DRUG-INDUCED PANCREATITIS

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Over the last 25 years there has been an explosion of new drugs introduced for the treatment of a variety of diseases. Due to the thoroughness of premarket drug evaluation in this country, when drugs are released for general use, they are generally safe and effective with well-known safety profiles. Drug-induced or drug-related pancreatitis is remarkably uncommon in light of the number of drugs prescribed. The relative rarity of drug-related pancreatitis makes it difficult for the clinician to obtain accurate information about rare complications of a drug, especially on newer drugs. This information usually accumulates by case report after the drug has been in general clinical use for some time. The FDA and the individual pharmaceutical companies are other possible sources of information. It is probably wise to consider any relatively new drug as a potential cause of drug-induced pancreatitis, and it is important to report well-documented cases in the medical literature, by letter or case report.

A classic review article by Mallory and Kern was published in 1980 [1]. They proposed criteria which should be met to prove a drug was a cause of pancreatitis. Based on the degree to which these criteria were met, a drug was then classified as having either a definite, probable or possible association with pancreatitis. This standard has generally been followed since in evaluating both new and old drugs. Proving a definite association requires that all the stipulations in Table 1 be met:

Table 1. Proof that a drug causes pancreatitis.

- Pancreatitis develops during treatment with the drug.
- Other likely causes of pancreatitis are not present.
- Pancreatitis resolves upon discontinuing the drug.
- Pancreatitis usually recurs upon readministration of the drug.

Helpful supportive information may include an increased incidence of pancreatitis in other patients compared to a control group or data in animal studies reporting an association. Because pancreatitis is a serious and occasionally fatal illness, readministration of the suspect drug is justified only if the drug is essential for the treatment of a serious illness. Therefore, it is common that rechallenge is not performed. In addition, it is difficult to evaluate the contributions which the underlying illness and the administration of other drugs make to the development of pancreatitis. In other words, the suspect drug may be a contributing rather than a causal factor. Drug-induced pancreatitis has no unique features that distinguish it from acute pancreatitis due to other causes. A careful history and a high level of suspicion are the best tools of the physician. Of course, making a diagnosis of drug-induced pancreatitis requires not only a high incidence of suspicion, but a thorough understanding of other causes of pancreatitis so that other possible etiologies can be evaluated.

The most common causes of episodes of acute pancreatitis in the United States are ethanol ingestion and passage of gallstones. Because the incidence of gallstones is high and biliary pancreatitis is common, a negative sonographic examination of the biliary tract is helpful

negative information in pursuing a diagnosis of drug-induced pancreatitis. Of course, in older patients, asymptomatic cholelithiasis and drug-induced pancreatitis may occasionally co-exist and clinical judgement will be needed to make therapeutic decisions.

Drug-induces pancreatitis is almost always acute. The rare cases of chronic pancreatitis purported to be from drugs are usually not well substantiated. The pathogenesis of drug-induced pancreatitis is usually unclear, but mechanisms suggested in Table 2 include many of the mechanisms proposed for other causes of pancreatitis.

Table 2. Possible mechanisms for drug-induced pancreatitis.

- Relative obstruction of the pancreatic duct
- Metabolic effects (i.e. hypercalcemia or hyperlipidemia)
- Immunosuppression
- Arterial thrombosis
- Direct cellular toxicity

DRUGS USED FOR AIDS

Patients with AIDS have an increased incidence of pancreatitis compared to the normal population. Clinical pancreatitis, usually mild, may occur in up to 20% of patients [2,3]. There are a number of factors in addition to alcohol and gallstones which are responsible for this increased incidence including drugs, hyperlipidemia [4], tumor and infections as well as direct effects of the HIV virus on the pancreas. Pancreatic abnormalities are even more commonly found at autopsy (Table 3).

Table 3. Autopsy findings in the pancreas in 139 patients with AIDS.

• Infections	14%
• Neoplasms	7%
• Drug-induced	5%
• Nonspecific changes	27%
Total Abnormal	53%

Evaluation of possible drug-induced pancreatitis in these complicated patients is not simple, and rechallenge with a suspected drug is only done occasionally with strong clinical indications. The anti-HIV drugs associated with pancreatitis are shown in Table 4.

Table 4. Anti-HIV Drugs Associated with Pancreatitis.

Definite	Probable
Didanosine (DDI)	Zalcitabine (DDC)
Pentamidine	

Definite Association with pancreatitis

Didanosine. 2',3'-dideoxyinosine (DDI) is a purine nucleoside analogue approved for treatment of human immunodeficiency virus. As soon as phase I clinical trials in patients with AIDS began, occasional cases of mild pancreatitis were observed [5-7]. DDI-associated pancreatitis appeared to be uncommon, with an initially reported incidence of about 3%. However, later studies indicate that the incidence of elevated amylase in DDI-treated AIDS patients may be much higher. In 51 homosexual men with AIDS receiving DDI (Table 5), 63% of patients had elevated serum amylases, and 23.5% of patients developed clinical pancreatitis [8]. Two patients died of complications of pancreatitis [8].

Table 5. Clinical pancreatitis and elevated serum amylase associated with DDI in men.

Study design: 51 homosexual men with AIDS. All patients used aerosolized pentamidine (Maxson,1991).

Results: Asymptomatic ↑ amylase - 39%
Clinical pancreatitis - 24%
Death from pancreatitis - 4%

In contrast, in a study of children with AIDS treated with DDI, clinical pancreatitis was unusual although amylase elevations occurred about as often as in the adult men in the previous study (Table 6)[9].

Table 6. Elevated amylase and pancreatitis associated with DDI in children.

Study Design: 43 children with AIDS treated with oral DDI for 24 weeks (Butler, 1991).

Results: Asymptomatic ↑ amylase - 44%
Clinical pancreatitis - 5%
Death from pancreatitis - 0%

Several clinical features that may allow some estimate of increased risk of DDI-associated pancreatitis in individual patients are described in Table 7.

Table 7. Possible predictors of DDI-associated pancreatitis in AIDS patients.

- severity of HIV disease
- drug-related hyperlipidemia
- increased dose of drug
- therapy longer than 10 weeks
- previous pancreatitis
- simultaneous use of pentamidine

Pentamidine. Pentamidine is a very old antibiotic used since the 1940's for the treatment of leishmaniasis and African trypanosomiasis. It was first used for treatment of *Pneumocystis carinii* in 1958 [10], and was the treatment of choice for this infection until the advent of trimethoprim-sulfamethoxazole [11]. Pentamidine was then used much less often, in part because of its high incidence of adverse reactions, including hypoglycemia from islet cell toxicity. In one study of 404 patients, 47% experienced at least one adverse reaction [12]. Pentamidine is now used extensively for prophylaxis and treatment of *P. carinii* in patients with AIDS. Murphey reported the first cases of pentamidine-associated pancreatitis in two patients with leukemias, both treated for *P. carinii* pneumonia [13]. Pancreatitis in these patients occurred in the second week of therapy with pentamidine and resolved within 10 days of discontinuing therapy. Rechallenge was not performed. In 1986, several cases of fatal pancreatitis were reported in patients with AIDS treated with pentamidine [14,15]. In 1989, the first case of pentamidine-associated pancreatitis recurring with rechallenge was reported [16]. In some of these cases, pancreatitis persisted for

some time after pentamidine was discontinued. Pauwels et al. suggested that this prolonged course may be due to its lipophilic nature; in his report an AIDS patient with pentamidine-associated pancreatitis had persistent levels of pentamidine in the serum for a month after therapy was discontinued [17]. Pentamidine is known to accumulate and persist in the pancreas in patients with AIDS for as long as one year after therapy is stopped [18]. Several patients have developed pancreatitis on long-term aerosolized pentamidine [19], which was developed to decrease systemic drug levels while maintaining prophylactic levels in the lung. In 2 patients, pancreatitis was exacerbated or recurred with rechallenge with aerosolized pentamidine [19]. The pathology of fatal pentamidine-induced pancreatitis in AIDS patients is somewhat unusual in that massive acinar and islet cell necrosis is present with minimal neutrophilic infiltrates, perhaps due to profound immunosuppression from HIV and concomitant zidovudine (AZT) therapy [20]. Both a high cumulative dose and individual hypersensitivity to pentamidine probably contribute to the risk of pancreatitis.

Table 8. Clinical features of pentamidine-associated pancreatitis.

