CLINICAL RESEARCH STUDY

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Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

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ABSTRACT

BACKGROUND: We sought to determine if controlled, prospective clinical data validate the long-standing belief that intravenous (IV) antibiotic therapy is required for the full duration of treatment for 3 invasive bacterial infections: osteomyelitis, bacteremia, and infective endocarditis.

METHODS: We performed a systematic review of published, prospective, controlled trials that compared IV-only to oral stepdown regimens in the treatment of these diseases. Using the PubMed database, we identified 7 relevant randomized controlled trials (RCTs) of osteomyelitis, 9 of bacteremia, 1 including both osteomyelitis and bacteremia, and 3 of endocarditis, as well as one quasi-experimental endocarditis study. Study results were synthesized via forest plots and funnel charts (for risk of study bias), using RevMan 5.4.1 and *Meta-Essentials* freeware, respectively.

RESULTS: The 21 studies demonstrated either no difference in clinical efficacy, or superiority of oral versus IV-only antimicrobial therapy, including for mortality; in no study was IV-only treatment superior in efficacy. The frequency of catheter-related adverse events and duration of inpatient hospitalization were both greater in IV-only groups.

DISCUSSION: Numerous prospective, controlled investigations demonstrate that oral antibiotics are at least as effective, safer, and lead to shorter hospitalizations than IV-only therapy; no contrary data were identified. Treatment guidelines should be modified to indicate that oral therapy is appropriate for reasonably selected patients with osteomyelitis, bacteremia, and endocarditis.

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KEYWORDS: Bacteremia; Endocarditis; Meta-analysis; Oral antibiotics; Osteomyelitis

INTRODUCTION

For many years, clinicians have assumed that intravenous (IV) antibiotics are necessary to successfully treat osteomyelitis, bacteremia, and endocarditis. This presumption stems from uncontrolled case series from the 1940s and 1950s and the limited bioavailability of the few oral antibiotics available at that time (ie, sulfanilamide, erythromycin, and tetracycline).[1-3] More modern drugs were not subjected to rigorous testing until the 1980s, by which time the culture of medicine had already established a deep, more than 30 years' old belief in IV-only therapy.[2,4,5] The necessity of IV-only therapy for these diseases has been enshrined in clinical and professional society guidelines, reinforcing long-standing inertia.

However, such guidelines do not cite controlled investigations in which IV-only therapy was established to be superior in efficacy to oral therapy. More recently, a number of studies have tested the hypothesis that we can safely

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switch to oral antibiotics once patients with these infections have stabilized. Therefore, we sought to determine if prospective, controlled investigations substantiate the long-standing clinical belief that IV-only therapy is superior to oral therapy for such infections, and if populations of patients who are likely to benefit from oral step-down therapy may be identified from such studies.

CLINICAL SIGNIFICANCE

- All 20 published randomized controlled trials comparing oral to intravenous (IV) therapy for osteomyelitis, bacteremia, and endocarditis demonstrated oral antibiotic therapy was at least as effective as IV.
- In no published studies was IV superior in efficacy.
- The data are overwhelmingly clear regarding the relative efficacy of oral to IV-only therapy for these diseases; it is time to change how we practice.

METHODS

Literature Search

In March 2021, we conducted a systematic review of the literature for prospective, interventional studies comparing IV-only vs oral antimicrobial therapy for serious, invasive bacterial infections. We searched PubMed for keywords: (oral, linezolid, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, trimethoprim, or clindamycin), and (osteomyelitis, bacteremia, or endocarditis), and publication type clinical trial. References within these articles were also evaluated to identify other relevant publications.

Eligibility Criteria, Data Extraction, and Outcomes

We included only prospective, interventional studies, either randomized controlled trials (RCTs) or quasi-experimental. We excluded retrospective, observational, uncontrolled, and noninterventional studies (in which treatment was not assigned by study protocol), as well as studies of prophylaxis and infections caused by nonbacterial pathogens. All studies were reviewed for eligibility by 3 authors who were also responsible for abstracting results (NWD, RAL, and BS).

A standardized form was used to identify and extract relevant characteristics of included studies. The primary outcome was successful therapy as defined by the absence of the respective clinical infection at the last time point of long-term follow-up. Other outcomes included rates of adverse events, mortality, duration of hospitalization, and relapse rates where available. Random effects meta-analysis of the included studies were graphically illustrated by forest plots using RevMan 5.4.1 freeware, and funnel plots were generated using *Meta-Essentials* freeware and methods[6] to assess for publication bias.

RESULTS

Study Selection

A total of 555 articles were identified from the initial search, of which 28 were prospective, interventional studies (Figure 1). Of these 27 RCTs and 1 quasi-experimental study, we excluded 2 RCTs of patients with bacteremia, 1 of which compared trimethoprim-sulfamethoxazole (TMP-SMX) vs IV vancomycin for invasive *Staphylococcus aureus* infections, and the other of that compared amoxicillin/clavulanate vs intramuscular ceftriaxone for febrile illness in small children.[7,8] The first study was excluded because the trial did not report that any patients actually received oral therapy (TMP-SMX was administered intravenously) and because there were concerns about external validity.[7] The second study was excluded because of extensive crossover of IV and oral therapy in both arms.[8] An additional 5 excluded RCTs enrolled multiple different types of infections, in which only a small numbers of patients had bacteremia or osteomyelitis (ie, ≤5 patients per treatment arm), or for the larger studies it was not possible to distinguish the outcomes of the subgroups of patients with bacteremia or osteomyelitis from those without.[9-13] None of the excluded trials reported significantly different outcomes between patients who received oral vs IV-only therapy. Ultimately, 20 RCTs and 1 quasi-experimental study were included in the analyses. Of the 20 RCTs, 1 was included in both the osteomyelitis and bacteremia analyses because clinical outcomes between groups were reported separately for both conditions in the same paper.[14]

