IV to Oral Antibiotic Conversion in Serious Infections and new choices of ABX

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Why do oral or IV to oral?

Cost-----$1-5,000/week in hospital or with Home Health
PICC line charge=$2800 charge, $776 reimbursement

Decrease in Central Line complications-15% in some studies
-infections, thrombosis, phlebitis
introductions of new organisms

Patients can return to normal activities earlier and easier
and overall have a healthier environment.

What is data that says it is or can be equally effective?

Used in Pediatrics for osteomyelitis, endocarditis, etc. since 1970's, as much because it allowed children to continue school and was safer to do at home than IV .

But few studies in adults as IV therapy was traditional

and an Infectious Disease Physician in private practice often used OPAT (Outpatient Parenteral Antibiotic Therapy) as a profit center for his practice and it is a good means of giving close follow up and insurance covered it.

I became interested in it and got our Pharm. D program involved while at Brackenridge, the County Hospital, in Austin

Drug Companies with new IV drugs would not fund IV therapy followed by an oral generic product, or a different class of drug

It would make study design difficult if failure or success occurred-Which drug had the major effect?

*** and all new drugs only have to show “non-inferiority” to its most similar competitor, not to any older drug.

Miles Labs were first company to demonstrate that Pseudomonas Osteomyelitis could be treated with parenteral, then conversion to oral ciprofloxicin when patient was eating and stable

In recent years, Linezolid for MRSA and VRE, IV then to oral has also been shown to be equally efficacious.

So what about studies that go from IV to oral with a similar class of drug, ex Oxacillin or Nafcillin IV to dicloxicillin po.

Or, from Vancomycin to po Clindamycin, or Trim Sulfa,
or Linezolid for MRSA

Or from Oxacillin or Ancef to high dose Cefuroxime or Cefdinir (Omnicef), both with good Pharmacokinetics, bioavailability, and antimicrobial activity against MSSA.
*****-But not Keflex – Cephalexin or other 1st Gen oral cephalosporins !!

Not many: Drug companies cannot afford to show that a short course of their new drug can give good results when converted quickly to a less expensive oral generic antibiotic.

No company that made IV synthetic penicillins studied conversion to high dose comparable drugs -had short half lives- q 4hr dosing without benemid (probenecid): Methicillin was generic, Oxacillin and Nafcillin IV were ending patent period.

Oral Nafcillin, Oxacillin, Dicloxicillin, Cloxicillin po were only studied to get indication for Skin and Soft Tissue infections at 250 or 500mg q 6 hours, i.e. 1-2 grams/d, not at 6-12 grams/d to get comparable steady state levels-Remember those doses!!

<u>There were no good first generation oral cephalosporins</u>
Keflex, Duracef, Ultracef, etc. all with high $MIC_{90\%s}$,8-10 mc/ml for Staph- Blood levels 3-6 mcgm/ml ---***(but not noted by the companies in their marketing)

Cefuroxime axetil (Zinocef iv), Ceftin po, was comparable to Ancef (cefazolin) but company only wanted to invest in Pedi URI-ENT indications for marketing oral form at low dose.

There were good drugs with potential for IV to PO
:
Trimethoprin-Sulfamethoxazole had great kinetics, well absorbed, was broad spectrum, with good ratios of blood and tissue levels including CNS, for MSSA, MRSA, most Strep, Gram negative rods except Pseudomonas
-**Became drug of choice in pediatric MRSA meningitis**

But only had 3 years to go on patent when first marketed and the only company studied oral indication was for urinary tract infection

Clindamycin HCl had both IV and po, but MRSA was not a problem when developed. Developed only as an anaerobe drug for abdominal sepsis with IV aminoglycosides ,
and **po,** got the usual Skin and soft tissue indication, but the early association with pseudomembranous colitis doomed it until we needed an alternative to vancomycin for MRSA.

Most drugs have good bioavailability

Oral Bioavailability*(*may vary due to dosage, DDIs, DFIs, formulation, fasting or not, patient-specific variable or other)

<50% Acyclovir (15%), Amoxicillin-clavulanic acid (30%), Azithromycin (40%), Cefixime (45%), Cefuroxime axetil (40%), Penicillin V (25%)

50-75% Amoxicillin (75%), Ampicillin (50%), Cefpodoxime proxetil (50%), Delafloxacin (60%), Dicloxacillin (70%), Valacyclovir (55%), Valganciclovir (60%)

>75% Ceftibuten (80%), Ciprofloxacin (80%), Clindamycin HCl (90%), Doxycycline (>90%), Fluconazole (>90%), Isavuconazonium sulfate (95%), Levofloxacin (100%), Linezolid (100%), Metronidazole (80%), Minocycline HCl (90%), Moxifloxacin (90%), Rifampin (90%), SMX-TMP (95%), Tedizolid (90%), Voriconazole (95%)

As previously stated, Ciprofloxacin was first drug to have the company study IV to oral in treatment of Pseudomonas osteomyelitis, and started the commercial interest

Now the new drugs being developed, some old, like Minocycline, now with an IV form , and a new tetracycline, Omadocycline, which has IV to PO studies and covers MRSA and enterococus, and many Gram Negatives,
as do the Gram positive spectrum quinolones Like levofloxacin, moxifloxacin, and the new delafloxacin which has MRSA and Pseudomonas coverage, but both new drugs are > $150/ day.

Moxifloxicin has recently gone generic, 20x better than levofloxacin
But not on any easily available sensitivity panel for our micro labs
.

One Company tried in late 60's-early 1970's, but resulted in a significant failure of IV to oral occurred and noted at Wilford Hall Air Force Base in San Antonio in early 1970's
with a first-generation cephalosporin named Cephradine in treatment of Staph endocarditis.

Blood levels were the same as cefazolin: Reliable or mean blood of 20mic/ml with 1gm q 8, 3-40 mic/ml with 2gm q 8 hr IV
And 1gm po cephradine→ mean blood level of 8-10mic/ml.

