What’s hot in infective endocarditis?

Partial oral endocarditis antibiotic treatment – the POET trial.

Claus Moser, MD, PhD
Department of Clinical Microbiology, Rigshospitalet.
Copenhagen University Hospital.
Denmark.

Stade de la Beaujoire, Nantes on July the 7th in 1998 last game for Denmark for the Laudrup brothers in the World Cup quarterfinal against Brasil (2-3).

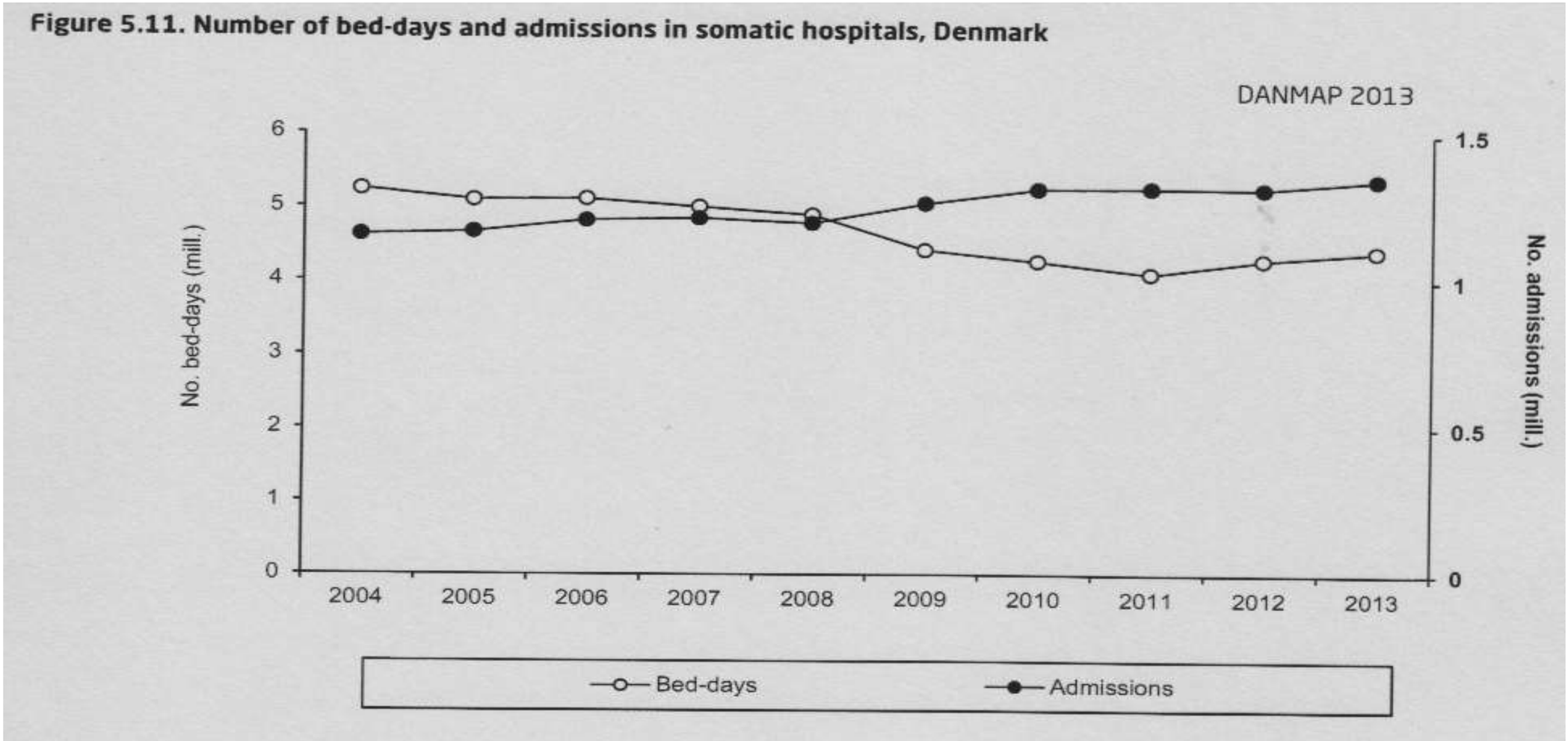
Recommended treatment of infectious left-sided endocarditis

- 4 to 6 weeks in-hospital
- iv antibiotics (iv lines)
- Work-up for endocarditis
- Work-up for primary focus
- Heart valve surgery ~50% of cases
- Daily ward rounds
- Careful monitoring - “Institutionalised” 24/7/4-6

Why try to reduce in-hospital treatment?

- The long admissions are associated with increased risk of complications
- Reductions in the length of hospital stay have been associated with improved outcome in other patient groups
- Reduce costs in the health care system

Length of stay and number of admissions in Denmark



From 2007 to 2013 we had a 3,000 hospital bed reduction (20%).

In 2017/18 the average length of stay is less than 3 days.

Jyllands Posten.-
P. 3-6-13

Glem ikke patienten på gangen

Op mod hver tredje medicinske afdeling har overbelægning hele året rundt.

LARS ENGBERG
formand for
Danske Patienter

GRETE CHRISTENSEN
formand for Dansk
Sygeplejeråd

POUL JASZCZAK
næstformand
i Lægeforeningen

Når en svækket ældre medicinsk patient bliver placeret ude på en kaotisk hospitalsgang eller foran elevatoren i træk og kulde, fordi der ikke er plads på sengestuerne, så vil de fleste nok mene, at vi har et alvorligt problem i det danske sundhedsvæsen. Ikke desto mindre er det virkeligheden på en del akutte og medicinske hospitalsafdelinger i landet.

Spørger man så de ansvarlige politikere i Danske Regioner, hvad den her utilfredsstillende situation skyldes, så lyder svaret, at vi netop i år har haft en særdeles hård og langvarig influenzaepidemi. Det er altså tale om force majeure, og patienter og sundhedsprofessionelle må bide tænderne sammen, for det er midlertidigt.

Nye tal fra Statens Serum Institut viser, at influenzaaktiviteten kun i en uge i år har været over middel. Dermed er det så som så med dokumentationen for, at det netop i år har været en ekstraordinær influenzaepidemi, der har varet i flere måneder.

Har nedlagt et stort antal senge

Hvad er så skyld i, at patienterne bliver placeret på gangene? Og hvorfor viser stikprøver, at op mod hver tredje medicinske afdeling har overbelægning hele året rundt?

En af hovedforklaringerne handler om, at regionerne har nedlagt et stort antal senge meget hurtigt, uden at kommunerne har nået at skabe et velfungerende sundhedsberedskab. Fra 2007-2012 har regionerne nedlagt næsten hver femte somatiske hospitalsseng. Det er langt hurtigere, end eksperterne havde anbefalet.

Ifølge Erik Juhl-udvalget, som blev nedsat af den daværende regering i 2008, og som havde til opgave at komme med ekspertanbefalinger til den nye sygehusstruktur, så skulle regionerne nedbringe antallet af senge med 20 pct. fra 2007-2020. Det svarer til en reduktion på knap 250 senge årligt. I stedet har regionerne skåret næsten 600 senge om året.

Hjælpepakke

Derfor kan det ikke komme som nogen stor overraskelse for Danske Regioner, at der mange steder ikke er plads til patienterne på sengestuerne. Derfor er der stort behov for, at der bliver taget hånd om problemerne hurtigst muligt, og derfor har vi som repræsentanter for patienter og sundhedsprofessionelle lavet en hjælpepakke mod overbelægning, hvor vi kommer med en række bud på løsninger.

Det bliver en falliterklæring

Der skal blandt andet indføres et her-og-nu-stop for nedlæggelse af medicinske senge, og her bør den økonomiaftale, som regeringen lige nu forhandler med regionerne, indeholde en målsætning om, at den massive nedlæggelse af senge bliver sat på standby i 2014. Samtidig skal økonomiaftalerne sikre, at regioner og kommuner i højere grad får incitamenter til at samarbejde.

Det er positivt, at regeringen vil omprioritere 250 mio. kr. til fælles sundhedsindsatser, men økonomiaftalerne skal også tage hånd om det problem, at incitamenterne i sundhedsvæsenet vender den forkerte vej. Regioner og kommuner bliver ganske enkelt ikke belønnet for at samarbejde, og det er en falliterklæring, hvis parterne forlader forhandlingsbordet uden en løsning, der skaber mere sammenhængende forløb for patienterne.

Vi har også været i foretræde for Folketingets sundhedsudvalg og fremlagt vores bud på, hvad der skal til for at løse overbelægningen, og det fik en positiv modtagelse af politikere fra begge sider af salen.

Samtidig har sundhedsminister Astrid Krag (SF) været i samråd på Christiansborg om hjælpepakken og overbelægning, og her lød meldingen fra ministeren, at hun havde svært ved at se, at det ikke skulle blive et tema ved økonomiforhandlingerne mellem regioner, kommuner og regeringen. Nu mangler vi bare, at der bliver sat handling bag, og opbakningen bliver udmøntet til reelle resultater for den enkelte ældre medicinske patient og de sundhedsprofessionelle i kommuner og på hospitaler.

Fokus på forebyggelse

Ingen tvivl om, at ministeren skal gå forrest. For det er klart, at både regioner og kommuner skal have rammerne, så sundhedsvæsenet kan håndtere patienterne, i takt med at antallet af ældre stiger markant, men regionerne og kommunerne skal også i højere grad forpligtes på at samarbejde og etablere de nødvendige senge, akutpladser og sundhedstilbud, så vi for alvor kan få gjort op med overbelægning.

Det er afgørende, at økonomiaftalerne sikrer, at der bliver sat fokus på sammenhæng og forebyggelse, så vi på længere sigt bliver færre borgere, der får en kronisk sygdom. Samtidig skal der laves nationale mål for folkesundheden, som regeringen flere gange har bebudet, men fortsat ikke har leveret.

Hvis politikerne endnu en gang bare lader stå til, vil vi desværre igen og igen kunne høre historien om overbelægning på medicinske afdelinger. For det skyldes ikke midlertidig influenzaepidemi. Det er en permanent tilstand mange steder i det danske sundhedsvæsen, og det er skabt af besparelser, nedlæggelse af sengepladser og manglende sundhedsberedskab i kommunerne. Vi skylder den ældre patient, der ligger ude på gangen, at gøre noget ved det.

”Oh no – I had just succeeded in closing the door.”

