Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Table 1: Distribution of microorganisms according to infective endocarditis classifications

	Native valve endocarditis (78%)				**PM and Def IE (5%)**	**Prosthetic valve IE (17%)**			**TOTAL**
	Community-acquired IE **55%**	Health care-associated **18%**		Drug abusers **5%**		Early (< 2 mths) **1.0%**	Mid term (2 – 12mths) **3.0%**	Late (> 12 mths) **13%**	
Pathogens		Nosocomial **15%**	Non-nosocomial **3%**						
Staphylococcus aureus	20/**20 %**	**44**/47%	**25**/42%	68/**81%**	**23%**	36/**0%**	**7%**	**25%**	**26 %**
CN Staphylococci	**4**/6%	12/**15%**	15/**25%**	**0**/3%	**54%**	**0**/17%	**27%**	**9%**	**10 %**
Oral streptococci*	**26**/28%	**7**/11%	**0**/6%	**4**/10%	**0%**	**0**/2%	**7%**	**11%**	**18 %**
Streptococcus bovis **	10/**18%**	**3 %**	3/**8%**	**0**/1%	**4%**	**0**/2%	**7%**	**9%**	**13 %**
Enterococcus	**9%**	**6**/14%	17/**42%**	**4**/5%	**0%**	7.5/**20%**	**7%**	**20%**	**10 %**
Pyogenic streptococci	**8%**	**0%**	**0%**	**4%**	**0%**	**0%**	**0%**	**3%**	**5 %**
Others	**6%**	**14%**	**0%**	**0/**3%	**16%**	**0%**	**33%**	**12%**	**8 %**
Negative-blood culture	**9.5**/11%	**9**/9 %	**0**/6%	**0**/5%	8%	17/**40%**	**13%**	**12%**	**9%**
Microorganism not identified	**5%**	**4.5%**	**0%**	**0%**	**0%**	**40%**	**13%**	**8%**	**5%**

Note: All figures refer to patients. Bold-typed values correspond to the 2008 French population-based study on definite IE.[1] Other values are based on tertiary care center IE studies reported in the literature.[2, 3] The percentage sum may not be 100% as some patients have more than 2 microorganisms responsible for IE and "microorganisms not identified" are also included in the "negative blood culture" group.

Native valve IE (NVE) is the most frequent form of IE (70 to 80%) [4-6]
Community-acquired IE in non-IDU patients is the most important group of IE, (50 to 70% of cases). Causative microorganisms are predominantly from the oral cavity (oral streptococci), the digestive tract (group D streptococci or *Enterococcus*), the skin (staphylococci), and the urinary tract in males (*Enterococcus*).
Health care-associated IE (excluding prosthetic valve IE) (HCA-IE) include nosocomial and non-nosocomial IE.[7] HCA-IE represents 25 to 35% of IE cases in industrialized countries.[1, 2, 7, 8] The affected population has more comorbidities, and is more frequently hemodialysis-dependent.[1, 2, 7-9] HCA-IE in-hospital mortality is 15 - 35%.[1, 7, 10]
Injection drug users (IDU) rate may be as high as 16% in recent series of IE in the USA.[1, 2, 8] Incidence (3.3/1000 IDUs-years) increases with daily drug use and in females. Majority are right sided IE [1, 2, 8]. Implantable defibrillator IE incidence is higher than PM IE one. A concomitant valve infection is observed in around 40% of the patients.[11] Bacteremia may be responsible for the concomitant inoculation of left-sided cardiac valves
Early **prosthetic valve IE** mainly results from valve inoculation at the time of surgery and is due to usual nosocomial microorganisms. Fungi are responsible for 10% of IE cases in some studies. Infection usually develops on the suture area between the prosthesis and the annulus and is often responsible for perivalvular abscess. Progressive endothelialization of the prosthetic valve is associated with a reduced risk of IE and a shift in IE-causing pathogens whose distribution becomes closer to that observed in NVE (Late prosthetic valve IE).
CN staphylococci: Coagulase negative Staphylococci.
* Oral (formerly viridans) streptococci include *S. sanguis, S. mitis, S. salivarius, S. mutans*, and *Gemella morbillorum*.
** *Streptococcus bovis/Streptococcus equinus* complex, formerly referred to as *Streptococcus bovis.*