Osteomyelitis

Eight RCTs, totaling 1321 patients, compared IV-only vs oral therapy for osteomyelitis (Table 1). All trials evaluated adult patients, and the majority excluded axial osteomyelitis, although the largest trial[15] included 39 patients with surgery for vertebral osteomyelitis/diskitis evenly distributed between treatment arms. Four of the trials[15-18] included patients with infected orthopedic hardware, all evenly distributed among oral and IV treatment groups. The largest trial of more than 1000 patients included 678 patients with foreign material, including 125 patients with infected prosthetic joints implants.[15] None of the trials included patients with osteomyelitis underlying a decubitus pressure ulcer, a condition for which antibiotics play little role.[22]

All trials reported microbiologic etiologies, with staphylococci followed by *Pseudomonas aeruginosa* as the most common monomicrobial organism. Six trials compared a fluoroquinolone (ciprofloxacin, ofloxacin, or fleroxacin), with or without an oral rifamycin to various IV regimens. One additional study[18] compared oral TMP-SMX plus rifampin to IV cloxacillin, while the largest osteomyelitis study[15] compared standard IV regimens to varied oral regimens including fluoroquinolones (37%), oral combinations (17%), penicillins (16%), and macrolides/lincosamide (13%).

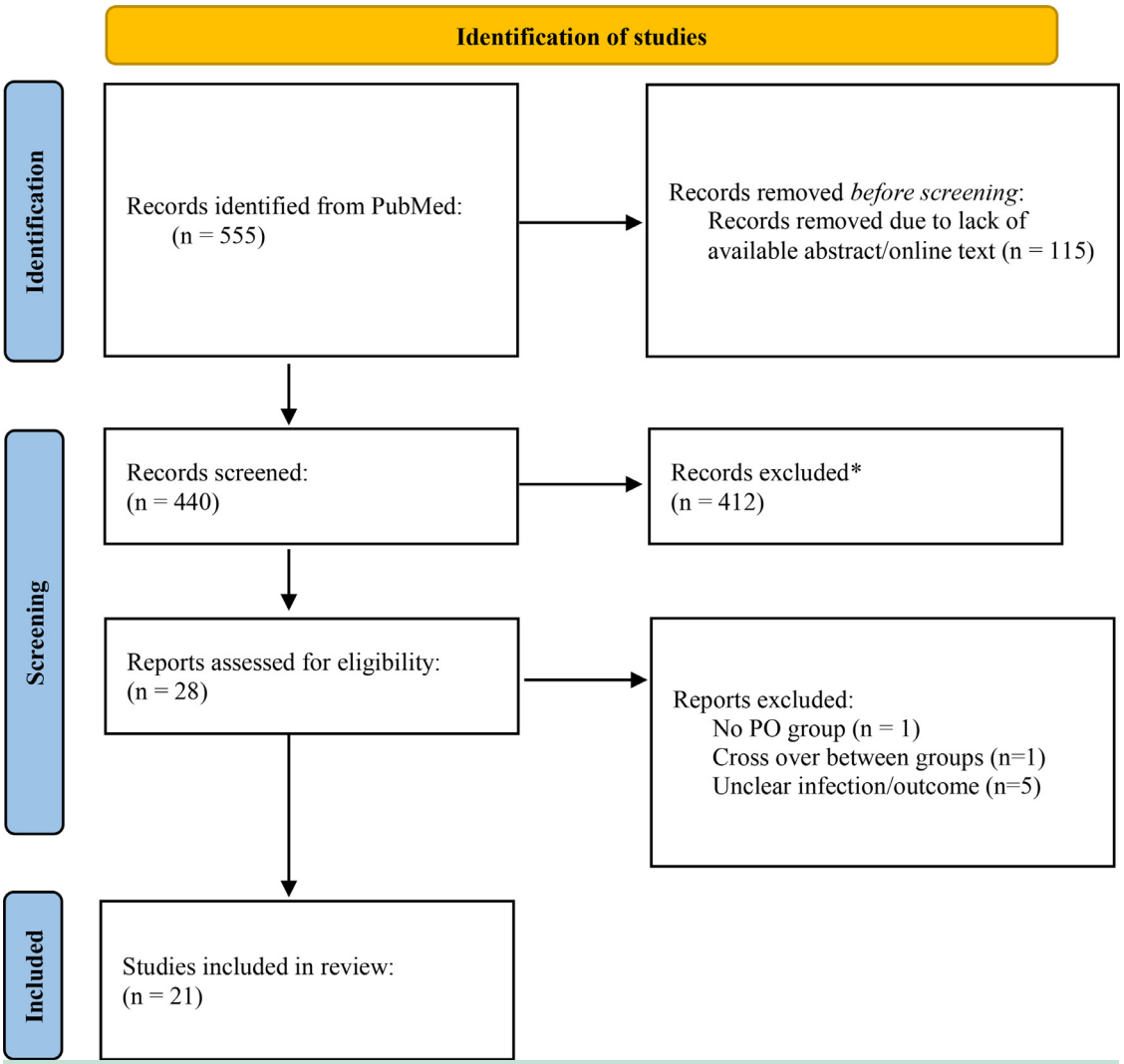

Figure 1 Flow chart for study inclusion. One RCT (Schrenzel 2004) was included in both the osteomyelitis and bacteremia sections because both patient populations were studied in the trial. *Excluded based on being retrospective or observational studies, noninterventional prospective studies (in which treatment with oral or IV was left to the discretion of the treating physician rather than being assigned by the protocol), studies of prophylaxis, studies of infections caused by nonbacterial pathogens, and single-arm or noncontrolled studies. IV = intravenous.