Options for modifying these regimens

- Reduce duration of iv antibiotic treatment
- Use *Outpatient Parenteral Antibiotic (Antimicrobial) Therapy* (OPAT) regimens
- - or – to maintain recommended duration, but in stable patients swap from an initial iv regimen to an oral regimen – in the out-patient clinic

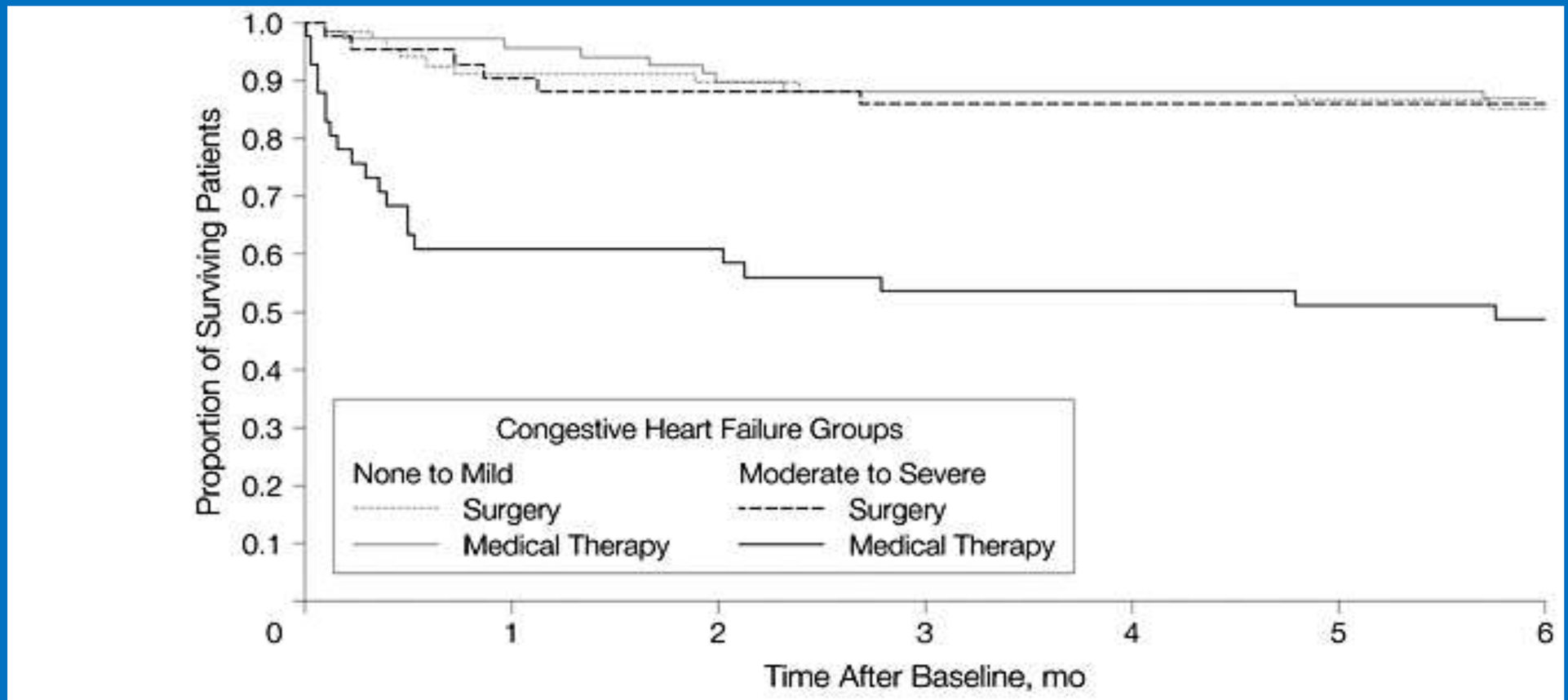
When to switch from iv in-hospital (IPAT) to out of hospital – OPAT?

Depends on ***timing*** of major adverse outcomes or complications in infectious endocarditis

- Death
- Heart failure
- Emboli

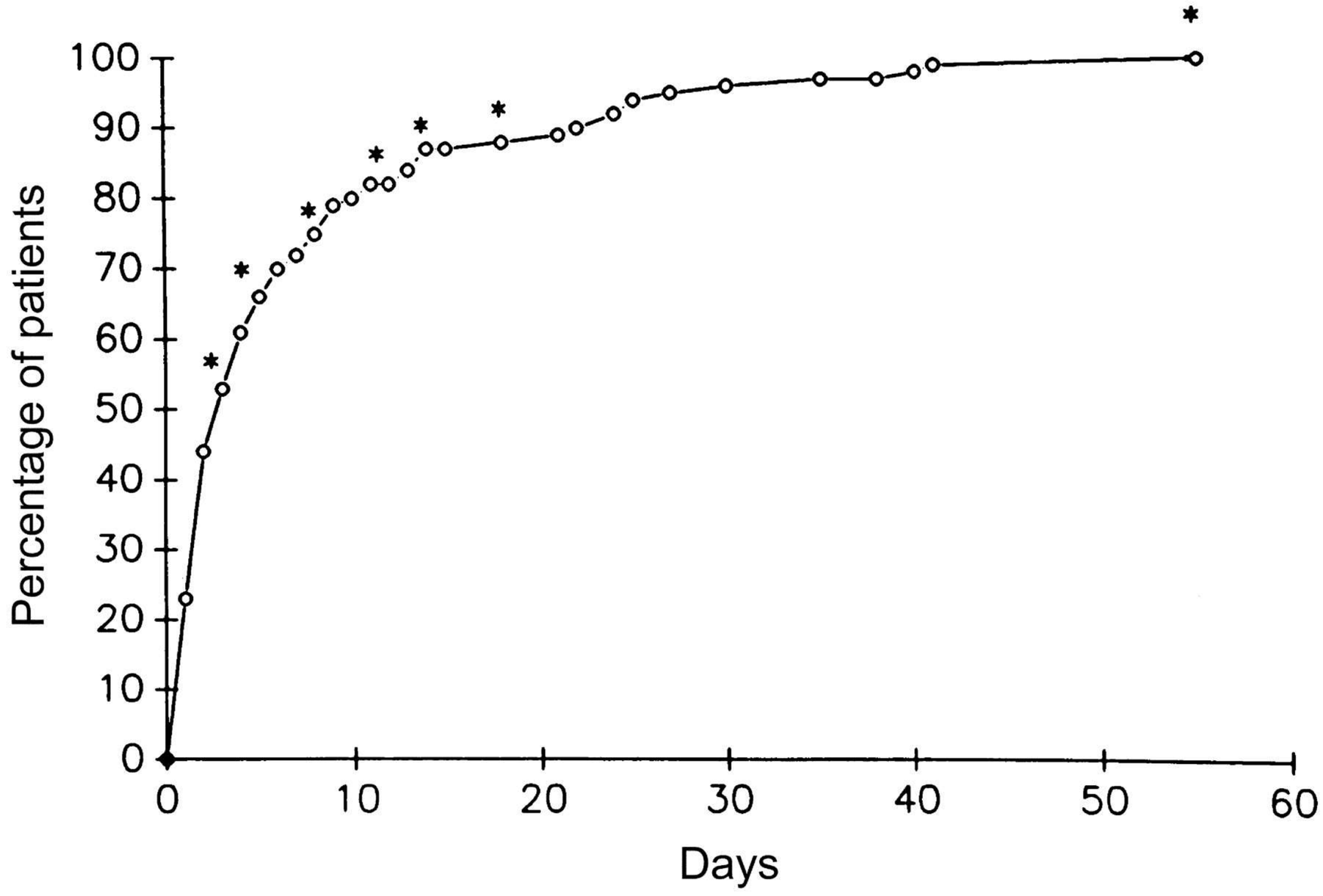
Impact of Valve Surgery on 6-Month Mortality in Adults With Complicated, Left-Sided Native Valve Endocarditis: A Propensity Analysis on whether valve surgery is associated with reduced mortality.

Vikram et al. JAMA 2003



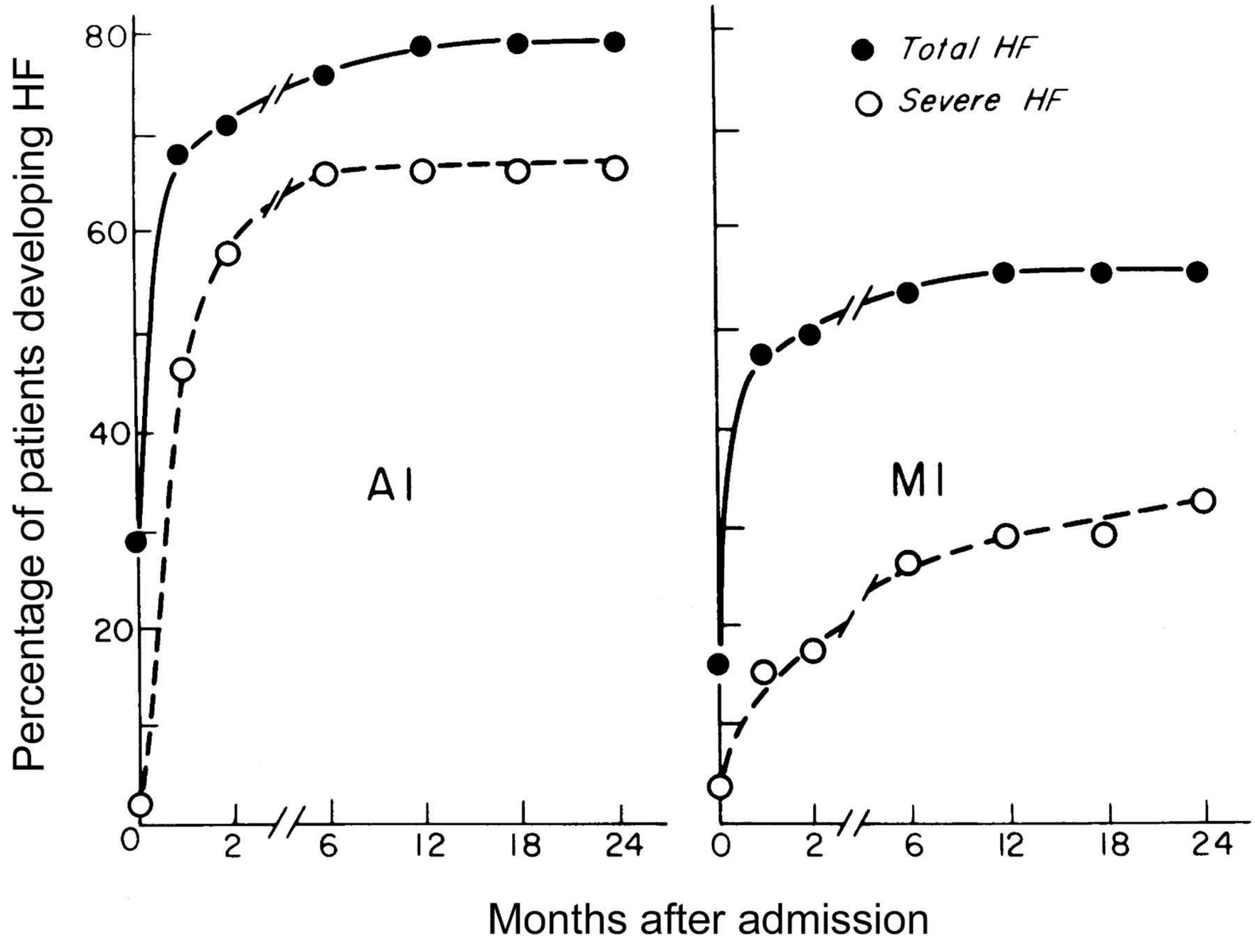
No. at Risk							
None to Mild CHF Group							
Surgery	67	60	59	58	58	57	56
Medical Therapy	68	64	61	59	59	59	57
Moderate to Severe CHF Group							
Surgery	42	37	36	35	35	35	35
Medical Therapy	41	24	24	21	21	20	19

Timing of fever in 123 patients with infective endocarditis in a Kaplan-Meier plot that shows cumulative frequency of defervescence.



