A-039

Pharmacologic Assessment of Guidelines on Gentamicin Use in Infective Endocarditis

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Background: To assess the relevance of guidelines on aminoglycosides use in the treatment of infective endocarditis. **Methods:** Patients with a Streptococcus spp, Staphylococcus spp or Enterococcus spp bacteraemia were included, excluding critically ill patients. Endocarditis treatment was initiated as recommended by US and European guidelines (gentamicin at 3 mg/kg/d, once daily dosing for Streptococcus spp, twice daily dosing for Staphylococcus spp or Enterococcus spp). If endocarditis wasn't confirmed, gentamicin was discontinued. Peak (Cmax), Trough (Cmin) and Minimum Inhibitory Concentration (MIC) were measured as well as creatinine level. Gentamicin regimen was considered efficient when inhibitory quotient (Cmax / MIC) was superior or equal to 12. **Results:** Among the 33 included patients, 88 peaks and 205 troughs were obtained. Modification of the initial regimens was required in 27 patients, because of insufficient peak (n=18) or excessive trough (n=9). Dosing at 5 mg/kg/d or more was significantly associated to efficient inhibitory quotient (39.3% of measured peaks, median (min-max)=9.5(0.8-44.7)) compared to 3 mg/kg/d (18.3% of measured peaks) median (min-max)=2.95(0.5-113.3)] (p=0.03). Staphylococci were more frequently associated with efficient inhibitory quotient (70.6%) compared Streptococci (21.7%) and Enterococci (0%) (p<0.001), due to lower MIC. Nineteen per cent of troughs (14 patients) were superior to 1. There was no significant association between once or two daily dosing and obtaining an efficient inhibitory quotient or a trough superior to one. Eight patients had a worsening of their renal function, and all 8 had nephrotoxic medication concomitant to gentamicin. **Conclusions:** Because of effective inhibitory quotients rarely obtained, recommended guidelines for gentamicin dosing regimens in infective endocarditis are inappropriate. Higher doses seem to be more appropriate to obtain efficiency from gentamicin. Dosing may be more important than frequency of administration.

K-277
Daptomycin Experience for Enterococcal Endocarditis

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Background: Daptomycin (DAP) is often used for patients (pts) with enterococcal endocarditis, although it is not approved for this indication and there are few supportive clinical data. This study examines the outcomes of pts with enterococcal endocarditis treated with DAP. **Methods:** All pts with enterococcal endocarditis were identified in CORE 2005-2009, a retrospective, multicenter, observational registry. Pts were assessed for outcome (cured, improved, failed, nonevaluable) at the end of DAP therapy. The evaluable population (EP) was the resulting cured, improved and failed pts. Pt characteristics are based on the EP. All pts were included in the safety analysis. Comparisons were made with Fisher's exact test.**Results:** There were 37 (73%) of 51 pts evaluable for outcome. The success rate was 76% (28/37; cured 43% n=16; improved 32% n=12). Pt demographics were: 62% male, 27% ≥ 66 yrs, 24% had an initial CrCl <30 mL/min, 16% on dialysis and 49% received DAP in an ICU. Most pts (65%) had left sided endocarditis, while 19% had an intracardiac foreign body present. 26 (70%) pts received at least one dose of combination therapy with the most common antibiotics: cefepime (n=6), gentamicin (n=5), ampicillin (n=5) and rifampin (n=5). The median (min, max) initial DAP dose was 6 mg/kg (3, 10; 19% ≥ 8 mg/kg). The median (min, max) DAP duration of therapy was 22 days (2, 61). Successful outcomes by pathogen: *E. faecium* (69%, 11/16), *E. faecalis* (75%, 12/16) and un-identified species (100%, 5/5). There was not a difference in success between vancomycin-resistant (73%, 11/15) and susceptible (77%, 17/22) (p=1.0). The median (min, max) time to clinical response in successfully treated pts was 4 days (1, 26); n=17. Successful outcomes were similar by DAP dose; < 8 mg/kg (77% (23/30) and ≥ 8 mg/kg (71% (5/7) (p=1.0). 5/51 pts (10%) experienced at least one possibly-related adverse event (AE) and 4 pts (8%) discontinued DAP due to AE. All cause mortality rate was 18% (9/51). **Conclusions:** In this cohort, DAP appeared to be a useful treatment for enterococcal endocarditis. Vancomycin resistance did not influence DAP success rates. Further studies are warranted.

