



Sulfonamides

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OVERVIEW

The sulfonamides represent a large class of antibiotics that have multiple clinical uses. The sulfonamides were the first effective antibiotics to be introduced into clinical medicine and have been in use continuously since the 1930's. They are considered bacteriostatic and appear to act by inhibition of bacterial biosynthesis of folic acid, which is needed for cell growth, at least in those bacteria that are sensitive to sulfonamides. Because humans rely upon dietary folic acid, they are usually resistant to the adverse effects of inhibition of folate synthesis. Sulfonamides have a wide range of antimicrobial activity against both gram-positive and -negative organisms. Unfortunately, bacterial resistance to sulfonamides is now common, and their use has decreased with the introduction of more potent classes of antibiotics. However, sulfonamides are still widely used especially for urinary tract infections in combination with trimethoprim and for treatment or prevention of parasitic (toxoplasmosis, pneumocystosis jiroveci) and malarial infections usually combined with trimethoprim or pyrimethamine. Sulfonamides with 5-aminosalicylic acid are the structural components of sulfasalazine, which is widely used for long term management of inflammatory bowel disease. The combination of sulfadoxine and pyrimethamine is used as prophylaxis against chloroquine-resistant malaria. Dapsone is a sulfonamide related drug that is used for the therapy of leprosy and dermatitis herpetiformis.

The sulfonamides are well known to cause idiosyncratic liver injury. Hepatotoxicity appears to be a class effect, in that virtually all sulfonamides used today have been linked to rare, but convincing cases of drug induced liver injury. The pattern of injury is variable, often mixed but it can be either hepatocellular or cholestatic. Most typically, the injury appears precipitously within one to three weeks of starting therapy, often preceded or accompanied by signs of hypersensitivity such as fever, rash, facial edema, lymphadenopathy, arthralgias, and eosinophilia or atypical lymphocytosis (or both). Hepatotoxicity from sulfonamides may represent a part of a spectrum of hypersensitivity due to sulfa-derived medications and have been linked to many cases of DRESS (drug rash with eosinophilia and systemic symptoms) as well as Stevens Johnson syndrome and toxic epidermal necrosis. The severity of injury varies widely. Most instances of sulfonamide related liver injury are mild-to-moderate in severity and self-limited in course. Cases with severe cholestasis may be prolonged and can lead to vanishing bile duct syndrome. Importantly, sulfonamides can cause acute liver failure, particularly in instances with a precipitous onset and hepatocellular pattern of serum enzyme elevations. Indeed, the sulfonamides remain one of the most common causes of drug induced acute liver failure and account for 5% to 10% of instances in many case series.

Formulations of sulfonamides currently in general use in the United States include sulfadiazine, sulfadoxine, and sulfisoxazole as well as the combination formulations including sulfasalazine and trimethoprim-sulfamethazole (TMP-SMZ, also referred to as co-trimoxazole). The term sulfonamide applies to derivatives of para-aminobenzene sulfonamide (sulfanilamide), which is composed of a benzene ring with a sulfate and amide

group at one end and an amide group at the other (para-position). These agents will be discussed as groups, rather than individual medications, and cases and references are combined.

Other important side effects of the sulfonamides include diarrhea, nausea, skin rash, headaches, and dizziness. Between 1% and 2% of patients have hypersensitivity responses to sulfonamides, but most of these are mild and self-limited and not associated with significant liver injury. Patients with HIV infection have higher rates of allergic reactions, but hepatotoxicity is uncommon even in this high-risk group. Rare serious side effects include severe allergic skin rashes, Stevens-Johnson syndrome, drug fever, serum sickness, agranulocytosis, aplastic anemia, nephritis, pancreatitis, confusion, ataxia and seizures. These adverse side effects can co-occur with hepatotoxicity.

Drug Class: [Antiinfective Agents](#)

The following links are to individual drug records.

- [Dapsone](#)
- [Sulfadiazine](#)
- [Sulfadoxine-Pyrimethamine](#)
- [Sulfamethoxazole-Trimethoprim](#)
- [Sulfasalazine](#)
- [Sulfinpyrazone](#)
- [Sulfisoxazole](#)

ANNOTATED BIBLIOGRAPHY

References updated: 05 December 2017

Zimmerman HJ. Sulfonamides. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 606-9.

(Expert review of the sulfonamides and sulfones published in 1999; sulfonamides are thought to cause clinically apparent liver injury in 0.5-1.0% of recipients generally with a sudden onset within 14 days of starting, often with immunoallergic features and a hepatocellular or mixed pattern of injury; mortality may be as high as 10%).

Moseley RH. Sulfonamides. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 463-82.

(Review of hepatotoxicity of antibiotics including sulfonamides).

Petri WA Jr. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1463-76.

(Textbook of pharmacology and therapeutics).

Lowe J, Smith M. The chemotherapy of leprosy in Nigeria; with an appendix on glandular fever and exfoliative dermatitis precipitated by sulfones. *Int J Lepr* 1949; 17: 181-95. PubMed PMID: 15399690.

(Summary of clinical results in using sulfones in 227 patients with leprosy described "Glandular fever and exfoliative dermatitis precipitated by sulfones" in the appendix: occurring mostly in adult men, the dermatitis in 2%, glandular fever in 12% which was marked by fever, lymphadenitis, splenomegaly and jaundice in some cases: initial description of sulfone-syndrome).

Fries J, Siragenian R. Sulfonamide hepatitis. Report of a case due to sulfamethoxazole and sulfisoxazole. *N Engl J Med* 1966; 274: 95-7. PubMed PMID: 5901208.

(60 year old woman developed jaundice after 4 days of sulfamethoxazole with fever, arthralgias and rash [bilirubin 8.4 mg/dL, ALT 360 U/L, Alk P 2.5 times ULN], with positive rechallenge within 30 hours of starting sulfisoxazole [AST 396 U/L, Alk P 1.5 times ULN]).

Dujovne CA, Chan CH, Zimmerman HJ. Sulfonamide hepatic injury. Review of the literature and report of a case due to sulfamethoxazole. *N Engl J Med* 1967; 277: 785-8. PubMed PMID: 6046676.

(Classic description of sulfonamide hepatotoxicity: case report of a 38 year old man who developed jaundice after 14 days of sulfamethoxazole [3rd exposure] with positive rechallenge; review of the literature on over 100 cases: usual latency of 1-4 weeks, shorter on rechallenge, rash and fever common).

Espiritu CR, Kim TS, Levine RA. Granulomatous hepatitis associated with sulfadimethoxine hypersensitivity. *JAMA* 1967; 202: 985-8. PubMed PMID: 5630747.

(24 year old man developed rash and jaundice within a week of starting sulfadimethoxine [bilirubin 4.2 mg/dL, AST 72 U/L, Alk P ~ twice ULN], liver biopsy showing granulomatous hepatitis; and rapid recovery).

Millikan LE, Harrell ER. Drug reactions to the sulfones. *Arch Dermatol* 1970; 102: 220-4. PubMed PMID: 4914268.

(50 year old man developed fever and cholestatic jaundice after a 4 week course of sulfone, resolving in a few weeks).

Das KM, Eastwood MA, McManus JP, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973; 289: 491-5. PubMed PMID: 4146729.

(Slow acetylators of sulfapyridine were more likely to have side effects and high serum levels).

Frisch JM. Clinical experience with adverse reactions to trimethoprim-sulfamethoxazole. *J Infect Dis* 1973; 128: Suppl: 607-12 p. PubMed PMID: 4271305.

(Review of postmarketing adverse event reporting on TMP-SMZ from 1968-72, 2151 reports, 32 hepatobiliary [1.5%]).

Rafoth RJ. Systemic granulomatous reaction to salicylazosulfapyridine (Azulfidine) in a patient with Crohn's disease. *Am J Dig Dis* 1974; 19: 465-9. PubMed PMID: 4151115.

(35 year old woman developed Stevens Johnson syndrome with minimal Alk P elevations, peak bilirubin 1.8 mg/dL, 19 days after starting azulfidine; liver and lymph node biopsies showed granulomas).

Tönder M, Nordöy A, Elgjo K. Sulfonamide-induced chronic liver disease. *Scand J Gastroenterol* 1974; 9: 93-6. PubMed PMID: 4453809.

(54 year old woman developed jaundice 4 weeks after starting TMP-SMZ [bilirubin 7.0 mg/dL, ALT 1180, Alk P twice normal], recurring with reexposure and after 1 day after "provocation test", the injury was not really chronic as all tests were normal in follow up after stopping).

Colucci CF, Lo Cicero M. Hepatic necrosis and trimethoprim-sulfamethoxazole. *JAMA* 1975; 233: 952-3. Letter. PubMed PMID: 1173911.

(80 year old man developed jaundice [bilirubin 10 mg/dL, ALT 135 U/L, Alk P 245 U/L] 10 days after a 10 day course of TMP-SMZ progressing to hepatic failure; massive hepatic necrosis on autopsy).

Brøckner J, Bøisen E. Fatal multisystem toxicity after co-trimoxazole. *Lancet* 1978; 1: 831. PubMed PMID: 85859.

(63 year old man had hypersensitivity reaction after 10 days of TMP-SMZ with multiorgan failure; liver component may have been due to shock and sepsis).

Callen JP, Soderstrom RM. Granulomatous hepatitis associated with salicylazosulfapyridine therapy. *South Med J* 1978; 71: 1159-60. PubMed PMID: 28568.

(36 year old woman developed drug-fever on sulfasalazine with minimal ALT elevations and granulomas on liver biopsy that resolved with discontinuation of drug, follow up biopsy was normal).