Six trials[14-18,20] demonstrated similar success rates between the IV and oral groups. One trial[21] actually showed significantly superior cure rates (69% vs 50%) for oral ofloxacin over IV imipenem/cilastin.

Severe drug reactions were either similar between treatment groups[13,15,16,18,20] or more frequent[17,19] in the IV group. Three studies also described line-related complications, including local cellulitis, phlebitis, and deep vein thrombosis unique to the IV group, ranging in frequency from 7% to 13%.[15,18,19] In by far the largest RCT conducted, patients in the IV arm had significantly higher adverse event rates, driven by line complications, as well as decreased patient satisfaction and longer durations of hospitalization.[15]

Meta-analysis of the 8 RCTs demonstrated a point estimate (95% confidence interval) of the difference in long-term treatment success of +1% (−3% to +5%) for oral vs IV therapy (Figure 2). Funnel plot analysis revealed no evidence of publication bias (Supplementary Figure 1A, available online).

In addition, 9 RCTs have been published in which oral antibiotics constituted the large majority of therapy in both arms for osteomyelitis with excellent outcomes.[23-31] These RCTs compared different durations or different oral antimicrobial agent, and included patients with vertebral osteomyelitis, diabetic foot infections, and prosthetic joint infections, with only short IV lead-in periods before patients were switched to oral therapy. Outcomes were favorable in these studies. Because these studies did not compare oral to IV therapy, they were not included in the meta-analysis; however, they do add important context regarding the real-world efficacy

Table 1 Prospective RCTs of Osteomyelitis

Author	Year	N	Inclusion and Exclusion*	Regimen Oral vs IV	Success† Oral vs IV	Complications Oral vs IV, n (%)	
Greenberg[19]	1987	30	Included: positive bacterial cultures (blood or bone) Excluded: malignant otitis externa, severity of disease requiring IV therapy	Ciprofloxacin vs standard IV	50% (7/14) vs 69% (11/16)	Relapse AEs	4 (28%) vs 1 (6%) 2 (14%) vs 6 (38%)
Gentry[17]	1990	59	Included: debrided OM Excluded: septicemia, MRSA	Ciprofloxacin vs βL + AG	77% (24/31) vs 79% (22/28)	Relapse AEs	6 (19%) vs 5 (18%) 1 (3%) vs 4 (14%)
Mader[16]	1990	26	Included: extra-axial OM with debridement and culture Excluded: severe renal or hepatic disease, antibiotics within 3 days	Ciprofloxacin vs βL/clindamycin + AG	79% (11/14) vs 83% (10/12)	AEs	7 (37%) vs 4 (29%)
Gentry[20]	1991	33	Included: biopsy confirmed OM Excluded: multiple sites of infection, retained prosthetic material, bacteremia	Ofloxacin vs cephalosporin	74% (14/19) vs 86% (12/14)	Relapse AEs	6 (19%) vs 5 (18%) 7 (37%) vs 4 (29%)
Gomis[21]	1999	32	Included: debrided chronic OM (extra-axial, sacral), 1 PJI	Ofloxacin vs imipenem	69% (11/16) vs 50% (8/16)‡	Serious AEs	0 (0%) vs 3 (19%)
Schrenzel[14]	2004	39	Included: *Staphylococcus aureus* bone and joint infection Excluded: chronic OM without debridement, retained foreign bodies, antimicrobials given >72 hours before enrollment				
				Fleroxacin + rifampin vs βL/vancomycin	82% (18/22) vs 65% (11/17)	Death AEs§	3 (4.4%) vs 5 (8.5%) 15 (22%) vs 5 (8%)
Euba[18]	2009	48	Included: surgical debridement for chronic extra-axial OM with or without foreign body Excluded: PJI, polymicrobial	TMP-SMX + rifampin vs cloxacillin	89% (24/27) vs 91% (19/21)‡	Relapse AEs	3 (11%) vs 2 (10%) 5 (18%) vs 3 (14%)
Li[15]	2019	1054	Included: extra-axial or vertebral OM, septic arthritis, PJI, fixation device infection	standard oral vs standard IV	87% (457/527) vs 85% (450/527)‡	Early discontinuation due to relapse Serious AEs	15 (3%) vs 1 (0.1%) 138 (26%) vs 147 (28%)
Totals (N = 8 RCTs)		1321		Oral: 84% (566/670) vs IV: 83% (543/651)			

AEs = adverse events; AG = aminoglycoside; βL = beta-lactam; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; OM = osteomyelitis; PJI = prosthetic joint infection; standard:= standard of care, within protocol specifications; RCT = randomized controlled trial; TMP-SMX: trimethoprim-sulfamethoxazole.

