 Hot Topics in Infectious Diseases

CSHP AGM

November 16, 2019

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Clinical Coordinator & ID Pharmacist, Sunnybrook Health Sciences Centre

Disclosures

- Consulting fee:
  - Sunovion Pharmaceuticals
- None relevant to today's talk

What's Hot?

NEJM. 2019; 380:415-24
NEJM.2019;38(5):487-89
NEJM. 2019;380:425-36
https://clinicaltrials.gov/ct2/show/NCT03005145
CID.2019;69(7):1091–8

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Partial Oral Therapy for Osteomyelitis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D., heyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Sc., Claus Moser, M.D., Ph.D., M.D., D.M.Sc.

Seven Versus 14 Days of Antib
for Uncomplicated Gram-
A Noninferiority Rand

Dafna Yahav,[1,2] [3] Fidi Koppel,[4] A
Antonel [1,2] Barak

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

travenous Antibiotics for Bone
Joint Infection

S. Walker, M.A. McNally, B.L. Atkins,
in, C. Scarborough, P.C. Matthews,
A. Taylor, B. Angus, I. Byren,
Mack, S. Hopkins, J. Folb,
Moran, A.F. Woodhouse,
thsing, J.A.T. Sandoe,
Cooper, C. Geue,
simakul,
Cooke,
tors*

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Home > Search Results > Study Record Detail

Save this study

Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03005145

Recruitment Status : Recruiting
First Posted : December 29, 2016
Last Update Posted : October 31, 2019

See Contacts and Locations

Sponsor:
Sunnybrook Health Sciences Centre

Information provided by (Responsible Party):
Sunnybrook Health Sciences Centre

H.
S. Staffo
I. Aggarwal,
N. McMeek
T.H.N. Wong, L.
E. Thwaites, P. Bejon,

https://goodticklebrain.com/shakespeare-index

IV or Not IV – That is the Question

- Paradigm shift in Infectious Diseases

- Re-evaluating the need for:
  - Long treatment durations and/or
  - Intravenous Therapy

NEJM.2019;38(5):487-89
Infect Dis 1998; 27:1247-54.
NEJM 1970; 282:198-206

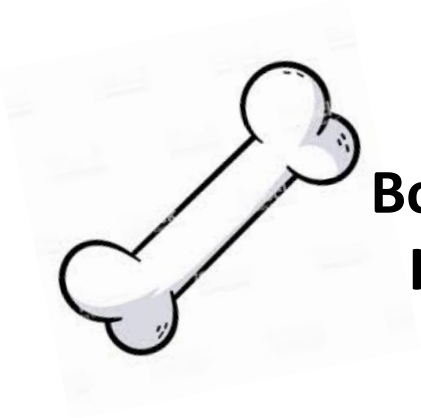
The Central Dogma of Deep-Seated Infections

Tenant #1: Intravenous

Tenant #2: For a long time (≥ 4-6 weeks)

Endocarditis

- Recommendations based on little evidence & derived in an era when pharmacokinetics of oral agents were not considered or well-studied



Bone & Joint Infections

- IV therapy not without challenges:
  - Longer hospitalizations
  - Complications (e.g. line-related infections /thrombosis)
  - IV drug users

- Some data to suggest that oral therapy may be “just as good” as IV

Objectives

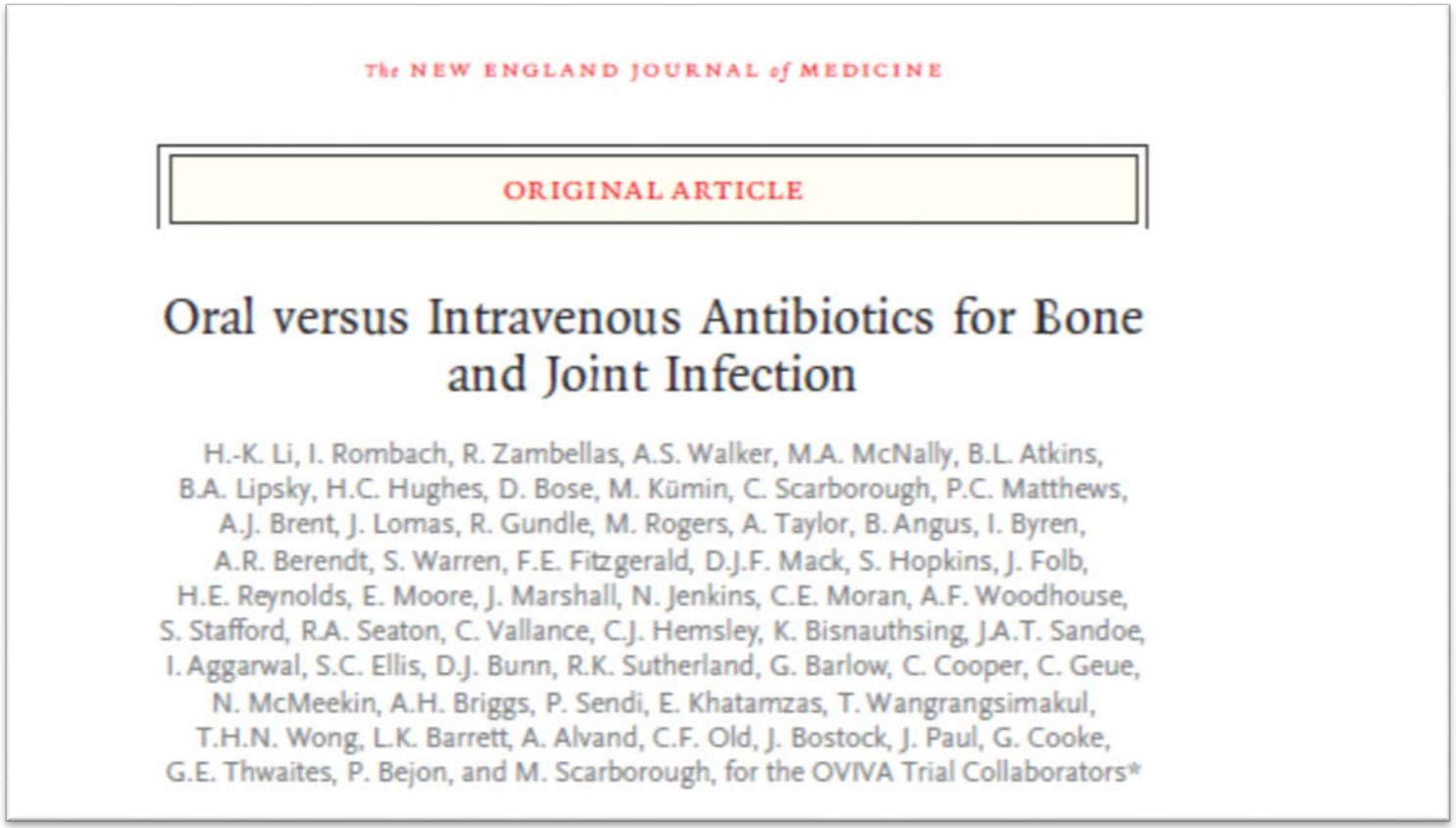
- Review contemporary data relating to oral therapy for the treatment of Bone and Joint Infections (OVIVA trial) and Infective Endocarditis (POET trial)
- Apply the evidence by the OVIVA and POET trials to a patient case
- Share our experiences with using oral therapy for the treatment of Bone & Joint Infections and Infective Endocarditis