Chester AC, Diamond LH, Schreiner GE. Hypersensitivity to salicylazosulfapyridine: renal and hepatic toxic reactions. *Arch Intern Med* 1978; 138: 1138-9. PubMed PMID: 27155.

(19 year old woman developed fever, rash, eosinophilia, adenopathy and jaundice arising 3 weeks after starting sulfasalazine [bilirubin 6.5 mg/dL, AST 1060 U/L], with accompanying nephritis, resolving after 2 weeks of prednisone).

Stevenson DK, Christie DL, Haas JE. Hepatic injury in a child caused by Trimethoprim-Sulfamethoxazole. *Pediatrics* 1978; 61: 864-6. PubMed PMID: 673549.

(16 year old boy developed rash and fever 7 weeks after starting TMP-SMZ [bilirubin 9.4 mg/dL, ALT 294 U/L, Alk P 880 U/L, 13% eosinophils], no mention of recovery).

Sotolongo RP, Neefe LI, Rudzki C, Ishak KG. Hypersensitivity reaction to sulfasalazine with severe hepatotoxicity. *Gastroenterology* 1978; 75: 95-9. PubMed PMID: 45581.

(19 year old woman developed nausea 2 weeks after starting sulfasalazine for inflammatory bowel disease followed by fever and rash [bilirubin 0.8 rising to 5.6 mg/dL, AST 109 U/L, Alk P 322 U/L, 10% eosinophils], treated with prednisolone and recovered in 1 month).

Jacobs E, Paulet P, Rahier J. Hypersensitivity reaction to sulfasalazine--another case. *Gastroenterology* 1978; 75: 1193. PubMed PMID: 30678.

(19 year old female with Crohn disease developed jaundice with high ALT levels, rash, fever, eosinophilia and lymphadenopathy after 8 weeks of sulfasalazine therapy, resolving within 4 weeks).

Kanner RS, Tedesco FJ, Kalser MH. Azulfidine- (sulfasalazine-) induced hepatic injury. *Am J Dig Dis* 1978; 23: 956-8. PubMed PMID: 31085.

(13 year old girl developed fever, rash, eosinophilia, lymphadenopathy and atypical lymphocytosis 3 weeks after starting sulfasalazine [bilirubin 4.1 mg/dL, AST 228 U/L, Alk P 149 U/L], rechallenge led to severe hepatocellular injury within 1 day).

Mihas AA, Goldenberg DJ, Slaughter RL. Sulfasalazine toxic reactions. Hepatitis, fever, and skin rash with hypocomplementemia and immune complexes. *JAMA* 1978; 239: 2590-1. PubMed PMID: 26816.

(26 year old man developed jaundice, fever, rash, adenopathy, atypical lymphocytosis and systemic symptoms 3 weeks after starting sulfasalazine for Crohn disease [bilirubin 1.5 mg/dL, ALT 680 U/L, Alk P 680 U/L, 12% eosinophils], resolving by 12 weeks with prednisone).

Gulley RM, Mirza A, Kelly CE. Hepatotoxicity of salicylazosulfapyridine: a case report and review of the literature. *Am J Gastroenterol* 1979; 72: 561-4. PubMed PMID: 43669.

(20 year old woman with Crohn disease developed fever 3 weeks after starting sulfasalazine accompanied by a mixed pattern of serum enzyme elevations without jaundice and had recurrence with a similar anicteric pattern 4 days after restarting).

Iwarson S, Lundin P. Multiple attacks of jaundice associated with repeated sulfonamide treatment. *Acta Med Scand* 1979; 206: 219-22. PubMed PMID: 495230.

(Four women, ages 20, 30, 35 and 68 years, who had repeated episodes of liver injury after sulfonamides with shortening of latency upon reexposure, but no worsening of injury [usually hepatocellular] or slowing of resolution, which ranged from 4-12 weeks).

Wormser GP, Keusch GT. Trimethoprim-sulfamethoxazole in the United States. *Ann Intern Med* 1979; 91: 420-9. PubMed PMID: 382938.

(Review of indications, efficacy and safety of TMP-SMZ).

Nair SS, Kaplan JM, Levine LH, Geraci K. Trimethoprim-sulfamethoxazole-induced intrahepatic cholestasis. *Ann Intern Med* 1980; 92: 511-2. PubMed PMID: 7362156.

(61 year old man with cholestatic hepatitis with minimal ALT and Alk P elevations after 10 days of TMP-SMZ, resolving in 2 months).

Ogilvie AL, Toghill PJ. Cholestatic jaundice due to co-trimoxazole. *Postgrad Med J* 1980; 56: 202-4. PubMed PMID: 7393813.

(70 year old woman with severe cholestatic hepatitis with vague previous history of exposure to TMP-SMZ and prolonged exacerbation with restarting treatment before full recovery).

Abi-Mansur P, Ardiaca MC, Allam C, Shamma'a M. Trimethoprim-sulfamethoxazole-induced cholestasis. *Am J Gastroenterol* 1981; 76: 356-9. PubMed PMID: 7325149.

(52 year old woman developed jaundice within 7 days of starting TMP-SMZ [bilirubin 11.2 mg/dL, ALT 78 U/L, Alk P 210 U/L], recovery within 2 months of stopping).

Coto H, McGowan WR, Pierce EH Jr, Thomas E. Intrahepatic cholestasis due to trimethoprim-sulfamethoxazole. *South Med J* 1981; 74: 897-8. PubMed PMID: 7256343.

(55 year old man developed fever and jaundice 1 week after stopping a 2 week course of TMP-SMZ [bilirubin 7.1 mg/dL, AST 86 U/L, Alk P 1341 U/L], resolving within 6 weeks of onset).

Frey HM, Gershon AA, Borkowsky W, Bullock WE. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; 94: 777-9. PubMed PMID: 7235421.

(17 year old boy with suspected leprosy developed rash followed by fever and jaundice [bilirubin 7.0 mg/dL, ALT 700 U/L] weeks after starting dapsone and thalidomide with atypical lymphocytosis, exfoliation, progressive liver failure, multiorgan failure and death).

Losek JD, Werlin SL. Sulfasalazine hepatotoxicity. *Am J Dis Child* 1981; 135: 1070-2. PubMed PMID: 6117199.

(13 year old boy with Crohn disease developed fever and rash 11 days after starting sulfasalazine with subsequent marked rise in AST [1743 U/L], but normal bilirubin and rapid resolution; positive rechallenge to single dose with rash, fever and minimal ALT elevation within 1 day).

Namias A, Bhalotra R, Donowitz M. Reversible sulfasalazine-induced granulomatous hepatitis. *J Clin Gastroenterol* 1981; 3: 193-8. PubMed PMID: 6113258.

(25 year old man developed fever and jaundice [bilirubin rising to 4.0 mg/dL, ALT to ~775 U/L] 19 days after starting sulfasalazine, resolving on prednisone within 6 weeks of stopping sulfasalazine; liver biopsy showed granulomas).

Ransohoff DF, Jacobs G. Terminal hepatic failure following a small dose of sulfamethoxazole-trimethoprim. *Gastroenterology* 1981; 80: 816-9. PubMed PMID: 7202951.

(70 year old man, with a history of rash after taking TMP-SMZ, developed rash followed by jaundice after 2 doses of TMP-SMZ with progressive acute liver failure [bilirubin 32 rising to 44 mg/dL, AST 2390 U/L, Alk P 270 U/L] and death, autopsy showing massive necrosis).

Steinbrecher UP, Mishkin S. Sulfamethoxazole-induced hepatic injury. *Dig Dis Sci* 1981; 26: 756-9. PubMed PMID: 7261840.

(53 year old woman developed fever and arthralgias followed by jaundice 3 days after 10 day course of sulfamethoxazole with mixed enzyme pattern and recovery in ~6 weeks, recurrence with retreatment – twice).

Tomecki KJ, Catalano CJ. Dapsone hypersensitivity. The sulfone syndrome revisited. *Arch Dermatol* 1981; 117: 38-9. PubMed PMID: 6450569.

(16 year old girl developed fever and fatigue followed by jaundice beginning 2 weeks after starting dapsone [50 mg/day] for acne [bilirubin 3.6 mg/dL, ALT 560 U/L, Alk P 449 U/L, 10% eosinophils], with hemolytic anemia, responding to prednisone, and resolving within 4 weeks).

Døssing M, Andreassen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. *Scand J Gastroenterol* 1982; 17: 205-11. PubMed PMID: 6982502.

(572 reports of drug induced liver injury from 1968-78 were analyzed, representing 6% of total adverse reaction reports and 12% of those that were fatal; halothane accounted for 25% of cases, chlorpromazine 9%, sulfonamides 9%, antituberculosis agents 7%, oxyphenisatin 4% and methyldopa 2%).

Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982; 4: 426-8. PubMed PMID: 6981160.

(Follow up of 40,000 patients admitted to 25 Boston hospitals from 1966-80, 1,121 received TMP-SMZ, and 91 [8%] had an adverse reaction, usually gastrointestinal upset [3.7%], skin rash [3.3%], fever [0.2%], no reports of liver injury or jaundice).

Kromann NP, Vilhelmsen R, Stahl D. The dapsone syndrome. *Arch Dermatol* 1982; 118: 531-2. PubMed PMID: 7092282.

(33 year old woman developed fever and rash 2 weeks and cholestatic liver enzyme elevations [AST 241 U/L, Alk P 1341 UL, bilirubin 1.3 mg/dL, and hepatic granulomata] 4 weeks after starting dapsone, accompanied by lymphadenopathy, atypical lymphocytes and leukamoid reaction, resolving within 8 weeks of stopping).

