Infective endocarditis
the Necker-enfants malades Paris experience

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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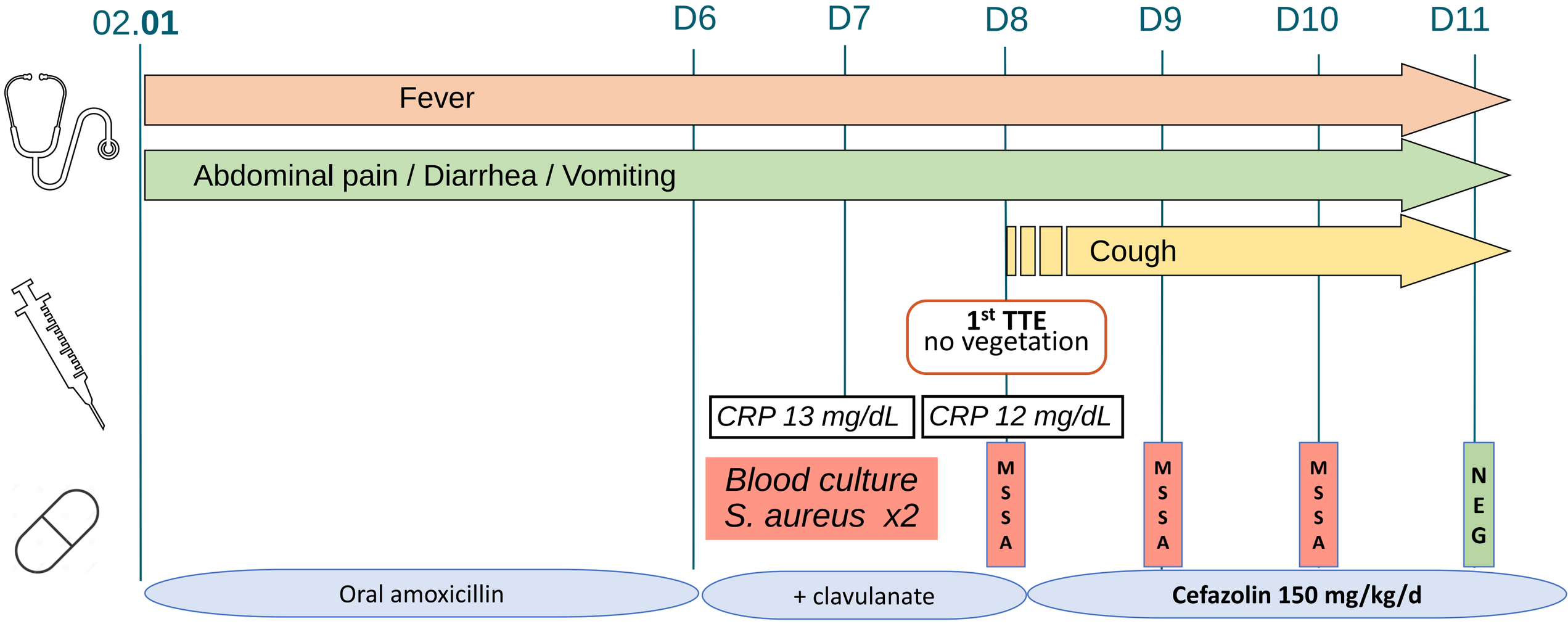
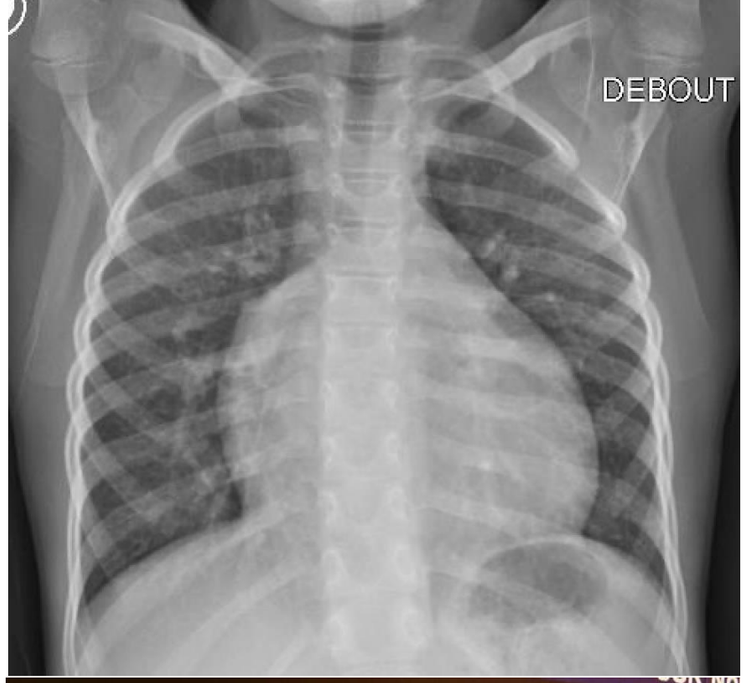
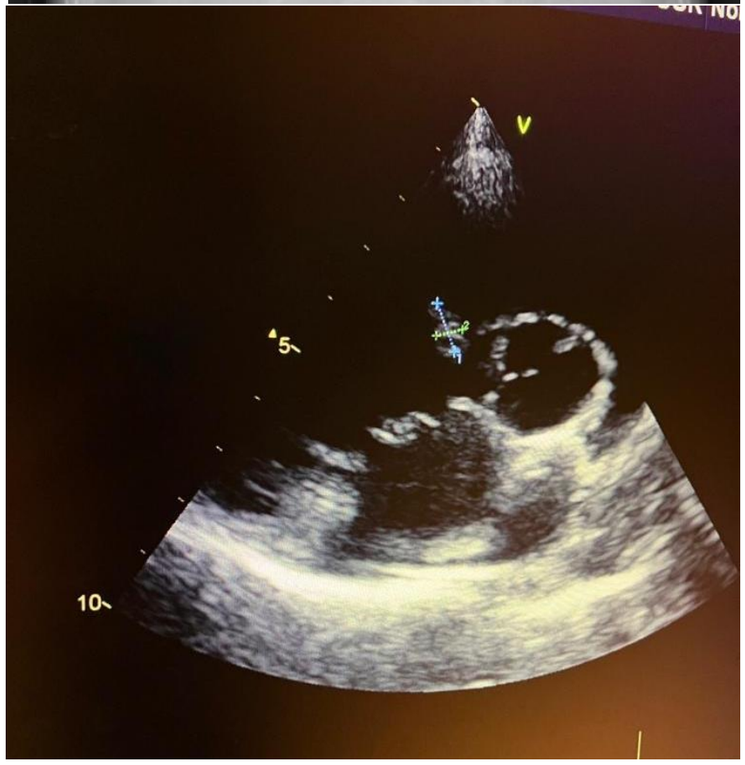
6-year-old female

