Current Evidence on Oral Antibiotics for Infective Endocarditis: A Narrative Review

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ABSTRACT

Infective endocarditis (IE) continues to be associated with high morbidity and mortality, even when treated with optimal antibiotic regimens. The selection of treatment depends on the causative pathogen, its antibiotic susceptibility profile, local and systemic complications and the presence of prosthetic materials or devices. Standard therapy typically involves 4–6 weeks of intravenous (IV) bactericidal therapy. However, there are instances in which IV antibiotic administration may be challenging due to cost, complications of IV access, adverse side-effects of the medication or concerns for misuse of the IV line. Current clinical guidance from the American Heart Association and the European Society of Cardiology cite scenarios where oral antibiotics can be considered for treatment of IE, though these situations are relatively infrequent and data to show their non-inferiority limited. Recently, a well-designed randomized clinical study reported favorable outcomes for partial oral antimicrobial therapy regimens given to patients with staphylococcal, streptococcal and enterococcal IE deemed clinically stable and without complications such as perivalvular abscess. Oral antibiotics, usually given in combination, were selected by infectious disease providers for their favorable pharmacologic properties and predicted bactericidal activity. There was a careful selection of patients who were transitioned to oral regimens. Before recommending routine use of oral antibiotics in the care of patients with IE, additional studies that better define eligible patients and that use regimens available in the countries that adopt this practice should be performed. If further studies confirm non-inferior outcomes with partial oral antibiotics for the treatment of IE, medical treatment could be delivered in a simpler, more costeffective manner, and likely with lower rates of adverse side-effects.

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INTRODUCTION

Infective endocarditis involves the endocardial surface of the heart, most often the heart valves. Annual incidence of IE is 3–9 cases per 100,000 in industrialized countries [1]. Increased risk is conferred by the presence of prosthetic valves, implanted cardiac devices, unrepaired cyanotic heart disease, a history of endocarditis and intravenous drug use (IVDU). In-hospital mortality is known to be 20% worldwide in patients with IE [2] [3], while 5-year mortality was nearly 50% in a population-based study performed in California and New York [4].

The selection of optimal therapy (medical or medical plus surgical) and duration for IE depends on the pathogen, its antibiotic susceptibility profile, the presence of prosthetic material or implanted cardiac devices, and the presence of complications such as perivalvular abscess. Standard therapy usually involves 4–6 weeks of IV antimicrobials [5]. Such therapy may entail prolonged hospital stays, especially in circumstances where the delivery of outpatient IV antibiotic therapy is not deemed safe or feasible because of challenges with finances, patient transportation or line maintenance. In such challenging circumstances oral antibiotic therapy is an attractive alternative. However, data to support the use of oral antibiotics in the treatment of IE are limited. In this narrative review, we discuss the results of early studies on the efficacy of such therapy, pertinent information contained in current practice guidelines and recent data on the outcomes of patients with IE treated with partial oral therapy. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

ORAL ANTIBIOTICS FOR IE FROM THE AMERICAN HEART ASSOCIATION AND EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

Current guidelines from the American Heart Association (AHA) mention the option of oral antibiotics in several scenarios based on previously published case series and several trials [5]. For the therapy of uncomplicated right-sided methicillin-sensitive *Staphylococcus aureus* (MSSA) IE in febrile persons with IV drug use, a small prospective randomized non-blinded study by Heldman et al. compared the use of a predominantly 4-week oral antibiotic regimen (ciprofloxacin plus rifampin) to conventional treatment with IV oxacillin or vancomycin plus gentamicin [6]. Nineteen patients received only oral therapy vs. 25 who received IV therapy, and all completed 28 days of inpatient treatment. There were four treatment failures (5% in oral vs. 12% in IV) based on blood cultures performed 1 week after completion of therapy ($p = 0.4$). Drug toxicity was more common in the parenterally treated group (3% in oral vs. 62% in IV; $p < 0.0001$). The authors concluded that for selected patients, oral ciprofloxacin plus rifampin was effective and associated with fewer adverse side effects than IV therapy. Dworkin et al. studied a similar oral regimen in right-sided IE [7]. In a non-comparative trial where study drugs were initiated after a mean of 34.4 h of conventional antibiotic for suspected IV drug-use related *S. aureus* IE (predominantly methicillin-susceptible), patients received approximately 1 week of IV ciprofloxacin which was then transitioned to high-dose oral ciprofloxacin for 3 weeks; oral rifampin was given throughout the whole treatment period. All ten patients who completed the study were cured based on resolution of symptoms and negative blood cultures at 4 weeks post therapy. Neither of these two studies led to widespread adoption of oral antibiotics for the treatment of staphylococcal endocarditis, in part due to very small sample sizes, non-comparative design for the latter and concern for decreasing susceptibility of *S. aureus* to ciprofloxacin over time.

