Like other antibiotics, ceftriaxone may interfere with the immunological response to the live orally ingested typhoid vaccine. Live-attenuated Ty21a vaccine should not be given until at least 3 days after the last dose of antibiotic and, if possible, antibiotics should not be started within 3 days of the last dose of Ty21a vaccine (Jackson *et al.*, 2015).

6. ADVERSE REACTIONS AND TOXICITY

Ceftriaxone is generally well tolerated. Adverse reactions of ceftriaxone are similar to those of other cephalosporins (Moskovitz, 1984).

6a. Hypersensitivity reactions and rash

Ceftriaxone can cause serious hypersensitivity reactions and should be used with caution in patients with a history of allergy to beta-lactam antibiotics (Roche, 2015). Life-threatening anaphylaxis developed in a 5-year-old boy with septic shock within minutes of receiving his first i.v. injection of ceftriaxone (Ernst *et al.*, 2002). Allergic rashes occur, but are uncommon (Marks, 1983). Hypersensitivity reactions in the form of skin rash, pruritus, fever, chills, or serum sickness have occurred in 2.7% of patients receiving i.m. or i.v. ceftriaxone (Moskovitz, 1984). The incidence is slightly higher in pediatric patients (3.3%). However, routine skin testing with a cephalosporin (e.g. ceftriaxone or cefotaxime) before its administration is not useful for predicting immediate hypersensitivity because of the extremely low sensitivity and low predictive value of the skin test (Yoon *et al.*, 2013). Serum sickness-like reaction after exposure to cefuroxime and ceftriaxone, which was reversible, has been reported (Baniasadi *et al.*, 2007). For a detailed discussion regarding beta-lactam allergy, see Chapter 3, Benzylpenicillin (penicillin G).

Rash was identified in 1.7% of patients with ceftriaxone therapy. Pruritus, chills, and fever have been reported rarely in < 1% (Roche, 2015). In other reports, skin rash occurs in < 2% of patients; however, skin rash was the most frequent reason for withdrawing the drug in safety studies (19/46) (Moskovitz, 1984). Pruritus (12.2%) and urticaria (11.1%) were the most common in one recent report of 2173 ceftriaxone-induced adverse events (Shalviri *et al.*, 2012). Severe or recurrent dermatologic adverse reactions, such as toxic epidermal necrolysis (Lam *et al.*, 2008) and fixed drug eruption (Ozkaya *et al.*, 2008), have also been reported with ceftriaxone therapy.

6b. Gastrointestinal side effects

Gastrointestinal events, primarily diarrhea, have been the most frequent adverse reaction associated with i.m. or i.v. ceftriaxone therapy. The incidence of gastrointestinal events is about 3.5%, with diarrhea occurring in 2.7% of adults and 5.6% of children (Moskovitz, 1984). Others have reported a rate of diarrhea as high as 10% of treated patients (del Rio *et al.*, 1983; Marks, 1983; Chonmaitree *et al.*, 1984; Congeni, 1984). Other gastrointestinal reactions have included nausea, vomiting, abdominal pain or discomfort, dysgeusia and flatulence, all occurring in < 1% of patients (Roche, 2015).

6c. *Clostridium difficile* diarrhea and effects on gut flora

C. difficile–related diarrhea has been highlighted as a risk of ceftriaxone use in a number of studies. Loo *et al.* (2005) showed that use of third-generation cephalosporins were a risk factor for *C. difficile*–associated diarrhea. Other authors have specifically found that ceftriaxone posed an independent risk for *C. difficile*–associated disease (Muto *et al.*, 2005; Baxter *et al.*, 2008). Studies in which ceftriaxone use has been reduced in hospitals have shown a concomitant reduction in cases of *C. difficile* infection (Khan and Cheesbrough, 2003; Thomas and Riley, 2003). *C. difficile* was grown from the feces in 25% of patients who received a single 2 g i.v. prophylactic dose of ceftriaxone before an elective surgical procedure; however, none developed diarrhea (Privitera *et al.*, 1991).

Ceftriaxone alters the normal flora in the body, notably in the gastrointestinal tract and vagina, leading to overgrowth or superinfections with yeasts or other organisms (Fekety, 1990). Suppression of intestinal microflora (enterobacteria, bifidobacteria, clostridia, and *Bacteroides*) occurs with ceftriaxone treatment but is usually reversible (Nilsson-Ehle *et al.*, 1985; Cavallaro *et al.*, 1992; Vogel *et al.*, 2001; Pletz *et al.*, 2004). Bodey *et al.* (1983) found that after the drug's administration there were no aerobic Gram-negative bacilli and were only 24% aerobic Gram-positive bacilli, and 10% of anaerobes still present in the bowel. Other authors have noted that after ceftriaxone treatment there is suppression of aerobic Gram-negative bacilli with overgrowth of yeasts and enterococci (de Vries-Hospers *et al.*, 1991). Samonis *et al.* (1993) also detected colonization by yeasts of the gastrointestinal tract in patients treated by ceftriaxone. After a course of ceftriaxone–metronidazole therapy, 17.1% of patients had colonization of the gut with ceftriaxone-resistant Enterobacteriaceae (DiNubile *et al.*, 2005), of which more than 50% were ESBL producers. Some ceftriaxone in the gut may be inactivated by fecal-inactivating enzymes; this may minimize the effect of ceftriaxone on fecal flora, but the degree to which this happens varies greatly between volunteers or patients (Welling *et al.*, 1992). In a study in 12 patients, the colonic microflora was found to normalize within 14 days of completion of treatment in all but one recipient (Nilsson-Ehle *et al.*, 1985). However, DiNubile *et al.* (2005) showed that 2 weeks after the end of a ceftriaxone–metronidazole course even higher numbers had colonization with a ceftriaxone-resistant Enterobacteriaceae than at the end of the therapy.

6d. Biliary pseudolithiasis

Although ceftriaxone is primarily eliminated by the kidneys, 10–40% is excreted unmetabolized into the bile (Shiffman *et al.*, 1990). Ceftriaxone concentrates in bile, resulting in a concentration 20–150 times that found in serum (Park *et al.*,