Treatments in Chronic Cholestasis in Children

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Key Words

Chronic cholestasis • Ursodeoxycholic acid • Rifampicin • Ion exchange resins • ω -3 fatty acids • N-acetyl cysteine • Opioid antagonist

Abstract

Few specific treatments for children with chronic cholestasis are available. Most therapy strategies relieve bile component retention or palliate some of the consequences of chronic cholestasis. Ursodeoxycholic acid is the most frequently used pharmacological agent in children with chronic cholestasis. This bile acid is administered at dosages between 10 and 30 mg/kg/day to patients with cystic fibrosis, inborn errors of bile acid metabolism, progressive familial intrahepatic cholestasis, sclerosing cholangitis, biliary atresia, Alagille syndrome, or those receiving total parenteral nutrition. Ursodeoxycholic acid mainly increases bile flow and has a membrane-stabilizing effect, reducing the toxicity of more hydrophobic bile acids. Rifampicin, an antibiotic, at dosages between 10 and 20 mg/kg/day is very efficient in relieving pruritus. Similar effects are obtained using nonabsorbable ion exchange resins. In addition, these molecules decrease the serum cholesterol levels contributing to reduce xanthomas. Replacement of some deficiencies created by total parenteral nutrition by administration of essential fatty acids or cysteine can prevent or contribute to improve the associated liver disorders. In some cholestatic diseases, surgical procedures can help to relieve the obstacle to the bile flow, as it is the case for portoenterostomy in patients with

biliary atresia. In cases of intrahepatic cholestasis, a clinical and biochemical improvement can be recorded after bile diversion or other procedure (ileum exclusion) limiting the absorption of bile acids by the intestine. In the future, the association of these different pharmacological agents, increasing the bile flow, protecting cell membranes, or restoring nutritional deficiencies, could contribute to an improvement in quality of life in children with chronic cholestasis and eventually delay the need of a more drastic therapy such as liver transplantation. Advances in gene therapy and hepatocyte transplantation could also be of great help; however, many years of intense research are still necessary before even a pilot study using one of these therapies can be considered on liver diseases resulting in chronic cholestasis.

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Chronic cholestasis in children is the consequence of a large variety of causes, and very few of them have a specific treatment. In most cases, medical or surgical therapies have been developed to prevent or treat complications secondary to bile component retention. Existing treatments are mostly supportive, trying to reduce the accumulation of bile acids in the organism and its consequences: progressive liver fibrosis, pruritus, hyperlipidemia and fatigue.

Reduced quantities of bile acids in the lumen of the intestine are responsible for fat malabsorption. Steatorrhea can become a cause of malnutrition and liposoluble vitamin deficiency in chronic cholestasis. Some therapies

Table 1. Available treatments for chronic cholestasis in children

Treatment	Indication	Contraindication	Side effects	Dosage
UDCA	influence on the pathogenesis of PFIC, CF, TPN; 'pruritus'	obstruction of bile ducts (e.g., failure of portoenterostomy in BA)	diarrhea	20–30 mg/kg/day
Rifampicin	'pruritus'	mycobacterium infection ¹		10–20 mg/kg/day
Nonabsorbable ion exchange resins	'pruritus' hypercholesterolemia	intestinal stenosis or subocclusion	constipation hyperchloremic acidosis	8–16 g orally daily divided in 2–3 times (increased progressively from 2 g orally daily)
Opioid antagonists	'pruritus'	–	withdrawal reactions	?
ω-3 fatty acids	TPN-induced liver disease	–	–	1 g/kg/day (increased progressively from 0.2 mg/kg/day)
NAC	TPN-induced liver disease	–	–	70–135 mg/kg/day (increased progressively from 20 mg/kg/day)

Associations of some of these drugs are usually required. BA = Biliary atresia.

described below, aiming to avoid the enterohepatic recirculation of bile acids, can aggravate this situation.

Pharmacological agents such as ursodeoxycholic acid (UDCA) and rifampicin improve choleresis by enhancing hepatocyte excretion of bile acids. Nonabsorbable ion exchange resins bind bile acids in the lumen of the intestine, decreasing its enterohepatic circulation. All these drugs increase choleresis and diminish pruritus and levels of cholesterol. Opioid antagonists have been proposed to treat pruritus; however, their limited availability, as well as their side effects, restricted their use in pediatrics (table 1).

