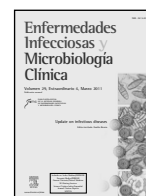




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New trends in infective endocarditis

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ABSTRACT

Keywords:

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Prognostic factors
Nosocomial endocarditis

The present article is an update of the literature on endocarditis. A multidisciplinary group of Spanish physicians with an interest in cardiac infections selected the most important papers produced lately in the field. Two of the members of the group discussed the content of each of the selected papers, with a critical review by others members of the panel. After a review of the state of the art papers from the fields of epidemiology, new causative microorganisms (bacterial and fungal), clinical findings including those in special patients, laboratory diagnosis, prognostic factors, nosocomial endocarditis, prophylaxis, new drugs and guidelines for antibiotic treatment were discussed by the group.

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Nuevos retos en endocarditis infecciosa

RESUMEN

Palabras clave:

Endocarditis
Diagnóstico
Tratamiento
Profilaxis
Factores pronósticos
Endocarditis nosocomial

Este artículo resume una actualización bibliográfica de las novedades más destacables de la endocarditis bacteriana. Un grupo multidisciplinario de médicos españoles con experiencia en las infecciones cardíacas seleccionó las publicaciones más importantes en este campo aparecidas recientemente en la bibliografía. El contenido de cada uno de los artículos seleccionados fue expuesto y discutido por 2 de los miembros del grupo, después del cual los miembros restantes efectuaron una revisión crítica. Después de la revisión, el grupo discutió las publicaciones sobre la epidemiología, los microorganismos causales poco frecuentes, el diagnóstico de laboratorio, la presentación en pacientes con problemas especiales, los factores pronósticos, la endocarditis nosocomial, la profilaxis antibiótica y las nuevas guías de tratamiento antibiótico, así como la utilización de nuevos antibióticos.

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State of the art

The clinical features of infective endocarditis (IE) as described by Osler have undergone many changes in developed countries¹⁻⁶. IE was a disease that commonly affected patients with predisposing valvular abnormalities caused by rheumatic carditis, and *viridans* group streptococci were the most common pathogens. This presentation is still seen in developing countries where rheumatic heart disease is prevalent. This group of at-risk patients is, however, being surpassed by new at-risk groups, including injection drug users, elderly people with valvular sclerosis, patients with cardiovascular prostheses, those with nosocomial exposure, and hemodialysis patients^{7,8}.

Staphylococci and streptococci account for the majority of the cases with notable trends toward a rising prevalence of staphylococcal skin flora caused by iatrogenic nosocomial infection, *Staphylococcus aureus* affecting intravenous drug users, and *Streptococcus bovis* in the elderly often associated with an underlying gastrointestinal neoplasm⁷⁻¹¹. Culture negative IE may be noted in up to one-third of cases^{12,13}. This most commonly is a consequence of prior antibiotic use, but an increasingly common scenario is infection by fastidious organisms with limited proliferation under conventional culture conditions¹⁴. Such organisms include *Coxiella*, *Bartonella*, *Legionella*, *Tropheryma whipplei*, fungi, and the HACEK group of bacteria (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella*)^{15,16}. In addition, the diagnosis of other slow growing microorganisms such as *Propionibacterium* is often missed due to the prolonged incubation (7-14 days) required for isolation from blood cultures¹⁷. Three to five sets of blood cultures, each from a separate venipuncture, incubated in both aerobic and anaerobic atmospheres, should be obtained over 24 hrs. If obtained before antibiotic administration, the initial sets of blood cultures will generally be positive in individuals with bacterial endocarditis within a 48 hr to 72 hr period¹⁸. The "microbiological adaptations" to the Duke criteria supported by the American Heart Association include the mere presence of a positive blood culture for *S. aureus*, regardless of whether community-acquired or not; a single positive blood culture for *Coxiella burnetii*; and a surrogate for positive blood cultures (antiphase 1 IgG antibody titre against *Coxiella* 1:800) helpful in establishing the diagnosis when blood cultures may be negative (culture-negative endocarditis)¹⁹. Currently, surgery is required in 20%-40% of patients with IE²⁰, but cultures of valvular tissue are generally unreliable due to prior antimicrobial therapy (false negatives) or to contamination during handling from resection to laboratory processing (false positives)^{21,22}. To overcome these limitations, several recent reports have demonstrated the utility of culture-independent universal 16S rRNA gene polymerase chain reaction (PCR) combined with sequencing in the diagnosis of IE and in the recognition of new IE pathogens²³⁻²⁶. To evaluate the serum levels and diagnostic value of cytokines and acute phase proteins in patients with infective IE have been the objectives of several studies. However, only IL 6 and CRP have been found consistently elevated in IE patients compared to non-infected controls²⁷.

Prosthetic valve endocarditis (PVE) is a rare but severe complication of valve replacement and has been reported to occur with 0.98% per patient-year incidence^{28,29}. The cumulative incidence at 5 years is 3% and at 10 years 5%, with a case-mortality rate ranging from 25 to 59% despite improvements in prophylaxis, diagnosis, and treatment^{30,31}. The best therapeutic option in PVE is still under debate. Although a medical surgical therapy is said to represent the best choice, medical therapy can be sufficient in some patients³²⁻³⁴.

Since 1954, prophylaxis has been the principal strategy used to decrease the incidence of the disease. According to the physiopathology of the infection, different national scientific societies have drawn up diverse guides mainly based on experimental animal models, though no randomized clinical studies have proved so far their efficiency³⁵⁻³⁹.

The current trend is to reduce the indication of IE prophylaxis to a limited number of procedures, mainly of the oral cavity and as long as there is an underlying at-risk heart condition.

The IE antimicrobial treatment is based on expert opinion consensus guides^{12,19,40-44}, of which the American Heart Association's is probably the most established. The last edition¹⁹, compared with the previous version from 1995, reports some changes owing to the resistance of most common microorganisms causing IE: *Streptococcus* sp, *Enterococcus* sp. and *Staphylococcus* sp. The 15-20% of group *viridans* *Streptococcus* sp. are now resistant to penicillin (minimal inhibitory concentration, MIC > 0.5 mg/mL) and patients with this type of endocarditis should now receive a combination of a betalactam (penicillin or ceftriaxone) and an aminoglycoside until definitive microbiology results are available⁴⁵. Some authors recommend the use of vancomycin when the MIC of penicillin and ceftriaxone is ≥ 4 μ g/mL⁴⁶.

The treatment of enterococcal endocarditis has also been reconsidered since the relatively often resistance to penicillin and the growing resistance to aminoglycosides and glycopeptides. The combination of penicillin, ampicillin or vancomycin with gentamicin or streptomycin during the complete episode has a synergic and bactericidal effect against this microorganism and it is classically considered the best choice of treatment. Recently, it has been proposed that a shorter aminoglycoside regime (only during 2-3 weeks) might be adequate⁴⁷. The bactericidal synergic effect against *Enterococcus* sp. disappear when the microorganism presents a high level resistance to aminoglycosides (≥ 500 μ g/mL for gentamicin or ≥ 1000 μ g/mL for streptomycin). The strains with high resistance to gentamicin (> 25%) show also crossed-resistance to netilmicin, kanamicin, tobramycin and amikacin and only a few (20-30%) are susceptible to streptomycin. When there is a total resistance to aminoglycosides a therapeutic regime consistently bactericidal is precluded. Based upon former studies, high ampicillin doses in continuous perfusion might cure the 30-40% of this type of endocarditis, always considering concomitant cardiac surgery whenever feasible. Combined ampicillin and ceftriaxone have shown a good activity in an experimental enterococcal endocarditis model^{48,49} and the clinical efficacy of this combination has been reported⁵⁰, becoming an alternative to more classically accepted therapy. The optimal treatment of endocarditis caused by multiresistant bacteria (considering resistance to penicillin, ampicillin, aminoglycosides and vancomycin), specially in the case of *Enterococcus faecium*, is not well defined.

New drugs as linezolid and daptomycin are increasingly been used with encouraging good results. Staphylococcal endocarditis is the entity where more changes have been described. On one hand, coagulase-negative staphylococci (CNS), classically associated with prosthesis, have been increasingly causing natural valve endocarditis, from an incidence of 3% to 8%^{41,52}. On the other hand, *S. aureus* clinical isolates, causing the 31.6% of the episodes, show a progressive resistance to methicillin^{53,54} and there is a growing number of community endocarditis due to methicillin-resistant *S. aureus* (MARSA), specially in the USA and frequently affecting patients with a history of intravenous drug abuse^{7,8,55-57}. This situation gave rise to a high use of glycopeptides, especially vancomycin, with its inherent problems of toxicity, poor tolerance, lower tissue diffusion and less efficacy, together with the decreasing methicillin-resistant *S. aureus* (MRSA) susceptibility to this antimicrobial and the known high mortality rate when MIC > 1 μ g/mL⁵⁹.