Another organism in the AHA practice guidelines for which an oral antibiotic is discussed is *Enterococcus faecium* resistant to the usual first-line agents (ampicillin, vancomycin and aminoglycoside). In this challenging IE scenario, linezolid, an oxazolidinone antibiotic that is considered bacteriostatic but with activity against vancomycin-resistant *Enterococcus* (VRE), is a Class IIb recommendation (Level of Evidence C) [5]. In a small number of patients,

linezolid was effective therapy for VRE IE [7]. Birmingham et al. reported cure in 17 of 22 cases treated with linezolid (77%) for *E. faecium* IE [8]. The advantage of using linezolid is that it is highly bioavailable when taken by mouth. However, because of its inhibition of monoamine oxidase, concern for the development of serotonin syndrome when used concomitantly with serotonergic neuropsychiatric medications impedes its use. Other adverse side effects that warrant close monitoring include thrombocytopenia and anemia; less commonly, lactic acidosis, peripheral neuropathy, and ocular toxicity can occur [9]. However, treatment failures with linezolid for Vancomycin-resistant *E. faecium* and *E. faecalis* IE have been reported [10]. Subsequently, the superiority of daptomycin over linezolid was demonstrated in a retrospective study of 644 cases of bloodstream infections due to VRE (adjusted risk ratio 1.15 [1.02–1.30]; $p = 0.026$) [11]. Therefore, linezolid is not considered first-line therapy for IE due to VRE, unless daptomycin non-susceptibility or intolerance is present.

Lastly, the AHA practice guidelines recommend the use of ciprofloxacin for native or prosthetic valve IE caused by the group of oral Gram-negative commensals referred to as the HACEK group (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*) (Class IIb recommendation, Level of Evidence C) [5]. The HACEK group is usually susceptible in vitro to fluoroquinolones [10]. A particular circumstance mentioned for their use is patient intolerance to ceftriaxone or other cephalosporin therapy. Very rarely, resistance to ciprofloxacin by members of the HACEK group has been described [12].

Practice guidelines of the European Society of Cardiology also cite the option of oral antibiotics in similar scenarios [13]. For right-sided *Staphylococcus aureus* IE in IV drug users, ciprofloxacin combined with rifampin is a secondary option, provided the strain is fully susceptible to both drugs, the case is uncomplicated and patient adherence is monitored carefully. For IE due to *S. aureus*, sulfamethoxazole/trimethoprim (IV for first week followed by oral for 5 weeks) and oral clindamycin are listed as alternative options (Class IIb recommendation, Level of Evidence C). For IE due to HACEK organisms, the European guidelines mention fluoroquinolones as a less well-validated alternative.

ADDITIONAL LITERATURE EVALUATING THE EFFICACY OF ORAL THERAPY FOR IE

To identify additional pertinent studies reporting the use of oral antibiotics for the treatment of IE, PubMed, Embase and Google Scholar were searched through April 2019. The PubMed search was as follows: (((((((("endocarditis"[MeSH Terms] OR "endocarditis"[All Fields]) AND ((((("anti bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR antibiotics[tw]) OR (anti bacterial agents[tw])) OR (antibacterial agents[tw])) OR (anti biotics[tw]))) AND ("administration, oral"[MeSH Terms] OR "oral"[All Fields])) NOT (dental[tw] OR dentist[tw] OR dentists[tw]))))) NOT ((animals[mh] NOT (humans[mh] AND animals[mh]))). This strategy was translated for Embase. PubMed and Embase searches limited to the last 10 years yielded 127 and 154 records, respectively including duplicates. Google Scholar identified an additional 22 records. For our narrative review we included all systematic reviews and prospective studies and excluded retrospective studies with study populations less than 30 patients, non-English and animal studies. We reviewed all titles and abstracts and narrowed the list to four relevant studies in the past 10 years. We found one systematic review published on the subject in 2014; we thoroughly reviewed its reference list for additional pertinent studies. This provided us with six relevant studies older than 10 years. These combined ten studies were included in this narrative review and are summarized in Table 1.