- Occurs rarely, probably more common in AIDS patients
- Mechanism: cellular toxicity/individual hypersensitivity
- Time of onset: IV as early as second week, oral or aerosolized may be months or longer
- Usually mild, may be fatal especially in AIDS patients
- Recurs with rechallenge

Possible Association with Pancreatitis

Zalcitibine. Dideoxycytidine (DDC) or zalcitabine is related to 2',3'-dideoxyinosine (DDI) and is likely to have similar side effects. Although no cases of zalcitibine-associated pancreatitis have been reported in the literature, data on file with the manufacturer (Hoffman-LaRoche) indicates that pancreatitis is a rare but serious complication (Personal communication cited in [21]).

ANTIBIOTICS.

Relatively few antibiotics have been reported to be associated with pancreatitis, considering the very large number of antibiotics and the frequency with which they are used. The antibiotics associated with pancreatitis are shown in Table 9.

Table 9. Antibiotics Associated with Pancreatitis

Definite	Probable	Possible
Stibogluconate	Metronidazole	Ampicillin
Sulfonamides		Erythromycin
Tetracyclines		Isoniazid
		Nitrofurantoin
		Rifampicin
		Roxithromycin

Definite association with pancreatitis.

Stibogluconate. Pentavalent antimony represents a drug which we now know is almost always toxic to the pancreas but which patients can generally tolerate. Obviously, a toxic drug like this will be used only until a safer and equally effective alternative is available. Pentavalent antimony, formulated as sodium stibogluconate or meglumine antimoniate, is a standard treatment for the leishmaniases, so is only occasionally used in the United States. Several sporadic cases of stibogluconate-associated pancreatitis were reported in the early 1990's, all in renal transplant patients [22]. Recently, Gasser et al. performed a prospective study of 17 patients treated with intravenous stibogluconate for leishmaniasis (Table 10)[23]. Serum amylase and lipase were drawn daily for 2 weeks and then twice weekly. Patients were asked daily about gastrointestinal symptoms.

Table 10. Prospective study of stibogluconate-associated pancreatitis.

Study design:	17 consecutive patients treated for leishmaniasis had serial lipase and amylase levels (Gasser, 1994).
Results:	16/17 (94%) had abnormal values of amylase or lipase 12/17 (70%) had clinical pancreatitis 6/6 (100%) had flares with rechallenge
Comment:	All patients with flares completed therapy

Serum amylase and lipase rose in 16 of 17 patients, and clinical pancreatitis occurred in 12 of 17 patients. Surprisingly, although symptoms recurred with rechallenge in 6 of 10 patients, patients improved on continued administration and all patients were able to complete therapy. The authors then retrospectively measured serum amylase and lipase on stored sera from 32

Peruvian patients treated with stibogluconate (n=24) or meglumine antimoniate (n=8). Eleven of 32 patients developed clinical pancreatitis, and amylase and lipase rose in 18 of 24 patients on stibogluconate and all 8 of the patients on meglumine antimoniate. Patients improved on continued treatment and all completed therapy.

Sulfonamides: sulfamethizole and trimethiprim-sulfamethoxazole. The first case of sulfonamide-induced pancreatitis was reported in 1963 by Barrett and Thier [24], in a patient treated first with tetracycline and then the sulfonamide antibiotic sulfamethizole for an abscess. She developed abdominal pain after a week of sulfamethizole which was then discontinued. On two subsequent occasions she developed both pancreatitis and culture-negative meningitis after taking only two tablets of sulfamethizole. Her symptoms resolved only a few days after the antibiotic was stopped on both occasions. This was felt to be a drug hypersensitivity reaction. Trimethoprim-sulfamethoxazole (TMP-SMX) is a newer sulfonamide-related agent which is used for a wide variety of infections. The first report of TMP-SMX-associated pancreatitis was made in 1986. A renal transplant patient developed pancreatitis one week after beginning therapy with TMP-SMX for a brain abscess due to *Nocardia* [25]. The patient had been taking azathioprine and prednisone for 5 years after renal transplant and furosemide for several months. First furosemide and next azathioprine were discontinued without improvement. The patient promptly improved after TMP-SMX was discontinued. Due to progression of the brain abscess, TMP-SMX was restarted with recurrence of pancreatitis which again resolved after the medication was discontinued. In another case, a 26-year-old man developed fulminant liver failure and pancreatitis after taking TMP-SMX for 5 days for an ear infection [26]. At autopsy, acute hepatic necrosis and hemorrhagic pancreatitis were found, probably due to a hypersensitivity reaction to the sulfa compound. Rechallenge was not performed. In a third case [27], pancreatitis developed after 6 weeks of TMP-SMX therapy for a brain abscess due to *Nocardia;* rechallenge was not performed. The sulfonamide-related diuretics and sulfasalazine will be discussed in the cardiovascular and gastrointestinal sections.

Tetracyclines. The earliest report of tetracycline-associated pancreatitis appeared in 1955 in patients who developed acute fatty liver of pregnancy [28]. Additional series of cases were reported in detail [29,30]. Renal failure often accompanied liver disease and pancreatitis. In 1967 Peters et al. reported a similar syndrome of tetracycline-associated fatty liver, pancreatitis and renal disease in nonpregnant patients [31]. To date at least four cases of tetracycline-induced pancreatitis have been reported in patients with no clinical or biochemical evidence of liver disease [32-34]. Rechallenge with recurrent pancreatitis occurred in two of the four patients. All four of these patients were 21 years of age or less. An additional 2 children were reported to have tetracycline-induced pancreatitis (no substantiation provided) [35]. It is unclear whether younger age predisposes to the development of pancreatitis or simply is associated with a more common use of tetracycline.

Probable association with pancreatitis

Metronidazole. Four well-documented cases of metronidazole-associated pancreatitis have been published since this widely used antibiotic was introduced in 1959.

Table 11. Metronidazole-associated pancreatitis.

- At least 4 reported cases
- By HMO prescription records, incidence no more than 4.6 cases/10,000 patients
- Onset within hours to days of starting therapy
- Rechallenge resulted in recurrence in 3/4 patients

In three cases, metronidazole was prescribed to young women for vaginal infections [36-38]. A fourth patient, a 63-year-old woman, received the antibiotic for Crohn's disease. In the first case [36], the unfortunate patient was survived inadvertent rechallenge three separate times 2,4 and 12 months after the first episode. On each occasion, recurrent pancreatitis was documented with laboratory studies. An ERCP after the second episode showed changes consistent with recurrent pancreatitis. The patients in the second and third reports also received inadvertent rechallenges after the initial episode with recurrent pancreatitis. A retrospective computer search of 6585 patients receiving metronidazole in a large HMO found no cases of pancreatitis requiring hospitalization [39], confirming that severe pancreatitis due to metronidazole is rare.

Possible association with pancreatitis

Ampicillin. There is a single case reported in a letter to the editor of a patient who developed pancreatitis 6 days after beginning ampicillin for a urinary infection [40]. She recovered 5 days after ampicillin was discontinued but developed pancreatitis again 4 days after rechallenge with ampicillin.

Erythromycin and Roxithromycin. Three cases of pancreatitis associated with erythromycin have been reported. In one case, the patient developed symptoms only 40 minutes after intravenous infusion of erythromycin lactobionate [41]. In two other cases [42,43], pancreatitis developed after an overdose of erythromycin. Although these cases seem reasonably solid, rechallenge has never been performed. There is a single report of roxithromycin-associated pancreatitis [44]; this patient had been taking erythromycin just before starting roxithromycin.

Nitrofurantoin. Nitrofurantoin-induced pancreatitis must be extremely rare since this is an old and widely used antibiotic. There is a single well-documented case report including rechallenge [45]. Rechallenge resulted in clinical pancreatitis only a few hours after a single small dose of nitrofurantoin. Transhepatic cholangiography at the time of the initial presentation showed dilated intrahepatic and common bile duct with smooth intrapancreatic narrowing; followup cholangiogram after resolution of symptoms was normal.

Isoniazid. Isoniazid, known for years as a hepatotoxic agent [46] has been cited several times in reviews over the last 20 years as a potential cause of pancreatitis. However, this appears to be due to repeated citations of the same report [47] which actually does not even mention

isoniazid, and frequent mention of "early reports" without substantiation. Ironically, a recent report has now presented a well-documented case of isoniazid-induced pancreatitis which included rechallenge [48]. A patient was treated for 14 days for gastrointestinal tuberculosis with isoniazid, rifampin and pyrazinamide. He developed acute pancreatitis confirmed with laboratory studies, CT scans and ultrasound. The biliary system was normal and other causes of pancreatitis were eliminated. A diagnosis of possible rifampin-induced pancreatitis was made and isoniazid was restarted 8 days later after recovery. Six hours later, the patient developed documented pancreatitis again. After recovery, he was uneventfully treated for tuberculosis with rifampin, pyrazinamide and ethambutol.