All the difficulties described on the IE therapy emphasize the need for searching for novel alternative antimicrobial agents⁵⁹⁻⁶³.

Linezolid. Linezolid is an oxazolidone approved for human clinical use in 2001 with an excellent activity for Gram positive microorganisms, including MRSA and vancomycin-resistant *Enterococcus* sp (VRE). Linezolid has a good biodisponibility and it can be used orally as a step-down therapy.

In the animal model, linezolid has shown efficacy for *S. aureus* endocarditis whether it is caused by methicillin-resistant or methicillin-susceptible strains^{64,65}. The continuous perfusion is associated with a bactericidal effect⁶⁶ and there is synergy in the combination with betalactams, even though both effects are pending of evaluation by randomized clinical studies.

Up to now, linezolid has not been evaluated by randomized, open-label clinical studies and data from reported cases in the literature show that linezolid has been mainly prescribed after previous antimicrobial failure or toxicity and mostly combined with other antimicrobials. IE caused by multiresistant Gram positive microorganism was one of the principal indications. In 2005, a review of VRE endocarditis described 5 of 19 patients treated with linezolid, reporting a favourable outcome in 4 of them⁶⁷⁻⁶⁹. One year later, a systematic review of linezolid-treated IE included 33 patients: 55% of them caused by MRSA or *S. aureus* with intermediate-resistance to vancomycin⁷⁰. There have recently been published 2 other literature reviews^{71,72} and a study where linezolid was used in post-cardiac surgery endocarditis caused by Gram positive microorganisms⁷³.

The American Heart Association (AHA) in the year 2005 recommended linezolid for the treatment of IE caused by *Enterococcus* sp. resistant to penicillin, aminoglycosides and vancomycin¹⁹. The year before, a guide of consensus elaborated by the Spanish Chemotherapy Society and Internal Medicine Society included the AHA indication and also IE caused by Gram positive microorganisms, especially MRSA, whenever intolerance or failure of previous antimicrobial treatment⁷⁴.

Daptomycin. Daptomycin is a new lipopeptide antibiotic that is rapidly bactericidal against most Gram-positive bacteria, even for stationary phase cultures⁷⁵.

Daptomycin was approved in the year 2006 by the FDA for the treatment of bacteraemia and right-side endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) or MRSA^{75,76}. The efficacy of daptomycin for the treatment of endocarditis caused by *S. aureus* and *E. faecalis* has been evaluated in several experimental models with rats and rabbits⁷⁷⁻⁸⁰. A significant reduction in the number of colony forming units has been reported, showing a good bactericidal activity even with higher microbial inocula⁸¹. Drug synergy has been described with gentamicin, cloxacillin and other betalactams antibiotics for the treatment of MRSA and with the association of ampicillin, gentamicin and rifampin for *Enterococcus* sp.^{82,83}.

Recently, a randomized study has been published showing the efficacy of daptomycin at a dose of 6 mg/Kg/d is compared with a standard treatment (that could include gentamicin) for the treatment of bacteraemia due to *S. aureus*⁸⁴. Fifty five of the 235 included patients presented definite endocarditis (35 of them corresponded to right-side endocarditis). Approximately one third of these patients were due to MRSA. The methodological strictness of the study to evaluate clinical and microbiological outcomes at 6 weeks after the end of treatment, underestimates the good results in both branches of the study. However, the efficacy in right-side endocarditis was 42%, similarly to the comparator group. The efficacy was greater with daptomycin when treating MRSA infections (50% vs. 42.9%). As for left-side endocarditis, the therapy was not effective in any of the arms of the study, probably due to the commented methodology and the low number of patients. Two other studies^{85,86} have been published where a systematic literature review and the current clinical experience with daptomycin are reported. In both of them, most patients were treated with antimicrobials before or during the administration of daptomycin which hampers the interpretation of results.

Below, a group of Spanish physicians with an interest in IE discusses the most remarkable papers produced in the area of IE during the last 3 years.

Epidemiology

Hill EE, Vanderschueren S, Verhaegen J, Herijgers P, Claus P, Herregods MC, et al. Risk factors for infective endocarditis and outcome of patients with *Staphylococcus aureus* bacteremia. *Mayo Clin Proc.* 2007;82**:1165-9.⁹**

The main objectives of this manuscript were to investigate the risk factors for *S. aureus* infective endocarditis (SAIE) and 6-month mortality in patients with *S. aureus* bacteremia (SAB).

This study consisted of patients who were diagnosed as having nosocomial or community-acquired SAB or SAIE between June 1, 2000, and December 31, 2005. Clinical characteristics of patients with SAB were compared with those of patients with SAIE, and predictors of mortality in patients with SAB were analyzed. Univariate analysis showed that unknown origin of SAB, a valvular prosthesis, a pacemaker, persistent fever, and persistent bacteremia were significantly associated with SAIE. In multivariable analysis, unknown origin of SAB (odds ratio [OR]: 4.2; 95% confidence interval [CI], 1.9-9.3; $P = .001$), a valvular prosthesis (OR: 9.2; 95%CI, 3.2-26.2; $P < .001$), persistent fever (OR: 3.1; 95%CI, 1.0-9.0; $P = .04$), and persistent bacteremia (OR: 6.8; 95%CI, 2.3-20.2- $P = .001$) were independently associated with SAIE. Six-month mortality was 8% in patients with SAB vs. 35% in patients with SAIE (OR: 6.5; 95%CI, 2.9-14.8; $P < .001$). In the univariate analysis, MRSA (OR: 7.2; 95%CI, 1.7 - 29.4; $P = .005$) was significantly associated with 6-month mortality in patients with SAB.

In conclusion, unknown origin of SAB, a valvular prosthesis, persistent fever, and persistent bacteremia were independently associated with SAIE in patients with SAB. In univariate analysis, MRSA was associated with 6-month mortality in patients with SAB. SAIE had a significantly higher mortality than SAB. The optimal management of SAB and SAIE deserves further study.

Comments. This report confirms the findings of previous investigations conducted during the past 3 decades that have examined the risk of IE in SAB. All studies published to date, including the current study, have one important limitation that has not been acknowledged, the so-called diagnostic suspicion bias. Accepting that a large proportion of patients with SAB do not undergo transesophageal echocardiography (TEE), the following question should be asked when the validity of these studies is appraised: who are the patients undergoing TEE? In clinical practice, physicians are more likely to suspect IE (and therefore to perform TEE) in patients with cardiovascular devices, including permanent pacemakers and prosthetic valves, persistent fever or bacteremia suggesting an endovascular focus, or an unknown source of bacteremia. Thus, these variables could have led to a diagnosis of IE and may not have been risk factors because of diagnostic suspicion bias.

Hsu RB, Lin FY. Methicillin resistance and risk factors for embolism in *Staphylococcus aureus* infective endocarditis. *Infect Control Hosp Epidemiol.* 2007;28**:860-6.¹⁰**

This retrospective cohort investigated the variables associated with hospital mortality and major embolism in 123 patients with definite IE caused by *S. aureus* from 1995 throughout 2005. Forty-eight cases (39%) were caused by methicillin-resistant isolates. Major embolism occurred in 45 patients (37%), the most frequent being pulmonary (22 patients), cerebral (21 patients) and peripheral (6 patients). Independent risk factors for embolism were injection drug use (IDU), presence of a cardiac vegetation with a size of 10 mm or greater, while nosocomial infection was protective. When the analysis was restricted to left-sided IE ($n=83$, embolism rate 29%), independent risk factors for an embolism were the presence of a cardiac vegetation with a size of 10 mm or greater and endocarditis due to methicillin-susceptible *S. aureus*. In-hospital death occurred for 32 patients (26%). Multivariate analysis selected the following variables as risk

factors for mortality: previous heart disease, previous or present hospitalization, diabetes mellitus, chronic renal insufficiency, and left-sided endocarditis.

In conclusion, methicillin-resistance was associated with diminished risk of embolisms in left-sided IE, and was not found to be associated with in-hospital death.

Comments. Some limitations of this study consist in the inclusion of cases from one single centre, as well as several variables (delay of initiation of therapy, antimicrobials used, and prosthetic IE) that were not analysed.

Etiology

Garzoni C, Nobre VA, Garbino J. *Candida parapsilosis* endocarditis: a comparative review of the literature. *Eur J Clin Microbiol Infect Dis.* 2007;26**:915-26.¹⁵**

This paper report the case of a 32-year-old man with history of prior intravenous drug (IVD) use hospitalized with IE due to *Candida parapsilosis* and review all 71 additional cases documented in the literature between 1968 and 2006. A retrospective analysis of the 72 *C. parapsilosis* cases (more than 16 years of age and definite IE according the modified Duke's criteria) compared to 52 recently reviewed cases of *C. albicans* endocarditis was conducted to identify organism-specific clinical peculiarities.

