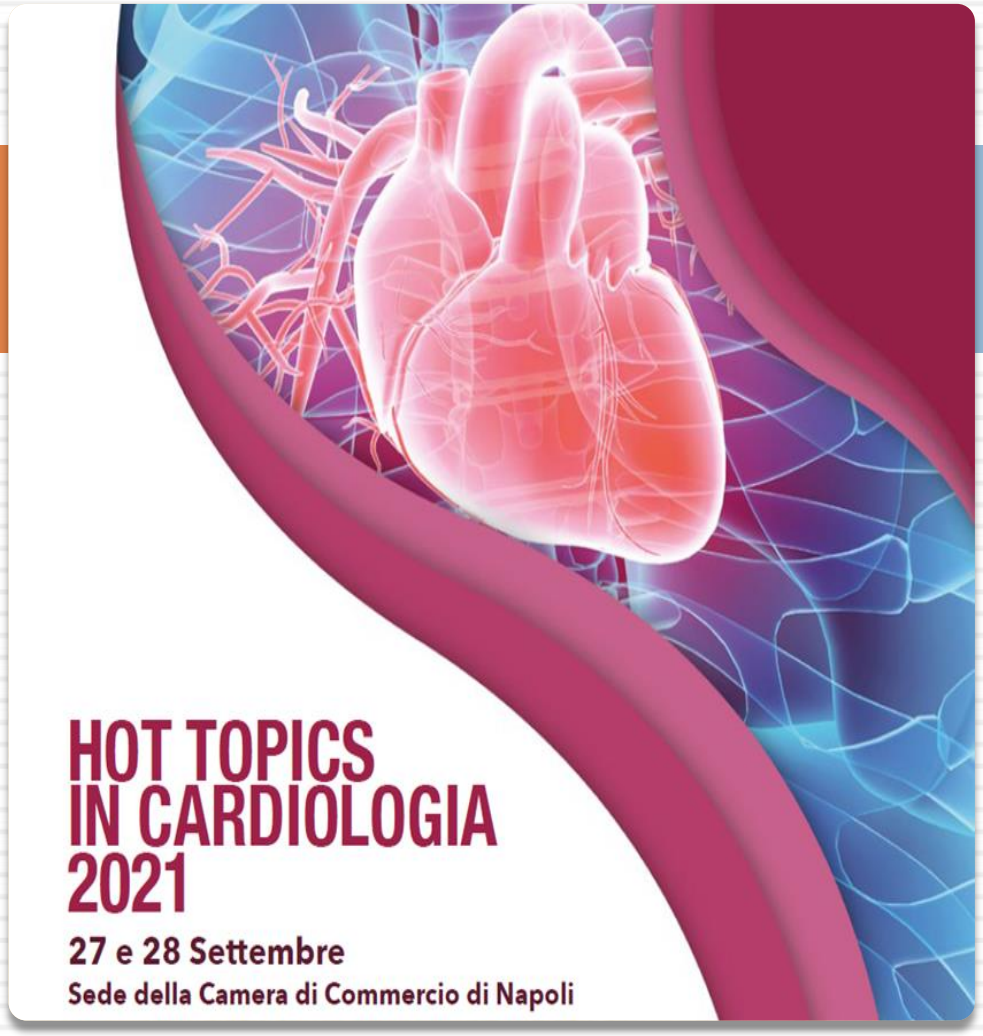

NUOVE PROSPETTIVE TERAPEUTICHE NELL'ANTIBIOTICO TERAPIA DELLE ENDOCARDITI INFETTIVE

Tiziana Ascione
Malattie Infettive
AORN "A.Cardarelli"
Napoli

MAYO CLINIC

Mayo Clin Proc. ■ XXX 2020;■(■):1-16 ■ https://doi.org/10.1016/j.mayocp.2019.12.008
www.mayoclinicproceedings.org

REVIEW

Infective Endocarditis: A Contemporary Review

Scott A. Hubers, MD; Daniel C. DeSimone, MD; Bernard J. Gersh, MBChB, DPhil;

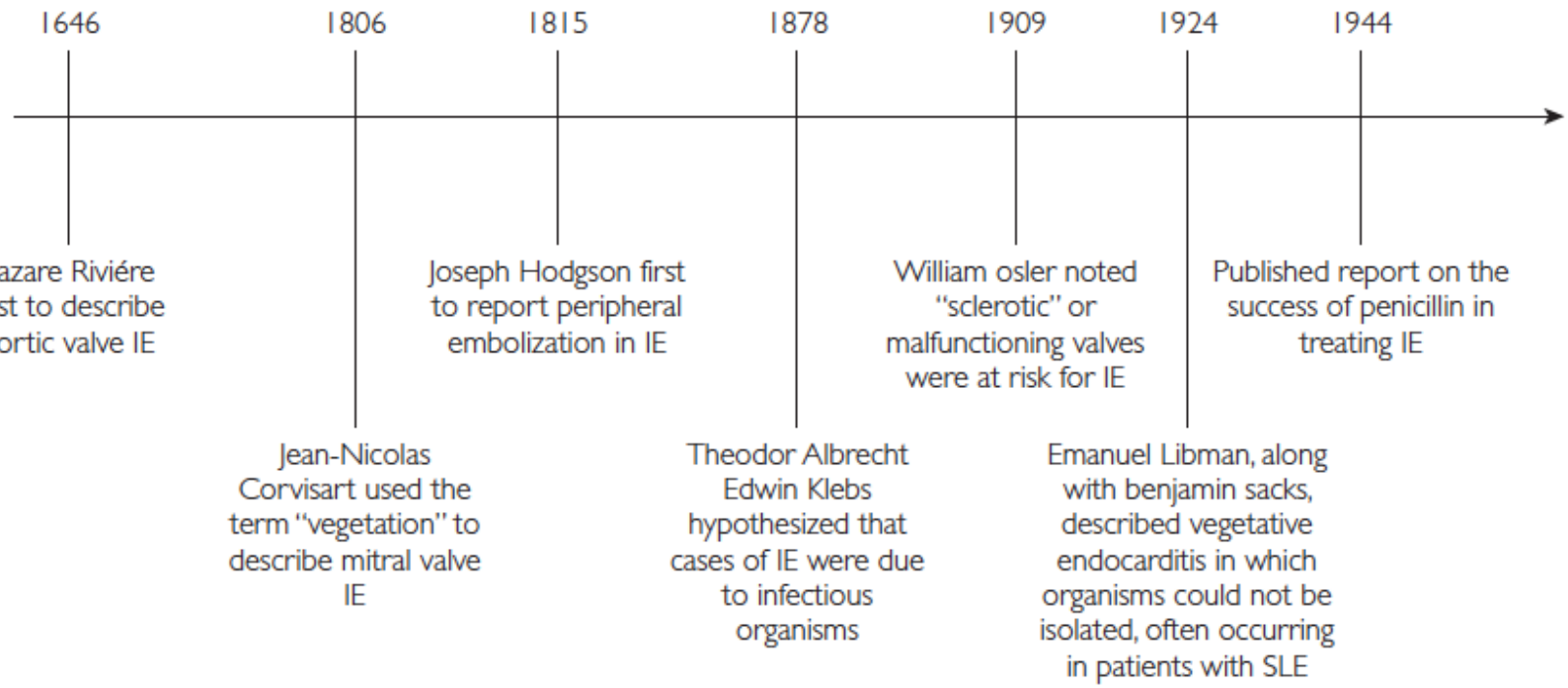

FIGURE 1. Timeline featuring major events in the history of IE. IE = infective endocarditis; SLE = systemic lupus erythematosus.

MAYO CLINIC

ORIGINAL ARTICLE

Clinical and Economic Burden of Hospitalizations for Infective Endocarditis in the United States

Mohamad Alkhouli, MD; Fahad Alqahtani, MD; Muhammed Alhajji, MD; Chalak O. Berzingi, MD; and M. Rizwan Sohail, MD

Mayo Clin Proc. ■ XXX 2019;■■(■):1-9 ■ https://doi.org/10.1016/j.mayocp.2019.08.023
www.mayoclinicproceedings.org

Clinical and Economic Burden of Hospitalizations for Infective Endocarditis

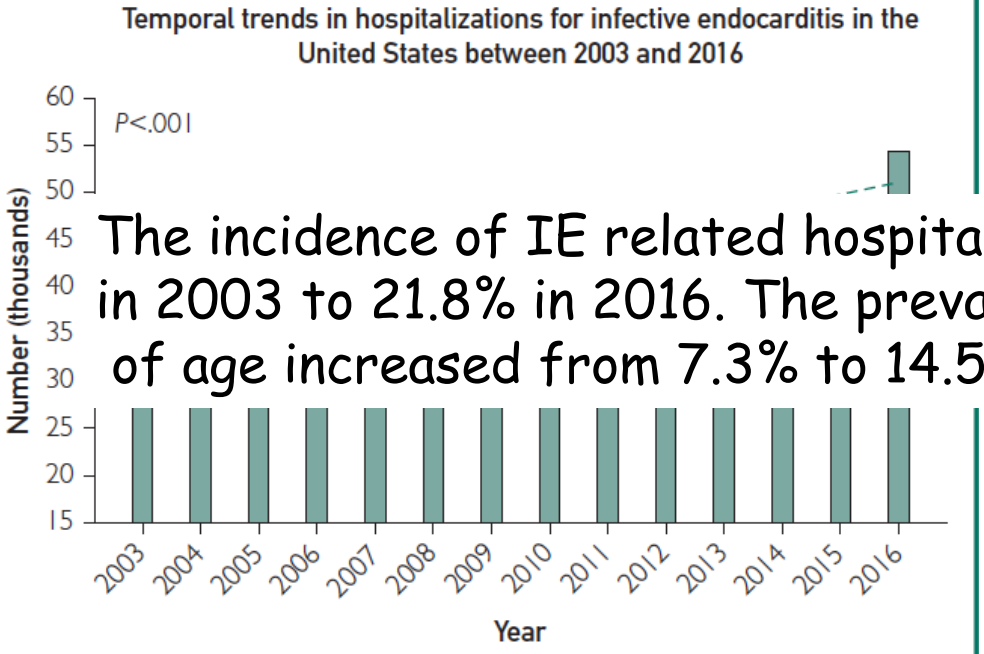

FIGURE 1. Temporal trends in hospitalizations for infective endocarditis in the United States between 2003 and 2016.

