursing facility to complete treatment when they could otherwise have been discharged home. Oral antibiotic selection and treatment courses were also determined by the multidisciplinary endocarditis team, in accordance with the previously approved protocol. Patient charts were then retrospectively reviewed by two physicians at least 60 days from their hospitalization.

Results

Between 1 November 2020 and 1 June 2021, 70 cases of IE diagnosed by the institution's multidisciplinary endocarditis team were identified. Fifty-nine cases were excluded from the oral therapy arm. We identified 11 cases of IE among 9 patients who were treated with partial oral therapy (Table 1). The median age was 32 years (IQR31–38) and 36.7% were women. The median Charlson Comorbidity Score was 0 (range 0–2). Nine of 11 cases were suspected to be caused by IVDU, with the remaining 2 cases thought to be secondary to a dental infection and thrombophlebitis, respectively. Seven patients were on medication-assisted treatment for opioid use disorder at the time of hospital discharge, with one patient on methadone therapy and the remaining six patients prescribed buprenorphine-based therapy. Nine cases involved patients with prior episodes of infective endocarditis, and seven involved prosthetic valves. Four cases involved the tricuspid valve, five cases involved the mitral valve and two cases involved the aortic valve.

Of the 11 cases, 9 had positive blood or valve cultures. Blood cultures were successfully sterilized in all cases prior to discharge. Ten cases had visible valve vegetations. The case without a definite vegetation along with both cases with negative blood cultures who did not undergo valve surgery met modified Duke criteria for definite endocarditis.[7] Seven patients experienced complications of endocarditis, including three patients who suffered embolic strokes. In five cases source control was pursued with surgical management. In four patients with prosthetic valve endocarditis secondary to IV drug use, redo surgery was not offered at the time of admission due to concerns about patients' ongoing substance use. In the remaining two patients, surgical indications were not present in one and surgery was deferred in the other due to increased surgical risk related to the patient's elevated BMI. Median total time on IV antibiotics was 13 days (IQR 4–22). The median time on oral antibiotics was 23 days (IQR 12–38). All patients completed a minimum of 28 days of total antibiotic treatment.

All patients survived to hospital discharge. Ten patients followed up with an infectious diseases provider for a post-hospitalization appointment, including five via telemedicine. The median duration of follow-up was 41 days (range 16–134 days). Five patients underwent outpatient laboratory evaluation while on oral antibiotics, which included a complete blood count in four cases, a complete metabolic panel in four cases, and a basic metabolic panel in one patient. Overall, oral therapy was well tolerated; none of the patients required a switch to alternative oral therapy due to adverse effects. Notably, two patients developed recurrent episodes of endocarditis in the setting of ongoing IVDU, including one diagnosed with a different aetiologic microorganism who re-presented 3 months after the index hospitalization and one who previously had culture-negative endocarditis and then presented 4 months after the first episode with *Streptococcus mitis* IE.

Reasons for partial oral treatment

Four patients desired discharge to home and were not approved by the health system's infusion or home care companies. One patient wished to discharge to a nursing facility for treatment

Table 1. Clinical characteristics and outcomes of patients with infective endocarditis treated with oral therapy