Larcen A, Lambert H, Janot C, Perarnaud J, Delorme N, Tonnel F. [Fatal hepatitis during sulfasalazine treatment] *Therapie* 1982; 37: 315-9. French. PubMed PMID: 6127817.

(17 year old with Crohn disease developed rash, eosinophilia and severe hepatocellular injury with jaundice [bilirubin 3.7 mg/dL, ALT 1050 U/L, Alk P 500 U/L] 3 weeks after starting sulfasalazine, progressing to acute liver failure and death).

Lawson DH, Paice BJ. Adverse reactions to trimethoprim-sulfamethoxazole. *Rev Infect Dis* 1982; 4: 429-33. PubMed PMID: 7051241.

(Review of world's literature on TMP-SMZ adverse drug reactions; common side effects are gastrointestinal upset and skin rash, liver injury is rare ~2% of reported adverse events).

Olsen VV, Loft S, Christensen KD. Serious reactions during malaria prophylaxis with pyrimethamine-sulfadoxine. *Lancet* 1982; 2: 994. PubMed PMID: 6127497.

(Briefly described case of 60 year old woman traveler who developed severe jaundice after 5 weeks of pyrimethamine-sulfadoxine [Fansidar] with fever and eosinophilia, ultimately recovered).

Koch-Weser J, Hodel C, Leimer R, Styk S. Adverse reactions to pyrimethamine/sulfadoxine. *Lancet* 1982; 2: 1459. PubMed PMID: 6129527.

(Industry response to letter by Olsen [1982] stressing the safety of Fansidar; among 1.5 million exposed persons, only 24 cases of liver reactions have been reported to sponsor).

Smith MD, Gibson GE, Rowland R. Combined hepatotoxicity and neurotoxicity following sulphasalazine administration. *Aust N Z J Med* 1982; 12: 76-80. PubMed PMID: 6123306.

(Two cases of hepatocellular injury arising 3 and 5 weeks after starting sulfasalazine with rash, fever, jaundice and neurologic signs of confusion, hallucinations and stiff neck, rapid recovery after stopping and with prednisone therapy).

Ghishan FK. Trimethoprim-sulfamethoxazole-induced intrahepatic cholestasis. *Clin Pediatr (Phila)* 1983; 22: 212-4. PubMed PMID: 6600661.

(5 year old girl developed rash, fever and jaundice one week after starting TMP-SMZ [bilirubin 6.5 mg/dL, ALT 44 U/L, Alk P 776 U/L], recovery within 2 weeks).

Lennard TW, Farndon JR. Sulphasalazine hepatotoxicity after 15 years' successful treatment for ulcerative colitis. *Br Med J (Clin Res Ed)* 1983; 287: 96. PubMed PMID: 6134567.

(37 year old man with ulcerative colitis developed asymptomatic elevations in Alk P [380 U/L] and AST [49 U/L] after 15 years of sulfasalazine use, with positive rechallenge, prednisone also used and issue of sclerosing cholangitis and autoimmune hepatitis not completely addressed).

Holdsworth CD. Sulphasalazine hepatotoxicity after 15 years' treatment. *Br Med J (Clin Res Ed)* 1983; 287: 759. PubMed PMID: 6137258.

(Letter in response to Lennard [1983] discussing possibility of sclerosing cholangitis in view of presence of ulcerative colitis).

Taffet SL, Das KM. Sulfasalazine. Adverse effects and desensitization. *Dig Dis Sci* 1983; 28: 833-42. PubMed PMID: 6136396.

(Review article on adverse effects of sulfasalazine with mention of 14 case reports of liver injury, 5 with positive rechallenge, some fatal and some with granulomas).

Fich A, Schwartz J, Braverman D, Zifroni A, Rachmilewitz D. Sulfasalazine hepatotoxicity. *Am J Gastroenterol* 1984; 79: 401-2. PubMed PMID: 6144268.

(52 year old woman and 32 year old man with inflammatory bowel disease had hypersensitivity reactions to sulfasalazine with ALT and Alk P elevations, but no jaundice, resolving with discontinuation).

Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; 100: 495-9. PubMed PMID: 6230976.

(Retrospective review of 38 HIV-positive patients treated with TMP-SMZ found 75% rate of dose limiting toxicity, 60% severe, and 20% had serum ALT elevations, starting within 1-2 weeks of starting).

Horák J, Mertl L, Hrabal P. Severe liver injuries due to sulfamethoxazole-trimethoprim and sulfamethoxydiazine. *Hepatogastroenterology* 1984; 31: 199-200. PubMed PMID: 6510880.

(Two case reports, 47 year old woman developed acute liver failure and died with onset of jaundice within 1 week of starting TMP-SMZ; 26 year old man developed prolonged jaundice arising 10 days after starting TMP-SMZ and slow recovery).

Thies PW, Dull WL. Trimethoprim-sulfamethoxazole-induced cholestatic hepatitis. Inadvertent rechallenge. *Arch Intern Med* 1984; 144: 1691-2. PubMed PMID: 6331808.

(54 year old man developed jaundice within 1 week of starting TMP-SMZ [bilirubin 5.0 mg/dL, ALT 255 U/L, GGT 198 U/L], resolving in 4 weeks with positive inadvertent rechallenge with 3 day latency).

Bartlett JC, Park H, Moe R. Hepatic toxicity associated with trimethoprim-sulfamethoxazole: report of a case. *J Am Osteopath Assoc* 1985; 85: 381-2. PubMed PMID: 3877712.

(67 year old developed rash, fever and nausea within 1 week of starting TMP-SMZ, but continued drug for 4 weeks when he was found to be jaundiced with bilirubin 9.8 mg/dL, AST 150 U/L, Alk P 332 U/L).

Farr M, Symmons DP, Bacon PA. Raised serum alkaline phosphatase and aspartate transaminase levels in two rheumatoid patients treated with sulphasalazine. *Ann Rheum Dis* 1985; 44: 798-800. PubMed PMID: 2865931.

(Two women, ages 71 and 72 years, had marked Alk P elevations [745 and >2000 U/L] starting within 1 week of starting sulfasalazine for rheumatoid arthritis, without allergic manifestations, resolving slowly).

Lazar HP, Murphy RL, Phair JP. Fansidar and hepatic granulomas. *Ann Intern Med* 1985; 102: 722. PubMed PMID: 3985527.

(Two women, aged 69 and 75 years, taking sulfadoxine and pyrimethamine for prophylaxis against malaria developed fever, rash and enzyme elevations with liver biopsies showing granulomas).

Selby CD, Ladusans EJ, Smith PG. Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). *Br Med J (Clin Res Ed)* 1985; 290: 113-4. PubMed PMID: 3155635.

(60 year old traveler developed fever and rash 3 weeks after starting Fansidar [bilirubin rising to 22.5 mg/dL, Alk P 809 U/L, ALT 89 U/L], dying two weeks later with severe rash and renal failure).

Curley RK, Macfarlane AW. Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine. *Br Med J (Clin Res Ed)* 1985; 290: 471-2. PubMed PMID: 2857586.

(Toxic epidermal necrolysis [TEN] arose after 9 days of sulfasalazine and subsequent jaundice with little information on enzymes; death appeared to be complication of TEN and corticosteroid use with herpes, septicemia and shock).

Beard K, Belic L, Aselton P, Perera DR, Jick H. Outpatient drug-induced parenchymal liver disease requiring hospitalization. *J Clin Pharmacol* 1986; 26: 633-7. PubMed PMID: 3793956.

(Survey of a Health Management Organization admissions over 5 years identified only 12 cases of drug induced liver injury, 1 due to sulfonamides [1:6400 exposures] and one to TMP-SMZ [1:12,706 exposures]).

Haines JD Jr. Hepatotoxicity after treatment with sulfasalazine. *Postgrad Med* 1986; 79: 193-4, 197-8. PubMed PMID: 2871549.

(42 year old man with Crohn disease had onset of rash, fever and abdominal pain 18 days after starting sulfasalazine followed by jaundice and progressive hepatic failure [ALT 3700 U/L, Alk P 619 U/L, bilirubin 18.4 mg/dL], leading to multiorgan failure and death; autopsy showed massive necrosis).

Jennings PE, Blandford RL, Rosenthal FD. Acute sulphasalazine hepatotoxicity. *Postgrad Med J* 1986; 62: 305-6. PubMed PMID: 2872666.

(37 year old man with severe hepatocellular injury [bilirubin 6.9 mg/dL, ALT 1994 U/L, Alk P 271 U/L] starting with rash 2 weeks after starting sulfasalazine, slow to resolve).

Johnson DA, Cattau EL Jr, Kuritsky JN, Zimmerman HJ. Liver involvement in the sulfone syndrome. *Arch Intern Med* 1986; 146: 875-7. PubMed PMID: 3963977.

(49 year old woman developed fever and malaise 2 weeks after starting dapsone [bilirubin 4.5 mg/dL, AST 2540 U/L, Alk P 177 U/L]; rapid response to prednisone in ~4 weeks, review of literature and FDA reports).

Leoung GS, Mills J, Hopewell PC, Hughes W, Wofsy C. Dapsone-Trimethoprim for *Pneumocystis carini* pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; 105: 45-8. PubMed PMID: 2940954.

(Experience in treating patients with known AIDS using dapsone-TMP; 6 of 15 patients had ALT elevations [peak 235 U/L] and 8 had rash, but none had jaundice).