Surgical interventions can be curative, as the Kasai intervention in some patients with biliary atresia, or palliative as the partial biliary diversion and the ilial exclusion in patients with Alagille syndrome or progressive familial intrahepatic cholestasis (PFIC). The latter could improve pruritus, decrease cholesterol retention and prevent evolution to cirrhosis.

Ursodeoxycholic Acid

UDCA (3α,7β-dihydroxy-5β-cholan-24-oic acid) is present in small quantities in human bile, up to 3%, and is the result of the 7β epimerization of chenodeoxycholic acid by colonic bacteria [1].

The β rather than the α hydroxy group at the 7th position gives UDCA a higher hydrophilicity when compared with chenodeoxycholic acid, its precursor. Thus, because of less hydrophobicity, UDCA is poor at micelle formation. In addition, it is poorly absorbed in the proximal intestine [1].

Mechanisms of Action

- Replacement of more hydrophobic bile acids at the circulating pool and at cell membranes. After 6 months of treatment at 10–12 mg/kg/day, UDCA represents 40–50% of the bile acid pool [2]. Because of their detergent capabilities, more hydrophobic bile acids are toxic for cell membranes, causing hepatocellular damage and an increase in cholestasis. UDCA has a membrane-stabilizing effect, reducing disruption of cholesterol-rich membranes [3].
- UDCA, but not its conjugated form taurodeoxycholate, decreases the toxicity of lipophilic bile acids on the function of the electron transport chain in a concentration-dependent form (up to 100 μmol/l), but increases bile acid-induced mitochondrial toxicity at higher concentrations [4].
- Interference in the ileum with the absorption of more toxic bile acids [2].
- UDCA is reabsorbed by the biliary epithelium in a protonated form and it is secreted again into bile (cholehepatic shunt) producing a hypercholeretic effect.

The protons absorbed lead to the formation of bicarbonate that is secreted and enrich the bile in this component [2].

- UDCA increases the bile salt-independent flow [1, 2].
- UDCA may stimulate transporter expression at the canalicular hepatocyte surface [5].
- A reduction in human leukocyte antigen class I expression at the hepatocyte surface has been reported [6].
- UDCA also suppresses interferon- γ -mediated induction of human leukocyte antigen class II expression via the glucocorticoid receptor-mediated pathway [7].

UDCA is responsible for very few and transitory side effects, such as diarrhea and skin reactions more probably due to drug adjuvants than to the active substance. However, it should be avoided or carefully administered to patients with an obstructive bile duct disease. In experimental animals with a ligation of the main bile duct, UDCA can aggravate bile infarcts [8]. In children with biliary atresia and unsuccessful Kasai intervention, UDCA can precipitate a liver failure.

UDCA is the most frequent drug used in children with chronic cholestasis. In several diseases, the benefit of the long-term administration of UDCA has not been proven beyond any doubt, as is the case for cystic fibrosis (CF). In other cases, the administration of the drug improves liver tests, but not the final outcome, as in patients with sclerosing cholangitis. In PFIC, it appears to stop the progression of the disease in some children and, associated with cholic acid, it is the treatment of choice in patients with inborn errors of the bile acid metabolism. In children with Alagille syndrome or biliary atresia, UDCA is mainly used to reduce symptoms such as pruritus.

Cystic Fibrosis

After 2 months of UDCA therapy, the presence of this bile acid represents between 25 and 42% of the pool, at the expense of cholic and chenodeoxycholic acids; these differences are dose dependent [9]. From these studies, it was concluded that the recommended dosage of UDCA is 20 mg/kg/day or greater [9].

UDCA stimulates the biliary secretory capacity in liver of CF patients, as determined by hepatobiliary scintigraphy [10]. Several pilot studies have shown that UDCA is responsible for an improvement in biochemical tests, mainly a decrease in serum levels of aminotransferases (ALT and AST) and γ -glutamyl transferase (GGT) [11]. In addition, liver inflammation and/or bile duct proliferation were improved after 2 years of UDCA therapy in control biopsies. UDCA administration also improves the nutritional state of young adults with CF and, in chil-

dren, ameliorates essential fatty acids and retinol status [12–14]. However, because of poor UDCA activity in micelle formation it did not affect steatorrhea [13]. If UDCA modifies the natural history of liver diseases in CF patients, it still remains to be studied in a large randomized prospective study. Encouraging results were recently reported on UDCA-induced arrest or even reversion of liver ultrasound lesions observed in patients with CF, in a long-term study [15].