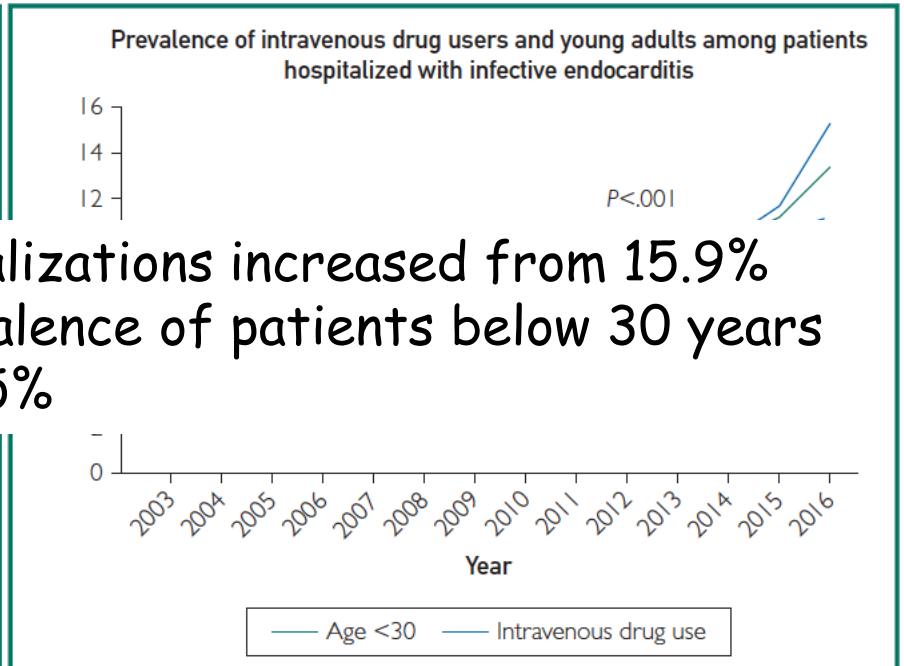

FIGURE 2. Temporal trends in the prevalence of young adults and intravenous drug users among patients hospitalized with infective endocarditis in the United States.

The incidence of IE related hospitalizations increased from 15.9% in 2003 to 21.8% in 2016. The prevalence of patients below 30 years of age increased from 7.3% to 14.5%

Mayo Clin Proc. ■ XXX 2019;■■(■):1-9 ■ https://doi.org/10.1016/j.mayocp.2019.08.023
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Clinical and Economic Burden of Hospitalizations for Infective Endocarditis

TABLE 1. Trends in the Baseline Characteristics and Prevalence of Comorbidities Among Patients Hospitalized With Infective Endocarditis Between 2003 and 2016

Baseline Characteristics	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	*P* value
Age, mean (SD)	59 (19)	59 (19)	60 (19)	59 (19)	61 (19)	61 (18)	61 (18)	61 (19)	60 (19)	59 (19)	58 (19)	57 (19)	57 (20)	55 (20)	<.001
< 30	7.3%	8.2%	7.8%	7.5%	6.7%	6.5%	6.6%	7.9%	8.2%	10.2%	10.9%	11.5%	12.6%	14.5%	<.001
31-50	25.1%	24.3%	22.8%	23.6%	22.1%	20.4%	20%	20.9%	20.3%	20.5%	22.1%	23.4%	21.9%	24.3%	
51-70	34.1%	34.5%	33.2%	35.4%	36.2%	38.5%	39.5%	38.2%	39.8%	38.7%	38%	36.5%	37.7%	35%	
> 70	33.5%	33.1%	36.2%	33.5%	35%	34.7%	33.9%	33%	31.7%	30.6%	29%	28.6%	27.9%	26.2%	
Female sex	42.7%	42.9%	41.1%	42.5%	42.2%	41.6%	41.2%	40.4%	40.9%	40.5%	39.2%	39.3%	39%	41.3%	<.001
Race															<.001
White	66.2%	69.2%	71.5%	68.7%	67.6%	70.9%	68.2%	68.5%	69.6%	71%	71.3%	72.4%	71.8%	73.2%	
Black															
Hispanic															
IV drug use															<.001
Diabetes															<.001
Hypertension															<.001
Coronary disea															<.001
Lung disease															<.001
Renal failure	18.3%	20.3%	22.6%	29%	29.5%	29.2%	31.2%	31.4%	34.3%	31.6%	28.7%	29.4%	29.5%	29.1%	<.001
ESRD on dialysis	NA	NA	NA	12.7%	13.3%	14.5%	15.9%	15.6%	17.6%	14.1%	12.5%	12.6%	12.0%	12.6%	<.001
Vascular disease	4.8%	5.4%	5%	5.2%	7.5%	11.7%	12.7%	12.1%	14.2%	14.1%	14.5%	15.9%	12.9%	14.9%	<.001
Anemia	23.2%	23.7%	24.7%	26.6%	30.3%	33.3%	35.4%	36.9%	41.5%	41.5%	41.2%	41.1%	42%	45.3%	<.001
Atrial fib/flutter	22.2%	21.8%	23.2%	22.8%	23.2%	18.7%	22.2%	22.4%	24.4%	25.4%	25%	25.4%	25.8%	25.9%	<.001
Prior sternotomy	9%	8.6%	8.5%	8.5%	8.6%	8.7%	11.9%	12%	13.1%	13.5%	12.3%	12.5%	12.6%	11.9%	<.001
Liver cirrhosis	2.5%	2.4%	2%	2.3%	2.9%	4.2%	5%	4.5%	5%	5.6%	5.6%	5.6%	5.5%	4.1%	<.001
Prior ICD	0.6%	0.7%	0.7%	1.1%	1.0%	1.4%	2.3%	2.1%	2.4%	2.4%	2.2%	2.5%	3.0%	2.4%	<.001
Prior pacemaker	3.3%	3.1%	2.7%	3.1%	2.9%	3.0%	4.0%	4.0%	4.0%	4.7%	4.0%	4.4%	4.8%	4.5%	<.001
Prosthetic valve	6.2%	5.0%	5.1%	5.0%	4.9%	5.0%	6.4%	6.5%	7.3%	7.6%	7.7%	8.2%	7.5%	7.3%	<.001

The annual volume of valve surgery for IE increased from 2003 to 2016 but the ratio of valve surgery to IE hospitalizations did not decrease 11.7 vs 11.8

Clinical and Economic Burden of Hospitalizations for Infective Endocarditis

TABLE 2. Trends in In-Hospital Mortality and Major Complications Among Patients Admitted With Infective Endocarditis Between 2003 and 2016

Clinical Outcomes	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	OR per year (95% CI)
Death															
Unadjusted	14.4%	13.2%	12.5%	12.9%	11.5%	13.2%	11.7%	11.9%	11.3%	10.8%	10.4%	10.5%	10.7%	10%	0.973 (0.971-0.975)
Adjusted	Ref	13.1%	12%	12.1%	10%	11.8%	10.6%	10.4%	9.7%	9.2%	9.1%	9.1%	9.3%	9.8%	0.970 (0.968-0.973)
Stroke															
Unadjusted	8.0%	7.9%	8.3%	7.9%	8.7%	9.3%	9.8%	10.5%	10.5%	10.6%	11.2%	11.5%	11.7%	13.2%	1.045 (1.042-1.047)
Adjusted	Ref	7.8%	8.4%	8.4%	8.1%	8.8%	9.1%	10.1%	10.0%	10.4%	10.8%	11.3%	11.9%	15.5%	1.047 (1.044-1.050)
New dialysis															
Unadjusted	3.1%	3.5%	3%	3.2%	3.4%	4%	4.8%	5.1%	4.5%	4.3%	3.8%	4.9%	4.7%	4.2%	1.030 (1.027-1.033)
Adjusted															0.963-0.971)
Septic shock															
Unadjusted															1.098-1.103)
Adjusted															1.089-1.095)
Mec. ventilation															
Unadjusted															1.048-1.052)
Adjusted	Ref	8.3%	7.0%	7.9%	8.2%	9.5%	10.3%	9.2%	8.7%	8.2%	8.1%	8.4%	10.6%	16.7%	1.038 (1.0351.045)
Tracheostomy															
Unadjusted	2.8%	2.7%	2.4%	2.0%	2.4%	2.7%	2.7%	2.4%	2.5%	2.6%	2.1%	2.6%	2.1%	2.4%	0.992 (0.988-0.996)
Adjusted	Ref	2.5%	2.4%	1.9%	2.4%	2.8%	2.8%	2.4%	2.6%	2.7%	2.2%	2.7%	2.2%	2.4%	0.996 (0.992-1.001)
Valve Surgery															
Unadjusted	11.7%	10.4%	9.9%	10.1%	9.9%	11.1%	11.4%	10.2%	10.7%	12.6%	12.4%	12.7%	12.3%	11.8%	1.018 (1.016-1.02)
Adjusted	Ref	9.6%	9.4%	10.2%	10.6%	11.9%	11.7%	10.5%	11.0%	12.5%	11.6%	11.7%	10.9%	10.5%	1.002 (1.00-1.005)

Mortality decreased from 14.4% to 10%
The expenditure on IE hospitalizations increased USD 1.48 billion in 2003 to USD 2.34 billion in 2016

Mayo Clin Proc. ■ XXX 2019;■■(■):1-9 ■ https://doi.org/10.1016/j.mayocp.2019.08.023
www.mayoclinicproceedings.org

Seminar

Infective endocarditis

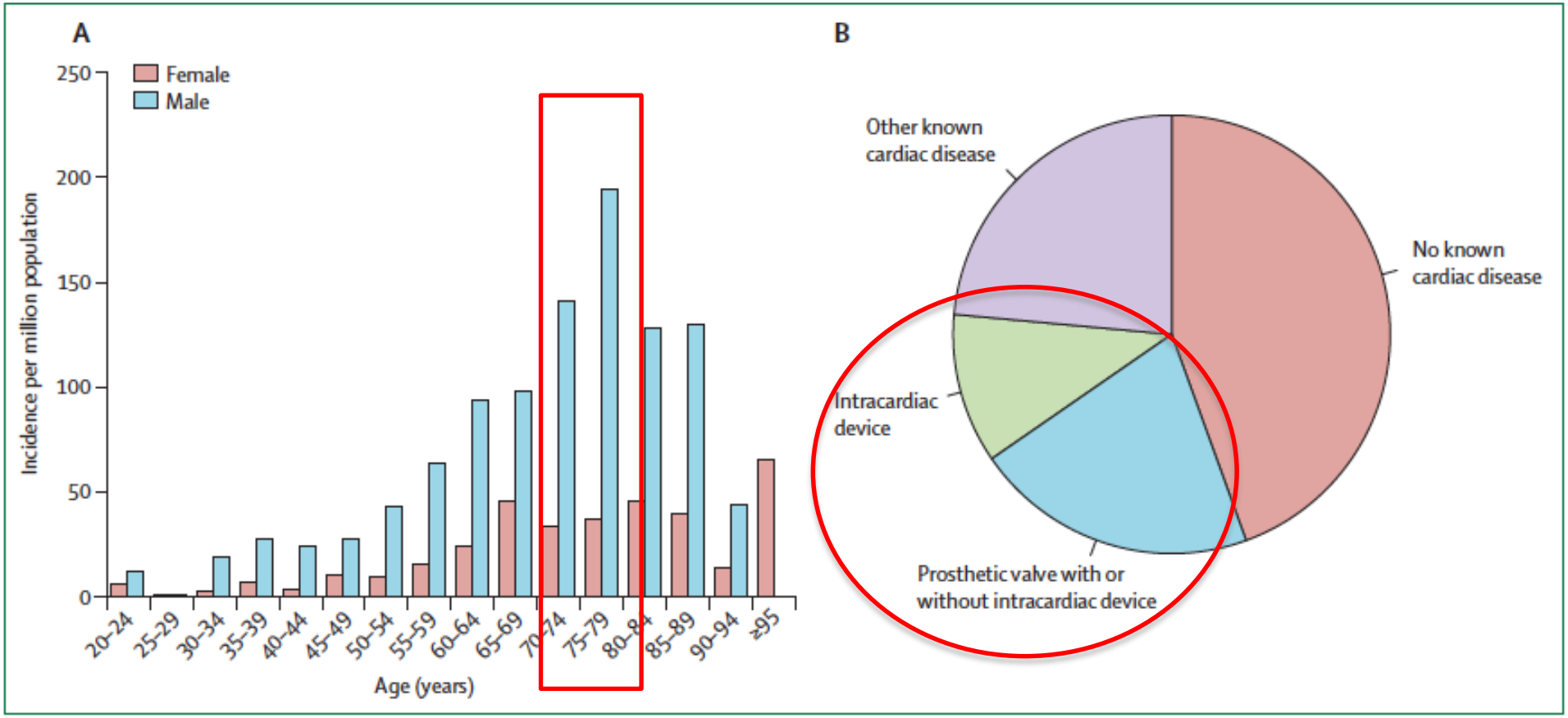
Thomas J Cahill, Bernard D Prendergast

Lancet 2016; 387: 882–93
Published Online September 2, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00067-7

