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ples, and Chonmaitree et al.⁵ found rhinoviruses in the middle ear fluid in three of 84 patients. According to Henderson et al.,² acute otitis media is more closely associated with infections with RSV, adenovirus, and influenza virus than with infections with rhinovirus.

Why the role of rhinoviruses in acute otitis media has not been shown earlier can be explained in several ways. The three studies^{2,5,8} that have reported rhinovirus isolations in patients with otitis may have been made during a season when no major rhinovirus outbreaks occurred in the community. Henderson et al.² diagnosed rhinovirus infection in only 48 of 2406 acute episodes of infection, and Chonmaitree et al.⁵ in four of 84 patients with acute otitis. Rhinovirus causes about 30% to 50% of all acute respiratory illness.⁶ We detected rhinovirus infection in 17% of patients with acute otitis media.

In addition to epidemiologic explanations, technical differences may explain some of the differences between the results of our study and earlier studies. The virus isolation samples were frozen at -70°C within 2 hours after sampling. A blind passage was done of negative HeLa Ohio cell cultures, which increased the sensitivity of virus isolation. Furthermore, secretions were aspirated from the nasopharynx through the nostrils and a large amount of mucus was usually obtained, from which a swab was taken for virus isolation. We suggest that this collection method may have contributed to the relatively high frequency of rhinovirus infections detected.

In addition to rhinovirus we found adenovirus and RSV in middle ear fluid, in agreement with our earlier studies⁴ and with those of others.^{1,3,5} The low rate of RSV isolation can be explained by the facts that the epidemic was only beginning at the end of the study and the direct detection of RSV antigen was not attempted.^{1,3,5} Virus as a sole pathogen was found in the middle ear fluid in seven (6%)

patients who had received no antibiotic treatment. This observation is in agreement with the studies of Sarkkinen et al.⁴ and Klein et al.,³ who found viruses as sole pathogens in 9% and 13%, respectively, of patients with acute otitis.

We conclude that rhinovirus infection is associated with acute otitis media. In some patients rhinovirus may be the only pathogen detectable in middle ear fluid.

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Early coagulopathy in severe iron poisoning

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Hepatotoxicity with resultant coagulopathy is a well-known complication of severe iron poisoning¹ and usually

occurs at least 24 hours after ingestion. Early gastrointestinal hemorrhage related to mucosal injury occurs within hours of overdose.¹ Any coincident coagulopathy would aggravate the gastrointestinal hemorrhage. Our observations support the presence of an early, reversible coagulopathy dependent on the serum iron concentration in poisoned patients.

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Table I. Coagulation studies in four patients with iron overdose

Patient	Age (yr)	Time after ingestion (hr)	Serum iron ($\mu\text{g/dl}$)	AST (U/L)	PT (sec)	Activated PTT (sec)
					Patient/control	Patient/control
1	2.5	28	244	>1,000	33/18	72/41
2	2.5	24	259	3,020	35/19	47/38
3	14	90	33	3,215	50/13	45/31
4	14	48	303	11,740	90/16	87/37
Normal			42-135	<50	C $\pm$ 2	C $\pm$ 5

C, Control.

Table II. Early coagulopathy studies in patients 1 and 2

Patient	Time after ingestion (hr)	Serum iron ($\mu\text{g/dl}$)	AST (U/L)	PT (sec)	Activated PTT (sec)
				Patient/control	Patient/control
1	8	5,270	218	20/13	93/38
	18	240	—	17/11	40/35
2	4	20,900	186	20/11	>120/34

AST	Aspartate aminotransferase
PT	Prothrombin time
PTT	Partial thromboplastin time

CASE REPORTS (Table I)

The four patients were all girls, and only one survived. The overdose was accidental in the two toddlers and intentional in the teenagers. Coagulation factor analyses done at 24 to 90 hours after ingestion demonstrated markedly depressed activities of factors V, VII, IX, and X without associated thrombocytopenia. This pattern is typical of a hepatotoxic coagulopathy. At the same time, serum transaminase activities were grossly elevated (AST >1000 to 11,740 U/L), indicative of severe hepatocellular damage, whereas the serum iron concentrations were only mildly elevated (33 to 303 $\mu\text{g/dl}$) and less than the total iron binding capacity.