Perimembranous ventricular septal defect — No surgery

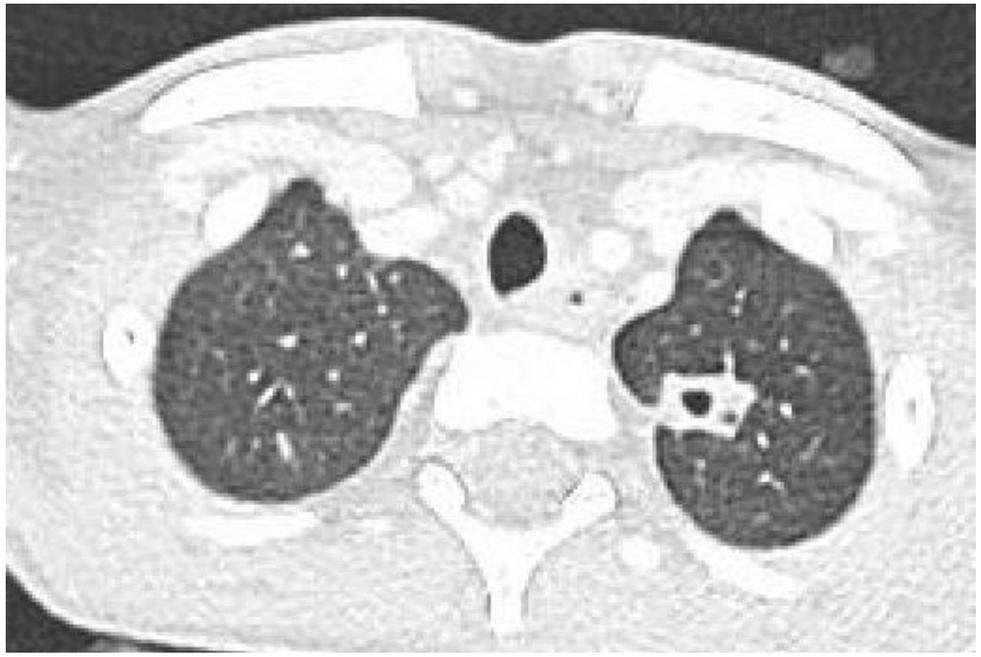
No travel abroad, lives in France

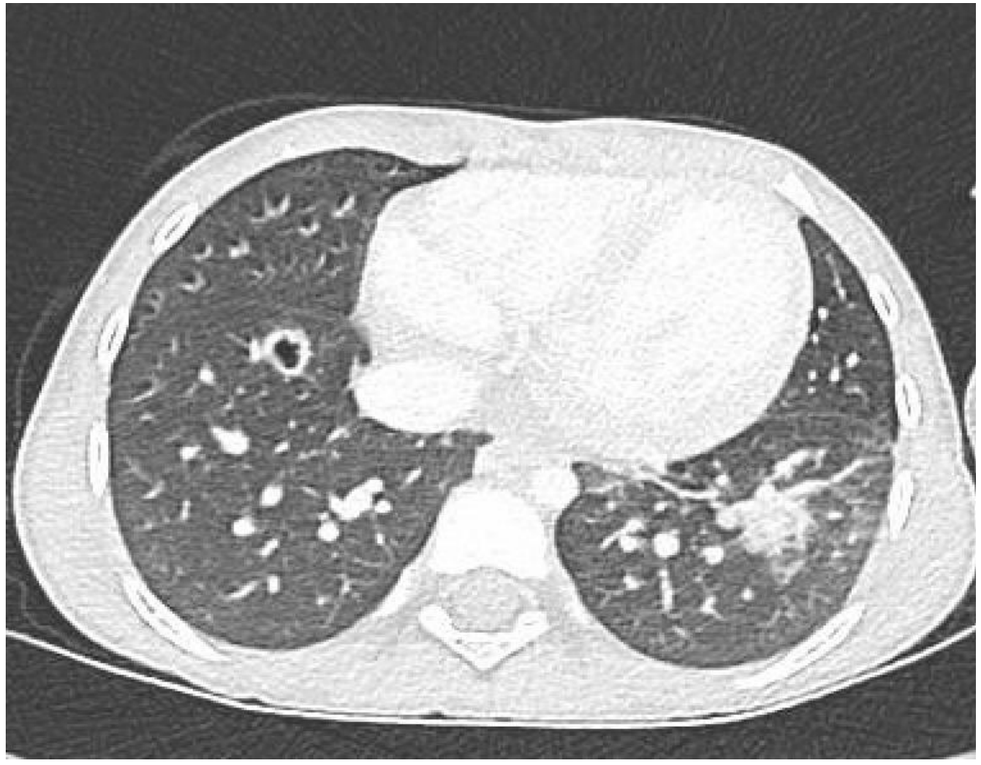






Right side
endocarditis 7 mm
tricuspid vegetation





Pre-opTOE

- **Good ventricular function, ventricular septal defect with left-right shunt**
- **Mobile vegetation (5x4 mm) on septal defect, tricuspid valve**

D17

Surgery

- **Vegetation removal - tricuspid deterioration**
- **Closing of the septal defect with a pericardic patch**

Evolution

- Clinical and biological improvement since 02.12
- Vegetation culture: *S. aureus*

D24

Oral Treatment ?

Pre-opTOE

- **Good ventricular function, ventricular septal defect with left-right shunt**
- **Mobile vegetation (5x4 mm) on septal defect and tricuspid valve**

D17

Surgery

- **Vegetation removal - tricuspid deterioration**
- **Closing of the septal defect with a pericardic patch**

Evolution

- Clinical and biological improvement since 02.12
- Vegetation culture: *S. aureus*

D24

Oral Treatment

Lefofloxacin + rifampicin

- After 14 days of IV cefazolin therapy, D7 of surgery
- Good outcome (no fever, decrease of inflammation)
- Difficulties to maintain a peripheral venous catheter
- Good predicted adherence to treatment

Iversen K. et coll. N Engl J Med 2019;380:415-24.

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

In subjects with clinically stabilized left heart IE, is oral switch as effective as continued IV therapy?

Method

- Multicentric randomized **non-inferiority trial** in Denmark
- Adults ≥ 18, left sided endocarditis, good response IV, *Streptococcus* sp, *Enterococcus faecalis*, *S. aureus* or CNS.
- *400 patients (201 oral group vs 199 IV group), randomization 1:1.*