https://www.amazon.com/Horse-Hip-Replacement-Featuring-Envelope/dp/B019T5TW6Y

Oral Therapy for Bone & Joint Infections

NEJM. 2019;380:425-36.

OVIVA Trial



The NEW ENGLAND JOURNAL of MEDICINE

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*

Study Objective:

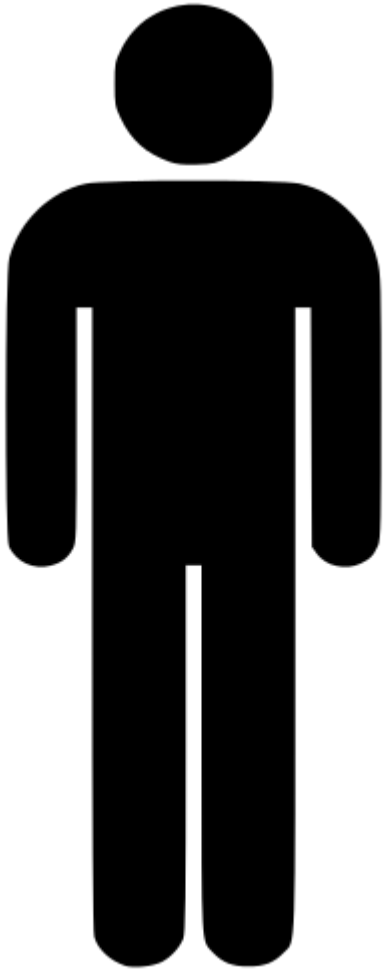
To determine whether oral whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for the management of complex orthopedic infections

OVIVA at a Glance….

- **Study Design**: multicenter, open-label**,** parallel-group, randomized, controlled non-inferiority study
  - 26 centres in the UK
- **Population:** n = 1054; adults with bone and joint infections
  - *Inclusion*: native OM, native joint infection, prosthetic joint infection, **orthopedic fixation device** infection, vertebral OM (± diskitis or soft tissue infection)
  - *Exclusion*: IE, *S. aureus* bacteremia, concomitant infection requiring IV therapy, **anticipated poor compliance**, suspected/confirmed mycobacterial/parasitic/fungal etiology
- **Intervention**:
  - IV vs. oral therapy for entire 6 week course (start of randomly assigned no more than 7 days after surgery or start of antibiotic therapy)
  - Antibiotics at the discretion of ID physician; assumed to be the most appropriate for the patient
- **Primary Outcomes**: definite treatment failure within 1 year of randomization
  - Presence of ≥ 1 clinical criterion (draining sinus tract/frank pus), microbiologic criterion (e.g. identical aspirate/biopsy microbiology), histological criterion (inflammatory infiltrate or microorganisms) ***adjudicated by 3 independent & blinded specialists**

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data)
http://clipartmag.com/person-outline-clipart

Meet the Average Joe (OVIVA Patient)



- 61 year old male
- Relatively healthy (few comorbidities
- Either chronic osteomyelitis OR **retained implant/device**
- Growing *Staphylococcus species*
- **Excellent patient – 90% medium/high adherence**

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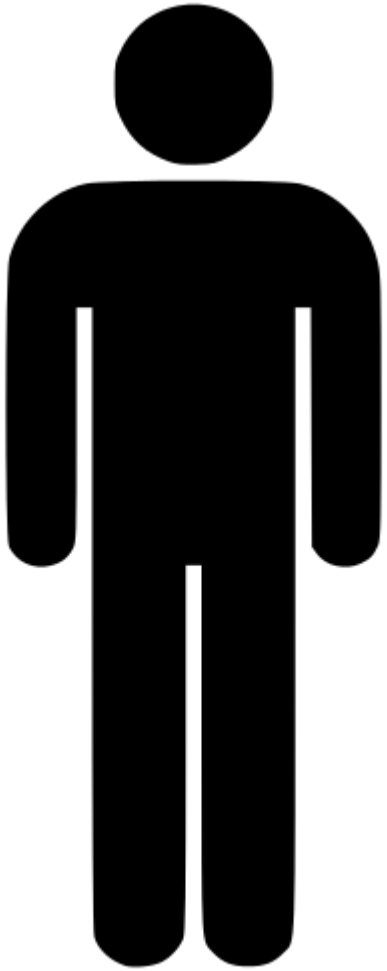