Department of Cardiology, Oxford University Hospitals, Oxford, UK (T J Cahill MRCP); **Department of Cardiology, St Thomas' Hospital, London, UK** (B D Prendergast FRCP)

Infective endocarditis occurs worldwide, and is defined by infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device. The causes and epidemiology of the disease have evolved in recent decades with a doubling of the average patient age and an increased prevalence in patients with indwelling cardiac devices. The microbiology of the disease has also changed, and staphylococci, most often associated with health-care contact and invasive procedures, have overtaken streptococci as the most common cause of the disease. Although novel diagnostic and therapeutic strategies have emerged, 1 year mortality has not improved and remains at 30%, which is worse than for many cancers. Logistical barriers and an absence of randomised trials hinder clinical management, and longstanding controversies such as use of antibiotic prophylaxis remain unresolved. In this Seminar, we discuss clinical practice, controversies, and strategies needed to target this potentially devastating disease.

Infective endocarditis



Lancet 2016; 387: 882–93

Infective endocarditis

Lancet 2016; 387: 882–93

- The causes and epidemiology of the disease have evolved in recent decades
- Increased prevalence in patients with indwelling cardiac devices
- The microbiology of disease has also changed and Staphylococci most often associated with health care contact have overtaken Streptococci
- Selection of optimal antibiotic therapy for IE due to MRSA with reduced susceptibility to vancomycin
- 1 year mortality remains at 30% at 30 days

Panel 1: Proportion of cases of infective endocarditis caused by different microorganisms from a French population-based cohort of 497 patients[2]

Staphylococci
Staphylococcus aureus: 26·6%
Coagulase-negative staphylococci: 9·7%

Streptococci and enterococci
Oral streptococci: 18·7%
Non-oral streptococci: 17·5%
Enterococci: 10·5%
Other: 1·6%

HACEK (haemophilus, aggregatibacter, cardiobacterium, *Eikenella corrodens*, kingella) microorganisms
1·2%

***Candida* species**
1·2%

Other*
6·0%

Polymicrobial (≥2 microorganisms)
1·8%

No microorganism identified
5·2%

PLOS ONE

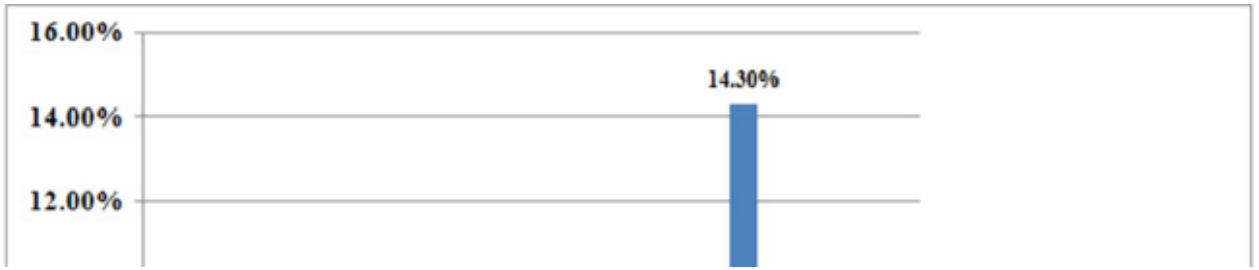
RESEARCH ARTICLE

Infective endocarditis post-transcatheter aortic valve implantation (TAVI), microbiological profile and clinical outcomes: A systematic review

Adnan Khan[1]*, Aqsa Aslam[1], Khawar Naeem Satti[2], Sana Ashiq[1]

1 Sharif Medical and Dental College, Lahore, Pakistan, 2 Senior Registrar Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan

Infective endocarditis post-TAVI, microbiological profile and clinical outcomes



The incidence of infective endocarditis varied from 0%-14.3% in the included studies, mean was3.25%. The average duration of follow-up was 474 days (1.3 years). *Enter*

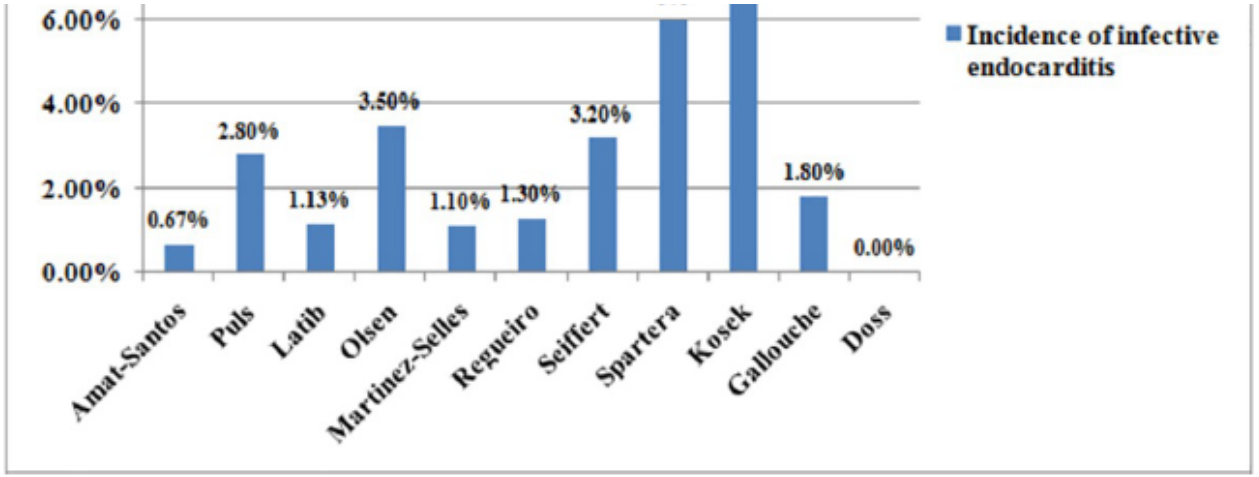
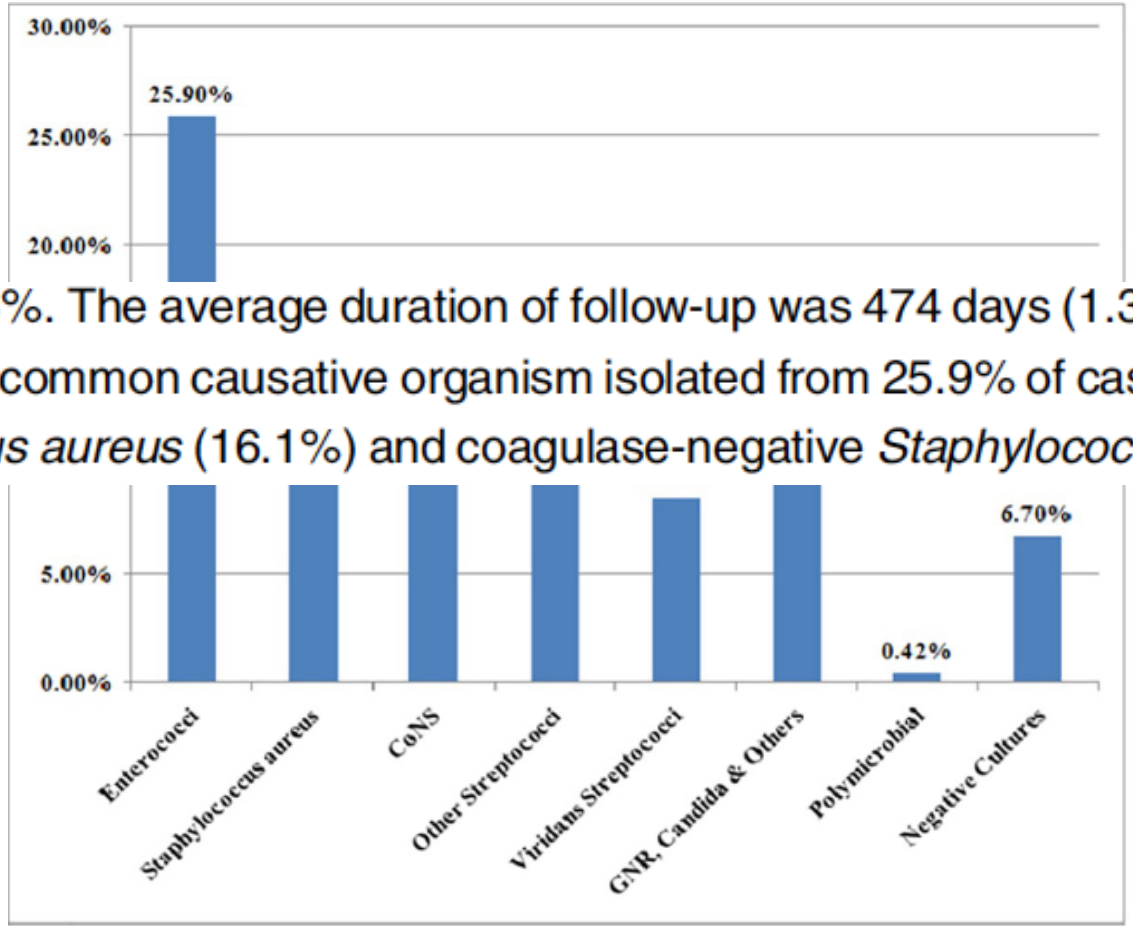


Fig 4. Percentage of post-TAVI infective endocarditis in studies included in the systematic review.

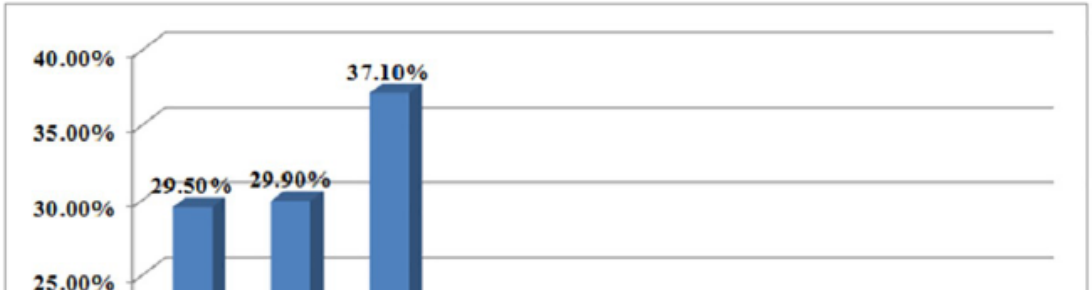
Infective endocarditis post-TAVI, microbiological profile and clinical outcomes



mean was3.25%. The average duration of follow-up was 474 days (1.3 years). *Enterococci* were the most common causative organism isolated from 25.9% of cases followed by *Staphylococcus aureus* (16.1%) and coagulase-negative *Staphylococcus* species (14.7%).