Case	Age, years/ sex	Comorbidities	CCI	Culture data	Source of endocarditis	Location of vegetation (size)	Complications of endocarditis	Surgery pursued (days following first +ve culture)	tx and duration (days)			Reason PO antibiotics pursued	Total duration of: tx (IV tx), days	Clinical outcome and comments (last endocarditis-related follow-up, days from discharge)
									empirical	targeted IV	targeted PO			
1	31/F	Recurrent UTIs, prior PWID	1	BCx −ve[a]	Suspect dental	Native MV (1.4 × 0.5 cm)	R MCA stroke, fetal demise	No surgical intervention	CRO (10) DAP (5)	N/A: culture negative	LZD+LVX (28)	No accepting facility, desired discharge to home	38 (10)	Completed oral antibiotics as prescribed and followed up with ID. No further known BSI or hospitalizations (17 days)
2	38/F	PWID, prior HCV, prior endocarditis	0	BCx +ve for MSSA	IVDU	MV (0.9 × 0.7 cm)	L frontal lobe, L thalamic, bilateral occipital strokes	MVR	VAN (10) CRO (4) CFZ (6)	OXA (19)	DCX+RIF (7; recommended for 16)	Desired to discharge to home	Estimated 36 (10)	Patient did not complete oral antibiotics (took for 1 week) and did not follow up with any providers. Readmitted with *E. faecalis* prosthetic valve endocarditis (Case 3) (75 days)
3	38/F	PWID, prior HCV, prior endocarditis	0	BCx +ve for *E. faecalis*	IVDU	Bioprosthetic MV (2.2 × 0.5 cm)	PICC-associated DVT	Redo MVR 3/10 (14)	VAN (1)	AMP (21) CRO (21) VAN (5)[b]	AMX+LZD (12)	Ongoing in-hospital substance use preventing PICC	39 (22)	Completed oral antibiotics as prescribed and followed up with ID and CT surgery. Patient developed recurrent endocarditis in the setting of ongoing IVDU with *Streptococcus gordonii* bacteraemia and candidaemia and passed away ∼5 months after treatment (64 days)
4	31/M	PWID, prior endocarditis	0	BCx +ve for MSSA	IVDU	Mechanical AV (2 × 1.5 cm)	Ascending aortic aneurysm	Redo AVR and pericardial patch repair of aneurysm (12)	VAN (2)	OXA (21); resumed (9) when readmitted for withdrawal symptoms	LZD+RIF (14)	Desired discharge to home	46 (32)	Completed oral antibiotics as prescribed and followed up with ID and CT surgery. No further known BSI or hospitalizations (16 days)
5	33/M	PWID, prior HCV, prior endocarditis	0	BCx −ve Valve cultures positive for *C. albicans*	Suspect IVDU	Bioprosthetic TV (0.5 × 0.4 cm + 0.7 × 0.6 cm)	*Candida* endophthalmitis	Redo TVR (7)	FLC (48) CAS (13) VAN (5) CRO (4)	CAS (13) FLC PO (48)	FLC (48)	*Candida* susceptible to FLC	48 (13)	Completed oral antibiotics as prescribed and followed up with ID, CT surgery and ophthalmology. Continued on suppressive dosing of FLC indefinitely. No further known BSI or hospitalizations (77 days)
6	19/F	PWID, prior endocarditis	0	BCx +ve for *E. faecalis*	IVDU	Bioprosthetic TV (0.4 × 0.5 cm)	Pacemaker lead infection	No surgical intervention	VAN (2)	N/A: patient refused further IV therapy	AMX+LZD (38)	Patient declined IV therapy	40 (2)	Completed oral antibiotics as prescribed. Followed up with CT surgery. Readmitted for candidaemia with CIED vegetation. Repeat BCx/lead cultures negative for *E. faecalis* (29 days)
7	32/M	PWID, HCV, prior endocarditis	0	BCx −ve	IVDU	Bioprosthetic TV (1.4 × 1.5 cm)	None	No surgical intervention	VAN (1) FEP (1)	N/A: culture negative	SXT+AMC (42)	Desire to leave hospital against medical advice	43 (1)	Completed oral antibiotics as prescribed. Followed up with ID. Readmitted with *S. mitis* prosthetic TV endocarditis, managed with IV antibiotics and transitioned to PO (Case 8) (134 days)

Continued

Table 1. *Continued*

Case	Age, years/ sex	Comorbidities	CCI	Culture data	Source of endocarditis	Location of vegetation (size)	Complications of endocarditis	Surgery pursued (days following first +ve culture)	tx and duration (days)			Reason PO antibiotics pursued	Total duration of: tx (IV tx), days	Clinical outcome and comments (last endocarditis-related follow-up, days from discharge)
									empirical	targeted IV	targeted PO			
8	32/M	PWID, HCV prior endocarditis	0	BCx +ve for *S. mitis*	IVDU	Bioprosthetic TV (1.6 × 0.9 cm)	None	No surgical intervention	VAN (4) FEP (1)	CRO (4)	LVX+AMX (37)	Desire to discharge to home	42 (4)	Antibiotic completion unknown. Followed up with ID. No further known BSI or hospitalizations (14 days)
9	30/M	PWID, prior endocarditis, migraines	0	BCx +ve for *S. mitis*	IVDU	Native MV (2.0 × 0.8 cm)	Mycotic aneurysm, osteomyelitis	MVR, debridement of vegetation, Physio ring placement (25)	N/A	CRO (15)	LZD+MXF (13)	Desire to leave hospital against medical advice	28 (15)	Completed oral antibiotics as prescribed. Patient also completed PO antibiotics for candidaemia. Followed up with ID, neurology and CT surgery. No further known BSI or hospitalizations (76 days)
10	56/M	CVA, HLD, atrial fibrillation	2	BCx +ve for MSSA	Suspect superficial thrombophlebitis vs dental	Native MV (1 × 0.8 cm)	None	No surgical intervention	N/A	OXA (34)	LZD (10)	Lost PICC, patient quarantined at home	44 (34)	Completed oral antibiotics as prescribed. Followed up with ID and CT surgery. No further known BSI or hospitalizations (41 days)
11	39/M	PWID, prior endocarditis	1	BCx +ve for *Streptococcus mutans*	IVDU	Suboptimal TEE, presumed prosthetic AV	Embolic R MCA stroke	No surgical intervention	CRO (10) DAP (2)	CRO (10)	AMX+MXF (23)	No accepting facilities, desire to discharge to home	33 (10)	Completed oral antibiotics as prescribed. Followed up with ID and CT surgery. No further known BSI or hospitalizations (25 days)

