Risk Factors, Complications, and Outcomes of Gallstones in Children: A Single-center Review

*Conor O. Bogue, †Amanda J. Murphy, ‡J. Ted Gerstle, §Rahim Moineddin, and *Alan Daneman

ABSTRACT

Background and Objective: The increasing use of sonography has resulted in an increase in the proportion of children with gallstones who are asymptomatic at the time of diagnosis. In adults, the literature supports expectant management of clinically silent gallstones. The evidence for this management approach in children is limited to a number of small series. Our objective was to review the risk factors, complications, and outcomes of gallstones at our institution, particularly in those patients who are asymptomatic at the time of initial diagnosis.

Materials and Methods: We reviewed 382 cases of gallstones in children. These patients were diagnosed with sonography. Data on age at diagnosis, presentation, sonographic findings, risk factors, complications, surgery, and follow-up were collected. A χ^2 test was used to compare the complication rates between symptomatic and asymptomatic groups. Descriptive statistics were used to analyze the sample.

Results: At diagnosis, 50.5% of children were asymptomatic; these patients were diagnosed at a mean age of 8.23 years. Compared with symptomatic patients, they were less likely to have a hemolytic anemia but more likely to have other risk factors, including cardiac surgery, leukemia and lymphoma, short bowel syndrome, or exposure to total parenteral nutrition or cephalosporins. These patients had a lower rate of complications than the symptomatic patients (4.6% vs 28.2% of symptomatic, $P < 0.0001$) and only 3.1% developed symptoms that necessitated surgery (vs 59.0% of symptomatic). Of the 58 (15.1%) diagnosed in infancy, 47 (81.0%) were asymptomatic. The infant group also had low rates of complications (8.6%) and cholecystectomy (1.7%). In cases with sonographic follow-up, resolution of gallstones was demonstrated in 16.5% of asymptomatic patients and in 34.1% of infants.

Conclusions: The data suggest that clinically silent gallstones in children and infants are associated with low rates of complications and can be managed conservatively, unless complications occur. Patients with sickle cell disease, spherocytosis, and elliptocytosis had high complication rates and required surgery more often.

Key Words: biliary calculi, children, choledocholithiasis, cholelithiasis, gallstones

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From the Departments of *Diagnostic Imaging and †Pediatric Laboratory Medicine, and ‡Division of General and Thoracic Surgery, The Hospital for Sick Children; and the §Department of Public Health Sciences, University of Toronto, Toronto, Canada.

Address correspondence and reprint requests to Dr Conor O. Bogue, Department of Diagnostic Imaging, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada (e-mail: cbogue@eircom.net).

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The diagnosis of gallstones in children is being made with increasing frequency (1–6) and the cause for this is multifactorial. One factor is the increased use of sonography in diagnosis and monitoring of gastrointestinal and genitourinary pathologies; this has led to increased detection of asymptomatic gallbladder calculi. In adults, it has been shown that only 7% to 25% of patients with asymptomatic gallstones develop symptoms necessitating surgery (7–11). In children, however, the literature on the natural history of asymptomatic gallstones is limited to a number of smaller series, which have suggested conservative management for those without symptoms (12,13). Our objective was to review the experience with gallstones at our institution, particularly in those patients who are asymptomatic at the time of initial diagnosis.

MATERIALS AND METHODS

Research Ethics Board approval (REB Application No. 1000010511) was obtained at our hospital to conduct a review of the medical and imaging records of inpatients and outpatients, 18 years old and younger, who were diagnosed with gallstones sonographically between January 2000 and June 2006. The records were reviewed up to the end of December 2006. We defined gallstones as echogenic foci in the gallbladder or bile ducts that produced posterior acoustic shadowing. We excluded patients with nonshadowing intraluminal material, because this could represent sludge or sludge balls.