Rifampicin. Rifampicin has been stated to cause pancreatitis [49] and this is sometimes cited in cases such as the one above but the case evidence is not strong.

CARDIOVASCULAR DRUGS.

Cardiovascular drugs that are associated with pancreatitis can be categorized as diuretics, antiarrhythmics or antihypertensives. The mechanisms of action for pancreatitis in these cases are unclear. A list of cardiovascular drugs associated with pancreatitis is shown in Table 12.

Table 12. Cardiovascular drugs associated with pancreatitis.

Definite	Probable	Possible
Furosemide	Bumetinide	Amiodarone
Thiazides	Chlorthalidone	Diazoxide
	Ethacrynic acid	Enalapril
	Methyldopa	Lisinopril
		Metolazone
		Procainamide

Definite association with pancreatitis

Furosemide. Furosemide is a sulfonamide-related compound. The first definite case of furosemide-associated pancreatitis was reported in 1975 [50]. A 64-year-old woman who was treated with furosemide after a myocardial infarction. Six weeks after treatment began, the patient developed clinical pancreatitis with elevated serum amylase and lipase. Symptoms persisted for two weeks and amylase levels continued to increase until furosemide was discontinued. The patient was markedly improved in 36 hours and completely recovered. A thorough evaluation for other causes of pancreatitis was unrevealing. The patient responded to rechallenge with a low dose of furosemide with recurrent pancreatitis beginning only a day after the drug was started. Almost immediately, several other cases were reported [51,52]. In one of these cases [52], hyperlipidemia was present initially but on rechallenge pancreatitis recurred without

hyperlipidemia. At least 8 cases of furosemide-associated pancreatitis have been reported in the literature; 5 of these patients had impaired renal function [53]. It has been proposed that diuretics such as furosemide may cause relative pancreatic ischemia by volume contraction; however, patients with volume contraction for many other reasons do not seem to have a predisposition to pancreatitis.

Thiazides. At least 17 cases of diuretic-associated pancreatitis, usually a thiazide diuretic, have been reported in pregnant patients [54]. Mortality for both mothers and infants was high, ranging from 30-50%. Pancreatitis in pregnancy from any cause carries a high mortality rate around 35%. Aside from cases associated with pregnancy, there at least seven well documented cases of thiazide-associated pancreatitis [54]. The doses of thiazide diuretic ranged from 250-1000 mg/day. The mean duration of treatment was 16 months. Several cases were fatal and at least two cases developed pancreatic abscesses.

Probable association with pancreatitis.

Bumetinide. Bumetinide, like furosemide, is a sulfonamide-related compound. It has been reported to cause serum amylase elevations, and in one case, pancreatitis when used as a substitute for furosemide in a patient with furosemide-associated pancreatitis [53].

Chlorthalidone. Chlorthalidone probably also causes pancreatitis but less commonly than the thiazide diuretics. There are only two well-documented cases in the literature [54], occurring with doses ranging from 50-200 mg/day.

Ethacrynic acid. There is a single fairly well documented report of pancreatitis associated with ethacrynic acid [55]; this has not been confirmed by subsequent reports.

Possible association with pancreatitis.

Amiodarone. A single case of pancreatitis associated with amiodarone has been reported [56]. This patient was a 67-year-old man receiving amiodarone for a ventricular arrhythmia. Abnormal liver enzymes were noted five months after starting amiodarone, but not reevaluated until more than 3 years later when he presented with apparent pancreatitis and massive ascites. Progressive liver failure was diagnosed. Over the next two months, he had persistent epigastric pain, nausea, vomiting and elevated serum amylase and lipase. Symptoms persisted for seven weeks after amiodarone was discontinued until his death of liver failure. Amiodarone is distributed widely and stored in fat, liver, lung and pancreas, which may account for persistence of symptoms after drug administration was stopped.

Diazoxide. A single case of pancreatitis has been reported by letter in a patient with renal failure and malignant hypertension [57]. Pancreatitis occurred four months after diazoxide was begun and resolved quickly after cessation. No rechallenge was performed and no further details were given regarding other risk factors for pancreatitis.

Enalapril and lisinopril. Enalapril was first reported to be associated with pancreatitis by letter[58]. In this case, symptoms developed shortly after the first dose and worsened 30 minutes after the second dose to the point that the patient was admitted to the hospital where pancreatitis was diagnosed. His illness resolved and rechallenge was not performed. The authors obtained information from the spontaneous reporting system of the FDA that about 20 other cases of enalapril-associated pancreatitis had been informally reported. Several other cases have now been reported in the literature [59,60]. In one case, symptoms developed within minutes of the first dose [59], while pancreatitis occurred after a month of enalapril in another case [60]. Rechallenge was not performed. The authors obtained information from the manufacturers that about 50 cases of enalapril-associated pancreatitis had been reported to them. In 1991, the first case of lisinopril-associated pancreatitis was reported by letter [61]. Similarly, the authors obtained reports from the manufacturers of 20 cases being reported to them of lisinopril-associated pancreatitis and an additional 15-30 reports of captopril-associated pancreatitis. Although some of the cases reported to the manufacturers probably would not withstand rigorous examination, the number of cases suggests that ACE inhibitors do cause pancreatitis. Several more cases of lisinopril-associated pancreatitis have now been reported in the literature [62,63]. The manufacturers of captopril, lisinopril and enalapril now list pancreatitis as a rare complication in package insert information.

Methyldopa. Two cases of methyldopa-associated pancreatitis have been reported by letter [64]. Both patients developed recurrent pancreatitis on rechallenge. One case is less clearcut because the patient was taking ampicillin and furosemide and had gallstones in the gallbladder.

Metolazone. Metolazone is a thiazide-like diuretic which has been reported to cause pancreatitis in two cases [65,66]. In the second case [66], the patient presented with hypercalcemia and pancreatitis. She recovered rapidly and serum calcium levels returned to normal after discontinuation of the drug. Rechallenge was not performed.

Procainamide. Procainamide-associated pancreatitis has been reported by letter in a patient who developed a high titer ANA and a positive LE cell preparation seven months after beginning procainamide [67]. Pancreatitis and the abnormal laboratory studies resolved after procainamide was discontinued. The patient restarted procainamide himself for palpitations, and returned again with pancreatitis and a high titer ANA and a positive LE cell preparation. Again, after stopping procainamide he made a rapid and complete recovery.

GI DRUGS

In addition to the drugs listed in Table 13 below, gastroenterologists often use antibiotics and immunosuppressive drugs, discussed elsewhere.

Table 13. GI drugs associated with pancreatitis.

Definite	Probable	Possible
Sulfasalazine 5-ASA	ERCP contrast	Diphenoxylate Cimetidine, Ranitidine Octreotide Phenolphthalein

Definite association with pancreatitis.

Sulfasalazine and 5-ASA. Sulfasalazine is an old drug synthesized in the 1930's for treatment of rheumatoid arthritis, with the idea of combining an antibiotic and a salicylate. Its major use today is for treatment of inflammatory bowel disease, particularly Crohn's colitis or ulcerative colitis. The drug has unusual pharmacokinetics; after bacterial cleavage, usually in the large intestine, into sulfapyridine and 5-ASA. Sulfapyridine is rapidly and almost completely absorbed but only about 25% of 5-ASA is absorbed from the colon. It was eventually learned that 5-ASA is the portion of the drug that is effective for inflammatory disease, while the sulfa moiety is responsible for most of the adverse reactions. If 5-ASA alone is given by mouth, it is rapidly absorbed and metabolized, thus sulfapyridine was serving as a carrier to deliver 5-ASA to the colon. 5-ASA is now available as mesalamine in the U.S., formulated as enteric-coated capsules or in a sustained-release preparation. Sulfasalazine is actually a rare cause of pancreatitis, with only a few cases reported in the literature in the 60 years since its introduction [68-70]. Pancreatitis did recur with rechallenge. In one case, the mechanism appeared to be an immune-mediated reaction [70]; the patient developed rash, fever and vomiting 2 weeks after starting sulfasalazine. This patient had massive hepatic necrosis in addition to pancreatitis and did not survive. Thus the sulfapyrazine portion of the drug seemed the likely cause of the pancreatitis. It now appears that 5-ASA may be a more significant cause of pancreatitis than sulfasalazine. After the introduction of 5-ASA alone, at least 7 cases of 5-ASA-associated pancreatitis have been reported [71-73]. Fever and rash did not occur in these cases and the pancreatitis appeared to be fairly mild. Two patients were rechallenged and had a recurrence of pancreatitis. Higher plasma levels of 5-ASA and its metabolites are achieved with oral 5-ASA than with sulfasalazine. 5-ASA enemas and sulfasalazine produce similar plasma 5-ASA and metabolite levels. In one interesting case, a patient who developed sulfasalazine-related pancreatitis had a recurrence after rectal 5-ASA administration [72].

