IV vs. Oral Antibiotics for Treatment of Infective Endocarditis Associated with IV Drug Use

By

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INTRODUCTION

The effects of the opioid crisis in the United States are well-established. It has reached epidemic proportions and causes immense personal, financial, psychological, and medical complications to those caught in its addictive clutches. Many users inject prescription and non-prescription opiates directly into their veins, allowing for 100% bioavailability and rapid onset of the drug's desired effects.[1] While most users are familiar with the very real possibility of death from an acute overdose, a lesser known, long-term complication that can result from intravenous drug use (IVDU) is a bacterial infection of the valves of the heart called infective endocarditis. The act of sharing or reusing needles, as well as improper cleansing of the skin can introduce bacteria directly into the bloodstream, which then seed the valves of the heart, resulting in IE.[2] This infection has the potential to cause significant chronic medical problems that are deleterious to quality of life, requiring multiple hospitalizations, extensive antibiotic therapy, and, in some 25-30% of cases, surgical management.[3] The mainstay of therapy for IE is long-term antibiotics, which is not always feasible or desirable for this patient population for several reasons. Most guidelines recommend four to six weeks of IV antibiotic treatment, therefore requiring these antibiotics to be administered via a peripherally inserted central catheter (PICC line).[4] The presence of a PICC line in a patient known to be an IV drug user makes discharge before completion of antibiotic therapy irresponsible due to the very real possibility of injecting illicit drugs into the patent venous access site. Cost is also a significant burden, to the patient and facility providing care which will be discussed briefly. This work will serve to analyze the epidemiology, pathophysiology, and treatment options for IV drug use associated infective endocarditis with the purpose of answering the question: *In adult*

intravenous drug users with native valve infective endocarditis, are oral antibiotics as effective in resolving infection and reducing complications as intravenous antibiotics? A secondary objective will include exploration of cost differences.

BACKGROUND

Epidemiology

It is estimated that 21 to 29% of patients with prescription opioids misuse them.[5] Approximately 4 to 6% of these patients will transition to heroin.[6] Between 2006 and 2013, heroin use in the United States has nearly doubled, and an estimate from the CDC states that deaths from heroin overdose nearly quadrupled from 2002 to 2014.[7] The population affected by infective endocarditis related to IVDU has changed in recent years, with an increasing frequency among patients younger than age 34, Caucasians, and females.[8] Between 2000 and 2013, the proportion of patients hospitalized for infective endocarditis whose infections were directly related to injection drug use increased from 7% to 12%. This represents an estimated growth from 3,578 cases per year to 8,530 cases per year nationally.[8] The CDC has also determined that in North Carolina, the incidence of hospitalizations for endocarditis among drug-dependent patients has increased twelve-fold since 2010.[9] In the general population, IE occurs primarily on the left-sided heart structures, more specifically the mitral and aortic valves.[10] Infective endocarditis involving these valves accounts for approximately 90 to 95% of all cases in the United States.[10] Interestingly, there is a well-established association of right-sided endocarditis in IV drug users. Of all cases of right sided infective endocarditis, is it estimated that approximately 76% occurred in IV drug users, and the tricuspid valve is involved

in 40 to 69% of those cases.[11] Not surprisingly, the prevalence of right sided infective endocarditis coincides with the population shown to be highest for IV drug use.[8]

Pathophysiology

Infective endocarditis is defined as an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect.[10] Its detrimental effects on the heart include severe valvular insufficiency, which may progress to congestive heart failure and myocardial abscesses.[12] Central to the concept of why infective endocarditis is so dangerous to patients is the production of endocardial vegetations. Vegetations are comprised of platelets, clotting factors, and inflammatory cells that are embedded with high concentrations of bacteria[12]. These are diagnosed by echocardiogram (Image 1). These vegetations are able to adhere to damaged endocardial tissues and are exceptionally difficult to eradicate, and therefore often require an extended course of antibiotic therapy or surgery in order to give the patient the best possible outcome.[12]