Demographic information, medical history, predisposing factors, presenting symptoms, imaging findings, and complications were recorded in all of the patients. Patients were divided into 2 groups based on their symptomatology at the time of their initial diagnosis. Patients were deemed ''asymptomatic'' if they had no symptoms, had symptoms that were not related to gallstones (eg, left lower quadrant pain), or had another confirmed cause for the symptoms (eg, intussusception causing abdominal pain). All of the other patients who had any symptom potentially related to gallstones were then included in the ''symptomatic'' group. These groups were then analyzed for differences in risk factors, complications, and management. Complications were assessed based on clinical and imaging findings. In those patients not requiring cholecystectomy, follow-up information was based on clinical and sonographic findings. At the authors' institution, patients not undergoing surgery are followed with an annual clinical and ultrasound assessment for 1 to 2 years. If they remain asymptomatic, they are only further followed up if symptoms develop. However, a longer duration of follow-up was available in many patients in this study when other diagnoses were under surveillance with abdominal ultrasound.

In those patients who required cholecystectomy, operative and pathology reports were reviewed and were then correlated with the sonographic findings. Chemical analysis of calculi is not routinely performed at our institution so this was not included in the study.

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Statistical Method

Descriptive statistics were used to describe the sample. Fisher exact or χ^2 test was used for assessing the association between the outcome, asymptomatic/symptomatic, and categorical predictors. Two independent sample t tests were used to assess the association between asymptomatic/symptomatic and continuous predictors. Logistic regression was used to quantify the impact of each predictor on the risk of being symptomatic and the probability of stone resolution while it was adjusted for age and sex. All of the tests were 2-sided and P values <0.05 were considered statistically significant. The statistical package SAS 9.2 (SAS Institute, Cary, NC) was used for data analysis.

RESULTS

Patient Demographics

A total of 382 patients were diagnosed with gallstones in the period reviewed and included 191 (50%) females and 191 (50%) males. Eighty-two (55%) of the patients who were 12 years of age or greater were female and 67 (45%) were male. There was no significant difference in the sex distribution ($P = 0.1156$). The age distribution is illustrated in Figure 1. The mean and standard deviation of the age in our patients was 9.3 and 5.7 years overall, 8.2 and 6.3 years in asymptomatic patients, and 10.5 and 4.7 years in symptomatic patients. Symptomatic patients were significantly older than asymptomatic patients ($P < 0.0001$).

There were 194 patients (88 females and 106 males) in the asymptomatic group. Males were more often asymptomatic than females, 55% versus 45%, but this did not reach statistical significance ($P = 0.0655$). The indications for ultrasound in the asymptomatic patients were investigation or follow-up of confirmed renal pathology 72 (37%), investigation or follow-up of confirmed bowel pathology 26 (13%), oncology 24 (12%), investigation or follow-up of liver pathology (masses, vascular, fungal work-up) 22 (11%), asymptomatic screening in patients at increased risk for forming gallstones (sickle cell disease, spherocytosis) 13 (7%), metabolic disease 10 (5%), assessment for congenital anomalies 7 (4%), gynecological pathology 6 (3%), VP shunt dysfunction 3 (2%), liver biopsy 2 (1%), and miscellaneous 9 (5%).

There were 188 patients (103 females and 85 males) in the symptomatic group. The symptoms reported by patients or parents included pain in 176 (94%), emesis in 20 (11%), jaundice in 13 (7%), fever in 11 (6%), irritability in 2 (1%), pale stools in 1 (<1%), and weight loss in 1 (<1%).

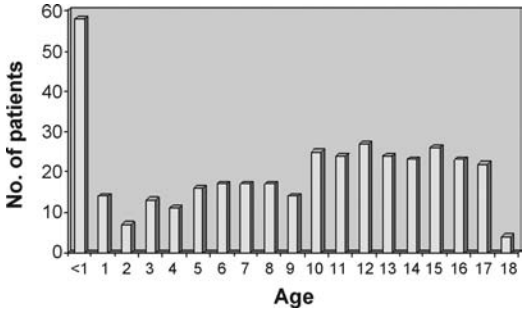

FIGURE 1. Age distribution of children with gallstones. The highest incidence is noted between birth and 1 year of age.