Table 14. Sulfasalazine and 5-ASA-associated pancreatitis.

- Both have been reported to cause pancreatitis
- In sulfasalazine-related pancreatitis, rechallenge with 5-ASA resulted in recurrence
- Both oral and enema forms of 5-ASA have been associated with pancreatitis

Probable association with pancreatitis.

ERCP contrast medium. ERCP is frequently associated with asymptomatic elevations in serum amylase. Clinical pancreatitis occurs in 1-5% of cases. Injury and edema of the papilla of Vater is one major cause of pancreatitis; the other causes are related to features relating to the contrast medium used. The volume of contrast medium injected is more important than the total amount used, since the total amount increases with difficulty in cannulation with spillage into the duodenal lumen. The risk of ERCP-associated pancreatitis is decreased by using a low-osmolality contrast medium [74]. The effects of the somatostatin analog octreotide on ERCP-associated pancreatitis are discussed later.

Table 15. Possible predictors of pancreatitis related to ERCP.

- Increasing number of pancreatic duct cannulations
- Necessity for sphincterotomy
- Increasing osmolality of contrast
- Pancreatic acinarization by contrast medium

Possible association with pancreatitis.

Cimetidine, Ranitidine. There are three cases of cimetidine-associated pancreatitis and one case of ranitidine-associated pancreatitis in the literature. The first two cases were reported in a letter [75]; two patients each developed pancreatitis a few weeks after beginning cimetidine therapy at 1000 mg/day. Rechallenge in both cases reproduced pancreatitis. A second more extensive report [76] described a patient on 800 mg/day of cimetidine who was hospitalized with generalized abdominal pain and hyperamylasemia. Over four weeks, the patient's symptoms continued but resolved rapidly after cimetidine was discontinued. Ranitidine has been reported to cause recurrent pancreatitis only once [77].

Diphenoxylate. Diphenoxylate is an antimotility agent for diarrhea now available without prescription. There is a single report made by letter linking diphenoxylate to pancreatitis [78]. This

patient developed pancreatitis on two separate occasions after taking diphenoxylate. She had previously had a cholecystectomy for gallstones. Perioperative cholangiography showed no stones but slight narrowing of the distal common bile duct. This was noted again on a transhepatic cholangiogram performed after third episode of pancreatitis which was not precipitated by diphenoxylate.

Octreotide. Octreotide is a long-acting analog of somatostatin which inhibits the release and/or actions of multiple hormones. FDA-approved indications include symptoms due to malignant carcinoid and VIP-secreting tumors. Octreotide has been suggested as a treatment for acute pancreatitis, but benefit has not been shown. Long-term octreotide is associated with a risk of gallstone formation, and at least one case of gallstone pancreatitis after a year of octreotide administration for acromegaly has been reported [79]. There is a single report of octreotide-associated pancreatitis in a patient treated acutely for AIDS-related diarrhea [80]. On the third day, the patient developed pancreatitis, which gradually resolved after octreotide was discontinued. He was not taking any other medications associated with pancreatitis, and the gallbladder was normal on ultrasound examination. The patient was not rechallenged, and since AIDS itself can cause pancreatitis, the association here is not convincing without corroboration by other cases. Octreotide has been suggested as an adjunct therapy prior to and after ERCP to decrease the risk of ERCP-associated pancreatitis. Two earlier studies [81,82] gave equivocal results, so a well-designed, randomized, controlled trial was carried out of octreotide intravenously prior to ERCP followed by subcutaneous injections postprocedure [83]. The investigators planned to randomize 220 patients each to the placebo and octreotide groups. The study was stopped after and interim analysis showed an increased incidence of pancreatitis in the octreotide-treated group. Although more common, pancreatitis was clinically less severe in this group and enzyme elevations were lower compared to placebo-treated patients developing pancreatitis.

Table 16. The effect of prophylactic octreotide on ERCP-related pancreatitis.

Study design: 84 ERCP patients randomized to placebo vs. octreotide (Sternlieb, 1992)

Results:
- Clinical pancreatitis - placebo 11%, octreotide 35%
- Pancreatitis milder in octreotide group
- Incidence of pancreatitis decreased with sphincterotomy

Phenolphthalein. Phenolphthalein is a common agent available without prescription for constipation. There is a single case of pancreatitis associated with excessive use of phenolphthalein [84].

IMMUNOSUPPRESSIVE DRUGS

As with most other drugs, pancreatitis is rarely associated with use of immunosuppressive drugs, however, a few of these drugs, L-asparaginase, azathioprine and 6-mercaptopurine, cause pancreatitis more frequently. A list of immunosuppressive drugs associated with pancreatitis is shown in Table 17.

Table 17. Immunosuppressive drugs associated with pancreatitis.

Definite	Probable	Possible
L-Asparaginase	Corticosteroids	Cisplatin
Azathioprine		Cyclosporine
6-Mercaptopurine		Cytarabine

Definite association with pancreatitis.

L-Asparaginase. L-asparaginase has been known for more than 20 years to be associated with pancreatitis [85,86], occurring in 8-18% of patients with a mortality reported to range from 1.8-4.6% [87]. Its major use is in lymphoproliferative disorders in children. Although rechallenge has not been performed for ethical reasons, it is generally accepted as a definite cause of pancreatitis due to its frequency and the fact that the patients receiving it have few if any other risk factors. Asparaginase is an enzyme which interferes with protein synthesis. It acts fairly selectively to deplete the essential amino acid L-asparagine in tumor cells which cannot manufacture this amino acid. However, side effects may result from damage to cells which are actively engaged in protein synthesis, such as pancreatic acinar cells.

Azathioprine and 6-Mercaptopurine. Azathioprine is a potent immunosuppressive agent used extensively for organ transplant patients and a variety of inflammatory diseases such as Crohn's disease. Initial reports of azathioprine-associated pancreatitis were made in renal transplant patients [88,89]. The etiologic role of azathioprine in causing pancreatitis was controversial, since most patients taking azathioprine are also taking corticosteroids. At the present time, the evidence that azothiaprine causes pancreatitis is stronger than the evidence for corticosteroids, although it is possible that the two drugs may have some synergistic effect. Azathioprine was first reported to be associated with pancreatitis in a patient with Crohn's disease in 1972 [90]. The patient was a 57-year-old woman who developed acute pancreatitis 3 weeks after azothiaprine was added to her medications which included prednisone (taken for several years). The prednisone was continued while azathioprine was stopped, resulting in resolution of her pancreatitis. Pancreatitis recurred on rechallenge with a small dose of azathioprine. Azathioprine-induced pancreatitis was subsequently described in several patients treated with azathioprine alone [91]. Documented pancreatitis developed in 5 of 113 (4.4%) of patients treated with azothiaprine but not prednisone in the National Cooperative Crohn's Disease

Study [92]. No pancreatitis was reported in the 132 patients taking sulfasalazine alone, the 146 patients taking prednisone alone, or the 178 patients taking placebo. 6-Mercaptopurine, a metabolite of azothiaprine, was then tried in a number of patients with inflammatory bowel disease, hoping that it would prove equally effective but safer. In 1986, a very large series of patients with inflammatory bowel disease treated with 6-MP was reviewed retrospectively [93]. In this series, 13 of 400 (3.25%) of patients developed pancreatitis. Seven of 13 patients were concomitantly receiving corticosteroids and 9 of 13 were receiving sulfasalazine. Twelve of 13 cases of pancreatitis occurred within 32 days of starting therapy, usually from 8-32 days. Rechallenge was performed in 7 of 13 patients with recurrence of pancreatitis in all patients within 2 weeks, usually within 1-2 days. The etiology of azothiaprine- and 6-MP-induced pancreatitis is felt to be hypersensitivity.

Table 18. Azathioprine and 6-MP-associated pancreatitis.

- Usually mild
- Usually occurs within weeks of starting therapy
- Almost always recurs with rechallenge
- Incidence in treatment of Crohn's disease is 3-4%

Probable association with pancreatitis.

