Gallstones in Intestinal Failure

Jeremy M.D. Nightingale and Mattias Soop

Key Points

1. Gallstones are more common in patients with intestinal failure (IF) 38% at 20 years of parenteral nutrition at home. They are also common in patients with a short bowel (21% over 10 years).
2. Most (76%) patients receiving home parenteral nutrition (PN) with gallstones develop complications.
3. Gallstone formation may relate to a high-calorie and/or lipid parenteral nutrition, a lack of oral intake, an ileal resection or disease, and certain medications (anticholinergics, opioids or octreotide).
4. Supersaturation of bile, nucleation, crystallization and reduced gall bladder contractility are the key factors that contribute to gallstone formation. In IF patients biliary stasis is most relevant and leads to gall bladder sludge and the formation of gallstones containing calcium bilirubinate.
5. Medical therapy is rarely used to prevent or dissolve gallstones in IF patients due to unpredictable absorption of medication and a lack of proven benefit.
6. Gallstones might be prevented changing the bile composition directly (e.g. ursodeoxycholic acid) or indirectly by increasing gut transit (e.g. cisapride) or changing the bowel flora (e.g. metronidazole).
7. Prevention could also be by maintaining regular gall bladder contraction with oral diet, cholecystokinin injections, rapid amino acid infusions, non-steroidal anti-inflammatory drugs (NSAID's) and avoiding octreotide.
8. Cholecystectomy is recommended if there are gallstones present and surgery is being performed for another reason.
9. Prophylactic cholecystectomy and/or sphincterotomy are not recommended if there are no gallstones.

Introduction

Gallstones (stones in the gallbladder or biliary ducts or both) are a major public health issue and are present in 10–15% of adults in the Western world and are overall more common in women [1]. Of those with gallstones (mainly cholesterol ones) about 25% will develop symptoms, in particular women [2]. Gallstones are of three main types: cholesterol stones, comprising about 75% of stones; pigment stones; and mixed. While pigment stones may predominate in patients with intestinal failure (IF), all types of stones can occur [3]. Gallstones may cause severe and life-endangering complications from cholecystitis (typically large stones >10 mm), biliary colic, obstructive jaundice (often multiple stones), pancreatitis (small stones), bowel obstruction (a large stone which passes from the gallbladder through a choledocho-duodenal fistula into the small bowel, where it may cause obstruction in the duodenum or terminal ileum) and rarely gallbladder cancer or a cholangiocarcinoma. Generally, gallstones greater than 1–1.5 cm and of a high number are most likely to cause symptoms.

(a) *Cholesterol gallstones* are composed of cholesterol, mucin, bile pigments, calcium salts and other compounds. The pathogenetic factors for cholesterol gallstones include a genetic background, female, older age, sedentary life style, high fat diet, lack of fibre, pregnancy (high number of childbirths), hormone replacement therapy. Insulin resistance, as occurs with obesity, metabolic syndrome and type 2 diabetes is a common aetiological component. A further contribution may be from factors within the gallbladder: hepatic hypersecretion of cholesterol, supersaturation of bile (precipitation of cholesterol

J. M.D. Nightingale (✉)
St Mark's Hospital, Harrow, Middlesex, UK
e-mail: Jeremy.nightingale@nhs.net

M. Soop
Head of Section of IBD and Intestinal Failure Surgery, Karolinska University Hospital and Karolinska Institutet at Danderyd Hospital, Stockholm, Sweden
e-mail: Mattias.soop@ki.se

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Fig. 1 Pigment type gallstone of 1 cm from a patient with a short bowel

crystals), a sluggish gallbladder, mucin and inflammatory changes in the gallbladder. Factors outside the gallbladder include slowing intestinal motility, increased intestinal absorption of cholesterol, and altered gut microbiota [4, 5].

In patients with IF (having PN or with a short bowel) however, the predominant type of gallstones found are pigment stones. Cholesterol may also play a part in gallstone formation in this group.

(b) Pigment gallstones (Fig. 1) are composed of calcium bilirubinate and are classically associated with haemolytic anaemia but do occur in other circumstances. In North India, where obesity is common, gallstones are primarily (>80%) cholesterol stones whereas in south India where most are vegetarian (less spices and fat) and non-obese, most (>60%) are pigment stones [1]. Liver disease (non-alcoholic fatty liver disease and cirrhosis) are also associated with pigment gallstones. Patients with cirrhosis have an incidence of 2–5% per year (most common if an alcoholic aetiology, a more severe cirrhosis and a longer duration of cirrhosis), which is four times that of the general population [5].

Epidemiology of Gallstones in Intestinal Failure

Gallstones are prevalent in patients with acute or chronic intestinal failure, and in chronic illnesses such as Crohn's disease, after intestinal resections and with the long-term use of parenteral nutrition (PN). Increased rates of cholelithiasis and cholecystitis have been shown also following trauma, burns, truncal vagotomy and pregnancy.

