Enterococcal PJI

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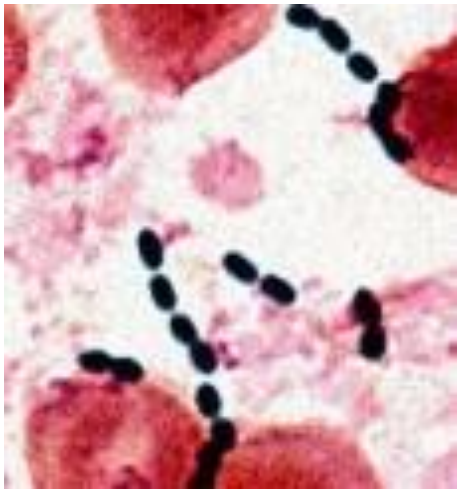
Enterococci: Gram-positive and round



- Formerly “streptococci” (but really quite different)
- Main clinical species : *E. faecalis* and *E. faecium*
- Mostly opportunistic pathogen (incl foreign bodies)
- Many antibiotics bacteriostatic or marginally bactericidal

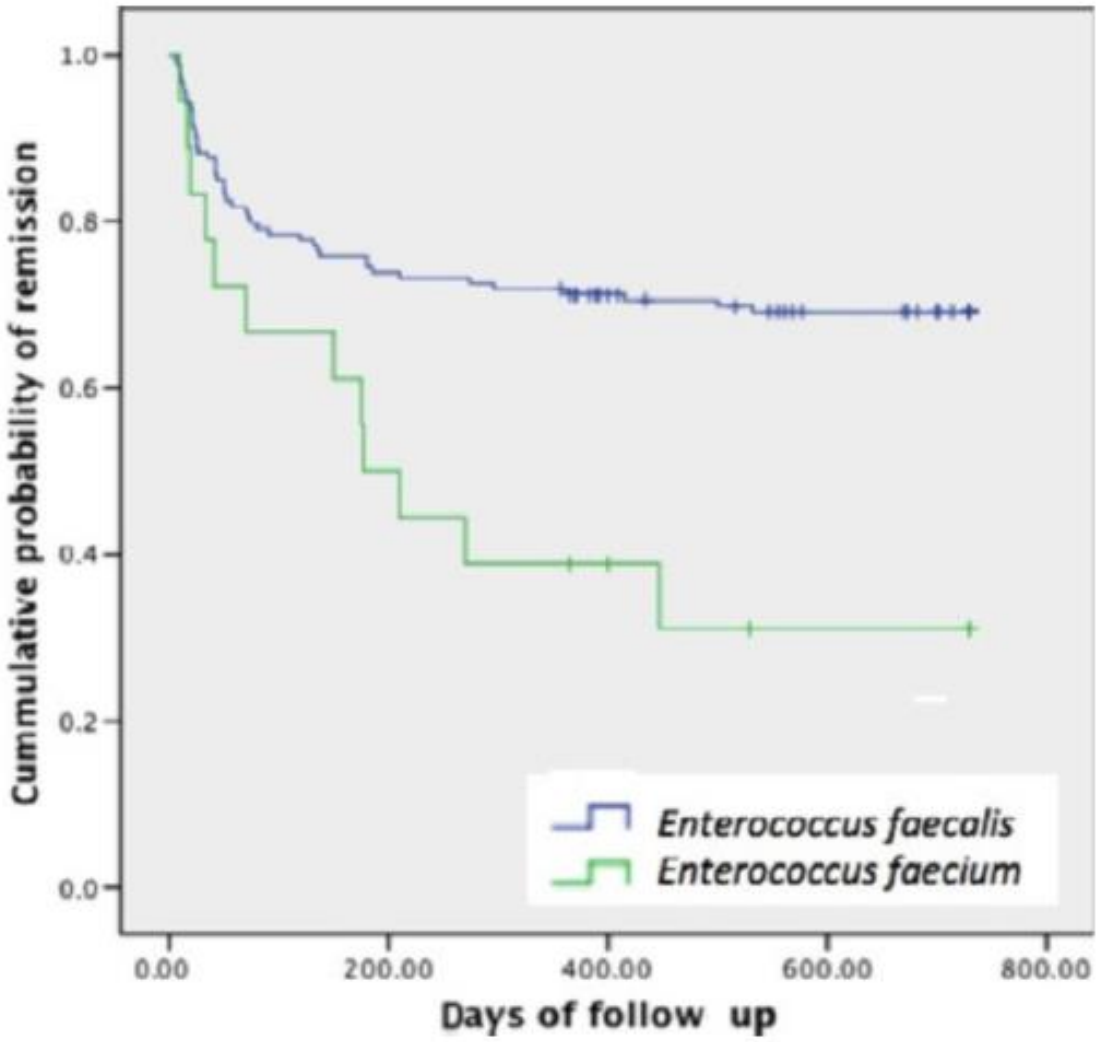
	E. faecalis	*E. faecium* community	*E. faecium* nosocomial
Amoxicillin, ampicillin	S	S	R
Vancomycin, teicoplanin	S	S	S
Daptomycin	S	S	S
Linezolid	S	S	S
Cotrimoxazole, ciprofloxacin, fosfomycin	Unreliable		
All other antibiotics	Intrinsically R to most		