- 61 year old male
- Relatively healthy (few comorbidities
- Either chronic osteomyelitis OR **retained implant/device**
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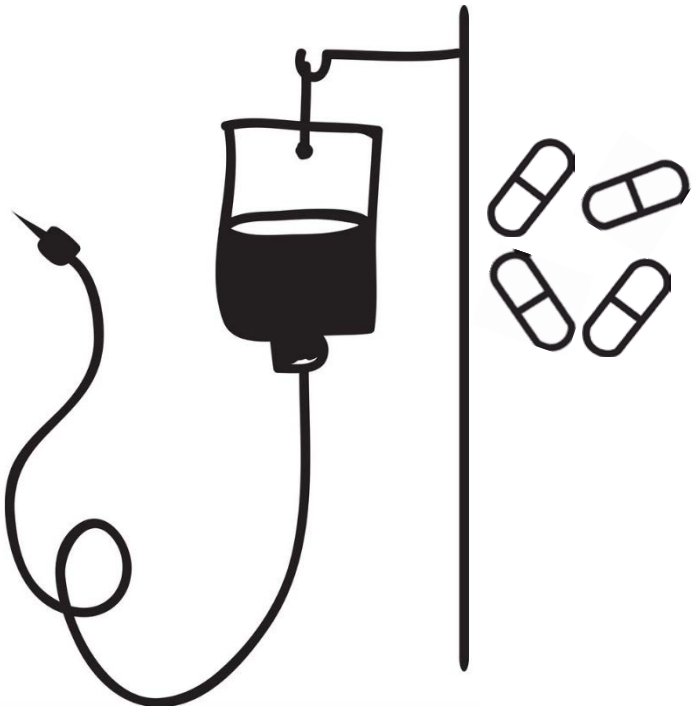
What was unrepresented?

Older patients
Multiple co-morbidities (T2DM, PVD)
Smokers
Vertebral OM
Pseudomonas (5%)
Gram negatives (20%)
MRSA (19 patients)

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data

Meet the Average Antibiotic Course



- **Total duration** of therapy ~**75 days** (~11 weeks)
  - i.e. ~80% of antibiotic courses were extended > 6 weeks
- ~**7 days of IV therapy**, followed by:
  - More IV therapy (IV arm) OR
  - Oral therapy (PO arm)
- Mostly monotherapy (10%)
- Antibiotics:
  - *IV therapy*: **glycopeptides/cephalosporins** (~70%)
  - *Oral Therapy*: **quinolones**/macrolides/lincosamides (~70%)

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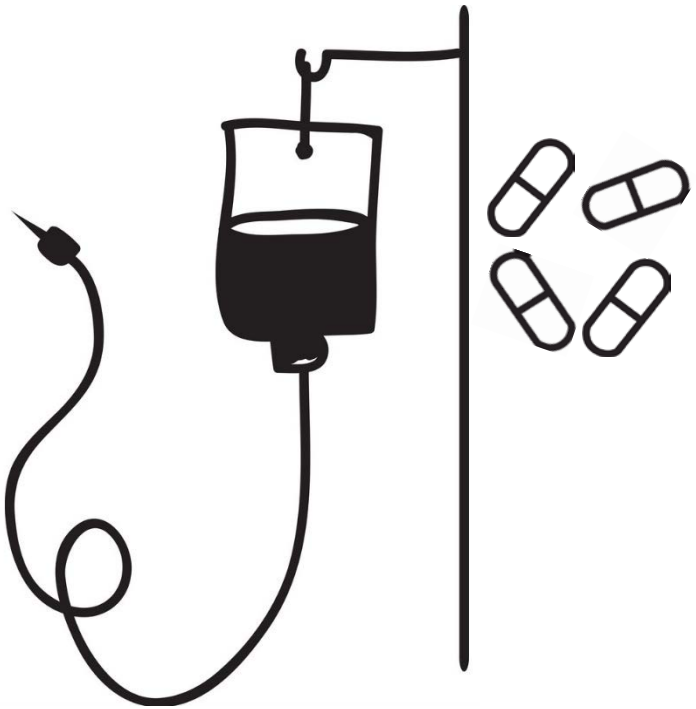

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- Little use of oral beta-lactams (penicillins - 14%)
- Adjunctive rifampin use ≥ 6 weeks greater in PO vs. IV arm (31.4 % vs. 22.9%)

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data

Primary Endpoint: Definitive Treatment Failure

Subgroup	Oral Group	IV Group	Risk Δ (90% CI; 95% CI)
ITT	13.3%	14.7%	-1.4% (−4.9 to 2.2%; −5.6 to 2.9%)
mITT	13.2%	14.6%	-1.5% (−5.0 to 2.1%; −5.7 to 2.8%)
Per protocol	13.1%	15.6%	-2.5% (−6.3 to 1.3%; −7.0 to 2.1%)
Worst-Case Sensitivity Analysis	16.1%	14.0%	2.1% (−1.5 to 5.7%; −2.2 to 6.4%)