Prothrombin time and activated partial thromboplastin time were also done within the first 24 hours in patients 1 and 2 (Table II). These data demonstrated a significant early coagulopathy with grossly elevated serum iron concentrations and very modest hepatic dysfunction. Patient 1 had a subsequent improvement in hemostasis with a fall in serum iron concentration. Hepatotoxic coagulopathy was then documented at 28 and 24 hours, respectively, after the ingestion.

DISCUSSION

All four patients had a severe hepatotoxic coagulopathy after 24 hours had elapsed. The depression of activities of factors V, VII, IX, and X is typical of this abnormality. The markedly elevated serum transaminase values and absence of thrombocytopenia support hepatic parenchymal damage rather than consumptive coagulopathy as the

cause. Coagulopathy resulting from iron-induced hepatic damage is well known. Its onset is usually delayed for at least 24 hours after iron ingestion, making the early coagulation abnormalities in patients 1 and 2 noteworthy. Both PT and activated PTT were grossly prolonged during the time of markedly elevated serum iron concentrations and minimal transaminase elevation. The coagulation measurements in patient 1 also improved coincident with a precipitous fall in serum iron concentration and prior to the onset of the hepatic coagulopathy. These observations are supported by a single case of an iron-poisoned patient in whom abrupt onset of a coagulopathy occurred within hours of iron ingestion.² Coagulation studies were comparable to those in patients 1 and 2, and the abnormalities were resolving by the time evidence of hepatic dysfunction appeared.

Thus there may be a biphasic coagulopathy in severe iron poisoning. The initial phase, occurring within hours of overdose, appears to be a functional, reversible, and serum iron concentration-dependent impairment of coagulation. The second, later phase is the well-known hepatotoxic coagulopathy of iron poisoning.

Previous *in vivo* studies in iron-poisoned rabbits³ and dogs⁴ have demonstrated a dose-related reversible dysfunction in coagulation of rapid onset, unrelated to shock or acidosis. Similar abnormalities have been demonstrated in *in vitro* studies in human plasma,^{4a} and the activated PTT prolongation was much greater than that of the PT, as in our patients 1 and 2. These effects were reversed after *in vitro* addition of a chelator to the test plasma. These data suggest a reversible interference with the function of

Factor activity (%)				Platelets (/cu mm)
V	VII, X	IX	VIII	
23	29	—	243	170,000
18	31	38	112	165,000
12	8	20	425	200,000
0	3	26	290	382,000
50-150	55-145	60-140	55-145	150,000-250,000

enzymes of the coagulation cascade. Free iron, not plasma protein bound iron, is considered responsible for oxidative damage to cellular and organelle membranes.⁵ It may also inhibit function of protease enzymes of the coagulation cascade.

Therapy for hemorrhage related to hepatotoxic coagulopathy involves coagulation factor replacement. If, however, there is functional impairment of coagulation factors because of peripheral inhibition by circulating free iron, it is unlikely the factor replacement or vitamin K would be beneficial. Thus therapy must include prompt removal of excess iron. Chelation therapy with deferoxamine is standard practice in severely iron-poisoned patients; unappreciated benefit may be the moderation of serious gastrointestinal hemorrhage. In many institutions rapid serum iron

analysis is not available. This has led to the use of other factors (leukocytosis, hyperglycemia, vomiting, diarrhea, and radiographic demonstration of iron within the gastrointestinal tract) as indicators of the severity of poisoning and the need for specific treatment.⁶ If additional experience confirms the presence of an early coagulopathy in severe iron poisoning, the presence of early coagulation abnormalities could also suggest the need for deferoxamine therapy.

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Marrow transplantation in chronic granulomatous disease: An update, with 6-year follow-up

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In 1984, we reported on the outcome of allogeneic bone marrow transplantation in an infant with chronic granulomatous disease.¹ This child has had low-level, stable, long-term mixed hematopoietic chimerism, and has been free of infection over the course of follow-up of 6 years.

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CASE REPORT

A 6-year-old Amish boy underwent an allogeneic bone marrow transplantation in March 1982 at age 5 months. The marrow was

CGD	Chronic granulomatous disease
DCF	2',7'-Dichlorofluorescein
PMN	Polymorphonuclear leukocyte
NBT	Nitroblue tetrazolium
PBSS	Phosphate-buffered saline solution

taken from his then 5-year-old HLA-identical healthy brother. His conditioning regimen before transplantation consisted of 2 mg/kg busulfan administered daily over 4 successive days, followed by cyclophosphamide, 50 mg/kg daily for 4 days. The