Enterococcal PJI

- Limited susceptibility / tough bacterium:
  - Higher probability of clinical failure?
  - Indication for 2-stage exchange, or DAIR possible?
  - Combination therapy w/ gentamicin or rifampicin?

Not all enterococci are equal

E. faecium worse outcome vs *E. faecalis*



N= 94, Tornero e.a. 2014

Enterococcal PJI vs other pathogens

Debridement, antibiotics, and implant retention (DAIR)

1e auteur	Period / location	Micro-organisms	N	Success
Rodriguez-Pardo 2014	2003-2010 16 centers Spain	Gram-negatives	174	79%
Lora-Tamayo 2013	2003-2010 17 centers Spain	*S. aureus* (MSSA and MRSA)	345	55%
Byren 2009	1998-2003 1 centers UK	*S. aureus* CoNS	60 31	78% 83%
Kuiper 2013	2004-2009 3 centers, NL	*S. aureus* CoNS	50 13	68% 31%
Tornero 2014	1999-2012 18 centers, 3 countries	**Enterococci** (54% polymicrobial)	94	**47%**
Duijff 2015	2009-2013, 1 center NL	**Enterococci** (80% polymicrobial)	44	**66%**

Larger studies with outcome per micro-organism (-group), follow-up minimum 2 years.

Tornero e.a. oral rifampicin

Rifampicin associated with remission in early PJI?

Age of implant at the moment of infection	Type of antibiotic	Remission (%)	Failure (%)	p value
≤30 days	Vancomycin	9 (36)	16 (64)	0.41
	Ampicillin	6 (40)	9 (60)	1
	Rifampin[a,b]	12 (60)	8 (40)	0.04
	Aminoglycoside[a]	3 (30)	7 (70)	0.49
	Linezolid	4 (80)	1 (20)	0.15
	Daptomycin	0	1	1
>30 days	Vancomycin	37 (65)	20 (35)	0.60
	Ampicillin	30 (67)	15 (33)	0.49
	Rifampin[a]	35 (58)	25 (42)	0.31
	Aminoglycoside[a]	20 (54)	17 (46)	0.20
	Linezolid	6 (46)	7 (54)	0.22
	Daptomycin	3 (43)	4 (57)	0.42

[a]In combination with one or more active antibiotics against enterococci.
[b]With vancomycin in six cases, with vancomycin and aminoglycoside in one case, with ampicillin and aminoglycoside in four cases, with linezolid in two cases and with other antibiotic in seven cases.

Enterococcal PJI: prosthesis exchange

		N	Success	Polymicrobial
El Helou 2008	2-stage	17	94%	No
Tornero 2014	1-stage	22	77%	+/- 54%
	2-stage	54	54%	
Castellani 2017	1 x 1-stage 5 x 2-stage		50%	?
Rasouli 2012	2-stage	18	50%	50%

N.B.: Different follow-up periods, entry criteria and definitions of failure.

UMC Utrecht

- End of 2014 – 2017
- 24 enterococcal infections (most were superinfection)
  - THP + KHP: 10 + 1
  - TKP: 7
  - Spondylodesis + internal fixation: 5 + 1
  - 20/24 (83%) polymicrobial

Outcome
- In follow-up: 12
- Persistance of *Enterococcus*: 2
- Suppression R/: 1
- (Re-)infection different micro-organism: 7
- Death at 1 and 6 months: 2

What does failure actually mean?