Of the 72 patients meeting the inclusion criteria of this review, 71% (51/72) were male, and the mean age was 48.73 years (± 15.8 years). Forty-one (57%) patients had isolated prosthetic valve involvement and 20% of patients were IVDA. Data on embolic or hemorrhagic complications were available for 64 (88.8%) of the 72 patients. Of these, 28 (43.8%) presented complications, with the most common sites being the lower limbs (ten; 35.7%) and the brain (six; 21.4%), followed by the lung (three; 10.7%) and the upper limbs (two; 7.1%). Seven (25%) of 28 patients presented intracranial hemorrhage, probably secondary to mycotic aneurysms.

The mortality rate was lower among patients undergoing adjunctive surgical therapy (33.3%) than among those treated only with antifungals (53.3%), but the difference was not statistically significant (OR: 0.4; 95 %CI, 0.2–1.1; $P = .14$). In the multivariate analysis an adjuvant surgical treatment was significantly associated with a better outcome (OR: 0.3; 95%CI, 0.1–1.0; $P = .05$).

The authors compared epidemiology, clinical findings and outcome of cases of *C. parapsilosis* endocarditis with 52 cases of *C. albicans* endocarditis and they did not find any significant differences.

Comments. This study presents several of the limitations that are common to retrospective studies. First, there is an important heterogeneity among included patients, and the clinical management of cases was not uniform. Second, data on patients treated with new antifungal compounds are scarce, thus precluding any definitive conclusion. Few patients received newer antifungal agents, and it would appear that more experience is required for their use in the treatment of *C. parapsilosis* endocarditis. These drugs may permit more efficient therapy since they are related to a higher efficacy and fewer side effects and could reduce the need of surgical treatment.

Lalani T, Person AK, Hedayati SS, Moore L, Murdoch DR, Hoen B, et al. *Propionibacterium* endocarditis: a case series from the International Collaboration on Endocarditis Merged Database and Prospective Cohort Study. *Scand J Infect Dis.* 2007;39**:840-8.¹⁷**

In this study, the authors used the International Collaboration on Endocarditis Merged Database (ICE MD), a multicenter retrospective database, as well as the ICE Prospective Cohort Study (ICE PCS), which is a prospective, multicenter, international registry of possible or definite IE episodes, according to the modified Duke

criteria, to identify patients with *Propionibacterium* endocarditis between 1985 and 2006. There were 2,212 cases of definite endocarditis in ICE MD and 2,760 cases in the ICE PCS database. Of these, 3,691 patients had native valve endocarditis, 923 had prosthetic valve endocarditis, and 219 had other types of endocarditis. *Propionibacterium* was the causative agent in 15 (0.3%) of the 4972 episodes. All of them had a definite endocarditis according to Duke's criteria. 14 of the 15 patients were male. Prosthetic valve endocarditis occurred in 13 of 15 cases and 3 patients had a history of congenital heart disease. Three patients developed cardiac abscesses. Most patients were treated with b-lactam antibiotics alone (penicillin) or in combination with clindamycin or aminoglycosides for 4 to 6 weeks. Overall, 10 of the 15 patients underwent valve replacement surgery and 2 patients died. Similar findings were noted when reviewing the literature

The authors compared the results to 28 cases previously reported in the literature between 1960 and 2006. Their conclusion was that *Propionibacterium* endocarditis usually occurs in male patients with prosthetic valves or congenital heart disease. Complications such as valvular dehiscence, cardiac abscesses and embolic phenomenon occur frequently. However, IE treatment may require a combination of medical (penicillin alone or in combination for 4 to 6 weeks) and surgical therapy. Overall, these patients have a good prognosis.

Comments. Actually, we should pay attention to "uncommon" and/or "slow growing" microorganisms that cause endocarditis such as *Propionibacterium*. The diagnosis of *Propionibacterium* endocarditis is often missed due to the prolonged incubation time (7–14 d) required for isolation of this microorganism from blood cultures, as well as the difficulty in differentiating whether positive blood cultures represent skin contamination or true bacteremia.

Chu VH, Miro JM, Hoen B, Cabell CH, Pappas PA, Jones P, et al; on behalf of the International Collaboration on Endocarditis-Prospective Cohort Study Group. Coagulase-negative staphylococcal prosthetic valve endocarditis--a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study. *Heart.* 2009;95**:570-6.⁸⁷**

The objective of this study is to describe the contemporary features of coagulase-negative staphylococcal (CoNS) prosthetic valve endocarditis (PVE). It is an observational study of prospectively collected data from a multinational cohort of patients with IE. Patients with CoNS PVE were compared to patients with *S. aureus* and viridans streptococcal (VGS) PVE.

The International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) is a contemporary cohort of patients with IE from 61 centres in 28 countries. Adult patients in the ICE-PCS with definite PVE and no history of injecting drug use from June 2000 to August 2005 were included. CoNS caused 16% ($n=86$) of 537 cases of definite non-injecting drug use-associated PVE. Nearly one-half ($n=33/69$, 48%) of patients with CoNS PVE presented between 60 days and 365 days of valve implantation. The rate of intracardiac abscess was significantly higher in patients with CoNS PVE (38%) than in patients with either *S. aureus* (23%, $P = .03$) or VGS (20%, $P = .05$) PVE. The rate of abscess was particularly high in early (50%) and intermediate (52%) CoNS PVE. In-hospital mortality was 24% for CoNS PVE, 36% for *S. aureus* PVE ($P = .09$) and 9.1% for VGS PVE ($P = 0.08$). Methicillin resistance was present in 68% of CoNS strains.

Comments. Nearly one-half of CoNS PVE cases occurred between 60 days and 365 days of prosthetic valve implantation. CoNS PVE was associated with a high rate of methicillin resistance and significant valvular complications.

Laboratory diagnosis

Marín M, Muñoz P, Sánchez M, Del Rosal M, Alcalá L, Rodríguez-Créixems M, et al; on behalf of the GAME Group. Molecular diagnosis of infective endocarditis by real-time broad-range polymerase chain reaction (PCR) and sequencing directly from heart valve tissue. *Medicine (Baltimore)*. 2007; 86:195-202.²⁶

Conventional microbiologic methods have important limitations in etiologic diagnosis of IE. As surgery is required in 20%-40% of patients with IE, and a considerable percentage of patients with IE have negative blood cultures and cultures of valvular tissue are generally unreliable due to prior antimicrobial therapy or contamination during surgery process, some recent studies have proposed the use of universal 16S rRNA gene polymerase chain reaction (PCR) combined with sequencing in heart valve tissue for the diagnosis of IE that require surgical treatment. However, experience in this field is limited, and the role of molecular techniques, PCR format and the methodology applicable to clinical laboratories has been not well defined previously.

Marín et al prospectively assessed the diagnostic yield of this technology for the diagnosis of IE in explanted heart valve tissue (HV) as part of the routine of a clinical microbiology laboratory, and compared it with conventional culture of blood or HV.

They analyzed 177 HV samples, 48 of them were from 35 patients with definite IE and 129 were from 120 patients undergoing valve replacement because of valvular dysfunction without IE. LightCycler technology with SYBR green was used for universal PCR and specific PCR assays were used to confirm broad-range PCR results.

For the 35 patients with IE, all of the HV samples except for 2 from the same patient gave positive PCR results. The microorganisms identified matched those isolated by blood culture in 31 cases. The other 3 patients had negative blood culture IE, but PCR made possible the detection of *Tropheryma whippelii*, *Bartonella quintana* and *Streptococcus gallolyticus*. Universal real-time PCR was negative in 123 samples (93.3%) of the control group. So, sensitivity, specificity, positive and predictive values for the diagnosis of IE of this real-time PCR method were 96%, 95.3%, 88.5%, and 98.4% respectively. There was a high percentage of contamination in the conventional HV cultures and correlation between blood cultures and HV culture was very poor.

Based on their results, the authors conclude that universal PCR method is more sensitive, specific, and rapid than conventional culture methods, and recommend its use to supplement blood and HV cultures at least in reference laboratories. On the other hand, conventional HV cultures are frequently responsible for false positive and false-negative results, and are not always useful to establish the etiology of IE.

Comments. This excellent study has nevertheless some limitations: the number of patients included with negative blood cultures is small, the election of the cycle number 31 as the cut-off to define contamination is in our opinion excessively empiric and needs external validation and, finally, the technical complexity of the method keeps it at the moment away from most clinical laboratories.