Mary-Margaret Andrews, and C. Fordham von Reyn Clin Infect Dis. 2001;33:203-209

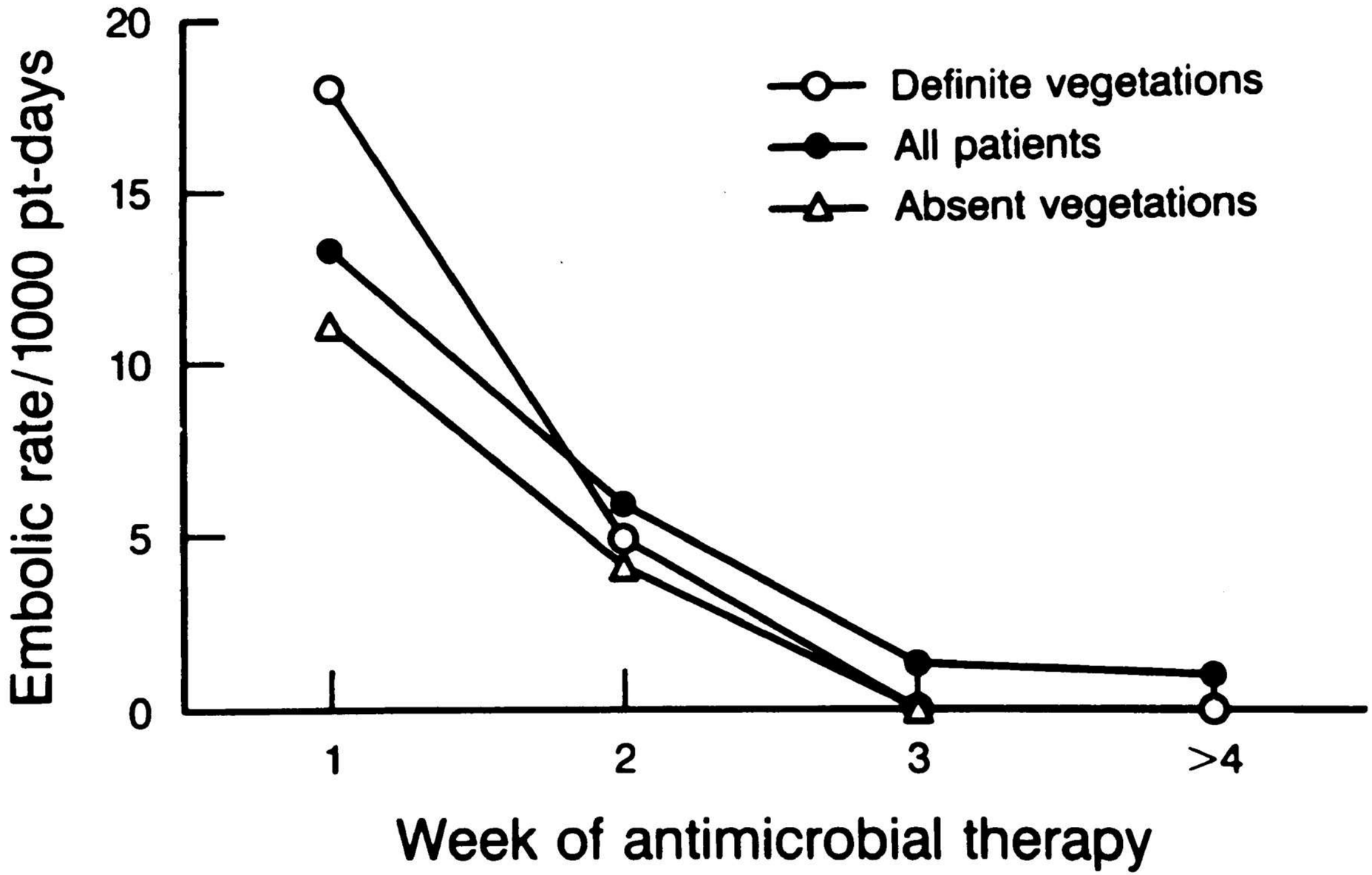
Clinical Infectious Diseases



Mary-Margaret Andrews, and C. Fordham von Reyn Clin Infect Dis. 2001;33:203-209

Clinical Infectious Diseases

Timing and incidence of embolic events in patients with infective endocarditis. pt-days, Patient-days.



Mary-Margaret Andrews, and C. Fordham von Reyn Clin Infect Dis. 2001;33:203-209

Clinical Infectious Diseases

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications of IE occur most frequently during this phase, and timely diagnosis is important for achieving optimal outcome.
	Preferred management: IPAT for 2 weeks.
	Exceptions: OPAT can be considered at 1 week for patients who meet the following 3 criteria: (1) infection with viridans streptococcal IE[a]; (2) medically stable condition without fever and with negative blood culture results, and stable electrocardiogram at time of proposed discharge; (3) no complications of IE and not in high-risk subgroup (see below).
Continuation phase (weeks 2–4 or 2–6)	Most patients who have not suffered complications of IE are likely to remain stable during the remainder of therapy, but side effects of parenteral antibiotic therapy may still occur.
	Preferred management: OPAT can be considered for the majority of patients who are medically stable (see above).
	Exceptions: IPAT should generally be continued for patients with any of the following characteristics: (1) complications of IE, such as congestive heart failure, conduction abnormality, mental status change, or evidence of perivalvular abscess on a transesophageal echocardiogram; (2) members of a high-risk subgroup: acute IE, aortic valve disease, prosthetic valve disease, or IE caused by *Staphylococcus aureus* or other virulent organisms.[b]
Essential elements of OPAT therapy	Patients should be educated and fully informed about the complications of IE and indications for and method of contacting their physician or IE care team.
	Patients and family should be reliable, compliant, and live close to the hospital.
	Routine postdischarge evaluation should include biweekly office or IE care team home visits during OPAT. Same-day evaluation by a member of the IE care team should be available for patients with recurrent fever or new symptoms.

[a] Expert consultation on individual patients may identify other low-virulence, low-risk organisms for which a similar approach may be taken.
[b] *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Neisseria gonorrhoeae,* beta streptococci, gram-negativebacteria, and fungi.

Mary-Margaret Andrews, and C. Fordham von Reyn Clin Infect Dis. 2001;33:203-209

Clinical Infectious Diseases

2015 ESC Guidelines for the management of infective endocarditis

(Habib et al. Eur Heart J 2015)

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	• Complications occur during this phase • Preferred inpatient treatment during this phase • Consider OPAT if: oral streptococci or *Streptococcus bovis*,[a] native valve,[b] patient stable, no complications
Continuation phase (beyond week 2)	• Consider OPAT if medically stable • Do not consider OPAT if: HF, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	• Educate patient and staff • Regular post-discharge evaluation (nurses 1/day, physician[c] in charge 1 or 2/week)[d] • Prefer physician-directed programme, not home-infusion model

Criteria that determine suitability of outpatient parenteral antibiotic therapy for infective endocarditis (Adapted from Andrews and von Reyn. CID 2001)

BMJ

BMJ 2013;346:f1585 doi: 10.1136/bmj.f1585 (Published 26 March 2013)

CLINICAL REVIEW

Outpatient parenteral antimicrobial therapy

Ann L N Chapman *consultant in infectious diseases*

ELSEVIER MASSON

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Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 44 (2014) 327–330

Short communication

Outpatient parenteral antimicrobial therapy for infective endocarditis: A cost-effective strategy

Traitement parentéral ambulatoire des endocardites infectieuses : une stratégie coût-efficace

A. Lacroix [a], M. Revest [a,d], S. Patrat-Delon [a], F. Lemaître [b,d], E. Donal [c], A. Lorléac'h [a], C. Arvieux [a], C. Michelet [a,d], P. Tattevin [a,*,d,e]

[a] *Service des maladies infectieuses et réanimation médicale, CHU Pontchaillou, 2, rue Le-Guilloux, 35033 Rennes cedex, France*
[b] *Département de pharmacologie clinique, CHU Pontchaillou, 35033 Rennes cedex, France*
[c] *Département de cardiologie et maladies vasculaires, CHU Pontchaillou, 35033 Rennes cedex, France*

OPAT saved 15,000 euros per patient

Speculation

Does a microbial agent exposed to an antibiotic die more if the antibiotic come into the body through

- a line in the vein compared to
- entering through the mouth?

Intravenous Followed by Oral Antimicrobial Therapy for Staphylococcal Endocarditis

RICHARD H. PARKER, M.D.; and BYRON E. FOSSIECK, Jr., M.D.; Washington, D.C.

Ann Intern Med 1980

N=33, Staph aur, cardiac murmurs,
16 days iv + 26 days oral; *all cured*

IV mainly nafcillin

Po mainly dicloxacillin or oxacillin

TREATMENT OF RIGHT-SIDED STAPHYLOCOCCUS AUREUS ENDOCARDITIS IN INTRAVENOUS DRUG USERS WITH CIPROFLOXACIN AND RIFAMPICIN

R.J. Dworkin [1], M.A. Sande, B.L. Lee, H.F. Chambers

Lancet 1989

Ciprofloxacin iv initially. N = 10, *all cured*

Oral Antibiotic Treatment of Right-sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy

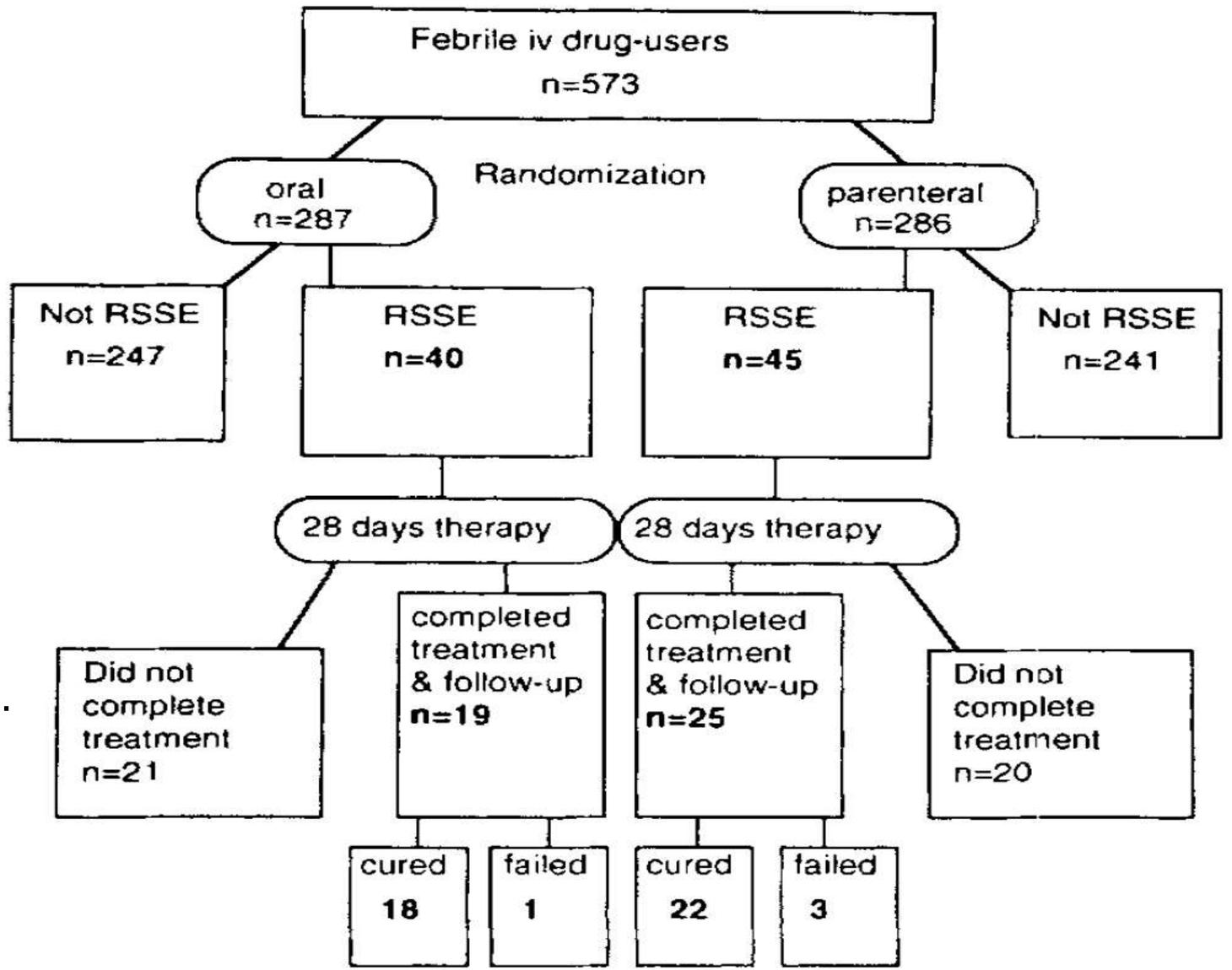
Alan W. Heldman, MD, Tina V. Hartert, MD, Stuart C. Ray, MD, Emile G. Daoud, MD, Thomas E. Kowalski, MD, Vincent J. Pompili, MD, Stephen D. Sisson, MD, William C. Tidmore, MD, Keith A. vom Eigen, MD, Steven N. Goodman, MD, PhD, Paul S. Lietman, MD, PhD, Brent G. Petty, MD, Charles Flexner, MD, *Baltimore, Maryland*

Am J Med 1996

RSSE:
Right-sided Staphylococcal endocarditis

Randomized to:
Po – ciprofloxacin and rifampicin,
IV oxacillin or vancomycin,
Both combined with gentamicin for 5 days.

4 weeks treatment.



Oral antibiotics for infectious endocarditis; Experience in our institution

Gender	Age	Microbial pathogen	Valve(s)/material involved	Peroral medication	Treatment duration (Parental/peroral)	Surgery	Outcome
Male	43	β-haemolytic streptocci group g	Prosthetic biological mitral valve	Fucidin and rimactan	13 days/28 days	No	Succes
Male	75	Staphylococcus epidermidis	Aortic and mitral valve	Linezolid and moxifloxacin	17 days/30 days	Yes prosthetic biological mitral and aortic valve	Succes
Male	62	Staphylococcus aureus	Mitral valve	Fucidin and linezolid	17 days/24 days	no	Succes
Male	56	Staphylococcus aureus	Prosthetic biological mitral valve	Fucidin and rimactan	29 days/15 days	no	Succes
Female	74	Streptococcus sangius	Mitral valve	Linezolid and moxifloxacin	15 days /17 days	no	Succes
Male	54	Staphyloccocus aureus	Aortic valve	Rimactan and linezolid	29 days/15 days	Yes prosthetic biological aortic valve	Succes
Male	78	Enterococcus faecalis	Prosthetic biological mitral valve	Linezolid	20 days/10 days	No	Succes
Male	67	Coagulase negative staphylococcus	Pacemaker electrode	Rimactan and linezolid	36 days/16 days	Yes, removal of infected electrode	Succes
Female	65	β-haemolytic streptocci group c	Aortic valve	Rimactan and linezolid	24 days/6 days	Yes, prosthetic biolocigal aortic valve	Succes
Female	44	Staphylococcus lugdunesis	Pacemaker electrode	Penicillin and linezolid	35 days/14 days	Yes, removal of infected electrode	Succes
Male	67	Salmonella	Aortic valve	Ciprofloxacin	42 days/21 days	Yes, prosthetic biolocigal aortic valve	Succes
Male	74	Coagulase-negative staphylococcus	Aortic and mitral valve	Penicillin	40 days/ 5 days	Yes, prosthetic biolocigal aortic and mitral valve	Succes

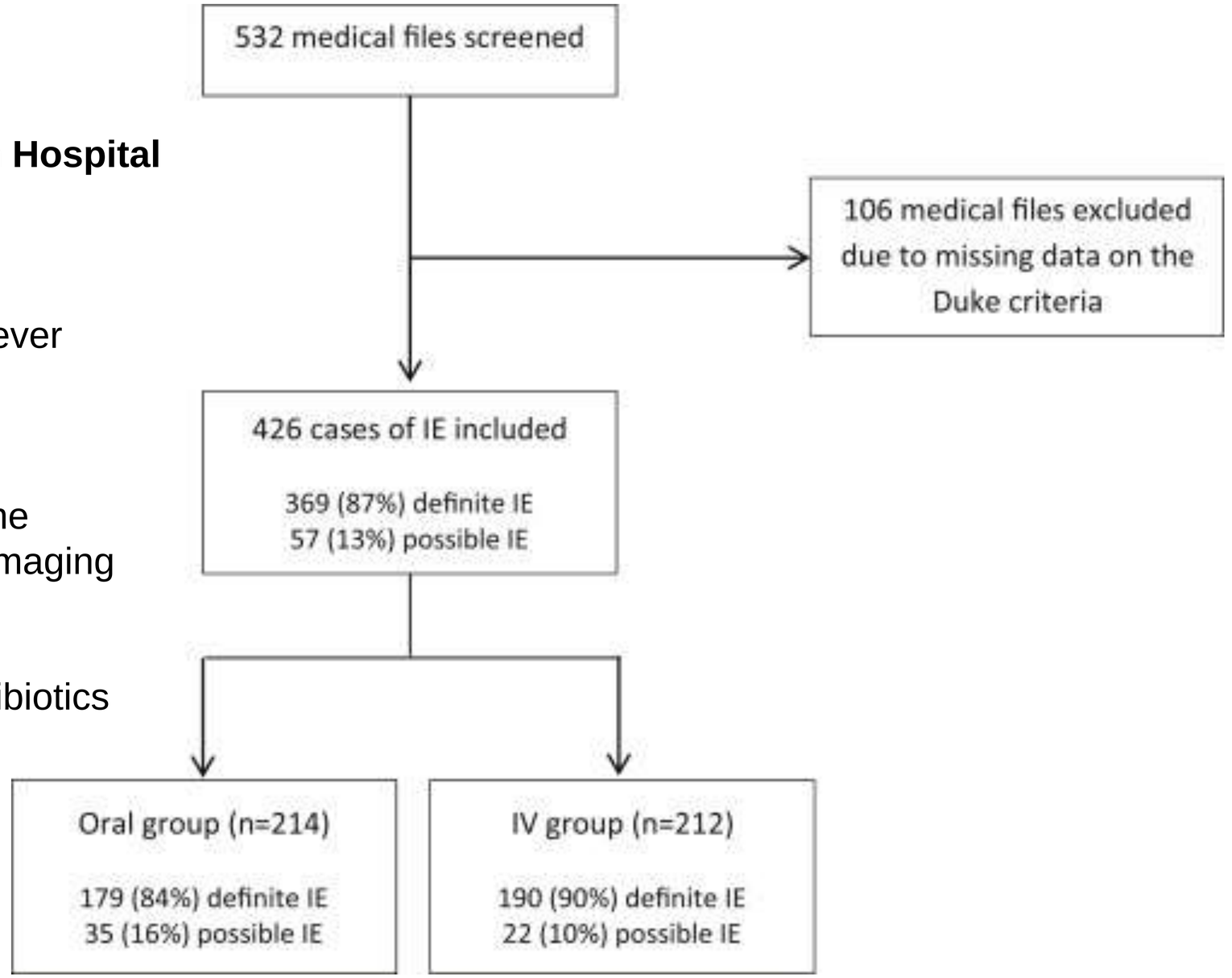
Iversen et al. Eur Heart J 2013.

Experience of switch to antibiotics in a patient cohort from 2000-13.

Georges-Pompidou European Hospital

Local protocols:
≥7 days iv
General conditionresolution of fever
Reduction CRP
Negative blood cultures
Normalization of leucocytosis
Normalization of serum creatinine
Disappearance or reduction of imaging abnormalities

If all fulfilled ->definitive oral antibiotics



Mzabi et al. *Clinical Microbiology and Infection* 2016 22, 607-612DOI: (10.1016/j.cmi.2016.04.003)

The oral regimens

Table 3
Oral antibiotic regimen according to microorganism identified

Microorganism	Antibiotic regimen
Streptococci ($n = 91$)	• Amoxicillin ($n = 84$; 92%) • Amoxicillin—clindamycin ($n = 4$; 4%) • Amoxicillin—rifampin ($n = 3$; 3%)
Staphylococci ($n = 54$)	• Clindamycin—(rifampin or fluoroquinolone) ($n = 15$; 28%) • Fluoroquinolone—rifampin ($n = 13$; 24%) • Amoxicillin—(rifampin or fluoroquinolone or clindamycin) ($n = 9$; 17%) • Fluoroquinolone ($n = 4$; 7%) • Amoxicillin ($n = 4$; 7%) • Clindamycin ($n = 4$; 7%) • Rifampin—(Bactrim or doxycycline) ($n = 2$; 4%) • Linezolid ($n = 2$; 4%) • Rifampin ($n = 1$; 2%)
Enterococci ($n = 23$)	• Amoxicillin ($n = 21$; 91%) • Amoxicillin—rifampin ($n = 2$; 9%)

Mzabi et al. *Clinical Microbiology and Infection* 2016 22, 607-612DOI: (10.1016/j.cmi.2016.04.003)