There are several well-studied mechanisms that help explain how and why IV drug users have an increased risk of developing infective endocarditis which we will discuss briefly. The repetitive exposure to particulate matter within solutions of IV drugs can cause damage to the valves, particularly the tricuspid valve which acts as a "screen" since it is anatomically the first structure exposed to the foreign injected matter.[12] Small particles and impurities in the injected solution may cross the pulmonary capillaries and abrade the endothelium of the mitral and aortic valves as well.[12] Direct introduction of bacteria from skin broken by a needle into the bloodstream is another origin of infective endocarditis. The incidence of cutaneous and nasal colonization with *Staphylococcus aureus* has been shown to be higher in IV drug users.

Staphylococcus aureus also happens to be the most commonly isolated pathogen in cases of infective endocarditis associated with IV drug use, although other organisms can be involved as well.[10] Additionally, there is potential for vasospasm caused by injected impure drugs, especially in the case of heroin mixed with vasospastic agents such as cocaine. This vasospasm creates a favorable environment for thrombus formation and bacterial aggregation.[12] These are the most extensively studied and plausible mechanisms, however further research is always warranted to discover more information.

The clinical presentation of right and left sided infective endocarditis are quite different. On physical examination, the majority of patients with right-sided infective endocarditis will exhibit a systolic murmur, but they are almost never pathologic[13], meaning that the murmur itself does not indicate structural heart disease. Pathologic murmurs are typically associated with left-side heart involvement. The expected characteristics of right-side involvement are fever, bacteria in the bloodstream, and as the infection progresses, multiple pulmonary emboli as the vegetations break free or cause a vascular insult and produce a clot.[13] Therefore, the patient may present with chest pain, dyspnea, cough and hemoptysis. If peripheral embolic events or neurological findings are present, it should draw suspicion toward left-sided heart involvement.[13]

It can be helpful to group complications of right-sided infective endocarditis into cardiac or pulmonary. Multiple sequelae of septic pulmonary emboli include: pulmonary infarction, pulmonary abscess, bilateral pneumothorax, pleural effusion, and empyema.[10] Fatal pulmonary hemorrhage can occur due to the rupture of aneurysms in the pulmonary arteries. These pulmonary emboli can also result in right ventricular dysfunction to the point of failure and

worsening tricuspid regurgitation from valvular incompetence. Tricuspid regurgitation has sequelae similar to that of septic pulmonary emboli, including right-sided chamber dilation, volume overload, and right ventricular failure. Other cardiac complications include the development of atrial fibrillation or atrial flutter.[14]

Current Treatment Guidelines

According to the *2015 American Heart Association (AHA) Guidelines for Infective Endocarditis in Adults*, the widely accepted standard of care for IE is 4 to 6 weeks of IV antibiotic therapy. Some less severe *Streptococcus* infections can be effectively treated with IV antibiotics for 2 weeks.[15] The choice of antimicrobials will, of course, vary depending on the causative microorganism. Table 1 shows a summary of the various IV antibiotic regimens recommended by the AHA for microorganisms causing IE. Antibiotics such as Penicillin G, nafcillin, oxacillin, and vancomycin require central access (as opposed to peripheral or midline catheters) if they are to be infused parenterally at standard concentrations for a period of time exceeding 2 weeks.[16] As Table 1 demonstrates, these IV medications are among the most common used to treat IE, especially if the causative microorganism is in the *Staphylococcus* or *Streptococcus* family.

