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REVIEW ARTICLE

# Asymptomatic Gallstones (AsGS) – To Treat or Not to?

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**Abstract** With ready availability of abdominal ultrasound, asymptomatic gallstones (AsGS) are being diagnosed with increasing frequency. Management decisions need to take into account the natural history of AsGS as well as the risks of cholecystectomy. Long-term follow up studies from the West have consistently shown that only a small minority of asymptomatic gallstones lead to development of symptoms or complications. Some sub-groups of patients (eg those with chronic hemolytic syndromes) have been shown to be at a higher risk of developing symptoms and complications and prophylactic cholecystectomy has been advised for them. Clear division of patients into low or high risk categories is still far from ideal and better identification of risk factors and risk stratification is needed. Overall, both open and laparoscopic cholecystectomy, are generally safe procedures. However, the incidence of bile duct injury (with all its serious consequences) continues to be higher with laparoscopic cholecystectomy and this should receive due consideration before offering prophylactic cholecystectomy to an asymptomatic patient who is not expected to receive any clinical benefit from it. Gallbladder cancer is rare in most of the developed world and prophylactic cholecystectomy has generally not been recommended to prevent development of GBC. Considering the wide geographical/ethnic variation in incidence of GBC across the world and the strong association of GBC with gallstones, it may not be prudent to extrapolate the results of studies of natural history of AsGS from one part of the world to another. Since northern India has one of the highest incidences of GBC in the world, it is imperative to have data on natural history of AsGS in patients from this area to allow formulation of precise guidelines for management of AsGs.

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The increasingly frequent detection of gallstones (GS) due to ubiquitous availability and use of diagnostic ultrasound for a wide range of abdominal complaints as well as 'routine check-ups', coupled with the recent advent and rapid establishment of laparoscopic cholecystectomy as the gold standard treatment of GS has refocussed attention on the issue of asymptomatic gallstones (AsGS). 'To treat or not to treat' is the Shakespearean dilemma which most surgeons face very often.

Optimal treatment of AsGS (essentially like any other clinical condition) would take into account the natural history of AsGS and weigh the potential benefit of treatment against the risk of the treatment – in this case, the morbidity and mortality of cholecystectomy. The clinical challenge in decision-making is to balance the projected prognosis of expectant management versus the risk, effort, inconvenience and cost of an immediate treatment 'for a particular patient'. By definition, a procedure is considered appropriate if its health benefits exceed its health risks by a sufficiently wide margin, thus making the procedure worth performing [1]. This review will attempt to summarize the information available in the literature regarding the natural history of AsGS in general as well as in special clinical situations, and the risks of cholecystectomy, to put the problem in perspective.

## Definition

GS that cause no GS-related symptoms or complications and are diagnosed during routine ultrasound for other abdominal conditions are called asymptomatic GS. Classically, pain due to GS (often erroneously labelled biliary 'colic') is felt in the right upper quadrant or epigastrium,

may radiate to the back or the right scapula, typically develops rapidly, is severe, steady and unrelieved by usual household remedies, change of position or passage of gas [2]. Whether 'dyspeptic symptoms' in the absence of typical biliary pain can be attributed to GS, remains a contentious issue. Complications include acute cholecystitis (which may evolve into empyema, progress to gallbladder (GB) perforation or even gangrene of the GB, cholangitis (due to common bile duct calculi) and pancreatitis. Despite a strong association, proof of a causal relationship between presence of GS and occurrence of gallbladder cancer (GBC) is lacking, and thus one may not club GBC with other complications of GS, but there is no denying the fact that in areas where incidence of GBC is high, including northern India, this possibility does hang like the proverbial sword of Damocles on the treating surgeon's mind. The fact remains that once diagnosed, GBC is a disease with dismal prognosis with cures being rare [3]. The feeling of dread that patients usually feel (and surgeons often second) whenever a possibility of GBC in future is even mentioned in a patient with AsGs, often strongly influences the choice of treatment.