Fig 5. Causative organisms of post-TAVI infective endocarditis. The in-hospital mortality

Infective endocarditis post-TAVI, microbiological profile and clinical outcomes



The mean in-hospital mortality and mortality at follow-up was 29.5% and 29.9%, respectively. The cumulative incidence of heart failure, stroke and major bleeding were 37.1%,

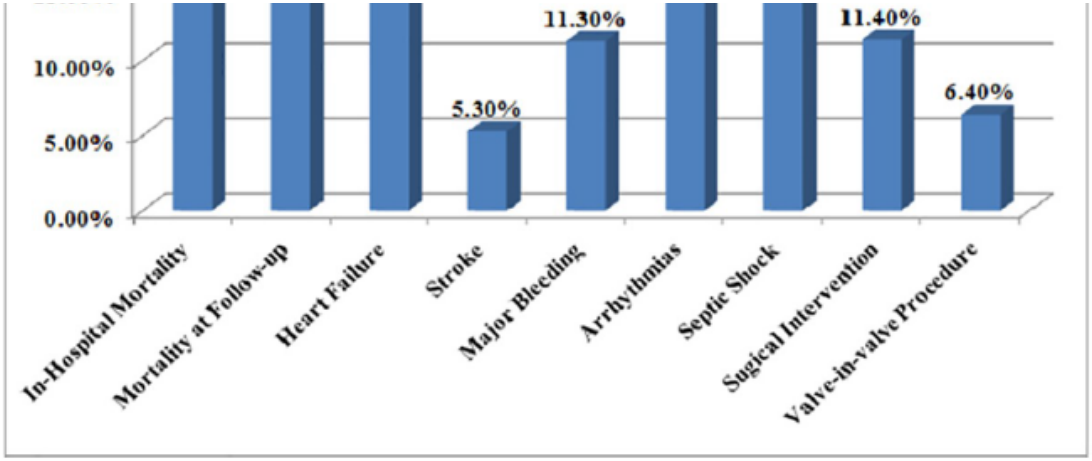


Fig 6. Clinical outcomes in patients of post-TAVI infective endocarditis. The incidence of infective endocarditis in

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Médecine et maladies infectieuses

Médecine et maladies infectieuses xxx (2016) xxx–xxx

General review

Analysis of the 2015 American and European guidelines for the management of infective endocarditis

Analyse des recommandations américaines et européennes de 2015 pour la prise en charge des endocardites infectieuses

P. Tattevin [a,*], J.-L. Mainardi [b]

[a] *Maladies infectieuses et réanimation médicale, CHU Pontchaillou, 35033 Rennes cedex, France*
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Received 23 January 2016; accepted 13 May 2016

Analysis of the 2015 American and European guidelines for the management of infective endocarditis

Table 1
Main first-line antibiotic therapies included in the 2015 European and American guidelines for the management of infective endocarditis.
Principales antibiothérapies de première ligne dans les recommandations européennes et américaines 2015 de prise en charge des endocardites infectieuses.

	2015 American guidelines	2015 European guidelines
Empirical antibiotic therapies	Depend on symptom evolution and epidemiological factors	Community-acquired (severe presentation): [a] ampicillin + (cl)oxacillin + gentamicin Nosocomial: vancomycin + gentamicin + rifampicin[b]
Native valve staphylococcal endocarditis	Methicillin-susceptible: (cl)oxacillin Methicillin-resistant: vancomycin or daptomycin	Methicillin-susceptible: (cl)oxacillin Methicillin-resistant: vancomycin or daptomycin Alternative (in both of the above situations): trimethoprim–sulfamethoxazole + clindamycin
Prosthetic valve staphylococcal endocarditis	Methicillin-susceptible: (cl)oxacillin + gentamicin b.i.d. or t.i.d. + rifampicin Methicillin-resistant: vancomycin + gentamicin b.i.d. or t.i.d. + rifampicin	Methicillin-susceptible: (cl)oxacillin + gentamicin o.d. or b.i.d. + rifampicin Methicillin-resistant: vancomycin + gentamicin o.d. or b.i.d. + rifampicin
Susceptible streptococcal endocarditis	"Two-week regimen": penicillin G or ceftriaxone + gentamicin (single daily dose) "Four-week regimen": penicillin G or ceftriaxone	"Two-week regimen": penicillin G or amoxicillin or ceftriaxone + gentamicin (o.d.) "Four-week regimen": penicillin G or amoxicillin or ceftriaxone
Susceptible enterococcal endocarditis	Regimen "A": penicillin G or ampicillin + gentamicin (2 or 3 uptakes/day) for 4 to 6 weeks Regimen "B": ampicillin + ceftriaxone for 6 weeks	Regimen "A": amoxicillin (4 to 6 weeks) + gentamicin (single daily dose for 2 to 6 weeks) Regimen "B": ampicillin + ceftriaxone for 6 weeks

[a] Including endocarditis of prosthetic valve implanted > 1 year earlier.
[b] Rifampicin is only indicated in the presence of a prosthetic valve and, according to some experts, should be introduced later on (5 to 7 days after antibiotic therapy initiation).

P. Tattevin, J.-L. Mainardi / Médecine et maladies infectieuses xxx (2016)

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Native-Valve Infective Endocarditis

Henry F. Chambers, M.D., and Arnold S. Bayer, M.D.

Table 3. Antimicrobial Regimens for Treatment of Native-Valve Infective Endocarditis.*

Microorganism and Regimen	Dose and Duration of Treatment†	Comments
Viridans streptococci, *Streptococcus gallolyticus*		
Penicillin MIC ≤0.12 μg/ml		
Penicillin G	12 million–18 million units/day intravenously in 4–6 divided doses for 4 wk	
Ceftriaxone	2 g intravenously once daily for 4 wk	
Vancomycin	30 mg/kg/day intravenously in 2–3 divided doses for 4 wk	
Penicillin G plus gentamicin	Penicillin G (12 million–18 million units/day intravenously in 4–6 divided doses) plus gentamicin (3 mg/kg intravenously once daily) for 2 wk	Avoid gentamicin in patients with preexisting renal disease, in the elderly, and in patients at risk for nephrotoxicity or ototoxicity (i.e., in those receiving other potentially nephrotoxic or ototoxic drugs)
Ceftriaxone plus gentamicin	Ceftriaxone (2 g intravenously once daily) plus gentamicin (3 mg/kg intravenously once daily) for 2 wk	Avoid gentamicin in patients with preexisting renal disease, in the elderly, and in patients at risk for nephrotoxicity or ototoxicity (i.e., in those receiving other potentially nephrotoxic or ototoxic drugs)
Penicillin MIC >0.12 to <0.5 μg/ml		
Penicillin G plus gentamicin	Penicillin G (24 million units/day intravenously in 4–6 divided doses for 4 wk) plus gentamicin (3 mg/kg intravenously once daily for 2 wk)	
Ceftriaxone plus gentamicin	Ceftriaxone (2 g once daily for 4 wk) plus gentamicin (3 mg/kg intravenously once daily for 2 wk)	If the ceftriaxone MIC of the isolate is ≤0.5 μg/ml, ceftriaxone alone is an option
Vancomycin	30 mg/kg/day in 2–3 divided doses for 4 wk	

Enterococci		
Ampicillin plus gentamicin	Ampicillin (12 g/day in 6 divided doses) plus gentamicin (3 mg/kg intravenously in 2–3 divided doses) for 4–6 wk	Not recommended for strains with high-level aminoglycoside resistance; limited data suggest that gentamicin can be discontinued after 2 wk
Penicillin G plus gentamicin	Penicillin G (24 million units/day intravenously in 4–6 doses) plus gentamicin (3 mg/kg intravenously in 2–3 divided doses) for 4–6 wk	Not recommended for strains with high-level aminoglycoside resistance; limited data suggest that gentamicin can be discontinued after 2 wk
Ampicillin plus ceftriaxone	Ampicillin (12 g/day in 6 divided doses) plus ceftriaxone (2 g every 12 hr) for 6 wk	Recommended for strains with high-level aminoglycoside resistance
Vancomycin plus gentamicin	Vancomycin (30 mg/kg/day in 2–3 divided doses) plus gentamicin (3 mg/kg/day in 2–3 divided doses) for 6 wk	Not recommended for strains with high-level aminoglycoside resistance; regimen of last resort because of toxicity
Methicillin-susceptible *Staphylococcus aureus*		Vancomycin or daptomycin is an option for patients who cannot receive beta-lactam antibiotics without adverse effects or with immediate hypersensitivity to beta-lactam antibiotics
Nafcillin or oxacillin	12 g/day intravenously in 6 divided doses for 6 wk	

Microorganism and Regimen	**Dose and Duration of Treatment†**	**Comments**
Methicillin-resistant *S. aureus*		
Vancomycin	30–60 mg/kg/day intravenously in 2–4 divided doses for 6 wk	The target 24-hr area under the concentration curve is 400–600 μg× hr/ml
Daptomycin	10 mg/kg/day intravenously once daily for 6 wk	
HACEK		
Ceftriaxone	2 g intravenously once daily for 4 wk	
Ciprofloxacin	800 mg/day intravenously or 1500 mg orally in 2 divided doses for 4 wk	
Levofloxacin	750 mg intravenously or orally once daily for 4 wk	

Comparison of Dual β-Lactam Therapy to Penicillin-Aminoglycoside Combination in Treatment of Enterococcus faecalis Infective Endocarditis

Abdelghani El Rafei MD , Daniel C. DeSimone MD , Aalap D. Narichania MD , M. Rizwan Sohail MD , Holenarasipur R. Vikram , Zhuo Li , James M. Steckelberg MD, MD , Walter R. Wilson MD , Larry M. Baddour MD