The problem was that there was an assumption that Cephradine was equal to Cefalothin in Kill power, but it was not:

MIC 90% of MSSA to Cephalothin(Keflin) was <0.5 micrograms/ml
Mic90% of MSSA to Cephradine was 8-12 micrograms/ml
SO,---→ back to Cephalothin with no oral equivalent

BUT,

To get a new oral antibiotic to market, studies done are only for skin and soft tissue infections, and community acquired pneumonias, and URI's.

Costs $500 to 900 million dollars to get drug to market, thus, the high cost of new antibiotics, ---now mostly developed by small startup companies. It is up to our judgement based on knowledge and experience to develop studies, or for us grunts in the field, to choose reasonable treatment regimens for more serious conditions.

Comparison of old and new in Skin and soft tissue infections – observed clinical response in Phase 3 or 4 studies

Trim-sulfa DS q12	vs Clinda 300q8	omadocycline	vs linezolid	delafloxacin	vs vanc – azthreonam IV
78.3% (Did not include Amoxicillin for added Strep coverage)	83.3	85	82.1	81.3	84.1
Cost* <$20/10d	$16-25	$1600	$55-1077	$1600	IV

*Good RX Pricing

Moxifloxicin is good to switch to if have only MSSA, gets only about 25%

Doxycycline = to or slightly better than Trim sulfa but noted lack of some strep coverage In a UT SW med school in 2007 but no statistical difference AAg&Chemotx 51(7) 2628 AmJ med2010 123 (10) p942 Tr-Sulf 91%,> Clinda > Cefalexin 74% response

Many prominent infectious disease physicians reviewed

and recommended oral switch IV to po or po alone for

serious infections if good micro, kinetics (absorption), monitoring

Pediatr Infect Dis J. 1987 Oct;6(10):951-3.

New era for orally administered antibiotics: use of sequential parenteral-oral antibiotic therapy for serious infectious diseases of infants and children.

McCracken GH Jr[1].

Author information

Abstract

Removal of the intravenous line, improvement of attitude and appetite and early discharge from the hospital can be achieved when sequential parenteral-oral antibiotic therapy is used appropriately to treat children with certain moderate to severe infections. Such antibiotic regimens are potentially indicated for suppurative skeletal infections, bacterial endocarditis, pneumonia with or without empyema, pyelonephritis and, perhaps, meningitis. To be effective, serum bactericidal activity against the causative pathogen after oral therapy must be comparable to that achieved after parenteral administration. Patient and parent compliance, adequate absorption and drug interactions are some of the factors that should be considered to assure a successful course of parenteral-oral antibiotic therapy.

But he was a Pediatrician so didn't get picked up in adult ID
And drug companies were developing IV only antibiotics

Back to Basics:

How can we evaluate the antimicrobial effect of an antibiotic ?

What is the “Kill ratio”?

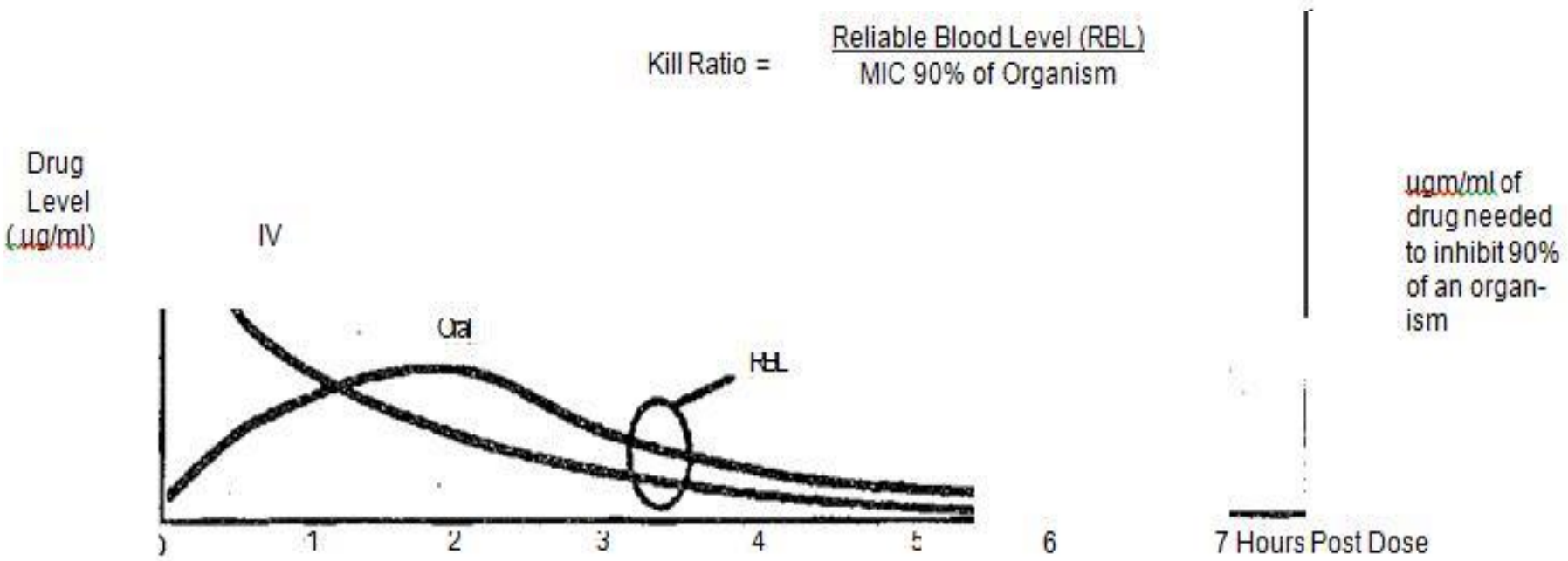
Easier for me to understand than AUC (area under curve)

Guidelines for Predicting the Effectiveness of an Antibiotic
Use of the "Kill Ratio" analysis

Therapeutic Index (T.I.) or "kill ratio": The Reliable Blood Level divided by the amount of antibiotic needed to inhibit the growth of 90% of strains of a particular bacteria:

Reliable Blood Level (mean) - about 1/3 of the 1-2 hour post-dose level.
MIC = Minimum Inhibitory Concentration in micrograms/ml of the antibiotic.
Need to know tissue levels relative to mean blood levels

$$\text{Kill Ratio} = \frac{\text{Reliable Blood Level (RBL)}}{\text{MIC 90\% of Organism}}$$



General Guidelines for Using the "Kill Ratio" Analysis of Antibiotics >10:1 = usually very good. Even if infected tissue levels are only 10% of serum drug levels, a 1:1 ratio of drug: MIC 90 is obtained in the infected site For penicillins, cephalosporins

> 4:1 = good penetration into most infected sites
> 1:1 = only adequate for skin and soft tissue infections
< 1:1 = only the more sensitive substrains will be consistently inhibited or killed

Fluoroquinolones and macrolides usually have ***higher tissue*** levels than mean or reliable blood levels. Same for tetracyclines

Table 1: Oral Antibiotics for Common Skin and Nasopharyngeal Organisms

DRUG	Pen VK V-CillinK Pen V	Cloxacillin Tegopen	Cephalexin Keftab	Cefaclor Ceclor	Erythro° PCE,	Clinda Cleocin	Amex Amoxil	Amox+Clav Augmentin	Trim-FSulfa Bactrim, Sepira	Cefuroxime • Ceftin	Cefixime Suprax	Cipro Cipro	
Dose (mg)	500 q6	500 q6	500 q6	500 q6	500 q6	300 q6	500 q8	500 q8 •	DS q12	500 q8	400 q24	500 q12	
Blood Level (ug/ml) -2 hour	5	12	16	12	1.4	5	8	8	80	10	2.5	2.4	
-trough	1	1	1	1	0.3	1	1	1	50	0.4	0.04	.02	
Reliable Blood Level (ug/ml) -	2	3	6	4	0.4(1.5 tissue	2	2	2	60 (sulfa)	3	0.8	0.8	
MIC° (ugm/m)													
Strep. pneu	0.02	- 0.2	3	3	0.04	0.2	0.12	0.03	3	0.25	0.29	1-8	
S. aureus	R	0.5	12	8	0.4	0.5	Ft	2	2	1	38	1	
H. Influ													
-Amp-S	1	Fl	-	2	1	?	0.5	0.5	-	0.25 -	0.05	-	
-Amp-	R	Ft	R	2	2	?	>64	2	3	0.25	0.4	0.01	
B. Cater													
Pen-S													
Anaerobes	0.1-3	1.10	?>8	?>8	0.4	2	0.1-3	0.1-3	Ft	<3	?	R	
Chlamydia	1				0.15			?+	Ft			2	
Legionella**					0.5							0.1-1	
Mycoplasma					0.01							0.4	
"Rifampin very active against Legionella													
AWP/Cost/day		<$2	$10	$17	<$1	$14	<$1	$10	<$1	$20	$7	$8	

Group A Strep $\frac{\text{Penicillin reliable blood level}}{\text{MIC 90 for Pen}} - \frac{2}{0.02}$ - Kill ratio = 100:1

$\frac{\text{Cephalexin reliable blood level}}{\text{MIC 90 for Cephalexin}} \quad \frac{6}{3}$ – Kill Ratio = 2 : 1

For Staph aureus (MSSA) Keflex –Cephalexin- had
MIC 90% of 12 mcgm/ml according to their company brochure

With mean blood levels of 6 mcgm/ml= Kill ratio of 0.5 or 1:2 in blood
with tissue levels expected of only 1-3mcgm/ml= kill ratio of <0.25= 1:4
--not the 4:1 you would like !!!

i.e. the same problem that the earlier cephalosporin, cephradine, had when
that company developed a n IV form from an earlier generation cephalosporin
without it having the "kill ratio" of cephalothin (Keflin), the first broadly
used IV cephalosporin.

As a historical note: I was blacklisted as a speaker for the company which
made Keflex
because I used it as my model to demonstrate the difference
between its "Kill ratio" and that of po Cloxacillin or Cefuroxime.

Thus my interest in IV to PO conversion to achieve good "kill ratios" began
In the early 1970's and I was able to expand that in Austin.

We published our results from my Austin experience from 1976 to 1986 in 1987.

The key was a good Phar D program, a good lab at Brackenridge Hosp that could do the old serum cidal test, and early on after my moving there as the only ID in town, two physicians with sons with acute Staph osteomyelitis who didn't want to miss school.

First was 21 yo with rt femur MSSA osteo, 12 grams oxacillin/d IV Switched to 8 grams/d Cloxicillin po + 1 gram probenacid at one week so he could go to medical school-became Chief of Heme-Onc at Univ of Arizona. Tx period 42 days

Second was 9 yo son of a classmate and orthopedic surgeon with MSSA sternal osteomyelitis, just when school was about to begin- 6 grams/d IV Oxacillin x1 week, then 6 weeks cloxacillin po+ probenecid to decrease renal excretion.

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 0022-1899/87/5505-0018$01.00

Oral Antimicrobial Therapy for Adults with Osteomyelitis or Septic Arthritis

Jimmy Black, Thomas Lynn Hunt, Paul John Godley, and Earl Matthew

From the College of Pharmacy, The University of Texas at Austin and the Central Texas Medical Foundation, Austin, Texas

We conducted a retrospective review of 21 adult patients with osteomyelitis and septic arthritis who were treated with high doses of oral antimicrobial agents, usually after an initial course of intravenous therapy. The mean duration of parenteral and oral therapy was 3.6 days and 43.0 days, respectively. Absorption of oral antibiotics was assessed by determining the trough serum bactericidal titers for the infecting organism; whenever feasible, the dosages were adjusted to achieve trough titers ≥1:8. The follow-up period ranged from six to 66 months (mean, 42.4 months). Eighteen of 21 patients had no clinical signs of recurrence after initial therapy. One patient with an infected joint prosthesis developed recurrent infection, and two patients had recurrences accompanied by sequestra. The mean duration of hospitalization was 13.4 days, and the mean duration of outpatient treatment was 31.9 days.