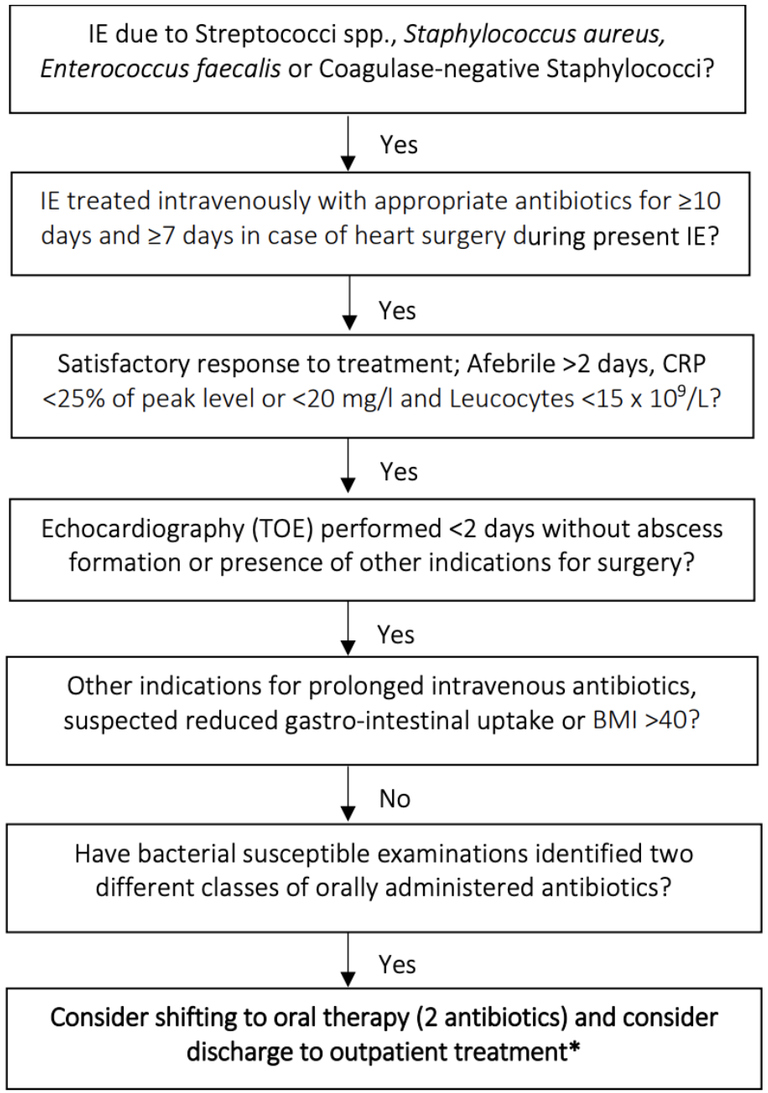
Exclusion

BMI>40	Other IV Antibiotics indication
Suspected reduced GI uptake	Suspected poor adherence

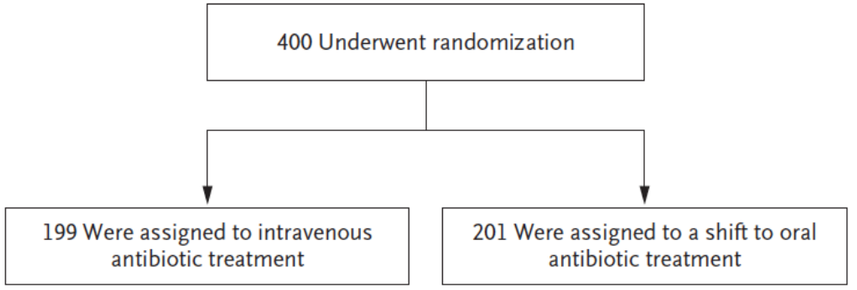
Composite primary endpoint

All-cause mortality	Clinically evident embolic events
Unplanned cardiac surgery	Relapse bacteremia

Up to 6 months after completion of antibiotic treatment



Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis



Median length of IV treatment :
17 days [IQR 12-24]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intravenous Treatment (N=199)	Oral Treatment (N=201)
Mean age — yr	67.3±12.0	67.6±12.6
Female sex — no. (%)	50 (25.1)	42 (20.9)
Body temperature — °C	36.9±0.45	37.0±0.44
Coexisting condition or risk factor — no. (%)		
Diabetes	36 (18.1)	31 (15.4)
Renal failure	25 (12.6)	21 (10.4)
Dialysis	13 (6.5)	15 (7.5)
COPD	17 (8.5)	9 (4.5)
Liver disease	7 (3.5)	6 (3.0)
Cancer	14 (7.0)	18 (9.0)
Intravenous drug use	3 (1.5)	2 (1.0)
Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Staphylococcus aureus‡	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci	10 (5.0)	13 (6.5)
Laboratory results at randomization		
Hemoglobin — mmol/liter	6.3±1.1	6.5±1.0
Leukocytes — $\times 10^{-9}$/liter	7.6±3.6	7.2±2.6
C-reactive protein — mg/liter	24.3±18.4	19.9±16.7
Creatinine — μmol/liter	124±112	141±164
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

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)
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)

Composite primary endpoint

IV Treatment (n=199)	Oral Treatment (n=201)
24 (12,1 %)	18 (9%)
Difference 3,1 (-3,4-9,6)	
Hazard Ratio (95% CI) 0,72 (0,37-1,36)	

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.