Landais C, Fenollar F, Thuny F, Raoult D. From acute Q fever to endocarditis: serological follow-up strategy. *Clin Infect Dis*. 2007; 44:1337-40.¹⁶

The authors perform a retrospective analysis of stored serum samples of patients with acute Q fever to establish clinical correlates. They study the kinetics of anti-phase I IgG from acute Q fever to the development of IE. Patients with anti-phase II IgG $\geq 1:200$ and anti-phase II IgM $\geq 1:50$ and known clinical course who met modified Duke Criteria (*C. burnetii* anti-phase I IgG ≥ 800 is considered a major criterion for diagnosis of IE) were selected. IgG, IgM, and IgA antibody titres were determined by indirect immunofluorescence. 22 patients,

14 male and 8 female, with a mean age of 59.7 years (range 44-76), were studied. Main manifestations of Q fever were fever in 5 (22.7%) patients, hepatitis in 14 (63.6%), and pneumonia in 3 (13.6%). Underlying illnesses were diabetes mellitus in 1, alcoholic intoxication in 1, and cancer in 2, with known prior cardiac disease in 17 (77.2%) patients. Chronic Q fever was symptomatic in 17 (77.2%) cases and was diagnosed a median of 3 months (range 1-48 months) after the acute episode. Clinical examination showed cardiac abnormalities in 11 (50%) patients, fever in 5 (22.7%), asthenia in 2 (9%), and purpura in 1 (4.5%). According to modified Duke criteria, 5 (22.7%) endocarditis were classified as "definitive", whereas 17 (77.2%) were "possible" cases. All patients developed phase I IgG titres ≥ 800 , 17 within 6 months of acute Q fever diagnosis. The main messages and recommendations of the article are to perform serologic follow-up at 3 and 6 months of acute Q fever and that anti-phase I IgG titres ≥ 800 are clearly associated to a high risk of endocarditis.

Comments. The selection methodology of cases is unclear and cannot rule out bias. Diagnostic specificity is sub-optimal as only in 1 patient was TEE performed at diagnosis of acute Q fever and only in 14 cases at diagnosis of IE. In addition, even applying the modified Duke criteria, only 5 of the selected cases could be classified as "definitive" and 17 as "possible". The results of the current study would have been more convincing in the presence of control group data, as, for example, patients with clinical and serologic follow-up, but without IE. Also, the existence of patients with low-titre *C. burnetii* endocarditis cannot be ruled out.

Image diagnosis

Feuchtnner GM, Stolzmann P, Dichtl W, Schertler T, Bonatti J, Scheffel, H et al. Multislice computed tomography in infective endocarditis: Comparison with transesophageal echocardiography and intraoperative findings. *J Am Coll Cardiol*. 2009;53:436-44.⁸⁸

Transesophageal echocardiography (TEE) is currently the reference imaging method for patients with suspected IE (IE). However, the procedure is semi-invasive; entails conscious sedation; and cannot be performed in patients with certain oropharyngeal, esophageal, or gastric conditions. With recent improvements in the resolution of computed tomography (CT) scanners, cardiac multislice CT might provide an alternative to TEE for visualizing valvular abnormalities in IE. Investigators recently compared the value of these methods for detecting such abnormalities.

Thirty-seven consecutive patients with clinically suspected IE underwent both TEE and CT imaging. Twenty-nine of these patients had definite IE and underwent cardiac surgery – 28 of them within 5 days of the imaging studies and one 6 weeks later. A total of 57 valves were included in the analysis, with intraoperative findings being the gold standard. Both TEE and CT correctly identified 26 of 27 patients with intraoperatively proven vegetations, and CT correctly classified 55 of 57 valves as having or not having vegetations. CT identified all nine paravalvular abscesses/pseudoaneurysms, whereas TEE identified eight. CT missed four small mitral valve perforations that were identified with flow analysis on TEE. However, CT revealed two vegetations on a prosthetic valve that were missed by TEE because of metal artifacts.

Comments. Confirmation of the imaging results by surgery is a strength of this investigation; however, the study population was highly selected and potentially subject to referral bias. Going forward, the choice of which imaging method to use will likely depend on patients' comorbid conditions and on the availability of the testing modalities. Of note, multislice CT imaging quality deteriorates with arrhythmias such as atrial fibrillation, and the technique requires use of iodinated contrast agents that are problematic in patients with renal dysfunction.

Duval X, Iung B, Klein I, Brochet E, Thabut G, Arnoult F, et al. on behalf of IMAGE (Resonance Magnetic Imaging at the Acute Phase of Endocarditis) Study Group. Effect of early magnetic resonance imaging on clinical decisions in infective endocarditis. *Ann Intern Med.* 2010;152:497-504.⁸⁹

Patients diagnosed with bacterial endocarditis in a Paris hospital were enrolled in a study to evaluate the role of brain magnetic resonance imaging (MRI) with angiography in their management. Of 274 cases screened, 130 were enrolled and had MRI performed within 7 days of admission. Cases were classified by the Duke criteria on study entry as definite (77 cases), probable (50 cases), and excluded (3 cases). Transesophageal echocardiography was performed in 121 cases, and transthoracic echocardiography alone was performed in 9 cases.

Endocarditis was on a native valve in 93 patients and on a prosthetic valve in 37 patients. Blood cultures were positive in 84%, with *S. aureus* in the blood of 28%. The unexpected finding was one or more abnormalities on MRI in 82%. Magnetic resonance angiography (MRA) was abnormal not only in all 16 patients with neurologic findings, but also in 90 of 114 (79%) patients without neurologic findings on admission. Lesions were cerebral aneurysms in 10 cases, abscesses in 8 cases, subarachnoid hemorrhage in 11 cases, large ischemic lesions in 33 cases, small ischemic lesions in 60 cases, intraparenchymal hemorrhagic lesions in 10 cases, and microhemorrhagic lesions in 74 cases. MRI was used to upgrade the classification of probable endocarditis to definite in 14 patients. All three cases classified as "excluded" by the Duke criteria after enrollment were changed to probable after MRI findings became available. Clinical management was often changed based on the unexpected findings of MRA. Whether outcome was altered by the management changes could not be determined.

Comments. A limitation of this study is the fact that this was the experience of one hospital. Also, patients were selected who did not need emergent valve replacement and could consent to the trial. Judging from the low incidence (12%) of neurologic findings in enrolled patients, it is likely that patients with sufficient neurologic findings on admission to warrant MRI had the procedure done before they could be enrolled in the study. Patients with azotemia likely were not given gadolinium and were excluded. Whatever the limitations are, the results of this study indicate a high prevalence of asymptomatic cerebral lesions accompanying bacterial endocarditis.

Special hosts' endocarditis

Cooper HL, Brady JE, Ciccarone D, Tempalski B, Gostnell K, Friedman SR. Nationwide increase in the number of hospitalisations for illicit injection drug-use-related infective endocarditis. *Clin Infect Dis.* 2007;45:1200-3.⁷

The Centers for Disease Control and Prevention National Hospital Discharge Survey database (NHDS) was analysed to seek for hospital admissions caused by IE in injection drug users (IDU) in the US from 1996 throughout 2003. A "specific" and a "sensitive" algorithm were developed to detect the cases. Data were stratified according to HIV infection status, and weight to reflect to US population. The analysis showed a significant increase of IE in all IDUs in the period 2002-2003 with respect to 2000-2001 using both algorithms, while a decrease of IE in HIV-infected IDUs was found. These results are not probably related with an increase in the IDU population or in the use of cocaine in the US since surveillance data do not support such changes. The authors state that the most probable causes are the use of methamphetamine (which actually increased during the study period) and a higher injection frequency among heroin injectors (associated with a decrease in the price of heroin).

Comments. The results of this study are surprising, since the frequency of IE in IDU had been decreasing during last years in most

countries, in association with a decrease in the IDU population and the fact that many previous heroin users are now in methadone programs or using alternatives ways of consuming heroin. Even though the authors had to "detect" the cases using indirect parameters (the algorithms), the results of both algorithms were consistent. The hypothesis for the causes of such an increase in the US is explained. While the use of methamphetamine is a new phenomenon, it would be interesting to have some information about the methadone programs in the US.

De Rosa FG, Cicalini S, Canta F, Audagnotto S, Cecchi E, Di Perri G. Infective endocarditis in intravenous drug users from Italy: the increasing importance in HIV-infected patients. *Infection.* 2007;35:154-60.⁸

This study analysed a retrospective multicenter cohort of 263 cases of IE in IDU in 54 Italian centres from 1986 throughout 1996; 100 were HIV-infected patients (median CD4 cell count, 182 per μ L). Only definite cases according to Duke's criteria were included. The most frequent etiology was *S. aureus* (59%; only 1.5% of them were methicillin-resistant) and *Streptococcus* (12%); there was right-sided and left-sided involvement in 63.5% and 43.7% of the cases, respectively. There were no significant differences between HIV-infected and HIV-uninfected patients in terms of aetiology, predisposing conditions, or prognosis. Only an isolated aortic valve localization was more frequent among HIV-negative patients (19.6% vs. 9%, $P=0.02$). Mortality rate was 16%; variables associated with mortality in multivariate analysis were any left-sided location (OR=5.2, 95%CI: 2.0-13.5) and age >35 years (OR:3.5; 95%CI: 1.4-9).