We measured Serum Bactericidal levels at trough
For our IV drug, for ex., patient on 2 gm q 4-6 Nafcillin,

Switched to po cloxicillin 2 gm q 8 for 24 hours,(+benemid)

Drew blood for serum cidal level at 6 and 8 hours post
Dose, then back to IV pending cidal levels.

Target was 1:8 serum cidal at trough,
and picked the po dosing interval that achieved that,
Or raised dose and retested.
Trough levels at equal interval usually better with po >IV

TODAY-Only vancomycin has easily measurable blood levels
Most micro labs, now automated, don't know what a "cidal" test is
.
Measured sulfa levels-now available through reference labs

What was Toxicity with high dose oral in our study group?

--2 persons with mild diarrhea-Cause was **lactose intolerance**

when they started drinking large amounts of milk for

their heartburn that was associated with the probenecid

--**21 patients,** two relapsed and had sequestra of dead bone

removed, and then did well.. One with prosthetic joint

Infected relapsed, joint replaced, retreated.

That paper didn't stimulate anything. Adult ID's suggested it, as below

Annu Rev Med. 1988;39:171-84.

Oral antibiotic therapy for serious infections.

Smith AL[1].

Author information

Abstract

After a pathogen has been identified and the antibiotic susceptibility determined, parenteral antibiotic administration can be replaced by the oral route for certain patients with meningitis, brain abscess, endocarditis, and skeletal infections. Antibiotics should be administered with the stomach empty and accompanied by 3 ml/kg of water. Direct instillation into the lumen of the small intestine may be advantageous with selected patients. Documenting adequate antibiotic absorption and ensuring compliance are essential to efficacious therapy.

And again, 10 years later,

Clin Infect Dis. 1997 Mar;24(3):457-67.

Oral administration of antibiotics: a rational alternative to the parenteral route.

MacGregor RR[1], Graziani AL.

Author information

Abstract

Much early experience with antibiotic therapy involved oral administration of sulfonamides, penicillins, tetracyclines, and chloramphenicol. Newer acid-labile, less-soluble agents created the need for intravenous (i.v.) administration, and i.v. technology (hyporeactive catheter polymers, infusion pumps, etc.) improved to where i.v. administration became normative for the treatment of serious infections. Recently, this preference is being reconsidered in light of agents that are highly effective orally, growing appreciation that i.v. treatment has serious complications, and economic pressures to provide the best care at the lowest cost. This article presents a brief history of administration routes and reviews the rationale for considering oral treatment for serious infections, including consideration of pharmacokinetics and minimum inhibitory concentrations. Published reports supporting the efficacy of orally administered antibiotics either as sole treatment or following an initial parenteral course are reviewed in detai and examples of programs that educate physicians about the rationale, acceptibility, and benefits of oral administration are given.

So, more reviews in 2006

Med Clin North Am. 2006 Nov;90(6):1197-222.

Oral antibiotic therapy of serious systemic infections.

Cunha BA[1].

⊕ Author information

Abstract

Traditionally, antibiotics have been administered intravenously (IV) for serious systemic infections. As more potent oral antibiotics were introduced, and their pharmacokinetic aspects studied, orally administered antibiotics have been increasingly used for serious systemic infections. Antibiotics ideal for oral administration are those that have the appropriate spectrum, high degree of activity against the presumed or known pathogen, and have good bioavailability. Oral antibiotics with high bioavailability, that is > or = 90% absorbed, achieve serum/tissue concentrations comparable to IV administered antibiotics at the same dose. The popularity of "IV to PO switch therapy" is possible because of the availability of many potent oral antibiotics with high bioavailability. Initial IV therapy is appropriate in patients who are in shock/have impaired intestinal absorption, but after clinical defervescence, completion of therapy should be accomplished with oral antibiotics. As experience with "IV to PO switch therapy" has accumulated, confidence in oral antimicrobics for therapy of serious systemic infections has continued to increase. The trend in treating serious systemic infections entirely with oral antimicrobial therapy will continue, and is clearly the wave of the future.

But the future had not arrived yet!!

Even these authors, experts in their field, made same mistake

that Air Force had, assumed all oral first generation oral

Cephalosporins had MIC's equal to IV Cephalothin (Keflin) or Cefazolin (Ancef), and that usual recommended doses

for skin and soft tissue infection (cellulitis)of 1-3gm/day was

somehow equal to 6-8 grams of IV Cefazolin for MSSA

And it is still true 40 years later, see below
excerpt from new ID Pharm D
antibiotic stewardship newsletter

Antibiotic Study Cheat Sheet

When You See...	Consider Using...
GRAM POSITIVES	
MSSA	Oral: cephalexin; IV: Oxacillin, nafcillin, cefazolin
MRSA	Oral: Bactrim, doxycycline, clindamycin, linezolid, tedizolid; IV: vancomycin, daptomycin, telavancin, dalbavancin, oritavancin, ceftaroline, tigecycline
Enterococci	Ampicillin, then vancomycin, then linezolid (VRE), daptomycin (VRE), or tigecycline (VRE)
Strep. pyogenes or *Strep. agalactiae*	Penicillin, clindamycin
Strep. pneumoniae or Viridans group Strep	Ceftriaxone, levofloxacin, amoxicillin-clavulanic acid (beware penicillin & macrolide resistance)

For IV to PO conversion to be successful,
comparable blood and
tissue levels, and, thus,
comparable killing power
have to be expected to be achieved!!