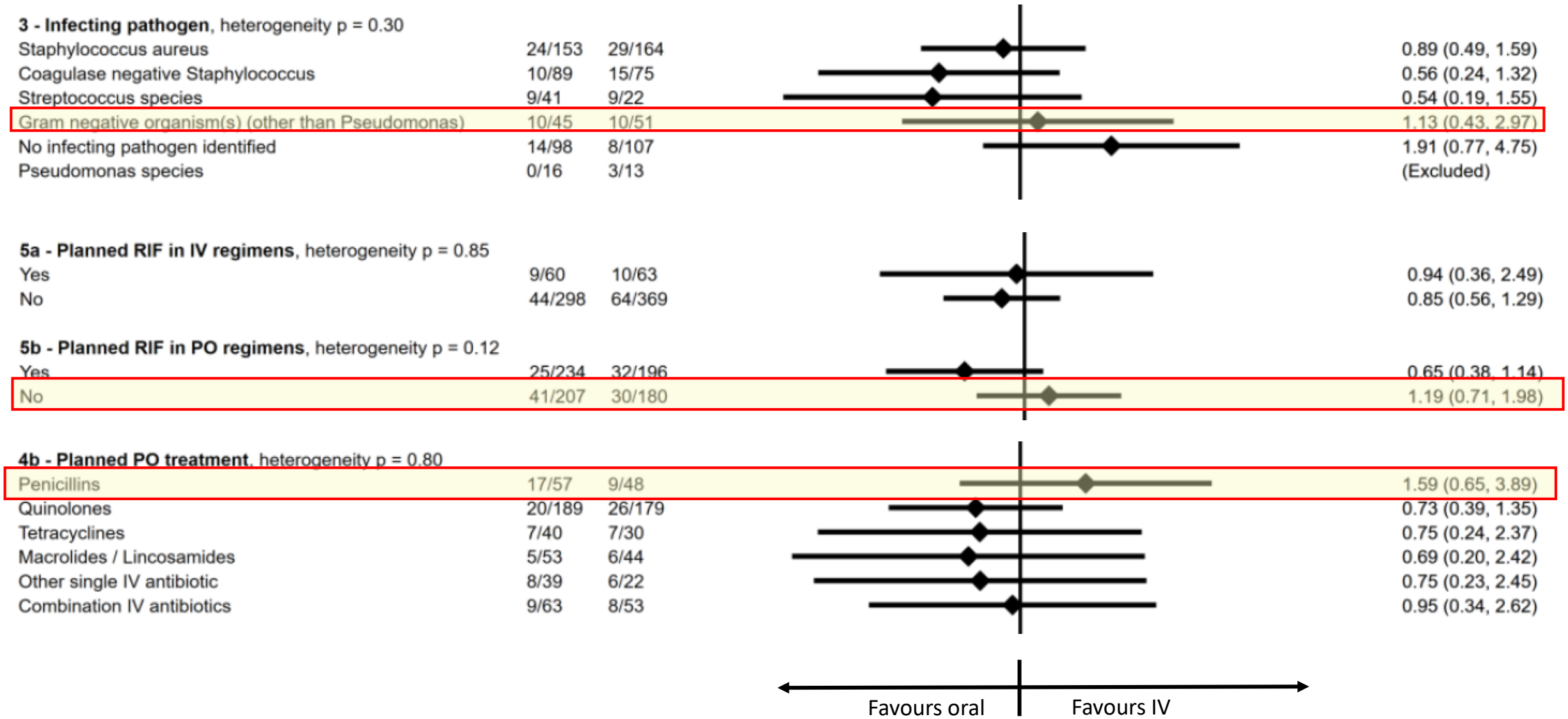
Met non-inferiority based on **either** 7.5% or 5% margin

Met non-inferiority based on 7.5% margin

*Non-inferiority margin initially set at 5%; reset at 7.5% at interim analysis

ITT – all randomized participants; missing endpoint data imputed (missing data for 39 patients- 3.7%)
mITT – all participants with complete endpoint data
Per protocol – participants who received at least 4 weeks of randomly assigned patients
Worst Case Sensitivity analysis: any missing data coded as: success (IV arm) and failure (oral arm)

OVIVA: What about those Subgroups?



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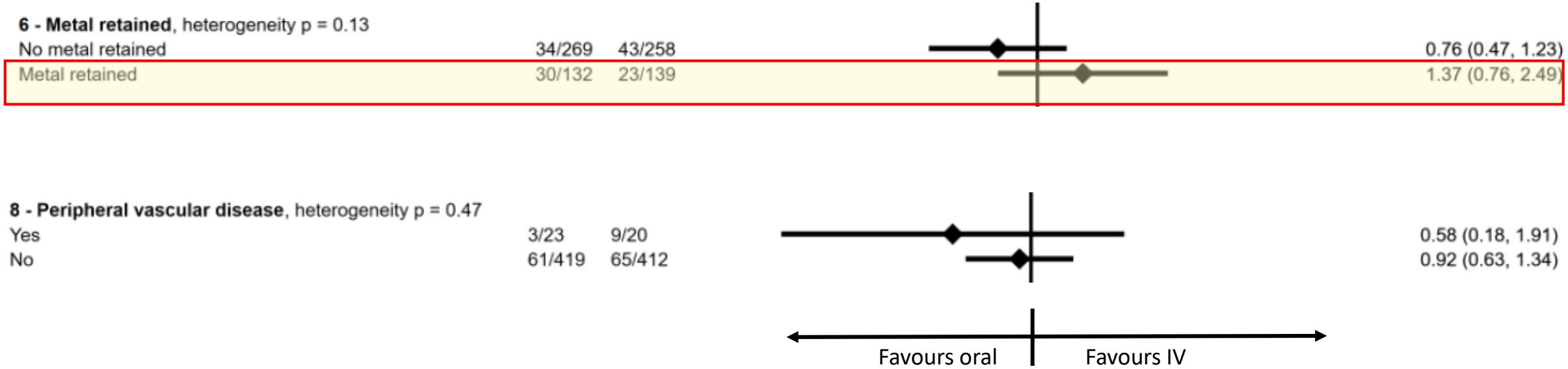

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Other Findings: Adverse Events

