6a. Musculoskeletal toxicity

One side effect that was apparent in experimental animals and in subjects in early trials with twice-daily dosing was skeletal muscle toxicity. Patients developed myopathy with elevated CPK, muscle pain, and weakness. The adverse skeletal muscle effects in dogs were characterized by degenerative/regenerative changes and elevated CPK. No fibrosis or rhabdomyolysis was evident. Severity was dose dependent, and all effects were fully reversible within 30 days of cessation of dosing (Package Insert, 2007). To guide the clinical dosing regimen with the potential for the least effect on skeletal muscle, two studies were conducted with dogs to compare the effects of repeated i.v. administration every 24 hours vs. every 8 hours for 20 days. The data from these studies suggest that increases in serum CPK activity and the incidence of myopathy were more closely related to the dosing interval (more severe effects with dosing every 8 hours than with every 24 hours) than to either the maximum concentration of the drug in plasma or the AUC. Once-daily administration appeared to minimize the potential for daptomycin-related skeletal muscle effects, possibly by allowing for more time between doses for repair of subclinical effects (Oleson *et al.*, 2000).

In humans, these adverse effects were also reduced when once-daily dosing was administered. In a later phase I study examining dosages up to 12 mg/kg once daily for 14 days, no skeletal muscle effects or CPK elevations were observed (Benvenuto *et al.*, 2006). In the phase III trials of cSSSI (Arbeit *et al.*, 2004), 0.2% of patients treated with daptomycin had symptoms of muscle pain or weakness associated with CPK elevations to greater than four times the upper limit of normal (Table 45.8). The symptoms resolved within 3 days, and CPK returned to normal within 7–10 days after discontinuing treatment. In the bacteremia/endocarditis trial (Fowler *et al.*, 2006), CPK elevations were significantly more common in the daptomycin-treated group than in the standard-therapy group (6.7% vs. 0.9%; $p = 0.04$). Among patients with normal baseline levels of CPK, elevations were noted in 23 of 92 patients who received daptomycin, compared with 12 of 96 patients who received standard therapy (25.0% vs. 12.5%; $p = 0.04$). Among patients with data that could be evaluated, 11 of 116 patients who received daptomycin had elevations in creatine kinase to more than 500 IU/l, compared with 2 of 111 patients who received standard therapy (9.5% vs. 1.5%; $p = 0.02$). Of these 11 patients receiving daptomycin, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Four of the 11 patients who received daptomycin had elevations that were greater than 10 times the upper limit of normal. Elevation of CPK led to the discontinuation of treatment with daptomycin in 2.5% of patients (Fowler *et al.*, 2006). In a group of 8 patients with asymptomatic elevated CPK receiving a mean daptomycin dosage of 7.75 mg/kg/day for a median duration of 42 days, the daptomycin dosing was withheld for 24 hours. After resuming the daptomycin 24 hours later, most often at the same dose, the elevated CPK values had resolved, and the 8 patients were able to complete the daptomycin therapy without further increases in CPK elevations (Burdette *et al.*, 2014).

The relationship between exposure to daptomycin and the probability of an elevation in CPK level was described in 108 patients, of whom 6 demonstrated a defined CPK elevation. Significant relationships between the minimum concentration of drug (C_{min}) and the area under the plasma concentration time curve and probability of CPK elevation were observed. C_{min} (breakpoint of 24.3 mg/l) was most significantly associated with CPK elevation ($p = 0.002$). The probabilities of a CPK elevation with a C_{min} of at least 24.3 mg/l and < 24.3 mg/l were 0.5 and 0.029, respectively. Increases in C_{min}, evaluated as a continuous variable, were also significantly associated with CPK elevation ($p = 0.01$). The probability of a CPK elevation was 0 and 0.01 after 7 days of treatment in patients with a C_{min} of at least 24.3 mg/l or < 24.3 mg/l, respectively. After 14 days, the probabilities were 0.5 and 0.025, respectively (Bhavnani *et al.*, 2010). In a subsequent study the correlation between C_{min} and CPK as described by Bhavnani *et al.* (2010) was used in Monte Carlo simulations to determine the probability of toxicity for various doses. The probabilities of toxicity with 6 mg/kg/day and 12 mg/kg/day were 3.3% and 17.7%, respectively (Soon *et al.*, 2013). Although the numbers in the study are relatively small, this suggests that both the C_{min} and the duration of therapy should be considered in determining the risk of an elevated CPK.

Rhabdomyolysis is an infrequent yet serious adverse effect. In four reported cases, this occurred after 7–10 days' therapy (Echevarria *et al.*, 2005; Kazory *et al.*, 2006; Papadopoulos *et al.*, 2006; King *et al.*, 2014; Patel *et al.*, 2007); in two cases it was associated with liver function abnormalities. Early-onset rhabdomyolysis has been reported in two cases.

6b. Peripheral nerve toxicity

In a study of daptomycin efficacy for S. *aureus* bacteremia/endocarditis, a total of 11 of 120 (9.2%) daptomycin-treated patients had adverse events categorized as peripheral neuropathy. In phase I studies examining dosages up to 12 mg/kg once daily of daptomycin for 14 days, no nerve conduction deficits or symptoms of peripheral neuropathy were observed, whereas in a small number of patients in phase I and phase II studies at doses up to 6 mg/kg, administration of daptomycin was associated with decreases in nerve conduction velocity and with adverse events (e.g. paresthesias, Bell palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In animals, effects of daptomycin on peripheral nerve—characterized by axonal degeneration and frequently accompanied by significant losses of patellar reflex, gag reflex, and pain perception—were observed at doses higher than those associated with skeletal myopathy. Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving daptomycin (Package Insert, 2007).