Older Antibiotics for oral conversion from IV:

For **MSSA-**

Dicloxicillin, oxacillin, cefuroxime, cefdinir, at 4-8 higher doses plus possibly probenecid

or Trim-Sulf, Clinda, Moxifloxicin

For **MRSA**-IV Vanc or other "me, toos", to Trim-Sulfa, or Clindamycin, or Doxycycline, or Linezolid. new are omadocycline, Delafloxicin

Strep- Amoxicillin or 2nd gen oral cephalosporin's or Macrolides
Clarithromycin is the best

Gram neg aerobic – trim-sulfa or fluroquinolone

Pseudomonas- Ciprofloxicin, or Delafloxacin ($$$)if sensitive

Resistant Gram neg- Fosphomycin- we will discuss more
-Minocycline,

VRE-Linezolid IV to Linezolid p.o. (now off patent), tedizolid $$$

- Ordering Higher p.o. doses than usual in serious infections requiring long term TX
  applies only to Penicillin and cephalosporin class
- Basically you give as high or almost as high oral dose as you would IV
- Or use lower and/or less frequent dosing plus probenecid to delay renal excretion.
- Examples:
- Instead of 3 gms Nafcillin q 6 hr. IV, give 2gm dicloxacillin q 6- 8 hr po
- + 1/2 of 500 mg probenecid q 12
- at$ 0.70/500mg cap = $ 12/day
- instead of 2 gm Cefazolin IV q 8hr, give 1.5 grams of Cefuroxime axetil
- 3- 500mg =1.5 gm Cefuroxime po q 8
- at $1.00-2.00/tablet x 9/d = $9-18/day

- Or at need for 20 million =+/- units Penicillin/ day IV(1000mg=1.6 million units) at
- 3 grams IV q 4-6 hr
- or if on 12-18 grams of Unasyn (ampicillin-sulbactam)
- instead give 8- grams/d po of Amoxicillin 500mg
- and add Amoxicillin/clavulanate at 1- 875 mg q 12
- as only need that 125mg of beta lactamase inhibitor bid to get
- needed anti anaerobe effect, otherwise gives bad diarrhea

What is minimal cost of the available antibiotics that can be used effectively for prolonged IV to PO Conversion? (using Good RX pricing with coupon at different pharmacy chains)

reg 10 day course	$$ daily high dose
Diclox 500qid- $28-405	4q8= $6 or >
Amox 500tid- $4-10	4q8= $5 or>
Cefuroxime 500q8- $20-30	3q8=$9-18
Above need higher dosing for serious deep infections	
Amox-Clav 875 bid $12-25 added to Amox	1q12= $2
Clindamycin 300 tid--$16-25- may need higher dose for serious infections	2q8=$3-6/d
	use regular dosing
Trim-sulfa DS q 12-- $4-12	1q12=$1
Doxycycline 100q12-$11-$30	1q12= $1-2
Omadocycline 450mg load, 150mg mg bid daily –price not listed but about $1650	1q12 >$150
Levofloxicin 500 q 12 - $15-80	1q12= $2
Moxifloxicin 400 qd-$25-94 (WG) (now generic)	1q24=$3-45
Gemifloxicin 300 qd-x7d $300	1qd=$50
Delafloxicin 450 q 12- not listed- but about $1600	1q12 >$150
Rifampin 300bid $20-$40	1q12=$2-4

Clindamycin dosage IV is 900 mg q 8 IV and
may probably should be given PO at more than the usual 300 mg q 8 hr. if used for serious infections, 600q 6 or 8 hours

And po minocycline has been given safely at 600 mg/d for acinitobacter infections with IV to po conversion rather than 100 mg bid
(so probably true for Doxycycline)

In very obese or large persons it may be reasonable to use mg/kgm dosing

2020 --The future has finally arrived, MAYBE??

Now there are two large recent studies from Europe

that show efficacy of IV to PO conversion

in endocarditis, septic joints, including prosthetic,

and osteomyelitis in adults

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

NEJM-2019;380; 425-436

METHODS

We enrolled adults who were being treated for bone or joint infection at 26 U.K. centers. Within 7 days after surgery (or, if the infection was being managed without surgery, within 7 days after the start of antibiotic treatment), participants were randomly assigned to receive either intravenous or oral antibiotics to complete the first 6 weeks of therapy. Follow-on oral antibiotics were permitted in both groups. The primary end point was definitive treatment failure within 1 year after randomization. In the analysis of the risk of the primary end point, the noninferiority margin was 7.5 percentage points.

NEJM-2019;380; 425-436

RESULTS

Among the 1054 participants (527 in each group), end-point data were available for 1015 (96.3%). Treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group. Missing end-point data (39 participants, 3.7%) were imputed. The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), indicating noninferiority. Complete-case, per-protocol, and sensitivity analyses supported this result. The between-group difference in the incidence of serious adverse events was not significant (146 of 527 participants [27.7%] in the intravenous group and 138 of 527 [26.2%] in the oral group; P=0.58). Catheter complications, analyzed as a secondary end point, were more common in the intravenous group (9.4% vs. 1.0%).

We found that appropriately selected oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks in the management of bone and joint infection, as assessed by treatment failure within 1 year. Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy.

Table S10: Overview of actual antibiotics (excluding rifampicin), as defined by agents used for more than one week during the initial six-week treatment period

	Participants randomized to IV Antibiotic* (N = 521)	Participants randomized to PO Antibiotic* (N = 523)	Total* (N = 1044)
Glycopeptides[a] (IV)	214 (41.1%)	22 (4.2%)	236 (22.6%)
Penicillins (IV)	38 (7.3%)	11 (2.1%)	49 (4.7%)
Cephalosporins (IV)	173 (33.2%)	8 (1.5%)	181 (17.3%)
Carbapenems (IV)	41 (7.9%)	5 (1.0%)	46 (4.4%)
Other single IV antibiotic	35 (6.7%)	2 (0.4%)	37 (3.5%)
Combination IV antibiotics	35 (6.7%)	6 (1.1%)	41 (3.9%)
Penicillins (PO)	8 (1.5%)	83 (15.9%)	91 (8.7%)
Quinolones[b] (PO)	33 (6.3%)	191 (36.5%)	224 (21.5%)
Tetracyclines[c] (PO)	4 (0.8%)	57 (10.9%)	61 (5.8%)
Macrolides / Lincosamide [d] (PO)	10 (1.9%)	68 (13.0%)	78 (7.5%)
Other single PO antibiotic (PO)	10 (1.9%)	54 (10.3%)	64 (6.1%)
Combination PO antibiotics (PO)	13 (2.5%)	87 (16.6%)	100 (9.6%)

The categories in this table were not mutually exclusive; 149 participants fell into more than one category and the data do not take account of adjunctive rifampicin which was analysed separately.