Inflammatory Bowel Disease

There is an increased prevalence of gallstones (25%) (detected by cholecystography and ultrasonography) in patients with Crohn's ileitis or ileo-colitis [6–9] and these occur with equal frequency in men and women [8, 10]. These stones often appear calcified on a plain abdominal radiograph [7]. Gallstones are more common in patients with ileitis than in those with ileo-colitis or colitis [11] and the likelihood may increase with the length of bowel resected [10], the duration of disease, previous surgery and the age of the patient [8, 12].

Patients with loss of functioning distal ileum due to disease or surgical excision have a disruption to the normal enterohepatic circulation of bile salts. It was estimated that the frequency of gallstones in patients with an ileal resection greater than 50 cm in length was 33%, compared to 17% in those who had undergone a lesser resection [10]. However, some studies suggest that the likelihood of gallstone formation is not related to the site of disease or resection but to the duration of disease and previous surgery [12].

Patients with ulcerative colitis (without operation) have on average a 7–14% prevalence of gallstones, marginally more than controls [9, 12, 13]. The risk of stones is higher after a panproctocolectomy and ileostomy formation [6, 14]. A large series of patients (180) who had an ileostomy following a panproctocolectomy showed gallstones in 24–25%, (three times the incidence that might have been expected in a population of this age and sex distribution), it was higher if more than 10 cm terminal ileum had been removed [15].

Short Bowel

Work at St Mark's Hospital showed that 17/27 (63%) men and 15/47 (32%) women with less than 200 cm small bowel remaining had either had a cholecystectomy or were found to have gall stones on an ultrasound examination. This study included subjects who were nutritionally autonomous and subjects who required parenteral nutrition (PN). There was no difference between those with a colon in continuity (15 (44%)) and those with a jejunostomy (17 (43%)) [16]. Another study showed that 72 of 345 patients (21%) who had a total small bowel length less than 104 cm (19% had a jejunostomy) developed gallstones over a 10 year period. PN dependence (34% of patients) and a very short length of

remaining jejunum were independent risk factors. 39% developed symptoms (23/28 (82%) acute cholecystitis/cholangitis and 5/28 (18%) acute pancreatitis) [15].

Parenteral Nutrition

Anecdotal reports in the 1970s suggested that PN might be associated with an increased incidence of both acalculous cholecystitis and cholelithiasis [17]. There were also descriptions of massively dilated gallbladders in patients receiving PN [18]. Later studies confirmed the association between PN and gallstone formation. In one study of patients receiving PN for a minimum of 3 months, 23% developed gallbladder disease after commencement of PN [19]. There was a 40% incidence of gallbladder disease in this group receiving PN, which is significantly greater than that in Crohn's disease or ileal resection patients not receiving PN. The same researchers also found that the risk of development of gallstones whilst on PN was greater in patients of less than 30 years old and in patients whose ileal resection had been performed less than 15 years previously. Research on a population of children on PN showed that 43% of children on long-term PN (mean duration 20 months) developed gallstones [20].

Subsequent studies also showed that long-term parenteral nutrition in both adults and children is commonly associated with gallstones (40%) [19–25], which in patients with a short bowel are often symptomatic [24]. Acalculous cholecystitis may occur but is less common [17, 23]. Gallstones were more common in men than women in one study [22].

Patients receiving PN frequently develop sludge and may go on to develop gallstones [21]. Dray et al. prospectively followed adult patients with a gallbladder in situ receiving HPN and 45/119 (38%) developed gallstones and/or biliary sludge (14 sludge alone), the probability of developing them was 21% at 1 year and 39% at 2 years. Eight of the 45 developed biliary complications. It was estimated that the incidence of biliary complications was 5% at 1 year and 10% at 2 years. No or negligible oral intake was associated with the development of gallstones. There was no difference in incidence between the sexes in this study [26].

Appleton showed that 17/63 (27%) of patients with no previous gallstones developed them over a median of 11 years of HPN. The cumulative incidence was 21% at 10 years, 38% at 20 years and 47% at 30 years. No less than thirteen of the 17 (76%) had symptoms (4 biliary colic, 4 acute pancreatitis, 2 common bile duct (CBD) stones, 1 cholangitis, 1 empyema/abscess) and 10 of these required surgical or endoscopic interventions. Increased energy content and the provision of lipid were predictors for cholelithiasis [27]. The authors concluded that complications from gallstones were so common that en-passent cholecystectomy is warranted when gallstones are present; in other words, during abdominal surgery for other reasons, the gallbladder should be removed if safe [27].

Biliary Sludge in PN and Crohn's Disease

Biliary sludge formation is an important stage in gallstone development and is associated with PN. Messing et al. reported a progressive increase in the incidence of biliary sludge from 6% after 3 weeks of PN to 50% between 4 and 6 weeks, and reaching 100% in patients receiving intravenous nutritional therapy for more than 6 weeks [21]. Sludge appears to precede gallstone formation; gallstones were then noted in six of 14 patients who developed sludge, while none of the patients without sludge developed gallstones. Interestingly, five of seven patients who earlier had sludge or gallstones were found to be free of both after a short period of oral refeeding [21].