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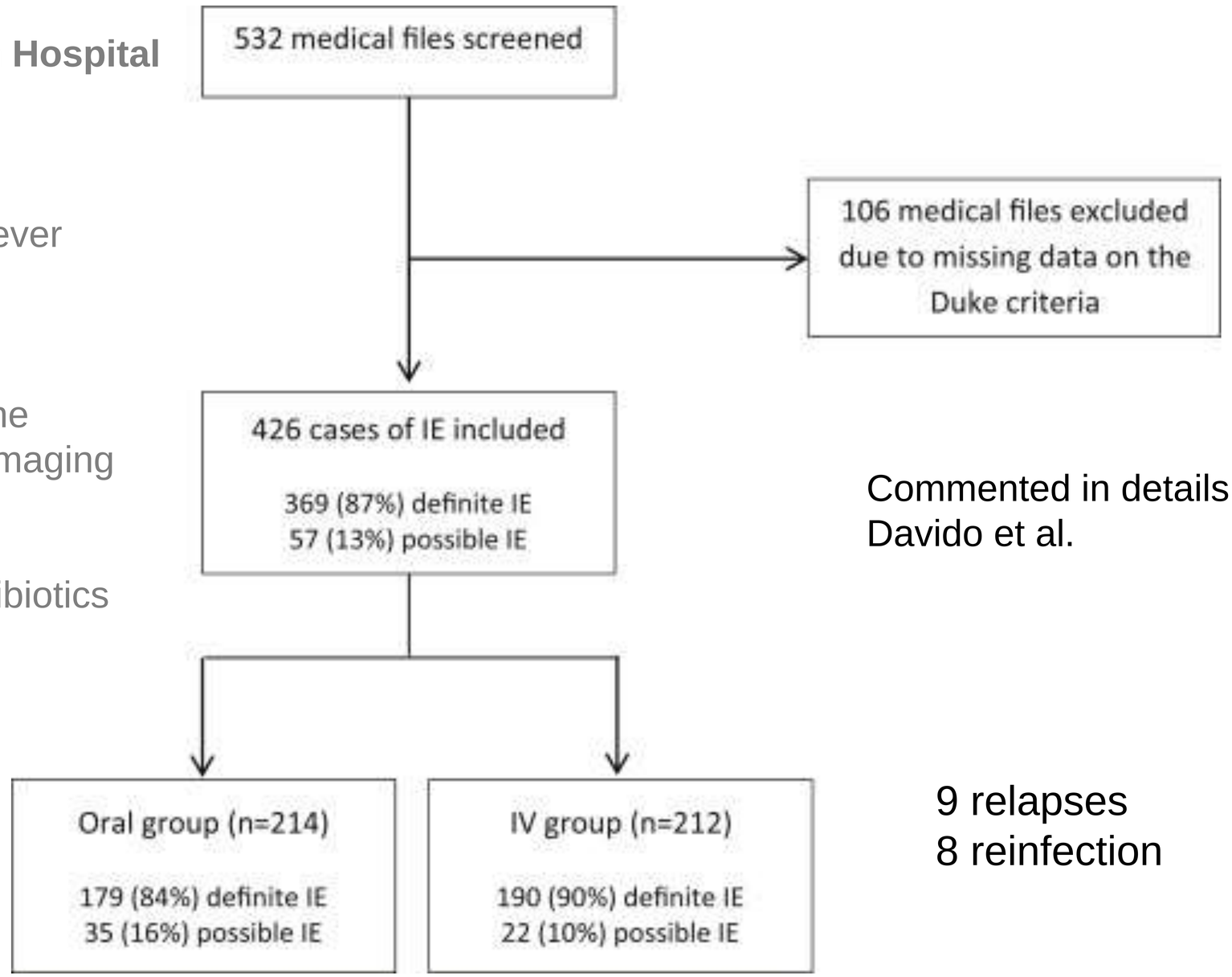


Commented in details in CMI 2017. Davido et al.

2 relapses
4 reinfections

9 relapses
8 reinfection

Fewer comorbidities and criteria of severity
Fewer with *S. aureus*

Mzabi et al. *Clinical Microbiology and Infection* 2016 22, 607-612DOI: (10.1016/j.cmi.2016.04.003)

Primary objective

To determine the safety and efficacy of ***partial*** oral antibiotic treatment of IE compared with traditional full-length parenteral antibiotic treatment

Design

- Un-blinded
- Prospective
- Randomised
- Multicenter, nationwide

Inclusion criteria 1

- Left-sided endocarditis based on the Duke criteria
- Infected with one of the following microorganisms (> ¾ of all left sided IE):
  - *Streptococcus spp*
  - *Enterococcus faecalis*
  - *Staphylococcus aureus*
  - Coagulase-negative staphylococci

Inclusion criteria II

- ≥ 10 days of appropriate parenteral antibiotic treatment overall, and at least 1 week of appropriate parenteral treatment after valve surgery
- T < 38.0 °C > 2 days
- C-reactive protein dropped to less than 25% of peak value or < 40 mg/L, and white blood cell count < 15 x 10^9/L during antibiotic treatment
- No sign of abscess formation revealed by trans-oesophageal echocardiography < 48 h before inclusion
- At least 10 days of antibiotic treatment had to remain at randomization

Exclusion criteria

- Body mass > 40
- Concomitant infection requiring iv antibiotics
- Suspected reduced GI absorption
- Inability to give informed consent
- Reduced compliance

Primary endpoint

- Combined endpoint within 6 months after antibiotic treatment was terminated
  - All-cause mortality
  - Unplanned cardiac surgery
  - Embolic events
  - Relapse of positive blood cultures with the primary pathogen

Secondary endpoints

- Quality of life after completion of antibiotic treatment
- Costs associated with management of endocarditis
- Shift of antibiotics during treatment
- Duration of antibiotic treatment
- Complications associated with intravenous catheters

Choice of antibiotics

Patients randomised to iv treatment:

- Treated according to guidelines from Danish Cardiac Society (DSC)

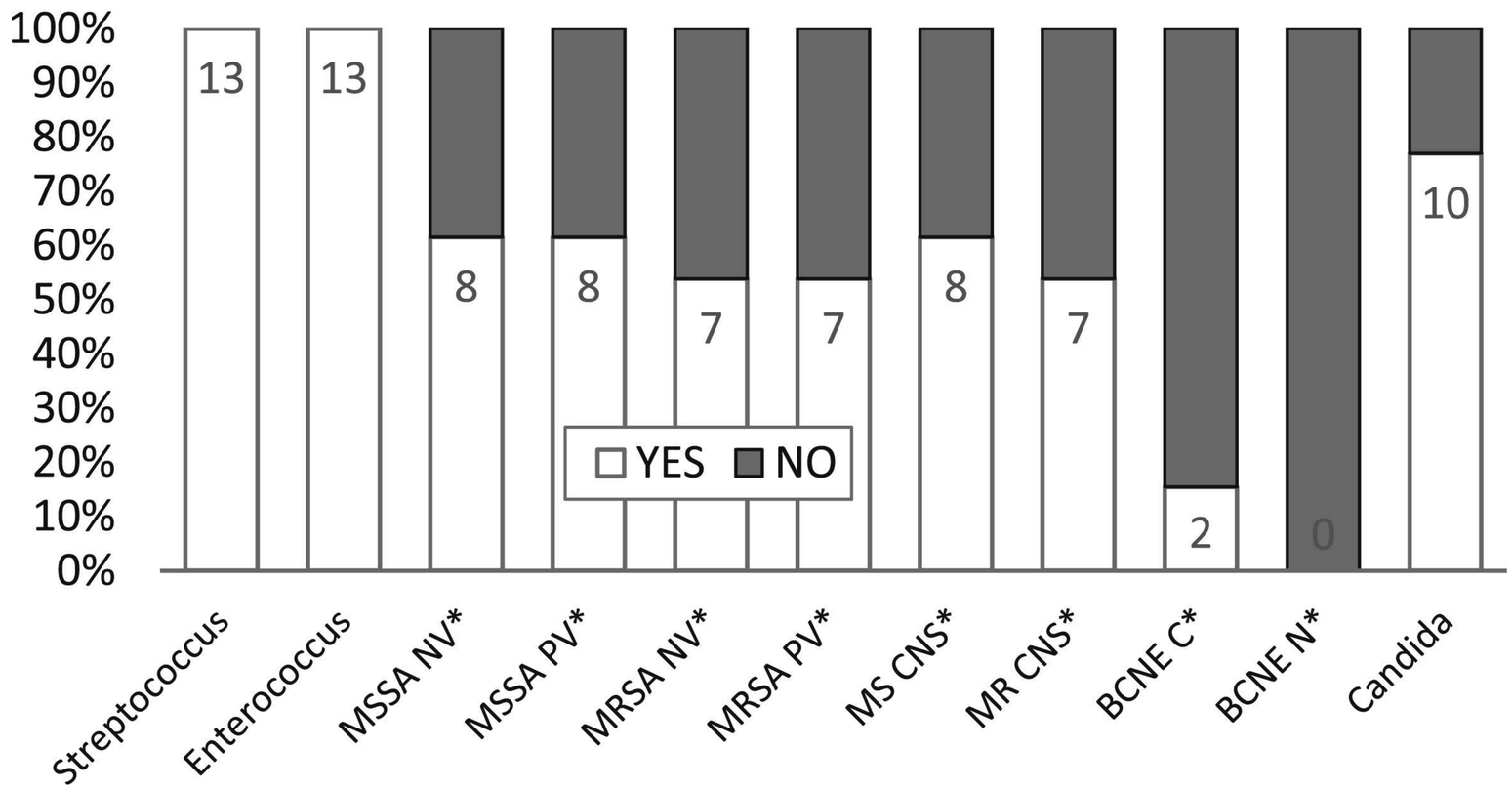
Patients randomised to oral treatment:

- Treated according to new study guidelines

International experts' practice in the antibiotic therapy of infective endocarditis is not following the guidelines

H. Tissot-Dupont, J.P. Casalta, F. Gouriet, S. Hubert, E. Salaun, G. Habib, M.P. Fernandez-Gerlinger, J.L. Mainardi, P. Tattevin, M. Revest, F. Lucht, E. Botelho-Nevers, A. Gagneux-Brunon, U. Snygg-Martin, K.L. Chan, J. Bishara, I. Vilacosta, C. Olmos, J.A. San Román, J. López, P. Tornos, N. Fernández-Hidalgo, E. Durante-Mangoni, R. Utili, M. Paul, L.M. Baddour, D.C. DeSimone, M.R. Sohail, J.M. Steckelberg, W.R. Wilson, D. Raoult

Clinical Microbiology and Infection
Volume 23, Issue 10, Pages 736-739 (October 2017)
DOI: 10.1016/j.cmi.2017.03.007



Antibiotics - Safety

- Minimal Inhibitory Concentration (MIC) determinations for relevant antibiotics (E-test)
- Pharmacokinetic profile in ***all*** patients
  - Day 1 (oral and i.v.)
  - Day 5 (oral – i.e. at steady state after shift from initial i.v. to oral)

Criteria for treatment in out-patients clinic

- No heart failure
- No significant arrhythmia or conduction defects
- No changes in cerebral status during admission
- No clinically identified embolic events during admission
- No other significant disabilities

Follow-up of out-patients

- Reports morning temp >38 ° C and other new symptoms to the ward
- Seen 2 (3) times a week
  - Clinically (+ ECG, BP, temp, SAT) (“ward round”)
  - Blood testings 3 times per week (CRP, WBC, haemoglobin, renal and hepatic parameters)