PII: S0163-4453(18)30191-9
DOI: 10.1016/j.jinf.2018.06.013
Reference: YJINF 4124

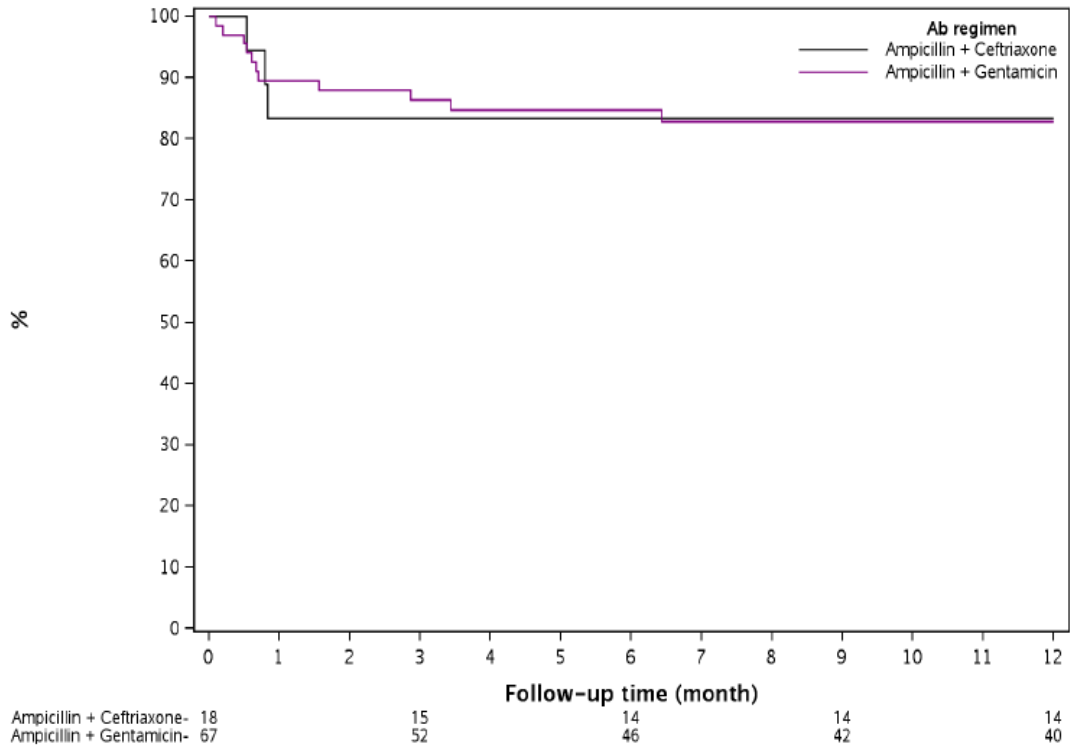
To appear in: *Journal of Infection*

Received date: 4 October 2017
Revised date: 20 June 2018
Accepted date: 25 June 2018

Comparison of Dual β-Lactam Therapy to Penicillin-Aminoglycoside Combination in Treatment of Enterococcus faecalis Infective Endocarditis

- 85 patients with *Enterococcus faecalis* endocarditis
- 67 pz Ampicillin + Gentamicin
- 18 pz Ampicillin + ceftriaxone
- 1 year mortality rate were similar in 2 groups
- Ampicillin + Ceftriaxone had lower rate of nephrotoxicity

Figure 1. Kaplan Meier 1-year Survival Curve by intention to treat groups



Journal of Infection 2018

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2019 VOL. 380 NO. 5

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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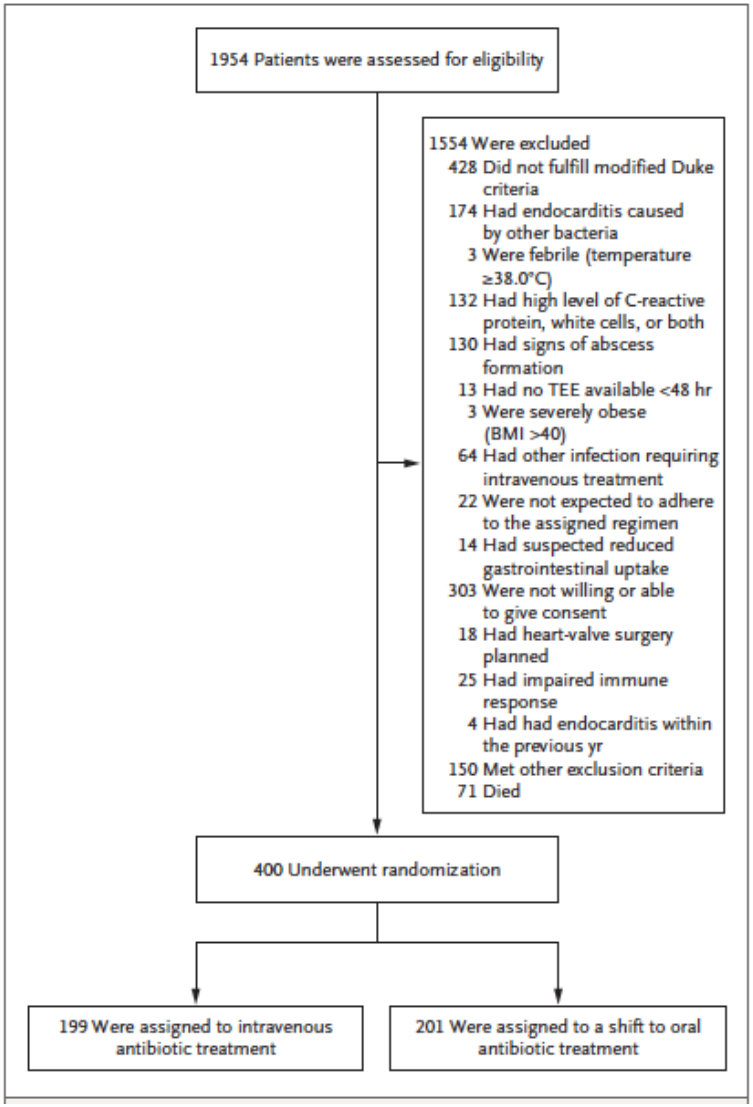
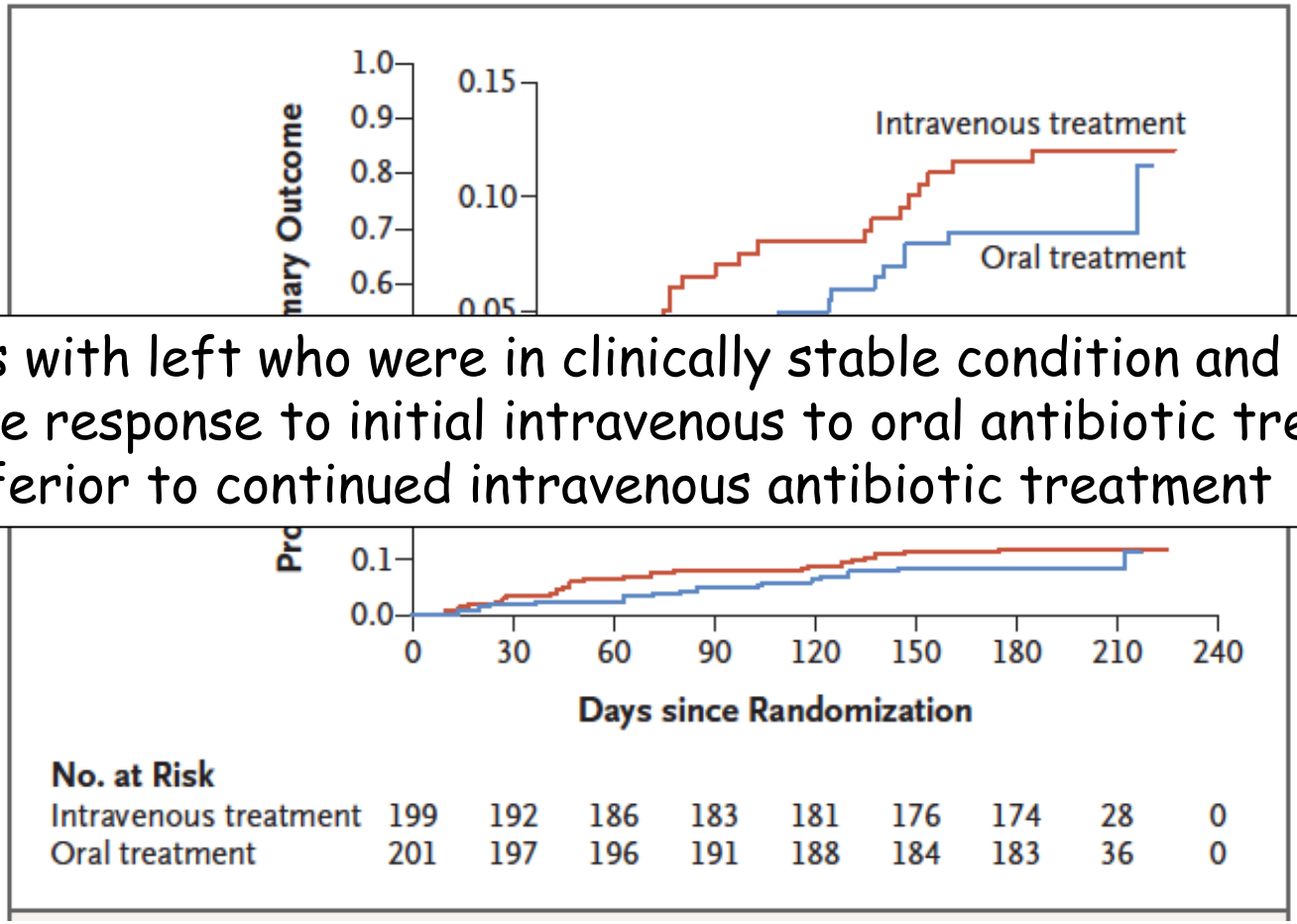
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

- A randomized study
- 400 patients
- Left Side Endocarditis
- 199 intravenous treatment
- 201 intravenous treatment
  + switch to oral antibiotic
- The patients shifted from
  iv to os on about day 17