In-Hospital and Long-Term Outcome of Left-Sided Infective Endocarditis (LSIE). The Influence of Methicillin-Resistant S. aureus Infection on Prognosis

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Background: The aim of this study was to describe in-hospital mortality and long-term outcome of LSIE patients. **Methods:** Prospective observational cohort study in a referral hospital between January 2000 and December 2011. The cohort consisted in 337 cases of infection on native valves (NVIE), and 101 on prosthetic valves (PVIE). Patients were followed-up until death, relapse, recurrence or last control. **Results:** The median age was 66 years (IQR 52-72), 39% had been transferred from other hospitals, and 31% acquired the infection in the healthcare setting. Etiology: streptococci 37%, staphylococci 33% (23/99 S. aureus were methicillin-resistant), enterococci 14%, and other 16%. At least one complication was observed in 83% of cases (congestive heart failure in 47%). Cardiac surgery was indicated in 73%, but performed in 40%. Overall in-hospital mortality was 29% (26% NVIE, 39% PVIE). For the whole series, S. aureus was an independent risk factor of in-hospital mortality (OR 2.0, 95%CI 1.2-3.5). In the subgroup of S. aureus LSIE, after adjustment for congestive heart failure, methicillin-resistance was a risk factor for in-hospital mortality (OR 2.62, 95%CI 1.02-6.76). The median length of follow-up in patients alive at discharge was 3.2 years (IQR 1-6 years). For the overall series, the actuarial survival at 1 year was 60% (64% NVIE, 49% PVIE), at 2 years 56% (59% NVIE, 43% PVIE), and at 5 years 48% (52% NVIE, 34% PVIE). Relapse occurred in 2.2% (95%CI 1.3%-5.5%), a median of 25 days after finishing treatment (IQR 7-42); and recurrence in 2.6%, (95%CI 1.3%-5%), with an incidence of 0.0067 episodes per patient-year (95%CI 0.0029-0.0133). **Conclusions:** LSIE is a disease with a high rate of in-hospital and long-term mortality, especially PVIE. Resistance to methicillin almost triples in-hospital mortality in S. aureus LSIE. However, relapse and recurrence are uncommon complications.

L1-1637
Endocarditis from *Enterococcus faecalis*

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Background: *E. faecalis* is the third cause (after *S. viridans* and *S. aureus*) of bacterial IE, accounting for 5-18% of the cases of native valve IE. The IE from Enterococcus has a subacute course and is present in elderly male sex patients. It affects mainly the aortic valve and is associated with fewer embolic events (EE). **Methods:** 61 episodes with native valve IE were analyzed out of 80 episodes of IE included in the patient cohort with IE. The episodes associated with intravascular devices were excluded. **Results:** *E. faecalis* was the second most frequent MO after *S. aureus* in our series and is the most frequent cause of the last 14 episodes, corresponding to the 50%. The average age of Group 1 was 63 (R- 40- 86) and that of Group 2 was 56 (R 17 - 88). The diagnosis of IE was defined in 16/17 (94%) episodes of Group 1 episodes, and 39/44 (87%) in Group 2. In all the episodes the IE was monomicrobial. The isolated *E. faecalis* were Ampicillin-sensitive, whereas 3 presented Aminoglycoside resistance. The duration of treatment in which they were completed was 4- 8 weeks, with only one recurrence. The places where endocardial affection was more frequent were the aortic and mitral valves without significant differences with Group 2. Vegetations were observed in the (TTE and /or TEE) echocardiograms performed at the time of diagnosis in 53 IE episodes: 16 (94%) in Group 1 and 37 (84%) in Group 2 without any differences in the size of the vegetations (> y < 10 mm in diameter). The EE in patients of Group 1 occurred in 2/17 patients whereas in Group 2 in 21/44, the difference between both groups being statistically significant (p = 0.02). The global mortality was 20 patients; 4 patients in Group 1 and 16 patients in Group 2. **Conclusions:** The *E. faecalis* is a frequent cause of native valve IE and it has increased in the last few years, the average age when it appears is higher, there are no differences in mortality, surgery, echocardiogram results and relapses, having a lower tendency to present embolic complications (p = 0.02).