There are considerably less data available on the prevalence of sludge in Crohn's disease itself without the concomitant use of PN but reduced gallbladder contractility, which predisposes to biliary sludge, has been demonstrated especially in those who have undergone ileal resection [28].

Biliary sludge also commonly develops rapidly in patients on an intensive care unit. Some of these patients had a previously recognized risk factor such as abdominal surgery or PN but neurosurgical procedures were also associated with sludge formation [29].

Pathogenesis of Gallstone Disease

Supersaturation of bile, nucleation and crystallisation, and reduced gall bladder contractility are the traditional factors that produce "lithogenic bile". In patients with IF the stones, while containing some cholesterol, are mainly of pigment type composed of calcium bilirubinate. The stones develop within biliary sludge, which has formed due to gallbladder stasis often due to a period of no or reduced oral intake. Biliary sludge contains calcium bilirubinate or unconjugated bilirubin, cholesterol monohydrate crystals and increased amounts of mucin glycoproteins [30]. Biliary sludge may disappear spontaneously but frequently evolves into gallstones [31]. Sludge may persist or recur in 50% of cases and gallstones may form in up to 14% of affected subjects over 3 years [25]. Calcium bilirubinate crystals, within biliary sludge, are more commonly found in men than women [32].

Supersaturation of Bile

While pigment stones are most common, cholesterol supersaturation is well researched and may occur and contribute to the genesis of gallstones [3]. Cholesterol is secreted into the bile canalicular lumina and subsequently taken up by biliary lipid vesicles with a cholesterol: phospholipid ratio of 0.34: 0.38, but the ratio is higher in lithogenic bile [33, 34]. Cholesterol, lecithin (the most abundant biliary phospholipid) and bile salts aggregate to produce mixed micelles and

vesicles in bile, in which the hydrophilic portions of these lipids are located peripherally with the hydrophobic portions orientated centrally in a hydrophobic domain, thus permitting lipid solubility in an aqueous environment [35]. Cholesterol solubility in bile has been defined using a triangular coordinate map comprising cholesterol, bile salts and phospholipids [36, 37]. Bile supersaturated with cholesterol may be a result of increased cholesterol secretion or decreased phospholipid or bile salt secretion. Cholesterol-rich vesicles play an important part in the formation of cholesterol crystals [38].

Nucleation and Crystallization

Bile contains both anti-nucleating and pronucleating factors, the balance of which is important in determining the likelihood of gallstone formation. Apolipoprotein A-1 and A-2, and a glycoprotein (120 kDa), all found in human bile, have been identified as anti-nucleating factors [39]. Pro-nucleating factors include both mucin glycoproteins [40] and non-mucin glycoproteins [41]. Mucin is thought to play a significant role in crystallization of cholesterol. The evidence for this comes from three main sources. First, mucin glycoproteins have been found in the matrix of cholesterol gallstones [42]. Second, mucin hypersecretion precedes crystallization of cholesterol in animal models [43] and probably humans [44]. Third, mucin has been shown to promote crystal nucleation in cholesterol supersaturated bile *in vitro*. Mucin may act as a nidus for crystal aggregation by entrapping cholesterol crystals or calcium bilirubin on non-glycosylated hydrophobic domains of the peptide chain of the mucin glycoprotein molecule [45].

In addition to mucin, several other non-mucin pronucleating factors have been identified *in vitro* such as amino peptidase N, a low-density lipoprotein particle, and haptoglobins.

Crystal growth in bile follows nucleation. Cholesterol monohydrate crystals are composed of bilayers of cholesterol bonded to a water layer. Rapid growth occurs as these crystals pack side-by-side in their long axis, resulting in plate-like monohydrate crystals. Cholesterol also precipitates in other forms such as helical, tubular and filamentous forms of non-hydrated cholesterol [46].

Gallbladder Contractility

As well as cholesterol supersaturation and mucin hypersecretion, reduced gallbladder contractility appears crucially important in cholelithiasis by allowing the cholesterol crystals entrapped in mucin to grow to a sufficient size to allow them to remain in the gallbladder. Early cholesterol crystals are likely to develop into macroscopic stones only if formed in the mucus layer adherent to the epithelium in gallbladders with reduced contractility.

It would appear that all three requirements—cholesterol/calcium bilirubinate supersaturation, increased nucleation rate mediated by mucin hypersecretion, and reduced gallbladder contractility—occurring simultaneously allow cholelithiasis to occur (the "triple defect of gallstone formation").

Pigment stones have been shown to be largely composed of calcium bilirubinate and other calcium salts. Less is known about the process of pigment stone formation than about cholesterol gallstones, but biliary stasis appears to play a major role. Unconjugated bilirubin concentration is higher in gallbladder bile in patients with pigment gallstones than in controls and it is likely that unconjugated bilirubin forms gallstones by precipitation in a similar fashion to that of cholesterol [47].