End point: treatment success after the end of therapy

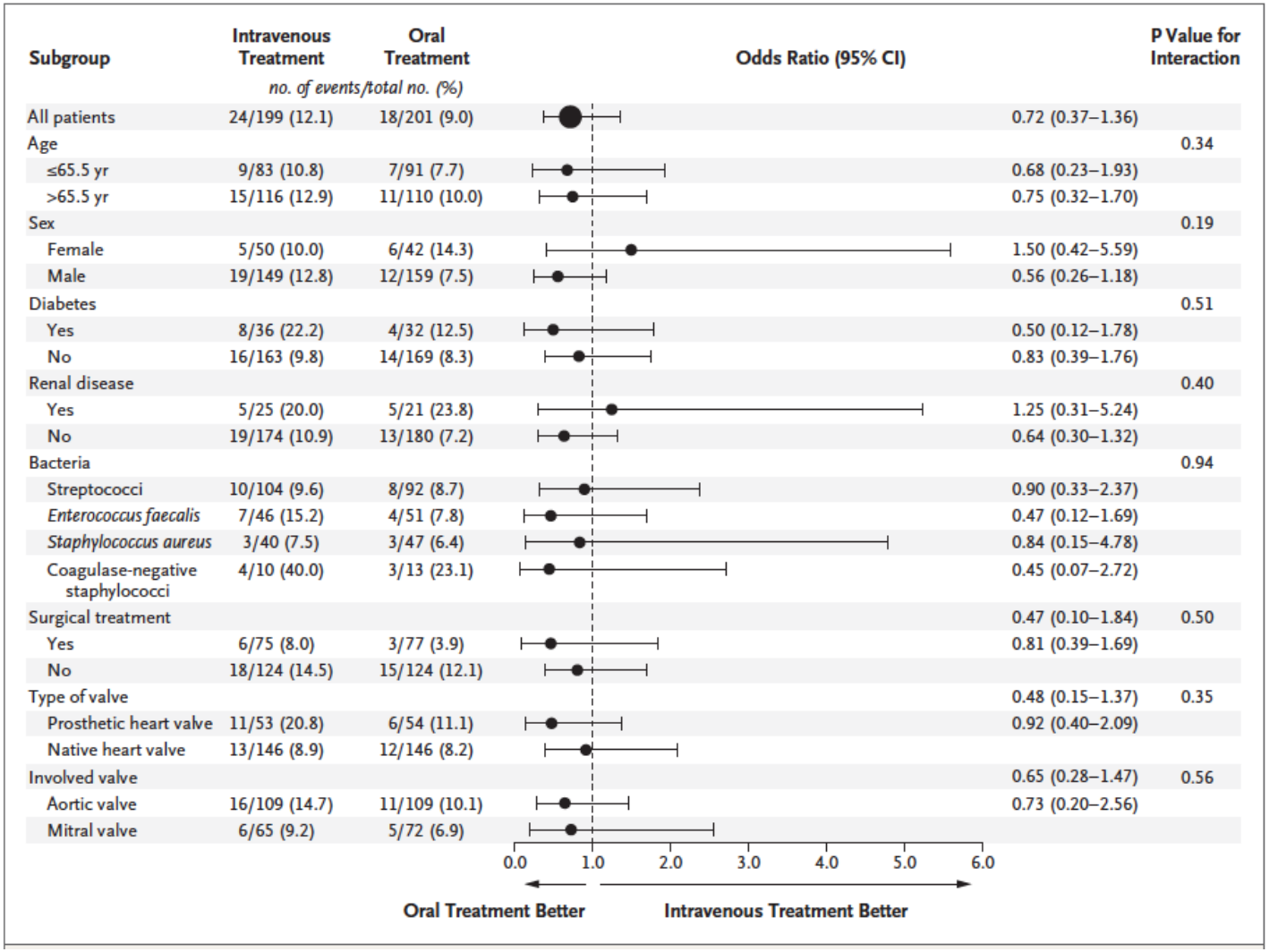


Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis



In Patients with left who were in clinically stable condition and who had an adequate response to initial intravenous to oral antibiotic treatment was non inferior to continued intravenous antibiotic treatment

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis



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)		

J Antimicrob Chemother
doi:10.1093/jac/dkaa106

Journal of Antimicrobial Chemotherapy

Oral antibiotics for infective endocarditis: a clinical review

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Oral antibiotics for infective endocarditis: a clinical review

Table 1. Pharmacokinetic and pharmacodynamic properties of amoxicillin given orally (PO) and IV[11–13]

	Amoxicillin	
Property	IV	oral
Peak serum levels	83–112 mg/L, 1 min after 500 mg IV injection	8–10 mg/L, 2 h after 500 mg PO dose
Duration of effective plasma concentration	after 500 mg IV dose, plasma concentration fell to 1 mg/L after 3.5 h	after 500 mg PO dose, concentration fell to zero after 6–8 h
Excretion	mainly urinary (58%–68% of PO dose excreted unchanged in urine during first 6 h)	
Pharmacokinetics	bioavailability 76.5%; low protein binding (17%)	
Published MIC values		
S. aureus (penicillin susceptible)	0.1 mg/L	
α-haemolytic streptococci	0.01 mg/L	
E. faecalis	0.5 mg/L	

- The study examines serum antimicrobial levels after oral and iv administration with reference to the MICs of relevant pathogens
- Safe levels of commonly used antibiotics.
- Pharmacological data offer reassurance for the safety of oral therapy

Clinical Microbiology and Infection 23 (2017) 697–703

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

New and improved? A review of novel antibiotics for Gram-positive bacteria

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New and improved? A review of novel antibiotics for Gram-positive bacteria

OLD DRUGS

Comparison							
Vancomycin	1958	N/A	2 g/24 h	€ 518	14	MRSA *E. faecium* PNS-SP BHS	VRE
Daptomycin	2003	2006	6 mg/kg/24 h	€ 1008	14	MRSA *E. faecium* (including VRE) PNS-SP BHS	
Ceftriaxone	1984	N/A	2 g/24 h	€ 110	10	BHS PNS-SP	MRSA CoNS *E. faecium*
Linezolid	2000	2000	600 mg/12 h	€ 1040	10	MRSA CoNS BHS *E. faecium*	

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New and improved? A review of novel antibiotics for Gram-positive bacteria

NEW DRUGS

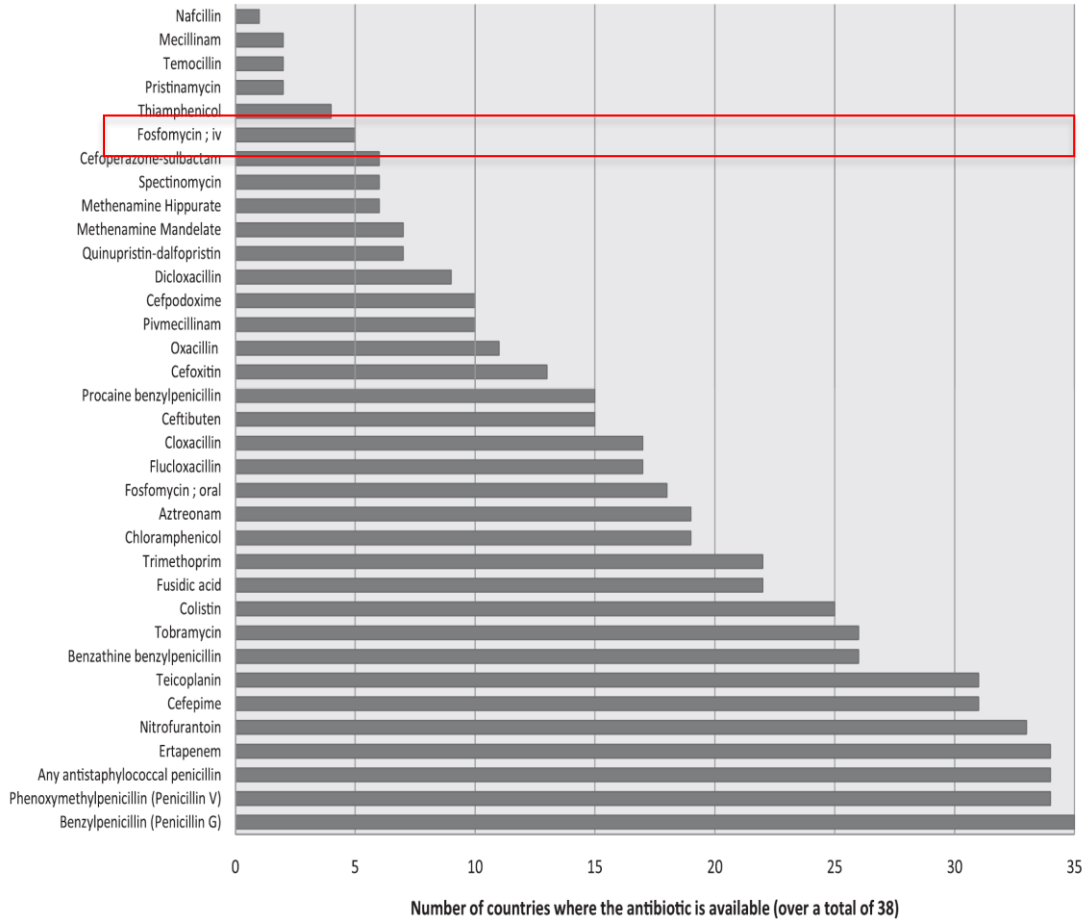
Table 1
Summary of approval status, dosage, approximate costs, and spectrum of activity of the antibiotics

Molecule	FDA approval	EMA approval	Dose (for normal renal function)	Total cost (for normal renal function and adult of ~70 kg)[a]	Typical treatment duration (days)	Spectrum of activity	Inactive against
Ceftaroline	2010	2012	600 mg/12 h	€ 1320	10	MRSA CoNS PNS-SP BHS *Haemophilus influenzae* *Enterococcus faecalis*	*Enterococcus faecium* VRE ESBL-E *Pseudomonas aeruginosa*
Ceftobiprole	not approved	not approved[b]	500 mg/8 h	€ 1990	10	MRSA CoNS PNS-SP BHS *H. influenzae* *P. aeruginosa*[c]	*E. faecium* VRE ESBL-E
Dalbavancin	2014	2015	1500 mg single dose (or 1000 mg followed 1 week later by 500 mg)	N/A	7–14	MRSA CoNS BHS *E. faecium*	VRE
Oritavancin	2014	2015	1200 mg single dose	€ 2260	10	MRSA CoNS BHS *E. faecium* (including VRE)	
Tedizolid	2014	2015	200 mg/24 h	€ 1008	6	MRSA CoNS BHS *E. faecium* (including VRE)	

M. Abbas et al. / Clinical Microbiology and Infection 23 (2017) 697–703

Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

Céline Pulcini,[1] Karen Bush,[2] William A. Craig,[3] Niels Frimodt-Møller,[4] M. Lindsay Grayson,[5] Johan W. Mouton,[6] John Turnidge,[7] Stephan Harbarth,[8] Inge C. Gyssens,[9,10] and the ESCMID Study Group for Antibiotic Policies



Fosfomycin

CID, 2012

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Clinical Appraisal of Fosfomycin in the Era of Antimicrobial Resistance

Sangeeta Sastry,[a] Lloyd G. Clarke,[b] Hind Alrowais,[a] Ashley M. Querry,[c] Kathleen A. Shutt,[a] Yohei Doi[a]

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Fosfomycin is recommended as one of the first-line agents for treatment of urinary tract infections (UTIs) in the latest guidelines endorsed by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). We evaluated the use of fosfomycin among inpatients at a tertiary care hospital between 2009 and 2013. UTI cases were defined using physician diagnosis and the National Healthcare Safety Network (NHSN) surveillance definitions. The number of patients treated with fosfomycin increased from none in 2009 to 391 in 2013. Among 537 patients who received fosfomycin for any indication during this period, UTI was the most common indication (74%), followed by asymptomatic bacteriuria (10%). All except 19 patients received a single dose of fosfomycin. *Escherichia coli* was the most common organism involved (52%). For 119 patients with UTIs, after exclusion of those with negative urine culture results, negative urinalysis results, receipt of additional agents, or indeterminate clinical outcomes, the clinical success rate at 48 h was 74.8%. Of 89 patients who met the criteria for NHSN-defined UTIs, 89.9% had successful outcomes. Recurrent infections occurred in 4.3% of cases, and mild adverse events were observed in 2.0%. All 100 randomly selected extended-spectrum β-lactamase (ESBL)-producing *E. coli* clinical isolates from this period were susceptible to fosfomycin. In conclusion, the use of fosfomycin has increased substantially since implementation of the updated guidelines at this hospital. Fosfomycin was used mainly for the treatment of physician-diagnosed UTIs, and the clinical outcomes were generally favorable. Fosfomycin maintained activity against *E. coli* despite the increased use of the agent.