## Burden of the Problem

The overall prevalence of GS disease in most developed nations, including US, UK, Italy and the Scandinavian nations, is between 10% and 20%. The prevalence increases with age in both males and females. At the age of 65, about 30% of women have GS, and by the age of 80 years, 60% of both males and females have GS. The large majority of these (70–85%) are asymptomatic [4]. In India, Khuroo et al. [5] reported a 6.1% (men 3.1% and women 9.6%) prevalence of GS in subjects above 15 years of age from Kashmir in northern India; 94% of these were asymptomatic at the time of diagnosis.

## Aim of Treatment (Prophylaxis)

When considering treatment of AsGS, one must not forget that the aim is not alleviation of a chronic or debilitating condition, but prevention of a potential future problem – biliary pain or biliary complications (including GBC). Hence, although we use the term 'treatment' what we actually do is 'prevention'. As is true for all prophylactic interventions, the expected risk to the patient should be near zero.

We would like to introduce a subtle difference between the terms 'prophylactic' cholecystectomy (to prevent symptoms and complications of GS, e.g., in reports from the West) and 'preventive' cholecystectomy (to prevent GBC, the issue more relevant in areas with high incidence rates of GBC).

## Treatment Options

From the most conservative to the most aggressive, treatment options may include – expectant management (wait and see); cholecystectomy if and when patient becomes symptomatic; selective cholecystectomy (in some cases) or routine cholecystectomy (in all cases). The advantages and disadvantages of the three approaches are summarized in Table 1.

## Natural History

> '*There is no innocent gallstone*' (William J Mayo, MD, 1904)

More than a century after the above statement, there is now enough evidence that most incidentally discovered, clinically silent GS rarely have clinical significance. In most western countries, majority of patients with AsGS remain asymptomatic throughout their lives and do not

**Table 1** Pros and cons of management strategies

| Advantages | Disadvantages |
|---|---|
| Expectant Management | |
| Avoids overtreatment | Potential for development of a serious complication while waiting |
| Avoids anaesthesia/surgery-related morbidity/mortality<br>Avoids unnecessary cost/workload for the health care system | Need to operate on an older patient (with co-morbidities) or in an emergent setting may increase morbidity and mortality |
| Routine Cholecystectomy | |
| Definitive cure | Overtreatment of a large number of patients |
| | Potential morbidity/mortality of anaesthesia/surgery |
| Generally a safe procedure with low morbidity and mortality, especially when performed in absence of complications | Increased cost/workload for the health care system |
| Selective Cholecystectomy | |
| Theoretically ideal – only subgroups at higher risk for development of symptoms or complications would be treated | Practically difficult – clear identification of high-risk subgroups still far from easy |

require any treatment. Autopsy studies show that more than 90% of autopsied patients with GS died from unrelated causes. Death as the ultimate complication from AsGS is very rare and usually occurs in the elderly as a consequence of biliary or postoperative complications.

In a significant study by Gracie and Ransohoff [6], 123 Michigan University faculty members, found to have GS on routine screening, were followed up for 15 years. At 5, 10 and 15 years of follow-up, 10%, 15% and 18%, respectively became symptomatic. The approximate rate at which the subjects developed biliary pain was 2% per year for the first 15 years without a subsequent decline over time; 0.3% of the cohort developed a biliary complication and in all of them, this was preceded by biliary colic [6]. The absolute risk of developing GBC was <1%. According to the Italian Group for Epidemiology and Prevention of Cholelithiasis study [2], the annual complication rate of initially asymptomatic patients was even less (0.3–1.2%).

A longitudinal follow-up study of AsGS showed that over a 20-year period, only 18% people developed biliary pain, and the mean yearly probability of development of biliary pain was 2% for the first 5 years, 1% during the second 5 years and 0.5% and 0.1% during the third and fourth 5 years, respectively; none of these individuals died of GS disease [7].