Table 1: AHA Recommendations for the Treatment Regimens of Endocarditis

Microorganism	*IV Antibiotic Regimen*
Penicillin-susceptible viridans *Streptococcus* or *Streptococcus bovis*	Penicillin G or ceftriaxone for 4 weeks or Penicillin G + gentamicin for 2 weeks or Ceftriaxone + gentamicin for 2 weeks or Vancomycin for 4 weeks

Relatively penicillin-resistant viridans *Streptococcus* or *S. bovis*	Penicillin G or ceftriaxone for 4 weeks, plus gentamicin for 2 weeks or Vancomycin for 4 weeks
Penicillin-resistant viridans *Streptococcus* or *S. bovis*	Ampicillin + gentamicin for 4 to 6 weeks
Oxacillin-susceptible staphylococci	Nafcillin or oxacillin for 6 weeks, plus gentamicin for 3-5 days (optional) or Cefazolin for 6 weeks, plus gentamicin for 3-5 days (optional)
Oxacillin-resistant staphylococcus	Vancomycin for 6 weeks
Enterococcus strains susceptible to penicillin, gentamicin, and vancomycin	Ampicillin + gentamicin for 4-6 weeks or Penicillin + gentamicin for 4-6 weeks or Vancomycin and gentamicin for 6 weeks
Enterococcus strains susceptible to penicillin, streptomycin, and vancomycin, and resistant to gentamicin	Vancomycin + streptomycin for 6 weeks
Enterococcus strains resistant to penicillin, but susceptible to aminoglycosides and vancomycin	Ampicillin/sulbactam + gentamicin for minimum of 6 weeks or Vancomycin + gentamicin for 6 weeks

METHODS

In order to address the clinical question at hand, the UNC Health Sciences Library links to the PubMed and CINAHL Plus databases were used. Within the PubMed database, the MeSH search builder was utilized and the following terms were added: "infective endocarditis", "intravenous drug users", "antibiotics", "oral antibiotics", and "intravenous antibiotics". In the CINAHL Plus database, a search was conducted to include the following terms: "infective endocarditis" AND "intravenous drug use" AND "antibiotics". For the latter search term, "Include Term in Subject Heading" was specified within the search bar to ensure the focus of the resulting articles would be on treatment options and efficacy.

For the clinical review on this topic, a retrospective cohort study, a systematic review, as well as a Cochrane review to compare and contrast have been selected. Included in the data analysis are multiple types of antibiotics, with emphasis placed on the route of administration, namely oral and intravenous. Infections whose etiologies were not related to IV drug use were not excluded since the organisms and the disease processes are similar, independent of the cause. Risk of bias in the included studies with respect to sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting was assessed using the Cochrane Collaboration's risk-of-bias assessment tool.

RESULTS

Mzabi et al (2016) presented a retrospective cohort study that aimed to determine whether a switch from parenteral to oral antibiotics following seven days of treatment with IV antibiotics was safe and effective for patients suffering from IE.[17] 426 cases of confirmed infective endocarditis were followed over a total of 13 years (from 2000 to 2013). The infectious agent in 88% of these cases was either *Staphylococcus spp.* or *Streptococcus spp*, and 6% of participants had isolated right-sided IE (although IVDU is not explicitly named as the cause). After an initial phase of IV antibiotic therapy, 214 patients (50%) were switched to an oral antibiotic at a median of 21 days after diagnosis of IE. Patients in the oral antibiotic cohort had fewer comorbidities such as heart failure or septic emboli at the start of the study. Oral antibiotics used were amoxicillin alone in 109 cases, or a combination therapy of clindamycin, fluoroquinolone, rifampin and/or amoxicillin in 46 cases, according to the susceptibility of the microorganisms. Analysis of these results concludes that a switch to oral antibiotics was not associated with an increased risk of mortality. During follow-up, four reinfections were

observed in the oral group compared to eight in the IV group. In this study, switching to oral administration was not associated with an increased risk of reinfection and is feasible in less severely ill patients.[17]