*All studies excluded children, pregnancy, and patients with organisms resistant to study drug.

†Success = absence of osteomyelitis at long term follow-up (most studies >1 year).

‡Outcomes by intention-to-treat.

§This study performed a subgroup analysis to determine treatment success, but AEs for the full study population regardless of site of infection, so the AE numbers are for the larger population from the study.

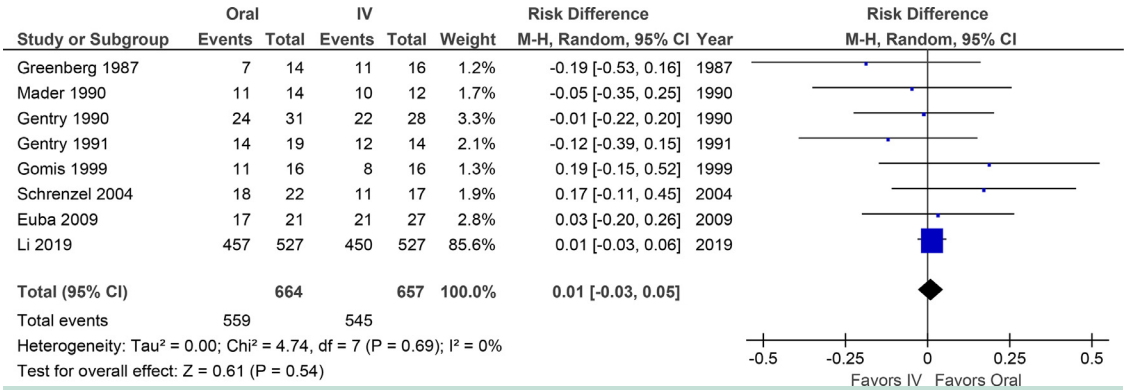

Figure 2 Meta-analysis forest plot of osteomyelitis treatment success. Overall treatment success was not significantly different.

of oral antibiotic therapy for a variety of types of osteomyelitis.

Bacteremia

Ten RCTs were identified totaling 705 patients randomized to either oral or IV therapy for nonendocarditis bacteremia (Table 2). Seven of the trials included only adults. Two trials enrolled only children[19,23] and 1 only neonates.[24] Sources of bacteremia were diverse across trials, including urinary,[32,33] respiratory,[32,34-37] skin and soft tissue,[32,36-38] biliary,[32,39] catheter-related[14,32,35,36,38,40] and primary/unknown.[14,32,35-37,40] Microbiologic etiologies included both gram-positive[14,34-38,40] and gram-negative[32,33,39] bacteremias. Across studies, *Escherichia coli* bacteremia was the most common among the gram-negative bacterial causes, followed by *Klebsiella pneumoniae*, whereas among the gram-positive cocci there was more equal distribution among methicillin-sensitive and -resistant *Staphylococcus aureus* (MSSA and MRSA), enterococci, coagulase-negative staphylococci (including methicillin-resistant strains), *Streptococcus pneumoniae,* and other streptococci.

Six bacteremia trials showed equivalent results for clinical success between IV-only and oral arms. However, 2 trials[35,36] showed nonstatistically significantly higher rates of success with oral therapy, and the remaining 2 studies demonstrated statistically significantly higher cure rates for oral over IV-only therapy.[34,37] No studies reported significantly higher cure rates of IV-only therapy.

Three studies[14,32,39] reported shorter hospital length of stay for oral therapy recipients compared to IV-only therapy, ranging from 1.5 to 11 days shorter.

Five RCTs reported similar overall rates of drug-related adverse events in both arms.[32,33,35,37,38] Two trials showed higher rates of vancomycin-related adverse events compared to oral linezolid, including rash, infusion reactions, and oral candidiasis.[36,40] Two trials reported IV therapy-only adverse effects directly related to IV drug infusion.[33,36]

Central nervous system side effects, hallucinations, and insomnia were more common in the fleroxacin arm compared to IV therapy recipients in 1 trial.[14] Notably, rates of cytopenias were similar in all trials of oral linezolid versus a comparator IV agent. Serious adverse events, including mortality, were similar between study arms in almost all of the studies, although 1 trial of patients who were intended to be enrolled with gram-positive bacteremia had unexpectedly higher mortality among linezolid recipients compared with IV vancomycin recipients.[38] On further analysis, excess mortality in that study was attributable to underlying gram-negative coinfection.

Meta-analysis of the 10 RCTs demonstrated a difference in long-term treatment success (95% confidence interval) for oral vs IV therapy of +7% (−1% to +15%) (Figure 3). Funnel plot demonstrated slight asymmetry; however, imputation to adjust for that asymmetry did not substantively alter the resulting treatment effect (Supplementary Figure 1B, available online).

Endocarditis

Three RCTs and 1 quasi-experimental trial were identified comparing oral stepdown vs IV-only therapy for infective endocarditis, including native and prosthetic valves, left- and right-sided, and cardiac devices endocarditis (Table 3).[41-45] In all cases, appropriate valvular surgical intervention or device removal was performed equally in both groups. While 3 trials focused only on specific etiologic organisms like *S. aureus*[42,45] or streptococci,[44] the largest trial[41] included a variety of causal bacterial organisms including *S. aureus*, streptococci, enterococci, and coagulase-negative staphylococci.