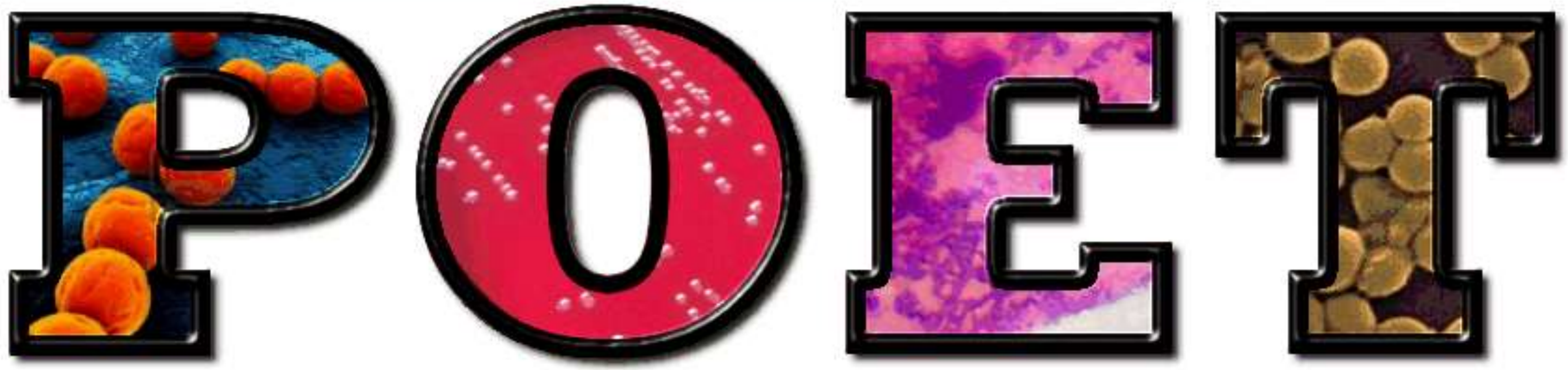
Follow-up after treatment

- 1 week (5-9 days)
- 1 month (25-35 days)
  Incl. transthoracic echocardiography
- 3 months (80-100 days)
- 6 months (170-190 days)
  Incl. transthoracic echocardiography

Statistics

- Estimated event rate 5-10%
  - All cause mortality 2-5%
  - Unplanned surgery 1-3%
  - Risk of embolic events 1-2%
  - Risk of relapse 1-3%
- Non inferiority margin 10%
- Power 90%
- One sided confidence interval 97.5%
- N=400 (1:1 inclusion)

Login



Case Report Form

Login på eCRF

Brugernavn:

Adgangskode:

Login

POET Sekretariatet
Att Kasper Iversen
Kardiologisk afd B, 2142
Rigshospitalet
Blegdamsvej 9
2100 København Ø

Telefon: 3545 9863 / 2871 2753
E-mail: poet@ecrf.dk

POET

01-001 100535-0227

Dataark

Deltageroversigt

Stamdata

Case Report Forms

Dokumenter

Indstillinger

Logout

- Indlæggelse
- Randomisering
- Ekkokardiografier
- Antibiotika
- Bivirkninger til antibiotika
- Ambulant behandling
- Udskrivelse
- Kontrolbesøg
- Farmakokinetik
- Events


POET

Study organization

- Steering committee:
  One representative per center
- Experts on antibiotics:
  One representative per region
- Safety monitoring board:
  - One cardiologist
  - One trialist
  - One specialist in infectious diseases

Oral antibiotics development - general

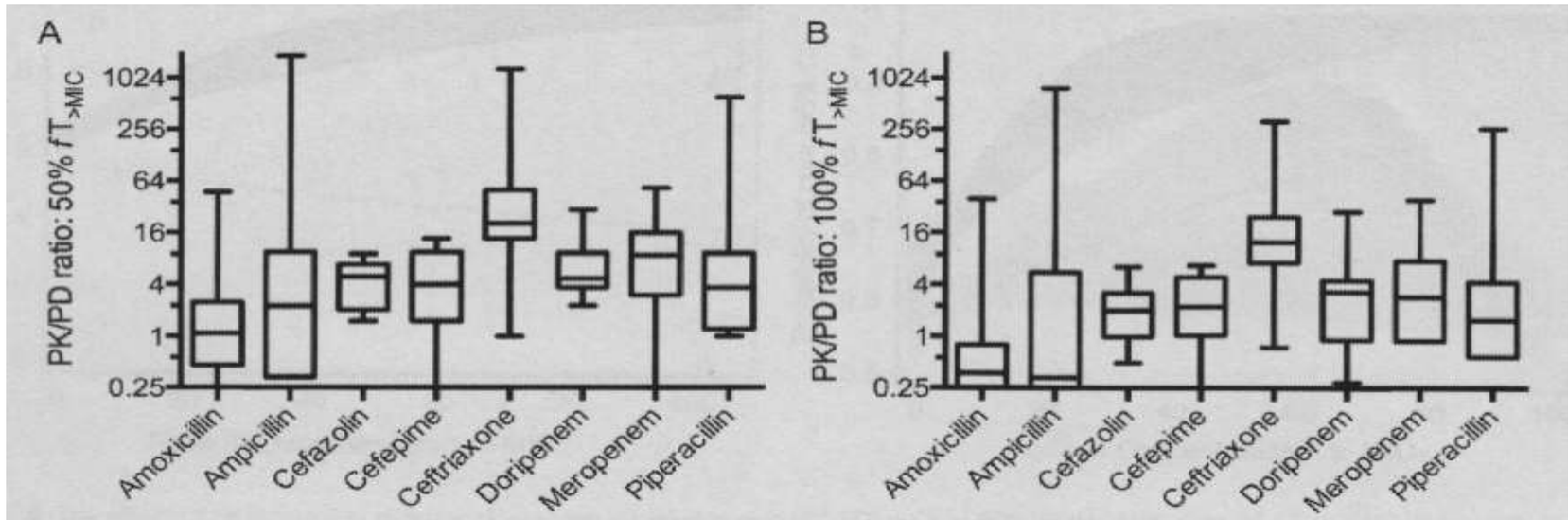
- Most pharmacokinetic data from “Antibiotics in Laboratory Medicine”. Ed Victor Lorian 5th. 2005. Otherwise relevant literature involved.
- Serum concentrations curves drawn
  - Lowest serum-concentration measured applied
  - Shortest $T_{1/2}$ applied
- In certain cases a theoretical serum concentration applied, based on a higher dosage.
- Single dosage kinetics.

Safety issues

- Treatment combinations (always 2 antibiotics) – purposes
  - Variations in pharmacokinetics (pharmacogenetic)
  - Reduce development of resistance
  - Potential additive/synergistic effects
  - Biofilm physiology
- Pharmacokinetic profile by HPLC on all patients (single and multiple dose kinetics) – reviewed by experts in clinical microbiology.

Pharmacokinetic variations are substantial.

(Roberts et al. CID 2014)



Antibiotic concentrationen relative to MIC in 361 critically ill patients after 50% and 100% of the dosing interval of eight different β-lactam antibiotics.

TABLE 1. Concentrations of antibiotics in sweat and blood of six healthy persons

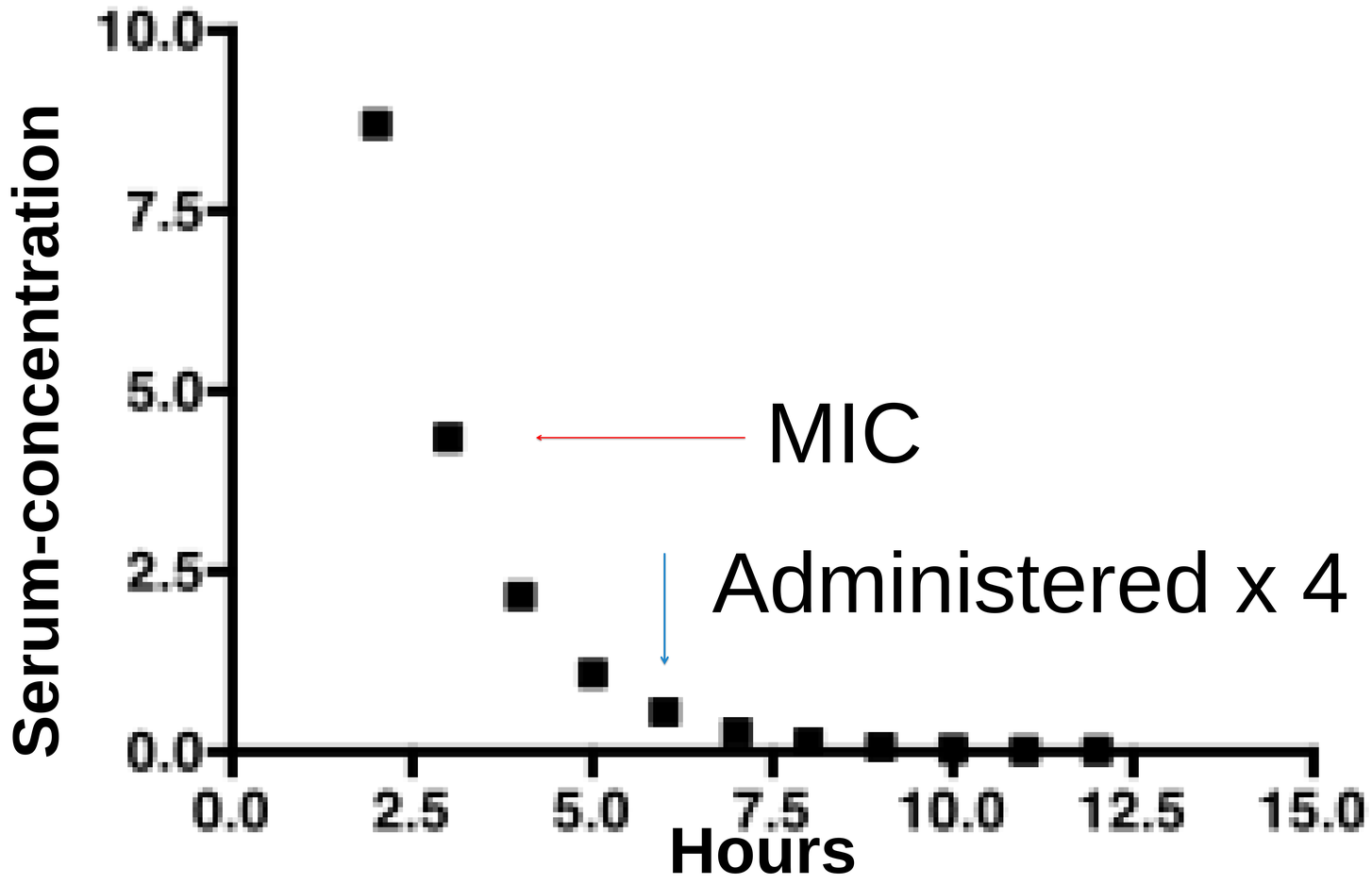
Drug	Dose (g)	C_{max} (μg/ml)/T (h) in[a]:			MIC_{90} (μg/ml) for[f]:	
		Blood	Axilla sweat	Forearm sweat	MSS	MRS
Benzylpenicillin	1.2	27/0.5 (9–44)	2.6, 2.1, 0.1[b]/0.5–2	1.5, 0.4[c]/0.5	0.03	0.03
Phenoxymethylpenicillin	1.2	8/1 (4.1–14)	0.4[d]/4	0	0.06	0.06
Cefuroxime	1.5	62/1 (40–113)	7.8[e]/0.5	3.1[e]/3	1–2	≥128
Ceftriaxone	2	372/1 (82–480)	8.9/0.5 (0.7–16.2)	2.5/0.5 (0.9–6.0)	4	≥128
Ceftazidime	2	360/1 (160–920)	28.4/0.5 (1.1–70)	11/2 (1.0–23)	4–8	≥128

[a] Mean peak concentration in serum or sweat (C_{max})/time after administration of drug. Ranges of C_{max} are given in parentheses.
[b] Three of six persons had measurable concentrations (all are listed) (lower limit of detection, 0.1 μg/ml).
[c] Two of six persons had measurable concentrations (both are listed) (lower limit of detection 0.1 μg/ml).
[d] One of six persons had a measurable concentration (shown) (lower limit of detection, 0.1 μg/ml).
[e] One of six persons had a measurable concentration (shown) (lower limit of detection, 0.4 μg/ml).
[f] MSS and MRS, methicillin-susceptible and methicillin-resistant staphylococci, respectively (data from reference 12).