Al-Omari et al (2014) conducted a systematic review of nine observational studies and two randomized controlled trials, all of which were determined to be the most applicable after applying very discerning exclusion criteria. The aim of this study was to determine the efficacy of oral antibiotic therapy in the treatment of IE, given that the role of oral antibiotic treatment for this condition is not well established. Seven of the observational studies evaluated the use of beta-lactams, ciprofloxacin with rifampin, or linezolid as appropriate in sensitivity studies in individual cases. The reported cure rates in these studies were between 77% and 100%, while two other observational studies using aureomycin or sulfonamide had failure rates exceeding 75%. A clinical trial comparing oral amoxicillin and IV ceftriaxone for IE from *Streptococcus spp.* reported a 100% cure rate, but the reporting had serious methodological limitations. One small clinical trial comparing oral ciprofloxacin and rifampin versus conventional intravenous antibiotic therapy for uncomplicated right-sided *S. aureus* IE in intravenous drug users reported cure rates of 89% and 90%, respectively. Drug toxicities were more common in the IV antibiotic group (62% versus 3%). Major limitations of this trial were small sample size, lack of allocation concealment, blinding at the delivery of the study drug(s) and assessment of outcomes[18]. Despite these limitations, it can be concluded that an oral regimen of amoxicillin, linezolid, or ciprofloxacin with rifampin could be considered when conventional IV antibiotic therapy is not possible.

A.W. Heldman et al (1996) conducted a prospective, randomized, non-blinded trial to compare the efficacy and safety of inpatient oral antibiotic treatment versus standard IV antibiotic treatment for right-sided staphylococcal endocarditis in IVDUs.

Oral therapy consisted of ciprofloxacin and rifampin. IV therapy was oxacillin or vancomycin, with gentamicin included for the first 5 days. Administration of other antibacterial drugs was not permitted during the treatment or follow-up periods. Patients with right-sided staphylococcal endocarditis participating in the trial received 28 days of inpatient therapy with the assigned antibiotics. Test-of-cure blood cultures were obtained during inpatient observation 6 and 7 days after the completion of antibiotic therapy, and again at outpatient follow-up 1 month later. Statistical data of the participants in this trial are as follows. Of 573 injection drug users who were hospitalized because of a febrile illness, 93 subjects had blood cultures positive for *Staphylococcus*. Of the 93 subjects with positive blood cultures, 85 fit diagnostic criteria for right-sided staphylococcal endocarditis. 44 of these 85 subjects completed inpatient treatment and evaluation including test-of-cure blood cultures. Nineteen patients received only oral antibiotics as their treatment, and 25 received only IV antibiotics. There were four treatment failures, one of them being from the oral antibiotic cohort and three from the IV antibiotic cohort. Drug toxicity was significantly more common in the IV treated group (oral, 3%; IV, 62%) consisting largely of oxacillin-associated increases in liver enzymes.[19] Given these results, it can reasonably be concluded that for selected patients with right-sided staphylococcal endocarditis, oral ciprofloxacin plus rifampin is effective and is associated with less drug toxicity than intravenous therapy.

DISCUSSION

After reviewing these studies, there are two discrepancies that must be addressed regarding the first cited study by Mzabi et al. This study differed from the other two in that there was a prerequisite period of IV antibiotics prior to switching to oral antibiotics, as compared to analyzing efficacy of oral antibiotics independently of IV antibiotics. The decision to switch to oral antibiotics was strongly correlated with other prognosis factors such as comorbidities and severity criteria. In addition, the timing of the IV to oral switch was highly variable from one patient to another. Furthermore, this study did not specify the etiology of IE as being from IV drug use. Rather, it focused on the infectious agent independent of cause. It must also be noted that while the Al-Omari and Heldman studies did include patients specifically noted to have IVDU associated IE, their sample sizes were very small.