In the 2 smaller studies, oral step-down and IV-only therapy resulted in similar outcomes, including no differences in mortality (no deaths in the former study, and none in the evaluable population in the latter study).[44,45] In the 2 larger studies, which included by far the largest RCT conducted, oral therapy was superior in efficacy, resulting in significantly lower long-term mortality and infectious relapse than IV-only therapy.[41-43] In no identified study was IV-only therapy superior in efficacy.

Table 2 Prospective RCTs of Bacteremia

Author	Year	N	Inclusion and Exclusion	Regimen Oral vs IV	Success* Oral vs IV	Complications Oral vs IV, n (%)
Gram-positive bacteria						
San Pedro[34]	2002	51	Included: age ≥13 years, suspected CAP with *Staphylococcus pneumoniae* bacteremia	Linezolid vs ceftriaxone/cefpodoxime	93% (27/29) vs 68% (15/22)	AEs† 218 (57%) vs 200 (55%)
Deville[40]	2003	36	Included: neonates up to 90 days old with gram-positive bacteremia Excluded: device that could not be removed, condition not appropriate for drug regimen	Linezolid vs vancomycin	80% (20/25) vs 64% (7/11)‡	AEs† 5 (12%) vs 6 (32%)
Jantausch[35]	2003	103	Included: age ≤12 years with bacteremia, including *Enterococcus, Staphylococcus aureus,* CoNS Excluded: device that could not be removed, condition not appropriate for regimen	Linezolid vs vancomycin	72% (54/75) vs 64% (18/28)‡	AEs† 20 (19%) vs 13 (28%)
Kaplan[36]	2003	80	Included: age ≤12 years with CRBSI, bacteremia caused by drug-resistant gram-positives Excluded: treated with active antibiotic >24 hours	Linezolid vs vancomycin	82% (47/57) vs 74% (17/23)	AEs† 40 (19%) vs 34 (34%)
Schrenzel[14]	2004	67	Included: adults with *S. aureus* or CoNS primary bacteremia or CRBSI Excluded: Excluded infections with foreign bodies retained	Fleroxacin + rifampin vs βL/vancomycin	87% (34/39) vs 89% (25/28)	Microbiologic failure rates for *S. aureus* 4 (14%) vs 2 (13%)
Wilcox[37]	2004	56	Included: age ≥13 years, gram-positive bacteremia Excluded: effective antibiotic therapy within 48 hours of study entry, infections requiring >28 days therapy	Linezolid vs teicoplanin	89% (23/26) vs 57% (17/30)	AEs† 121 (56%) vs 110 (51%)
Wilcox[38]	2009	166	Included: age ≥13 years, gram-positive CRBSI Excluded: catheter could not be removed, endovascular or other infection, antibiotic within 72 hours before study entry	Linezolid vs vancomycin	75% (70/93) vs 81% (59/73)	AEs† 244 (67%) vs 230 (63%)
Gram-negative bacteria						
Amodio-Groton[32]	1996	50	Included: adults with gram-negative bacteremia Excluded: severe renal impairment, strict anaerobes, nonbiliary abdominal source, critically ill, neutropenia, AIDS	Ciprofloxacin vs ciprofloxacin (72 hours after any upfront IV agent)	83% (20/24) vs 77% (20/26)	AEs† 1 (4%) vs 2 (8%)

Table 2 (*Continued*)

Author	Year	N	Inclusion and Exclusion	Regimen Oral vs IV	Success* Oral vs IV	Complications Oral vs IV, n (%)	
Monmaturpoj[33]	2012	17	Included: 82 adults with pyelonephritis (17 bacteremic) Excluded: severe hepatic or renal disease, immune-compromised hosts	Cefditoren vs ceftriaxone	100% (6/6) vs 91% (10/11)	AEs†	4 (10%) vs 2 (5%)
Park[39]	2014	59	Included: adults with bacteremic, obstructive acute cholangitis with successful biliary decompression Excluded: critical illness, biliary drainage in prior 2 weeks, need for surgery, immune-compromise, bacteremia complications of liver abscess or endocarditis	Ciprofloxacin vs std IV	93% (27/29) vs 93% (28/30)	Relapse	1 (3%) vs 0 (0%)
						30-day mortality	0 (0%) vs 0 (0%)
Totals (N = 10 RCTs)		685	Oral: 81% (328/403) vs IV: 77% (216/282)				

AEs = adverse events; CAP = community-acquired pneumonia; CoNS = coagulase negative staphylococci; CRBSI = catheter-related bloodstream infection; std = standard of care, within protocol specifications; IV = intravenous.

*Success classified as clinical resolution of infection.

†These studies performed a subgroup analysis to determine success of antimicrobials for bacteremia, but AEs for the full study population regardless of site of infection, so the AE numbers are for the larger population from the study;

‡Analysis by intention-to-treat

Adverse events were similar in most trials with a few exceptions. Slightly higher rates of acute kidney injury associated with TMP-SMX + clindamycin (5% vs <1%) compared to IV standard were reported in 1 trial,[42] although another[45] showed significantly higher rates of liver toxicity (mostly oxacillin-related) and acute kidney injury with IV therapy. All 4 studies demonstrated shorter lengths of inpatient hospitalization in their oral therapy arms.