Comments. HIV infection does not appear to have a significant effect on mortality. However, the study has some limitations that should be taken into account. The situation of HIV infection was not stratified according to their CD4 cell count or AIDS diagnosis. Also, TEE was performed only in 2 patients, and was probably scarcely used during the study period.

Naber CK, Erbel R. Infective endocarditis with negative blood cultures. *Int J Antimicrob Agent.* 2007;30 Suppl 1:S32-6.¹³

Naber and Erbel review the current published knowledge of IE with negative blood cultures (BCN-IE). The issues mentioned and discussed in the article are: a) BCN-IE carries a worse prognosis than blood culture-positive IE; b) causes for negativity of BC are previous administration of antibiotics, fastidious organisms (rare and difficult to culture bacteria), and non-IE. Duke criteria may be improved by serologic testing, depending on local prevalence of organisms. PCR in blood is currently not recommended because of lack of standardization of methodology and background bacterial contamination. A general consideration is made: increases in sensitivity, i.e. addition of serologic data, may be associated with reductions in specificity; c) regarding antibiotic therapy, the substitution of oxacillin or a second-generation cephalosporin for ampicillin is proposed, although based on the frequency of staphylococci in blood culture positive endocarditis. Empiric vancomycin therapy may be indicated if, based on local prevalence, MRSA is a concern, although newer therapeutic options should be considered. Daptomycin is discussed in depth in relation to the recent publication of a trial on *S. aureus* bacteremia in which daptomycin is compared to vancomycin. There is no evidence favouring the use of combination therapy with gentamicin. Surgery was independently associated with reduced in-hospital mortality.

Comments. The manuscript underscores some important aspects of BCN-IE. However, the text is intensely biased. Unfortunately, almost all data, comments and recommendations, particularly the

sections on antibiotic management, are derived from publications of series of blood culture-positive IE and are therefore not grounded.

Prognostic factors

Fernández-Guerrero ML, Goyenechea A, Verdejo C, Roblas RF, De Górgolas M. Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*. 2007; 86:363-77.¹¹

Enterococcal etiology represents the third cause of IE and retains a significant mortality. Previous studies have analyzed the factors associated with mortality in enterococcal endocarditis, but the role of hospital acquisition of the infection has not been assessed. The present study was designed to analyze risk factors associated to mortality in enterococcal endocarditis. A cohort-based study was carried-out in a university hospital in Madrid, Spain, including all the patients with an episode of enterococcal endocarditis, attended by the authors of this study, between January 1998 and December 2005. Cases were included according to the modified Duke criteria, being definite in all cases (n=44). Only the first episode of endocarditis was included to carry out the analysis of mortality-associated factors; thus, three second episodes occurring in three patients were excluded. In all the 44 cases, endocarditis was left-sided; 27 and 17 were on native and prosthetic valves, respectively. Twelve out of 44 cases were hospital-acquired. All patients, except two, received effective antimicrobial treatment and 18 (40.9%) needed valve replacement due to cardiac failure.

Eight of 44 patients (18.1%) died due to the infection, the mortality rate being 22.2% and 11.7% in native and prosthetic valve endocarditis, respectively. In the univariate analysis, factors associated to mortality were advanced age ($P=.05$), the presence of one or more comorbidities (OR: 3.2; 95%CI, 1.1-9-39), cardiac failure (OR: 1.61; 95%CI, 1.15-2.25), and hospital acquisition of endocarditis (OR: 8.05; 95%CI, 1.50-43.2). In the stepwise logistic regression analysis, only hospital acquisition of endocarditis remained as an independent factor associated to mortality.

Comments. This study stresses the importance of hospital acquisition in enterococcal endocarditis, above all in terms of vital prognosis, and, as a consequence, the importance of adequate antimicrobial prophylaxis in situations with risk of enterococcal bacteraemia in patients with impaired cardiac valves. Perhaps the long period of inclusion of the patients in the cohort and the single institution based study might be limitations that may be resolved with the analysis of cases in homogeneous multi-centre based studies.

San Román JA, López J, Vilacosta I, Luaces M, Sarriá C, Revilla A, et al. Prognostic stratification of patients with left-sided endocarditis determined at admission. *Am J Med.* 2007;120:369 e1-7.³⁴

The prognosis of patients with left-sided endocarditis remains poor despite the progress of surgical techniques. Identification of high-risk patients within the first days after hospital admission would permit a more aggressive therapeutic approach.

This is a prospective multicenter study to find out the clinical, microbiologic, and echocardiographic characteristics available within 72 hours of admission that might define the profile of high-risk patients. Of 444 episodes, 317 left-sided endocarditis cases were included and 76 variables were assessed. Events were surgery in the active phase of the disease and in-hospital death. A stepwise logistic regression analysis was undertaken to determine variables predictive of events. In the multivariate analysis they found the following variables to be significant: patient referred from another hospital (OR: 1.8; CI, 1.1-2.9), atrioventricular block (OR: 2.5; CI, 1.1-5.9), acute

onset (OR: 1.7; CI, 1.1-2.9), and heart failure at admission (OR: 2.3; CI, 1.4-3.8). When the echocardiographic and microbiological variables statistically significant in the univariate analysis were introduced in the model, the presence of heart failure at admission (OR: 2.9; CI, 1.8-4.8), periannular complications (OR: 1.8; CI, 1.1-3.1), and *S. aureus* infection (OR: 2.0; CI, 1.1-3.8) retained prognostic power. Risk could be accurately stratified when combining the 3 variables with predictive power: 0 variables present, 25% risk; 1 variable present, 38-49% risk; 2 variables present, 56-66% risk; and 3 variables present, 79% risk.

In conclusion, the risk of patients with left-sided endocarditis can be accurately stratified with the assessment of variables easily available within 72 hours of admission to the hospital.

Comments. This model can help clinicians care for patients with endocarditis and predict their risk. The 3 cornerstones in the diagnosis of endocarditis are pivotal regarding prognosis: clinical examination, blood cultures and echocardiography. Patients with heart failure, periannular complications and/or *S. aureus* infection should be closely followed. For this reason, institutions without surgical possibilities should refer patients with endocarditis to tertiary care centres without delay.

Nosocomial endocarditis

Wang A, Athan E, Pappas PA, Fowler VG Jr, Olaison L, Paré C, et al; for the International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA.* 2007;297:1354-61.²⁹

Infection of prosthetic valves is uncommon but carries an important morbidity and mortality. Because much of the knowledge on the epidemiologic, clinical and prognostic characteristics of prosthetic valve endocarditis (PVE) comes from single institutions, the present study was carried out with the following objectives: a) to analyze the prevalence, clinical characteristics, and outcome of PVE, with attention to health-care associated infection; and b) to determine risk-factors associated with in-hospital mortality. Data for the study comes from the International Collaboration on Endocarditis (ICE). The cohort for this study was collected from June 2000 to August 2005 and enrolled 3250 patients from 61 centres in 28 countries (United States, South America, Europe, Middle East, South Africa, Australia, New Zealand and Asia). For the purpose of this study, only definite endocarditis cases (modified Duke criteria) and the first episode from each patient were included. Informed consent from the patients was obtained. A standard case report was used in all sites, developed by the ICE-Prospective Cohort Study (ICE-PCS), which has 275 variables according to previous definitions. Early PVE was defined as that occurring in the 60 days after the prosthetic valve implantation. Health-care associated infection in PVE was defined as nosocomial or non-nosocomial health-care associated infection. For the univariate statistical analysis the chi-square and Wilcoxon tests were used. An equation model was created to determine variables independently associated with in-hospital mortality; the fit of the final regression model to the data was evaluated by the Hosmer-Lemeshow test.

PVE accounted for 20.1% of all definite endocarditis episodes (556 out of 2670 cases). Aortic and mitral valves were the most affected. The most frequent causative microorganisms were: *S. aureus* (23%, 35.9% in early PVE), CNS (16.9%), *Enterococcus* spp. (12.8%, mostly in late PVE) and group viridans *Streptococcus* (12.1%, mainly in late PVE). Health care-associated PVE was present in 203 (36.5%) of the overall cohort. In-hospital death occurred in 127 (22.8%) patients and was predicted by older age, health care-associated infection (OR: 1.62; 95%; 95%CI, 1.08-2.44; $P=.02$), *S. aureus* infection (OR: 1.73; 95%CI, 1.01-2.95; $P=.05$), and complications of PVE, including heart failure

(OR: 2.33; 95%CI, 1.62-3.34; $P < .001$), stroke (OR: 2.25; 95%CI, 1.25-4.03; $P = .007$), intracardiac abscess (OR: 1.86; 95%CI, 1.10-3.15; $P = .02$), and persistent bacteremia (OR: 4.29; 95%CI, 1.99-9.22; $P < .001$).