Corticosteroids. By 1980, 40 cases of corticosteroid-associated pancreatitis had been reported in the literature [1]. This association has been controversial. In 1981, Steinberg and Lewis published a detailed analysis of 36 of these cases [94], rejecting them as supportive evidence for steroid-induced pancreatitis for a variety of reasons (on other medications linked to acute pancreatitis, having other significant risk factors, or not having adequately excluded other significant risk factors.) One of the major pieces of evidence lacking was a case of recurrent pancreatitis on rechallenge. More recently, a case of dexamethasone-associated pancreatitis has been reported documenting recurrence of pancreatitis on two separate rechallenges [95]. This patient, a 50-year-old man, was receiving dexamethasone for Hodgkin's lymphoma for clinical signs of spinal cord compression. The patient developed pancreatitis after 5 days of dexamethasone therapy, which was then discontinued, because his physicians decided his symptoms were due to compression fracture due to lytic lesions eventually diagnosed as fibrohistiosarcoma. Dexamethasone was restarted on two separate occasions for clearcut evidence of spinal cord compression. On each occasion, clinical and laboratory signs of pancreatitis recurred. Biliary disease was eliminated by radiographic studies. Although the patient was on multiple other medications, the temporal association between dexamethasone and pancreatitis was striking.

Cisplatin. There are only two cases linking cisplatin to pancreatitis in the literature [96,97]. The more detailed and convincing report describes a 9-year-old boy who developed pancreatitis on the third of three monthly cycles of cisplatin/adriamycin [97] for metastatic osteosarcoma. CT

and ultrasound examinations of the biliary tract were normal, and no other risk factors were present. Adriamycin has not been implicated in pancreatitis, but cisplatin has been reported to cause asymptomatic hyperamylasemia. Rechallenge with cisplatin was not performed.

Cyclosporine. Cyclosporine has been reported to cause asymptomatic hyperamylasemia and hyperlipasemia in renal transplant patients [98]. All of these patients had abnormal creatinine clearances (range, 11-65 ml/min) and were receiving low dose prednisone. Serum amylase is known to be elevated in some patients with decreased renal clearance. In another report [99], 105 patients treated for renal transplant with cyclosporine and prednisolone were prospectively observed for pancreatitis or hyperamylasemia. Results were compared to historical controls of 180 renal transplant patients treated with azathioprine and cyclosporine. Pancreatitis occurred in 0.5% of azathioprine-treated patients and in 3.8% of cyclosporine-treated patients. The two cyclosporine-treated patients who had high trough levels of cyclosporine died of complications of pancreatitis. The other two patients improved with either a change to azathioprine or a reduction in cyclosporine dose. Asymptomatic hyperamylasemia occurred in 16.2% of patients; no changes in creatinine clearance occurred associated with this hyperamylasemia.

Cytarabine. Cytarabine has been reported to be associated with pancreatitis in a number of patients receiving the drug within a few weeks or months after therapy with L-asparaginase [86,100]. The authors raised the possibility that subclinical pancreatic damage by cytarabine might predispose to pancreatitis with subsequent exposure to asparaginase. Subsequently, 2 of 30 patients receiving high dose cytarabine without previous exposure to L-asparaginase were reported [101]. Biliary disease was excluded by ultrasound in both patients, but rechallenge was not performed.

NEUROPSYCHIATRIC DRUGS

The neuropsychiatric drugs associated with pancreatitis are shown in Table 19.

Table 19. Neuropsychiatric drugs associated with pancreatitis.

Definite	**Possible**
Valproic acid	Carbamazepine Clozapine Ergotamine

Definite association with pancreatitis.

Valproic acid. At least 25 cases of valproic acid-associated pancreatitis had been reported in the literature by 1990 [102-106], including cases of concomitant liver failure [86]. Recurrence with rechallenge has been reported multiple times. Recently, Asconape reported on the clinical

features of valproic acid-associated pancreatitis in 39 cases [107]. A total of 39 cases were gathered from the literature, from the authors' practices and from a survey of physicians interested in the treatment of epilepsy. It is of interest that 53 of 366 of these physicians (14.5%) reported having seen a case of valproic acid-associated pancreatitis; none of these 53 cases had been reported previously. Of these 53 cases, only 12 were included in the review after completed case reports were returned. These findings are summarized in Table 20.

Table 20. Valproic acid-associated pancreatitis.

Study design: Review of 39 cases of valproic acid-associated pancreatitis (Asconape, 1993).

Results:
- 43% of cases occurred within 3 months of therapy
- 69% of cases occurred within 1 year of therapy
- 76% of cases were receiving multiple drugs
- 8% of cases were fatal
- Rechallenge commonly resulted in recurrence

Possible association with pancreatitis

Carbamazepine. Carbamazepine is a drug related to the tricyclic antidepressants, particularly amitriptyline; it is used for seizure disorders. There is one published case of carbamazepine-induced pancreatitis [108] and another case of elevated serum amylase and lipase related to carbamazepine [109]. In the first case [108], a 73-year-old woman developed nausea, anorexia, malaise and headache 4 weeks after beginning carbamazepine. Symptoms continued over the next six weeks until carbamazepine was discontinued after an elevated serum amylase was found. Evaluation including CT visualization of the biliary tree did not reveal other risk factors for pancreatitis. The authors report that a telephone call to the manufacturer revealed three other possible cases of carbamazepine-induced pancreatitis, not clearly documented. In the second case, a 5-year-old boy took an accidental overdose of an unknown amount of carbamazepine which had been discontinued five months before. He had elevated serum amylase and lipase levels, but no significant symptoms of pancreatitis. An abdominal ultrasound was normal. No rechallenge was performed.

Clozapine. Clozapine is a relatively new antipsychotic agent most often used when patients are unresponsive to or intolerant of other neuroleptic agents. There are two cases reported in letters of acute pancreatitis associated with clozapine [110,111]. In the first case [110], pancreatitis occurred after 12 days of clozapine. Evaluation including abdominal ultrasound and CT scan showed pancreatitis but a normal biliary tree. No rechallenge was performed. In the second case [111], pancreatitis occurred on a combination of clozapine and valproic acid. Pancreatitis continued after valproic acid was stopped but resolved several days after clozapine was stopped. Rechallenge with clozapine alone resulted in a recurrence of abdominal pain, but pancreatitis was not documented with laboratory or imaging studies.

Ergotamine. There is a single case of probable ischemic pancreatitis related to a suicidal overdose of ergotamine [112]. The patient presented comatose with cold, pulseless extremities. He was intubated and treated with sodium nitroprusside. He developed marked elevations of liver enzymes consistent with ischemia as well as large increases in serum amylase and lipase. Abdominal CT scan showed necrosis of the pancreatic tail. All laboratory studies returned to normal after 14 days.

RHEUMATOLOGY DRUGS

The drugs used for rheumatologic conditions that are associated with pancreatitis are listed in Table 21.

Table 21. Rheumatology drugs associated with pancreatitis.

Definite	Probable	Possible
Sulindac	Salicylates	Acetaminophen Colchicine Gold Ketoprofen Mefenamic acid Oxyphenbutazone Peroxicam

Definite association with pancreatitis.

Sulindac. Sulindac is the nonsteroidal antiinflammatory agent (NSAID) most clearly associated with pancreatitis. A letter reporting a possible case of sulindac-associated pancreatitis was first published in 1980 [113]. Another report by letter soon appeared reporting a case of sulindac-associated pancreatitis that recurred twice with rechallenge [114]. She had taken a thiazide diuretic and conjugated estrogens for many years. Evaluation for other causes was not performed. Other cases, also including rechallenge, have now been reported [115-118]. Pancreatitis usually occurs within a few weeks or months of starting therapy, but in one case, onset occurred five years after taking sulindac [117]. In one case [116], the patient developed fatal toxic hepatitis and toxic epidermal necrolysis syndrome associated with pancreatitis. Two cases of sulindac-induced pancreatitis have been reported in which symptoms were suggestive of gallstone pancreatitis and hyperbilirubinemia developed [118]. One case recurred after inadvertent rechallenge with identical signs and symptoms. The authors hypothesize that injury to bile duct canniculi as well as papillary edema could cause the hyperbilirubinemia.

Probable association with pancreatitis.

Salicylates. The only salicylate reported to cause pancreatitis is 5-ASA, reviewed under GI drugs.

Possible association with pancreatitis.

Acetaminophen. Pancreatitis associated with acetaminophen has been reported only rarely, and always in the context of an acetaminophen overdose [119,120]. Since acetaminophen overdoses are exceedingly common, acetaminophen must be generally quite safe for the pancreas.

Colchicine. There is one case of pancreatitis associated with a colchicine overdose [121]; rechallenge was not performed.