Serious Adverse Events

- Overall, not significantly different between groups (~27%)
  - IV catheter-related complications: 9.4% (IV arm), 1.0 % (oral arm)
  - Gastrointestinal: 9.5% (IV arm), 5.8% (oral arm)
  - *C. difficile*-associated diarrhea: 1.7% (IV arm), 1.0% (oral arm)

Hospitalization-Days

- Significantly longer in the IV vs. oral arm (14 days vs. 11 days; $p<0.001$)

Cost Effectiveness Analysis:

- Estimated cost savings of **~$3,500 per patient** in the oral arm
  - Antibiotic costs, administration of antibiotics (equipment, staff time), hospitalized bed days

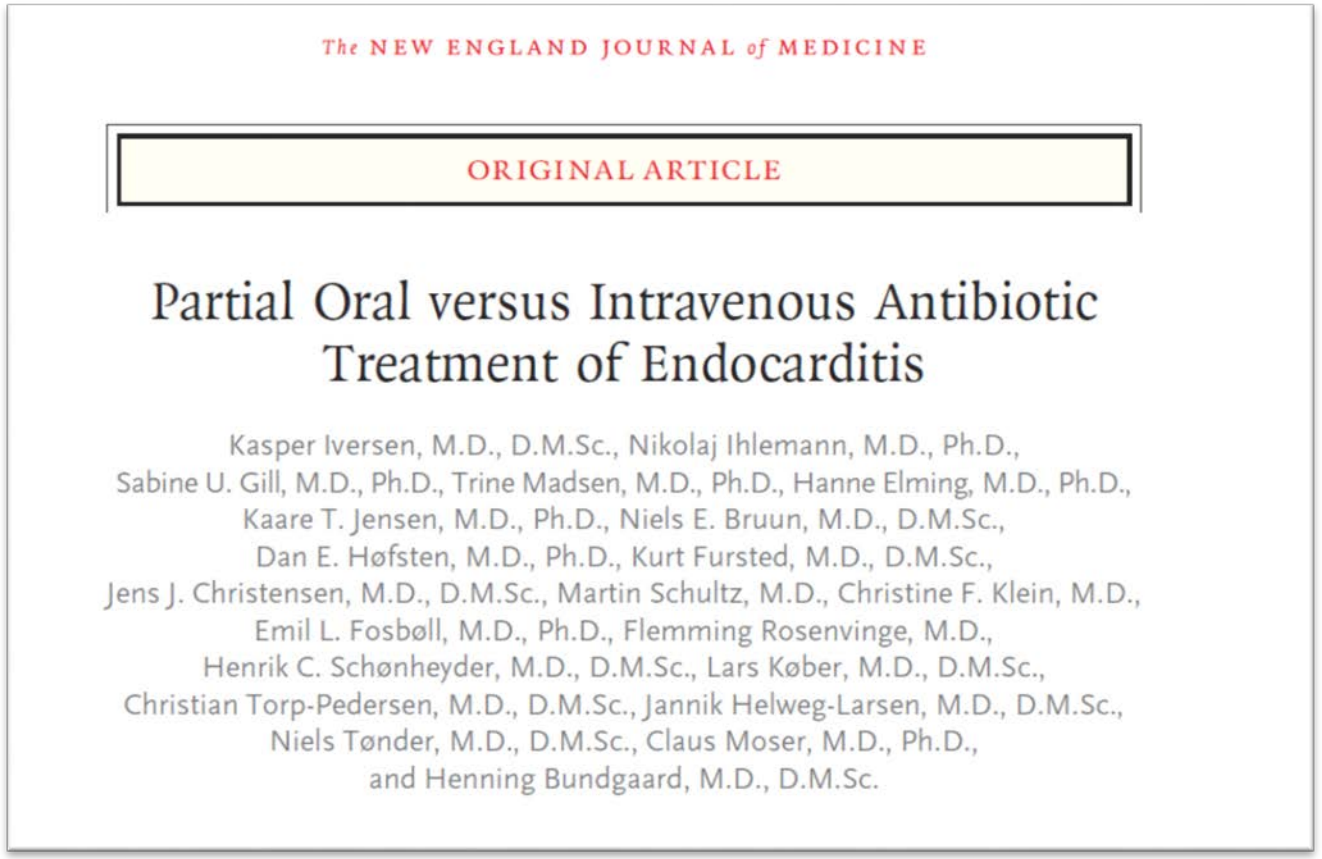
OVIVA – Study's Conclusions

"We found that appropriately selected oral antibiotic therapy was non-inferior 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"

https://thriveglobal.com/stories/how-to-heal-from-a-broken-heart/

Oral Therapy for Endocarditis

Poet Trial



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Study Objective:

To determine whether a shift from intravenous to oral antibiotics would result in efficacy and safety similar to those with continued intravenous treatment in patients with endocarditis of the left-side of the heart

Poet at a Glance….

- **Study Design**: multicenter, **open-label,** randomized, controlled non-inferiority study
  - Cardiac Centres in Demark 
- **Population:** n = 400; adults with <u>left-sided</u> bacterial endocarditis
  - *Inclusion*: Adult (≥ 18 years) , **stable,** infected with Streptococci*, Enterococcus faecalis,* Staphylococcus aureus *or* Coagulase-negative staphylococci, **≥ 10 days of appropriate parenteral antibiotic treatment**, T < 38.0 °C > 2 days, CRP < 25% peak value or < 20 mg/L, and white blood cell count < 15 x 10^9/L during antibiotic treatment, **no abscess, TTE & TTE** within 48 hours of randomization
  - *Exclusion*: Body mass index > 40, concomitant infection requiring intravenous antibiotic therapy, inability to give informed consent to participation, suspicion of reduced absorption, **anticipated non- compliance**

Poet at a Glance(cont)....