- Labadie H, Beaugrand M, Ferrier JP. [Hepatitis and mononucleosis syndrome related to the ingestion of salazosulapyridine]. *Rev Med Interne* 1986; 7: 35-40. French. PubMed PMID: 2871605.
- (25 year old developed fever and rash 7 days after starting sulfasalazine with atypical lymphocytosis, but negative EBV testing [bilirubin 1.5 mg/dL, ALT 1035 U/L, Alk P 250 U/L]).*
- MacGilchrist AJ, Hunter JA. Sulphasalazine hepatotoxicity: lack of a hypersensitivity response. *Ann Rheum Dis* 1986; 45: 967-8. PubMed PMID: 2878646.
- (50 year old woman with rheumatoid arthritis developed anorexia and abdominal pain 11 weeks after starting sulfasalazine; no features of hypersensitivity [bilirubin normal, ALT 1449 U/L, Alk P 230 U/L], resolving within 17 days of stopping).*
- Murphy RL, Phair JP. Systemic reaction to pyrimethamine-sulfadoxine. *J Fam Pract* 1986; 22: 375-6. PubMed PMID: 3958686.
- (75 year old woman developed fever, rash, eosinophilia and cholestatic liver enzymes [AST 53 U/L, Alk P 364 U/L] without jaundice after 4 weeks of pyrimethamine-sulfadoxine therapy; liver biopsy showed granulomas).*
- Poland GA, Love KR. Marked atypical lymphocytosis, hepatitis, and skin rash in sulfasalazine drug allergy. *Am J Med* 1986; 81: 707-8. PubMed PMID: 2876632.
- (38 year old man developed rash, fever, myalgias, and facial edema with eosinophilia, atypical lymphocytosis and liver test abnormalities, within 2 weeks of starting sulfasalazine [bilirubin 2.8 mg/dL, ALT 202 U/L, Alk P 465 U/L], resolving rapidly with prednisone).*
- Ribe J, Benkov KJ, Thung SN, Shen SC, LeLeiko NS. Fatal massive hepatic necrosis: a probable hypersensitivity reaction to sulfasalazine. *Am J Gastroenterol* 1986; 81: 205-8. PubMed PMID: 2869683.
- (15 year old boy developed severe hepatocellular injury and rash starting within 2 weeks of starting sulfasalazine, treated with prednisone and relapse of jaundice and rash when tapered; patient died of acute hemorrhage, probably from corticosteroids rather than hepatic injury).*
- Tanner AR. Hepatic cholestasis induced by trimethoprim. *Br Med J (Clin Res Ed)* 1986; 293: 1072-3. PubMed PMID: 3094778.
- (49 year old woman developed TMP/SMZ induced cholestatic hepatitis with latency of 3 weeks and resolution in 8 weeks, developed similar pattern after five days of TMP alone).*
- Wejstal R, Lindberg J, Malmvall BE, Norkrans G. Liver damage associated with fansidar. *Lancet* 1986; 1: 854-5. PubMed PMID: 2870335.
- (Seven cases of jaundice attributed to sulfadoxine/pyrimethamine [Fansidar] prophylaxis against malaria; cases arose after 2-12 weeks of therapy, were usually hepatocellular and 6 were jaundiced [bilirubin 0.7-15.2 mg/dL, Alk P 1-2 times normal, ALT 20-90 times normal], resolving within 4-12 weeks of stopping).*
- Berg PA, Daniel PT. Co-trimoxazole-induced hepatic injury--an analysis of cases with hypersensitivity-like reactions. *Infection* 1987; 15 Suppl 5: S259-64. PubMed PMID: 3501774.
- (Review of hepatotoxicity of TMP-SMZ with detailed descriptions of cases in the literature).*
- Lawrence WA, Olsen HW, Nickles DJ. Dapsone hepatitis. *Arch Intern Med* 1987; 147: 175. PubMed PMID: 3800520.
- (19 year old woman developed fever and jaundice 24 days after starting dapsone [bilirubin 9.8 mg/dL, ALT 2745 U/L, Alk P 201 U/L] with signs of acute liver failure, but ultimately spontaneous resolution).*
- Oliver RM, Rickenbach MA, Thomas MR, Neville E. Intrahepatic cholestasis associated with co-trimoxazole. *Br J Clin Pract* 1987; 41: 975-6. PubMed PMID: 3509795.

- (65 year old man developed jaundice 4 weeks after starting TMP-SMZ therapy [bilirubin 4.5 mg/dL, AST 114 U/L, Alk P > 500 U/L], resolving within 3 months of stopping).*
- Zitelli BJ, Alexander J, Taylor S, Miller KD, Howrie DL, Perez TH, Van Thiel DH. Fatal hepatic necrosis due to pyrimethamine-sulfadoxine (Fansidar). *Ann Intern Med* 1987; 106: 393-5. PubMed PMID: 2949680.
- (15 year old girl developed fever, rash and jaundice after third weekly dose of pyrimethamine-sulfadoxine [bilirubin rising from 0.6 to 8.5 mg/dL, ALT 763 U/L, Alk P 669 U/L, atypical lymphocytosis]; patient ultimately died of acute liver failure).*
- Alberti-Flor JJ, Hernandez ME, Ferrer JP, Howell S, Jeffers L. Fulminant liver failure and pancreatitis associated with the use of sulfamethoxazole-trimethoprim. *Am J Gastroenterol* 1989; 84: 1577-9. PubMed PMID: 2596461.
- (26 year old man developed acute liver failure and pancreatitis 5 days after starting TMP-SMZ while also taking 4.5 grams of acetaminophen daily, which may have contributed to the liver injury).*
- Coumaros D, Georges C, Zerbe S. Salicylazosulfapyridine (SASP) hepatitis: role of 5-aminosalicylic acid (5-ASA). *Scand J Gastroenterol* 1989; 24 (suppl 158): 132-3. Not in PubMed
- (26 year old woman found to have elevated ALT [5.5 times ULN] 1 year after starting sulfasalazine, not resolving until both sulfonamide and 5-ASA were stopped).*
- Kumar VV, Mahesh BV, Raju VK, Devi KR. Trimethoprim induced intrahepatic cholestasis. *Indian Pediatr* 1989; 26: 181-3. PubMed PMID: 2753538.
- (10 year old boy developed jaundice 10 days after starting TMP-SMZ [bilirubin 8.0 mg/dL, AST 80, Alk P 5 times ULN] with rapid resolution; 3 months later a course of TMP alone led to jaundice within 1 week with similar pattern of serum enzyme elevations).*
- Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; 298: 82-6. PubMed PMID: 2563951.
- (In a multicenter controlled trial of 5-ASA [mesalazine] vs sulfasalazine in 164 patients, the two agents had similar efficacy, but there were fewer hypersensitivity effects with mesalazine; nevertheless, 3% of 5-ASA treated patients developed raised ALT values and one developed hepatitis with jaundice).*
- Muñoz SJ, Martinez-Hernandez A, Maddrey WC. Intrahepatic cholestasis and phospholipidosis associated with the use of trimethoprim-sulfamethoxazole. *Hepatology* 1990; 12: 342-7. PubMed PMID: 2167870.
- (60 year old woman developed jaundice 4 days after starting TMP-SMZ [bilirubin 20.5 mg/dL, Alk P 502 U/L, AST 188 U/L], not resolving until 6 months after stopping).*
- Jayalakshmi P, Ting HC. Dapsone-induced liver necrosis. *Histopathology* 1990; 17: 89-91. PubMed PMID: 2146206.
- (42 year old man developed fever, rash and jaundice 6 weeks after starting dapsone for photodermatitis [bilirubin 6.8 mg/dL, ALT >500 U/L, Alk P 656 U/L, 21% eosinophils] with liver and renal failure, dying 3 days after admission, autopsy showing extensive coagulative necrosis).*
- Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; 83: 82-5. PubMed PMID: 2138674.
- (Spontaneous reporting of serious liver injury in 1:75,000 prescriptions for pyrimethamine-dapsone [Maloprim] for malaria prophylaxis in the UK).*
- Ramanan C, Ghorpade A, Manglani PR. Dapsone syndrome. *Indian J Lepr* 1991; 63: 226-8. PubMed PMID: 1838381.

Cockerill FR, Edson RS. Trimethoprim-sulfamethoxazole. *Mayo Clin Proc* 1991; 66: 1260-9. PubMed PMID: 1749295.

(Review of pharmacology, efficacy and safety of TMP-SMZ).

van der Ven AJ, Koopmans PP, Vree TB, van der Meer JW. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; 338: 431-3. PubMed PMID: 1678095.

(Hypothesis paper on the high rates of hypersensitivity to sulfonamides among AIDS patients).

Brooks H, Taylor HG, Nichol FE. The three week sulphasalazine syndrome. *Clin Rheumatol* 1992; 11: 566-8. PubMed PMID: 1362531.

(53 year old man with rheumatoid arthritis developed fever, rash, atypical lymphocytes, eosinophilia and low complement levels, similar to serum sickness 2 weeks after starting sulfasalazine [bilirubin 6.0 rising to 8.9 mg/dL, ALT 231 U/L, Alk P 706 U/L], with slow recovery despite corticosteroids).

Hautekeete ML, Bourgeois N, Potvin P, Duville L, Reynaert H, Devis G, Adler M, et al. Hypersensitivity with hepatotoxicity to mesalazine after hypersensitivity to sulfasalazine. *Gastroenterology* 1992; 103: 1925-7. PubMed PMID: 1360436.