Table I

	Group 1 (17) *Enterococcus* spp.	Group 2 (44)
Age	63 (R 40-86)	56 (R 17-88)
Blood culture	17	40 (91%)
Vegetation	16 (94%)	37(84%)
≥ 10 mm	11 (69%)	23 (62%)
Defined IE	16 (94%)	39 (88%)
Surgery	4 (23%)	14 (32%)
Embolism	2 (12%)	21 (48%)

Comparison of High Dose Daptomycin (DAP) and Dose Optimized Vancomycin (VAN) for MRSA Bacteremia and Infective Endocarditis (IE)

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Objective: Dose-optimization of antimicrobial therapy has been suggested to improve patient outcomes in serious MRSA infections. Our objective was to evaluate outcomes of patients treated with high-dose DAP or optimized VAN from a multicenter randomized double-blind trial. **Methods**: Patients with bacteremia and or right-sided IE were randomized to receive DAP 10 mg/kg/day vs. VAN optimized for troughs of 15-20 mg/L. Safety incl. muscle toxicity and nephrotoxicity was monitored throughout. Clinical and microbiological characteristics were also collected. Modified intent-to-treat population included pts with MRSA isolated; clinical cure was evaluated at the end of therapy (EOT). **Results**: 36 patients received treatment; 19 DAP and 17 VAN. 15 pts were in mITT. Demographics were similar except sex (males 68% in DAP, 77% in VAN). Median age was 51 years (range 20, 94). Of the 30 patients with confirmed diagnosis, 57% were treated for bacteremia, 43% for IE. CrCL was > 80 ml/min in 69% of the patients. Median dose: 9.97 mg/kg/day DAP and 2.25 g/day VAN. Median VAN trough: 20.63 mg/L. Overall safety: 2/19 (10%) patients who received DAP had elevations in CPK > 10 x ULN on therapy; 1 discontinued, 1 completed 28 d. 4/17 (23%) patients had decreased renal function during VAN therapy; 2 discontinued. 15 patients (9 DAP, 6 VAN) with MRSA were included in mITT. Clinical cure at EOT was 67% (6/9) for DAP and 50% (3/6) for VAN. Median time to clearance was 4 days in DAP; less then 50% of VAN patients achieved clearance. Mean LOS after start of study drug was 7.6d for DAP and 10.8d for VAN. Microbiology: DAP MIC range 0.125-0.5, VAN MIC range 0.5-2, agr group 1 (67%), 2 (13%), 3 (13%); 60% were mec type 4 and USA 300 or 400. No hVISA was identified by macro Etest. **Conclusion**: DAP at a dose of 10 mg/kg/d in MRSA bacteremia and IE was generally safe and well tolerated and associated with a rapid bacterial clearance. Further research comparing higher dosages of DAP and VAN is warranted.

L1-1639
578 Endocarditis in French Region: Epidemiology, Mortality and Cost

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Background: We conducted an epidemiological and economic study of infective endocarditis (IE) for 2007-2009 in the Center Region of France, using the regional hospital database (PMSI). **Methods:** We extracted hospital discharge (HD) data for IE from the PMSI, with a definition using IE-related diagnosis codes. We calculated the positive predictive value (PPV) of the definition and the frequency of definite IEs according to the Duke criteria, using hospital reports from a sample of 243 patients. Sensibility (Se) was calculated from a sample of 492 HDs with a code of transesophageal echocardiography, valvular surgery or removal of pacemaker. Incidence, comorbidities, microbiology, risk factors for death, length of stay and charges were also analyzed. **Results:** The analysis was focused on 807 HDs (578 patients). PPV and Se of the definition were 87.4% and 90%, respectively. Frequency of definite IEs was 74,4%, IC95 [67.9%-80.9%]. The annual average incidence standardized for age and sex, adjusted on PPV and frequency of definite IEs, was 45.4 cases per million residents. Mean age was 68.2 years. Streptococci and staphylococci were the main coded agents (39.8% and 29.1%, respectively). A valvular surgery was performed in 19.4% of cases. The hospital mortality was 17.6%. In the multivariate analysis, risk factors for mortality included age (p<0,001), staphylococcal infection (p<0.001) and hemorrhagic stroke (p=0.002). The average length of hospital stay was 30 days and the average cost was 15 281 euros (20 103 dollars) per HD. **Conclusion:** We reported a higher IE incidence rate than the French national study of 2008 (45.4 vs 31 cases per million residents). Comorbidities and microbiological characteristics were comparable to published data. Valvular surgery was considerably less frequent than in the published data (near 50%) whereas mortality was similar. The economic analysis shows that IE imposes a heavy cost on society. Medico-administrative databases are a reliable tool for epidemiology, thanks to their exhaustiveness ; however, their use requires a validation step to determine the Se and PPV of the cases definition.