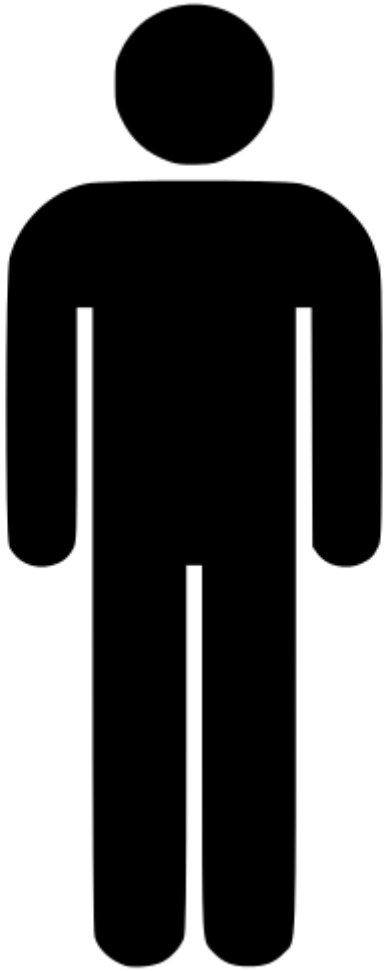
- **Intervention**:
  - Random assignment ratio to continued IV antibiotic treatment or to a shift to oral therapy
    - In accordance with guidelines of the European Society of Cardiology,Danish Society of Cardiology
  - Oral antibiotics: **moderate to high bioavailability, two antibiotics** from **different drug classes** with **different antimicrobial mechanisms of action** and **different metabolization**
  - **Plasma antibiotic levels** of oral agents were obtained on Day 1 & Day 5; dose adjustments made if necessary

- **Participate follow up:**
  - Oral therapy group: assessed in outpatient clinics, **2-3 times per week** throughout oral treatment phase; **end-of-treatment TEE** (transesophageal echocardiography) to assess sufficient response to treatment
  - Followed at outpatient clinics at 1 week, and at months 1, 3 and 6 months after completion of antibiotic therapy

- **Primary Outcomes**: composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen
  - from randomization through 6 months after antibiotic treatment was completed ***adjudicated by blinded cardiologists and ID specialists**

NEJM. 2019; 380:415-24.
http://clipartmag.com/person-outline-clipart

Meet the Average Joe (POET Patient)



- 67 year old male
- 1 comorbidity
- VGS aortic native valve endocarditis
- Did not undergo valve replacement
- Clinically stable
- Able to make frequent outpatient visits/week

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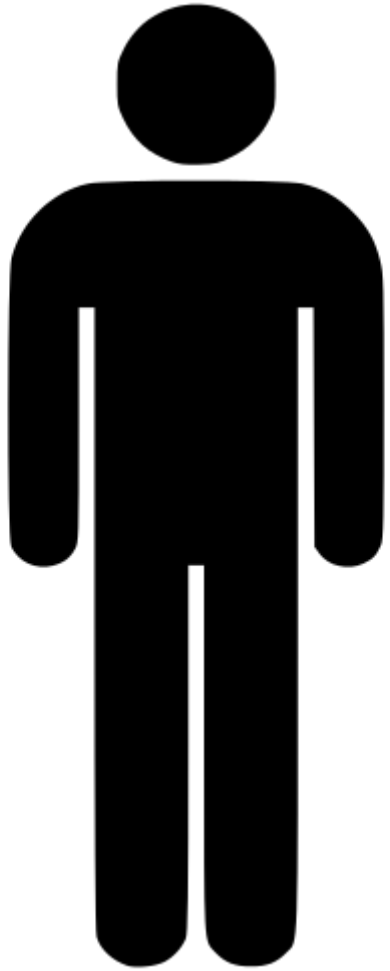

- 67 year old male
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What was unrepresented:
Prosthetic valve IE (~25%)
Enterococci (~25%)
Staphylococcus (~20%) – NO MRSA
IV drug users (n=5; 1%)

Note: that 80% of patients screened were deemed ineligible (common reasons: expected non compliance, lack of availability to follow-up, elevated inflammatory markers)!

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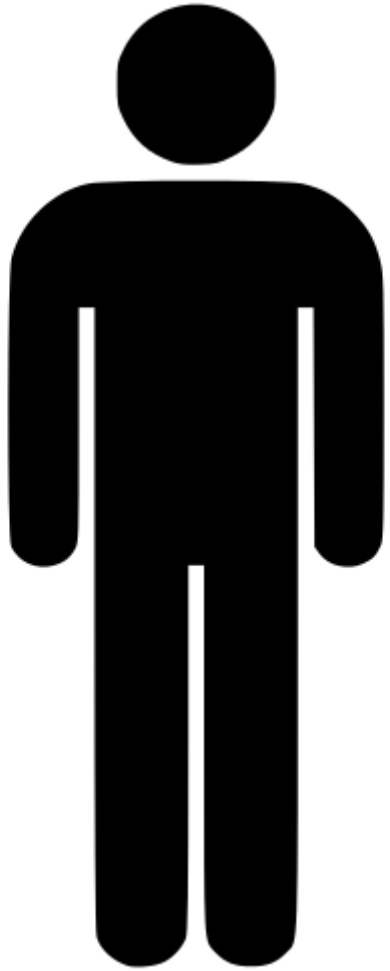

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"Rock solid humans immunologically, who responded immediately to treatment and got better fast"

-Dr. Mark Crislip
(host of Puscast)

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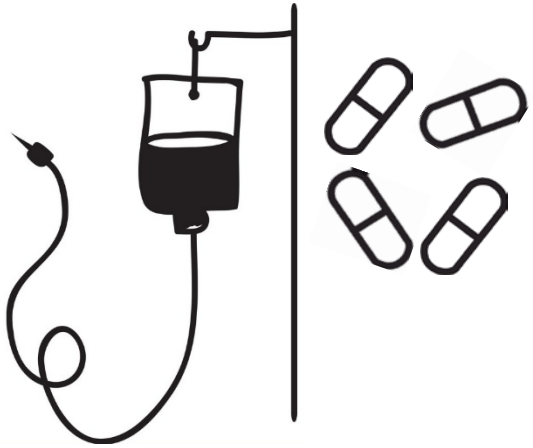
Meet the Average Antibiotic Course