Schein et al. retrospectively studied, before widespread availability of penicillin, 81 patients with predominantly streptococcal endocarditis treated with oral sulfonamides [14]. The duration of therapy was widely variable (10 days to 14 weeks). The cure rate was a dismal 10% when evaluated at several years' follow-up.

Table 1 Previous studies evaluating oral antibiotic therapy for IE

References Location Year of publication	Design Follow up (f/u)	Cases description	Definition of IE	Microbiology	Therapy	Outcome
Schein et al. [14] USA 1948	Retrospective F/u 2–8 years	81 NVIE	Not explained	*Streptococcus* spp. (94%) *S. aureus* (1%) *Enterococcus* spp. (1%) *H. influenzae* (4%)	Oral sulfonamides for 10–14 days	Cure rate 10%
Pinchas et al. [15] Israel 1983	Prospective F/u 3 months to 12 years	11 NVIE all left-sided IE	Fever and pre-existing valvular heart disease and multiple positive blood cultures	*Streptococcus viridans* (100%)	High dose oral ampicillin for 6 weeks with probenecid for the first 4 weeks and IM streptomycin for the first 2 weeks	Cure rate 90%
Chetty et al. [16] South Africa 1988	Prospective F/u 3 years	15 NVIE	Characteristic clinical features and any of the following: positive blood cultures or vegetations on echocardiogram	*Streptococcus* spp. (60%) Culture negative (40%)	High dose oral amoxicillin for 6 weeks (47% received also probenecid)	Cure rate 87%
Dworkin et al. [27] USA 1989	Prospective F/u 4 weeks	13 IVDUs with NVIE all right-sided IE	More than two positive blood cultures and any of the following: vegetations on echocardiogram or pulmonary infiltrates/effusion or tricuspid insufficiency murmur or no other identifiable source for the infection	*S. aureus* (100%)	IV ciprofloxacin and oral rifampin for 1 week followed by oral ciprofloxacin and oral rifampin for 3 weeks	Cure rate 77%
Stamboulian et al. [17] Argentina 1991	Prospective, randomized, open label F/u 3–6 months	30 NVIE (15 patients received oral vs. 15 patients received IV therapy) all left-sided IE	More than two positive cultures and any of the following: new or changing regurgitation murmur or predisposing heart disease or vascular phenomena or valvular vegetation on echocardiogram	*Streptococcus viridans* (50%) *Streptococcus bovis* (50%)	IV or IM ceftriaxone for 2 weeks followed by high dose oral amoxicillin for 2 weeks vs. IV or IM ceftriaxone for 4 weeks	Cure rate 100% in both arms

Table 1 continued

References Location Year of publication	Design Follow up (f/u)	Cases description	Definition of IE	Microbiology	Therapy	Outcome
Heldman et al. [6] USA 1996	Prospective, randomized, open label F/u 5 weeks	85 IVDUs with NVIE (40 patients received oral therapy group and 45 received IV therapy) all right-sided IE	More than two positive blood cultures and any of the following: valvular vegetations on echocardiogram or evidence of pulmonary emboli on chest x ray or tricuspid insufficiency murmur or no other identifiable source for the infection	MRSA (5%) MSSA (89%) CoNS (6%)	Oral ciprofloxacin and rifampin for 4 weeks vs. IV oxacillin or vancomycin (IV gentamicin for the first 5 days) for 4 weeks	Cure rate 95% in oral vs. 88% in IV, $p = 0.4$ Treatment toxicity: 3% in oral vs. 62% in IV/ $p < 0.001$
Demonchy et al. [18] France 2011	Retrospective	66 IE (19 patients received oral therapy and 45 patients received IV therapy)	Modified Duke criteria	Staphylococci 32% Streptococci 38% Enterococcus faecalis 3% HACEK 2% Candida 3% Polymicrobial 12% Others 11%	Antibiotics were switched to oral therapy after 18 ± 9 days of IV therapy For Staphylococcus aureus, three patients with fluoroquinolones, three patients with linezolid, six patients with combinations of fluoroquinolones, rifampin or clindamycin For streptococcus, four patients with amoxicillin, three patients with combination of amoxicillin, rifampin, or clindamycin	Mortality was 0% in oral switch vs. 21% in patiebts without oral switch. There was no significant difference ($p = 0.052$)

