with diarrhea/loose stools (4–5% of patients), nausea (3%), and abdominal pain (2–3%) being the most frequently reported. With the 2 g extended release formulation, the reported rates are nausea 17%, diarrhea/loose stools 18–55%, vomiting 4%, and abdominal pain 36% (Chandra *et al.*, 2007; Okayasu *et al.*, 2011). The incidence of gastrointestinal reactions due to azithromycin is lower, compared to erythromycin (Periti *et al.*, 1993). The mechanism for the gastrointestinal effects is macrolide-induced endogenous release of motilin, which stimulates motilin receptors and has a prokinetic effect on the gut (Catnach and Fairclough, 1992).

6b. Hepatotoxicity

Transaminase elevation occurs during azithromycin treatment in 7% of patients but is reversible upon completion of the therapy (Vergis *et al.*, 2000). In large prospective studies, azithromycin has been associated with an increased risk of idiosyncratic drug-induced liver injury, particularly in patients with pre-existing liver disease (Chalasani *et al.*, 2015; Molleston *et al.*, 2011). Liver injury is more commonly hepatocellular than cholestatic and usually occurs 1 to 3 weeks after initiation of azithromycin therapy (Martinez *et al.*, 2015). Liver injury is usually reversible, but chronic liver injury, and complications leading to liver transplantation or death can occur (Martinez *et al.*, 2015).

6c. Cardiac effects

Macrolides have been associated with prolongation of cardiac repolarization (prolongation of the QT interval). The molecular mechanism appears to be a blockade of the hERG channel-dependent potassium current in myocyte membranes (Roden, 2008). These interactions may give rise to polymorphic ventricular tachycardia, torsades de pointes, or ventricular fibrillation. In a rat model, the capacity of various macrolides to induce QTc prolongation was ranked as follows: erythromycin > clarithromycin > roxithromycin > azithromycin (Ohtani *et al.*, 2000). In an early meta-analysis of six randomized trials comparing azithromycin to placebo in almost 14 000 patients with established coronary disease—an inherently high-risk group—azithromycin use was not associated with increased mortality (Baker and Couch, 2007). Following several published case reports of azithromycin-associated QT interval prolongation (Matsunaga *et al.*, 2003; Russo *et al.*, 2006), sometimes leading to torsade de pointes (Huang *et al.*, 2007; Kezerashvili *et al.*, 2007), Ray *et al.* (2012) evaluated the effect of azithromycin on the risk of death in a Tennessee Medicaid cohort aged 30–74 years. The study found that a 5-day course of azithromycin was associated with an increased risk of cardiovascular death, particularly in patients with a high baseline risk of cardiovascular disease, versus control patients who were taking amoxicillin (Ray *et al.*, 2012). In a cohort of U.S. veterns, a group with a higher rate of comorbidities, azithromycin was associated with higher mortality and increased rates of serious arrhythmia, compared to control patients who were taking amoxicillin (Rao *et al.*, 2014). In a nationwide Taiwanese study, the use of azithromycin was associated with an increased risk of ventricular arythmia and cardiovascular death, compared to amoxicillin–clavulanate use (Chou *et al.*, 2015). However, these findings were not confirmed in a large nationwide Danish study that included the general population aged 18–64 years who had low risk of cardiovascular disease, and used patients treated with penicillin V as the comparion group (Svanstrom *et al.*, 2013). In addition, a study of elderly patients hosptitalized for pneumonia found that pneumonia treatment that included azithromycin was associated with lower mortality and a smaller risk of myocardial infarction than pneumonia treated with other antibiotics (Mortensen *et al.*, 2014). Single dose azithromycin 1 g used for the treatment of sexually transmitted infections has not been associated with increased risk of cardiac death (Khosropour *et al.*, 2014). Although the data on the cardiovascular safety of azithromycin remain inconclusive, the absolute risk of serious arrhythmia in most patients is extremely small. However, because the drug does carry risk, the decision to initiate azithromycin treatment should be based on a careful evaluation of the pre-existing comorbidities, risk factors for arrhythmia, or QT prolongation, and concomitant medication use. If azithromycin is unavoidable in these patients, reversible causes of QT prolongation can be abated, and the dose and duration of azithromycin limited. Monitoring with electrocardiogram can also be performed periodically during therapy.

6d. Ototoxicity

Reversible ototoxicity has been reported in patients receiving long-term azithromycin therapy for *M. avium* infection, and 8 days of intravenous azithromycin for pneumonia (Bizjak *et al.*, 1999; Wallace *et al.*, 1994). Clinicians should be aware that irreversible hearing loss has also been reported with low-dose oral azithromycin for a urinary tract infection (Ress and Gross, 2000). There have also been case reports of ototoxicity occurring in patients with HIV (Tseng *et al.*, 1997). Guinea pig models have shown reversible reductions in transiently evoked otoacoustic emissions with clarithromycin and azithromycin, but not erythromycin (Uzun *et al.*, 2001). The authors attribute this to transient dysfunction of outer hair cells in the inner ear.

6e. Hypersensitivity reactions

Allergic reactions including anaphlylaxis, eosinophilia, fever, and skin eruptions are rarely reported for macrolides (Mori *et al.*, 2014; Periti *et al.*, 1993; Sriratanaviriyakul *et al.*, 2014; Taylor *et al.*, 2003); but when they do occur, they usually resolve promptly with treatment cessation. Azithromycin is more allergenic than clarithromycin in children (Barni *et al.*, 2015). Pharmaceutical workers exposed to powdered substances involved in azithromycin synthesis may develop allergic contact dermatitis as a result of patch testing (Lopez-Lerma *et al.*, 2009; Milkovic-Kraus *et al.*, 2007).