Risk Factors

Figure 2 illustrates the risk factors in our patients, which are recognized to predispose individuals to gallstones. In the group of asymptomatic patients there was at least 1 risk factor in 94 of 194 (48%). There were strong age- and sex-adjusted associations between having a history of cardiac surgery ($P = 0.0002$), exposure to cephalosporins ($P = 0.0002$), diuretic therapy ($P < 0.0001$), or total parenteral nutrition (TPN; $P < 0.0001$) as risk factors, and having asymptomatic gallstones. In the symptomatic group, there was at least 1 recognized risk factor in 91 of 188 (48%). The risk factors with significant age- and sex-adjusted associations with symptomatic status were sickle cell disease ($P < 0.0001$), spherocytosis ($P = 0.0008$), and trisomy 21 ($P = 0.0281$). Sickle cell disease and spherocytosis together accounted for 37% of these patients. In both groups, 52% of patients had no identifiable risk factor.

Complications

In the group that was initially asymptomatic, complications developed in only 9 of 194 (5%): choledocholithiasis in 6, pancreatitis in 2, and acute cholecystitis in 1. Three of the 6 patients with choledocholithiasis passed the stones spontaneously and did not have further complications. The other 3 required intervention. This included a 9-month-old girl with a history of prematurity and cutis marmorata telangiectatica congenita, who was managed successfully with endoscopic retrograde cholangiopancreatography (ERCP) for stone removal and sphincterotomy; a 16-year-old boy with antiphospholipid syndrome who required ERCP followed by cholecystectomy; and a 12-year-old girl with a history that included hemophagocytic lymphohistiocytosis, macrophage activation syndrome, and acute renal failure, who passed common bile duct stones but required cholecystectomy for persistent pain due to gallbladder stones.

One of the 2 patients with pancreatitis was a 2-year-old boy with a history of bone marrow transplantation for Hurler syndrome; he responded to medical therapy and did not have a recurrent episode in 3 years of follow-up. The other, a 17-year-old boy with a history of portal vein thrombosis, portal hypertension, and a Rex shunt required a cholecystectomy.

The single patient with clinical and sonographic evidence of acute cholecystitis was a 7-month-old boy with a history of bone marrow transplantation for Hurler syndrome. This episode was resolved with hospitalization, bowel rest and intravenous fluids,

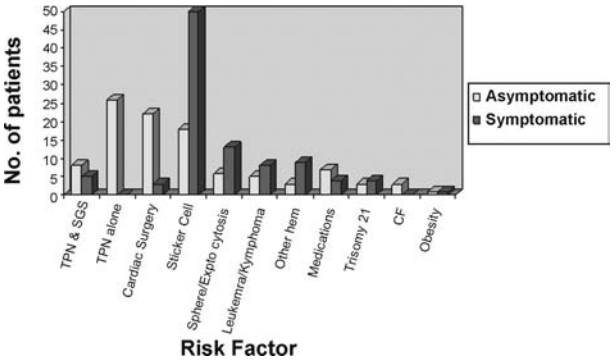

FIGURE 2. Frequency of risk factors in asymptomatic and symptomatic patients. CF = cystic fibrosis; SGS = short gut syndrome; TPN = total parenteral nutrition.

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antibiotics, and analgesia. There was no recurrence of symptoms at 2-year follow-up.

In the patients who were symptomatic at initial diagnosis, complications were more frequent, occurring in 54 of 188 (29%) ($P < 0.0001$). These included choledocholithiasis (without cholecystitis or pancreatitis) in 21, acute cholecystitis in 12, and acute cholecystitis with choledocholithiasis in 7. Acute pancreatitis developed in another 13, 5 of whom also had choledocholithiasis and 1 of whom had acute cholecystitis and choledocholithiasis. The remaining patient had clinical and sonographic evidence of chronic cholecystitis.

Of the 34 patients in this group who developed choledocholithiasis, the stones were passed spontaneously in 19 and ERCP was required in 15. In the 20 patients who had acute cholecystitis, 4 were managed with hospitalization, bowel rest and intravenous fluids, antibiotics, and analgesia and did not have interval cholecystectomy. Cholecystectomy was required in the remaining 16. The 7 patients with pancreatitis (without choledocholithiasis or acute cholecystitis) were managed conservatively. The patient with chronic cholecystitis required cholecystectomy.