(21 year old woman developed rash 3 weeks after starting sulfasalazine, recurring 1 day after starting mesalazine [5-ASA] alone [bilirubin 2.5 mg/dL, ALT 102 U/L, Alk P 560 U/L]; went on to develop liver failure, but ultimately survived).

Kowdley KV, Keeffe EB, Fawaz KA. Prolonged cholestasis due to trimethoprim sulfamethoxazole. *Gastroenterology* 1992; 102: 2148-50. PubMed PMID: 1587437.

(Two women, ages 43 and 48 years, developed prolonged cholestasis after exposure to TMP-SMZ with latency to onset of rash of 4 days, but 2-3 weeks to onset of jaundice [bilirubin 3.6 and 27.1 mg/dL, ALT 422 and 63 U/L, Alk P 229 and 306 U/L], requiring 12 and 18 months to recover).

Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. *J Intern Med* 1992; 232: 133-8. PubMed PMID: 1506809.

(Adverse drug reaction reports in Denmark from 1978 to 1987; 62 cases [5%] were attributed to either TMP-SMZ or SMZ alone).

Mohle-Boetani J, Akula SK, Holodniy M, Katzenstein D, Garcia G. The sulfone syndrome in a patient receiving dapsons prophylaxis for *Pneumocystis carinii* pneumonia. *West J Med* 1992 Mar; 156: 303-6. PubMed PMID: 1595261.

(35 year old man with HIV and HBV infection developed fever and jaundice 6 weeks after starting dapsons prophylaxis [bilirubin 3.7 mg/dL, ALT 650 U/L, Alk P 229 U/L, 10% atypical lymphocytes], which began to resolve within days of stopping; review of 21 cases in the literature, all occurred within 2 months of starting, all with fever and most with jaundice).

Leroux JL, Ghezail M, Chertok P, Blotman F. Hypersensitivity reaction to sulfasalazine: skin rash, fever, hepatitis and activated lymphocytes. *Clin Exp Rheumatol* 1992; 10: 427. PubMed PMID: 1356682.

(45 year old woman with rheumatoid arthritis developed fever, rash and facial edema 3 weeks after starting sulfasalazine [no mention of bilirubin, ALT 39 U/L, Alk P 212 U/L, eosinophils 50%], with rapid recovery upon stopping).

Reeve PA, Ala J, Hall JJ. Dapsone syndrome in Vanuatu: a high incidence during multidrug treatment (MDT) of leprosy. *J Trop Med Hyg* 1992; 95: 266-70. PubMed PMID: 1386634.

(An increase in the rate of dapsone syndrome occurred with introduction of multidrug therapy of leprosy [dapsone, clofazimine, rifampin], occurring in 24% of 37 patients and with fatality rate of 11%).

Lons T, Richardet JP, Machayekhi JP, Dalbergue B, Trinchet JC. [Granulomatous hepatitis caused by dapsone]. *Gastroenterol Clin Biol* 1992; 16: 293. French. PubMed PMID: 1582552.

(73 year old woman developed fever and weakness 5 months after starting dapsone [bilirubin 1.8 mg/dL, ALT 3.3 times ULN, Alk P 1.6 times ULN], liver biopsy showed granulomas with giant cells, symptoms and laboratory test abnormalities resolving with stopping dapsone and increasing corticosteroids).

Malnick SD, Atali M, Israeli E, Abend Y, Geltner D. Trimethoprim/sulfamethoxazole-induced rash, fever, abnormal liver function tests, leukopenia, and thrombocytopenia. *Ann Pharmacother* 1993; 27: 1139-40. PubMed PMID: 8219452.

(54 year old woman developed rash, fever and cytopenia with minimal ALT elevations 5 days after starting TMP-SMZ).

Carr A, Tindall B, Penny R, Cooper DA. Patterns of multiple-drug hypersensitivities in HIV-infected patients. *AIDS* 1993; 7: 1532-3. PubMed PMID: 8280426.

(Survey of 108 AIDs patients for history of allergic reactions to antibiotics, 39% reported allergy to sulfonamides, often cross reactive, but not always [dapsone vs TMP-SMZ]).

Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. *Ann Intern Med* 1993; 119(7 Pt 1): 576-83. PubMed PMID: 8363168.

(In Medicaid records between 1980-87, 107 patients were hospitalized for acute hepatitis of unknown cause, 8 had received TMP-SMZ, estimated risk from sulfonamides was <1 per 100,000 prescriptions).

Altraif I, Lilly L, Wanless IR, Heathcote J. Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) after administration of clindamycin and trimethoprim-sulfamethoxazole. *Am J Gastroenterol* 1994; 89: 1230-4. PubMed PMID: 8053440.

(Two case reports; 30 year old man developed TMP-SMZ induced allergic hepatitis with jaundice evolving into a prolonged cholestatic syndrome with ductopenia).

Pickert CB, Belsha CW, Kearns GL. Multi-organ disease secondary to sulfonamide toxicity. *Pediatrics* 1994; 94: 237-9. PubMed PMID: 8036081.

(13 year old boy developed rash during 3 week course of TMP-SMZ followed 10 days later by fever and pharyngitis with eosinophilia [25%], AST 252 U/L, GGT 210 U/L and renal failure with slow recovery).

Lindgren A, Olsson R. Liver reactions from trimethoprim. *J Intern Med* 1994; 236: 281-4. PubMed PMID: 8077884.

(Summary of Swedish adverse drug reaction reports of 21 cases of liver injury due to TMP alone; latency 5 to 24 days, all recovered, similar onset as to TMP-SMZ, but no details given).

Chalasanani P, Baffoe-Bonnie H, Jurado RL. Dapsone therapy causing sulfone syndrome and lethal hepatic failure in an HIV-infected patient. *South Med J* 1994; 87: 1145-6. PubMed PMID: 7973902.

(34 year old woman with HIV infection developed rash, fever and jaundice 1 month after starting dapsone for P. jiroveci prophylaxis [bilirubin 3.1 rising to >20 mg/dL, AST 1186 U/L, 15% eosinophils], with subsequent progressive injury, hepatic failure and death).

Barnard GF, Scharf MJ, Dagher RK. Sulfone syndrome in a patient receiving steroids for pemphigus. *Am J Gastroenterol* 1994; 89: 2057-9. PubMed PMID: 7942736.

(66 year old man developed fever, rash and liver abnormalities beginning 2 weeks after starting dapsone [peak bilirubin 4 mg/dL, ALT 550 U/L, Alk P 380 U/L], resolving within 4 weeks of stopping).

- Risse L, Bernard P, Brosset A, Enginger V, Bedane C, Bonnetblanc JM. [Disulfone hypersensitivity syndrome]. *Ann Dermatol Venereol* 1994; 121: 242-4. French. PubMed PMID: 7832554.
- Lau G. A fatal case of drug-induced multi-organ damage in a patient with Hansen's disease: dapsone syndrome or rifampicin toxicity? *Forensic Sci Int* 1995; 73: 109-15. PubMed PMID: 7797183.
- (71 year old man developed jaundice 7 weeks after starting dapsone [bilirubin 23.8 mg/dL, ALT 211 U/L, Alk P 385 U/L, eosinophils 15%] with severe rash, exfoliation, multiorgan failure and death 10 days after presentation).*
- Puri AS, Gupta R, Ghoshal UC, Khan E, Aggarwal R, Naik SR. Hepatic injury in sulfone syndrome: hepatitis or cholestasis? *Indian J Gastroenterol* 1995; 14: 20. PubMed PMID: 7860114.
- (23 year old man developed fever, rash and jaundice 1 month after starting triple therapy for leprosy using dapsone [bilirubin 6.8 mg/dL, ALT 187 U/L, Alk P 376 U/L, 10% eosinophils], resolving after exfoliative dermatitis within 6 weeks of stopping and later tolerating rifampin and clofazimine).*
- Jick H, Derby LE. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy* 1995; 15: 428-32. PubMed PMID: 7479194.
- (Boston database on 232,390 patients given TMP-SMZ and 266,951 given TMP alone; rates of hepatic events similar with both drugs: 3.8-5.2/100,000 exposed persons).*
- Simma B, Meister B, Deutsch J, et al. Fulminant hepatic failure in a child as a potential adverse effect of trimethoprim-sulphamethoxazole. *Eur J Pediatr* 1995; 154: 530-3. PubMed PMID: 7556317.
- (5 year old given TMP-SMZ and then amoxicillin-clavulanate and two weeks later developed jaundice [bilirubin 20.5 mg/dL, ALT 546 U/L, Alk P 538 U/L], progressing to liver failure and need for emergency transplantation).*
- George DK, Crawford DH. Antibacterial-induced hepatotoxicity. Incidence, prevention and management. *Drug Saf* 1996; 15: 79-85. PubMed PMID: 8862966.
- (Review of hepatotoxicity from antibiotics including sulfonamides indicating that transient increases in aminotransferase levels occur in 10% of patients, but that clinical liver injury is rare, in one study <1,100,000 prescriptions).*
- Prussick R, Shear NH. Dapsone hypersensitivity syndrome. *J Am Acad Dermatol* 1996; 35 (2 Pt 2): 346-9. PubMed PMID: 8698924.
- (22 year old woman developed fever, rash and lymphadenopathy 5 weeks after starting dapsone [bilirubin 3.0 mg/dL, ALT 342 U/L, Alk P 138 U/L], responding to prednisone and resolving within 6 weeks of stopping).*
- Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years' experience. *N Z Med J* 1996; 109: 315-9. PubMed PMID: 8816722.
- (Adverse drug reaction reports identified 943 liver injuries over 21 years in New Zealand; TMP-SMZ accounted for 29 (ranking 9th), 1 case being fatal).*
- García Rodríguez LA, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. *Pharmacotherapy* 1997; 17: 721-8. PubMed PMID: 9250549.
- (Review of studies of drug induced liver injury from the UK general practice database identified 23 cases of liver injury from TMP-SMZ among 232,390 users giving an incidence rate of 3.2 per 100,000 prescriptions, a rate similar to comparable antibiotics).*
- Cribb AE, Pohl LR, Spielberg SP, Leeder JS. Patients with delayed-onset sulfonamide hypersensitivity reactions have antibodies recognizing endoplasmic reticulum luminal proteins. *J Pharmacol Exp Ther* 1997; 282: 1064-71. PubMed PMID: 9262376.