The success of antibiotics in controlling bacterial growth and replication is dependent on: a) The susceptibility of the pathogen to the anti-infective that is used; b) The pharmacokinetics of this drug (i.e. whether its bioavailability and distribution allow it to reach the site of infection in sufficient concentration); and, c) Appropriate duration of therapy.[18] Although the pharmacokinetic profile of oral ampicillin is known to be suboptimal, the studies in which this antibiotic was used reported high rates of cure in patients with IE.[20] This is likely explained by the fact that the organisms causing IE in those series were mainly streptococci and staphylococci, and that large doses of oral ampicillin were used. Oral amoxicillin, on the other hand, has excellent bioavailability (>90%) and low binding to serum proteins (17%), which maximizes its tissue penetration[21], which is needed to effectively sterilize dense vegetations found in IE. Typical doses of oral amoxicillin (1 g q8h) produce peak and 6-hour serum

concentrations of 16ug/ml and 1.1 ug/ml, respectively.[22] Further, adding probenecid 1 g to each dose of amoxicillin increases its peak and trough serum concentrations by 30% and 4-fold, respectively.[22] Therefore, while pharmacological considerations make oral amoxicillin a plausible alternative for the treatment of IE caused by susceptible bacteria, the clinical evidence supporting this approach is still not robust.[18] However, because streptococci continue to be a leading cause of infective endocarditis (40% - 60% of native valve endocarditis in the community setting)[14] and oral amoxicillin is inexpensive and widely available, this therapeutic approach should be further investigated in adequately designed clinical trials.

Staphylococcus aureus is the leading cause of IE among those who acquired the infection in healthcare settings and among IV drug users, and the second most prominent cause of community acquired IE.[23] Ciprofloxacin has bactericidal activity against *S. aureus* and a strong pharmacokinetic profile when given orally (70% bioavailability and serum protein binding rate of 30%), but the emergence of resistance during treatment of *S. aureus* IE is well described.[24] Similarly, rifampin is bactericidal against *S. aureus*, has almost complete oral bioavailability, and shows little binding to serum proteins; however, it also has a low threshold for the development of spontaneous resistance during therapy.[25] Newer fluoroquinolones such as levofloxacin and moxifloxacin also have a strong pharmacologic profile when given orally and are bactericidal against *S. aureus,* and in contrast to ciprofloxacin, the development of in-vivo resistance appears rare.[26] Therefore, it would also be reasonable to consider the oral administration of these drugs in future studies for the treatment of this infection.

Oral linezolid has excellent pharmacologic profile (bioavailability >99% and serum protein binding rate 30%) and there is a growing body of evidence of its efficacy in serious

infections caused by Gram-positive cocci.[27] The promising results with the use of oral linezolid for the treatment IE reported by Al-Omari et al[18] warrant further confirmation in clinical trials.

The guidelines that have been followed for years have demonstrated a limited role for oral antibiotics in the treatment of infective endocarditis. These opinions, however, were largely based on theoretical considerations and anecdotal experience. The findings of this work challenge the guidelines, however there are limitations. In order for the use of oral antibiotics to become a largely accepted practice incorporated into guidelines, higher quality and more consistent studies should be performed. Standard outcome measures and objective measures of response to treatment should also be defined and applied in all future studies to ensure universally high-quality data collection and analysis.

Cost is a significant burden to the patient, treatment facility, and the overall medical system as a whole. There is little information available at this time specifically detailing the cost in treating IVDUs related IE, however there is one study that provides insight into the financial consequences of such an infection. A 12-month retrospective chart review was conducted at Jackson Memorial Hospital in Miami, Florida from 2013 to 2014. During this period, 423 patients were admitted for IVDU associated infections. Only 8% of these patients had private insurance. State-funded Medicaid programs were billed for 41% of patients. Federally-funded Medicare was billed for 15% of patients. Of the IVDUs in the cohort, 36% were completely uninsured. Further financial impact such as lost wages is beyond the scope of this paper. Care for indigent patients at Jackson Memorial Hospital is supported by the taxpayers of Miami-Dade County via a 0.5% sales tax levied since 1991 for the Public Health Trust. During this study, the

majority of the 423 patients had infections involving skin and soft tissue, with 13% of cases being confirmed IE. The adjusted mean charge for patients without IE was $71,581. The adjusted mean charge for patients with IVDU related IE was significantly higher at $180,314[28]. No data is provided on exact treatment in this study, however it is stated that all IE patients received IV antibiotics as part of their therapy.