Gold. Two cases of gold-related pancreatitis have been reported by letter [122]. Both cases were women who had received gold orally or intramuscularly for about 5 weeks. The biliary system was normal by ERCP in the first case except for slight extrinsic compression of the distal common bile duct consistent with mild enlargement of the pancreatic head. Ultrasound showed no stones or biliary ductal dilatation in the second case. CT scan showed diffuse pancreatic enlargement in both cases. Both patients developed fever and eosinophilia peaking at 25% and 19% respectively, implicating an allergic mechanism as causing the pancreatitis. Rechallenge was not performed.

Other NSAIDS. With the exception of sulindac, discussed previously, NSAID-induced pancreatitis must be quite rare since the number of patients using these drugs is enormous. Indomethacin [47], mefenamic acid [123], and oxyphenbutazone [124] and ketoprofen [125] have each been reported once to be associated with pancreatitis. None of these cases included rechallenge. Pancreatitis occurred days to weeks after therapy began. Piroxicam has also been reported once in the literature to have probably induced pancreatitis [126]. This patient, a woman also being treated with prednisone for an unspecified type of arthritis, was rechallenged with return of symptoms but laboratory studies were not performed in conjunction with symptoms. Of interest, by 1986, 10 cases of piroxicam-associated pancreatitis had been reported to the manufacturer [126]. Details of these cases were not given, but all patients had other risk factors for pancreatitis, although some of the risk factors given were use of drugs with fairly tenuous links to pancreatitis (cimetidine, acetaminophen, propoxyphene). A report of a postmarketing surveillance program performed in the United Kingdom revealed only one case of piroxicam-associated pancreatitis in 17,676 patients receiving piroxicam [127]; this case was a patient who developed pancreatitis secondary to a piroxicam-associated gastric ulcer, which does not qualify as drug-induced pancreatitis.

MISCELLANEOUS DRUGS

A few other drugs have been reported to be associated with pancreatitis (Table 2).

Table 22. Miscellaneous drugs associated with pancreatitis.

Definite	Possible
Estrogen	Isotretinoin Tryptophan

Definite association with pancreatitis.

Estrogen. Use of estrogens alone or in combination with progestins is associated with acute pancreatitis, first reported in 1970 [128]. The patients are women who may be any age but are often young, without other obvious risk factors. The onset of pancreatitis is quite variable, occurring from 2 to 78 weeks after initiation of estrogen therapy [129]. Clearly most cases are due to estrogen-induced hyperlipidemia, a well recognized cause of pancreatitis. Occasionally pancreatitis occurs in a patient on estrogens without documented hyperlipidemia. In one such case, widespread vascular thrombosis presumably related to estrogen use was found at autopsy [130].

Possible association with pancreatitis.

Isotretinoin. Isotretinoin is a retinoid derivative used widely for the treatment of cystic acne as well as some other skin conditions. There are two reported cases of isotretinoin-associated pancreatitis reported in the literature; in both cases the patients had isotretinoin-induced hyperlipidemia [131,132]. In the first case, the patient was also taking estrogen, making it difficult to be sure isotretinoin was definitely involved [131]. In the second case, a 30 year old woman developed pancreatitis 6 weeks after beginning isotretinoin [132]. She had marked hyperlipidemia which gradually resolved over 3 months after stopping isotretinoin. Lipoprotein electrophoresis showed type IV hyperlipidemia. Extensive evaluation for biliary disease including ERCP was unremarkable. This patient had a history of transient hypertriglyceridemia during pregnancy.

Phenformin. At least 6 cases of phenformin-associated pancreatitis have been reported in the literature [133]. Five of the six patients had lactic acidosis complicating their illness. Phenformin is known to occasionally cause lactic acidosis without obvious associated illness. Probably because other effective treatment of diabetes mellitus exist, none of these patients were rechallenged with phenformin.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

by health professionals of adverse events and product problems

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Triage unit sequence #

Page ___ of ___

A. Patient Information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ___ lbs or ___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ___ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ___
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 #2
2. Dose, frequency & route used #1 #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 ☐ yes ☐ no ☐ doesn't apply #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 ☐ yes ☐ no ☐ doesn't apply #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ___
5. Expiration date (mo/day/yr)
6. model # ___ catalog # ___ serial # ___ lot # ___ other # ___
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) ☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Also reported to
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

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Report experiences with:

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- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

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- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

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- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 for more information or to report quality problems
- 1-800-822-7967 for a VAERS form for vaccines

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REFERENCES

1. Mallory A, Kern F Jr. Drug-induced pancreatitis: a critical review. Gastroenterology 1980; 78:813-820.
2. Clas D, Falutz J, Rosenberg L. Acute pancreatitis associated with HIV infection. Can Med Assoc J 1989; 140:823.
3. Schwartz MS, Brandt LJ. The spectrum of pancreatic disorders in patients with the acquired immune deficiency syndrome. Am J Gastroenterol 1989; 84:459-462.
4. Grunfeld C, Kotler DP, Hamadeh R, Teirney A, Wang J, Person RN Jr. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1989; 86:27-31.
5. Dolin R, Lambert JS, Morse GD, et al. 2',3'-Dideoxyinosine in patients with AIDS or AIDS-related complex. Rev Infect Dis 1990; 12(Suppl 5):S570-575.
6. Yarchoan R, Mitsuya H, Pluda JM, et al. The National Cancer Institute phase I study of 2',3'-dideoxyinosine administration in adults with AIDS or AIDS-related complex: analysis of activity and toxicity profiles. Rev Infect Dis 1990; 12(Suppl 5):S522-533.
7. Rozencweig M, McLaren C, Beltangady M, et al. Overview of phase I trials of 2',3'-dideoxyinosine (ddI) conducted on adult patients. Rev Infect Dis 1990; 12(Suppl 5):S570-S575.
8. Maxson CJ, Greenfield SM, Turner JL. Acute pancreatitis as a common complication of 2',3'-dideoxyinosine therapy in the acquired immunodeficiency syndrome. Am J Gastroenterol 1992; 87:708-713.
9. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. N Engl J Med 1991; 324:137-144.
10. Ivady G, Paldy L. A new form of treatment of interstitial plasma-cell pneumonia in premature infants with pentavalent antimony and aromatic diamidines. Monatsschr Kinderheilkd 1958; 106:10-14.
11. Hughes WT, Kuhn S, Chaudhary S, et al . Successful chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1977; 297:1419-1426.
12. Walzer PD, Perl DP, Krogstad DJ, et al . Pneumocystis carinii pneumonia in the United States: Epidemiologic, diagnostic and clinical features. Ann Intern Med 1974; 80:83-93.
13. Murphey SA, Josephs AS. Acute pancreatitis associated with pentamidine therapy. Arch Intern Med 1981; 141:56-58.
14. Salmeron S, Petitpretz P, Katlama C. Pentamidine and pancreatitis. Ann Intern Med 1986; 105:140-141.
15. Zuger A, Wolf BZ, El-Sadr W, Simberkoff MS, Rahal JJ. Pentamidine-associated fatal acute pancreatitis. JAMA 1986; 256:2383-2385.
16. Schwartz MS, Cappell MS. Pentamidine-associated pancreatitis. Dig Dis Sci 1989; 34:1617-1620.
17. Pauwels A, Eliaszewicz M, Larrey D, et al. Pentamidine-induced acute pancreatitis in a patient with AIDS. J Clin Gastroenterol 1990; 12:457-459.
18. Donnelly J, Bernard EM, Rothkotter H, Gold JWM. Distribution of pentamidine in patients with AIDS. J Infect Dis 1988; 157:985-989.