Biliary Sludge

Biliary sludge may be an important intermediate factor in the formation of gallstones [45]. Sludge was initially identified by ultrasonography as low amplitude echoes without acoustic shadowing which layered in the most dependent portion of the gallbladder [48] (Fig. 2). Biliary sludge is an amorphous precipitant of mucin glycoproteins, bile pigment granules (calcium bilirubinate), cholesterol crystals, small stones, protein and lipids. An ever-present constituent of biliary sludge in humans is calcium bilirubinate or unconjugated bilirubin. Cholesterol monohydrate crystals and a marked increase in the amount of mucin are found in biliary sludge [45]. They also noted that the cholesterol and phospholipid concentration in bile from sludge-forming patients was no different to that of normal controls and gallstone patients [45].

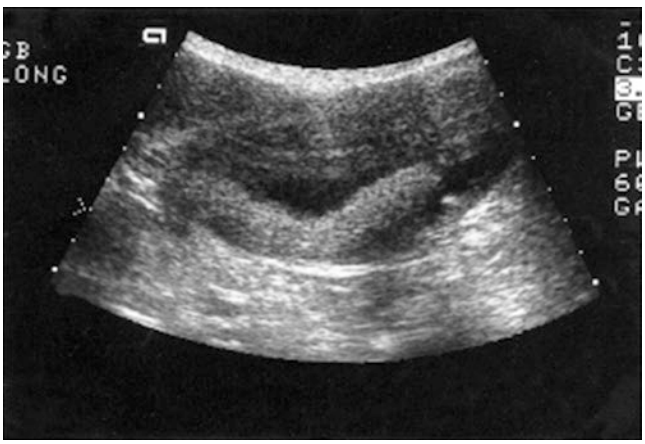

Fig. 2 Ultrasound image of the gallbladder in longitudinal section showing layering of sludge without acoustic shadowing (courtesy of Professor M. J. Lee, Radiology Department, Beaumont Hospital, Dublin 9)

Several possible factors leading to biliary sludge formation are cited in the literature including biliary stasis (due to no or little oral intake), use of total parenteral nutrition, mucin hypersecretion, bile infection and acute illness. A definite association between development of biliary sludge and gallbladder stasis has been noted especially in patients receiving total PN with no oral intake [24].

The exact mechanism of sludge formation has not yet been elucidated but one theory is that decreased gallbladder contractility leads to bile becoming progressively more concentrated due to water absorption and the cholesterol vesicular carriers becoming enriched in cholesterol content and depleted of lecithin and other phospholipids. Crystals of cholesterol are thus formed, and calcium salts (especially bilirubinate) precipitate secondary to stasis as well. Thus, sludge may form. Prolonged stasis and further growth may lead to the development of gallstones [49]. Biliary sludge may disappear spontaneously or have a fluctuating course but it frequently evolves into gallstones [50]. It would appear that sludge may persist or recur in at least 50% of cases and that gallstones may form in up to 14% of affected subjects over 3 years [51]. Biliary sludge always represents a pathological process and cholecystitis is common [52].

Intestinal Microbiota

Bile acids are cholesterol-derived molecules that can be modified by the gut microbiota and can act as signaling molecules to regulate metabolic and physiological processes. The gut microbiota releases many enzymes that can modify the bile acids such as bile salt hydrolases (7α-dehydroxylase, and hydroxysteroid dehydrogenase). These enzymes can change the gut microbiota composition, and thus alter the bile acids (more secondary bile acids) and so predispose to gallstone formation. A slower gut transit time also allows more secondary bile acids to be manufactured.

Pathogenesis of Gallstones in Intestinal Failure

Gallstones in IF patients may occur due to ileal disease/resection, fasting, PN, surgery, rapid weight loss or drug treatments (Fig. 3). Bacterial overgrowth may have a role.

Surgery, weight loss and parenteral nutrition may all involve prolonged fasting. The main drugs that are causative are anticholinergic agents, opioid analgesics or octreotide. Other factors may include poor cholecystokinin secretion and less physical activity.

Ileal Disease/Resection

While disruption of the enterohepatic circulation and consequent loss of bile salts should lead to an increase in cholesterol saturation (relates to concentrations of cholesterol, bile salts and phospholipids); this was the case in some studies of patients with "ileal dysfunction or resection" [53, 54] but not in others [53]. A reduced amount of deoxycholic acid and an increased amount of ursodeoxycholic acid are found in the bile of patients with ileal Crohn's disease [54, 55]. Bilirubin concentrations are two- to threefold higher in patients with ileal disease compared to those with no ileal disease [54, 55] while phosphatidylcholine levels are not different [54]. The majority of patients (children and adults) who undergo ileal resection and require long-term PN develop pigment gallstones [56]. Of note, some researchers have found normal or even low cholesterol saturation of bile after resection of ileum [55]. In patients with Crohn's disease gallbladder contractility is reduced after a fatty meal [31, 57], which may contribute to the formation of biliary stasis. The fasting gallbladder volume is decreased and fasting plasma cholecystokinin levels are surprisingly increased in patients with Crohn's disease of the large bowel and patients after an ileocecal resection) [58].