According to the National Institute of Health consensus conference report, 10% of patients develop symptoms during the first 5 years and 20% by 20 years [8].

McSherry et al. [9] followed 135 asymptomatic men and women with GS who were subscribers to the Health Insurance Plan of Greater New York. Of them, 10% developed symptoms and only 7% required cholecystectomy over a median follow-up of 46.3 months.

Similar findings have been reported more recently from Norway and Italy [10, 11], and one could extrapolate that after 20 years, approximately two-thirds of individuals with AsGS would remain symptom free [6, 7, 9, 12–14] (Table 2). The data suggest that clinically silent GS in children and infants too are associated with low rates of complications and can be managed conservatively, unless complications occur. Spontaneous resolution of GS has been reported in 16.5% of infants and children with AsGS [15].

To summarize, most studies (all from the West with low incidence rates of GBC), mainly conducted in the 1980s, indicate the following:

- Progression from asymptomatic to symptomatic disease is relatively low, ranging from 10–25% over a period of 5–15 years.
- The longer the patients remain asymptomatic, the less likely they are to develop symptoms.
- Majority of patients rarely develop severe, potentially life-threatening complications, such as acute suppurative cholangitis or severe acute pancreatitis, without first having at least one episode of biliary pain.

## Is the Natural History of AsGS Uniform Across Geographical Areas and Ethnic Groups?

There are indicators to suggest that this may not be so (*vide infra*), especially as far as development of GBC is concerned.

There are, unfortunately, no large studies on the natural history of AsGS from high-GBC-incidence areas to prove this beyond doubt. Individuals, especially females from Chile, have been reported to develop symptoms of GS disease at a younger age and >50% of them become symptomatic [16, 17]. In fact, since Chile has one of the highest incidence rates of GBC in the world, cholecystectomy is usually advised for GS between the ages of 30–40 years in women and 40–50 years in men, irrespective of the presence or absence of symptoms [17]. No data on natural history of AsGS is, however, available from India.

## Risk Stratification

Attempts have been made to stratify risk in patients with AsGS to identify patients in whom natural history and evolution may be different and who are at

- increased risk of conversion from asymptomatic to symptomatic disease.
- increased risk of developing complications.
- increased suspicion/risk of developing GBC.

**Table 2** Natural history of asymptomatic GS

| Series | Patients | Years of follow-up | Biliary pain (%) | Biliary complications (%) | Annual risk of biliary pain |
|---|---|---|---|---|---|
| Gracie and Ransohoff [6] | 123 | 15 | 18 | 2 | 2 |
| McSherry et al. [9] | 135 | 4 | 10 | 0 | – |
| Friedman et al. [7] | | 20 | 18 | | 2.5–5 |
| Cucchiaro et al. [14] | 125 | 5 | 25 | 3 | – |
| Wada and Imamura [12] | 680 | 13 | 20 | – | – |
| Halldestam et al. [13] | 123 | 7 | 6 | 4.8 | – |

Factors that have been reported to confer a higher risk of progression from asymptomatic to symptomatic disease and/or complications include age <55 years, smoking, female sex, greater body weight, presence of three or more GS, and presence of floating stones [7, 18]. Other workers have observed that life expectancy >20 years, calculi >2 cm in diameter, calculi <3 mm and patent cystic duct, non-functioning GB and perioperative detection of incidental stones are the risk factors for progression to symptomatic/complicated GS disease [4, 19]

Higher risk of developing GBC has been reported in patients with GS and associated polyps >1 cm, calcified GB (13–22%), large stones >3 cm (10 times risk) [20, 21], GB packed with stones [22] and ethnic groups in high-incidence GBC areas [21, 23, 24].

Despite such attempts, it is difficult, if not impossible, to clearly identify patients who will develop complications and timings of such a development.