Supplementary Table 2: Recommended antibiotic regimens for most frequent situations of IE.
Guidelines are adapted from the guidelines by the European Society of Cardiology. [12] Significant differences with the AHA guidelines are acknowledged in the Comments.
Dosages are for adult patients with normal renal function

Sub-table 2A: Initial treatment of IE before or without pathogen identification

Antibiotic	***Dosage and Route***	***Duration (weeks)***	***Comments***
Native valves			
Ampicillin-sulbactam,	*12 g/day IV in 4 doses*	*4-6*	*Patients with blood-culture negative IE should be treated in consultation with an infectious disease specialist*
or			
amoxicillin-clavulanate,	*12 g/day IV in 4 doses*	*4-6*	
with			
gentamicin [(a)]	*3 mg/kg/day IV in 2 or 3 doses.*	*4-6*	
Vancomycin [(b)]	*30 mg/kg/day IV in 2 doses*	*4-6*	*This regimen is intended to patients unable to tolerate beta-lactams.*
with *gentamicin* [(a)]	*3 mg/kg/day IV in 2 or 3 doses.*	*4-6*	
with *ciprofloxacin*	*800 mg/day IV in 2 doses*		*Ciprofloxacin is not uniformly active on Bartonella spp. Consider adding doxycycline if Bartonella spp. is likely.*
	or 1000 mg/day orally in 2 doses	*4-6*	
Prosthetic valves (early, < 12 months post surgery)			
Vancomycin [(b)]	*30 mg/kg/day IV in 2 doses*	*6*	*If no clinical response, surgery and maybe extension of the antibiotic spectrum to gram-negative pathogens must be considered*
with *gentamicin* [(a)]	*3 mg/kg/day IV in 2 doses*	*2*	
with *rifampin*	*1200 mg/day orally in 2 doses*	*6*	
Prosthetic valves (late, ≥ 12 months post surgery)			
Same as for native valves			

Sub-table 2B: Antibiotic treatment of IE due to staphylococci

Antibiotic	***Dosage and Route***	***Duration (weeks)***	***Comments***
Native valve IE			
<u>Methicillin-susceptible staphylococci</u>:			
Oxacillin or Cloxacillin or Nafcillin	*12 g /day IV in 4-6 doses*	*4-6*	*The use of gentamicin is optional (e.g. in patients with severe sepsis) and at most limited to 3 days. In the guidelines by the BSAC and those by the IDSA for MRSA bacteremia, the use of gentamicin is no longer recommended for staphylococcal native valve IE.*[13, 14]
±			
Gentamicin [(a)]	*3 mg/kg/day IV in 2 doses*	*3 days*	
<u>Penicillin-allergic patients or methicillin-resistant staphylococci</u>:			
Vancomycin [(b)]	*30 mg/kg/day IV in 2 doses*	*4-6*	*Cefazolin 6 g/day in 3 doses is an alternative to Vancomycin in the AHA guidelines*
±			
Gentamicin [(a)]	*3 mg/kg/day IV in 2 doses*	*3 days*	
Prosthetic valve IE			
<u>Methicillin-susceptible staphylococci</u>:			
Oxacillin or Cloxacillin or Nafcillin	*12 g /day IV in 4-6 doses*	*<u>≥</u> 6*	*Rifampin increases the hepatic metabolism of warfarin and other drugs.*
***with** rifampin* [(c)]	*1200 mg/day IV or orally in 2 doses*	*<u>≥</u> 6*	*The clinical benefit of adding gentamicin is not clearly established but is recommended for PVE, in combination with Rifampin.*
***with** gentamicin* [(a)]	*3 mg/kg/day IV in 2 or 3 doses*	*2*	
<u>Penicillin-allergic patients and methicillin-resistant staphylococci</u>:			
Vancomycin [(b)]	*30 mg/kg/day IV in 2 doses*	*<u>≥</u> 6*	
***with** rifampin* [(c)]	*1200 mg/day IV or orally in 2 doses*	*<u>≥</u> 6*	
***and** gentamicin* [(a)]	*3 mg/kg/day IV or IM in 2 or 3 doses*	*2*	