By meta-analysis, oral therapy was significantly more likely to result in treatment success and mortality, with a treatment difference (95% confidence interval) of +8% (+3% to +14%) (Figure 4). Funnel plot revealed no evidence of publication bias (Supplementary Figure 1C, available online).

DISCUSSION

All 20 RCTs, and a single quasi-experimental study, found that oral antibiotics were at least as effective as IV therapy for the treatment of osteomyelitis, bacteremia, and endocarditis. Indeed, multiple of the studies found that oral was more effective than IV therapy for bacteremia and

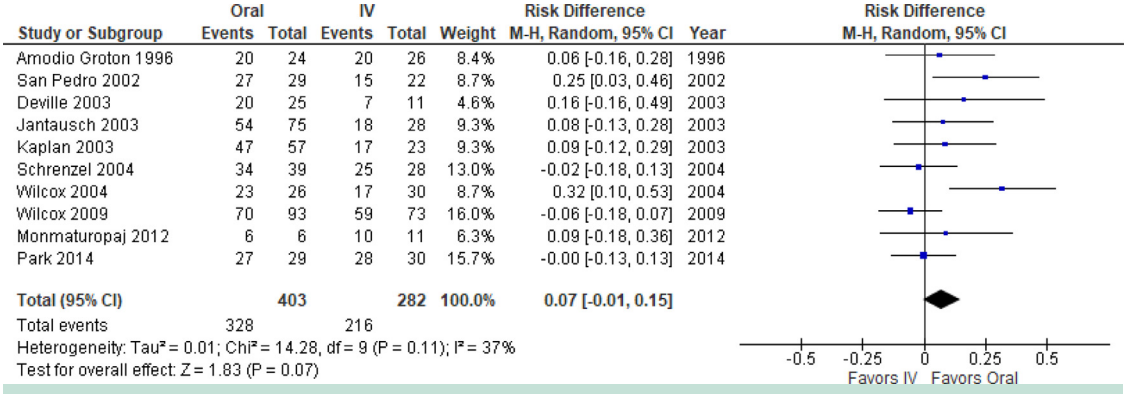

Figure 3 Meta-analysis forest plot of bacteremia treatment success. Overall treatment success was not significantly different, although the confidence interval favored oral therapy.

Table 3 Prospective Controlled Studies of Infective Endocarditis

Author	Year	N	Inclusion and Exclusion Criteria	Regimen Oral vs IV	Success Oral vs IV	Reported Complications Oral vs IV, n (%)	
Stamboulian[44]	1991	30	Included: native valve IE due to penicillin-susceptible streptococci Exclusion: cardiovascular risk factors, prosthetic valves	2 weeks ceftriaxone then 2 weeks amoxicillin vs 4 weeks ceftriaxone	100% (15/15) vs 100% (15/15)	Relapse AEs	1 (7%) vs 0 (0%) 1 (7%) vs 1 (7%)
Heldman[45]	1996	44	Included: adult injection drug users with right-sided staphylococcal IE (95% MSSA) Excluded: left-sided IE, prosthetic device, pregnant, intubated	Ciprofloxacin + rifampin vs standard IV	95% (18/19) vs 88% (22/25)	AEs	1 (3%) vs 24 (62%)
Iversen[41]/Bungaard[43]*	2019	400	Included: IE of any valve, including prosthetic valves and pacemakers due to streptococci, *Enterococcus faecalis, Staphylococcus aureus* or CoNS Excluded: unstable patients	Standard oral vs standard IV	73% (146/199) vs 62% (125/201)	AEs	10 (5%) vs 12 (6%)
Tissot-Dupont[42]†	2019	341	Included: IE of any valve, including prosthetic value due to *S. aureus* (including MRSA)	IV TMP-SMX + clindamycin for 7 days transitioned to oral vs. standard IV	81% (138/171) vs 70% (119/170)	Relapse AEs	7 (4%) vs 10 (6%) 27 (16%) vs 16 (9%)
Totals (N = 3 RCTs) + 1 quasi-experimental		474	815	Oral 77% (179/233) vs IV 67% (162/241)	Oral 78% (317/404) vs IV 68% (281/411)		

AEs = adverse events; CoNS = coagulase-negative staphylococci; IE = infective endocarditis; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA =methicillin-sensitive *Staphylococcus aureus;* TMP-SMX: trimethoprim-sulfamethoxazole.

*Iversen et al reported 6-month follow-up, and Bungaard et al. reported median 3-year follow-up of the same study patients. Outcomes shown are from the longer term follow-up.

†This was a quasi-experimental, pre-post study.

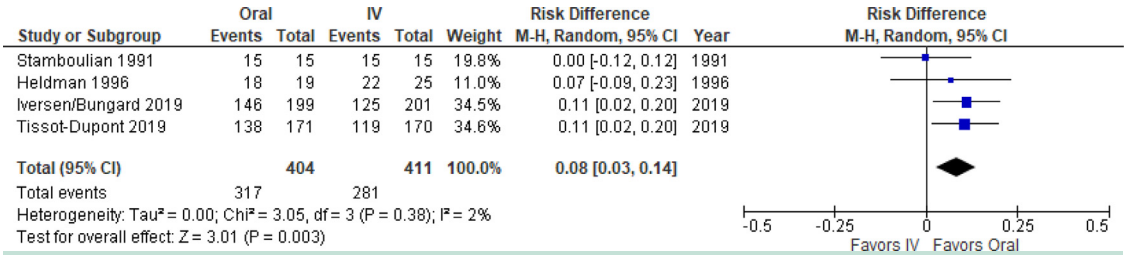

Figure 4 Meta-analysis forest plot of endocarditis treatment success. Oral therapy was significantly more effective.

endocarditis, including for mortality. No contrary data were identified.