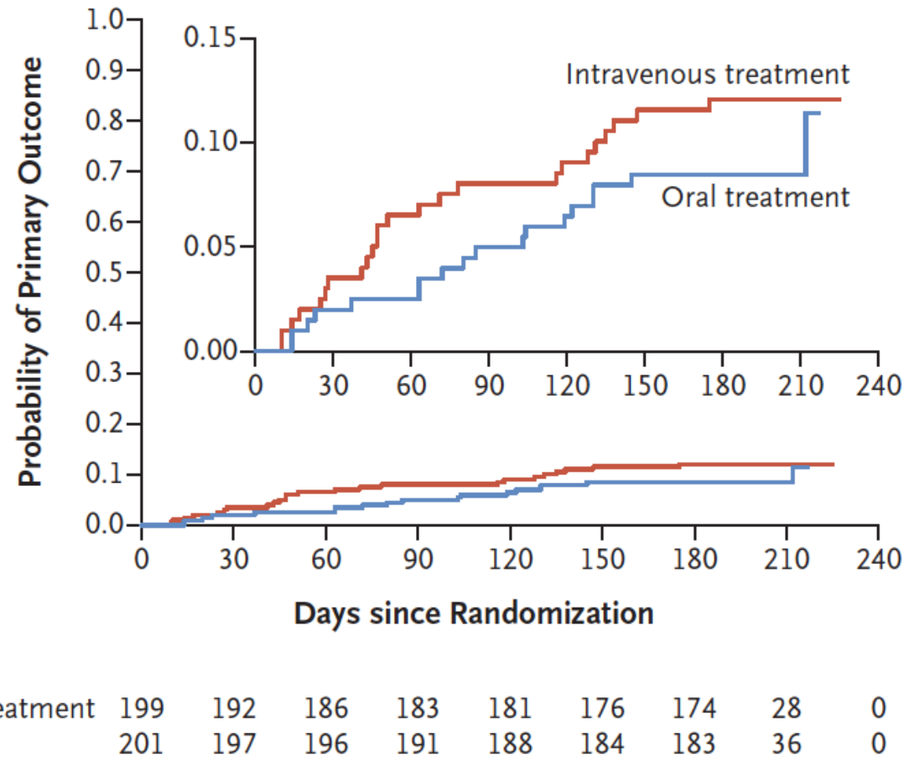


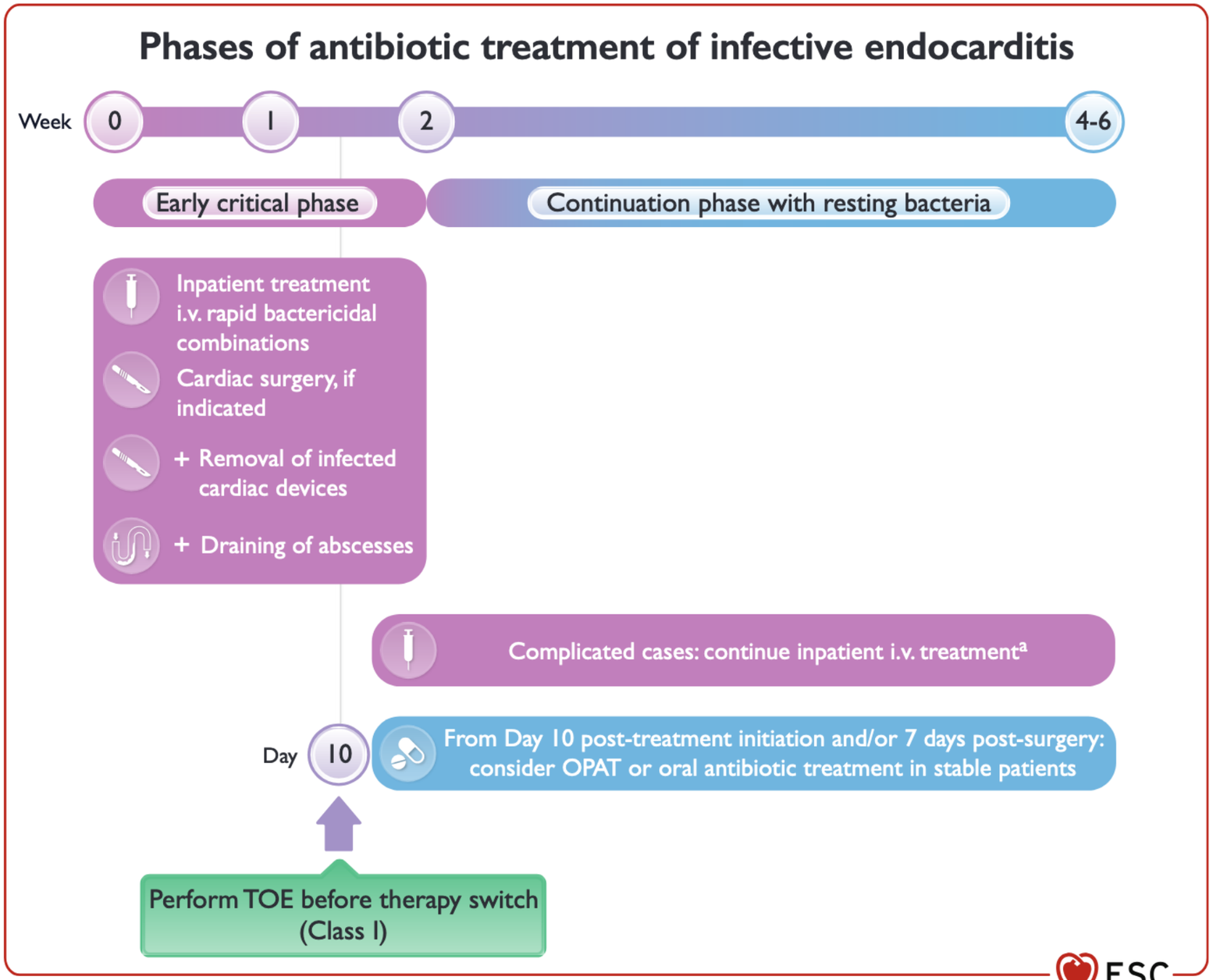
Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment. The inset shows the same data on an enlarged y axis.