Relation Between Specific Bacteria, Echocardiographic Findings, And Surgical Findings In Patients Undergoing Cardiac Surgery Due To Infectious Endocarditis

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Background: Echocardiographic (ECHO) findings in patients with infectious endocarditis (IE) affect decisions regarding valve surgery. Information about the relation between ECHO and surgical findings is limited. Information is also lacking regarding the effect of different bacteria on the reliability of ECHO compared to surgical findings. **Methods:** Clinical, bacteriological, ECHO and surgical findings were reviewed for 80 patients who underwent valve surgery because if IE during 2004-2011. IE was diagnosed according to the modified Duke criteria. Blood cultures (BC) were performed for all patients. Patients with negative blood cultures were evaluated for Q fever by serology. All patients underwent transesophageal ECHO (TEE). Surgical findings were considered different from TEE results if there was a difference in ≥1 in the number or type of infected valves, number of vegetations, size of vegetations (≥5 mm), and number of abscesses. Descriptive statistics, chi square and Fisher exact tests were used when appropriate. **Results:** Mean age was 55 years. 26% had a prosthetic valve. Causative agents were Staphylococcus aureus in 24%, Streptococcus viridans sp. in 20% and Enterococcus sp.in 10%. 18% had culture negative endocarditis. Mitral and aortic valves were involved in 56% and 45% respectively. TEE demonstrated vegetations in 84%, a new valvular leak in 61%, and abscesses in 30%. 23% had an embolic event. In 42% of patients TEE results differed from surgical findings. Despite this difference surgical procedure remained appropriate for most patients. S. viridans IE was associated with a disproportionate high number of discrepancies between TEE and surgical findings compared to other bacteria (63% vs. 38%, p=0.07). Agreement in the number of vegetations was 75% for S. viridans vs. 92% for other bacteria (p<0.0001) and for abscesses 50% for S. viridans vs. 75% for other bacteria (p=0.009). **Conclusion:** Significant differences exist between ECHO and surgical findings but these differences usually do not affect the appropriateness of surgery. Discrepancies were much more frequent in patients with S. viridans IE compared to other bacteria.

Beta-Haemolytic Streptococcal Infective Endocarditis (BHIE). Characteristics and Outcomes from a Large, Multi-national Cohort

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Background: The aim of this study was to describe the clinical characteristics and outcome of patients with BHIE in a large, international, cohort of patients. **Methods**: Patients hospitalized with definite or possible endocarditis by the International Collaboration on Infective Endocarditis Prospective Cohort Study in 64 hospitals from 28 countries were included. Characteristics and outcome of S. pyogenes (SPIE) and S. agalactiae IE (SAIE) patients were compared with those of oral streptococcci IE (OSIE). **Results**: 1509 IE episodes enrolled were due to streptococci: 928 (62%) OSIE, and 173 (12%) BHIE (12 SPIE, 111 SAIE, and 50 other).

Comparison between BHIE and OSIE episodes

Characteristic	SPIE (n=12)	SAIE (n=111)	OTHER BHIE (n=50)	OSIE (n=928)
Median Age, Years (IQR)	35.0 (26.1-68.3)*	61.1 (48.5-74.0)*	54.7 (42.9-68.6)	56.7 (40.7-71.1)
Diabetes	0/12	24/111 (22%)*	8/49 (16%)	101/927 (11%)
I.V. Drug Use	5/12 (42%)*	3/111 (3%)	1/48 (2%)	44/923 (5%)
Admission Delay >1 Month	0/11*	11/109 (10%)*	5/50 (10%)*	377/883 (43%)
Prosthetic IE	2/12 (17%)	20/109 (18%)	14/50 (28%)**	166/894 (19%)
CHF	6/12 (50%)	32/111 (29%)	18/49 (37%)	250/915 (27%)
Stroke	0/12	30/111 (27%)*	11/50 (22%)	123/916 (13%)
Surgery Performed	6/12 (50%)	54/111 (49%)	16/50 (32%)	397/924 (43%)
In-Hospital Mortality	2/12 (17%)	20/111 (18%)*	7/50 (14%)	75/928 (8%)

*P<0.05 as compared with SOIE. **P=0.07 as compared with SOIE. In the whole streptococcal IE series, after adjusting by congestive heart failure, beta-haemolytic infection was an independent risk factor for in-hospital mortality (OR 2.11; 95%CI 1.33-3.36; P=0.002). **Conclusions**: BHIE is uncommon in a large, multinational series of IE. SPIE and SAIE have clearly differentiated clinical patterns with a worse prognosis than SOIE patients.