Comments. This multicenter study includes an important number of PVE cases, and identifies changes in the trends of some etiologic agents and factors associated to in-hospital mortality. The main limitation of the study lies in the global analysis, with conclusions appropriate for some countries but probably non-valid for others. Some caveats are: a) arbitrary grouping for the analysis of some countries; b) the high frequency of *S. aureus* depends on some regions, probably due to the organization of their health systems, which varies among countries; c) there are differences in mortality among countries that, although non-significant, deserve specific analysis to implement intervention strategies; and, finally, d) mortality is only analyzed during in-hospital stay and may not reflect true outcomes.

Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Barsic B, Bouza E, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008; 168:2095.⁹⁰

IE is increasingly common in Western countries, especially among people aged ≥ 65 . A better understanding of the epidemiology of IE in this population could help to inform management and prevention strategies. Investigators recently analyzed data from a large, multinational, prospective cohort study to evaluate the clinical features, risk factors, and outcomes of IE in older patients.

Of 2759 consecutive IE patients enrolled between 2000 and 2005, 1056 (38%) were aged ≥ 65 . Compared with those aged 18 to 64, older patients were more likely to have healthcare-associated IE (39% vs. 29%; $P < .001$). Fifty-six percent of older IE patients had invasive procedures during the 6 months before IE onset, compared with only 39% of younger ones ($P < .001$). *S. aureus* was the most common pathogen in both age groups. CNS, enterococci, *S. bovis*, and MRSA were more common in older patients, whereas viridans-group streptococci were more common in younger ones. Older IE patients were less likely to have vegetations or embolic, vascular, or immune-mediated manifestations (e.g., stroke, Janeway lesions, Osler nodes, Roth spots).

Compared with younger IE patients, older ones had lower rates of surgical treatment (39% vs. 54%; $P < .001$) and higher rates of in-hospital mortality (25% vs. 13%; $P < .001$). Age ≥ 65 was an independent risk factor for in-hospital death in the multivariate analysis.

Comments. The high proportion of healthcare-associated IE cases among older patients suggests that increasing efforts to prevent healthcare-associated infections should help to reduce IE incidence in this population. Furthermore, the combination of higher IE mortality and lower surgical-intervention rates raises an interesting question: Are the increased operative risks associated with advanced age preventing older IE patients from receiving potentially life-saving surgical therapy?

Benito N, Miró JM, De Lazzari E, Cabell CH, Del Río A, Altclas J, et al. on behalf of ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med. 2009; 150:586-94.⁹¹

The clinical profile and outcome of nosocomial and non-nosocomial health care-associated native valve endocarditis are not well defined. The objective of this study was to compare the characteristics and outcomes of community-associated and nosocomial and non-nosocomial health care-associated native valve endocarditis. This was a prospective cohort study, with 61 participating hospitals in 28 countries. Patients with definite native

valve endocarditis and no history of injection drug use who were enrolled in the ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) from June 2000 to August 2005.

Health care-associated native valve endocarditis was present in 557 (34%) of 1622 patients (303 with nosocomial infection [54%] and 254 with non-nosocomial infection [46%]). *S. aureus* was the most common cause of health care-associated infection (nosocomial, 47%; non-nosocomial, 42%; $P = .30$); a high proportion of patients had MRSA (nosocomial, 57%; non-nosocomial, 41%; $P = .014$). Fewer patients with health care-associated native valve endocarditis had cardiac surgery (41% vs. 51% of community-associated cases; $P < .001$), but more of the former patients died (25% vs. 13%; $P < .001$). Multivariable analysis confirmed greater mortality associated with health care-associated native valve endocarditis (incidence risk ratio, 1.28 [95%CI, 1.02-1.59]).

Comments. The authors conclude that more than one third of cases of native valve endocarditis in non-injection drug users involve contact with health care, and non-nosocomial infection is common, especially in the United States. Clinicians should recognize that outpatients with extensive out-of-hospital health care contacts who develop endocarditis have clinical characteristics and outcomes similar to those of patients with nosocomial infection. Still, patients were treated at hospitals with cardiac surgery programs. The results may not be generalized to patients receiving care in other types of facilities or to those with prosthetic valves or past injection drug use.

Prophylaxis

Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A Guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736-54.³⁹

The American Heart Association (AHA) has made recommendations for the prevention of IE for over 50 years. In 1955 the first AHA document was published, and the most recent AHA document on IE prophylaxis was published in 1997. Many authorities and societies have questioned the efficacy of antimicrobial prophylaxis to prevent IE.

IE is uncommon but life-threatening; prevention is preferable to treatment of established infection. Certain underlying cardiac conditions predispose to it. Bacteremia caused by organisms known to cause IE occurs commonly in association with dental, gastrointestinal (GI) or genitourinary (GU) tract procedures. Antimicrobial prophylaxis was thought to be effective in humans for prevention of IE associated with dental, GI, or GU tract procedures.

However, IE much more likely to result from frequent exposure to random bacteremias associated with daily activities. Prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo a dental, GI, or GU tract procedure. The risk of antibiotic-associated adverse events exceeds the benefits from prophylactic antibiotic therapy. Maintenance of oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE. Today, *S. aureus* is the most frequent cause of IE, and the origin is now most commonly health-care related. Prevention starts with adequate treatment of bacteremic infection and removal of any intravenous device present. The vast majority of patients with IE have not had a dental procedure within two weeks before the onset of symptoms of IE.

Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable include: a) prosthetic cardiac valve or prosthetic material used for cardiac repair; b) previous IE; c) congenital heart disease (unrepaired cyanotic congenital heart defect (CHD) including palliative shunts and conduits; completely repaired CHD with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure, and repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)); d) cardiac transplantation recipients who develop cardiac valvulopathy.

Only a small fraction of IE is due to dental manipulation. Most cases of IE are related to poor daily hygiene and mastication. A septic mouth increases the risk of secondary bacteremia. The emphasis should be placed on good dental care, not on prophylaxis. Only in high-risk cases should antibiotic prophylaxis be offered. In cases of incision or biopsy of respiratory mucosa, prophylaxis can be contemplated even in the absence of objective confirmation of efficacy. Finally the old indication of antibiotic prophylaxis in cases of GI and GU manipulation is no longer recommended.

Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation*. 2009;119:1541-51.⁹²

The American Heart Association (AHA) has released a new guideline, endorsed by the American Academy of Pediatrics, which focuses on the prevention of rheumatic fever (RF) and on diagnosis and treatment of acute group A streptococcal (GAS) pharyngitis. Also included in the scientific statement are prophylaxis recommendations for recurrent RF and bacterial endocarditis and discussion of poststreptococcal reactive arthritis and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Although much of the information is not new, the report confirms many recommendations in the AAP Committee on Infectious Diseases' Red Book. Highlights of the report include the following:

One third of acute RF episodes result from streptococcal infections that are not evident.

GAS pharyngitis primarily affects children between ages 5 and 15 years. Infants with GAS infections might present with excoriated nares or purulent nasal discharge. Acute RF is rare in children younger than 3 years.

Microbiological confirmation is necessary to differentiate GAS pharyngitis from pharyngitis caused by other pathogens. Neither rapid antigen tests nor traditional throat culture can differentiate between people who have GAS infection and those who are carriers.

Antigen tests are very specific, but sensitivity is unacceptably low. If a patient has a negative rapid test but the clinician has a high index of suspicion for GAS pharyngitis, a culture should be performed.

Treatment is indicated for patients with acute pharyngitis and either a positive antigen test or a positive culture. In general, follow-up cultures are not recommended.

Repeated courses of antibiotics are rarely indicated in asymptomatic children who continue to be culture positive for GAS.

Comments. This report highlights a number of important points: GAS pharyngitis is one of the few infectious diseases in which penicillin V can be administered twice daily and amoxicillin once daily. If a rapid antigen test is negative but the pretest probability is

high (e.g., the patient has sudden onset of sore throat, fever, and pharyngeal exudate), a culture should be performed. Acute RF and the common signs and symptoms of GAS pharyngitis are rare in children younger than 3 years, so you can be more selective about culturing than in older children.

Guidelines and review

Yung D, Kottachchi D, Neupane B, Haider S, Loeb M. Antimicrobials for right-sided endocarditis in intravenous drug users: a systematic review. *J Antimicrob Chemother*. 2007;60:921-8.⁹³

Objective: systematic review of the evidence of clinical cure with antimicrobials in native valve right heart endocarditis in intravenous drug users.

Materials and methods: the publications were sought through computerized searches of MEDLINE (1966-2006), EMBASE (1980-2006), Cochrane Central Register (2006, issue 3) and hand search of selected publications. There were no limits on language or type of publication.

Selection criteria: randomized control trials evaluating the clinical and microbiological cure of right heart endocarditis using single or combination antimicrobial treatment were identified. The primary outcomes of interest were the clinical and microbiological cure or failure between 2 weeks and six months after treatment. Patients with extrapulmonary metastatic complications due to endocarditis were excluded.