	Failures N=	Re-infection enterococcus	Infection different PMO	Other / unclear
El Helou	12	3	5 (36%)	4
Tornero	78	?	?	?
Rasouli	9	?	≥2 (≥22%)	?
UMCU	10	3	7 (70%)	-

Tornero e.a. 2014

- In particular early infections problematic
- Polymicrobial infection and *E. faecium* associated with failure
- DAIR in late infections, success in 4/8 patients

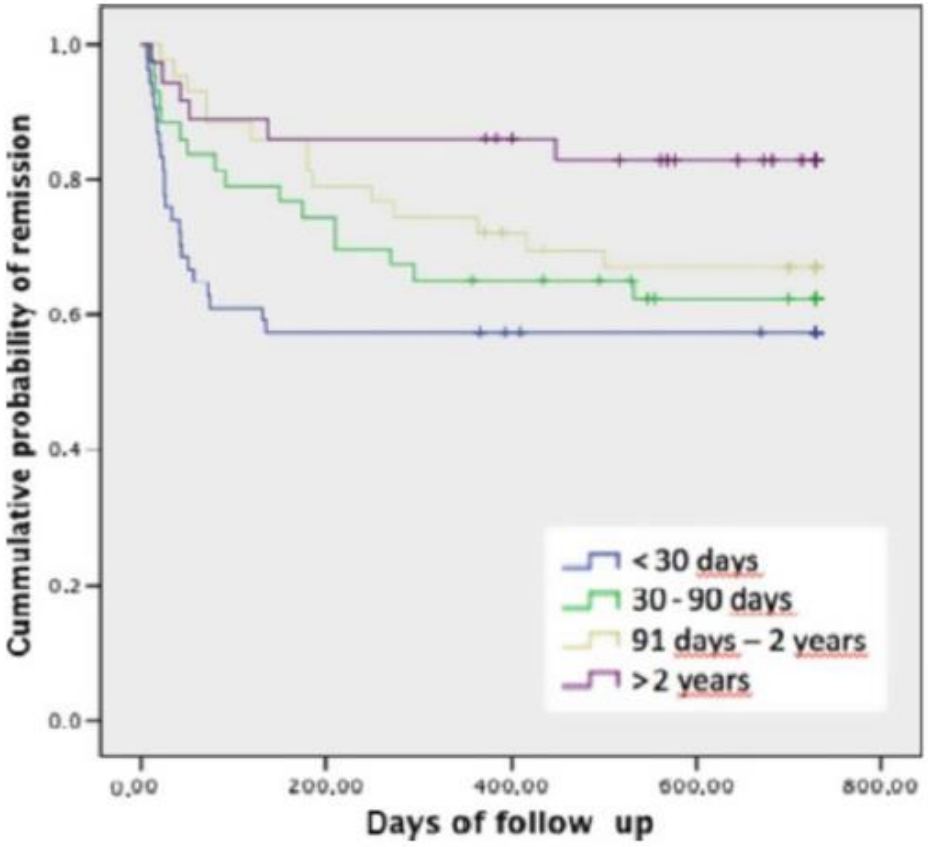
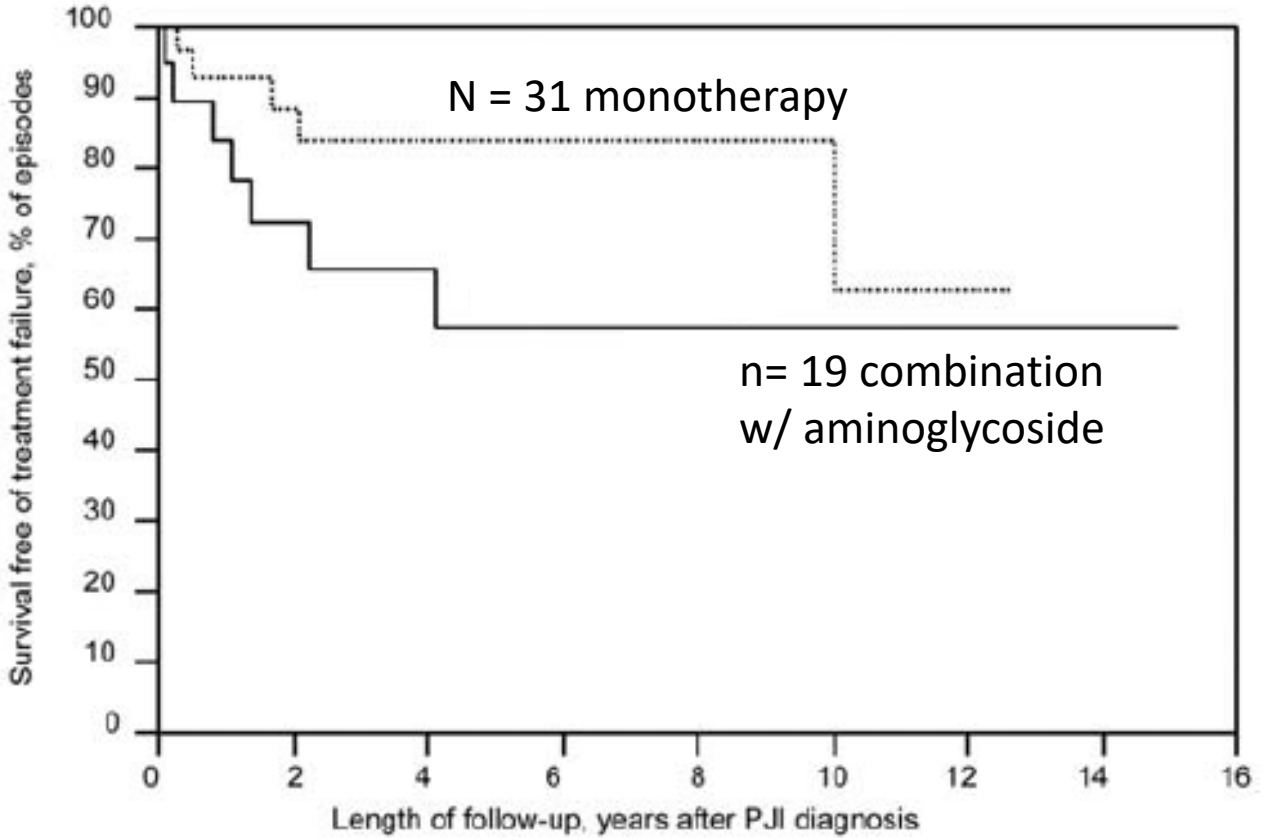