Table 1 continued

References Location Year of publication	Design Follow up (f/u)	Cases description	Definition of IE	Microbiology	Therapy	Outcome
Mzabi et al. [19] France 2016	Retrospective Median follow up was 5 months after diagnosis	426 IE (214 patients received oral vs. 212 patients received IV) Left heart 335 (79%) Right heart 27 (6%) Permanent pacemaker 52 (12%) Intra-cardiac device 12 (3%) Native valve 262 (62%) Prosthetic valve 100 (23%) Bio-prosthesis 53 (12%) Mechanical prosthesis 47 (11%)	Duke criteria	Streptococci 171 (40%) Oral streptococci 99 (23%), *Streptococcus bovis* 42 (10%) Pyogenic streptococci 24 (6%) Other *Streptococci* spp. 6 (1%) MSSA 67 (16%) MRSA 14 (3%) CoNS 48 (11%) Enterococci 50 (12%) HACEK 21 (5%) *Bartonella* spp. 14 (3%) *Coxiella burnetii* 8 (2%) Other microorganisms 28 (7%) No microorganisms identified 5 (1%)	Oral therapy group received IV therapy for median duration of 21 days after diagnosis For streptococci, Amoxicillin (92%) Amoxicillin + clindamycin (4%) Amoxicillin + rifampin (3%) For Staphylococci, Clindamycin + (rifampin or fluoroquinolone) (28%) Fluoroquinolone + rifampin (24%) Amoxicillin + (rifampin or fluoroquinolone or clindamycin) (17%) Fluoroquinolone (7%) Amoxicillin (7%) Clindamycin (7%) Rifampin + (Bactrim or doxycycline) (4%) Linezolid (4%) Rifampin (2%) For Enterococcus, Amoxicillin (91%) Amoxicillin + rifampin (9%)	Mortality rate at follow up of 90 days after treatment was 4/144 (2.7%) in oral vs. 20/170 (11.7%) in IV therapy

Table 1 continued

References Location Year of publication	Design Follow up (f/u)	Cases description	Definition of IE	Microbiology	Therapy	Outcome
Iversen et al. [20] Denmark 2018	Randomized, non-inferiority, multicenter trial. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen. F/u 6 months	400 IE (201 patients received oral therapy and 199 patients received IV therapy) all left-sided endocarditis	Duke criteria	Pathogens in oral Abx group _Streptococcus_ spp. 92 (45.8%) _E. faecalis_ 51(25.4%) _S. aureus_ 47 (23.4%) CoNS 13 (6.5%)	Amoxicillin or linezolid for penicillin and methicillin susceptible _S. aureus_ or coagulase negative staph; Dicloxacillin or linezolid for methicillin susceptible _S. aureus_ or coagulase negative staph; linezolid for methicillin resistant _S. aureus_; Amoxicillin or linezolid for E. Faecalis; Amoxicillin or linezolid for streptococci with MIC for penicillin < 1; Moxifloxacin for streptococci with MIC for penicillin > 1	The primary composite outcome at 6 month-follow up was 18/201 (9%) in oral vs. 24/199 (12.1%) in IV therapy (odds ratio 0.72; 95% CI 0.37–1.36)
Bundgaard et al. [21] Denmark 2019	Follow up data of the study by Iversen et al. above F/u 3.5 years	Same as above	Same as above	Same as above	Same as above	The primary composite outcome was 76/201 (38.2%) in IV group and 53/199 (26.4%) in oral group. (hazard ratio 0.64, 95% CI 0.45–0.91)