(Comprehensive review of the major and minor side effects of sulfonamides including discussion of mechanisms).

Rieder MJ, King SM, Read S. Adverse reactions to trimethoprim-sulfamethoxazole among children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 1997; 16: 1028-31. PubMed PMID: 9384334.

(Single center survey; 40% of 25 children with HIV treated with TMP-SMZ developed short latency onset allergic reactions, none hepatic).

Stoschus B, Meybehm M, Spengler U, Scheurlen C, Sauerbruch T. Cholestasis associated with mesalazine therapy in a patient with Crohn's disease. *J Hepatol* 1997; 26: 425-8. PubMed PMID: 9059966.

(30 year old man developed nausea and jaundice 4 months after starting mesalazine [5-ASA] [bilirubin 6.0 mg/dL, ALT 393 U/L, Alk P 201 U/L]; no hypersensitivity features; resolving within 6 weeks of stopping therapy).

Yao F, Behling CA, Saab S, Li S, Hart M, Lyche KD. Trimethoprim-sulfamethoxazole-induced vanishing bile duct syndrome. *Am J Gastroenterol* 1997; 92: 167-9. PubMed PMID: 8995964.

(57 year old man developed vanishing bile duct syndrome after acute hepatic injury [bilirubin 2.0 rising to 40.4 mg/dL, ALT 465 U/L, Alk P 295 U/L] arising within 1 week of starting TMP-SMZ; no allergic features; ultimately underwent liver transplantation).

Besnard M, Debray D, Durand P, Cézard JP, Navarro J. Sulfasalazine-induced fulminant hepatitis in pediatric Crohn's disease: report of two cases. *J Pediatr Gastroenterol Nutr* 1998; 26: 119-20. PubMed PMID: 9443132.

(2 cases of 10 year olds [1 boy, 1 girl] developing fever, rash, arthralgias and eosinophilia 2-3 weeks after starting sulfasalazine, both progressing to acute liver failure).

Brett AS, Shaw SV. Simultaneous pancreatitis and hepatitis associated with trimethoprim-sulfamethoxazole. *Am J Gastroenterol* 1999; 94: 267-8. PubMed PMID: 9934769.

(34 year old woman developed fever and abdominal pain on TMP-SMZ [bilirubin 1.6 mg/dL, ALT 216 U/L, Alk P 158 U/L], resolving in 2 months; history of previous episode).

Deltenre P, Berson A, Marcellin P, Degott C, Biour M, Pessayre D. Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. *Gut* 1999; 44: 886-8. PubMed PMID: 10323894.

(65 year old man developed elevated ALT levels [8-12 times ULN] without jaundice after 6 months of mesalazine therapy that continued for 10 months and was associated with autoantibodies [ANA 1:500, SMA 1:200] and chronic hepatitis on biopsy; resolved rapidly once drug was stopped).

Ilario MJ, Ruiz JE, Axiotis CA. Acute fulminant hepatic failure in a woman treated with phenytoin and trimethoprim-sulfamethoxazole. *Arch Pathol Lab Med* 2000; 124: 1800-3. PubMed PMID: 11100060.

(60 year old woman developed acute liver failure while receiving both phenytoin and TMP-SMZ).

Windecker R, Steffen J, Cascorbi I, Thürmann PA. Co-trimoxazole-induced liver and renal failure. Case report. *Eur J Clin Pharmacol* 2000; 56: 191-3. PubMed PMID: 10877016.

(48 year old man developed jaundice [bilirubin 10.2 mg/dL, ALT 723 U/L, Alk P 413 U/L], with bone marrow and renal failure 6 days after 10 day course of TMP-SMZ, ultimately recovering within 6 months).

Lau G, Kwan C, Chong SM. The 3-week sulphasalazine syndrome strikes again. *Forensic Sci Int* 2001; 122: 79-84. PubMed PMID: 11672959.

(34 year old woman developed fever, rash, and lymphadenopathy 17 days after starting sulfasalazine, with subsequent hepatocellular jaundice [bilirubin 8.9 mg/dL, ALT 10,000 U/L, Alk P 515 U/L], progressing to liver failure and death).

Kaluarachchi SI, Fernandopulle BM, Gunawardane BP. Hepatic and haematological adverse reactions associated with the use of multidrug therapy in leprosy--a five year retrospective study. *Indian J Lepr* 2001; 73: 121-9. PubMed PMID: 11579648.

(Review of side effects of multidrug therapy of leprosy in 3333 patients identified 25 cases of toxic hepatitis, usually within first 3 months of starting, some related to rifampin but details not provided).

Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; 51: 536-9. PubMed PMID: 12235076.

(Survey of adverse drug reaction reporting on 5-ASA vs sulfasalazine – UK from 1991-8 – found sulfasalazine more commonly causes liver injury ~0.6 vs 0.32/100,000 exposures).

Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; 36: 451-5. PubMed PMID: 12143055.

(All adverse drug reactions from French region from 1997-2000 found 34 cases of liver injury, 40 drugs involved, 2 possibly due to sulfasalazine).

Mainra RR, Card SE. Trimethoprim-sulfamethoxazole-associated hepatotoxicity - part of a hypersensitivity syndrome. *Can J Clin Pharmacol* 2003; 10: 175-8. PubMed PMID: 14712321.

(24 year old woman developed fever, eosinophilia and jaundice while taking multiple herbal medications and after a brief course of TMP-SMZ [bilirubin 10.0 mg/dL, ALT 2479 U/L, Alk P 472 U/L], severe course but ultimate recovery).

Zaman F, Ye G, Abreo KD, Latif S, Zibari GB. Successful orthotopic liver transplantation after trimethoprim-sulfamethoxazole associated fulminant liver failure. *Clin Transplant* 2003; 17: 461-4. PubMed PMID: 14703931.

(23 year old man developed liver injury arising within 7 days of starting TMP-SMZ [bilirubin rising from 0.8 to 6.9 to 10.3 mg/dL, ALT 1706 U/L], evolving rapidly into acute liver failure and need for transplant).

Itha S, Kumar A, Dhingra S, Choudhuri G. Dapsone induced cholangitis as a part of dapsone syndrome: a case report. *BMC Gastroenterol* 2003; 3: 21. PubMed PMID: 12911838.

(40 year old man developed fever, rash and jaundice 3 weeks after starting dapsone [100 mg/day] [bilirubin 14.4 mg/dL, ALT 127 U/L, Alk P 141 U/L, 6% eosinophils], with subsequent desquamation and improvement on stopping).

Lee KB, Nashed TB. Dapsone-induced sulfone syndrome. *Ann Pharmacother* 2003; 37: 1044-6. PubMed PMID: 12841817.

(42 year old HIV-positive man developed fever, rash and jaundice 4 weeks after starting dapsone [100 mg/day] [peak bilirubin 5.7 mg/dL, ALT 255 U/L, Alk P 2078 U/L], resolving within 8 weeks of stopping).

Halmos B, Anastopoulos HT, Schnipper LE, Ballesteros E. Extreme lymphoplasmacytosis and hepatic failure associated with sulfasalazine hypersensitivity reaction and a concurrent EBV infection--case report and review of the literature. *Ann Hematol* 2004; 83: 242-6. PubMed PMID: 13680174.

(34 year old man with Crohn disease developed fever, rash, atypical lymphocytosis and hepatic failure after 1 day of restarting sulfasalazine, [bilirubin rising from 4.0 to 10.4 mg/dL, AST 1628 U/L, 10% eosinophilia], with apparent beneficial response to prednisone).

Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol* 2004; 172: 448-53. PubMed PMID: 15247700.

(Review article on side effects of antibiotics used in pediatric urologic practice).

Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am* 2004; 24: 477-90, vii. PubMed PMID: 15242722.

(Review of mechanisms of hypersensitivity to sulfonamides).

de Abajo FJ, Montero D, Madurga M, Rodriguez LAG. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Brit J Clin Pharm* 2004; 58: 71-80. PubMed PMID: 15206996.

(Analysis of General Practice Research Database from UK on 1.6 million persons from 1994-2000 found 128 cases of drug induced liver injury [2.4/100,000 person-years]; sulfasalazine was taken by 4 of 128 cases [3%], compared to 5 of 5000 controls [adjusted odds ratio 25.5]).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. *Liver Transpl* 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, 3 of which were attributed to sulfasalazine and 1 to TMP-SMZ).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scand J Gastroenterol* 2005; 40: 1095-101. PubMed PMID: 16165719.

(Among 103 cases of fulminant drug induced liver injury reported to a Swedish registry between 1966 and 2002, 6 cases were attributed to TMP-SMZ, 3 to sulfonamides and 1 to sulfasalazine [~10% overall]).