## Special Subgroups

### Chronic haemolytic Syndromes

Natural history of GS in patients with chronic haemolytic syndromes (e.g., sickle cell disease) differs from other patients with AsGS in a number of ways. Onset of GS is at a younger age and, therefore, there is an increased life-time risk of developing complications; 50% develop complications in 3–5 years after diagnosis. Biliary complications of GS and veno-occlusive crises may present with similar manifestations (pain, fever, leucocytosis and jaundice, thus confounding diagnosis. In fact, biliary complications often precipitate veno-occlusive crises. Also, emergency surgery for complications is associated with significantly higher morbidity, mortality and increased hospital stay [25]. Elective, prophylactic cholecystectomy is thus recommended on diagnosis of GS before development of symptoms or complications.

### Transplant Recipients

Treatment of AsGS in patients undergoing transplantation assumes importance because of the need for postoperative immunosuppression. Some of the immunosuppressive drugs such as cyclosporine and tacrolimus are prolithogenic. The difficulty in diagnosis of acute cholecystitis, because of possible masking of signs and symptoms due to immunosuppression, leading to delay in diagnosis, may lead to increased morbidity and mortality. The aim of prophylactic cholecystectomy is to remove a possible septic focus that may cause severe complications in an immune-suppressed patient. Also, the mortality of emergency cholecystectomy has been reported to be higher in patients on immunosuppression.

Despite these theoretical considerations, recent studies in patients with renal transplant suggest no increase in morbidity, mortality or graft loss with expectant management of AsGS and cholecystectomy only when they become symptomatic [26, 27]. Kao et al. [28] reported a comparative mortality of 5:1,000 deaths for prophylactic postcardiac transplant cholecystectomy compared to a figure of 80:1,000 deaths and 44:1,000 deaths for pretransplant cholecystectomy and expectant management, respectively. By and large, most recent studies report favourable results of expectant management in patients undergoing cardiac and bone marrow transplantation [29] and suggest that cholecystectomy after onset of symptoms is safe.

## Perioperative Discovery

In patients with AsGS who undergo unrelated abdominal surgery, a high (up to 70%) incidence of biliary symptoms and/or complications following surgery has been reported. It has been observed that cholecystectomy is required in up to 40% of these patients within one year of the initial operation. A prophylactic cholecystectomy at the time of the initial operation is usually advised [30–33]. However, it should be performed only if cholecystectomy does not add to the risk, patient has been informed and consent taken for the additional procedure; it requires planning for incision and is contraindicated when a prosthetic material is being used.

## Diabetes Mellitus

In the past, patients with diabetes mellitus (DM) were thought to be at a higher risk for developing GS as well as complications of GS such as acute cholecystitis, and the subsequent perioperative morbidity and mortality was reported to be significantly higher in patients with DM. It was also thought that the associated autonomic neuropathy in people with diabetes might delay the diagnosis of complications such as acute cholecystitis – prophylactic cholecystectomy was, therefore, recommended. More recent studies, however, have refuted most of these suppositions. Decision analyses using these new data have shown that prophylactic cholecystectomy is of no clear benefit and should not be routinely recommended for diabetics with AsGS. It is now believed that available data, although limited, indicate that asymptomatic patients with DM do not benefit from screening for GS and that cholecystectomy should only be performed in cases of symptomatic cholelithiasis, as is the case of the general population [34, 35]. The degree of additional operative risk of operating patients with DM for acute cholecystitis too has been revisited and studies do not justify recommending chole-

cystectomy in diabetics with AsGS. Early surgery, however, is highly recommended in diabetics with symptomatic GS and acute cholecystitis [36].

### Cirrhosis of Liver

Liver cirrhosis is a well-documented risk factor for the formation of GS. These are most often bilirubinate stones, representing, most probably, chronic haemolysis caused by ongoing hepatic necrosis and hypersplenism. However, in most of these patients, the GS are asymptomatic and surgery is rarely required. When indicated for symptoms or complications, cholecystectomy is associated with a risk of high morbidity in these patients, especially in the advanced stages of cirrhosis.