Follow-up

In the 194 children in the group who were initially asymptomatic, clinical follow-up was available in 187 (96%). The mean (±SD) follow-up time was 3.21 ± 1.71 years (range 0.08–7.0 years). Of these patients, 91 (47%) had sonographic follow-up, for 1.58 ± 1.46 years (range 0.04–6.0 years). Follow-up sonography showed that gallstones were no longer evident in 17 (19%) children. Resolution of stones was documented sonographically at a mean of 14 months (range 0.08–3.75 years) after diagnosis. In the remaining 74 (81%) there were no significant changes in the sonographic appearance of the stones in the gallbladder. In 7 patients (4%) follow-up was limited or unavailable (3 died, 3 transferred to adult services, and 1 was followed up elsewhere).

Of the 188 children who were initially symptomatic, 77 were managed nonoperatively. Clinical follow-up was available in 76 of 77 (99%) for a mean duration of 3.2 ± 1.67 years (range 0.5–6.67 years). Of these patients, 42 (55%) had sonographic follow-up for 1.62 ± 1.77 years (range 0.02–6.67 years). In these patients the gallstones were sonographically no longer evident in 12 of 42 (29%) at a mean of 0.75 years (range 0.08–2.5 years) after diagnosis. In the remaining 30 of 42 (71%) there was no significant change in the sonographic appearance of the stones in the gallbladder. In 1 patient, follow-up was unavailable because he was transferred to an adult service. The only factor associated with an increased probability of stone resolution was young age. Of the 29 cases in which the stones resolved, 14 were less than or equal to 1 year of age.

Operative Treatment (Cholecystectomy)

Cholecystectomy was required in 122 patients (66 females and 56 males). The mean interval from diagnosis to surgery was 23 weeks. The mean age at which patients underwent cholecystectomy was 11.5 years.

The cholecystectomy rate was considerably lower in the asymptomatic group than in the symptomatic group (11 of 194 [6%] vs 111 of 188 [59%], $P < 0.0001$). Of these, 3 had prophylactic cholecystectomy performed at the time of splenectomy for spherocytosis and 2 had concurrent cholecystectomy at the time of their recipient hepatectomy during liver transplantation. Therefore, only 6 of 194 (3%) patients had surgery for complications related to gallstones. In the symptomatic group, cholecystectomy was required for ongoing pain in 93 of 188 (50%) and for associated complications of the stones in 18 of 188 (10%).

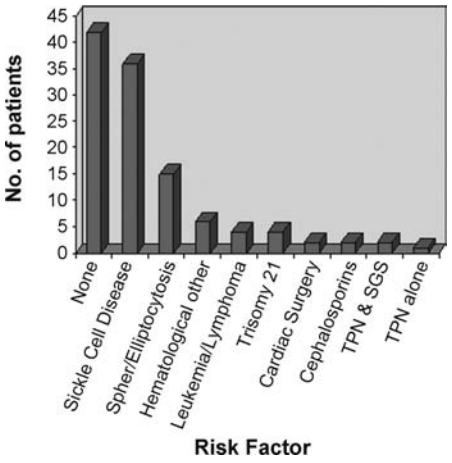

FIGURE 3. Frequency of risk factors in patients requiring cholecystectomy.

Figure 3 correlates the presence of risk factors in the 122 patients who had a cholecystectomy. There was no identifiable risk factor in 34%. Sickle cell disease, spherocytosis, and elliptocytosis together accounted for 42% of cases.

Gallstones in Infants

Demographics and Risk Factors

There were 58 of 382 (15%) patients who were 1 year of age or younger at diagnosis, including 8 who were <1 month old. Eleven of 58 (19%) were symptomatic at diagnosis and the remaining 47 of 58 (81%) were clinically silent. The risk factors in the symptomatic and asymptomatic groups are illustrated in Figure 4. At least 1 risk factor was identified in 40 of 58 children (69%). The risk factor profile in this age group differed from the overall group with a greater contribution from cardiac surgery, TPN, and medications. One patient in this age group had a diagnosis of sickle cell disease, but also had additional risk factors including extensive small bowel resections for necrotizing enterocolitis requiring TPN and treatment with cephalosporins.

