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Partial outpatient oral antibiotic treatment of infective endocarditis is non-inferior to inpatient intravenous antibiotic therapy

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Partial outpatient oral antibiotic treatment of infective endocarditis is non-inferior to inpatient intravenous antibiotic therapy

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ABSTRACT A clinical decision report using:

Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *N Engl J Med.* 2019; 380:415-424. https://doi.org/10.1056/NEJMoa1808312

for a patient with infective endocarditis and intravenous drug use with desire to leave the hospital.

Keywords: *infective endocarditis, antibiotics, addiction*

Clinical-Social Context

Joseph Podolski (pseudonym) is a 27-year-old white man who presented to the emergency department with joint pain, fever and fatigue. Past medical history includes injecting heroin “all over” his body and infrequent medical visits. He was tachycardic and febrile with a chest x-ray read as bilateral pneumonia versus septic emboli. Blood cultures were drawn and he began empiric antibiotic therapy for both pneumonia and endocarditis. His workup was negative for Covid-19 and HIV. After admission to the hospital an echocardiogram showed a 1.1cm x 1.3cm vegetation on the pulmonic valve and cardiothoracic surgery, cardiology, infectious disease and addiction medicine were consulted. Infective endocarditis (IE) was diagnosed and blood cultures resulted with methicillin resistant staphylococcus aureus. His intravenous antibiotic regimen was adjusted according to susceptibility results. The team discussed his substance use with him and he explained he did not share needles but did reuse needles after sterilizing them with lime juice. He had never attempted treatment and stated, “I don’t want to stop” using heroin, partially for fear of withdrawal symptoms which he had experienced previously.

After a few days of inpatient therapy cardiothoracic surgery requested that Mr. Podolski undergo a transesophageal echocardiogram (TEE) for better visualization. Mr. Podolski was very nervous about being in the hospital and declined the procedure initially because of this. In conversation, he explained he had “too much to take care of at home” and wanted to leave in spite of his ongoing intravenous antibiotic therapy. The severity of his condition was explained to him as well as the need for longer duration of antibiotics and the risk of death if untreated. He told the team he lives at home with his sister and was intentionally vague when asked about why he wanted to leave so urgently but was insistent on doing so.

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Clinical Question

Can outpatient oral antibiotic treatment of infective endocarditis be an acceptable alternative to inpatient intravenous antibiotic treatment for patients who wish to leave the hospital?

Research Article

Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *N Engl J Med.* 2019; 380:415-424. https://doi.org/10.1056/NEJMoa1808312 [1]

Description of Related Literature

PubMed was searched first with the query “endocarditis” AND “oral” AND “intravenous” AND “antibiotics”. This returned 67 results and only articles that compared parenteral therapy with oral antibiotic therapy were reviewed in depth. A total of 2 clinical trials were found that were relevant to this scenario, Iversen et al.[1] and Heldman et al.[2] A second search using MeSH with terms “endocarditis, bacterial/drug therapy AND oral AND intravenous returned 100 results with subsequent filter for randomized controlled trial revealing the same trials. The other articles in the search were predominately review articles, meta-analysis or systematic reviews and were examined for further context. McCarthy and Avent discussed the benefits of oral antibiotics over intravenous agents as having lower cost, absence of cannula-related infections and earlier discharge from the hospital.[3] Several reviews mentioned Iversen et al. in their citations. One such meta-analysis from Rezar et al. also concluded that partial oral therapy was non-inferior to IV therapy for non-critically ill patients in left or right IE.[4] This paper referenced a study by Mzabi et al.[5], which appeared related and was set aside for further investigation. Chowdhury et al. published a clinical decision paper referencing Iverson et al. that used expert opinion to argue both for and against use of partial oral antibiotic therapy in a case of infective endocarditis.[6] The remainder of the articles tended to be general reviews or not relevant to the clinical question. One topic of note covered by certain reviews included the use of lipoglycopeptides discussed by Tobudic et al.[7], which are promising but require further study.

As MRSA was seen in Mr. Podolski, this was searched specifically using the query (endocarditis) AND (MRSA) with an article filter for Clinical Trial, Meta-Analysis and Randomized Controlled Trial, returning 38 results. Otome et al. was reviewed indicating that medical management is acceptable versus surgical management regarding large vegetation sizes in right sided IE but was not a direct fit for the clinical question.[8] Other articles were not applicable.

Of the three articles set aside, Iverson et al. was the best article for investigation as a randomized multicenter clinical trial of 400 patients. Mzabi et al. was a single center cohort study of 426 cases.[5] Heldman et al. was a smaller prospective randomized non-blinded trial of 85 patients with right sided infective endocarditis but noted its population was predominantly African American males and had high rates of concomitant HIV infection unlike Mr. Podolski.[2]

A final search via Google Scholar was performed for related articles to Iversen et al. and 101 results returned. Outpatient parenteral antimicrobial therapy was a topic of interest but ultimately not the best fit for the clinical question as seen in Suzuki et al.[9] Additional studies of interest were Vroon et al. and Dworkin et al.[10,11] Bundgard et al.[12] was a follow up related to Iversen et al. and was reviewed. Vroon et al. used the Iversen et al. criteria for patient selection but was a retrospective observational study of 119 patients.[10] Dworkin et al. was an older study of 14 patients with right sided IE whose findings concurred with the other articles but was underpowered relative to the others.[11] Overall, the studies indicated that oral therapy for IE can be effective in right or left sided disease. The strongest study was Iverson et al., which was chosen in spite of its focus on left sided disease as no data were seen suggesting oral therapy’s efficacy differed between such cases.

