8 mg/kg of daptomycin, and 8 of 21 (38.1%) for comparator patients. In conclusion, daptomycin at 6 and 8 mg/kg given for up to 6 weeks was safe and appeared to be effective in managing staphylococcal prosthetic joint infection using a two-stage revision arthroplasty technique in a total of 49 patients (Byren *et al.*, 2012).

Several other authors also report clinical success rates in the treatment of periprosthetic joint infection; however, all the studies included a limited number of patients (18–72) and did not compare them with treatment with other antibiotics (Roux *et al.*, 2016; Corona Pérez-Cardona *et al.*, 2012; Perrottet *et al.*, 2015; Lora-Tamayo *et al.*, 2014). Clinical success rates varied from 50–87%. One retrospective study combined the i.v. use of daptomycin with bone cement containing daptomycin after the two-stage revision arthroplasty and included 22 patients with periprosthetic joint infections with methicillin-resistant staphylococci. In the first stage, 10% daptomycin (weight of daptomycin per weight of bone cement) was incorporated into polymethylmethacrylate bone cement, and systemic daptomycin (6 mg/kg) was administered postoperatively for 14 days. In the second stage, 2.5% daptomycin was used in the bone cement. The minimum followup was 2 years or until recurrence of infection. The infecting organisms included MRSA in 10 patients, MRSE in 8 patients, and methicillin-resistant coagulase-negative staphylococci in 4 patients. The mean followup was 33.7 months (range 24–51 months). The treatment success rate was 100%. Only 1 patient developed asymptomatic transient elevation of the CPK level (Kuo *et al.*, 2016).

The data between January 2006 and April 2012, with followup to 2014 in the EU-CORE, were retrospectively evaluated. Clinical outcomes were assessed as success (cured or improved), failure, or nonevaluable. Of 6075 patients enrolled, 638 (median age, 63.5 years) had primary infections of osteomyelitis or orthopedic device infections, 224 had nonprosthetic osteomyelitis, 208 had osteomyelitis related to a permanent or temporary prosthetic device, and 206 had orthopedic device infections. The most commonly isolated pathogen was *S. aureus* (214 [49.1%]; 24.8% were MRSA). Overall, 455 (71.3%) patients had received previous antibiotic therapy. Patients underwent surgical interventions, including tissue (225 [35.3%]) and bone (196 [30.7%]) débridement, as part of their treatment. The overall success rate for daptomycin treatment was 81.8%. Clinical success rates were 82.7% and 81.7% in *S. aureus* and in coagulase-negative staphylococcal infections, respectively. Differences in clinical success rates for various infection types have been identified. The highest cure rate has been found for infection with temporary prosthetic devices (89.6%), followed by nonprosthetic infections (79.9%) and permanent prosthetic device–related osteomyelitis (78.1%). Clinical success rates were similar when daptomycin was prescribed as first-line treatment (80.1%) or as second-line treatment (83.1%) (Malizos *et al.*, 2016). A previous analysis of the CORE database indicated that failures were more likely if surgical débridement was not performed (24% vs. 5%; $p = 0.045$). The clinical success rate for patients treated with an initial daptomycin dose of > 4 mg/kg was significantly higher than for patients treated with an initial dose ≤ 4 mg/kg (88% vs. 65%; $p= 0.013$) (Lamp *et al.*, 2007). The cure rates as described by Malizos *et al.* (2016) were comparable to the rates reported in other smaller studies (Liang *et al.*, 2014; Seaton *et al.,* 2013b).

7d. Central nervous system infections

EXPERIMENTAL MENINGITIS

In an infant pneumococcal meningitis rat model, the effect on brain damage due to inflammation was studied. Rats were treated with ceftriaxone alone, with daptomycin before ceftriaxone, and with rifampin before ceftriaxone. Brain damage was studied by measuring chemokines and cytokines in the CSF and histomorphometry, and hearing loss were assessed after 3 weeks. Daptomycin plus ceftriaxone vs. ceftriaxone significantly ($p < 0.04$) lowered CSF concentrations of monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and interleukin 6 at 6 hours as well as macrophage inflammatory protein 1α, interleukin 6, and interleukin 10 at 22 hours after initiation of therapy and led to significantly ($p < 0.01$) less apoptosis and significantly ($p < 0.01$) improved hearing capacity (Grandgirard *et al.*, 2012). Adjuvant daptomycin could therefore offer added benefits for the treatment of pediatric pneumococcal meningitis. Another study also showed an additional effect for the combination of ceftriaxone plus daptomycin (Egermann *et al.*, 2009). In the comparison of daptomycin and vancomycin in a rabbit MRSA meningitis model, after 8 hours of treatment the antibacterial effect of these two drugs was similar. The doses of daptomycin used in the rabbits were comparable to human doses of 6 mg/kg (Bardak-Ozcem *et al.*, 2013).

HUMAN MENINGITIS

There is very limited experience with daptomycin in the treatment of human meningitis or ventriculitis. Several cases have been described in the literature, as reviewed by Vena *et al.* (2013). Daptomycin in these cases is combined with other antibiotics such as vancomycin, rifampicin, linezolid, gentamicin, tigecyclin, or levofloxacin. Doses used in these cases vary considerably, also dependent on the renal function. The highest i.v. dosage was 24 mg/kg/day divided over six doses, combined with 2.5 mg of daptomycin administered intraventricularly (Jaspan *et al.*, 2010). An additional intraventricular dose was administered in one other case, but in a dose of 10 mg daily (Erritouni *et al.*, 2012). One of the 11 cases described by Vena *et al.* (2013) was not cured (Wahby *et al.*, 2012). This particular patient was treated with daptomycin, 6 mg/kg every 48 hours (peritoneal dialysis), and serum as well as CSF concentrations at 24 hours after the dose were undetectable (Wahby *et al.*, 2012). In another case, different concentrations of daptomycin were measured for samples taken from two external ventricular drains (EVDs). The output of the EVDs differed also. The right EVD produced 20 ml and the left EVD 45 ml since the last dose or sample. The concentrations of daptomycin in samples taken from these EVDs were