19. Murphy RL, Noskin GA, Ehrenpreis ED. Acute pancreatitis associated with aerosolized pentamidine. Am J Med 1990; 88:53N-56N.
20. Klatt EC. Pathology of pentamidine-induced pancreatitis. Arch Pathol Lab Med 1992; 116:162-164.
21. Underwood TW, Frye C. Drug-induced pancreatitis. Clin Pharm 1993; 12:440-448.
22. Halim MA, Alfurayh O, Kalin ME, Dammas S, Al-Eisa A, Damanhouri G. Successful treatment of visceral Leishmaniasis with allopurinol plus ketoconazole in a renal transplant recipient after the occurrence of pancreatitis due to stibogluconate. Clin Infect Dis 1993; 16:397-399.
23. Gasser RA, Magill AJ, Oster CN, Franke ED, Grogl M, Berman JD. Pancreatitis induced by pentavalent antimonial agents during treatment of Leishmaniasis. Clin Infect Dis 1994; 18:83-90.
24. Barrett PVD, Thier SO. Meningitis and pancreatitis associated with sulfamethizole. N Engl J Med 1963; 268:36-37.
25. Antonow DR. Acute pancreatitis associated with trimethoprim-sulfamethoxazole. Ann Intern Med 1986; 104:363-365.
26. 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; 84:1577-1579.
27. Bartels RHMA, Van der Spek JAN, Oosten HR. Acute pancreatitis due to sulfamethoxazole-trimethoprim. South Med J 1992; 85:1006-1007.
28. Ober WB, LeCompte PM. Acute fatty metamorphosis of the liver associated with pregnancy. Am J Med 1955; 19:743-758.
29. Schultz JC, Adamson JSJr, Workman WW, Norman TD. Fatal liver disease after intravenous administration of tetracycline in high dosage. N Engl J Med 1963; 269:999-1004.
30. Kunelis CT, Peters JL, Edmondson HA. Fatty liver of pregnancy and its relationship to tetracycline therapy. Am J Med 1965; 38:359-377.
31. Peters RL, Edmondson HA, Mikkelsen WP, et al . Tetracycline induced fatty liver in nonpregnant patients. Am J Surg 1967; 113:622-632.
32. Elmore MF, Rogge JD. Tetracycline-induced pancreatitis. Gastroenterology 1981; 81:1134-1136.
33. Torosis J, Vender R. Tetracycline-induced pancreatitis. J Clin Gastroenterol 1987; 9:580-581.
34. Nicolau DP, Mengedoht DE, Kline JJ. Tetracycline-induced pancreatitis. Gastroenterology 1981; 81:1134-1136.
35. Jordan SC, Ament ME. Pancreatitis in children and adolescents. J Pediatr 1977; 91:211-216.
36. Sanford KA, Mayle JE, Dean HA, Greenbaum DS. Metronidazole-associated pancreatitis. Ann Intern Med 1988; 109:756-757.
37. Celifarco A, Warschauer C, Burakoff R. Metronidazole-induced pancreatitis. Am J Gastroenterol 1989; 84:958-960.
38. Plotnick BH, Cohen I, Tsang T, Cullinane T. Metronidazole-induced pancreatitis. Ann Intern Med 1985; 103:891-892.

39. Friedman GD, Selby JV. How often does metronidazole induce pancreatitis? Gastroenterology 1990; 98:1702-1703.
40. Hanline MH. Acute pancreatitis caused by ampicillin. South Med J 1987; 80:1069.
41. Hawksworth CRE. Acute pancreatitis associated with infusion of erythromycin lactobionate. Brit Med J 1989; 298:190 (Letter).
42. Berger TM, Cook WJ, O'Marcaigh AS, et al . Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. Pediatrics 1992; 90:624-626.
43. Gumaste VV. Erythromycin-induced pancreatitis. Am J Med 1989; 86:725.
44. Souweine B, Fialip J, Ruivard M. Acute pancreatitis associated with roxithromycin therapy. DICP Ann Pharmacother 1991; 25:1137.
45. Nelis GF. Nitrofurantoin-induced pancreatitis: report of a case. Gastroenterology 1983; 84:1032-1034.
46. Scharer L, Smith JP. Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 1969; 71:1113-1120.
47. Guerra M. Toxicity of indomethacin. Report of a case of acute pancreatitis. JAMA 1967; 200:222-223.
48. Rabassa AA, Trey G, Shukla U, Samo T, Anand BS. Isoniazid-induced acute pancreatitis. Ann Intern Med 1994; 121:433-434.
49. Maxson K. Side effects of rifampicin: a clinical study. Scand J Respir Dis (Suppl) 1973; 82:8-52.
50. Jones PE, Oelbaum MH. Frusemide-induced pancreatitis. Brit Med J 1975; 1:133-134.
51. Strunge P. Frusemide-induced pancreatitis? Brit Med J 1975; 3:434(Letter).
52. Call T, Malarkey WB, Thomas FB. Acute pancreatitis secondary to furosemide with associated hyperlipidemia. Dig Dis Sci 1977; 22:835-838.
53. Stenvinkel P, Alvestrand A. Loop diuretic-induced pancreatitis with rechallenge in a patient with malignant hypertension and renal insufficiency. Acta Med Scand 1988; 224:89-91.
54. Eckhauser ML, Dokler MA, Imbembo AL. Diuretic-associated pancreatitis: a collective review and illustrative cases. Am J Gastroenterol 1987; 82:865-870.
55. Schmidt P, Friedman IS. Adverse effects of ethacrynic acid. N Y State J Med 1967; 67:1438-1442.
56. Sastri SV, Diaz-Arias AA, Marshall JB. Can pancreatitis be associated with amiodarone hepatotoxicity? J Clin Gastroenterol 1990; 12:70-77.
57. De Broe M, Mussche M, Ringoir S, Bosteels V. Oral diazoxide for malignant hypertension. Lancet 1972; 1:1397 (Letter).
58. Tilkemeier P, Thompson PD. Acute pancreatitis possibly related to enalapril. New England Journal of Medicine 1988; 318:1275-1276 (Letter).
59. Pedro-Botet J, Miralles R, Coll J, et al . Captopril versus enalapril: cough versus pancreatitis. DICP Ann Pharmacother 1990; 24:438-439 (Letter).
60. Roush MK, McNutt RA, Gray TF. The adverse effect dilemma: quest for accessible information. Ann Intern Med 1991; 114:298-299.
61. Dabaghi S. ACE inhibitors and pancreatitis. Ann Intern Med 1991; 115:330-331 (Letter).
62. Maliekal J, Drake CF. Acute pancreatitis associated with the use of lisinopril. Ann Pharmacother 1993; 27:1465-1466.

63. Standridge JB. Fulminant pancreatitis associated with lisinopril therapy. South Med J 1994; 87:179-181.
64. Van der Heide H, Ten Haaft MA, Strickler BH. Pancreatitis caused by methyldopa. Brit Med J 1981; 282:1930-1931.
65. Fuchs JE, Keith MR, Galanos AN. Probable metolazone-induced pancreatitis. DICP Ann Pharmacother 1989; 23:711 (Letter).
66. Anderson PE, Ellis GG, Austin SM. Metolazone-associated hypercalcemia and acute pancreatitis. Am J Med Sci 1991; 302:235-237.
67. Falko JM, Thomas FB. Acute pancreatitis due to procainamide-induced lupus erythematosus. Ann Intern Med 1975; 83:832-833.
68. Block MB, Genant HK, Kirsner JB. Pancreatitis as an adverse reaction to salicylazosulfapyridine. N Engl J Med 1970; 282:380-82.
69. Faintuch J, Mott CB, Machado MCC. Pancreatitis and pancreatic necrosis during sulfasalazine therapy. Int Surg 1985; 70:271-272.
70. Rubin R. Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. Am J Gastroenterol 1994; 89:789-791.
71. Fiorentini MT, Fracchia M, Galatola G. Acute pancreatitis during oral 5-aminosalicylic acid therapy. Dig Dis Sci 1990; 35:1180-1182.
72. Isaacs KL, Murphy D. Pancreatitis after rectal administration of 5-aminosalicylic. J Clin Gastroenterol 1990; 12:198-199.
73. Sachedina B, Saibil F, Cohen LB, Whittey J. Acute pancreatitis due to 5-aminosalicylate. Ann Intern Med 1989; 110:490-492.
74. Cunliffe WJ, Cobden I, Lavelle MI, Lendrum R, Tait NP, Venables CW. A randomized prospective study comparing two contrast media in ERCP. Endoscopy 1987; 19:201-202.
75. Wilkinson ML, O'Driscoll R, Kiernan TJ. Cimetidine and pancreatitis. Lancet 1981; 1:610-611 (Letter).
76. Nott DM, DeSousa BA. Suspected cimetidine-induced acute pancreatitis. Brit J Clin Pract 1989; 43:264-265.
77. Herrmann R, Shaw RG, Fone DJ. Ranitidine-associated recurrent acute pancreatitis. Aust NZ J Med 1990; 20:243-4.
78. McCormick PA, O'Donoghue D, Brennan N. Diphenoxylate and pancreatitis. Lancet 1985; 1:752 (Letter).
79. Sadoul JL, Benchimol D, Thyss A, Freychet P. Acute pancreatitis following octreotide withdrawal. Am J Med 1991; 90:763-764.
80. Gradon JD, Schulman RH, Chapnik EK, Sepkowitz DV. Octreotide-induced acute pancreatitis in a patient with acquired immunodeficiency syndrome. South Med J 1991; 84:1410-1411.
81. Bordas JM, Toledo V, Rodes MJ. Prevention of pancreatic reactions by bolus somatostatin administration in patients undergoing endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy. Hormone Res 1988; 29:106-108.
82. Deschner K, Kalloo A, Collen M, et al . Somatostatin: An evaluation of its utility as adjunctive medication for ERCP. Gastrointestinal Endosc 1989; 35:149.