Using SORT criteria by Ebell et al. the literature regarding use of oral antibiotic therapy for infective endocarditis is a Strength of Recommendation A[13] based on a meta-analysis by Rezar et al.[4] showing this treatment to be non-inferior to IV therapy.

Critical Appraisal

From 2011 to 2017 the Partial Oral Treatment of Endocarditis (POET) trial screened 1954 patients over 18 years old with Duke criteria indicating infectious endocarditis across multiple cardiac centers in Denmark. 400 met inclusion criteria and 201 patients

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were randomized 1:1 to partial oral antibiotic therapy with 199 sorted to intravenous antibiotic therapy. After diagnosis and initial intravenous antibiotics in the hospital, the oral group was switched to 2 oral antibiotics of differing mechanisms, based on bacterial species and drug susceptibility. Oral therapy patients were treated outpatient when feasible and had follow-up 2-3 times per week while on antibiotics. On termination of antibiotic treatment both groups were out of the hospital and were subsequently followed for 6 months. Notable exclusion criteria included reduced compliance and lack of TEE. Demographics including age, sex, comorbid conditions, pathogen, laboratory results, foreign implants and type of cardiac involvement were well distributed considering the number of variables and the sample size.

The results of the study demonstrated non-inferiority of partial oral therapy versus standard intravenous therapy regarding the primary composite outcomes of all-cause mortality, unplanned surgery, embolic events and relapse of bacteremia. A primary outcome occurred in 12.1% in the intravenous group and 9.0% in the oral group (Odds Ratio, 0.72; 95% Confidence Interval 0.37 to 1.36). The difference between groups was 3.1% (P=0.40) indicating non-inferiority criteria were met. The rate of adverse effects from the antibiotics was 6% in the IV group and 5% in the oral group with no significant difference (P=0.66). According to SORT criteria, this result is Level 1 quality as the POET trial is a high quality randomized controlled trial examining patient oriented evidence with adequate follow up of 6 months. Additionally, the findings are consistent with the related literature.

Notable weaknesses of the study included the limited selection of only four bacterial species that can cause IE. There were no included cases of MRSA, a relatively common cause of IE in the United States seen in Mr. Podolski. Right sided endocarditis was also excluded from this study, though the literature from Rezar et al. seems to indicate oral therapy is an acceptable treatment for right or left sided disease. 22 patients were excluded for compliance concerns, possibly impacting the generalizability of the results and thereby the recommendation in practice. These factors introduce some selection bias, possibly making the results less representative for Mr. Podolski and an American population.

The study design generated ample power of 90% with a strong effect of treatment size given IE's high fatality rate when untreated and the efficacy of antibiotics. No number needed to treat or harm was provided. Blinding was not performed due to the study involving the route of administration and the addition of sham antibiotic treatment being unethical in a disease with such high mortality rates that has an effective treatment. For potential participation bias, 303 patients screened were not willing or able to consent, which could include patients who were from minority populations and reticent of experimentation. The study groups were also exposed to different lengths of stay in the hospital and therefore varying risk of nosocomial secondary infection.

Clinical significance was adequately considered with ongoing morbidity and death being primary outcomes of relevance. Partial oral antibiotic therapy is feasible to perform in the United States, though the studies population was different from Mr. Podolski's case in a number of ways. The most notable include the average age of 67 and 35% of the patients having at least 1 major comorbidity.

Analysis was done using the intention to treat principle, which improves the strength of the trial, though supplemental per-protocol and sensitivity analyses were also done that showed a similar outcome. Attrition bias was unlikely to be a factor as no patients were lost to follow up or left the study though 4 patients did cross over from oral to intravenous therapy citing preference (2), nausea (1) or new infection (1). The trial was registered prospectively and the study protocol was followed. Funding was provided by grants from several Danish non-profit foundations with one investigator also receiving grant funding from Bayer for unrelated projects.

Clinical Application

The conclusions from this study show that some patients with infective endocarditis can be safely switched to outpatient oral antibiotic therapy after initial intravenous antibiotics and leave the hospital. Although this study's clinical-social circumstances varied slightly from Mr. Podolski's case, they should be an indicator that outpatient therapy would likely be equally efficacious for him as in-patient intravenous therapy. In particular, as he is younger and healthier than the averages of the study he would likely have a high chance of treatment success.

The clinical options were presented to Mr. Podolski and it was recommended he first complete a TEE and the short course of intravenous antibiotics before considering any outpatient treatment options. The ability to be home during treatment as well as the risk of less frequent monitoring was discussed with Mr. Podolski. He ultimately

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decided against remaining in the hospital to continue treatment and left for home against medical advice and without treatment in fear of withdrawal symptoms.

New Knowledge Related to Clinical Decision Science

The field of Clinical Decision Science asks practitioners to consider more than solely the clinical trial data. This case highlights the importance of ensuring someone's social needs and home life are discussed in a non-judgmental way in order to find the root cause of substance use, which is noted in a paper by Steffes as being effective in building long-term physician-patient relationships.[14] Additionally this clinical decision report highlights the need for clinicians to ask themselves about the stigma associated with illicit drug use by their patients and how that affects clinical decision making.[14] Would outpatient therapy be considered in similar cases if doctors are unaware of their own biases? Multiple sequential decisions are required to care for this patient and if the team was better able to elicit this information we may have been more successful in convincing him to proceed with treatment instead of leaving the hospital especially since the POET trial and related studies suggested it was possible to send him home with oral therapy. Had he been older with more serious comorbidities our thinking may have favored an inpatient course anyway and our conversation would have been different and more urgent that he must stay. Management could also change if he was not competent to make his own decisions and did not comprehend the negative effects of forgoing treatment. This case encourages physicians to look for options that fit individual patients and circumstances, especially considering the social factors at play.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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