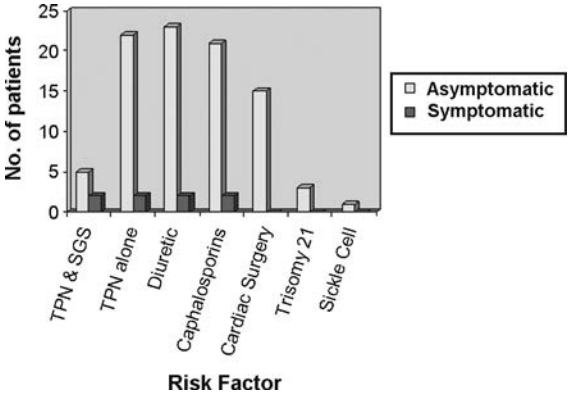

FIGURE 4. Risk factors in infants. SGS = short gut syndrome; TPN = total parenteral nutrition.

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Complications

Of the 58 infants, 5 developed complications: cholecystitis in 3 (1 of whom also had choledocholithiasis) and isolated choledocholithiasis in 2. None developed pancreatitis. All 3 with cholecystitis were managed with hospitalization, bowel rest and intravenous fluids, antibiotics, and analgesia and none required cholecystectomy or ERCP. Of the 2 with isolated choledocholithiasis, 1 required ERCP and the other passed the stone spontaneously but required interval cholecystectomy.

Follow-up

Clinical follow-up only was available for 17 of 58 infants (29%) and sonographic and clinical follow-up was available for the other 41 of 58 (71%). On follow-up sonography, gallstones were no longer evident in 14 of 41 (34%) and in 2 patients only sludge remained. Disappearance of stones was documented at a mean of 9 months (range 0.08–2.5 years) after initial diagnosis. In the remaining 25 of 41 (61%), there was no significant change in the sonographic appearance of the gallbladder or the stones.

DISCUSSION

This article reviews the experience with 382 children with gallstones at our institution during a 6.5-year period. It is not possible to determine the true incidence of gallstones in the pediatric age groups (infant, child, and adolescent) because the total number of patients who had abdominal sonography in this period is not available and only those individuals who were referred to our radiology department for evaluation were included.

We only included patients with intraluminal echogenic foci in the biliary tree that caused acoustic shadowing. Intraluminal echogenic foci, which do not cause a shadow, could represent sludge or ''sludge balls'' and were excluded. It has been suggested that sludge is not a forme fruste of cholelithiasis but a different process with separate predisposing factors (12). We acknowledge, however, that some stones may not cause a shadow (14) and that the application of this criterion may have led to the erroneous exclusion of some patients.

We have compared our data with a previous series from our institution (15) in which there were 133 cases of gallstones diagnosed between 1979 and 1985. These data show that the frequency of gallstones in these age groups has indeed increased in our institution and concurs with the literature, which suggests that gallstones are being recognized with increasing frequency in children (1–6).

One reason for the increasing frequency is the increasing use of abdominal sonography in children (13,16–18), which has also led to an increased detection of gallstones in patients without symptoms at initial diagnosis. There probably is also a true increase in frequency because a number of the recognized etiologies have become more prevalent in recent years; cardiopulmonary bypass operations are more frequently performed, survival after small bowel resection has improved, and the use of TPN, cephalosporins, and furosemide has increased (19). The increase in childhood obesity may also be a factor; obesity has been reported to account for 8% to 33% of gallstones observed in children (4,20).

Previous studies have shown a female predominance with increasing age (5,12,21) and some authors have found a large female predilection (1) of up to 22:1 in adolescents (22). In the present series the sex ratio was equal overall and, surprisingly, in the subset of 12 years of age or older, only 55% were female.

Reports in the literature have documented that most gallstones in children are diagnosed in the second decade but that there is also a large number found in infancy (5,20,23). The overall age distribution of our patients concurs with the literature, as 15.2% were under 1 year of age and there were more adolescents ages 10 to 18 years than there were children ages 1 to 9 years (200 vs 126). The mean age in our patients was 9.4 years; children in the asymptomatic group had a mean age of 8.2 years, which was somewhat younger than the mean age (10.2 years) in the symptomatic group.