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High Activity of Fosfomycin and Rifampin against Methicillin-Resistant *Staphylococcus aureus* Biofilm *In Vitro* and in an Experimental Foreign-Body Infection Model

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Infectious Diseases Service, Department of Medicine, University Hospital Lausanne, Lausanne, Switzerland[a]; National Institute of Infectious Diseases Prof. Dr. Matei Bals, Bucharest, Romania[b]; Institut de Biologie des Hôpitaux de Nantes, Service de Bactériologie-Hygiène, CHU de Nantes, Nantes, France[c]; Septic Surgical Unit, Department of Surgery and Anesthesiology, University Hospital Lausanne, Lausanne, Switzerland[d]; Center for Musculoskeletal Surgery, Charité-University Medicine, Berlin, Germany[e]

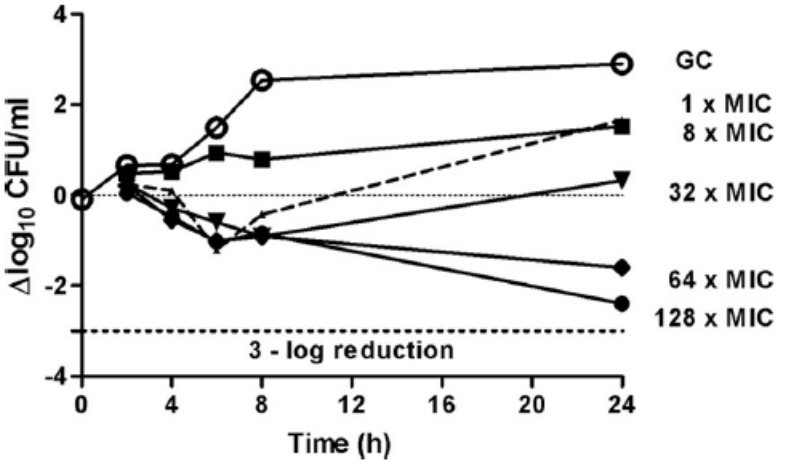
May 2014 Volume 58 Number 5 Antimicrobial Agents and Chemotherapy p. 2547–2553

Fosfomycin against MRSA biofilm in vitro

TABLE 1 Antimicrobial susceptibility of MRSA strain ATCC 43300 determined by Etest and microcalorimetry

Antimicrobial	Etest MIC (μg/ml)	MHIC (μg/ml) for MRSA[a]		
		Planktonic	Biofilm	Biofilm/planktonic
Fosfomycin	1	32	4,096	128
Daptomycin	0.125	0.125	40	320
Vancomycin	1	1	>1,024	>1,024
Rifampin	0.04	0.08	164	2,050
Tigecycline	0.125	0.125	128	1,024

[a] MHIC, minimal heat inhibitory concentration determined by microcalorimetry.



- Highest eradication of MRSA implant associated infections was achieved with fosfomycin
- Application in the treatment of prosthetic valve IE

May 2014 Volume 58 Number 5 Antimicrobial Agents and Chemotherapy p. 2547–2553

Clinical Infectious Diseases

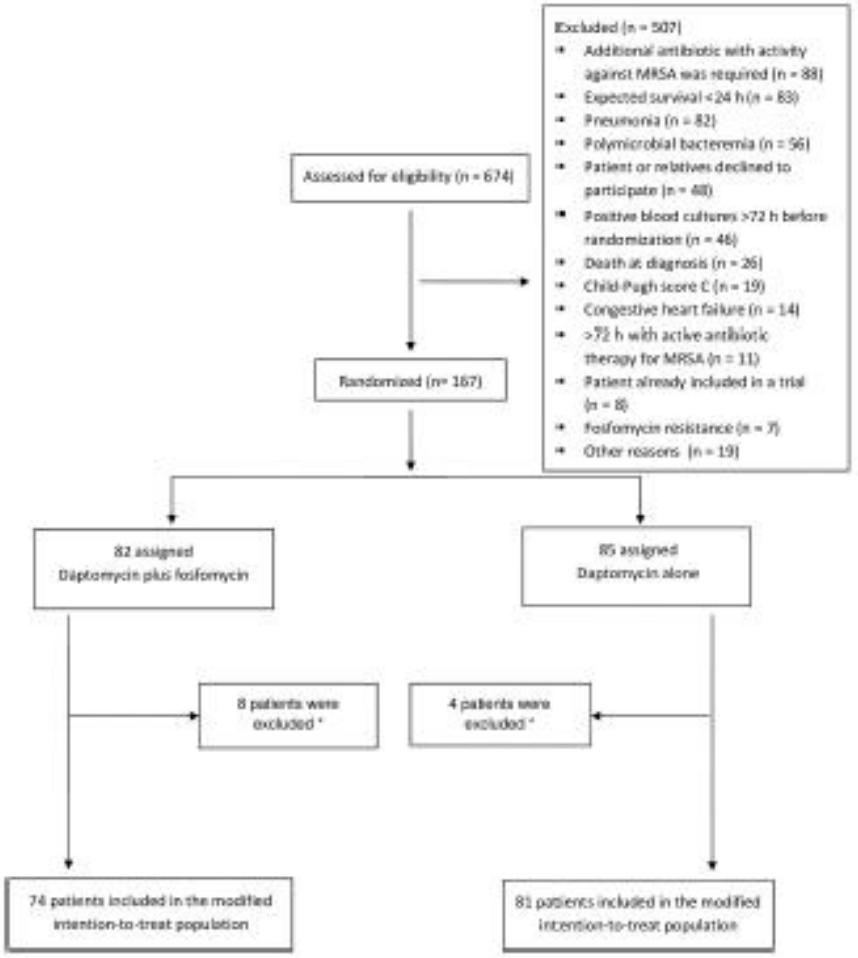
MAJOR ARTICLE

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Miquel Pujol,[1,a] José-María Miró,[2,a] Evelyn Shaw,[1] Jose-María Aguado,[3] Rafael San-Juan,[3] Mireia Puig-Asensio,[4] Carles Pigrau,[4] Esther Calbo,[5] Miguel Montejo,[6] Regino Rodriguez-Álvarez,[6] María-Jose Garcia-Pais,[7] Vicente Pintado,[8] Rosa Escudero-Sánchez,[8] Joaquín Lopez-Contreras,[9] Laura Morata,[2] Milagros Montero,[10] Marta Andrés,[11] Juan Pasquau,[12] María-del-Mar Arenas,[12] Belén Padilla,[13] Javier Murillas,[14] Alfredo Jover-Sáenz,[15] Luis-Eduardo López-Cortes,[16] Graciano García-Pardo,[17] Oriol Gasch,[18] Sebastian Videla,[19] Pilar Hereu,[19] Cristian Tebé,[20] Natalia Pallarès,[20] Mireia Sanllorente,[19] María-Ángeles Domínguez,[21] Jordi Càmara,[21] Anna Ferrer,[22] Ariadna Padullés,[22] Guillermo Cuervo,[1] and Jordi Carratalà[1,a]; for the MRSA Bacteremia (BACSARM) Trial Investigators

Daptomycin Plus Fosfomycin Versus Daptomycin Alone

- A randomized (1:1) study
- 167 patients
- MRSA Bacteremia
- MRSA Endocarditis
- 85 Daptomycin
- 82 Daptomycin + Fosfomycin
- 6 weeks of therapy
- End point: treatment success after the end of therapy



Daptomycin Plus Fosfomycin Versus Daptomycin Alone

Table 2. Primary and Secondary Outcomes

Outcome	Daptomycin Plus Fosfomycin, No. of Patients/Total (%)	Daptomycin Alone, No. of Patients/Total (%)	Relative Risk (95% CI)
Primary endpoint			
Treatment success at TOC	40/74 (54.1)	34/81 (42.0)	1.29 (.93–1.8)
Secondary endpoints			
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)	0.15 (.04–.63)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)	−6.2 (−11.4 to −.9)[a]
Positive blood cultures at TOC	0/74 (0.0)	4/81 (4.9)	−4.9 (−9.7 to −.2)[a]
Microbiological failure at TOC	0/74 (0.0)	9/81 (11.1)	−11.1 (−18.0 to −4.3)[a]
No. of episodes of complicated bacteremia at TOC	12/74 (16.2)	26/81 (32.1)	0.51 (.28–.94)
Any AE leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)	3.56 (1.21–10.44)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)	0.55 (.14–2.12)
Overall mortality at TOC	18/74 (24.3)	22/81 (27.2)	0.9 (.53–1.54)

Daptomycin Plus Fosfomycin Versus Daptomycin Alone

Table 3. Reasons for Treatment Failure at Test of Cure

Reason for Treatment Failure	Daptomycin Plus Fosfomycin, No. (%) of Patients (n = 74)	Daptomycin Alone, No. (%) of Patients (n = 81)	Proportion Difference (95% CI)	*P* Value[a]
Treatment failure[b]	34 (45.9)	47 (58.0)	−12.1 (−27.7 to 3.6)	.133
Mortality at TOC	18 (24.3)	22 (27.1)	−2.8 (−16.6 to 10.9)	.687
Clinical failure[c]	0 (0.0)	3 (3.7)	−3.7 (−7.8 to .4)	.247[d]
Microbiological failure	0 (0.0)	9 (11.1)	−11.1 (−18.0 to −4.3)	.003[d]
Any AE leading to treatment discontinuation	13 (17.6)	4 (4.9)	12.6 (2.8–22.5)	.012
Additional antimicrobial therapy administered before TOC[e]	9 (12.1)	19 (23.4)	−11.3 (−23.2 to .6)	.068
Lack of blood cultures at TOC	8 (10.8)	4 (4.9)	5.9 (−2.6 to 14.4)	.172
Loss to follow-up	1 (1.3)	3 (3.7)	−2.4 (−7.2 to 2.5)	.622[d]

Diagnostic Microbiology and Infectious Disease 98 (2020) 115153

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

In vitro activity of ceftaroline and ceftobiprole against clinical isolates of Gram-positive bacteria from infective endocarditis: are these drugs potential options for the initial management of this disease?

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ARTICLE INFO

Article history:
Received 19 January 2020
Received in revised form 16 July 2020
Accepted 20 July 2020
Available online 28 July 2020

Keywords:
Ceftaroline
Ceftobiprole
Infective endocarditis

ABSTRACT

The in vitro activity of ceftaroline and ceftobiprole was assessed against 77 Gram-positive bacterial isolates recovered from patients diagnosed with infective endocarditis (IE). Our data confirm that these drugs are highly in vitro active against the most common agents of IE including methicillin-resistant *Staphylococcus aureus*, methicillin-resistant coagulase-negative staphylococci, and *Streptococcus* spp., with no significant differences between them. Also, ceftaroline and ceftobiprole have demonstrated a good activity against *Enterococcus faecalis* (MIC_{90} 0.75 μg/mL and 0.5 μg/mL, respectively). The spectrum of these drugs together with the in vitro and in vivo data on them related with IE published in the scientific literature places them as potential options for the initial management of this disease.

International Journal of Antimicrobial Agents 53 (2019) 644–649

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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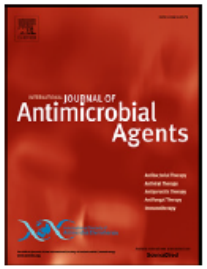

Ceftaroline fosamil for the treatment of Gram-positive endocarditis: CAPTURE study experience

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Ceftaroline in IE

- 55 patients with Gram positive endocarditis
- MRSA 77.3%
- MSSA 25%
- CoNS 50%
- Ceftaroline
  - first line therapy 7.3%
  - second line therapy 70.6%
  - monotherapy 41%
- Clinical success was observed in 39/55 (70.9%)

International Journal of Antimicrobial Agents 53 (2019) 644–649

Table 3
Clinical success rates for ceftaroline fosamil treatment among patients with Gram-positive infective endocarditis.