Høiby N, et al. AAC 2000.

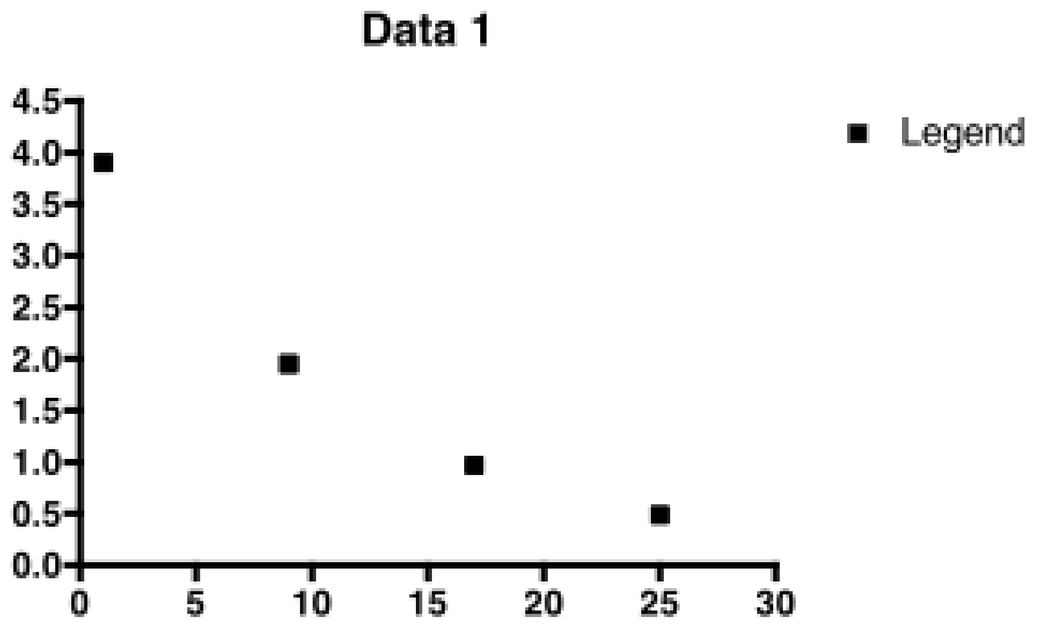
Amoxicillin

Concentration curve



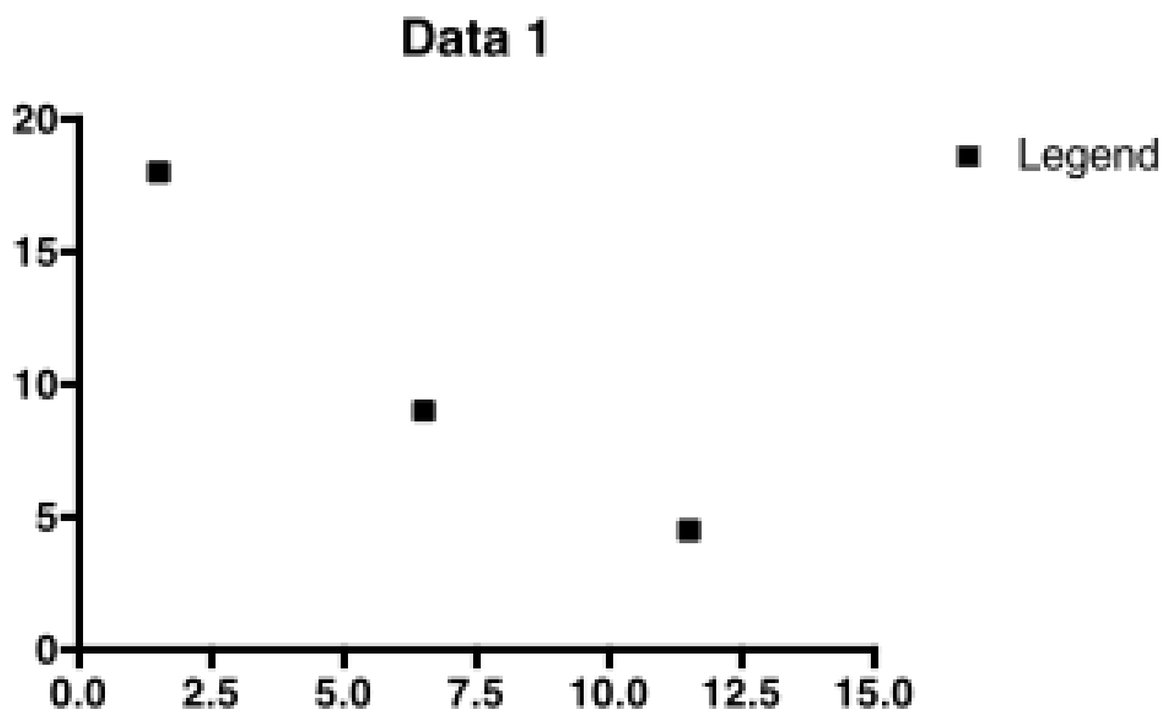
1 g oral. Serum-conc after 2 h (single dose). $T_{1/2}$ 1 h.
MIC set at 4 mg/L for enterococci.
MIC set at 0.125 mg/L for other bacteria.

Moxifloxacin



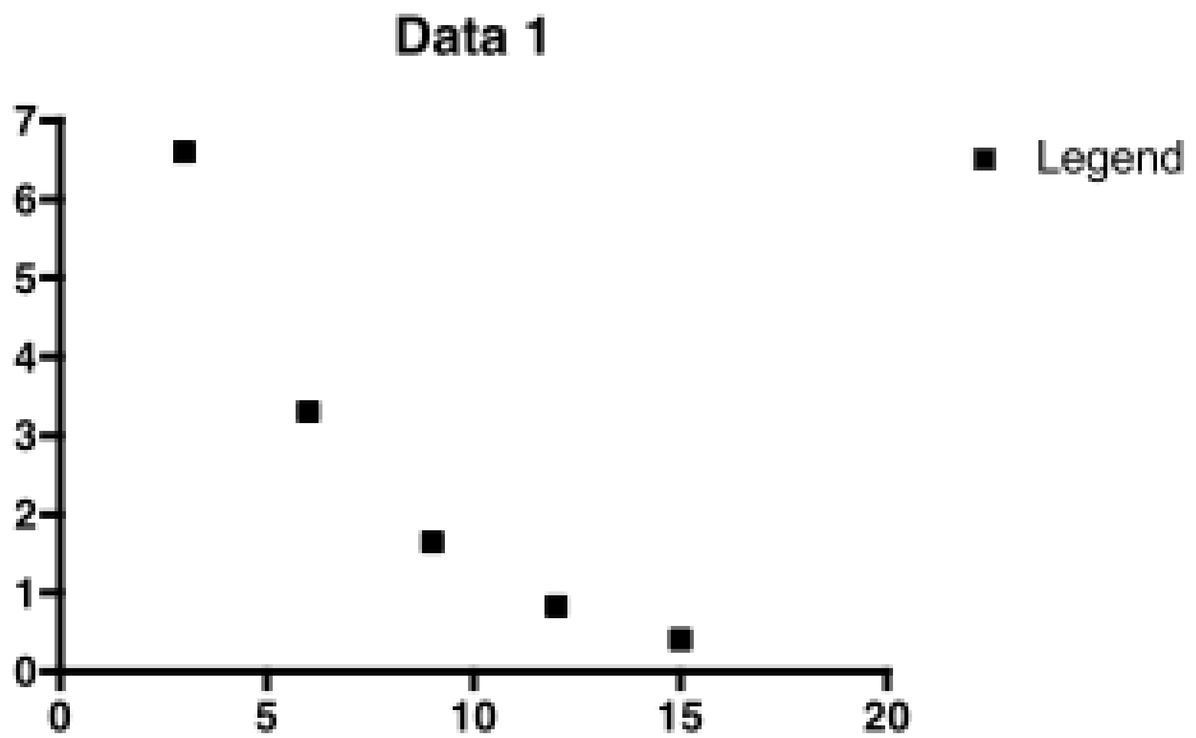
0.4g po. Serum-conc after 1,4h (multiple doses). $T_{1/2}$ 8h.
MIC 0.5 mg/L.
Administered once/24h.

Linezolid



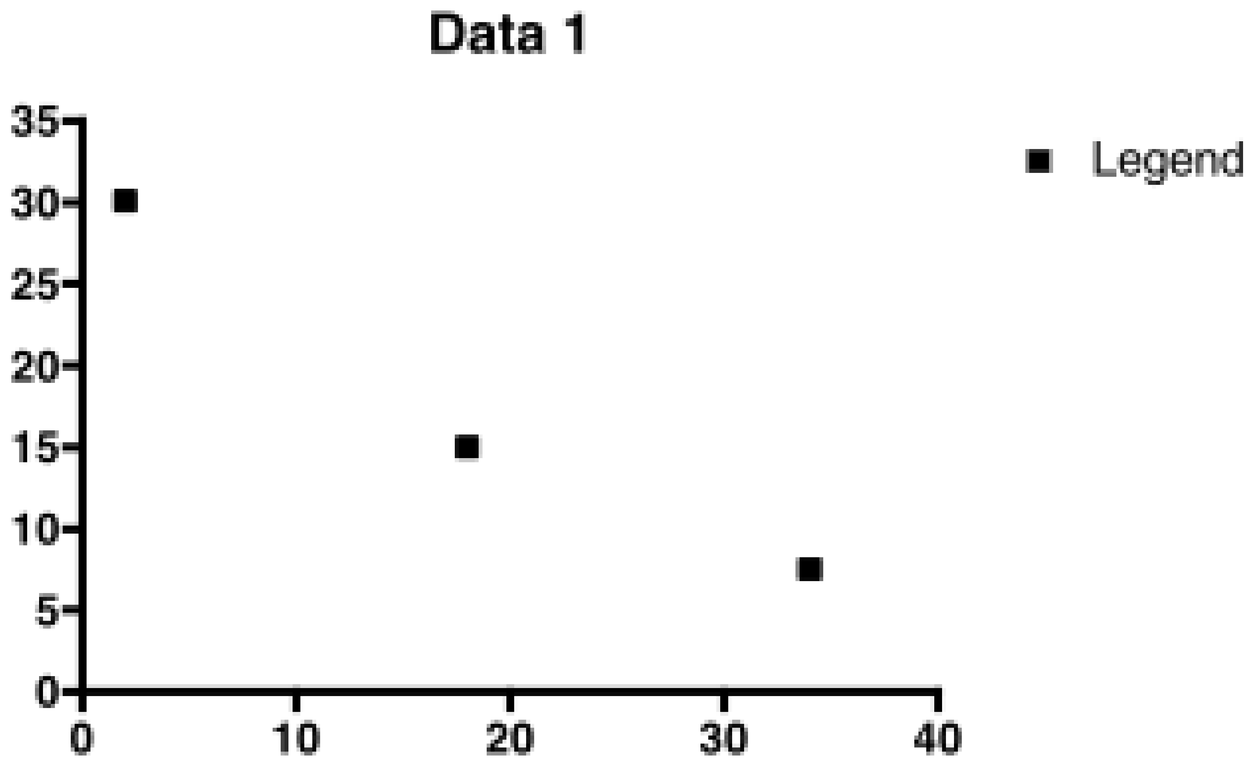
0.6g po. Serum-conc after 1-2h (multiple doses). $T_{1/2}$ 5h.
MIC 4 mg/L.
Administered as 0.6 g/12h.