Total Parenteral Nutrition

Fasting associated with total parenteral nutrition (TPN) leads to bile stasis related to lack of stimulation of the bile acid-dependent and -independent bile flow. In a model of TPN-induced cholestasis, the intravenous administration of UDCA improved bile flow and reduced bilirubin levels [16]. Similar encouraging results were recorded in a pilot study of children with intractable diarrhea depending on TPN, but tolerating UDCA at the dosage of 30 mg/kg/day in 3 daily doses [17].

In very low birth weight infants with TPN-associated cholestasis, UDCA at doses of 10–30 mg/kg/day reduces the duration and intensity of cholestasis [18]. In most of these patients, intestinal complications, including partial resections of the bowel, preclude the standard use of UDCA. Eventually, a very fractionated daily dosage of the medication can be well tolerated, avoiding diarrhea. Unfortunately, the UDCA intravenous form is not commercially available.

Inborn Errors of Bile Acid Metabolism

Two main forms of bile acid synthesis defect are responsible for chronic cholestasis in children: the 3-oxo- Δ^4 -steroid 5 β -reductase deficiency and the 3 β -hydrosteroid- Δ^5 -oxireductase/isomerase deficiency. Hepatotoxicity is probably due to the accumulation of bile acid precursors and the lack of primary bile acids. To reduce the synthesis of toxic molecules, the activity of cholesterol 7 α hydroxylase, the rate-limiting enzyme in endogenous bile acid synthesis, must be inhibited.

Most patients respond only partially to UDCA treatment alone; association of cholic acid (250 mg/day) is therefore indicated. The administration of chenodeoxycholic and cholic acids has also been proposed in these patients. The latter treatment can lead to a faster improvement in the liver injury [19].

Progressive Familial Intrahepatic Cholestasis

UDCA is a valuable initial treatment for patients with PFIC when administered orally at doses between 20 and

30 mg/kg/day. Similar improvement was observed no matter the PFIC type, meaning patients with normal (PFIC types 1 and 2) or increased levels (PFIC type 3) of serum GGT. In patients with normal GGT, an improvement in parameters of cholestasis was observed in 61% of cases and in 71% of those with type 3 PFIC [20]. The duration of the disease prior to the beginning of the UDCA treatment could influence these results; early diagnosis and initiation of UDCA therapy could further improve the final outcome. In some patients, the improvement, even if complete, is only transitory, and the cholestasis reappears some years after the beginning of UDCA.

In patients with less deleterious mutations in genes responsible for types 1 or 2 of PFIC, a benign recurrent intrahepatic cholestasis is observed. In benign recurrent intrahepatic cholestasis patients, UDCA treatment fails in preventing a cholestatic episode, but could improve some of the symptoms (e.g., pruritus) [21].

Sclerosing Cholangitis

An initial pilot study of UDCA in patients with well-developed sclerosing cholangitis showed an improvement in liver tests. Later, a statistically significant difference in the serum levels of ALT/AST/GGT was observed between UDCA and placebo-treated patients with sclerosing cholangitis during a study of 3 years of follow-up [22]. An improvement in pruritus and fatigue was also observed, but the difference was not significant. Unfortunately, more recent results in a randomized, double-blind study comparing UDCA (13–15 mg/kg/day) with placebo showed no differences in treatment failure (progression of the disease, death or liver transplantation). This study confirmed an improvement in liver tests, but concluded that UDCA did not offer clinical benefits to patients with sclerosing cholangitis [23]. Thus, low dosages of UDCA apparently do not modify the progression of this disease. A very recently published study showed that, on the contrary, high doses of UDCA were associated with an improvement in survival and a trend toward stability/improvement in the histological stage in a relatively small group of patients with sclerosing cholangitis [24].

Despite these results, new trials could be proposed using high dosages of UDCA very early in the evolution of sclerosing cholangitis, and particularly in patients with small duct disease. When the disease affects the main bile ducts (as in most cases), probably, the disturbance in the bile flow can contribute irreversibly to the aggravation of the liver disease. The larger experience in the use of UDCA in chronic cholestatic diseases was obtained in

adult patients with primary biliary cirrhosis, a severe form of intrahepatic cholangiopathy [25]. Different groups showed controversial results with UDCA therapy, partially explained by the different time in the evolution of the disease at the starting of treatment. The dose of UDCA administered also appears to play a role in the influence of this medication on the final outcome. This vast experience should be considered in planning new trials in patients with sclerosing cholangitis.