Clinical success, *n*/*N* (%)	Patients (*n*=55)
Overall clinical success	39/55 (70.9)
Line of therapy	
First-line	3/4 (75.0)
Second-line or later	36/51 (70.6)
Treatment setting	
General hospital ward	19/23 (82.6)
ICU	20/32 (62.5)
Type of endocarditis	
Right-sided	21/26 (80.8)
Left-sided	17/25 (68.0)
Bilateral	1/4 (25.0)
BMI (kg/m^2)	
Underweight (<18.5)	1/1 (100)
Normal (18.5–24.9)	11/14 (78.6)
Overweight (25.0–29.9)	8/15 (53.3)
Obese (≥30)	17/23 (73.9)
Type of bacterial infection	
MRSA	34/44 (77.3)
MSSA	1/4 (25.0)
CoNS	3/6 (50.0)
Type of therapy	
Monotherapy	19/23 (82.6)
Concurrent therapy	20/32 (62.5)
Risk factor	
IDU	17/21 (81.0)
IVD	16/24 (66.7)
Dosing regimen	
q8h	16/23 (69.6)
q12h	24/35 (68.6)
q24h	2/3 (66.7)
Treatment duration (days)	
<11	14/26 (53.8)
≥11	25/29 (86.2)

International Journal of Infectious Diseases 81 (2019) 210–214

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Multicenter clinical experience of real life Dalbavancin use in gram-positive infections

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Multicenter clinical experience of real life Dalbavancin use in gram-positive infections

Table 1
Demographic information (n = 101).

Variable	n (%)
Age, y, median (range)	65 (11–93)
Sex	
Male	57 (56.4)
Female	44 (43.6)
Infection type	
PJI	32 (31.7)
Osteomyelitis (including vertebral osteomyelitis)	30 (29.7)
Endocarditis	25 (24.8)
Native valve	15 (14.9)
Prosthetic valve	6 (5.9)
Cardiac implantable electronic device	4 (4)
ABSSSI	11 (10.9)
CRBSI	3 (3)
Pathogens	
CNS	28 (33)
MSSA	14 (16)
MRSA	8 (9)
Enterococci	7 (8)
Streptococci	5 (6)
Propionibacterium acnes	4 (5)
>1 gram-positive pathogen	16 (15.8)
Mixed infection (gram-positive plus gram-negative)	5 (5)
Dalbavancin regimen	
1 × 1500 mg	24 (23.8)
1 × 1500 mg d1 + d8	14 (13.9)
1 × 1500 mg d1 + d8 and in week 8	3 (3)
1 × 1000 mg d1 followed by 500 mg weekly	43 (42.6)
1 × 1000 mg every 14d	3 (3)
Other regimens	14 (13.9)

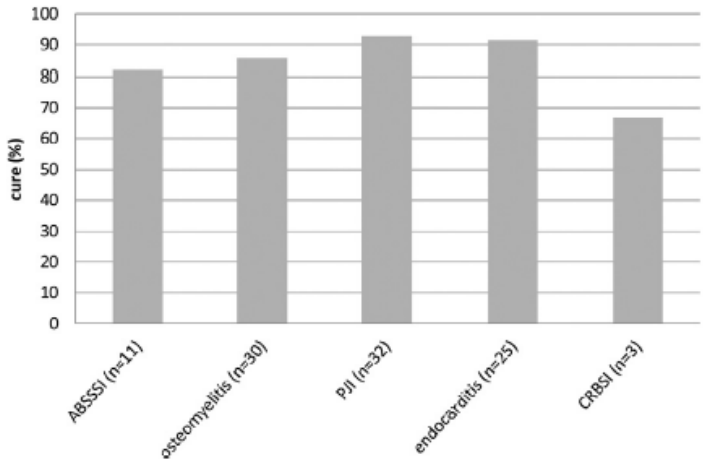

Figure 1. Percentage of cured patients in different indications for dalbavancin use.

- Dalbavancin prolonged half life
- IE off label indications
- Success rate was high 89%,
- Good tolerability and safety

International Journal of Infectious Diseases 81 (2019) 210–214

Hidalgo-Tenorio *et al.*
Ann Clin Microbiol Antimicrob (2019) 18:30
https://doi.org/10.1186/s12941-019-0329-6

Annals of Clinical Microbiology and Antimicrobials

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DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection produced by gram-positive cocci

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DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection

Table 1 Characteristics of patients with infective endocarditis

	N = 34
Age, median (IQR)	73 (63–81)
Male, n (%)	25 (73.5)
Charlson index, n (%)	2 (1–4)
Type of infection, n (%)	
Definite IE	31 (91.2)
Early prosthetic	5 (14.7)
Late prosthetic	10 (29.4)
Pacemaker lead	8 (23.5)
Valve affected, n (%)	
Aortic	17 (50)
Mitral	8 (23.5)
Tricuspid	1 (2.9)
Causative organism, n (%)	
MSSA	7 (20)
MRSA	3 (8.6)
CNS	15 (42.9)
E. faecalis	3 (8.6)
Streptococcus spp.	7 (20)
Patient received prior antibiotic therapy, n (%)	34 (100)
Days of previous antibiotic treatment, median (IQR)	28 (17–35)
Prior antibiotic therapy, n (%)	
Daptomycin	24 (68.6)
Ceftriaxone	10 (28.6)
Linezolid	3 (8.6)
Vancomycin	8 (22.9)
Surgery, n (%)	12 (34.3)
Surgery before administering DBV	11 (91.6)
Reason for DBV administration, n (%)	
1000 mg 1 day	5 (14.7)
1500 mg (1 day)	12 (35.3)
1000 mg (1 day), 500 mg (8 days), 500 mg (15 days)	1 (2.9)
1500 mg (1 day), 1000 mg (15 days)	3 (.8)
1500 mg (1 day), 1000 mg (15 days, 30 days, 45 days)	1 (2.9)
1000 mg (1 days), 500 mg every week/9 weeks	1 (2.9)
1500 mg (1 days), 1000 mg every 2 weeks/10 weeks	1 (2.9)
DBV-covered days, median (IQR)	14 (14–21)
Clinical cure, n (%)	34 (100)
Microbiological cure, n (%)	33 (97.1)
Follow-up blood cultures:	17 (48.6)
Negative follow-up blood cultures	17 (100)
IE-related death, n (%)	
During hospitalisation	0
At 12 months	0
Relapse, n (%)	0

Conclusions: DBV is an effective consolidation antibiotic therapy in clinically stabilized patients with IE and/or BSI. It proved to be a cost-effective treatment, reducing the hospital stay, thanks to the pharmacokinetic/pharmacodynamic profile of this drug.

Infection (2020) 48:323–332
https://doi.org/10.1007/s15010-020-01415-6

REVIEW

Infections causing stroke or stroke-like syndromes

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Received: 14 January 2020 / Accepted: 20 March 2020 / Published online: 1 April 2020

Infections causing stroke or stroke-like syndromes

- Stoke-like presentation can be reported in 25% of endocarditis
- Diagnosis impact in terms of antibiotic treatment choices and outcome
- Probability of survival of patients with infective endocarditis according to the presence or absence of neurologic complication

Infection (2020) 48:323–332
https://doi.org/10.1007/s15010-020-01415-6

Stroke-like presentation of endocarditis

The incidence of neurologic complications in patients suffering an infective endocarditis was investigated in a large Spanish study collecting retrospective data of more than 1200 cases from 8 reference centres [30]. The study highlighted that 340 (25%) patients with infective endocarditis experienced neurologic complications and that ischaemic events accounted for 56% of these cases. Small embolism with transient neurologic symptoms was reported in the majority of ischaemic cases, but those with more severe presentation frequently had multiple embolisms and involvement of both brain hemispheres. Moreover, haemorrhagic events were reported in 60 cases (18%), with a high percentage of cases with primary haemorrhage. On the basis of the multivariate analysis of the factors associated with brain embolism during endocarditis, *Staphylococcus aureus* and a vegetation size > 30 mm were associated with both ischaemic or haemorrhagic events and those with an age > 70 years reported more frequently haemorrhagic events. The results of this study demonstrated that stroke-like presentations can be reported in many cases with endocarditis, suggesting particular attention for patients presenting with an oligosymptomatic stroke and fever.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Parallels between Cancer and Infectious Disease

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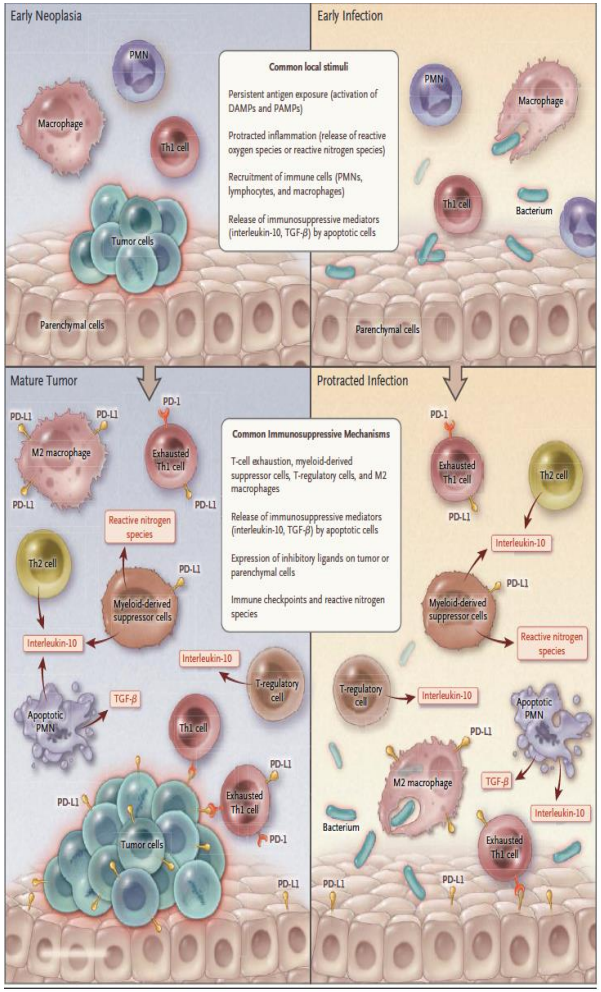

Parallels between Cancer and Infectious Disease

Early Neoplasia Vs Early Infection

Infectious diseases and cancer have multiple similarities. Both infectious organisms and cancer cells express many proteins that are recognizable by host T cells,[1] and both elicit T-cell–mediated inflammation. An essential aspect of T-cell homeostasis is that the responses of these cells must eventually diminish to avoid toxicity from excessive T-cell proliferation and cytokine release. Unfortunately, this can lead to a loss of appropriate T-cell responses, especially in advanced cancer and chronic infections.

Mature Tumor Vs Chronic Infection

N ENGL J MED 371;4 NEJM.ORG JULY 24, 2014

The New England Journal of Medicine