Using oral antibiotics as opposed to the well-established IV regimens has significant cost-saving potential where appropriate. For example, referencing the 2015 AHA guidelines (see Table 1), it is appropriate to treat IE caused by oxacillin-susceptible *S. aureus* (OSSA) with a 6-week course of IV oxacillin. According to a 2011 study by Weiland et al in which oxacillin was used, daily charges for 4g every 6 hours and supplies (not including staff) is $249, with a 6 week course totaling $11,329.[29] Using the same causative organism, OSSA, in another example, the conclusion of Al-Omari et al[18] can guide oral treatment. In this situation, 1g of oral levofloxacin daily is an appropriate alternative to IV therapy. According to the drugs.com price guide (November 2018), two 500mg levofloxacin tablets cost $10.13[30] which is the daily cost for an appropriate dose in a patient with IE. Therefore, a 6-week course would total $425.46.

It is also necessary to consider treatment setting in the population of IVDUs. Inpatient therapy is an option and may be required depending on severity of illness; however, it is inevitably the most expensive, and carries its own set of risks such as hospital acquired infections. Outpatient parenteral therapy (OPAT) is an option for some patients in the general population.[16] However, a history of illicit injection drug use frequently raises questions about the appropriateness of OPAT. Allowing a patient outside of a supervised facility presents the

risk of using their PICC line to directly inject other substances. No clear-cut guidelines exist, and the practitioner must weigh the risks and benefits in each case. Furthermore, the patient must be compliant and have the physical ability to complete OPAT. Either the patient, a family member, or a designated friend must have the cognitive ability and manual dexterity to infuse antibiotics. The patient's home must have a telephone, running water and, if necessary, a refrigerator for medications.[16] These added variables associated with OPAT make oral antibiotic therapy that much more desirable when possible.

CONCLUSION

These studies have demonstrated that oral antibiotics in the treatment of uncomplicated infective endocarditis, especially when they are associated with *S. aureus* and *Streptococcal spp.*, are suitable alternatives to the AHA guidelines. The oral regimens can be just as effective, and in some cases, a much better option. As mentioned previously, the more common infectious agents seen in IE from IV drug use are *S. aureus* and *Streptococci*. However, it must be restated that the study with the largest sample size cited within this work relied on an IV regimen for 3 weeks prior to a switch to oral antibiotics. Additionally, the participants deemed appropriate to receive an oral antibiotic regimen had fewer comorbidities or less severe valvular disease than others in the same study. There are instances in which the options of effective intravenous antibiotics are limited, such as in patients with multiple allergies, resistant bacteria, or the maintenance of prolonged intravenous access is not desirable. Oral antibiotic regimens can be initiated inpatient, with the potential for quicker discharge and the ability to continue treatment from home. IV antibiotic courses require hospitalization, usually for the duration of treatment.

Remaining at the forefront of all is our obligation as healthcare providers to our patients, to educate them on the potential negative outcomes of illicit IV drug use, as well as facilitating, to the best of our ability, substance use counseling and rehabilitation.