TABLE 2. Outcome according to the type of surgical management and type of infection

Age of implant at the moment of infection	Surgery	Remission (%)	Failure (%)	p value
≤30 days	Debridement	20 (41.6)	28 (58.4)	1
	Exchange	2 (40)	3 (60)	
31–90 days	Debridement	12 (46.2)	14 (53.8)	0.58
	Exchange	6 (37.5)	10 (62.5)	
91 days to 2 years	Debridement	8 (66.7)	4 (33.3)	0.72
	Exchange	16 (57.1)	12 (42.9)	
>2 years	Debridement	4 (50.0)	4 (50.0)	0.02
	Exchange	23 (92.0)	2 (8.0)	

Combination therapy with aminoglycosides?

- Enterococcal endocarditis: evidence for combination therapy
- 50 cases monomicrobial enterococcal PJI 1969-99 (retrosp)
  - 34% 2-stage exchange, 46% resection, 10% salvage of prothesis
  - Possibly selection bias: older age → less aminoglycosides



12 failures:
-3 same strain
-5 different bacterium
-4 unclear

El Helou e.a.
Clin Inf Dis 2008

Antibiotic (combination) regimens other studies

	Rifampicin	Aminoglycosides
Tornero e.a.	45%	26%
Duiff e.a.	Not specified[1]	0%
Rasouli e.a.	0%?[2]	12%
UMCU	21%[1]	0%

[1]Rifampicin for treatment of co-infecting micro-organisms.
[2]Therapy specified as “AB for Enterococcus PJI”

Suggested AB-regimens (DAIR / 1-stage)

- Pro-Implant foundation

Peni S: Ampicillin + gentamicin +/- fosfomycin IV → amoxicillin 3x1 g p.o.

Peni R: Vancomycin/daptomycin + gentamicin +/- fosfomycin IV
→ linezolid (2x600 mg), max 4 wks

- IDSA (enterocci may be indication for 2-stage)

Peni S: Penicillin/ampicillin +/- gentamicin → penicillin or amoxicillin 3 x 0.5g p.o.

Peni R: Vancomycin +/- gentamicin

- UMCU, CWZ Nijmegen, (and most Dutch centers?)

Peni S: Amoxicillin 4-6 x 2g → amoxicillin 3 x 1 g p.o.

Peni R: Full treatment vancomycin IV

Delphi consensus meeting 2013

- Discussion and voting by experts
- "Regimens containing rifampicin, when feasible, should be used in gram-positive PJI (...)." 87% agree
  - "Experience with oral antibiotics is scarce in streptococcal and enterococcal PJI but it is reasonable to use a β-lactam with a high oral bioavailability (**amoxicillin** for enterococci); and, since rifampin is active against streptococci, it is reasonable to recommend the addition of rifampin. Indeed, recent *in vitro* data showed that linezolid or **ciprofloxacin combined with rifampin** had better activity against enterococal biofilms than ampicillin or ampicillin plus rifampin; therefore, these combinations are potential alternatives."

- No clinical evidence ciprofloxacin or rifampicin enterococcal PJI

In conclusion

- Enterococcal PJI associated w/ high chance therapeutic failure
  - *E. faecium*
  - Mixed infection

  } Risk factors
- DAIR possible
- 2-stage exchange: high failure rate compared w/other mo's
  - Failure often not due to enterococci...
  - Enterococcal infection mostly indication of patient condition?
- No clinical evidence for combination therapy
- Urgent need for data comparing treatment modalities