We divided the patients into 2 groups based on symptoms. The first group of patients had clinically silent or asymptomatic gallstones. Our confidence in classifying these asymptomatic patients was high. The symptomatic group then included all of the other patients who had any symptoms or clinical signs (pain, fever, vomiting, jaundice, and pale stools, and, in infants, irritability) potentially related to the presence of gallstones. As a result, this second group contains a large spectrum of symptoms, ranging from classic biliary colic to nonspecific symptoms, such as vomiting or vague abdominal pain. We acknowledge that the gallstones in some of these patients may not have been the cause of the symptoms. This is especially true of infants, in whom symptom assessment is even more difficult. This limitation of the present study reduces the strength of any statements made about the symptomatic group. Other limitations of this study are its retrospective design and the limited average follow-up period of 3.2 years.

At the time of diagnosis, 51% of our patients were clinically asymptomatic. This is lower than the 66% to 82% reported in adults (24,25) but greater than the 40% reported by Wesdorp et al (12) in children. The greater percentage of asymptomatic patients in our study may reflect the continually increasing use of abdominal sonography in pediatrics for reasons other than biliary disease.

The rate of significant complications of gallstones was lower in our asymptomatic group compared with the symptomatic group (5% vs 28%, $P < 0.001$). This finding is consistent with that of earlier studies (12). Accordingly, the asymptomatic group had a lower cholecystectomy rate for symptoms than the symptomatic group (3% vs 59%). It is also noteworthy that 41% of patients who were initially symptomatic did not require surgery during our period of follow-up. In these patients, who had a single symptomatic episode with rapid resolution of symptoms and no recurrence, a trial of nonoperative management was successful. Other factors, which may have influenced the decision to manage nonoperatively, include patient or parent objections to surgery or high operative risk due to comorbidities. Because the strength of any conclusions regarding the symptomatic group is reduced due to the inclusion of patients with nonspecific symptoms, we cannot advocate nonsurgical management for these patients based on this study. Cholecystectomy remains the standard of care for children with symptomatic gallstones.

Some studies have suggested that pancreatitis is the most common complication of gallstones in children (1,5), whereas others have found that acute cholecystitis or obstructive choledocholithiasis was more common (6,26). In our patients, choledocholithiasis was the most common, followed by acute cholecystitis.

Resolution of gallstones was documented in 17% of our asymptomatic patients who had sonographic follow-up, which gives credibility to the argument for conservative management of these patients. The resolution rate in our symptomatic patients who had sonographic follow-up appears to be higher at 29%, but this is distorted by the reduction in the denominator due to the 111 cholecystectomies in this group. If surgical patients are included, then this figure falls to only 6%. Another potential confounding factor is that some asymptomatic gallstones may have also been included in this group due to nonspecific symptoms. Young age was the only factor associated with an increased rate of stone resolution. Resolution or disappearance of gallstones on sonography has been

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well documented in infants but not in children older than 1 year of age. In the present series, we documented disappearance of the stones in 34% of follow-up ultrasounds in patients 1 year or younger and in 13% of patients older than 1 year. This observation in our infants is close to the 33% observed in infants by Schirmer (27) but is lower than the 50% to 75% resolution rate reported by some other authors (17,28). These latter higher rates may be explained by a potentially greater sample bias in these smaller series of only 10 and 4 patients, respectively. There is no literature on gallstone resolution in older children, and to the best of our knowledge, there is no explanation to date for the mechanism of disappearance of gallstones on sonographic examinations. We assume that these stones undergo some sort of dissolution possibly due to alterations in bile composition and/or removal of the stimulating factor for stone formation. In none of our patients was there any definite clinical evidence of biliary pain or obstructive jaundice to suggest passage of the stones through the common bile duct. However, it is impossible to exclude asymptomatic passage of the stones through the duct.

TPN therapy and cardiac surgery were the most common risk factors in the asymptomatic group. TPN is a well-recognized risk factor for gallstone formation, especially in children with associated ileal disease or resection. With both of these risk factors, gastrointestinal function is abnormal with the development of bile stasis and the disappearance of the normal enterohepatic circulation of bile salts (4). The incidence of biliary calculi in children requiring TPN for 3 months or more has been found to be as high as 43% (29). Cardiac bypass is thought to lead to gallstone formation by causing acute hemolysis. It has also been postulated that cyclosporine and azathioprine may contribute to lithogenesis in the heart transplant population (26). Although this has not been a major risk factor in other series, it was so in this study, largely due to the large cardiac surgical practice at our institution.