Much data suggests that ileal resection results in alteration of bilirubin rather than cholesterol metabolism so resulting in pigment gallstone formation (Table 1). Ileal resection

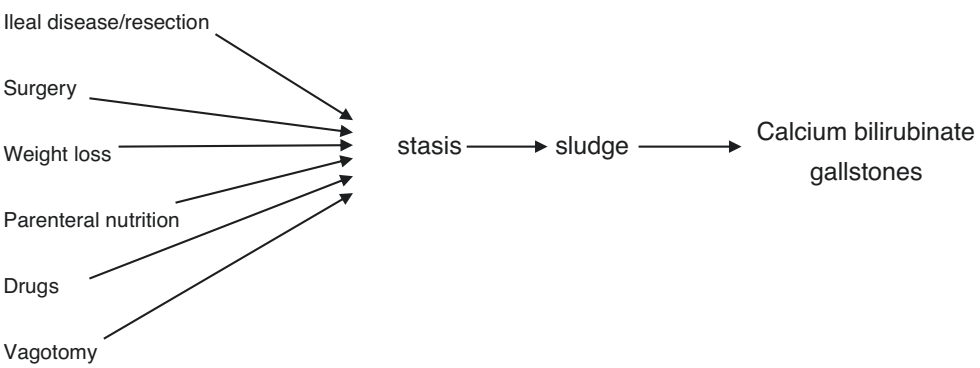

Fig. 3 Pathogenesis of gallstones in patients with intestinal failure

Table 1 Gallstones in Crohn's disease: disturbance of cholesterol or bilirubin metabolism?

Researchers	Year	Subjects	Main findings
Dowling RH, Bell GD, White J [53]	1972	Patients with Crohn's disease	Increased cholesterol saturation index
Dowling RH, Mack E, Small DM [59]	1971	Rhesus monkey's ileal resection	Cholesterol supersaturation Lithogenic bile model
Kelly TR, Klein RL, Woodford JW [60]	1972	Prairie dog's ileal resection	Increased cholesterol/ phospholipid ratio
Pitt HA, Lewinski MA, Muller EL, Porter-Fink V, Den Besten L [61]	1984	Prairie dog's Ileal resection	Pigment gallstones Increased bilirubin concentration in bile
Brink MA, Slors FM, Keulemans YCA, et al. [62]	1999	Patients with Crohn's disease or ileal resection	Increased bilirubin levels in bile, probably secondary to enhanced colonic uptake of bilirubin

in the prairie dog led to the development of pigment gallstones in 44% of animals compared to none in the control group [61]. Calcium bilirubinate crystals were found in up to 94% of animals who underwent ileal resection and in none of the control groups. It was noted that calcium and total bilirubin concentrations in bile were significantly greater in ileal-resected animals.

Data from patients with ileal resection receiving TPN have shown that there is a predisposition to development of pigment gallstones. Analysis of stones from adults and children who have had significant ileal resection necessitating long-term parenteral nutrition shows that pigment rather than cholesterol stones form in the majority of these patients [56].

Research in humans has shown that there is a three- to tenfold increase in bilirubin levels (unconjugated and conjugated) in gallbladder bile in patients with ileal disease and/or resection for Crohn's disease compared to patients with ulcerative colitis or Crohn's colitis [62]. Biliary bilirubin concentrations correlated positively with the anatomic length of resection and duration of ileal disease. This shows that there is an increase in the enterohepatic cycling of bilirubin secondary to enhanced uptake of bilirubin in the colon. This may explain the increased risk of pigment gallstone formation in patients with terminal ileal Crohn's disease and after an ileal resection.

There are several proposed mechanisms for reduced gallbladder contractility in Crohn's patients. Reduction in intestinal release of cholecystokinin or other peptides due to proximal small bowel disease may be a factor [63]. The number of argentaffin cells in colonic mucosa in patients with ulcerative colitis is reduced [64]. Reduction in levels of peptide YY concentration in the colonic mucosa of patients with ulcerative colitis and Crohn's disease has also been demonstrated [65]. Thus, changes in peptide secretion by small and large bowel may occur in Crohn's disease and may influence gallbladder contractility.

In contrast to the increased prevalence of gallstones in women compared to men in the general population, female sex does not seem to be a risk factor for gallstones in Crohn's disease [10]. In fact, some data suggest a higher prevalence of gallstones in men receiving PN compared to women [22]. Men with a short bowel with or without a retained colon have a much higher prevalence of gallstones than women [16].

A diagnosis of CD, intestinal surgery, prolonged NSAID use, disease activity and duration and bowel stenosis have been associated with cholecystonephrolithiasis in IBD [66].

