(Package Insert, 2007). In such circumstances for cSSSI and *S. aureus* bloodstream infections, doses of 4 and 6 mg/kg, respectively, are given every 48 hours. No additional doses are required for patients undergoing hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration, although it is advised to administer daptomycin after hemodialysis (Package Insert, 2007). Dosages are derived from patient studies using the calculated creatinine clearance by the Cockroft and Gault equation using actual body weight. Using pharmacokinetic data, a dose of 6 mg/kg every 48 hours for patients with *S. aureus* bloodstream infections and creatinine clearance of < 30 ml/min or receiving hemodialysis or continuous ambulatory peritoneal dialysis provides appropriate daptomycin exposure for this indication; this will not be the case for patients receiving 4 mg/kg every 48 hours (Chaves *et al.*, 2014). This recommendation would be in conflict with hemodialysis administered three times a week, however. Butterfield *et al.* (2013) analyzed the pooled data from three pharmacokinetic studies of patients on hemodialysis (Salama *et al.*, 2010; Benziger *et al.*, 2011; Patel *et al.*, 2011). In total 26 patients were included, and they all received a dose of 6 mg/kg/day after dialysis. With the use of Monte Carlo simulations, two interdialytic periods were evaluated. Their recommendation was to use the standard doses of 4 and 6 mg/kg for the interdialytic period of 48 hours. When an interdialytic period of 72 hours is used, they advise to increase the doses by 50%. Therefore, for the dose of 4 mg/kg, the recommendation is to use 6 mg/kg every 72 hours, and the dose of 6 mg/kg should be increased to 9 mg/kg every 72 hours (Butterfield *et al.*, 2013).

Several studies have been performed with patients during continuous renal replacement therapy. Corti *et al.* (2013) described nine critically ill patients and reviewed the literature. Dosing recommendations varied in this special population; because of the limited data available, therapeutic drug monitoring was recommended. On the other hand, Preiswerk *et al.* (2013) retrospectively reviewed seven cases of continuous renal replacement therapy and also concluded that the recommended dose should be at least 6 mg/kg/day, but possibly 8 mg/kg/day for critically ill patients. They also recommended therapeutic drug monitoring to prevent underdosing. A summary of these studies is provided in Table 45.3.

## PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Subjects with moderate hepatic impairment receiving daptomycin do not require an adjustment in daptomycin dose or dose regimen. A single-dose, matched-controlled study was designed to evaluate the pharmacokinetics of daptomycin in adults (18–80 years) with moderately impaired hepatic function (Child-Pugh class B, $n = 10$). Subjects were administered a single i.v. dose (6 mg/kg of total body weight) over 30 minutes. A normal volunteer control group matched by weight (±25 lb/11 kg), age (±10 years), and sex was included in this study for comparison with the hepatic function–impaired group. The pharmacokinetic parameters of daptomycin were similar in both groups (Dvorchik, 2004).

## OLDER ADULTS

Changes in the pharmacokinetics of daptomycin in the elderly are attributable to changes in renal function, because age *per se* is not a significant factor. The pharmacokinetics of daptomycin was evaluated after a single 30-minute i.v. infusion of 4 mg/kg to groups of young adult (18–30 years) and geriatric (≥ 75 years) volunteers. With increased age, there were increases in the area-under-the-concentration-time-curve (AUC) extrapolated to infinity and the terminal elimination half-life. Systemic clearance (CL) and renal clearance both decreased with increasing age. The observed changes seen in CL between the two cohorts were most likely a result of changes in renal function, as estimated by creatinine clearance (Cockroft and Gault formula). No statistically significant differences were observed between the two groups in the maximum plasma concentration ($C_{max}$) or the volume of distribution at steady state (Dvorchik and Damphousse, 2004).

## OBESE PATIENTS

Daptomycin may be dosed based on total body weight, and no adjustment in daptomycin dose or dosing regimen should be required based solely on obesity (Dvorchik and Damphousse, 2005). The absolute volume of distribution ($V_z$ and $V_{ss}$) and plasma CL for daptomycin (4 mg/kg of total body weight) were higher in moderately obese (body mass index = 25–39.9 kg/m$^2$) or morbidly obese (body mass index ≥ 40 kg/m$^2$) subjects than in nonobese matched controls. Daptomycin plasma half-life, the fraction of the dose excreted unchanged in urine, and daptomycin absolute renal clearance (ml/h) were unchanged as a function of obesity. The rate of change of $V_z$ and CL with increasing body mass index was greater when these pharmacokinetic parameters were expressed in absolute terms than when they were normalized for total or ideal body weight. This suggests that increases in body mass associated with obesity are proportionally higher than the corresponding increases in $V_d$ and CL. Exposure to daptomycin in obese subjects ($C_{max}$, AUC) was increased by 25% and 30%, respectively, compared with nonobese matched controls, well within the range that was previously determined to be safe and well tolerated (Dvorchik and Damphousse, 2005).

## PERITONEAL ADMINISTRATION

Although intraperitoneal administration of daptomycin is off label, there are several case reports, as reviewed by Gilmore *et al.* (2013). A total of seven cases have been included, of which four used an intraperitoneal loading dose (most frequently, 100 mg/l dialysate volume), and the maintenance dose was most often 20 mg/l dialysate volume. All patients were clinically cured. One of the cases was a patient with peritoneal dialysis-associated peritonitis who was treated with intraperitoneal administration of a daptomycin dose of 7 mg/kg after peritoneal dialysis because no vascular access was available. The plasma concentrations were measured 15 minutes, 30 minutes, 3.5 hours, and 25 hours after injection. All concentrations were above the $MIC_{90}$ for MRSA, and the 3.5- and 25-hour samples were above 10 mg/l (Bahte *et al.*,