+ve, positive; −ve, negative; AMC, amoxicillin/clavulanic acid; AMP, ampicillin; AMX, amoxicillin; AV, aortic valve; AVR, aortic valve repair; BCx, blood cultures; BSI, bloodstream infection; CAS, caspofungin; CCI, Charlson Comorbidity Index; CFZ, cefazolin; CIED, cardiovascular implantable electronic device; CRO, ceftriaxone; CT surgery, cardiothoracic surgery; CVA, cerebral vascular accident; DAP, daptomycin; DCX, dicloxacillin; DVT, deep venous thrombosis; FEP, cefepime; FLC, fluconazole; HLD, hyperlipidaemia; ID, infectious diseases; LVX, levofloxacin; LZD, linezolid; MV, mitral valve; MVR, mitral valve repair; MXF, moxifloxacin; OXA, oxacillin; PICC, peripherally inserted central catheter; PO, per os (by mouth); PWID, person who injects drugs; R MCA, right middle cerebral artery; RIF, rifampicin; TEE, transoesophageal echocardiogram; SXT, trimethoprim/sulfamethoxazole; tx, treatment; TV, tricuspid valve; TVR, tricuspid valve repair; UTI, urinary tract infection; VAN, vancomycin.

[a]Cultures collected after 48 h of antibiotic treatment.

[b]Patient transitioned to vancomycin for 5 days due to concern for ceftriaxone- or ampicillin-related drug fever.

but there were no accepting facilities. Two patients had documented patient-directed discharges. One patient declined IV therapy. One patient was initially discharged home on IV antibiotics and developed a PICC complication that necessitated a transition to oral antibiotic therapy. One patient was discharged to a medical respite programme with a PICC and then requested early discharge from this facility and was transitioned to an oral regimen. One patient with *Candida albicans* endocarditis who underwent tricuspid valve replacement was treated with oral fluconazole given the high bioavailability of this medication.[8]

Discussion

In this case series, we highlight the successful treatment of 11 IE cases, including 9 secondary to IVDU, with partial oral antibiotic therapy. This study primarily evaluated patients with comorbid IVDU, a population frequently excluded from other studies assessing the role of oral antibiotic therapy. Although small, this retrospective series demonstrates the real-world applicability of a step-down approach to endocarditis treatment, previously outlined in a randomized controlled trial by Iversen *et al*.[2] In that study, all patients received at least 10 days of IV antibiotic therapy prior to transitioning to oral treatment. Notably three patients in this series received <10 days of IV treatment before switching to an oral regimen. This finding suggests there may be a subset of patients in which even shorter durations of IV treatment are necessary and should be an area of further investigation. The duration of treatment was guided by a multidisciplinary endocarditis team using an evidence-based approach. When possible, patients with native valve streptococcal endocarditis or culture negative endocarditis were treated with ∼28 days of therapy, per American Heart Association guidelines.[1] Additionally, patients who underwent surgical intervention were at times treated with 2 weeks of therapy from their operative date, provided they had no other metastatic sites of infection.[9]

There are several patient and health system barriers to providing treatment to endocarditis PWIDs. As highlighted by this study, five patients desired discharge either home or to a nursing facility but were denied by either the nursing facility or by home infusion and home care companies. This finding is consistent with other published research from Massachusetts, which demonstrated that 37.4% of opioid-use disorder hospitalizations in that state were associated with at least one referral rejection that included discriminatory content from a post-acute care facility.[10] Without transitioning to an oral regimen these patients would likely have stayed in the hospital for the entirety of their antibiotic course. In addition to the costs to the healthcare system, long hospital stays also increase the risk of patient-directed discharge, which may be as high as 20% in patients with IVDU-related endocarditis.[11]

Although there were no relapsed infections with the initial microorganism, one patient developed recurrent IE with a new bacterium and one patient who previously had culture negative endocarditis developed endocarditis due to *S. mitis*. Both of these cases occurred in the setting of ongoing IVDU. While partial oral antibiotic treatment can be effective, if the underlying substance use disorder is not addressed patients will remain at continued risk for subsequent IE episodes. All patients in the cohort who had associated IVDU were seen by the hospital's addiction medicine consult service. All seven patients were also initiated on medication-assisted treatment, including one who was treated with methadone and six treated with buprenorphine. The concurrent use of rifampicin has the potential to induce metabolism of methadone and the patient discharged on methadone was monitored closely as an inpatient after initiation of rifampicin to ensure they did not develop precipitated opiate withdrawal.

This limited retrospective case series builds upon the established literature, including a 400 patient randomized control trial, which has demonstrated the non-inferiority of partial oral antibiotic treatment compared with IV therapy for IE. Our findings suggest that it may be reasonable for providers to consider a step-down approach in IE patients, including those with IVDU or those who would prefer to avoid the potential complications of long-term IV antibiotic administration.

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Transparency declarations

All authors contributed to the manuscript and have no conflicts of interest to disclose.

Supplementary data

Appendix S1 is available as Supplementary data at *JAC-AMR* Online.

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