Fasting and Parenteral Nutrition

Patients who have a reduced or absent oral intake (e.g. if having total PN) may experience long periods when food-stimulated intestinal hormone secretion (e.g. cholecystokinin) is not activated. Cholecystokinin secretion in response to a meal is significantly decreased in short bowel patients [67]. This may result in gallbladder stasis and the rapid formation of biliary sludge [21, 50, 68]. As reviewed above, the incidence of biliary sludge rapidly increases from 6% at three weeks of TPN to 50% between four and six weeks, and 100% after 6 weeks [21]. The sludge gradually disappears when oral refeeding is begun [21]. Gallstones will have started to become apparent by 4 months [21]. Bile is not supersaturated consequent on TPN [69], but bile flow is impaired [70] and gallbladder emptying during both continuous and cyclic infusions is reduced [71]. A medium/long chain triglyceride mixture in a PN regimen may be more likely to cause biliary sludge than one of long chain triglycerides alone [67]. In children on PN, cholelithiasis may be associated with a massively dilated gallbladder [18].

Bile flow is impaired when PN is given [70]. Current evidence suggests that bile is not supersaturated as a consequence of PN [69], but that prolonged stasis may be the key pathogenetic mechanism for increased cholelithiasis. The evidence for the dominant role of stasis in this scenario comes from several sources. Gallbladder contractility measured by ultrasound is reduced in patients receiving parenteral feeding [71]. The cholesterol saturation index in bile in prairie dogs receiving PN is not increased but gallbladder stasis is noted [72].

Improved radiological imaging has lent itself to the investigation of gallbladder disease. Radionuclide imaging of the gallbladder revealed biliary tract abnormalities in 92% of patients who received PN [73]. Ultrasonographic measurements of gallbladder motility during use of PN showed that, while maximal gallbladder volume was similar in PN patients and controls, gallbladder emptying was significantly reduced in parenterally fed patients during both continuous and cyclic infusion [71].

The mechanism underlying impaired gallbladder contractility in patients receiving PN is unclear. In one animal model using cholesterol-fed ground squirrels, agents which bypassed receptors and their subsequent interactions with calcium channels in the sarcolemma can restore gallbladder contractility in gallstone disease [74]. This suggested that bile saturated with cholesterol causes excessive integration of cholesterol into the sarcolemma, thus changing its functional characteristics. The primary smooth muscle defect in this animal model would appear to involve the sarcolemmal membrane, rather than the intracellular signal transduction pathways or contractile apparatus [73].

The finding of biliary sludge and potential for gallstone formation during PN has also been documented during fasting after surgery. Ultrasound studies have provided evidence of the relationship between prolonged periods of fasting and gallbladder sludge formation in patients who have undergone gastrointestinal surgery [68].

Is gallbladder Stasis Alone Sufficient to Cause Gallbladder Disease in Patients Receiving PN?

In untreated coeliac disease, the gallbladder enlarges, contractility after a fatty meal is reduced and biliary sludge may occur [75, 76]. Reduced gallbladder contractility in response to a fatty meal has been noted in coeliac disease. This defect appears to correlate well with decreased cholecystokinin secretion [77]. Furthermore, gallbladder emptying improves after successful treatment with a gluten-free diet [77]. However, no increase in the prevalence of cholelithiasis has been found in patients with coeliac disease despite impaired gallbladder contractility. Thus, factors other than gallbladder stasis may be important in the development of gallstones but the lack of enteric stimulation of bile flow and impaired gallbladder contractility secondary to the absence of significant oral intake may be the primary factors in biliary sludge and gallstone development during PN use.

Type of Feed

In adults those receiving parenteral lipid were at greatest risk of stones [27]. In children on PN there was a higher prevalence of sludge on pure soya lipid. Predictors for sludge in these children were young age at PN, lack of enteral feed, and a motility disorder with stoma [78].

Surgery

Major abdominal (not involving the biliary system) [79], cardiac valve replacement surgery [80] and a period in an intensive care therapy [29] all predispose to gallstone development with an equal sex incidence. This is again likely to be due to bowel rest causing biliary stasis, biliary sludge and the formation of gallstones.

Many factors appear to influence development of gallstones in patients with inflammatory bowel disease who undergo surgery, including gender, episodes of fasting, TPN and the type of surgery involved. Particular operations such as ileal resection, which interfere with the enterohepatic bile salt cycle, are more likely to lead to gallstone formation. Major abdominal surgery itself (not involving the biliary system) also appears to accelerate gallstone development in some patients. Indeed, in one retrospective study of gallstone formation after major abdominal surgery, surgery and age were the only statistically significant independent predictors of gallstone development during follow-up [79].

The possible mechanisms responsible for gallstone formation in patients who have undergone major abdominal surgery outside the biliary tract. Lee et al. found that sludge preceded gallstone formation in six of 14 sludge-forming patients receiving TPN [51]. Gallbladder stasis and bowel rest were felt to be important factors in sludge development. Patients on intensive care units (who undergo periods of fasting) are predisposed to sludge development.

Harrison et al. found that patients who underwent valve replacement surgery for rheumatic heart disease had a gallstone prevalence of 39% compared to 12% in a matched control population [80]. No difference in the degree of haemolysis between the two groups was detected; undermining the suggestion that excess haemolysis might be the cause of increased cholelithiasis in the surgical group.