Sickle cell disease, spherocytosis, and elliptocytosis were the most common risk factors in the symptomatic group, accounting for 37%. Overall, 25% of cases of gallstones were associated with congenital hemolytic anemia. In the past, hemolytic disease was thought to account for the majority of gallstones in children. However, in recent years, studies have found that this proportion has fallen to 20% to 25% (4,6) because the other risk factors become more prevalent. Symptoms were present in 76% and 68% of patients with sickle cell disease and spherocytosis, respectively, and cholecystectomy was required in 72% and 100% of these patients, respectively.

Obesity has been reported to be a frequent risk factor in older children (1,4,12). The rate of obesity in our group was extremely low (<1%). However, it has been shown that obesity is underdiagnosed in children. Riley at al (30) found that children with a body mass index between the 85th and 94th percentiles were diagnosed as overweight during only 4% to 8% of clinic visits. As a result, the true level of obesity and its role as a risk factor may be underestimated in this retrospective study. Parity is also a recognized risk factor for the development of cholelithiasis (2,22), but this was not observed in the present study.

Cystic fibrosis and inflammatory bowel disease have previously been included among the significant risk factors for gallstone disease in children (12,26), but these were not common in our series. Only 3 asymptomatic patients had cystic fibrosis. One patient with ulcerative colitis had asymptomatic gallstones but had cholecystectomy during liver transplant for primary sclerosing cholangitis. The single patient with Crohn disease was asymptomatic and required no surgical intervention.

The literature has documented that cholelithiasis is also being diagnosed with increasing frequency in the neonatal period and infancy (2). This is highlighted by comparing the present series, in which 58 (15%) patients were younger than 1 year of age, to our previous series between 1979 and 1985, in which there were only 20 patients in this age range (15). The recognized risk factors in infants include TPN, ileal disease, prematurity, dehydration, diuretics, hepatic immaturity, and cephalosporin therapy. Hemolytic disorders are less common in infants (18,31). In the present series, diuretics, TPN, and cephalosporins had been administered to 49%, 47%, and 45% of patients, respectively. The other commonly identified risk factor was cardiac surgery, which was present in 32% of cases. Short bowel syndrome was less common, and no patient had hemolytic anemia as the only risk factor. These risk factors are similar to those reported elsewhere (15–17), as well as our previous unpublished series (Fig. 5).

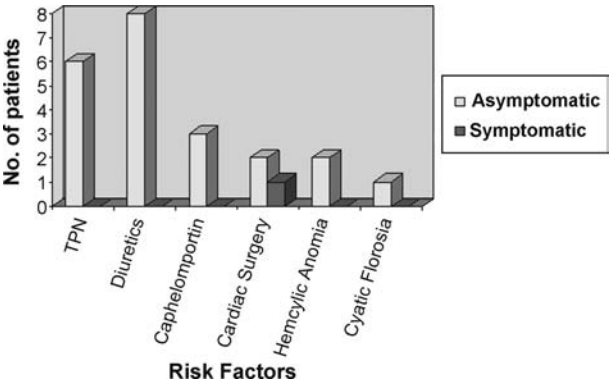

FIGURE 5. Risk factors for development of gallstones in infants diagnosed at the Hospital for Sick Children between 1979 and 1984 (unpublished).

The complication rate in infancy was low at 9% (5 of 58) with equal rates of acute cholecystitis and bile duct obstruction from choledocholithiasis. This agrees with the favorable prognosis observed by most authors (17,18,26,28) after early reports of high complication rates of gallstones in infancy (3,29). Cholecystectomy was required for symptoms in 1 case (2%) and performed during liver transplant in another. The low complication rate and high resolution rate, even in initially symptomatic infants, support nonoperative management in this age group.

In the adult population there is evidence to support the conservative management of gallstones (11). Based on the data from our large series, we conclude that clinically asymptomatic gallstones in the pediatric population are associated with relatively low rates of complications and may, therefore, be safely managed without surgical intervention.

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