Results: 7 randomized control trials were identified (1 comparing single antimicrobial therapies, 4 comparing combination and single therapies, 2 comparing combination therapies). There was a short course treatment arm in 3 of the studies. 1 trial compared short with long course treatments.

This systematic review did not find any statistically significant benefit between any antimicrobial regimens and all studies were scored as having a moderate to severe risk of bias.

Comments. There is no evidence at present to support any specific antimicrobial regimen over others in the treatment of right heart endocarditis in intravenous drug users. Given the absence of definitive randomized controlled trials evidence, short-course cloxacillin alone is reasonable.

Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG; Paul-Ehrlich-Society for Chemotherapy), Deutsche Gesellschaft für Kardiologie, Herz-und Kreislaufforschung (DGK; German Society for Cardiology, Heart, and Circulatory Research). German Guidelines for the diagnosis and management of infective endocarditis. *Int J Antimicrob Agent*. 2007;29:643-57.⁴³

Objective: German guidelines for the diagnosis and treatment of IE, issued by the Working Group on Infective Endocarditis of the Paul Ehrlich Society and the German Societies of Cardiology and Cardiovascular Surgery, Infectious diseases, Intensive Care, Microbiology and Hygiene, and Internal Medicine.

These guidelines analyze the definition and classification of IE, as well as the diagnostic criteria (clinical, microbiological and histological), role of transthoracic and transesophageal echocardiogram, therapeutic regimens, indications for intravenous ambulatory treatment, management of complications and indications for surgery.

Comments. These guidelines do not provide any new contribution when compared with the 2005 AHA guidelines. We should like to point out the description of the collection and transportation of blood cultures for the diagnosis of IE and the diagnostic methods for fastidious microorganisms.

Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;121**:458-77.⁹⁴**

The use of cardiovascular implantable electronic devices (CIEDs), such as pacemakers and defibrillators, has markedly increased as indications expand and the population ages. However, the incidence of CIED infections has risen even faster, despite technological advances in implantation procedures and in the devices themselves. Accordingly, the AHA has updated its scientific statement on prevention and management of these infections.

Key points:

- Citing recent research, the authors identify several risk factors for CIED infection: immunosuppression, including renal dysfunction, diabetes, and corticosteroid use, oral anticoagulation use, coexisting illness, Perioperative factors (including failure to administer perioperative antibiotic prophylaxis, preoperative fever, and preprocedural temporary pacing), dDevice revision or replacement, coexisting indwelling hardware, including bloodstream infections related to such hardware and operator inexperience.
- Staphylococcal species account for 60% to 80% of CIED infections, roughly split between *S. aureus* and CNS.
- Class I diagnostic recommendations, nearly all based on expert consensus, include drawing at least two sets of blood cultures before initiating antibiotic therapy, Gram stain and culture of the generator pocket and lead tip, and transthoracic echocardiography in cases of positive blood culture or high suspicion of endocarditis.
- Device removal may be avoided if infection is superficial and does not involve any hardware. In such cases, 7 to 10 days of oral antistaphylococcal therapy is reasonable. However, if any part of the device is infected, complete removal of all hardware is recommended.
- Of course, prophylaxis with an antibiotic that has in vitro activity against staphylococci should immediately precede all CIED placements.

Comments. Given the significant morbidity and mortality associated with CIED infections, physicians must be extremely alert about preventing them. The focus should be on appropriate selection of patients and timing of implantation; use of preoperative antibiotics and sterile implantation techniques; and diligent, guideline-recommended postoperative care.

Community-acquired MRSA

Millar BC, Prendergast BD, Moore JE. Community-associated MRSA (CA-MRSA): an emerging pathogen in infective endocarditis. *J Antimicrob Chemother*. 2007;61**: 1-7.⁵⁵**

CA-MRSA is primarily associated with skin and soft tissue infections; however, sporadic cases of severe infections such as bacteremia with septic shock, necrotizing pneumonia and, more recently, endocarditis have been reported.

The major objectives of this article are: *a*) to review the published cases of CA-MRSA endocarditis to date; and *b*) evaluate the current international guidelines recommendations for its antibiotic management.

In order to identify CA-MRSA cases a thorough search of the PubMed Search Engine was carried out, seeking articles that were in print by July 2007.

In order to evaluate recommendations on antibiotic management, three relevant International Guidelines, such as the American Heart Association, the British Society for Antimicrobial Chemotherapy, and the European Society of Cardiology guidelines were reviewed regarding antibiotic therapy for IE caused by MRSA.

Twenty-three cases of endocarditis due to MRSA were identified. Most cases were described in the US, were caused by the genotype USA 300, were community-acquired and involved young, healthy population; however, a large proportion of cases had antecedents of diverse types of skin lesions or IV drug abuse. All cases were associated with native valves, most often the tricuspid valve. These 23 cases were compared with 248 cases of native valve MSSA and 43 cases of native valve MRSA endocarditis taken from published results of the International Collaboration on Endocarditis (ICE) merged database. This comparison showed that CA-MRSA and MSSA endocarditis were very similar regarding their demographic and clinical characteristics, although mortality associated with CA-MRSA was markedly lower (13%, vs. 23.2% for MSSA and 37.2% for MRSA).

Obviously, according to the revised guidelines, the antibiotic management of CA-MRSA endocarditis requires an approach similar to that of MRSA endocarditis, as a result of the resistance of CA-MRSA to beta-lactam agents.

The article has the merit of having collected and updated the available information about this emerging infection, although it is difficult to draw any firm conclusions on the epidemiological trends and outcome of CA-MRSA endocarditis in the next future.

Tsigrelis C, Armstrong MD, Vlahakis NE, Batsis JA, Baddour LM. Infective endocarditis due to community-associated methicillin-resistant *Staphylococcus aureus* in injection drug users may be associated with Panton-Valentine leukocidin-negative strains. *Scandinavian J Infect Dis*. 2007;39**:299-302.⁵⁶**

The authors of this paper hypothesise that CA-MRSA isolates which cause IE in injection drug users (IDUs) are distinct from CA-MRSA strains which cause endocardial infection as a complication of skin and soft tissue infections. They present a case of CA-MRSA endocarditis in a 41 year-old IDU man and review previous cases of MRSA endocarditis reported (Medline search of English language from Jan 1999 to Aug 2006) with molecular data available on SCCmec typing, with or without data on PVL gene testing.

Overall, they found 6 cases fulfilling the inclusion criteria. There were 3 cases among IDUs (including their own case) and other 3 cases in patients with complicated skin and soft tissue infections (non IDUs).

When they compared IDUs and non IDUs cases, apart from the different valves involved, the major difference was the presence or absence of Panton-Valentine leukocidin (PVL) genes. The strains recovered from IDUs with IE due to community-acquired MRSA did not produce PVL, contrary to MRSA strains causing endocarditis as a complication of skin and soft tissue infection. All isolates from IDUs had the SCCmec type IV, and all patients survived. It is well known that PVL genes are present in the large majority of CA-MRSA isolates that cause skin and soft tissue infections. Similarly, PVL genes are also often found in MSSA isolates, especially in those causing skin and soft tissue infections and pneumonia, but are rarely found among those causing endocarditis. Whether there is an association between IDU and PVL-negative CA-MRSA strains among endocarditis cases remains speculative.

Comments. Further studies are needed to confirm these findings and to know their possible clinical implications.

New treatments

Muñoz P, Rodríguez-Creixems M, Moreno M, Martín M, Ramallo V, Bouza E; and the GAME Study Group. Linezolid therapy for infective endocarditis. *Clin Microbiol Infect*. 2007;13**:211-5.⁷²**

This report describes nine patients with endocarditis treated with linezolid and 33 similar cases from the medical literature. All 42 patients except one had a severe underlying condition, with the most common being previous heart disease (62%) and renal insufficiency

(26%). The mean age was 63 years (range: 1-82), and 63% of patients were male. Endocarditis was left-sided in 76% of cases and occurred on a prosthetic valve in 33% of cases. Multiresistant bacteria predominated, including MRSA ($n=11$), *S. aureus* with reduced vancomycin susceptibility ($n=11$), and vancomycin-resistant enterococci ($n=7$). The most important reasons for administering linezolid were previous failure of a more conventional antimicrobial regimen (60%), intolerance of previous treatment (28%) and sequential therapy (12%). Thirty-eight patients had received previous therapy for a mean of 30 days (range: 4-90). Nevertheless, 22 patients refractory to treatment were persistently bacteremic when linezolid therapy was commenced. Linezolid was administered for a mean of 37 days, but longer for refractory patients (46 vs. 24 days; $P < .01$). Surgery was performed on 12 patients, and other drugs were given in combination with linezolid to 11 patients. Adverse effects were uncommon, but nine patients had thrombocytopenia and one had diarrhoea. None of the patients experienced severe or permanent side effects, and no relationship was found between toxicity and duration of linezolid therapy. The mean follow-up period was 8.5 months, and the outcome was considered to be successful for 33 (79%) patients. The response was satisfactory for eight of 11 patients with MRSA, and for seven of 11 patients with endocarditis caused by *S. aureus* with reduced susceptibility to vancomycin. Endocarditis caused by vancomycin resistant enterococci also showed a high response rate to linezolid, with four of five cases cured. Related death occurred in six (14%) patients, and was more common in patients with comorbidities.