Rifampin often Rc as an addition because of biofilm effect in vitro,
but no good clinical data to support

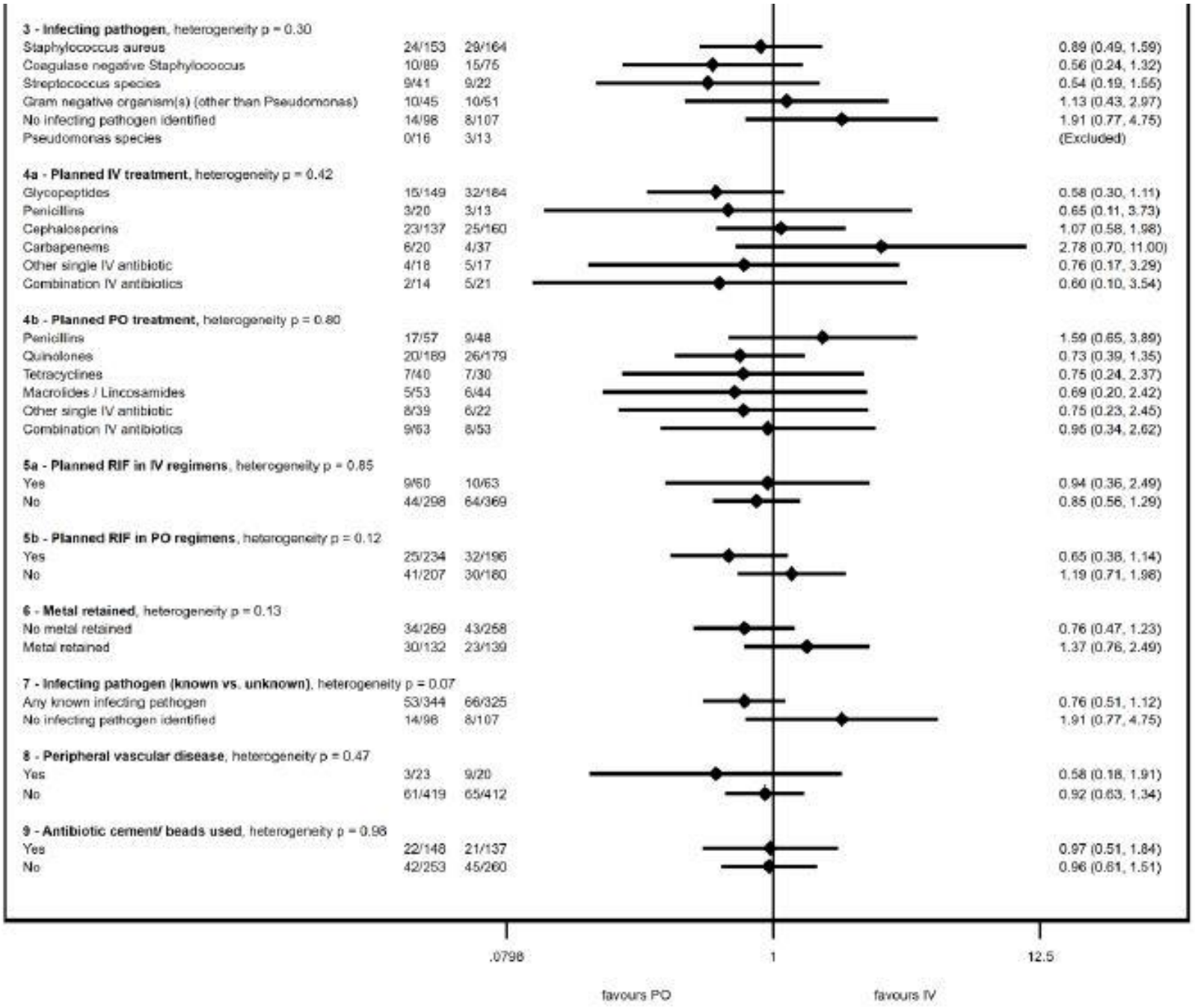
Table S11: Actual rifampicin use in 1049 participants

Observed rifampicin use[a]	Randomized to IV Antibiotic* (N=523)	Randomized to PO Antibiotic* (N=526)	Total* (N=1049)
No rifampicin use	310 (59.3%)	233 (44.3%)	543 (51.8%)
<2 weeks[b]	21 (4.2%)	36 (6.8%)	57 (5.4%)
2 to 6 weeks[b]	72 (13.8%)	92 (17.5%)	164 (15.6%)
>6 weeks[b]	120 (22.9%)	165 (31.4%)	285 (27.2%)

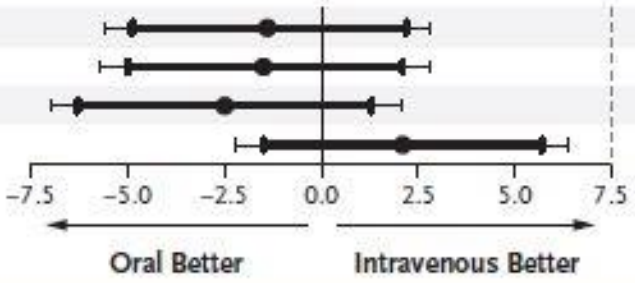
**Frequency and percentages are displayed*