Biliary Atresia

An early preliminary study using UDCA after hepatic portoenterostomy showed that this drug was effective in patients with a good postoperative bile drainage, resulting in lower total bile acid levels and better weight gain [26]. Long-term administration of UDCA significantly improves the final outcome after Kasai portoenterostomy, more patients cleared jaundice and survived with their native liver. In children without recovery of a good bile flow after portoenterostomy, UDCA administration can lead to faster development of liver injury, and eventually, precipitates a liver failure [27].

Alagille Syndrome

Few reports are available on the use of UDCA in patients with Alagille syndrome. Improvement in the jaundice and pruritus was found, as well as a decrease in circulating lipid levels and a decrease in xanthomas [28]. No controlled study is available; however, UDCA is widely prescribed to these patients. The influence of this bile acid in the natural history of the disease is still unknown.

Rifampicin

Rifampicin decreases the bile acid concentration in hepatocytes, by competing with its uptake. Furthermore, this antibiotic induces microsomal enzymes that promote the 6 α -hydroxylation and subsequent 6 α -glucuronidation of toxic bile acid.

Initial clinical experience using this antibiotic for the treatment of pruritus was given in adults with a primary biliary cirrhosis, showing a significant relief from pruritus in a majority of patients [29]. In children with chronic cholestasis, a double-blind crossover study showed the efficacy of rifampicin in alleviating pruritus during a period of up to 6 months [30]. Subsequently, 2 studies on pediatric patients with refractory pruritus treated by rifampicin confirmed those initial results [31, 32]. No im-

provement in biochemical features of cholestasis was recorded in most treated children with different causes of chronic cholestasis.

The recommended dosage of rifampicin is 10–20 mg/kg/day in 2 daily doses. Few side effects were reported. However, rifampicin is an enzymatic inducer of microsomal enzymes. Several forms of cytochrome P450 isoenzyme activity are increased by rifampicin administration; therefore, the rate of metabolism of several drugs can be accelerated.

It was proposed that UDCA and rifampicin have complementary effects that may justify a combination of both agents in the treatment of patients with cholestatic diseases [33].

Nonabsorbable Ion Exchange Resins

These molecules are not absorbable from the gastrointestinal tract and release chloride and bind bile acids in the lumen of the intestine, diminishing their enterohepatic recirculation. Nonabsorbable ion exchange resins augment cholesterol excretion via enhanced conversion to bile acids. These drugs can decrease the bile acid pool by approximately 40%. Trihydroxy bile acid dissociates rapidly from these molecules and can be absorbed in the ileum.

Cholestyramine (orange-flavored granules) has been used for some decades and has been proven to be effective and safe. However, palatability is poor, limiting the tolerability to this drug. Therefore, compliance is erratic in the best of cases. When nasogastric tubes are indicated for enteral feeding, the administration of cholestyramine through this pathway has been shown to be well tolerated and successful in decreasing serum cholesterol levels and improving pruritus (fig. 1).

In children, cholestyramine can be started at a dosage of 2–4 g twice daily and then increased to 8–16 g daily in 2 or 3 divided doses. Cholestyramine binds other acids or negatively charged substances, which explains most of its interaction with many drugs.

Colestipol in granules or tablets has not been used frequently in children. Indications and precautions in its use are similar to those described for cholestyramine.

Colesevelam hydrochloride (in the form of a nonabsorbable hydrogel or tablet) is probably the best tolerated of these drugs, but unfortunately, it is not available everywhere [34]. This drug has enhanced the specificity, greater affinity and higher capacity for binding bile acids compared with the 2 other nonabsorbable ion exchange resins mentioned above.

Fig. 1. In this boy with Alagille syndrome, cholestyramine was administered by a nasogastric tube, indicated for enteral feeding. Dramatic decrease in serum cholesterol levels and shrinking of xanthomas was observed. Pruritus improved with the association of rifampicin with the treatment. No modifications in biochemical parameters of cholestasis were recorded.

Nonabsorbable ion exchange resins can interfere with the intestinal absorption of other drugs, like UDCA. This particular problem should be considered when treating a patient with chronic cholestasis. In addition, the time of administration should be well established to allow a maximal capture of bile acids and to avoid interaction with other drugs including fat-soluble vitamins. Other drugs should be given 1 or 4–6 h after cholestyramine.

Main side effects are constipation and hyperchloremic acidosis due to the large quantities of chloride released in the gastrointestinal lumen and absorbed instead of bicarbonate. The latter can be particularly severe in patients with Alagille syndrome, frequently showing previous renal problems.