ESC 2023

- ✓ *Critical phase*: **at least 10 days of i.v.** treatment is required (OPAT restricted indication)
- ✓ *Continuation phase* : **beyond 10 days of therapy and 7 days post-surgery:** OPAT/step-down oral therapy may be feasible (left sided)

Contraindications:
- Heart failure
- Severe valvular regurgitation, vegetations >10 mm, progression, or local complications
- Neurological involvement
- Renal impairment
- Malabsorption
- PWID



ESC 2023… Abx adapted to children?

Table S9 **Combinations of antibiotics for oral step-down treatment**

Penicillin-and methicillin-susceptible *S. aureus* & CoNS	Methicillin-susceptible *S. aureus* & CoNS	Methicillin-resistant CoNS	*E. faecalis*	Penicillin-susceptible streptococci	Penicillin-resistant streptococci
Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Dicloxacillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2
Amoxicillin 1 g × 4 Fusidic acid 750 mg × 2	Dicloxacillin 1 g × 4 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2
Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2		Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1
Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2		Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	Linezolid 600 mg × 2 Rifampin 600 mg × 2	
Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2		Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	

Always in combination
Attention should be paid to the recommended dosage

Necker Hospital Cohort Study

- **Oral switch : why such a crucial question in children?**
  - **PRO:** difficult to get an IV access; tolerance for IV ttt; accidental removal…
  - **CONS:** Few PK/PD studies, no clinical trials, poor adherence to PO ttt, reliability of parents (long treatment!), limited "pediatric-specific" medications

Need for pediatric studies

ELSEVIER

The Lancet Infectious Diseases
Volume 16, Issue 8, August 2016, Pages e139-e152

Review

Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines

Brendan J McMullan BMed [a b], David Andresen MMedSci [c d], Christopher C Blyth MBBS [e f g j], Minyon L Avent PharmD [h], Asha C Bowen PhD [e f i j], Philip N Britton MBBS [k m], Julia E Clark BMBS [n u], Celia M Cooper BMBS [o], Prof Nigel Curtis PhD [p q r], Emma Goeman MBBS [a], Briony Hazelton MBBS [d e], Gabrielle M Haeusler MBBS [s t], Ameneh Khatami MD [k], James P Newcombe MBBS [a], Joshua Osowicki MBBS [p q], Pamela Palasanthiran MD [a b], Mike Starr MBBS [p r], Tony Lai BPharm [l], Clare Nourse MD [n u], Joshua R Francis MBBS [v]…
Dr Penelope A Bryant PhD [p q r]

Protocol

- ✓ **Retrospective, observational, single-center study using routine care data**
- ✓ **In Necker – Enfants malades : Reference centre for paediatric cardiology**
  - National network for complex congenital heart defects, Inherited & Rare Cardiac Diseases Center
  - Medical-surgical ward: **36 beds and** ICU: **26 beds**

- ✓ **Objectives:** To describe the characteristics of patients with IE who either did or did not receive an oral antibiotic switch,

  with a focus on treatment failures.

  Treatment failure: Any of the following events within 3 months after therapy:
  - Death (all cause) at 1 and 3 months
  - Microbiological relapse
  - Unplanned cardiac surgery
  - New embolic events
  - Treatment modification due to insufficient clinical response