Rifampicin



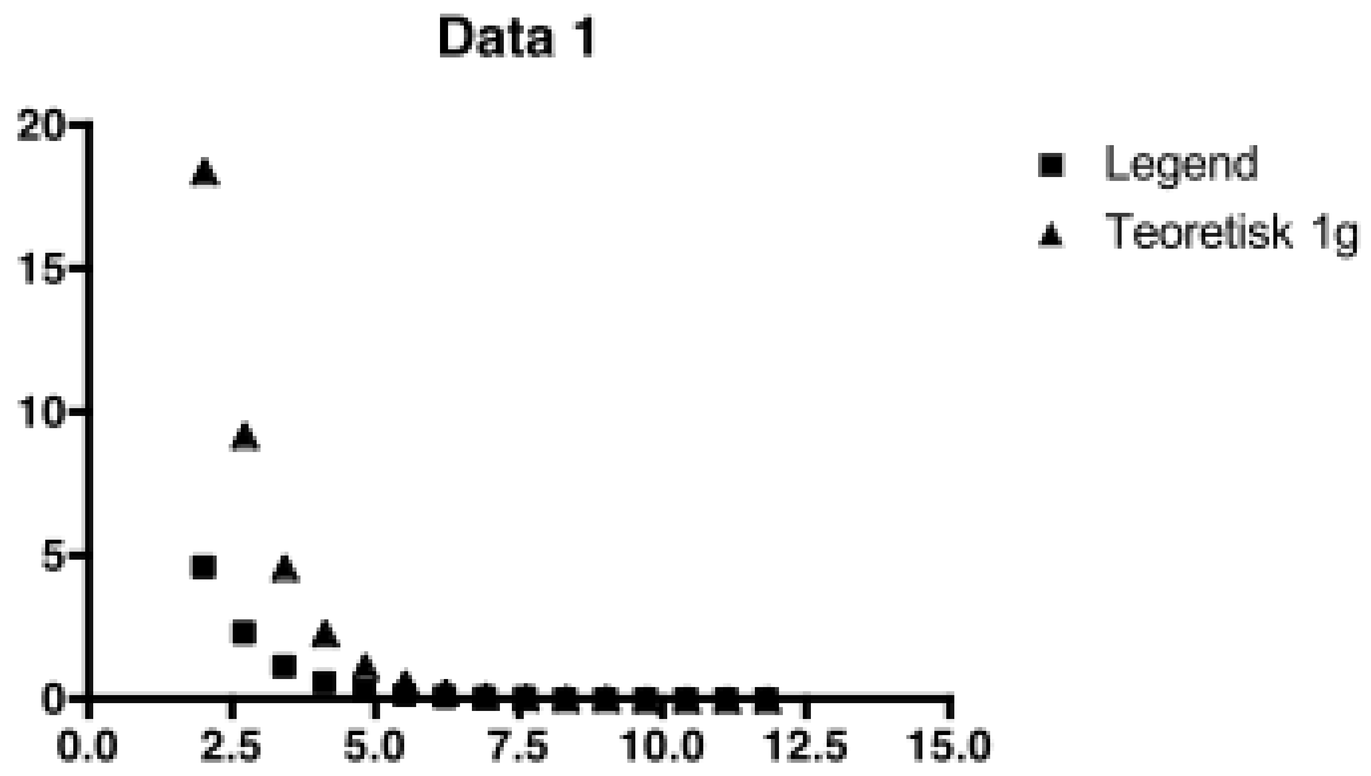
0.6g po. Serum-conc after 3h (multiple doses). $T_{1/2}$ 3h.
MIC 0,064 mg/L.
Administered as 0.6g/12h.

Fucidic acid



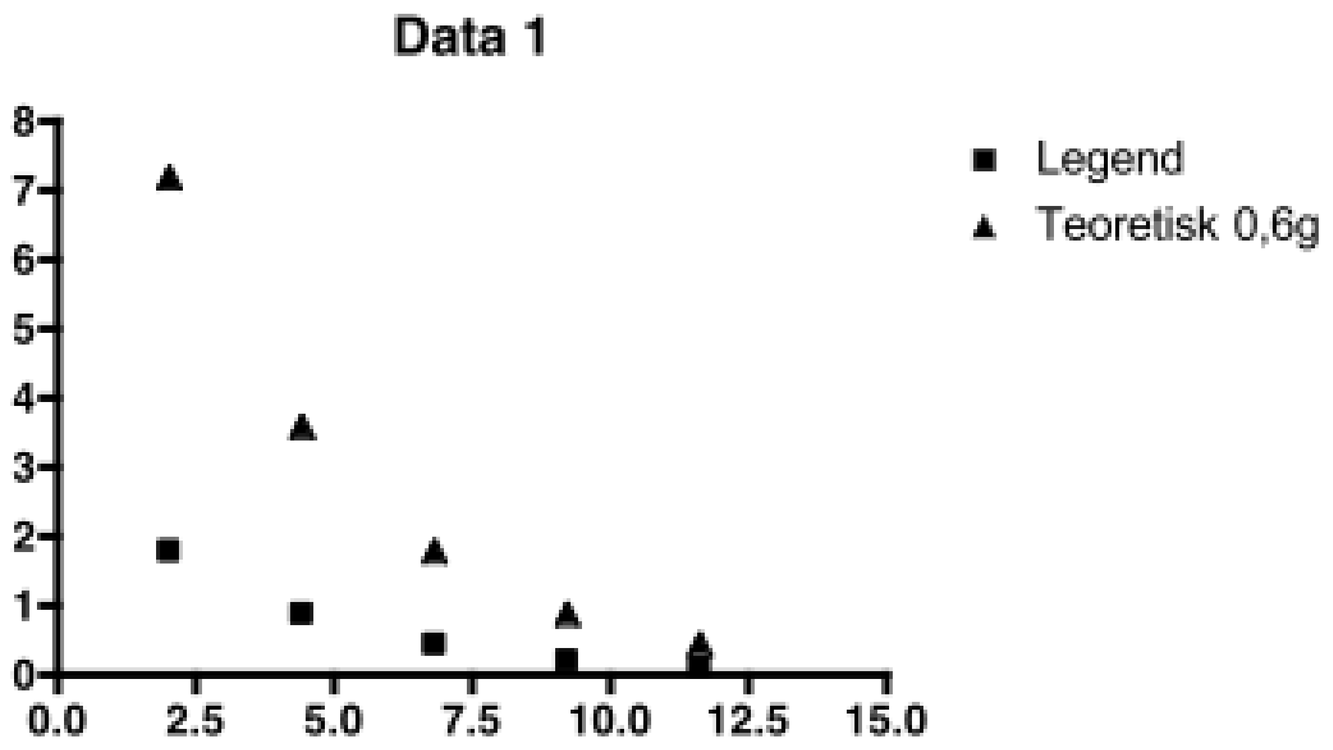
0.5g po. Serum-conc after 2.1h (single dose). $T_{1/2}$ 16h.
At multiple doses the serum-conc is stable above 100mg/L.
MIC 2 mg/L.
Administered as 0.5g/8h.

Dicloxacillin



0.25g po. Serum-conc after 2h (single dose). $T_{1/2}$ 0.7h.
Theoretical 1g dose inserted in the figure.
MIC 1.5 mg/L.
Administered as 1g/6h.

Clindamycin



0.15g po. Serum-conc after 2h (single dose). $T_{1/2}$ 2.4h.
Theoretical 0.6g dose inserted in the figure.
MIC 0.25 mg/L.
Administered as 0.6g/8h.

Regimens *Staphylococcus aureus* and CoNS.

Penicillin sensitive

1) Amoxicillin 1 g x 4 and fucidic acid 0.75 g x 2/rifampicin 0.6 g x 2

2) Linezolid 0.6 g x 2 and fucidic acid 0.75 g x 2/rifampicin 0.6 g x 2

Methicillin sensitive (Penicillin resistant)

1) Dicloxacillin 1 g x 4 and fucidic ac. 0.75 g x 2/rifampicin 0.6 g x 2

2) Linezolid 0.6 g x 2 and fucidic ac. 0.75 g x 2/rifampicin 0.6 g x 2

Methicillin resistant

1) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2/rifampicin 0.6 g x 2

2) Alternative regiments depending on patterns of resistance

Regimen

Enterococcus faecalis

1) Amoxicillin 1 g x 4 and (rifampicin 0.6 g x 2)/moxifloxacin 0.4 g x 1

2) Linezolid 0.6 g x 2 and (rifampicin 0.6 g x 2)/moxifloxacin 0.4 g x 1

Regimens

Non-hemolytic streptococci, hemolytic streptococci and *Streptococcus pneumoniae*

Amoxicillin sensitive

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2/moxifloxacin 0.4 g x 1

2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2/moxifloxacin 0.4 g x 1

Amoxicillin resistant

1) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

2) Moxifloxacin 0.4 g x 1 and rifampicin 0,6 g x 2/clindamycin 0.6 g x 3

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Partial oral treatment of endocarditis

(Am Heart J 2013;165:116-22.)

Financing

The Danish Heart Foundation,

The Capitals Research Foundation

Au revoir on June 26th in Russia.

General concept of inclusion

- The patient is clinically stable
- The infection is well-controlled
- The valve lesion(s) are stable
- Only certain bacterias

European Heart Journal (2009) **30**, 2369–2413
doi:10.1093/eurheartj/ehp285

Guidelines on the prevention, diagnosis, and treatment of infective endocarditis

Table 18 Criteria which determine suitability of outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications occur during this phase. Preferred inpatient treatment during this phase. Consider OPAT: if oral streptococci, patient stable, no complications.
Continuation phase (beyond week 2)	Consider OPAT: if medically stable. Do not consider OPAT: if heart failure, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	Educate patient and staff. Regular post discharge evaluation (nurses 1/day, physician in charge 1–2/week). Prefer physician-directed program, not home-infusion model.

Adapted from Andrews and von Reyn.[159]

Reasons for in-hospital treatment in infectious endocarditis 1

- To treat optimally to reduce the high mortality rate – 9-40%
  - Cardiac complications
    - Worsening valve lesions
    - Abscess formation
    - Heart failure
    - Conduction defects (AV-block) and arrhythmia
    - Pericarditis – myocarditis
  - Assessing need for - and timing of surgery

Reasons for in-hospital treatment in infectious endocarditis 2

- To treat other (associated) infections
- To treat co-morbidities; dialysis, strokes, COPD, DM
- To reduce and treat complications
  - Treatment failure
  - Emboli – neurological complications
  - Acute renal failure
  - Splenic abscess
  - Drug fever and other treatment related complications