Descloux E, Argaud L, Dumortier J, Scoazec JY, Boillot O, Robert D. Favourable issue of a fulminant hepatitis associated with sulfasalazine DRESS syndrome without liver transplantation. *Intensive Care Med* 2005; 31: 1727-8. PubMed PMID: 16283166.

(45 year old woman developed rash 15 days after starting sulfasalazine and subsequently developed fever, eosinophilia and progressive liver injury leading to liver failure and death; autopsy showed massive necrosis).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al.; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; 129: 512-21. PubMed PMID: 16083708.

(Reports to a Spanish network between 1994-2004, included 461 cases of drug induced liver disease; sulfonamides were not mentioned in the top 19 causes [drugs with 5 or more cases]).

Garcia Rodriguez LA, Ruigomez A, Jick H. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scand J Gastroenterol* 2005; 40: 1095-1101. PubMed PMID: 16165719.

(Among 103 cases of fulminant drug induced liver injury reported to a Swedish registry between 1966 and 2002, 6 cases were attributed to TMP-SMZ, 3 to sulfonamides and 1 to sulfasalazine [~10% overall]).

Alves-Rodrigues EN, Ribeiro LC, Silva MD, Takiuchi A, Fontes CJ. Dapsone syndrome with acute renal failure during leprosy treatment: case report. *Braz J Infect Dis* 2005; 9: 84-6. PubMed PMID: 15947852.

(39 year old woman developed fever 23 days after starting dapsone [100 mg/day] and one week later developed jaundice [direct bilirubin 1.8 mg/dL, ALT 137 U/L] and renal failure, with slow recovery on prednisone after stopping).

Abidi MH, Kozlowski JR, Ibrahim RB, Peres E. The sulfone syndrome secondary to dapsone prophylaxis in a patient undergoing unrelated hematopoietic stem cell transplantation. *Hematol Oncol* 2006; 24: 164-5. (51 year old woman with acute myelogenous leukemia and hematopoietic cell transplantation developed fever and hemolytic anemia PubMed PMID: 16639690.

followed by rash and jaundice on dapsone therapy [bilirubin 7 mg/dL, ALT 203 U/L], dying 3 weeks later).

- Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. *Dig Liver Dis* 2006; 38: 33-8. PubMed PMID: 16054882.
- (Survey of drug induced liver fatalities reported to WHO database between 1968-2003 revealed 4690 reports – 89% from the US; 21 drugs were associated with more than 50 cases each, including TMP-SMZ [ranking 10th]).*
- Teo L, Tan E. Sulphasalazine-induced DRESS. *Singapore Med J*. 2006; 47: 237-9. PubMed PMID: 16518561.
- (49 year old woman developed purpuric rash and eosinophilia after 4 weeks of sulfasalazine therapy accompanied by serum enzyme elevations [ALT 171 U/L, Alk P 115 U/L] but no jaundice, rapidly resolving after stopping).*
- Kouklakis G, Mpoumponaris A, Zezos P, Moschos J, Koulaouzidis A, Nakos A, Pehlivanidis A, et al. Cholestatic hepatitis with severe systemic reactions induced by trimethoprim-sulfamethoxazole. *Ann Hepatol* 2007; 6: 63-5. PubMed PMID: 17297432.
- (30 year old man developed fever and rash 2 weeks after stopping a 15 day course of TMP-SMZ [bilirubin 2.9 mg/dL, ALT 456 U/L, Alk P 223 U/L], resolving within 3 months of onset).*
- Jobanputra P, Amarasena R, Maggs F, Homer D, Bowman S, Rankin E, Filer A, Raza K, Jubb R. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. *BMC Musculoskelet Disord* 2008; 9: 48. PubMed PMID: 18405372.
- (Ten cases of sulfasalazine hepatotoxicity identified in a UK rheumatology service over 7 year period; usual onset in 2-42 days, 7 with rash, 3 eosinophilia, 5 cases in blacks, two patients required liver transplantation; estimated frequency of 4 per thousand patients exposed).*
- Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.
- (Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, 9 were due to TMP-SMZ, which ranked 4th as a cause).*
- Crowell CS, Melin-Aldana H, Tan TQ. Fever, rash, and hepatic dysfunction in a 3-year-old child: a case report. *Clin Pediatr (Phila)* 2008; 47: 517-20. PubMed PMID: 18509155.
- (3 year old boy with rash, fever, cough and 19% atypical lymphocytes was thought to have Kawasaki disease or mononucleosis, but later found to have received TMP-SMZ 1 week before onset [bilirubin 1.6 mg/dL, ALT 354 U/L, Alk P 351 U/L], rapid response to corticosteroids).*
- Jobanputra P. BSR DMARD monitoring guidelines: sulfasalazine. *Rheumatology (Oxford)* 2008; 47: 1587-8. PubMed PMID: 18723518.
- (Letter in response to published guidelines on sulfasalazine stressing the severe, but rare complication of hepatitis [0.4%] which can lead to acute liver failure).*
- Ranawaka RR, Mendis S, Weerakoon HS. Dapsone-induced haemolytic anaemia, hepatitis and agranulocytosis in a leprosy patient with normal glucose-6-phosphate-dehydrogenase activity. *Lepr Rev* 2008 Dec; 79 (4): 436-40. PubMed PMID: 19274991.
- (21 year old man developed fever and agranulocytosis 5 months after starting multidrug therapy of leprosy [bilirubin 2.4 mg/dL, ALT 282 U/L], which resolved within 1 month of stopping and he later tolerated long term rifampin and clofazimine therapy).*
- Hanses F, Zierhut S, Schölmerich J, Salzberger B, Wrede CE. Severe and long lasting cholestasis after high-dose co-trimoxazole treatment for *Pneumocystis pneumonia* in HIV-infected patients--a report of two cases. *Int J Infect Dis* 2009; 13: e467-9. PubMed PMID: 19299179.

(Two patients with HIV infection and pneumocystis pneumonia developed elevations in Alk P and bilirubin while on TMP-SMZ, but both also had CMV infection and multiple complications, and abnormalities persisted long term).

Sheen YS, Chu CY, Wang SH, Tsai TF. Dapsone hypersensitivity syndrome in non-leprosy patients: a retrospective study of its incidence in a tertiary referral center in Taiwan. *J Dermatolog Treat* 2009; 20: 340-3. PubMed PMID: 19954390.

(Among 361 patients without leprosy treated with dapsone over a 54 month period, hypersensitivity syndrome developed in 6 [2%], including 4 women and 2 men, arising after 8-36 days with fever and rash; 5 had liver involvement [bilirubin 1.2 to 4.7 mg/dL, ALT 62 to 1064 U/L, Alk P 297-1072 U/L], none fatal, all resolving symptomatically within 30 days).

Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. *J Hepatol* 2009; 50: 511-7. PubMed PMID: 19155082.

(Among 685 patients identified an average of 10 years after an episode of drug induced liver injury, 23 [3.4%] had continuing liver disease, 8 with cirrhosis; none were attributed to a sulfonamide).

Gutierrez M, Filippucci E, Bugatti L, Bertolazzi C, Grassi W. [Severe drug hypersensitivity syndrome due to sulphasalazine in patient with rheumatoid arthritis]. *Reumatismo* 2009; 61: 65-8. Italian. PubMed PMID: 19370190.

(60 year old man with rheumatoid arthritis developed rash, facial edema and fever 32 days after starting sulfasalazine [bilirubin normal, ALT 74 U/L, Alk P 142 U/L, 6% eosinophils], resolution with prednisone).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. *Br J Clin Pharmacol* 2010; 70: 721-8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, TMP-SMZ accounting for 48 cases [0.5%] for an adjusted odds ratio of 1.3).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010; 105: 2396-404.

PubMed Citation (313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; dapsone accounted for 17 cases [5.4% of which 2 were fatal, and TMP-SMZ accounted for 7 cases [2.2%], but none were fatal).

Lens S, Crespo G, Carrión JA, Miquel R, Navasa M. Severe acute hepatitis in the DRESS syndrome: Report of two cases. *Ann Hepatol* 2010 Apr-Jun; 9 (2): 198-201. PubMed PMID: 20526017.

(Two cases of DRESS syndrome; case 1, a 29 year old woman who developed fever, rash, eosinophilia and jaundice 8 weeks after starting sulfasalazine [bilirubin 13.5 mg/dL, ALT 1117 U/L, Alk P 1171 U/L, INR 3.2] with signs of hepatic failure, but ultimate recovery on corticosteroids within 21 days; case 2 attributed to levetiracetam).

García-Aparicio J, Herrero-Herrero JI. [Toxic hepatitis following sequential treatment with cotrimoxazol, levofloxacin, doxycycline and sertraline in a patient with a respiratory infection]. *Farm Hosp* 2010; 34: 152-4. Spanish. PubMed PMID: 20471573.

(65 year old woman developed jaundice shortly after having received TMP-SMZ as well as doxycycline and levofloxacin for a urinary tract infection [bilirubin 3.5 rising to 14.2 mg/dL, ALT 937 U/L, Alk P 373 U/L], resolving within 3 months of onset).

Bell TL, Foster JN, Townsend ML. Trimethoprim-sulfamethoxazole-induced hepatotoxicity in a pediatric patient. *Pharmacotherapy* 2010; 30: 539. PubMed PMID: 20412003.

(9 year old boy developed fever and abdominal pain without rash 14 days after starting a course of TMP-SMZ [bilirubin 0.6 mg/dL, ALT 624 U/L, Alk P 153 U/L, 9% eosinophils], resolving within a week of stopping).