[a] *The most commonly prescribed doses of rifampicic were 300mg BD (388 prescriptions) and 450mg BD (133 prescriptions).*
[b] *Based on the longest continuous period of use.*

i.e. made no difference


Favors PO
Favors IV
3 - Infecting pathogen, heterogeneity p = 0.30
Staphylococcus aureus 24/153 29/164 0.89 (0.49, 1.59)
Coagulase negative Staphylococcus 10/89 15/75 0.56 (0.24, 1.32)
Streptococcus species 9/41 9/22 0.54 (0.19, 1.55)
Gram negative organism(s) (other than Pseudomonas) 10/45 10/51 1.13 (0.43, 2.97)
No infecting pathogen identified 14/98 8/107 1.91 (0.77, 4.75)
Pseudomonas species 0/16 3/13 (Excluded)
4a - Planned IV treatment, heterogeneity p = 0.42
Glycopeptides 15/149 32/184 0.58 (0.30, 1.11)
Penicillins 3/20 3/13 0.65 (0.11, 3.73)
Cephalosporins 23/137 25/160 1.07 (0.58, 1.98)
Carbapenems 6/20 4/37 2.78 (0.70, 11.00)
Other single IV antibiotic 4/18 5/17 0.76 (0.17, 3.29)
Combination IV antibiotics 2/14 5/21 0.60 (0.10, 3.54)
4b - Planned PO treatment, heterogeneity p = 0.80
Penicillins 17/57 9/48 1.59 (0.65, 3.89)
Quinolones 20/189 26/179 0.73 (0.39, 1.35)
Tetracyclines 7/40 7/30 0.75 (0.24, 2.37)
Macrolides / Lincosamides 5/53 6/44 0.69 (0.20, 2.42)
Other single IV antibiotic 8/39 6/22 0.75 (0.23, 2.45)
Combination IV antibiotics 9/63 8/53 0.95 (0.34, 2.62)
5a - Planned RIF in IV regimens, heterogeneity p = 0.85
Yes 9/60 10/63 0.94 (0.36, 2.49)
No 44/298 64/369 0.85 (0.56, 1.29)
5b - Planned RIF in PO regimens, heterogeneity p = 0.12
Yes 25/234 32/196 0.65 (0.38, 1.14)
No 41/207 30/180 1.19 (0.71, 1.98)
6 - Metal retained, heterogeneity p = 0.13
No metal retained 34/269 43/258 0.76 (0.47, 1.23)
Metal retained 30/132 23/139 1.37 (0.76, 2.49)
7 - Infecting pathogen (known vs. unknown), heterogeneity p = 0.07
Any known infecting pathogen 53/344 66/325 0.76 (0.51, 1.12)
No infecting pathogen identified 14/98 8/107 1.91 (0.77, 4.75)
8 - Peripheral vascular disease, heterogeneity p = 0.47
Yes 3/23 9/20 0.58 (0.18, 1.91)
No 61/419 65/412 0.92 (0.63, 1.34)
9 - Antibiotic cement/ beads used, heterogeneity p = 0.98
Yes 22/148 21/137 0.97 (0.51, 1.84)
No 42/253 45/260 0.96 (0.61, 1.51)
.0798
1
12.5
favours PO
favours IV

Subgroup	Oral Group	Intravenous Group	Risk Difference (90% CI; 95% CI)
	patients with treatment failure/ total no. of participants		
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)



Conclusion:

We found that appropriately selected oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks in the management of bone and joint infection, as assessed by treatment failure within 1 year. Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy.

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Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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METHODS

In a randomized, noninferiority, multicenter trial, we assigned 400 adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics to continue intravenous treatment (199 patients) or to switch to oral antibiotic treatment (201 patients). In all patients, antibiotic treatment was administered intravenously for at least 10 days. If feasible, patients in the orally treated group were discharged to outpatient treatment. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 months after antibiotic treatment was completed.

PHARMACOKINETICS

To ensure that patients received sufficient doses of antibiotics, blood samples for the measurement of plasma levels of orally administered antibiotics were obtained on day 1 after the administration of a single dose (30 minutes and 1, 2, 4, and 6 hours after administration) and on day 5, after the administration of multiple doses (with the assumption that a steady state would have been achieved by this time). Samples were also obtained from patients in the intravenously treated group on day 1. Samples were analyzed with the use of high-pressure liquid chromatography. For safety considerations, the first dose

Used only 4 grams/d Dicloxicillin, rather than 8
Otherwise std doses of other antibiotics

Breakdown of bacterial species for each of the elements of the composite outcome

	All-cause mortality		Unplanned cardiac surgery		Embolic event		Relapse of positive blood culture	
	IV treatment n=13	Oral treatment n=7	IV treatment n=6	Oral treatment n=6	IV treatment n=3	Oral treatment n=3	IV treatment n=5	Oral treatment n=5
Streptococci	7 (54%)	3 (43%)	2 (33%)	4 (66%)	2 (67%)	2 (67%)	0	0
E faecalis	2 (15%)	1 (14%)	0	0	0	0	3 (60%)	3 (60%)
S aureus	2 (15%)	2 (28%)	3 (50%)	1 (17%)	0	0	2 (40%)	1 (20%)
CNS	2 (15%)	1 (14%)	1 (17%)	1 (17%)	1 (33%)	1 (33%)	0	1 (20%)