The evaluated trials used a wide array of antimicrobial therapy, offering reassurance that oral efficacy is not limited to only 1 or 2 classes of drugs. Nevertheless, not all oral antimicrobial options are likely to be effective for treating these diseases, and clinicians should use oral regimens that have been demonstrated to have favorable efficacy in published studies.

For osteomyelitis, most of the published efficacy data were with fluoroquinolones or TMP-SMX, with or without adjunctive rifampin.[1,18] The addition of rifampin is important when treating *S. aureus* infections with fluoroquinolones due to the high rate of quinolone resistance emerging with monotherapy.[1,46] Furthermore, the majority of adverse events from oral therapy in published RCTs were due to fluoroquinolones, and there have been rising concerns about fluoroquinolone toxicity in general.[47,48] Thus, if alternative agents are available (eg, TMP-SMX, linezolid for <4 weeks, amoxicillin for *Streptococcus*, etc.), these may be preferrable to minimize toxicities. Nevertheless, clinicians may underestimate the dangers of prolonged IV catheterization, and the data demonstrate that IV catheter complications are at least as frequent, and potentially more dangerous, than fluoroquinolone complications.

The typical published dose of TMP-SMX for osteomyelitis has been 7.5 mg/kg/d (2 double-strength tablets twice daily for a 70-kg patient).[1] Clindamycin has also been studied extensively in pediatric osteomyelitis,[49-52] and both clindamycin (600 mg thrice daily or 450 mg 4 times daily) and linezolid (600 mg twice daily) achieved high cure rates in numerous observational studies of adult osteomyelitis[1,24,53] and were options in the largest RCT for osteomyelitis.[15] Caution should be used when administering linezolid for more than 2-3 weeks due to toxicities such as cytopenias, which are reversible, and neuropathy, which may be irreversible with prolonged dosing. All these drug options have excellent oral bioavailability and bone penetration. In contrast, oral β-lactams and doxycycline achieve low blood levels and have relatively poor bone penetration compared to these other options.[1] Caution may be warranted in selecting these drugs for treating osteomyelitis, although 10%-15% of patients in the largest RCT for osteomyelitis did receive them.[15]

Treatment options for bacteremia and endocarditis are similar to osteomyelitis.[2] One major exception is the need to avoid using up front TMP-SMX monotherapy to treat *S. aureus* bloodstream or endocarditis infections, in contrast to osteomyelitis.[7,54] However, Tissot-Dupont et al[42] demonstrated that a combination of TMP-SMX plus clindamycin, followed by step-down oral therapy with TMP-SMX was effective for treating endocarditis (indeed it was superior to the IV control group). Thus, TMP-SMX may be reasonable to use as an oral step-down option after initial IV therapy has stabilized the patient and cleared their bacteremia.

The amount of IV antimicrobial therapy that was administered prior to initiation of oral therapy varied dramatically across the trials. Some studies administered no IV therapy per protocol prior to initiation of oral therapy.[14,45] Other studies ranged between 7 and 14 days of IV therapy prior to oral therapy. Thus, there is no specific duration of required IV lead-in defined by the identified studies.

Why oral therapy might be superior in efficacy to IV therapy for bacteremia/endocarditis remains uncertain. Harm from the long-term IV catheter could contribute to treatment failures. Furthermore, retaining plastic catheters could make clearance of bacteremia more difficult and serve as a nidus for relapse. Further study is warranted to determine if there is a pathophysiological basis for clinical superiority of oral regimens, generally. Such research is in line with recent trends challenging other aspects of traditional management of these patients, such as the increasing movement to short-course therapy[26,31,55-59] and the necessity or not of follow-up blood cultures.

Limitations

A primary limitation of the meta-analysis is that many of the RCTs included were small. However, for each disease, at least 1 large RCT completed within the last decade anchored the meta-analyses. Furthermore, concerns raised about the quality of the 20 individual RCTs must be tempered by the fact that not a single prospective study was identified demonstrating superiority of IV therapy. Finally, the relative paucity of MRSA infections in these published RCTs may be of concern. Although that is a limitation, and caution should always be taken in treating invasive MRSA

infections, there is a logical fallacy to the argument that clinicians should be comfortable treating MSSA but not MRSA infections with oral therapy. The IV options for MSSA (β-lactams) are considerably more effective than the primary IV option for MRSA infections (vancomycin).[60,61] The *mecA* methicillin-resistance mechanism does not alter the antimicrobial activity of fluoroquinolones, TMP-SMX, clindamycin, linezolid, or rifampin. Thus, if these oral options are at least as effective as the IV therapy for MSSA infections, they logically must be at least as effective as the less effective IV therapy for susceptible MRSA infections.

CONCLUSION

Building off a previously proposed algorithm,[2] we suggest it is reasonable to consider oral therapy for osteomyelitis, bacteremia, and endocarditis when all of the following criteria are met:

1) The patient is clinically and hemodynamically stable.
2) Surgical or procedural source control has been achieved if possible, with no persistent bacteremia.
3) The patient is likely to be able to tolerate and absorb oral medications.
4) A published regimen is available with clinical outcomes data for targeted pathogens.
5) There are no psychosocial or logistical reasons to prefer IV therapy.