83. Sternlieb JM, Aronchick CA, Retig JN, et al. A multicenter, randomized, controlled trial to evaluate the effect of prophylactic octreotide on ERCP-induced pancreatitis. Am J Gastroenterol 1992; 87:1561-1566.
84. Lambrianides AI, Rosin RD. Acute pancreatitis complicating excessive intake of phenolphthalein. Postgrad Med J 1984; 60:491-492.
85. Land VJ, Sutow WW, Fernvach DJ, Lane DM, Williams TE. Toxicity of L-asparaginase in children with advanced leukemia. Cancer 1972; 30:339-347.(abstract)
86. Weetman RM, Baehner RL. Latent onset of clinical pancreatitis in children receiving L-asparaginase therapy. Cancer 1974; 34:780-785.(abstract)
87. Nguyen DL, Wilson DA, Engelman ED. Serial sonograms to detect pancreatitis in children receiving l-asparaginase. South Med J 1987; 80:1133-1136.
88. Johnson WC, Nasbeth DC. Pancreatitis in renal tranplantation. Ann Surg 1970; 171:309-314.
89. Woods JE, Anderson CF, Frohnert PP, Petrie CR. Pancreatitis in renal allografted patients. Mayo Clin Proc 1972; 47:193-195.
90. Nogueira JR, Freedman MA. Acute pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology 1972; 62:1040-1041.
91. Kawanishi H, Rudolph E, Bull FE. Azathioprine-induced acute pancreatitis. N Engl J Med 1977; 289:357.
92. Sturdevant RAL, Singleton JW, Deren JJ, Law DH, McCleery JL. Azathioprine-related pancreatitis in patients with Crohn's disease. Gastroenterology 1979; 77:883-886.
93. Haber CJ, Meltzer SJ, Present DH, Korelitz BI. Nature and course of pancreatitis caused by 6-mercaptopurine in the treatment of inflammatory bowel disease. Gastroenterology 1986; 91:982-986.
94. Steinberg WM, Lewis JH. Steroid-induced pancreatitis: does it really exist? Gastroenterology 1981; 81:799-808.
95. Levine RA, McGuire RF. Corticosteroid-induced pancreatitis: a case report demonstrating recurrence with rechallenge. Am J Gastroenterol 1988; 83:1161-1164.
96. Calvo DB, Patt YZ, Wallace S, et al . Phase I-II trial of percutaneous intra-arterial cis-diammine dichloroplatinm (II) for regionally confined malignancy. Cancer 1980; 45:1278-1283.
97. Bunin N, Meyer WH, Christensen M. Pancreatitis following cisplatin: a case report. Cancer Treat Rep 1985; 69:236-237.
98. Prevost X, Myara I, Cosson C, Duboust A, Moatti N. Asymptomatic hyperamylasemia after cyclosporine therapy in patients with renal transplants. Transplant Proc 1988; 20:555-558.
99. Yoshimura N, Nakai I, Ohmori Y, et al. Effect of cyclosporine on the endocrine and exocrine pancreas in kidney transplant recipients. Am J Kidney Dis 1988; 12:11-17.
100. Altman AJ, Dinndorf P, Quinn JJ. Acute pancreatitis in association with cytosine arabinoside therapy. Cancer 1982; 49:1384-1386.
101. Siemers RF, Friedenberg WR, Norfleet RG. High-dose cytosine arabinoside-associated pancreatitis. Cancer 1985; 56:1940-1942.
102. Binek J, Hany A, Heer M. Valproic-acid-induced pancreatitis. J Clin Gastroenterol 1991; 13:690-693.

103. Parker PH, Helinek GL, Ghishan FK, Greene HL. Recurrent pancreatitis induced by valproic acid. Gastroenterology 1981; 80:826-828.
104. Wyllie E, Wyllie R, Cruse RP, et al . Pancreatitis associated with valproic acid therapy. Am J Dis Child 1984; 138:912-914.
105. Lott JA, Bond LW, Bobo RC, McClung HJ, Murray RD. Valproic acid-associated pancreatitis: report of three cases and a brief review. Clin Chem 1990; 36:395-397.
106. Ford DM, Portman RJ, Lum GM. Pancreatitis in children on chronic dialysis treated with valproic acid. Pediatr Nephrol 1990; 4:259-261.
107. Asconape JJ, Penry JK, Dreifuss FE, Riela A, Mirza W. Valproate-associated pancreatitis. Epilepsia 1993; 34:177-183.
108. Soman M, Swenson C. A possible case of carbamazepine-induced pancreatitis. Drug Intell Clin Pharm 1985; 19:925-927.
109. Tsao CY, Wright FS. Acute chemical pancreatitis associated with carbamazepine intoxication. Epilepsia 1993; 34:174-176.
110. Martin A. Acute pancreatitis associated with clozapine use. Am J Psychiatry 1992; 149:714 (Letter).
111. Frankenburg FR, Kando J. Eosinophilia, clozapine and pancreatitis. Lancet 1992; 340:251 (Letter).
112. Deviere J, Reuse C, Askenasi R. Ischemic pancreatitis and hepatitis secondary to ergotamine poisonining. J Clin Gastroenterol 1987; 9:350-352.
113. Goldstein L, Laskin DA, Ginsberg GH. Sulindac associated with pancreatitis. Ann Intern Med 1980; 93:151 (Letter).
114. Lilly E. Pancreatitis after administration of sulindac. JAMA 1981; 246:2680 (Letter).
115. Memon AN. Pancreatitis and sulindac. Ann Intern Med 1982; 97:139 (Letter).
116. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. J Rheumatol 1983; 10:512-513.
117. Zygmunt DJ, Williams JJ, Bienz SR. Acute pancreatitis associated with long-term sulindac therapy. West J Med 1986; 144:461-462.
118. Weaver GA, Bordley J, Guiney WB, D'Accurzio A. Chronic pancreatitis with cyst formation after prednisone and thiazide treatment. Am J Gastroenterol 1982; 77:164-168.
119. Caldarola V, Hasset JM, Hall AH. Hemorrhagic pancreatitis associated with acetaminophen overdose. Am J Gastroenterol 1986; 81:579-582.
120. Mofenson HC, Caraccio TR, Nawaz H. Acetaminophen induced pancreatitis. Clin Toxicol 1991; 29:223-230.
121. Freeman JS, Panebianco PS. Colchicine overdosage: report of a case. J Am Osteopath Assoc 1982; 82:252-254.
122. Eisemann AD, Becker NJ, Miner PB, Fleming J. Pancreatitis and gold treatment of rheumatoid arthritis. Ann Intern Med 1989; 111:860-861 (Letter).
123. Van Walraven AA, Edels M, Fong S. Pancreatitis caused by mefanamic acid. Can Med Assoc J 1982; 126:894 (Letter).
124. Bosch JA, Valdes M, Oristrell J, et al . Oxyphenbutazone-induced sialadenitis, intrahepatic cholestasis, and pancreatitis. Acta Gastroenterol Belg 1985; 48:529-530.
125. Cobb TK, Pierce JR. Acute pancreatitis associated with ketoprofen. South Med J 1992; 85:430-431.

126. Haye OL. Piroxicam and pancreatitis. Ann Intern Med 1986; 104:895 (Letter).
127. Jick H, Derby LE, Garcia Rodriguez LA, Jick SS, Dean AD. Nonsteroidal antiinflammatory drugs and certain rare, serious adverse events: a cohort study. Pharmacotherapy 1993; 13:212-217.
128. Bank S, Marks IN. Hyperlipaemic pancreatitis and the pill. Postgrad Med J 1970; 46:576-88.
129. Parker WA. Estrogen-induced pancreatitis. Clin Pharm 1983; 2:75-79.
130. Foster ME, Powell DEB. Pancreatitis, multiple infarcts and oral contraception. Postgrad Med J 1975; 51:667-669.
131. Flynn WJ, Freeman PG, Wickboldt LG. Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. Ann Intern Med 1987; 107:63.
132. McCarter TL, Chen YK. Marked hyperlipidemia and pancreatitis associated with isotretinoin therapy. Am J Gastroenterol 1992; 87:1855-1858.
133. Chase HS Jr, Mogan GR. Phenformin-associated pancreatitis. Ann Intern Med 1977; 87:314-315.