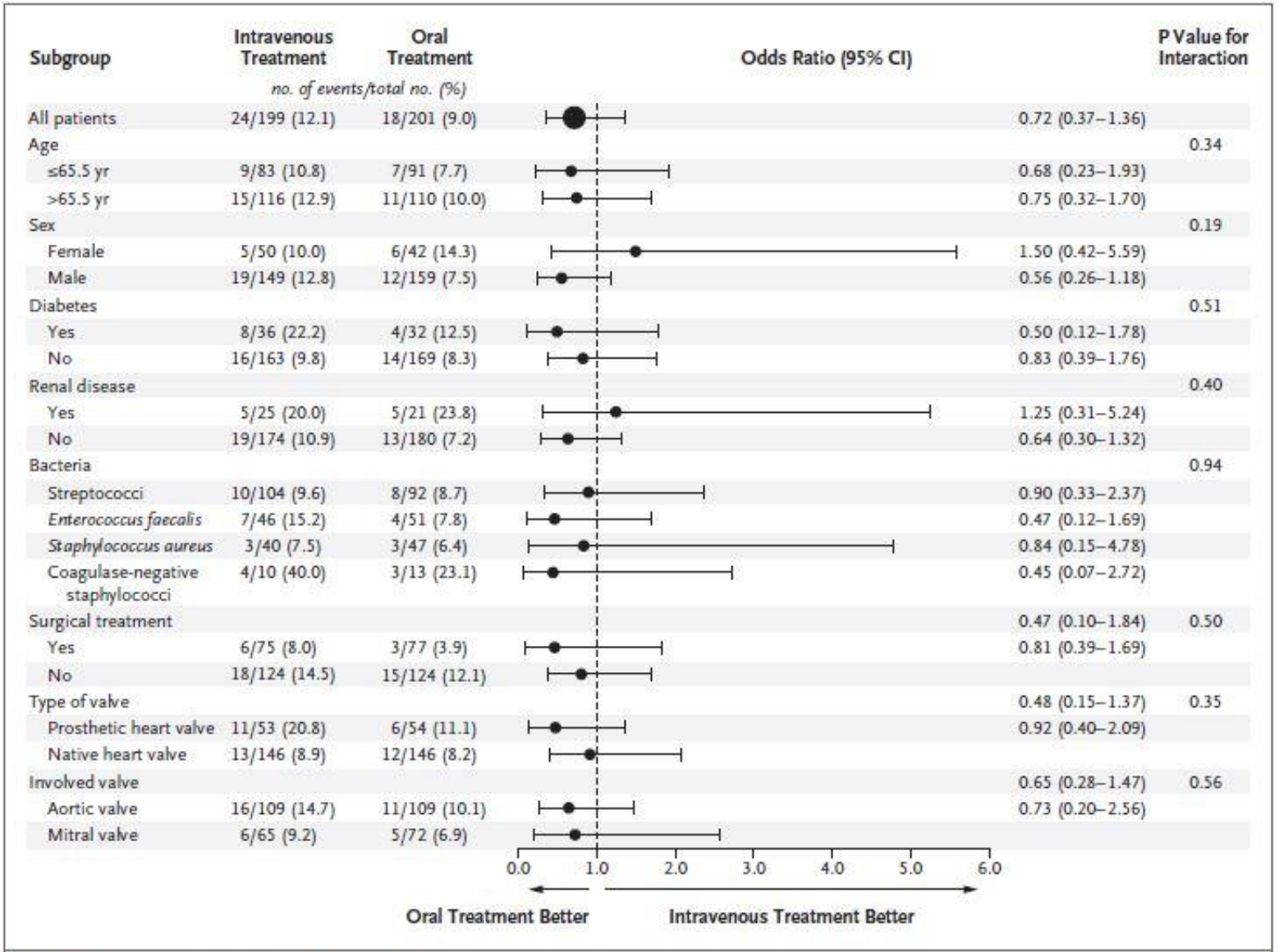

Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

Antibiotic regimens in the POET trial.

	Oral regimens	Frequency n (%)
Staphylococcus aureus	Dicloxacillin and rifampicin	15 (33)
	Amoxicillin and rifampicin	13 (29)
	Moxifloxacin and rifampicin	3 (7)
	Amoxicillin and fusidic acid	2 (4)
	Dicloxacillin and fusidic acid	2 (4)
	Fusidic acid and linezolid	2 (4)
	Rifampicin and linezolid	2 (4)
	Penicillin and rifampicin	1 (2)
	Amoxicillin and clindamycin	1 (2)
	Ampicillin and rifampicin	1 (2)
	Moxifloxacin and fusidic acid	1 (2)
	Moxifloxacin and linezolid	1 (2)
	Linezolid and clindamycin	1 (2)
Enterococcus faecalis	Amoxicillin and moxifloxacin	24 (47)
	Amoxicillin and linezolid	13 (25)
	Amoxicillin and rifampicin	6 (12)
	Moxifloxacin and linezolid	5 (10)
	Amoxicillin and ciprofloxacin	2 (4)
	Amoxicillin	1 (2)

DOSES:
Diclox 1 gmq6
Amox 1gm q6
Rifampin 0.6gm q 12
Linezolid 0.6 q12
Clinda 0.6 q8
Moxiflox 0.4 q 24
Fusidic acid 0.75 q12

Streptococci	Amoxicillin and rifampicin	47 (52)
	Amoxicillin and moxifloxacin	12 (13)
	Rifampicin and linezolid	8 (9)
	Moxifloxacin and linezolid	8 (9)
	Amoxicillin and linezolid	7 (8)
	Penicillin	3 (3)
	Ampicillin and moxifloxacin	1 (1)
	Ampicillin and rifampicin	1 (1)
	Dicloxacillin and moxifloxacin	1 (1)
	Moxifloxacin and clindamycin	1 (1)
	Moxifloxacin and vancomycin	1 (1)
Coagulase negative staphylococci	Fusidic acid and linezolid	5 (38)
	Rifampicin and linezolid	4 (31)
	Amoxicillin and linezolid	1 (8)
	Dicloxacillin and rifampicin	1(8)
	Moxifloxacin and linezolid	1(8)
	Rifampicin and Fusidic acid	1(8)

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (−1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (−3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (−2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (−3.1 to 3.1)	0.97 (0.28 to 3.33)

* Six patients, three in each group, had two outcomes.
† For details about relapse of the positive blood culture, see the Supplementary Appendix.

In conclusion, in patients who had endocarditis on the left side of the heart caused by streptococcus, *E. faecalis*, *S. aureus*, or coagulase-negative staphylococci and who were in stable condition, a shift from intravenously administered to orally administered antibiotic treatment was noninferior to continued intravenous antibiotic treatment.

RESULTS

After randomization, antibiotic treatment was completed after a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group (P=0.48). The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P=0.40), which met noninferiority criteria.

CONCLUSIONS

In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

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Conclusion ? On use of oral antibiotics rather than IV

They work and are proven useful and are safer than IV

Need self responsible patients who can eat

Assure that they receive enough the drug
for the time period they need to take them with easy refill,
esp. indigent patients, at the proper high doses needed
****Cell phone alarms make great reminders to take meds.

Same close monitoring (like follow CRP for decrease
in inflammatory response with treatment whether IV or oral)

And follow for any signs of malabsorption or intolerance
which could effect efficacy.

Do we have time for more?