Preliminary results - Epidemiology

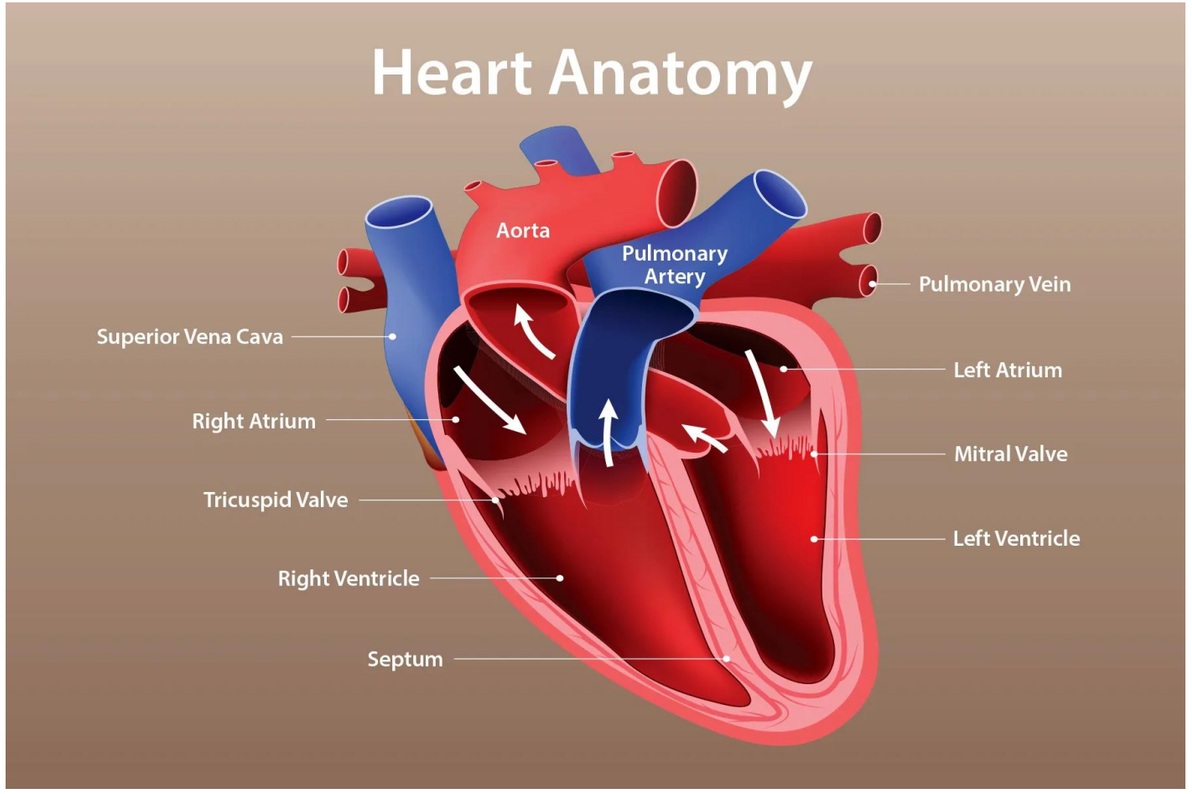
54 cases identified

- Median age: 9 years (IQR 3-14)
- Male predominance: 61%
- Congenital heart disease: 66%
- Previous cardiac surgery: 50%

- Immunocompromised: 9.3%
- Community infection : 81.2%

- Tricuspid valve : 19
- Pulmonary valve : 5
- RDPA Tube : 9
- Mitral valve: 15
- Aortique valve : 6