Opioid Antagonists

Naloxone and nalmefene are the first 2 opioid antagonists tested in adults with primary biliary cirrhosis, attempting to relieve pruritus [35, 36]. The use of these substances was based on the possible role of the central nervous system in the pruritus observed in patients with cholestasis. Enkephalin class substances (endogenous opioids) may be potential mediators in the involvement of the nervous system.

Fig. 2. In this girl with PFIC (low GGT), a partial biliary deviation was carried out. An almost complete normalization of biochemical liver tests was recorded. Relapse of symptoms and signs of cholestasis were observed 2–3 years after surgery. Hepatobiliary scintigraphy showed that the bile flow was almost exclusively directed to the stoma bag. This case showed that the liver disease progressed despite bile diversion and UDCA treatment.

A placebo-controlled single-blinded trial of naloxone proved that this medication reduced the scratching activity in cholestatic patients. The main problems with this drug were the need of intravenous perfusions due to its very short half-life and a possible opiate withdrawal syndrome at the end of the perfusion [35].

Nalmefene can be administered orally (but this form is not available everywhere). Improvement in the perception of pruritus was reported in most treated patients because of its longer duration of action when compared with naloxone. This medication can be associated with severe withdrawal symptoms, which is apparently dependent on the dosage used. Marked exacerbation of pruritus when the drug was suddenly discontinued was also reported [36].

Naltrexone can also be administered orally. In a randomized trial of naltrexone versus placebo, a significant decrease in daytime and nighttime itching was reported. Opiate withdrawal syndrome was observed in half of the patients receiving naltrexone [37].

No series on the use of opioid antagonists in children with chronic cholestasis has been published. Therefore, it is impossible to conclude on its indication in the pediatric population. From adult experiences, these drugs are dif-

ficult to administer and it is hard to avoid side effects when discontinued.

ω-3 Fatty Acids

Liver disease associated with TPN in children with intestinal failure can lead to cirrhosis and liver failure. In some patients, when UDCA is absorbed, an improvement in liver tests has been recorded. More spectacular results were obtained by replacing soy oils in fat emulsions with fish oils. Children receiving a solution enriched in ω-3 fatty acids showed a dramatic improvement in the liver disease [38].

Recently, a 4-year-old boy followed at our institution had a resection of most of his small intestine, because of a volvulus. This child developed a severe liver disease on TPN and was enrolled on the waiting list for a liver transplant. Parenteral fish oil was started (Omegaven), and 3 months later, he was removed from the waiting list, and 6 months later, showed normal serum levels of conjugated bilirubin [V. Marchand, pers. commun.].

N-Acetyl Cysteine

Liver disease in the long-term TPN population is the consequence of a variety of factors. Oxidative stress appears to play a major role in the etiology and in the persistence and aggravation of cholestasis. Cellular concentrations of glutathione is an essential defense against this harmful process. Cysteine is an important precursor of intracellular glutathione; however, low levels of cysteine are found in currently used aminoacid solution.

N-acetyl cysteine (NAC) can be used as a precursor of cysteine. When NAC was added to the parenteral nutrition solution, at dosages of 70–135 mg/kg/day, a normalization or marked decrease in serum-conjugated bilirubin levels was recorded [39]. This improvement in liver cholestasis was associated with a normalization of glutathione in red blood cells, suggesting that the cellular concentration of this antioxidant molecule played a major role in the decrease in the liver injury.

Surgical Procedures

Biliary Diversion and Ileal Exclusion

More than 30 years ago, Alagille and Odièvre, at Bicêtre Hospital in France, described the efficacy of bili-

ary drainage by cholecystostomy in patients with PFIC and Alagille syndrome. Unfortunately, because of local complications on the skin around the drain, this type of external bile drainage could not be kept for a long time [40].

In the 80s, a technique of partial biliary diversion was developed, using 10–15 cm of jejunum interposed between the gallbladder and the skin. This procedure was permanent and allowed the partial deviation of the bile flow to an external stoma bag for years. A clinical and biochemical improvement was reported in patients with Alagille syndrome [41]. In children with PFIC, the partial biliary diversion resulted in an improvement in growth, relief of pruritus and correction of biochemical anomalies of cholestasis [42, 43]. In some cases, the dramatic improvement was transitory, followed by a relapse of the cholestasis and the requirement of liver transplantation after 4–5 years of the initial bile deviation (personal observations) (fig. 2). In other cases, the complete improvement was only obtained if UDCA was given as a coadjuvant therapy.