Chisholm-Burns MA, Patanwala AE, Spivey CA. Aseptic meningitis, hemolytic anemia, hepatitis, and orthostatic hypotension in a patient treated with trimethoprim-sulfamethoxazole. *Am J Health Syst Pharm* 2010; 67: 123-7. PubMed PMID: 20065266.

(37 year old man developed fever and rash 8 days after starting TMP-SMZ [bilirubin 2.3 mg/dL, ALT 1290 U/L, Alk P not given], with hemolytic anemia, resolving in 2 weeks).

Khokhar OS, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. *Dig Dis* 2010; 28: 508-18. PubMed PMID: 20926880.

(Review of liver toxicity of drugs for inflammatory bowel disease; sulfasalazine is cited as causing an acute hypersensitivity like reaction with fever, rash and liver involvement, and both a granulomatous and a cholestatic form of liver injury and rarely acute liver failure).

Rogler G. Gastrointestinal and liver adverse effects of drugs used for treating IBD. *Best Pract Res Clin Gastroenterol* 2010; 24: 157-65. PubMed PMID: 20227029.

(Review of GI and liver side effects of drugs of inflammatory bowel disease; sulfasalazine is listed as causing "abnormal liver function" tests in 4% of patients).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 12 due to sulfonamides [9%], 9 from SMZ/TMP and 3 sulfasalazine).

M

olleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; for the Drug-Induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN Prospective Study. *J Pediatr Gastroenterol Nutr* 2011; 53: 182-189. [PubMed Citation](#) (Among 30 children with drug induced liver injury enrolled in a prospective US database between 2004 and 2008, 15 were due to antibiotics including 1 from sulfamethoxazole).

Devarbhavi H, Karanth D, Prasanna KS, Adarsh CK, Patil M. Drug-Induced liver injury with hypersensitivity features has a better outcome: a single-center experience of 39 children and adolescents. *Hepatology* 2011; 54: 1344-50. PubMed PMID: 21735470.

(Between 1997 and 2010, 450 cases of drug induced liver injury were seen at a single center in India, including 45 cases in children [9%], among whom the most common causes were antituberculosis drugs [n=22, 50% mortality], anticonvulsants [phenytoin 10, carbamazepine 6], and dapsone 4; others included 1 case each due to TMP-SMZ, ciprofloxacin, amoxicillin and Ayurvedic agents).

Bollaert M, Jeulin H, Waton J, Gastin I, Tréchet P, Rabaud C, Schmutz JL, et al. [Six cases of spring DRESS]. *Ann Dermatol Venereol* 2012; 139: 15-22. French. [PubMed Citation](#)

(Description of 6 cases of DRESS syndrome arising during a single one month period, all with reactivation of herpes virus infections [EBV, HHV-6, HHV-7 or CMV] and due to different medications, including amoxicillin, allopurinol, carbamazepine, trimethoprim-sulfamethoxazole and multiple antibiotics).

Anelli MG, Scioscia C, Grattagliano I, Lapadula G. Old and new antirheumatic drugs and the risk of hepatotoxicity. *Ther Drug Monit* 2012; 34: 622-8. PubMed PMID: 23128910.

(Review of liver injury caused by antirheumatic agents; sulfasalazine can cause liver injury in 1:1000 recipients, usually arising in the first month of treatment often with immunoallergic features and with typical signs of DRESS syndrome in some patients).

Descamps V. [Drug reaction with eosinophilia and systemic symptoms (DRESS)]. Rev Prat 2012; 62: 1347-52. French. PubMed PMID: 23424909.

(Review of clinical features of DRESS syndrome in French).

Sempera S, Lammert C, Talwalkar JA, Sanderson SO, Poterucha JJ, Hay JE, Wiesner RH, Gores GJ, Rosen CB, Heimbach JK, Charlton MR. Frequency, clinical presentation, and outcomes of drug-induced liver injury after liver transplantation. Liver Transpl 2012; 18: 803-10. PubMed PMID: 22389256.

(Among 29 cases of suspected drug induced liver injury occurring in patients after liver transplantation, 11 [38%] were attributed to TMP-SMZ the mostly commonly implicated agent).

Cangemi DJ, Donovan ST, Johnson MM. 62-year-old man with painless jaundice and hyponatremia. Mayo Clin Proc 2013; 88: e49-53. PubMed PMID: 23726406.

(62 year old man developed jaundice shortly after 4 day course of TMP-SMZ for cellulitis [bilirubin 25.8 mg/dL, ALT 425 U/L, Alk P 1515 U/L], resolving within 3 months of onset).

Ng CT, Tan CK, Oh CC, Chang JP. Successful extracorporeal liver dialysis for the treatment of trimethoprim-sulfamethoxazole-induced fulminant hepatic failure. Singapore Med J 2013; 54: e113-6. PubMed PMID: 23716163.

(17 year old man developed fever and rash 28 days after starting TMP-SMZ for acne [bilirubin 3.0 rising to 19.2 mg/dL, ALT 1660 U/L, Alk P 227 U/L, eosinophils 670/ μ L], progressing to hepatic failure, but ultimate recovery without liver transplantation within 2 months of onset).

Pirklbauer M, Gruber J. [DRESS syndrome following sulfasalazine treatment.]. Z Rheumatol. 2013 Dec 14. [Epub ahead of print] German. PubMed PMID: 24337150.

(33 year old woman with juvenile idiopathic arthritis developed fever, rash and dyspnea with cough 4 weeks after starting sulfasalazine [bilirubin not given, ALT 117 U/L, GGT 422 U/L], with pulmonary manifestations of DRESS syndrome, resolving with prednisone therapy).

Girelli F, Bernardi S, Gardelli L, Bassi B, Parente G, Dubini A, Serra L, Nizzoli M. A new case of DRESS syndrome induced by sulfasalazine and triggered by amoxicillin. Case Rep Rheumatol 2013; 2013: 409152. PubMed PMID: 23936716.

(53 year old woman developed fever and lymphadenopathy 6 weeks after starting sulfasalazine for spondylitis, with subsequent rash and oral ulcers [bilirubin 2.7 mg/dL, ALT 350 U/L, Alk P 2959 U/L], improving with prednisone therapy).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 2 that were attributed to TMP-SMZ).

Garcia A, Yi NJ, Lee KB, Lee JM, Choi YR, Suh SW, You T, et al. Fulminant hepatitis linked to dapsone hypersensitivity syndrome requiring urgent living donor liver transplantation: a case report. Pediatr Transplant 2014; 18: E240-5. [PubMed Citation](#)

(12 year old girl developed fever and rash 3 weeks after starting dapsone, which was followed by jaundice and liver failure [bilirubin 1.8 rising to 19.6 mg/dL, ALT 131 U/L, Alk P not given, INR rising to 2.6], undergoing urgent living-donor liver transplantation, explant showing submassive necrosis).

Yang JJ, Huang CH, Liu CE, Tang HJ, Yang CJ, Lee YC, Lee KY, Tsai MS, et al. Multicenter study of trimethoprim/sulfamethoxazole-related hepatotoxicity: incidence and associated factors among HIV-infected patients treated for *Pneumocystis jirovecii* pneumonia. *PLoS One* 2014; 9: e106141. [PubMed Citation](#)

(Among 284 HIV infected patients treated with SMZ/TMP for P. jirovecii pneumonia, 152 [53%] developed liver test abnormalities which was attributed to SMP/TMP in 47 [17%] of whom 3 [1%] developed jaundice, but none died of liver failure).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. *Ann Hepatol* 2014; 13: 231-9. [PubMed PMID: 24552865](#).

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, including 39 attributed to antimicrobial agents, but none to dapsone).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52.e7. [PubMed Citation](#)

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 2 cases were attributed to dapsone, with time to onset of 1-2 months, hepatocellular enzyme elevations, one with jaundice, both resolving after stopping dapsone but both were considered only probable).

Schulkes KJ, Tervaert JW, Rijken F, Haas LE. Dapsone hypersensitivity syndrome not related to G6PD deficiency. *BMJ Case Rep* 2015; 2015. pii: bcr2015212742. [PubMed Citation](#)

(55 year old woman developed fever, cough and rash 4 weeks after starting dapsone [bilirubin 0.9 mg/dL, ALT 150 U/L, Alk P 213 U/L, INR 1.4] with pulmonary infiltrates, resolving with prednisone therapy within 4 weeks of stopping dapsone).

Chalasani N, Reddy KRK, Fontana RJ, Barnhart H, Gu J, Hayashi PH, Ahmad J, et al. Idiosyncratic drug induced liver injury in African-Americans is associated with greater morbidity and mortality compared to Caucasians. *Am J Gastroenterol* 2017; 112: 1382-8. [PubMed Citation](#)

(Among 985 patients enrolled in a US prospective database of drug induced liver injury between 2004 and 2016, SMZ/TMP was the most implicated medication among 144 African Americans [7.6%], but ranked fifth among 841 Caucasians [3.6%] behind amoxicillin-clavulanate, nitrofurantoin, anabolic steroids and isoniazid).

Ferrajolo C, Verhamme KM, Trifirò G, 't Jong GW, Picelli G, Giaquinto C, Mazzaglia G, et al. Antibiotic-induced liver injury in paediatric outpatients: a case-control study in primary care databases. *Drug Saf* 2017; 40: 305-15. [PubMed Citation](#)

(In a large database, population based, case control study from Europe, sulfonamides were being used in 0.5% of children with new-onset, unexplained acute liver injury compared to 0.1% of controls yielding an adjusted odds ratio of 24.2).