_IE_ infective endocarditis, _NVIE_ native valve infective endocarditis, _IV_ intravenous, _IVDU_ intravenous drug users, _MSSA_ methicillin-sensitive _Staphylococcus aureus_, _MRSA_ methicillin-resistant _Staphylococcus aureus_, _CoNS_ coagulase negative _Staphylococcus_, _HACEK_ (_Haemophilus aphrophilus_, _Actinobacillus actinomycetemcomitans_, _Cardiobacterium hominis_, _Eikenella corrodens_, _Kingella kingae_)

A few decades later, Pinchas et al. [15] reported outcomes of 11 patients with uncomplicated *Streptococcus viridans* endocarditis who received 6 weeks of oral ampicillin with 2 weeks of concurrent intra-muscular streptomycin and 4 weeks of probenecid. All blood cultures taken after treatment were negative and they remained free from recurrences during follow-up at 3 months to 12 years.

Progressing along the chronology of publications included in this report, a prospective study by Chetty et al. assessed outcomes of 15 patients with uncomplicated ampicillin-susceptible *Streptococcus* IE treated with 6 weeks of high-dose oral amoxicillin [16]. Twelve (80%) patients responded to treatment and remained well at 3 years. There were three deaths; one at day 7 due to sudden aortic cusp rupture, and two later deaths due to pulmonary and cerebral embolism. One patient relapsed 8 weeks after oral therapy and responded to conventional IV treatment.

In the late 1980s, Stamboulian et al. conducted a prospective, randomized study of 30 patients with penicillin-susceptible streptococcal IE [17] to assess partial oral therapy. Fifteen patients received ceftriaxone for 4 weeks while the other 15 received the same dose of ceftriaxone for 2 weeks followed by oral amoxicillin for 2 weeks. Clinical cure was achieved in all patients in both groups. Broad exclusion criteria were applied, including the presence of heart failure, severe aortic insufficiency, conduction system abnormalities, recurrent thromboembolic disease and prosthetic valve endocarditis.

Moving into the new millennium, Demonchy et al. [18] conducted a retrospective study of adult patients with endocarditis hospitalized between 2007 and 2009. In a total of 66 patients, 19 (29%) patients received an oral antibiotic after 18 ± 9 days of IV antibiotics. A switch to oral antibiotic therapy was not associated with increased risk of mortality compared to those who had only IV therapy (0% mortality in oral switch vs. 21% without, $p = 0.052$).

A significantly larger retrospective study with 426 patients treated for IE between 2000 and 2012 was published by Mzabi et al. [19]. Treatment followed the European IE guidelines except that switching to oral antibiotics was allowed after 7 days of IV therapy if the patient's general condition had improved. In all, 214 patients fulfilled these criteria after a median of 21 days on IV therapy. These patients had fewer comorbidities, less-severe disease, and were less likely to be infected with *S. aureus* than those who remained on IV therapy. Among patients transitioned to oral therapy (median follow-up, 9 months), two relapses, four reinfections, and 16 deaths occurred; among those who continued on IV antibiotics, nine relapses, eight reinfections, and 76 deaths occurred (median follow-up, 3 months). A multivariate analysis that controlled for age, sex, pathogen type and comorbidities indicated that switching to oral treatment was not associated with excess risk for relapse or reinfection. This study suggested that the use of oral antibiotics for a portion of treatment of IE was non-inferior to a full course of IV therapy for some patients.

A recent study that has generated much interest regarding the benefits of relatively early transition to oral antibiotics is the Partial Oral vs. Intravenous Antibiotic Treatment (POET) study conducted by Iversen et al. [20]. This was a randomized, prospective, multicenter non-inferiority trial conducted in Denmark between 2011 and 2017. From 1954 patients screened because of suspected IE, 400 patients (20%) with left-sided endocarditis fulfilled modified Duke criteria and were randomly assigned to IV or oral therapy after an initial 10 days of IV therapy. Common reasons for exclusion were inability to meet the modified Duke criteria (28%), lack of consent (19%), and infection with bacteria not included in the study protocol (11%). The primary endpoint was a composite of all-cause mortality, relapse of bacteremia after 6 months, embolic events, and other complications. The two groups were well balanced with regard to baseline characteristics. In patients treated with partial oral therapy, the causative organisms were *Streptococcus* spp. (45.8%), *Enterococcus faecalis* (25.4%), *S. aureus* (23.4%) and coagulase negative staphylococci (6.5%). Methicillin-resistant *S. aureus* was rare. All patients were followed for 6 months. The composite outcome occurred in 12.5% of the IV group versus 9% of the oral therapy group (odds ratio 0.72; 95% confidence interval 0.37–1.36).