- **Median Duration of therapy:** ~35 days (~ 5 weeks)
- **Median Duration of IV Therapy**: ~ 17 days (> 2 weeks!)
- **Patient Disposition**: 19 days in hospital (~ 3 weeks)
  - In Denmark, IV home therapy is not available

Pathogen	Antibiotic Therapies Used
Streptococci [mostly VGS] **_Enterococcus faecalis_** **_Staphylococcus aureus NB. No MRSA_** **CNST**	• Amoxicillin 1 g QID + fusidic acid • Amoxicillin 1 g QID + rifampin • Amoxicillin 1 g QID + moxifloxacin • Linezolid + fusidic acid • Linezolid + rifampin • Linezolid + moxifloxacin • Moxifloxacin + rifampin • Moxifloxacin + clindamycin • Dicloxacillin 1 g QID + rifampin • Dicloxacillin 1 g QID+ fusidic acid

***4 patients crossed over from po → IV;No cross-over from IV → po**

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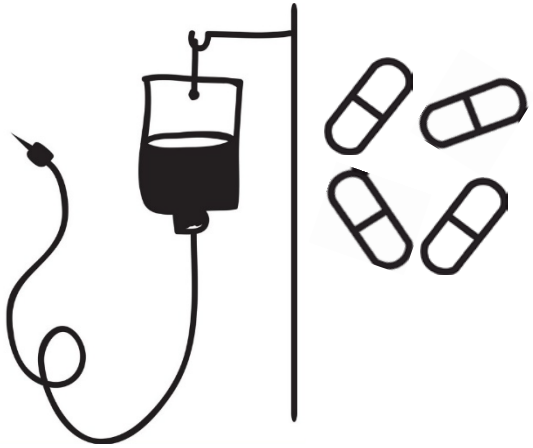
Meet the Average Antibiotic Course



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- **Amoxicillin** - (very) high dose amoxicillin to compensate for low bioavailability -? GI tolerability
- **Linezolid** – bone marrow suppression
- **Fusidic acid** - not available in Canada
- **FQs** - increasing concern of toxicities of (e.g. aortopathies)
- **Rifampin** – not everyone can take (drug interactions, hepatotoxicity)

Pathogen	Antibiotic Therapies Used
Streptococci [mostly VGS]	• Amoxicillin 1 g QID + fusidic acid • Amoxicillin 1 g QID + rifampin • Amoxicillin 1 g QID + moxifloxacin • Linezolid + fusidic acid • Linezolid + rifampin • Linezolid + moxifloxacin • Moxifloxacin + rifampin • Moxifloxacin + clindamycin • Dicloxacillin 1 g QID + rifampin • Dicloxacillin 1 g QID+ fusidic acid
Enterococcus faecalis	
***Staphylococcus aureus* NB. No MRSA**	
CNST	

***4 patients crossed over from po → IV;No cross-over from IV → po**

POET: Primary Outcome

Primary outcome:

12.1% (IV) vs. 9.0% (Oral); △ = 3.1% [**95% CI, -3.4 to 9.6; p =0.40**]* ⊥

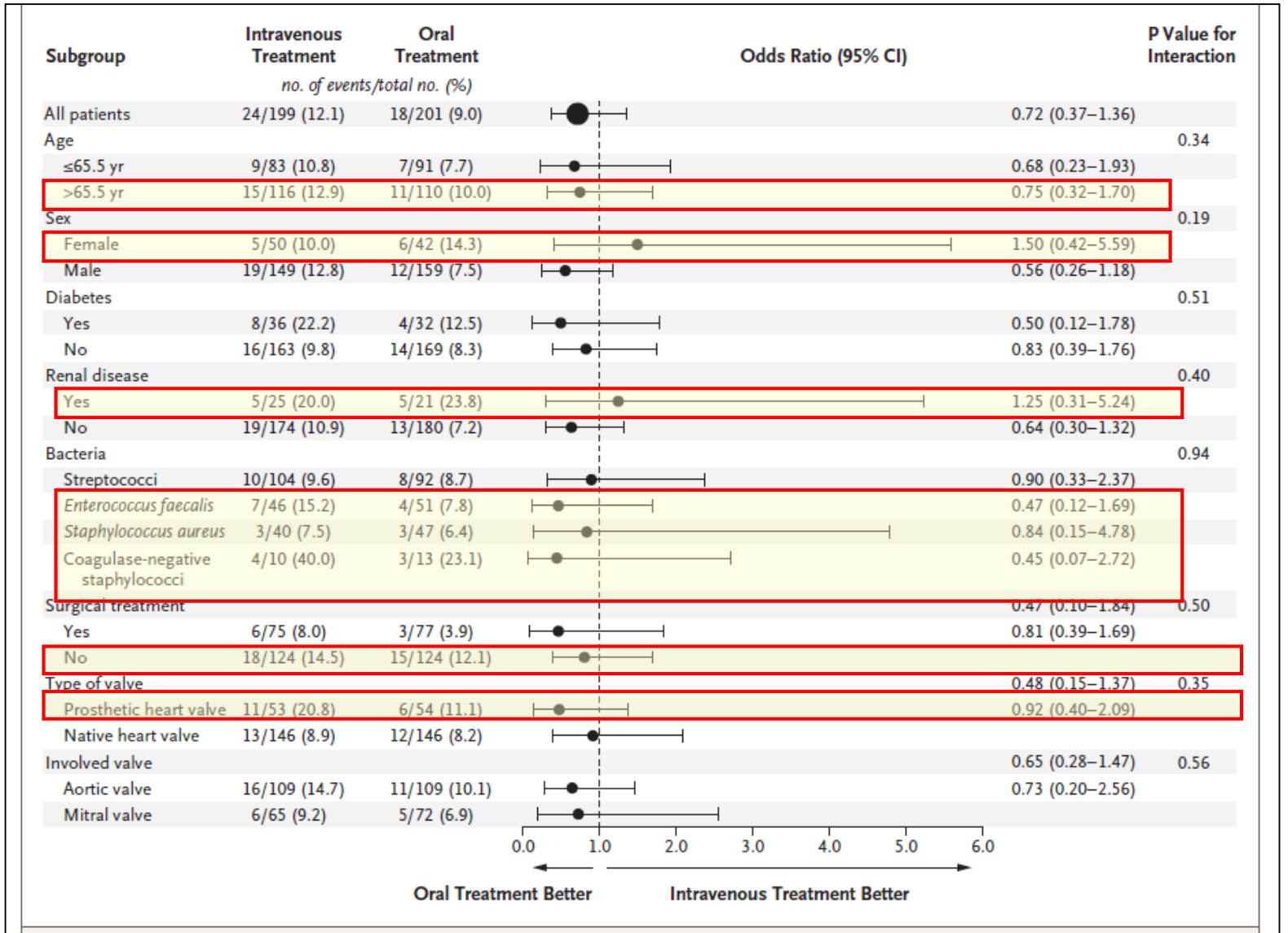
*met non-inferiority criterion of 10% (?in favour of oral therapy)