This finding has important practical and financial implications, and identification of patients at risk for development of gallstones postoperatively might encourage the use of prophylactic measures such as earlier enteral feeding or administration of cholecystokinin.

Rapid Weight Loss

Cholesterol gallstones are common (40%) in morbidly obese patients and this figure increases with a diet causing rapid weight loss or after weight reducing surgery [81]. 38% of patients undergoing gastric by-pass surgery developed gallstones and a further 12% developed gallbladder sludge [82] and these formed during the time of maximal weight loss. Reduced gallbladder motility is likely to be the most important factor but cholesterol saturation also increases [82]. A significant increase in the gallbladder volume occurred in obese patients taking a low-energy, low-fat diet after 10 days [83], and could be secondary to minimal cholecystokinin secretion or to excess secretion of pancreatic polypeptide or somatostatin (gallbladder wall relaxants).

The proposed factors involved in gallstone formation during weight loss include impaired gallbladder motility and modifications in biliary nucleation. Twenty-one obese patients were placed on a low-calorie, low-fat diet for weight

reduction purposes [83]. A significant increase in the gallbladder volume after 10 days ingestion of this diet was noted, and was attributed to poor gallbladder contractility secondary to minimal stimulation of cholecystokinin secretion or to excess secretion of gallbladder wall relaxants such as pancreatic polypeptide or somatostatin [84, 85].

Drug Treatments

The use of narcotics [86] and anti-cholinergics [87] both of which reduce gallbladder contractility, in patients receiving PN has led to an increase in gallbladder disease. Narcotics, by reducing bile flow through the sphincter of Oddi, encourage gallbladder stasis, and anti-cholinergics have been shown to antagonize the protective effect of sphincterotomy on gallstone formation—both lending strong support to the idea of gallbladder stasis playing the most important role in gallstone formation. Loperamide inhibits gallbladder contraction in healthy subjects at daily doses of 16 mg [88] and inhibits pancreatic and biliary secretions in patients with a short bowel at 6 mg daily [89].

Octreotide, a long-acting somatostatin analogue often used in the treatment of a high output jejunostomy, increases the risk of cholelithiasis [87]. It reduces post-prandial gallbladder contractility [90] secondary (more lithogenic) bile acids are formed by intestinal bacteria [91] and it inhibits cholecystokinin secretion.

Cholecystectomy and Sphincterotomy

As several risk factors have been identified for cholelithiasis in patients with a short bowel, namely ileal resection (especially if fewer than 120 cm of intestinal remnant is left), resection of the ileo-colonic junction, long-term PN and the presence of Crohn's disease itself, a role for prophylactic cholecystectomy in patients with a short bowel has been suggested [92]. In patients with a short bowel, cholelithiasis is usually symptomatic, often complicated by inflammation or bile duct stones, and is associated with a significant morbidity and mortality postoperatively.

The cumulative incidence for cholecystectomy in patients with Crohn's disease after an ileal resection was 0.5% at 1 year, 2.4% at 5 years, 4.6% at 10 years, and 10.3% after 20 years with a higher rate in women, and higher than in the general population [93]. Prophylactic cholecystectomy should be considered when an abdominal procedure is being done in patients with IF and gallstones [27]. The rationale for performing such an en-passent cholecystectomy is the markedly increased incidence of complications to gallstones in IF (76% in one study) [27]. Cholecystectomy is not without problems; however, as a postoperative bile leak may interfere with the healing of any new intestinal anastomosis. Longer-term, it may shorten gut transit time (mainly by accelerating colonic transit) and so increase dependency on PN. These sequelae which may be due to a change in bile acid composition (more diarrheogenic secondary bile acids) develop early and persist for at least 4 years [94]. Furthermore, some data suggest that patients who have a short bowel and a cholecystectomy may be more prone to liver fibrosis/cirrhosis [95].

Medical Prevention and Dissolution Therapies

There are many therapies that may prevent cholesterol gallstones (Table 2). It is more difficult for pigment stones. The studies/reports suggest that cholesterol gallstones can be prevented by giving statins, ezetimibe, w3 polyunsaturated fatty acids, liraglutide and many herbal, complementary or alternative medicines [1]. Dietary factors that may prevent the development of cholesterol gallstones include a vegetarian diet, polyunsaturated or monounsaturated fat, fiber, and caffeine. In the past direct contact dissolution of cholesterol stones was done by infusing methyltertbutylether via a cannula into the biliary tree. Experimentally calcium bilirubinate stones can be dissolved in a mixture of glycerol octanoate and EDTA [96], but no practical method of dissolving them have been used in human clinical trials.

The role of medical treatments for gallstones has diminished, but may on occasions, be considered an alternative to cholecystectomy in those patients who are not suitable for surgery. The main medical treatment for gallstones, used alone or in combination with extracorporeal shockwave lithotripsy, is an oral bile salt (originally chenodeoxycholic acid then subsequently ursodeoxycholic acid).