Sub-table 2C:Antibiotic treatment of IE due to oral streptococci and group D streptococci			
Antibiotic	***Dosage and Route***	***Duration (weeks)***	***Comments***
<u>Penicillin-susceptible (MIC <0.125 mg/l) oral and group D streptococci</u>			
Standard treatment			
Penicillin G	*12-18 million U/day IV in 6 doses*	*4*	*Preferred in patients > 65 years or with impaired renal function.*
or			
Amoxicillin[(d)]	*100 mg/kg/day IV in 4-6 doses*	*4*	*Gentamicin (3 mg/kg/day IV or IM in 1 dose) should be added fort he first 2 weeks in prosthetic valve IE*
or			
Ceftriaxone[(e)]	*2 g/day IV or IM in 1 dose*	*4*	
Two-week treatment (for non complicated native valve IE)			
Penicillin G	*12-18 million U/day IV in 6 doses*	*2*	*Absence of complications includes no extracardiac infectious foci, normal renal function, and no surgical treatment.*
or			
Amoxicillin[(d)]	*100 mg/kg/day IV in 4-6 doses*	*2*	
or			
Ceftriaxone[(e)]	*2 g/day IV or IM in 1 dose*	*2*	
with			
Gentamicin[(f)]	*3 mg/kg/day IV or IM in 1 dose*	*2*	
In beta-lactam allergic patients			
Vancomycin[(g)]	*30 mg/kg/day IV in 2 doses*	*4*	
<u>Penicillin-relatively resistant (MIC 0.125 – 2 mg/l) strains[h]</u>			
Standard treatment			
Penicillin G	*24 million U/day IV in 6 doses*	*4*	
or			
Amoxicillin[(d)]	*200 mg/kg/day IV in 4-6 doses*	*4*	
with			
Gentamicin[(f)]	*3 mg/kg/day IV or IM in 1 dose*	*2*	
In beta-lactam allergic patients			
Vancomycin[(g)]	*30 mg/kg/day IV in 2 doses*	*4*	

Sub-table 2D:Antibiotic treatment of IE due to Enterococcus spp.

Antibiotic	***Dosage and Route***	***Duration (weeks)***	***Comments***
<u>Beta-lactam and gentamicin susceptible strains (for resistant isolates see [i,j,k])</u>			
Amoxicillin[d]	*200 mg/kg/day IV in 4-6 doses*	*4-6*	*6-week therapy recommended for patients with*
***with** gentamicin[a]*	*3 mg/kg/day IV or IM in 2 doses.*	*4-6*	*>3 months symptoms.*
or			
Vancomycin[g]	*30 mg/kg/day IV in 2 doses*	*6*	
***with** gentamicin[a]*	*3 mg/kg/day IV or IM in 2 or 3 doses.*	*6*	

Sub-table 2E: Antibiotic treatment of IE due to selected fastidious organisms[l]

Pathogens	***Proposed therapy***	***Treatment outcome***
Brucella spp.	*Doxycycline (200 mg/24h)* *plus cotrimoxazole (960 mg/12h)* *plus rifampin (300-600/24h)* *for ≥ 3 months orally*	*Treatment success defined by an antibody titre <1:60*
Coxiella burnetii (agent of Q fever)	*Doxycycline (200mg/24h)* *plus hydroxychloroquine (200-600mg/24h) [m] orally* ***or*** *Doxycycline (200mg/24h)* *plus quinolone (ofloxacin, 400mg/24h) orally* *for ≥ 18 months*	*Treatment success defined by anti-phase I IgG titer <1:200, and IgA and IgM titers <1:50*
Bartonella spp.	*Ceftriaxone (2g/24h) or amoxicillin[d] (12g/24h) IV* *or Doxycycline (200mg/24h) orally* *for 6 weeks* ***with*** *Gentamicin (3mg/24h) IV* *for 3 weeks[a]*	*Treatment success expected in ≥ 90%. Combination with an aminoglycoside is key to cure*
Tropheryma whipplei *(agent of Whipple's disease)*	*Cotrimoxazole[n]* *Penicillin G (1.2 MU/24h) and streptomycin (1g/24h) IV* *for 2 weeks, then cotrimoxazole orally* *for 1 year* ***or*** *Doxycycline (200mg/24h) with hydroxychloroquine (200-600mg/24h) orally* *for ≥ 18 months*	*Long-term treatment, optimal duration unknown.*