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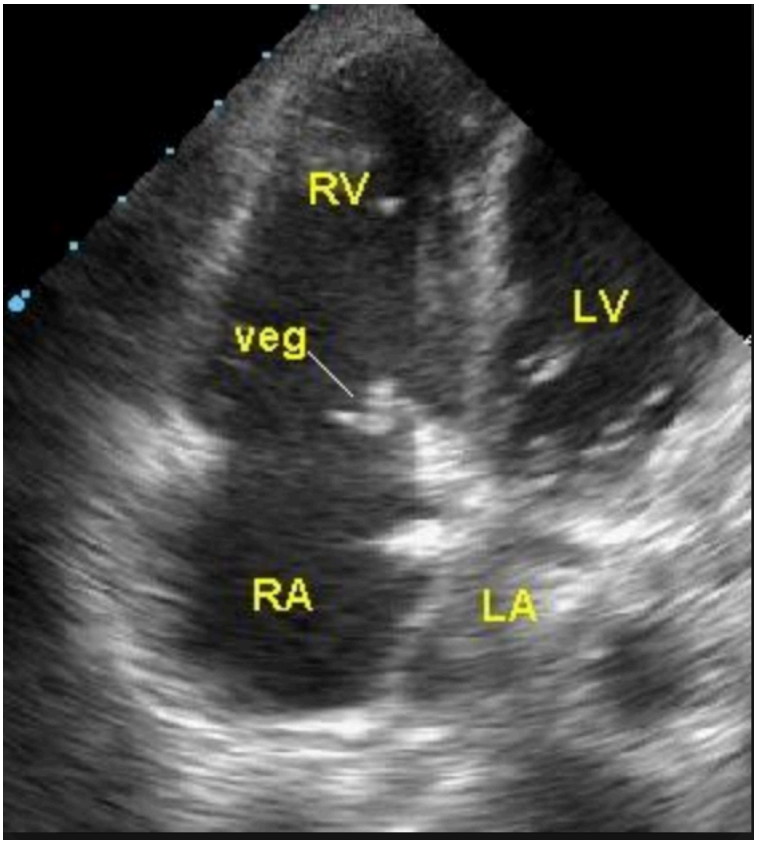
Appendix

Image 1: Echocardiogram demonstrating a large vegetation in a patient with infective endocarditis. Photo credit: https://www.rcemlearning.co.uk/references/endocarditis/



Cochrane Tool for Risk of Bias:

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Mzabi 2016	High	Unclear	High	Low	Low	Low	Unclear
Al-Omari 2014	High	High	High	High	Low	High	Low
Heldman 1996	Low	Low	High	Low	Unclear	Low	Unclear

Characteristics of Included Studies

Author, year	Study Design	Sample Size	Key Measures	Key Findings
Mzabi, 2016	Retrospective Cohort Study	426	• 214 patients (50%) were switched to oral route at a median of 21 days after diagnosis of IE. • Oral antibiotics were amoxicillin alone in 109 cases or a combination therapy of clindamycin, fluoroquinolone, rifampicin and/or amoxicillin in 46 cases, according to the susceptibility of the microorganisms.	A switch to oral antibiotics following a course of IV was not associated with an increased risk of mortality or reinfection.
Heldman, 1996	Prospective, Randomized, Non-blinded Trial	93	• Febrile injection drug users were assigned to begin oral or IV treatment on admission, before blood culture results were available. • Oral therapy consisted of ciprofloxacin and rifampin. Parenteral therapy was oxacillin or vancomycin, plus gentamicin for the first 5 days.	For selected patients with right-sided staphylococcal endocarditis, oral ciprofloxacin plus rifampin is effective and is associated with less drug toxicity than is intravenous therapy.
Al-Omari, 2014	Observational Study	85	• Seven observational	The use of oral ciprofloxacin in

			studies evaluating the use oral beta-lactams, oral ciprofloxacin in combination with rifampin, and linezolid for the treatment of IE caused by susceptible bacteria reported cure rates between 77% and 100%.	combination with rifampin for uncomplicated right-sided S. aureus IE in IVDUs is supported by one small clinical trial of relatively good quality and could be considered when conventional IV antibiotic therapy is not possible.
Tookes, 2015	Retrospective Chart Review	349	• Discharge records/billing for all emergency department visits and inpatient hospitalizations were queried for drug abuse AND infection AND hospitalization between July 1, 2013 and June 30, 2014.	Injection drug use-related bacterial infections represent a significant morbidity for IDUs in Miami-Dade County and a substantial financial cost to the county hospital.