A technical variant was later reported, in which the appendix vermiformis was used as a conduit between the gallbladder and the skin, with very good results [44].

In a recent publication, another way of obtaining a partial deviation of the bile flow was described. In 3 patients with Alagille syndrome, 15% of the terminal ileum was excluded using a stapled division and ileocecal anastomosis. The rationale of the procedure is to avoid the site of maximal absorption of bile acids in the bowel. A decrease in cholesterol levels, an improvement in pruritus and a reduction in xanthomes sizes were observed [45].

All of these surgical procedures should be avoided in patients that have already developed a cirrhosis. Important bleeding from neo-varices at sites of anastomosis is a very frequent complication. In addition, in patients with advanced liver disease, the benefits of such procedures are not demonstrated.

Hepaticoportenterostomy

The surgical intervention described by Kasai in the 1950s became the first and only procedure able to restore the bile flow in patients with biliary atresia.

Normalization of serum bilirubin, within 3 months of portoenterostomy, has been found to indicate a good long-term prognosis. This occurs in around 50–60% of operated infants, with a better outcome when the inter-

vention has been carried out early in life [46]. Other factors at the time of the portoenterostomy can modify the final outcome such as the degree of the liver fibrosis and the characteristics of the extrahepatic remnant. The prognosis of the Kasai intervention in a patient with polysplenia malformation syndrome associated with biliary atresia has been worse in some centers and similar to biliary atresia without malformations in others [47]. In the postoperative period, the development of cholangitis can also worsen the prognosis.

Because of the presence of inflammatory infiltrate in the liver of these patients, it was proposed that the use of anti-inflammatory drugs could arrest the progression of the disease. Unfortunately, several recent publications of pilot and double-blind randomized studies showed that the use of high doses of steroids after Kasai intervention did not increase survival of the native liver [48, 49].

Ten-year survival is between 30 and 54% in different centers around the world; around 25% at 20 years, and 10% at 30 years [50–53]. All patients develop a cirrhosis, with the associated complications of portal hypertension: gastrointestinal bleeding, hypersplenism and hepatopulmonary diseases.

Liver transplantation has improved the overall survival of children with biliary atresia and failure of the Kasai intervention. Currently, the success of this therapy is responsible for a survival rate of 90% [47].

Perspectives

Eventually, 2 future therapies could definitely cure some inherited diseases responsible for chronic cholestasis: gene therapy and/or hepatocyte transplantation. In the case of gene therapy, after initial years of hope, disappointing results in most trials and serious side effects retarded its progression and further development. In the case of the liver, it is not known how many cells should express a specific gene to avoid the development of symptoms and signs of a particular disease and impede its progression. Many problems need to be solved before we can even think of a trial concerning a cholestatic liver disease.

Hepatocyte transplantation has already been attempted in some human beings. Partial correction of liver-inherited diseases was observed in animal models. Normal hepatocytes have an advantage over the repopulation of the liver against cells carrying a mutated and possibly lethal gene. Correction of the PFIC type 3 in a mouse model was reported and stayed stable for a long time [54]. This

therapy is confronted with the availability of normal hepatocytes, the need of immunosuppressive therapy and the question on the fate of remaining mutated cells. The risk of tumors developing in the long-term follow-up represents a considerable concern.

The use of ω -3 fatty acid cholestasis of different origins should be explored. Deficiency in essential fatty acids has been reported in patients with cholestasis of different etiologies, e.g., Alagille syndrome and CF. This feature is most probably a consequence of severe steatorrhea. Extraintestinal pathways of administration have been proposed, but without much success. Intravenous, periodic administration could be indicated in some cases.

Oxidative stress is almost constantly associated with cholestasis. It can be hypothesized that in these children, the retention of bile components, the malabsorption responsible for malnutrition and deficiency of essential fat-

ty acids and oligoelements lead to malformation of different cellular mechanisms of protection. In the latter, the deficiency in glutathione can be included. NAC administration could be of great help in several cholestatic processes, as an adjuvant therapy.

Future trials should test the potential benefit of ω -3 fatty acids and NAC in children with chronic cholestasis. Both of these therapies show very few side effects, being well tolerated in children.

Many of the drugs described above could be associated in the treatment of chronic cholestasis in order to diminish the liver injury and/or to relieve harmful symptoms of these disorders. Drugs with different mechanisms of action can be associated with an adequate nutritional support, individualizing the therapy according to the etiology of the cholestasis and the current status of a particular child.

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