33 (61%) right heart



Preliminary results - Microbiology

Staphylococci

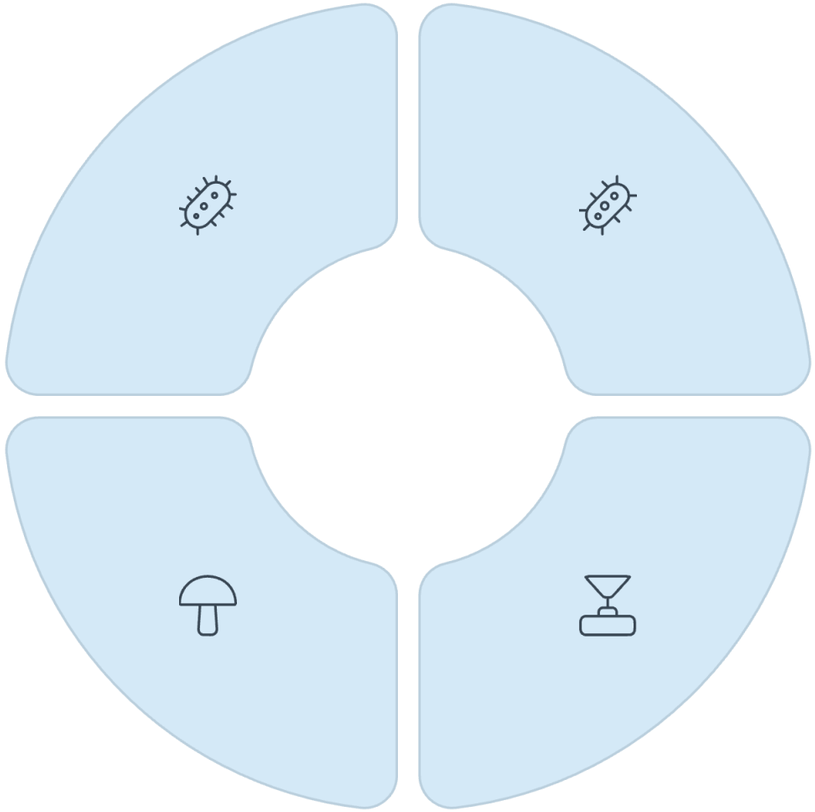
45.4% of cases

- *S. aureus : 33.1%*
- CoNS: 12.3

Other/Culture-negative

16.7% of cases

- Fungal: 3.7%
- Culture-negative: 12.9%



Streptococci

25% of cases

- Viridans group: 14.8%
- Pneumococcal : 5.5%
- Deficient : 3.7%

Gram-negatives

12.9% of cases

- HACEK: 11%
- Enterobacteriaceae: 1.9%

Preliminary results – clinical presentation

87.4%

Fever

Most common presenting symptom, but often low-grade in our cohort

64.3%

Heart Murmur

New or changing murmur, particularly in patients with pre-existing cardiac conditions

43.1%

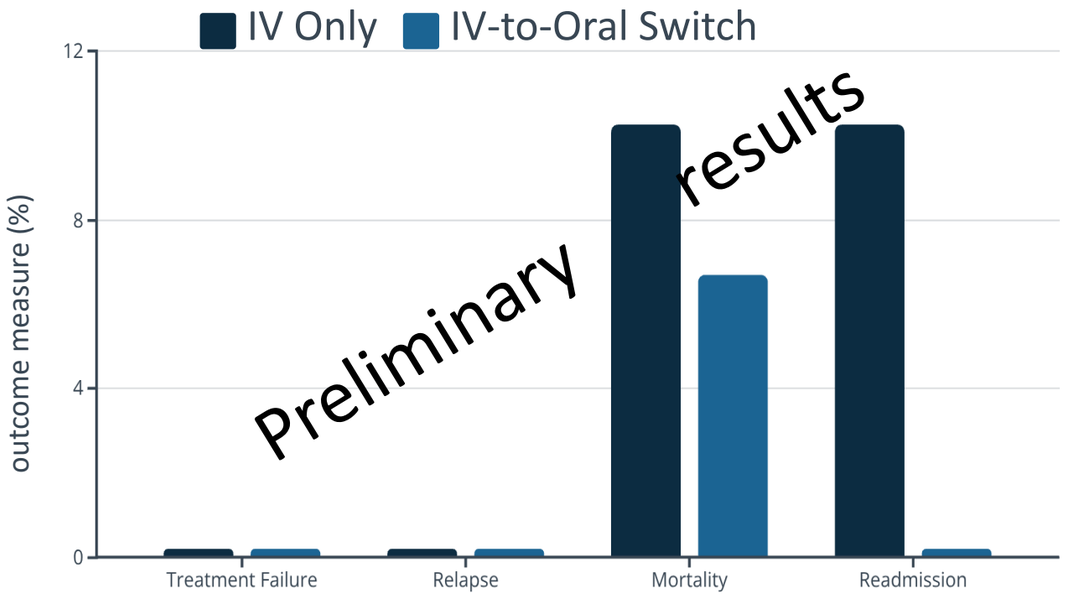
Extracardiac

Cough, abdominal pain and arthralgia occurred in decreasing frequency

Clinical pearl: Up to 23% of our pediatric patients presented with non-specific symptoms only (fatigue, poor feeding, weight loss), delaying diagnosis by a median of 7 days.

Preliminary results - IV-to-Oral Switch : Outcomes

- **54 patients with definite IE at the moment eligible for evaluation**
- 15 patients **(27.8%)** switched to oral therapy after **median 14 days of IV**
- Most common oral regimens:
  - Amoxicillin (streptococcal IE)
  - Levofloxacin + rifampin (MSSA/MRSA)
  - Linezolid + rifampin (MRSA/ConS)
- **No oral switch : HACEK, undocumented cases and patients with cerebral embolism**



Key finding: Early transition to oral therapy in carefully selected patients seems to be comparable

RESULTS NEED TO BE CONSOLIDATED : ongoing+++

Key Takeaways: The Necker Hospital Experience

Epidemiology

Increasing incidence with predominance in patients with CHD and indwelling catheters. Unique pediatric risk factors require targeted prevention strategies.

Diagnosis

Modified Duke criteria with greater sensitivity for pediatric population. Clinical suspicion must remain high despite atypical presentations.

Treatment

Early transition to oral therapy is safe in selected patients, reducing hospital stays and catheter-related complications without compromising outcomes.

Multidisciplinary Approach

Collaboration between microbiologists, infectious disease specialists, cardiologists, and pharmacists essential for optimal management.

Next steps: : Prospective studies!

Do you feel ready for oral step down in infective endocarditis?

Early Oral Switch Therapy for Infective Endocarditis in Children: An International Cross-Sectional Survey on Current Use in Clinical Practice

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