In summary, there are now 20 RCTs and a quasi-experimental study that unanimously demonstrate that oral therapy is at least as effective as IV-only therapy for osteomyelitis, bacteremia, and endocarditis. Furthermore, oral therapy is safer, results in superior patient satisfaction, and markedly decreases length of hospital stay and cost.[15] It is time for evidence to overcome anchor bias and inertia in medicine. These findings should be incorporated into treatment guidelines to help drive change to clinical practice, indicating that oral therapy is a reasonable option for these diseases in reasonably selected patients.

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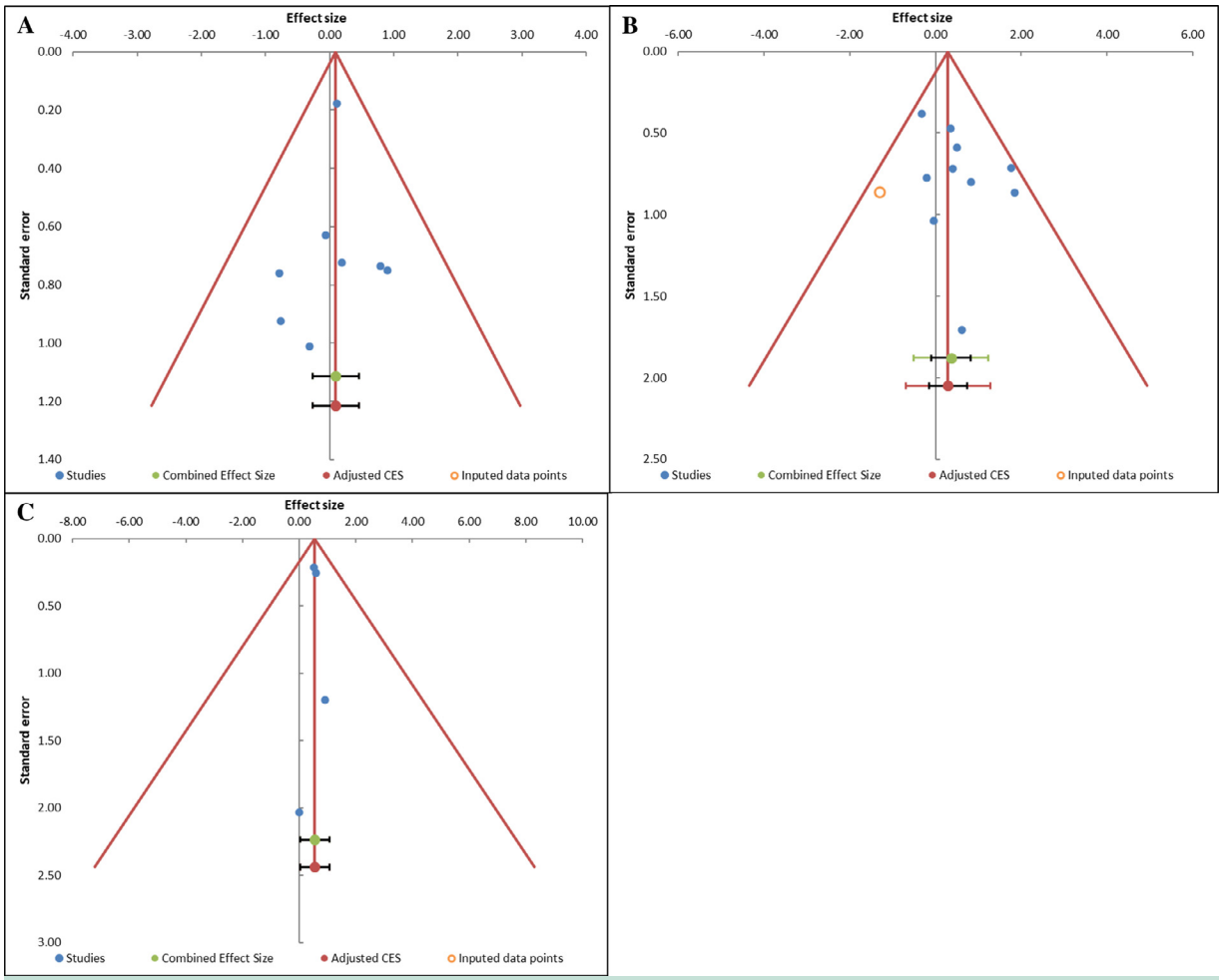
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.10.007.



Supplemental Figure 1 Funnel plots of effect size. **(A)** Osteomyelitis studies. **(B)** Bacteremia studies. **(C)** Endocarditis studies. No asymmetry was found for osteomyelitis or endocarditis, so there are no imputed data points. For bacteremia, there was slight asymmetry detected in the funnel plot, and a single imputed data point corrected that asymmetry. For each graph, adjusted CES is shown, which demonstrates how the relative efficacy changes with an imputed data point. Because there was no asymmetry or imputed data points for osteomyelitis or endocarditis, the adjusted CES = the primary CES. For bacteremia, the single imputed data point resulted in minimal change to the CES, indicating no meaningful effect of the asymmetry on estimated effect. Funnel plots were drawn with *Meta-Essentials* freeware and methods.[1] CES = combined effect sizes.