⊥ robust in sensitivity analysis that accounted for cross-over from oral to IV therapy

Component of Primary Outcome	IV Treatment (n=199)	Oral Treatment (n=201)	Risk Δ (95% CI)
All- cause mortality	6.5%	3.5%	3.0% (-1.4 to 7.7)
Unplanned cardiac surgery	3.0%	3.0%	0% (-3.3 to 3.4)
Embolic event	1.5%	1.5%	0%(-2.4 to 2.4)
Relapse of positive blood culture	2.5%	2.5%	0% (-3.1 to 3.1)

Met non-inferiority (10%)

POET: What about those Subgroups?



Subgroup	Intravenous Treatment	Oral Treatment	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All patients	24/199 (12.1)	18/201 (9.0)	0.72 (0.37–1.36)	
Age				0.34
≤65.5 yr	9/83 (10.8)	7/91 (7.7)	0.68 (0.23–1.93)	
>65.5 yr	15/116 (12.9)	11/110 (10.0)	0.75 (0.32–1.70)	
Sex				0.19
Female	5/50 (10.0)	6/42 (14.3)	1.50 (0.42–5.59)	
Male	19/149 (12.8)	12/159 (7.5)	0.56 (0.26–1.18)	
Diabetes				0.51
Yes	8/36 (22.2)	4/32 (12.5)	0.50 (0.12–1.78)	
No	16/163 (9.8)	14/169 (8.3)	0.83 (0.39–1.76)	
Renal disease				0.40
Yes	5/25 (20.0)	5/21 (23.8)	1.25 (0.31–5.24)	
No	19/174 (10.9)	13/180 (7.2)	0.64 (0.30–1.32)	
Bacteria				0.94
Streptococci	10/104 (9.6)	8/92 (8.7)	0.90 (0.33–2.37)	
Enterococcus faecalis	7/46 (15.2)	4/51 (7.8)	0.47 (0.12–1.69)	
Staphylococcus aureus	3/40 (7.5)	3/47 (6.4)	0.84 (0.15–4.78)	
Coagulase-negative staphylococci	4/10 (40.0)	3/13 (23.1)	0.45 (0.07–2.72)	
Surgical treatment			0.47 (0.10–1.84)	0.50
Yes	6/75 (8.0)	3/77 (3.9)	0.81 (0.39–1.69)	
No	18/124 (14.5)	15/124 (12.1)		
Type of valve			0.48 (0.15–1.37)	0.35
Prosthetic heart valve	11/53 (20.8)	6/54 (11.1)	0.92 (0.40–2.09)	
Native heart valve	13/146 (8.9)	12/146 (8.2)		
Involved valve			0.65 (0.28–1.47)	0.56
Aortic valve	16/109 (14.7)	11/109 (10.1)	0.73 (0.20–2.56)	
Mitral valve	6/65 (9.2)	5/72 (6.9)		

NEJM. 2019; 380:415-24
NEJM. 2019; 380:415-24 (Supplement)

POET: Adverse Events

- Adverse effects: 6% (IV) vs. 5% (oral); p =0.66

Side Effect	Intravenous Treatment n=12	Oral Treatment n=10	
Gastrointestinal, n(%)	0 (0%)	3 (30%)	?Courtesy of high dose amoxil and dicloxacilin
Renal Failure, n(%)	0 (0%)	1 (10%)	
Hepatic Failure, n(%)	0 (0%)	1 (10%)	
Bone marrow suppression, n(%)	2 (17%)	4 (40%)	?Courtesy of linezolid
Allergy, n(%)	10 (83%)	1 (10%)	

POET: Study's Conclusion

"In patients with endocarditis on the side of the heart caused by streptococcus, *E. faecalis*, *S. aureus* or coagulase-negative staphylococci who were in clinically stable condition and who had an adequate response to initial treatment, a shift from initial intravenous to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment"

Questions or Comments?

Further Reading

- OVIVA Trial (N Engl J Med.2019;380:425-36)
- POET Trial (N Engl J Med 2019; 380:415-424)
- Editorial: “Partial Oral Therapy for Osteomyelitis and Endocarditis — Is It Time?” N Engl J Med 2019; 380:487-489