Adverse effects from antibiotics were reported in 12 (6%) patients in the IV treatment group and 10 (5%) patients in the oral therapy group ($p = 0.66$). The results suggested that an oral antibiotic switch is an option for the management of stable patients with IE. In addition, Bundgaard et al. [21] performed a post hoc long-term follow-up review of these patients. After a median follow up of 3.5 years, the primary composite outcome had occurred in 76 patients in the intravenously treated group (38.2%) and in 53 patients in the orally treated group (26.4%) (hazard ratio 0.64, 95% confidence interval 0.45–0.91).

Al-Omari et al. [22] conducted a systematic review on oral antibiotic therapy for endocarditis in 2014 before Mzabi's study and the POET study were published. Their main finding was that cure rates for endocarditis caused by susceptible organisms treated with well-matched oral antibiotic regimens ranged between 75 and 100%. However, they noted that a majority of the studies included in their analysis had poor methodological quality and broad heterogeneity in study populations and study design. These factors prevented them from calculating any meaningful pooled estimates.

DISCUSSION

Current practice guidelines for IE recommend IV therapy for most episodes. However, recent studies have shown IV antibiotics might not be necessary for the entirety of the treatment course, depending on clinical circumstances of the case. There are multiple risks and high costs associated with extended courses of intravenous antibiotics, including procedural complications from intravenous lines, central-line associated infections, and thrombosis [23]. Outpatient parenteral antibiotic therapy (OPAT) allows patients to receive parenteral antimicrobials outside of acute care hospitals. Internationally, OPAT utilization has considerably increased, since its introduction in the 1970s, to treat a variety of infections [24]. It is estimated that more than 250,000 patients receive OPAT annually, and its use is growing by more than 10% annually in the United States [25]. Previous

studies have demonstrated OPAT-related adverse events occur in about 25% of patients and most commonly involve antibiotic reactions, hematologic or gastrointestinal adverse effects, or IV access complications [26]. Oral antimicrobial therapy for endocarditis would offer several potential benefits including lower costs, fewer side effects and greater ease for patients.

The study by Mzabi et al. [19] indicated non-inferior outcomes for patients transitioned to oral antibiotics when good clinical response had been achieved while on IV therapy, but the retrospective nature and broad range of days before transition to oral therapy makes application of the data a challenge. The POET study [20], a well-designed prospective randomized trial of patients with Gram-positive left-sided IE provides stronger evidence that in select patients, carefully chosen oral antimicrobial regimens produce non-inferior outcomes compared to all-IV therapy. There was intensive clinical assessment of the patients, including a TEE shortly before transition to oral therapy, Infectious Disease expertise rendered for the selection of oral regimens, and very close outpatient follow-up. Of note, MRSA was not significantly represented in the oral group and few patients had IVDU as a risk factor for IE. Therefore, the findings may not reflect the patient profiles in other countries, including the US. The fact that only 20% of the screened population was randomized is one reason that widespread adoption of partial oral antibiotic therapy is premature until further studies validate the findings and confirm which features of patients with IE allow for the safe transition to oral treatment. On the basis of these recent data, targeted oral therapy likely has a role in the treatment of selected patients with left-sided IE, but more information is needed to recommend its widespread adoption.

CONCLUSIONS

There is increasing evidence that in some patients with IE, transition to oral antibiotics after achieving a clinical response with IV therapy may have good efficacy and reduced adverse side-effects when compared to all-IV

therapy. If such positive outcomes are confirmed in further studies with good delineation regarding patient and oral regimen options, the benefits would include significantly lower costs to the healthcare system, reduced risks of adverse side-effects associated with prolonged intravenous access, and ease for the patient.

ACKNOWLEDGEMENTS

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