indigestion, 158 (1.6%); rash, 110 (1.1%); urticaria 9, anaphylaxis 1, *Candida* superinfection 98 (1%), altered liver function tests 3, and jaundice 1 (Croydon, 1984).

The majority of the safety data for amoxicillin–clavulanic acid has been obtained with the earlier formulations, mostly given three times daily. The 875-mg/125-mg twice-daily regimen appears to have a similar safety profile to the 500-mg/125-mg three-times-a-day dosing (White *et al.,* 2004). A lower incidence of diarrhea with the former dosing (2.9% vs. 4.9%) (Calver *et al.,* 1997) likely relates to the lower clavulanic acid daily dose. The new pharmacokinetically enhanced 2000-mg/125-mg twice-daily formulation appears to have comparable adverse events to the 875-mg/125-mg twice-daily preparations (White *et al.,* 2004).

6a. Gastrointestinal side effects

In an analysis of 38,500 patients in clinical trials a similar range of side effects occurred, with upper gastrointestinal events 2.5% (nausea 1.4%) and diarrhea (3.4%) the most common (Neu *et al.,* 1993). Diarrhea has been reported more commonly (about 10%) by others and is attributed primarily to the clavulanic acid component (Bush and Johnson, 2000) because both this and other gastrointestinal side effects, such as nausea and vomiting, seem to be more common with amoxicillin–clavulanic acid than with amoxicillin alone (Iravani and Richard, 1982; Pien, 1983; Conner, 1985). With the twice-daily dosing schedules and 125-mg individual doses of clavulanic acid (vs. 250-mg doses), gastrointestinal toxicity is lessened (Crokaert *et al.,* 1982; Lawrence and Shanson, 1985). Administration with food may reduce the severity of gastrointestinal-adverse events (Bush and Johnson, 2000). Antibiotic-related diarrhea associated with *C. difficile* can also occur and ranges from mild diarrhea to fulminant pseudomembranous colitis. In nursing home residents, the highest rate of antibiotic-related diarrhea was associated with amoxicillin–clavulanic acid prescriptions (Gillespie *et al.,* 2015), and amoxicillin–clavulanic acid was also identified among the high-risk antibiotics associated with *C. difficile* infection in the elderly residents of a Scottish care home (Marwick *et al.,* 2013). In a human gut model, rapid *C. difficile* ribotype 027 germination and toxin production occurred after amoxicillin–clavulanic acid instillation (Chilton *et al.,* 2012) and logarithmic gut microbiota changes were observed. Finally, amoxicillin–clavulanic acid administered before meals into the small bowel induces duodenal contractions, suggesting possible use as a prokinetic agent (Gomez *et al.*, 2012).

6b. Rashes

The incidence of rashes (1.1%) noted by Croydon (1984) was surprisingly low because amoxicillin alone is associated with a higher frequency of rashes. A higher frequency of rashes was noted in one study in which 116 females were given amoxicillin–clavulanic acid; rashes were observed in 4.1% (Iravani and Richard, 1982). Rashes and fever also occurred more frequently in HIV-infected patients given amoxicillin–clavulanic acid (Van der Ven *et al.,* 1994). Among patients with immediate hypersensitivity reactions to amoxicillin–clavulanic acid, approximately 30% may be due to selective reactions to the clavulanic acid component (Torres *et al.,* 2010). Cross-reactivity with other beta-lactams has not been reported, and it is suggested that in these patients other beta-lactams could be used (Torres *et al.,* 2016). Liquid formulations of amoxicillin–clavulanic acid usually contain sodium benzoate as an excipient, and in a challenge study of children with cutaneous reactions to the suspension, positive (mainly urticarial) responses were seen as frequently to the excipient as to amoxicillin–clavulanic acid (Mori *et al.,* 2012). Other rare dermatological adverse events include linear IgA bullous disease (Ho *et al.,* 2007) and reactions observed with ampicillin-class antibiotics, such as erythema multiforme, exfoliative dermatitis, pruritus, pemphigus (Baroni *et al.,* 2012), and Stevens-Johnson syndrome (Fathallah *et al.,* 2013).

6c. Hepatotoxicity

There are a number of reports of amoxicillin–clavulanic acid–induced cholestatic jaundice (Thompson *et al.,* 1995; Beraldo *et al.,* 2013), including with a fatal outcome (Hebbard *et al.,* 1992; Ersoz *et al,,* 2001). Risk factors include male sex, the elderly, treatment duration (Cundiff and Joe, 2007), and concomitant hepatotoxic drugs (Yasici *et al.,* 2015); although cases have also been reported in children, including a vanishing bile duct syndrome (Smith *et al.,* 2005). The overall estimated risk of hepatoxicity is 1:10,000 to 1:100,000. Hepatotoxicity is more likely attributable to the clavulanic acid component and is a non-dose-related hypersensitivity, usually cholestatic but sometimes a hepatocellular reaction, in which the onset can occur weeks after stopping the drug; recovery over weeks to months generally occurs (Cundiff and Joe, 2007). Several studies have identified an association between liver injury and HLA genotype, including class II DRB1*15:1 and class I HLA-A*02:01 (Donaldson *et al.*, 2010; Lucena *et al.*, 2011; Stephens *et al.,* 2013). Kim *et al.* (2015) described amoxicillin and clavulanic acid T-cell responses in patients with liver toxicity and generated component-specific CD4+ and CD8+ clones; it is interesting that clones were not activated by flucloxacillin, piperacillin, or benzyl penicillin.

6d. Other adverse reactions

Other uncommon to rare adverse events include interstitial nephritis, eosinophilia, leucopenia, thrombocytopenia (Mansour *et al.,* 2014), agitation, convulsions, insomnia and hyperactivity, and anaphylactoid and hypersensitivity reactions (see Chapter 5, Ampicillin and amoxicillin). A case of Kounis syndrome (Ralapanawa and Kularatne, 2015) (acute coronary syndrome concurrent with hypersensitivity reaction) has been reported in a 74-year-old man shortly after receiving i.v. amoxicillin–clavulanic acid. It was surprising that in a study of drug-induced QTc interval prolongation, amoxicillin–clavulanic acid was found to be associated with higher QTc