Timing of Antibiotic and Surgical Treatment of Q-fever Endocarditis

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Background: Data is limited regarding the correct timing for surgical intervention in Q fever endocarditis (QFE). In particular it is not known if early surgery prior to starting appropriate antibiotic therapy affects patients' outcomes. **Methods:** Between 2004-2011 patients who underwent valve surgery due to QFE at the Sheba Medical Center were identified. Patients' files were reviewed. QFE was diagnosed according to the modified Duke criteria. **Results:** During the study period 137 valve procedures due to endocarditis were performed. 8 cases (5.8%) of QFE were diagnosed (5 males and 3 females). Mean age was 53 years. 6 patients underwent aortic valve replacement (AVR) (including 2 root replacements with composite graft), one underwent mitral valve replacement (MVR) and 1 underwent AVR with MVR. 3 patients had native valve endocarditis and 5 patients had prosthetic valve endocarditis. The main echocardiographic finding was paraprosthetic leak or bioprosthetic deterioration with few signs of endocarditis such as cardiac vegetations. In 2 patients minimal abscess formation was noted. Blood culture results remained negative in all patients. All patients had a positive serology to *Coxiella burnetii* and in one case PCR performed on the resected valve was positive. Treatment of QFE was started prior to surgery (3-8 weeks) in 3 patients, during the week prior to surgery in 2 patients, during the week after surgery in one patient and 5-12 weeks after surgery in 2 patients. All patients received doxycycline and hydroxychloroquine for a prolonged period. We observed no operative mortality and one in-hospital death. The patient who died began antibiotic treatment 5 weeks after surgery and died a few days later due to cardiac arrest. Mean follow-up was 36±23 months. No late deaths occurred. In surviving patients prosthetic valve function was normal and none required additional surgery. **Conclusions:** Q fever endocarditis should be suspected in patients with abnormal native or prosthetic valves without leukocytosis and negative blood cultures. In most patients delay in antibiotic treatment in relation to the surgery did not seem to affect outcomes.

B-646

Relationship Between in vitro Vancomycin Susceptibility in Biofilms and Treatment Outcomes in Experimental Endocarditis due to Methicillin-Resistant *Staphylococcus aureus*

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Background: Vancomycin (VAN) is commonly used to treat MRSA infections. However, high rates of VAN treatment failure in MRSA infections caused by VAN-susceptible (S) strains (MICs < 2 µg/ml) have been increasingly reported. We studied potentially relevant mechanism(s) of such "in vivo resistance" to VAN treatment amongst VAN-S strains. **Methods:** Ten VAN-S MRSA clinical bloodstream isolates previously categorized for their VAN responsiveness in an experimental infective endocarditis (IE) model were assessed in vitro for: VAN binding; biofilm formation (± sub-lethal VAN exposure); biofilm composition; susceptibility to VAN killing (in the presence or absence of catheter segments); and cell wall thickness. **Results:** As a group, the five strains categorized as VAN-responsive in the IE model (`Responders' [Rsp]) significantly differed from the five 'Non-Responders' (Non-Rsp) in terms of: higher VAN binding (p = 0.03); and lower survival of a 10^7 cfu/ml inoculum with VAN at 15 µg/ml in the presence and absence of plastic catheter segments (p = 0.004 for the absence plastic catheter segments; p ≤ 0.05 for four of five Rsp strains in the presence of plastic catheter segments). Cell wall thickness was similar among the 10 strains. Biofilm formation was higher (but not significantly different) in Non-Rsp vs Rsp. Biochemical analyses revealed a significantly higher biofilm protein (but not carbohydrate or DNA) content in Non-Rsp vs Rsp strains (p = 0.04). Interestingly, sublethal VAN induced significantly more biofilm formation in Non-Rsp vs controls (without sublethal VAN exposure; p = 0.004), but not Rsp strains. **Conclusions:** These results suggest that the capacity of VAN-S MRSA strains to induce biofilm formation and survive VAN exposures within biofilms may closely correlate with VAN treatment outcomes of endovascular infections.