association with daptomycin therapy was identified during postmarketing safety surveillance. A study investigating 30 commercially available thromboplastin reagent kits detected interaction of clinically relevant daptomycin concentrations with two recombinant thromboplastin reagents that led to falsely prolonged patient prothrombin time/international normalized ratio results (Webster *et al.*, 2008).

6. ADVERSE REACTIONS AND TOXICITY

Daptomycin has relatively few side effects (Table 45.8). Data from manufacturer-sponsored trials are available for 1667 treated patients. Most adverse events were described as mild or moderate in intensity. In phase III cSSSI trials, daptomycin was discontinued in 15 of 534 (2.8%) patients owing to an adverse event, whereas comparators were discontinued in 17 of 558 (3.0%) patients. Treatment-emergent adverse events were more common in patients older than 65 years of age than in patients younger than 65 years (Arbeit *et al.*, 2004). In an *S. aureus* bacteremia/endocarditis trial, daptomycin was discontinued in 20 of 120 (16.7%) patients because of an adverse event, whereas the comparator was discontinued in 21 of 116 (18.1%) patients (Fowler *et al.*, 2006). The most common adverse events with onset before 14 days were similar to those occurring between 15 and 28 days and after 28 days (Rege *et al.*, 2013). The main side effects from the various cSSSI trials with daptomycin, 4 mg/kg/day, are shown in Table 45.8.

In the pooled analysis of the Cubicin Outcomes Registry and Experience (CORE) and the European Cubicin Outcomes Registry and Experience (EU-CORE) methodology, including the data in the registry from Europe, the USA, Latin America, and Asia, a total of 11,557 patients was treated with daptomycin between 2004 and 2012. Safety was assessed for up to 30 days after treatment. Adverse events and serious adverse events possibly related to daptomycin therapy were reported in 628 (5.4 %) and 133 (1.2 %) patients, respectively (Seaton *et al.*, 2016).

Two meta-analyses including 6 and 13 trials, respectively, evaluated the incidence of adverse events in comparison with other antibiotics. The analyses did not agree on the overall incidence of adverse effects as compared with other antibiotics. The first meta-analysis found daptomycin to have a similar treatment-related adverse events incidence in comparison with other antibiotics, mainly vancomycin and teicoplanin (OR: 1.06; 95% CI: 0.71–0.59; $p = 0.76$; $I^2 = 41\%$) (Wang *et al.*, 2014). In contrast, in the other meta-analysis it was found that daptomycin-treated patients had fewer adverse effects in total (He *et al.*, 2014). Both analyses found more patients receiving daptomycin with significant elevations in CPK (OR: 1.95; 95% CI: 1.04–3.65; $p = 0.04$; $I^2 = 0\%$) (Wang *et al.*, 2014). He *et al.* (2014) also focused on renal impairment and found that daptomycin caused a significantly lower incidence of renal impairment. Subgroup analysis indicated that daptomycin was significantly associated with a higher incidence of CPK elevation and fewer renal impairments among the population with a mean age ≤ 60 years and receiving a dose of daptomycin ≥ 6 mg/kg/24 hours (He *et al.*, 2014).

Table 45.8. Incidence of most frequent adverse events on daptomycin treatment (> 2%) vs. comparator agents from phase III cSSSI studies.

	Daptomycin, 4 mg/kg (n = 534) (%)	Comparator[a] (n = 558) (%)
Constipation	6.2	6.8
Reaction at the injection site	5.8	7.7
Nausea	5.8	9.5
Headache	5.4	5.4
Diarrhea	5.2	4.3
Insomnia	4.5	5.4
Rash	4.3	3.8
Vomiting	3.2	3.8
Abnormal liver function tests	3.0	1.6
Pruritus	2.8	3.8
Elevated creatine kinase	2.8	1.8
Fungal infections	2.6	3.2
Hypotension	2.4	1.4
Urinary tract infection	2.4	0.5
Dizziness	2.2	2.0
Renal failure	2.2	2.7
Anemia	2.1	2.3
Dyspnea	2.1	1.6

[a]Comparators were antistaphylococcal penicillins (flucloxacillin, nafcillin, oxacillin, 4–12 g/day i.v. in divided doses) and vancomycin 1 g every 12 hours i.v.

Abbreviation: cSSI: complicated skin and skin structure infection.

Adapted from Arbeit *et al.* (2004).

A study in 119 patients receiving daptomycin at home described adverse effects in 8 patients. In 3 of these patients a rash occurred; 1 had leucopenia, 3 had elevated creatine kinase levels, and 1 had a clinical adverse event. The researchers also compared the rate of adverse events during home therapy in a group of patients receiving vancomycin and found a 60% lower rate of antimicrobial adverse events and an 80% lower rate of antimicrobial interventions than in similar patients receiving vancomycin (Shrestha *et al.*, 2014). Seaton *et al.* (2013a) also found outpatient use to be safe. Ease of administration of daptomycin via a daily 2-min injection and its efficacy and safety combine to make it an attractive treatment option for outpatient parenteral antimicrobial therapy.

Although the use of daptomycin in children is not recommended in the official labels and the optimal dose still needs to be determined, it has been used. Concerning the safety of daptomycin, some data suggest that rates of adverse events in children are similar to those in adults (Garazzino *et al.*, 2016; Syriopoulou et *al.*, 2016).