[(a)] Renal function and serum gentamicin concentrations should be monitored once/week (twice/week in patients with renal failure). Trough concentrations should be < 0.5 mg/l.
[(b)] Serum vancomycin concentrations should achieve 20-30 mg/L at pre-dose (trough) level and 30–45 mg/L at post-dose level (peak; 1 h after infusion is completed).
[(c)] Rifampin is believed to play a special role in prosthetic device infection because it helps eradicate bacteria attached to foreign material. Rifampin should always be combined with another effective antistaphylococcal drug to mimize the risk of resistant mutant selection.
[(d)] or Ampicillin, same dosage.
[(e)] Preferred option for outpatient therapy
[(f)] Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, trough concentrations should be < 1 mg/l.
[(g)] Serum vancomycin concentrations should achieve 10–15 mg/L at pre-dose (trough) level and 30–45 mg/L at post-dose level (peak; 1 h after infusion is completed).
[(h)] For strains resistant to penicillin (MIC > 2 mg/l), regimens recommended for enterococcal IE (subtable 2d) should be used.
[(i)] <u>High-level resistance to gentamicin (MIC >500 mg/l)</u>: if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in 2 equally divided doses. Otherwise, use more prolonged course of β-lactam therapy. The combination of ampicillin (12 g/ 24h) with ceftriaxone (2g twice daily) was recently suggested for high-level gentamicin-resistant E. faecalis.[15] but also for non-highly gentamicin-resistant strains.[16]
[(j)] <u>beta-lactam resistance</u>: (i) if due to beta-lactamase production, replace ampicillin with ampicillin-sulbactam or amoxicillin with amoxicillin-clavulanate; (ii) if due to PBP5 alteration, use vancomycin-based regimens.
[(k)] <u>Multi-resistance to aminoglycosides, β-lactams and vancomycin</u>: suggested alternatives are: (i) linezolid 2x600 mg/day IV or orally for <u>≥</u>8 weeks (monitor hematological toxicity), (ii) β-lactam combinations including imipenem plus ampicillin or ceftriaxone plus ampicillin for <u>≥</u>8 weeks.
[(l)] Optimal duration of treatment of IE due to these pathogens is unknown. The durations presented are based on selected case reports and experts' opinion.
[(m)] Doxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine concentrations (target 0.8-1.2 mg/L)) is significantly superior to doxycycline.
[(n)] Treatment of Whipple IE remains highly empirical. Successes have been reported with long-term (> 1 year) cotrimoxazole therapy.

Supplementary Table 3: Recommended antibiotic prophylaxis regimens for dental procedures

			Single dose within 60 minutes preceding the procedure	
		Antibiotic	**Adults**	**Children**
No allergy to beta lactams				
Oral intake	possible	Amoxicillin	2 g p.o.	50 mg/kg p.o.
	not possible	Ampicillin	2 g i.v.	50 mg/kg i.v.
Allergy to beta lactams				
Oral intake	possible	Clindamycin (1)	600 mg p.o.	20 mg/kg p.o.
	not possible	Clindamycin (2)	600 mg i.v.	20 mg/kg i.v.

(1) alternatively Cephalexin: 2 g i.v. for adults or 50 mg/kg i.v. for children

(2) alternatively Cefazolin or Ceftriaxone: 1 g i.v. for adults or 50 mg/kg i.v. for children

Cephalosporins should not be used in patients with history of anaphylaxis, angioedema, or urticaria after Penicillin and Ampicillin intake

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