Changing Bile Composition

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) and chenodeoxycholic acid may, in addition to being used to help cholestatic IFALD, have roles in both prevention and dissolution of gallstones in patients with intestinal failure. Chenodeoxycholic acid was

Table 2 Prevention of gallstones and biliary sludge

Cholecystectomy and/or sphincterotomy	
Change bile composition	
• Directly	Ursodeoxycholic acid
• Indirectly	
– Change intestinal microflora	Antibiotics (Metronidazole)
– Increase gut transit	Prokinetics (Cisapride)
Prevent biliary stasis (promote gallbladder emptying)	
• Enteral feed	
• Cholecystokinin	
• Rapid amino acid infusions	
• NSAID's	
• Avoid octreotide	

used first but due to a dose-dependent increase in aminotransferases, an increase in serum low-density lipoprotein cholesterol and the development of bile salt-induced diarrhoea, it was superseded by ursodeoxycholic acid (urso stands for bear from which it is derived) and has been successfully used for patients to dissolve gallstones.

UDCA decreases biliary cholesterol saturation by 40–60% (i.e. makes cholesterol more soluble and less able to crystalize), by inhibition of cholesterol absorption in the intestine, reducing cholesterol secretion into bile and reducing the concentration of several crystallization-promoting factors (for example, amino-peptidase N, haptoglobin and some immunoglobulins) [97–99]. In addition UDCA decreases the toxicity of bile acids which can damage cell membranes and cause cholestasis [100].

UDCA is most effective in patients with good gallbladder function (and a patent cystic duct) who have few small non-radio-opaque cholesterol stones (<10–20 cm in size). UDCA has been used successfully to reduce the number of episodes of pancreatitis due to microscopic gallstones or biliary sludge [100]. The bile salt therapy may be required for more than 6 months. The problem of UDCA is that there is a high recurrence rate of gallstones of 30–50% at 5 years and 50–70% at 12 years, after successful treatment [101].

UDCA has not been studied in IF patients in whom there may be major problems with absorption.

Increase Gut Transit or Change Intestinal Microflora

Slow intestinal transit results in more primary bile acids being converted by bacteria to the more lithogenic secondary bile acids. Cisapride increases gastrointestinal transit rate (reversing any changes of octreotide treatment) and changes bile composition [91]. Thus it or another prokinetic drug could be useful in preventing gallstones in patients with intestinal failure due to small bowel dysfunction.

Metronidazole, by suppressing anaerobic intestinal organisms, reduced the rise in liver enzymes associated with parenteral nutrition in Crohn's disease [102]. This may be another simple way of reducing the chance of developing gallstones.

Prevent Biliary Stasis (Promote Gallbladder Emptying)

Oral Diet, Cholecystokinin, Rapid Amino Acid Infusions

As discussed cholestasis is an important contributor to the formation of gallstones and in part may be due to a lack of oral intake and thus reduced cholecystokinin which stimulates gallbladder contraction. cholecystokinin levels are low after a meal in patients with a short bowel and receiving PN [63]. Thus an oral diet and cholecystokinin injections could be a good preventative option in patients having PN with no or little oral intake. In prairie dogs, daily injections of cholecystokinin [30], or sphincterotomy [31], prevented gallstone formation. Data from human studies suggest that use of cholecystokinin in patients receiving TPN stimulates gallbladder emptying and prevents stasis and subsequent sludge formation [32, 72]. The prophylactic use of cholecystokinin in adult patients receiving total (no oral intake) PN, especially those with an ileal resection in whom the incidence of gallstone formation is increased may be beneficial. In children of whom 10% develop mostly asymptomatic gallstones while having total PN, cholecystokinin-octapeptide prophylaxis did not prevent the PN-associated gallstones forming. In addition, URDA did not dissolve gallstones, once identified [103].

The use of rapid infusion of amino acids [104–106] for example 125 mL of an aminoacid mixture (Synthamin 14 without electrolytes) over 5 min (2.1 g/min) produced a 64% reduction in gallbladder volume within 30 min [105]. A rapid infusion prevents the formation of biliary sludge [106].

Aspirin and Non-steroidal Anti-inflammatory Drugs

Studies involving the cholesterol-fed prairie dog showed that use of high-dose aspirin prevented gallstone recurrence after successful dissolution therapy. A decrease in mucin glycoprotein involved in nucleation was found and, as aspirin is an inhibitor of prostaglandin formation, it was suggested that secretion of mucin might be prostaglandin-mediated [107]. However, research in the same model showed that, at therapeutic doses, non-steroidal anti-inflammatory drugs (NSAIDs) had minimal effect on the production of mucin by the gallbladder [108].

NSAIDs may prevent gallstone formation by a prokinetic effect on the gallbladder. In a human study, subjects with gallstone disease given therapeutic doses of indomethacin had increased post-prandial gallbladder emptying [109]. This effect was not seen in healthy control subjects. The concentration of various eicosanoids in the gallbladder wall changes with bile cholesterol supersaturation and chronic inflammation and it may be that inhibitors of prostaglandin formation such as NSAIDs promote the production of prokinetic leukotrienes or prostaglandins in diseased but not in healthy gallbladders.

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