Comments. A high successful outcome was achieved with linezolid. It can be argued that cure could be attributed to the use of previous or concomitant antibiotics prescribed to the patients. However, this seems unlikely, as most of the patients had refractory disease with persistent bacteraemia when linezolid therapy was initiated, despite prolonged previous standard treatment. Nevertheless, this possibility cannot be excluded in patients for whom linezolid was used as consolidation therapy, particularly as the duration of therapy for endocarditis is not clearly established.

The limited published reports suggest that linezolid may offer a therapeutic alternative for the treatment of IE due to resistant Gram-positive bacteria or may be used in those patients who do not tolerate glycopeptides. Although most of the reported patients with IE treated with linezolid were cured or improved, it should be considered that there is always a possible bias for publication of case reports with successful treatment. Randomized controlled trials would be necessary to clarify the efficacy of linezolid in the treatment of this condition and to exclude possible underreporting of side-effects.

Colli A, Campodonico R, Gherli T. Early switch from vancomycin to oral linezolid for treatment of Gram-positive heart valve endocarditis. *Ann Thorac Surg.* 2007;84**:87-91.⁷³**

This is a retrospective study conducted from February 2002 to August 2005 based on the analysis of a preformed hospital database. All patients presenting with active native or prosthetic valve left-sided endocarditis caused by resistant Gram positive bacteria who underwent surgical intervention for at least one valve replacement or repair were included.

The diagnosis of endocarditis at baseline was determined with the use of the modified Duke criteria.

All patients were treated before surgical intervention with IV vancomycin (target vancomycin blood level was between 10 and 15 mg/L) for at least 24 hours. After the intervention, patients were treated with continuous infusions of vancomycin to achieve a plateau blood concentration of 20 to 25 mg/L.

If the patient fulfilled early switch criteria (ability to take oral medications, clinical improvement, no requirement of intravenous antimicrobials, normalizing white blood count and no linezolid

contraindications), oral linezolid 600 mg every 12 hours was initiated and continued for 3 weeks. Patients underwent clinical and microbiologic follow-up at 30 days, 6 months, and 1 year after intervention.

During the study period, 14 patients were included, and the mean age was 52 ± 16 years. Ten patients were admitted with New York Heart Association class III criteria, and 4 patients fulfilled New York Heart Association class IV criteria. The most frequent indication for early surgical treatment was worsening heart failure (8 patients, 60%) and inability to control the infection (6 patients, 40%). Twelve patients (85%) presented with an active native valve endocarditis, and 2 patients (15%) presented with an active prosthetic valve endocarditis. Twelve patients (85%) presented preoperatively with positive blood cultures, and 2 patients (15%) had negative preoperative blood cultures. Eight patients (60%) presented with MRSA (MIC >2 mg/L), and 4 patients (30%) presented with penicillin-resistant viridans streptococci (MIC >0.5 mg/L). In the 2 patients (15%) with culture-negative endocarditis, pathogens were identified in the culture of the resected valves. In both cases, multidrug-resistant enterococci (resistant to penicillin MIC >16 mg/L, resistant to gentamicin MIC >500 mg/L and vancomycin susceptible MIC <4 mg/L) were identified.

Six patients (40%) presented with vegetations on the aortic valve, 6 patients (40%) on the mitral valve, and 1 (7%) on both the aortic and mitral valves. The 2 patients with prosthetic valve endocarditis (1 mitral and 1 aortic) presented with prosthesis dehiscence. The mean intensive care unit and total hospital stay were 3.1 ± 2.3 days and 10.5 ± 3.4 days, respectively. Early switch to oral linezolid occurred after 5.3 ± 4.7 days from the surgical intervention. Follow-up was completed in 100% of the study patients and all the blood cultures performed at follow-up were negative. Neither there were cases of recurrent endocarditis during the follow-up period nor drug-related complications. No operative deaths within 30 days of the procedure occurred. These were 2 late deaths, resulting in an overall late mortality of 14.3%.

Comments. This study shows that the combination of aggressive surgical treatment and the early switch from intravenous vancomycin to oral linezolid for treatment of active Gram positive endocarditis is safe and effective, and reduces infection relapses, vancomycin use, hospital length of stay, and economic costs. However, limitations are: the inclusion of a selected group of patients who underwent surgical intervention, the single institution design, the small sample size and the retrospective analysis. Thus, validation of these results will require further clinical investigations with multicenter randomized trials.

Levine DP, Lamp KC. Daptomycin in the treatment of patients with infective endocarditis: experience from a registry. *Am J Med.* 2007;120** 10 Suppl 1:S28-33.⁸⁶**

The Cubicin Outcomes Registry and Experience (CORE) 2004 was a retrospective observational chart review of the cases of patients receiving daptomycin for any indication in 45 US institutions.

Among the 1,160 CORE 2004 patients, 49 patients (4.2%) had a diagnosis of IE. Of these, 26 (53%) had left-sided endocarditis (LE), 11 (22%) had right-sided endocarditis (RE), and 12 (24%) had both LE and RE. Data on patients with both LE and RE were combined with those on patients with LE alone. The median dose for LE was 6 mg/kg (range, 4 to 7 mg/kg) and for RE, 4 mg/kg (range, 4 to 6.4 mg/kg). Nonetheless, the majority of patients (55%) received daptomycin at a dose of >6 mg/kg, with a greater number of patients in the LE subgroup than in the RE subgroup (63% vs. 27%; $P = .046$) receiving daptomycin at doses of >6 mg/kg.

Overall results were good with 31 (63%) of the patients being reported as clinical success. Patients in the LE subgroup had a slightly

higher rate of clinical success presumably because of the higher doses in that subgroup. Median times to clinical response based on signs and symptoms were 4 and 5 days for the LE and RE group, respectively. A remarkable finding is that clinical success was independent of the type of Gram positive microorganism, including MRSA and *Enterococcus* sp.

Comments. As in other retrospective studies, there are several limitations in this study, the main being that patients do not comprise an homogeneous group (the diagnosis of endocarditis was determined by individual investigators, and diagnostic criteria, such as echocardiography and/or Duke criteria, were not collected); no information on cardiac surgical procedures was retrieved and therefore the influence of surgery on outcomes cannot be assessed; outcome evaluation was not done based on follow-up data, so relapsing infections could not be determined, hence limiting the conclusions.

Gavaldà J, Len O, Miró JM, Muñoz P, Montejo M, Alarcón A, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. *Ann Intern Med.* 2007; 146:574-9.⁵⁰

In a previous experimental model the authors reported in vitro and in vivo synergism with combined ampicillin and ceftriaxone against *Enterococcus faecalis* with high-level aminoglycoside resistance (HLAR), so they conduct this observational, multicenter, open-label clinical trial in patients with endocarditis caused by *E. faecalis* with or without HLAR to validate their results.

Patients received intravenous ampicillin, 2 g every 4 hours, plus intravenous ceftriaxone, 2 g every 12 hours, for 6 weeks. Ceftriaxone was given just after the ampicillin infusion.

Twenty one patients comprised the HLAR *E. faecalis* group and 22 the non HLAR group. Overall the clinical and microbiological cure rate was 71.4% and 72.7% at the end of treatment in the HLAR and non-HLAR enterococcal endocarditis groups, respectively, and these percentages were 71.4% and 63.6% after 3 months. Treatment-related mortality rate was 28.6%, which is similar to that in other enterococcal endocarditis series. On the basis of these results the authors conclude that combined treatment with ampicillin and ceftriaxone at a dosage of 2 g every 12 hours may be the treatment of choice for endocarditis caused by HLAR *E. faecalis*. Results were also very good in patients with non-HLAR endocarditis although two patients presented with a relapsing infection, which amounts to a higher rate of complications in this group. For this reason caution must be advised in this subset of patients before the universal recommendation of this alternative treatment can be made.

The combination of ampicillin and ceftriaxone was shown to be effective and safe for treating HLAR *E. faecalis* endocarditis and could be a reasonable alternative for patients with non-HLAR *E. faecalis* endocarditis who are at increased risk for nephrotoxicity.

Conflict of interest

In the past 5 years, B. Almirante has received grant support from Gilead Sciences, Pfizer, and the Instituto de Salud Carlos III. He has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Janssen and Novartis.

J. Rodríguez-Baño has received honoraria for lectures and advisory work from Pfizer and Novartis, and receives research funding from the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III – co-financed by European Regional Development Fund “A way to achieve Europe” ERDF, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008).

The remaining authors declare they have not any conflict of interest.

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