The natural history of AsGS in patients with cirrhosis has been addressed in several studies [37–39]. The consensus is that although the prevalence of AsGS is high in this population, majority of patients do not go on to become symptomatic. The risk of GS becoming symptomatic has been reported to be significantly lower in men and in alcoholic cirrhosis than in cirrhotic women, especially in the presence of a positive family history and advanced age [38]. The risk of development of complications is low, but the mortality associated with acute episodes of cholecystitis is high. Incidental cholecystectomy is not justified in cirrhotic patients with AsGS, but close follow-up with early elective operation when symptoms supervene should be recommended [37, 40].

### Common Bile Duct Stones

The subgroup of patients with AsGS who have associated common bile duct stones is reported to be at a higher risk (up to 50%) of developing potentially severe complications, and thus recommended for a prophylactic cholecystectomy [41].

### Gallbladder Cancer

The association between GS and GBC remains an unsolved conundrum. The parallels in epidemiology between the two are striking. Risk of GBC has been reported to increase with increasing size of GS and with increasing number of stones [20, 21] – especially if the stones occupy a significant volume of the GB [22]. Progressive changes in GB wall from chronic cholecystitis, hyperplasia, metaplasia, dysplasia, carcinoma in situ to invasive cancer have been reported from Chile – the time course of which lends credence to a gradual progression from chronic inflammation to dysplasia to invasive carcinoma [42]. The incidence of GBC is also reported to be higher in patients with xanthogranulomatous cholecystitis and Mirizzi's syndrome – both associated with long-standing GS disease [43–45]. The relationship between GS and GBC is likely to be complex, as is evident from the fact that many geographical areas where GS are common do not have a high prevalence of GBC and that not all GBCs are associated with stones (Table 3).

One of the unique features of GBC is the striking geographic, ethnic and gender variation in the worldwide incidence, suggesting a strong influence of genetic and environmental factors.

In most countries of the Western hemisphere, GBC is rare. The highest incidence rates of GBC are found in northern India and Pakistan, East Asia (Korea and Japan), eastern Europe (Slovakia, Poland and Czech Republic) and South America (Columbia and Chile). Areas of low incidence include western Europe and North America [48]. In India, GBC is one of the most common causes of cancer-related mortality in women in the northern and north-eastern states. Age-specific incidence of GBC in women in Delhi varies from 8/100,000 to 48/100,000 [49]. *The highest recorded truncated incidence rate for GBC in the world is seen in Delhi* [49, 50]. The rates in southern India are strikingly low (1/100,000 per year) in comparison. Patients with GS in northern India have been reported to develop GBC at an earlier age [51]. In areas of high prevalence, GBC is one of the most common gastrointestinal cancers, especially in women, and contributes significantly to cancer-related mortality.

GBC is amongst the most frequently observed cancers in native populations of North and South America – this population has an increased prevalence of GS also at an earlier age. It has been reported that *North American Indian women develop GBC with a greater frequency than heavy smokers develop lung cancer* [19].

Considering the uniformly dismal prognosis of GBC unless diagnosed early and the absolute prevention that cholecystectomy offers, a case has been made for preventive cholecystectomy, especially in young healthy women with AsGS in northern India [49]. Considering an estimated prevalence rate of 4%, offering preventive cholecystectomy

**Table 3** Asymptomatic GS and the risk of GBC

| Series | Number of patients | Follow up | No. of GBC |
|---|---|---|---|
| Ransohoff and Gracie [46] | *n*=1,000 AsGS | 7,000 patient years | No GBC |
| Maringhini et al. [47] | *n*=2,583 AsGS | 13.3 years | 5 GBC |
| GREPCO [2] 1995 | *n*=118 AsGS | 10 years | 1GBC |

*AsGS* asymptomatic gallstones, *GBC* gallbladder cancer

even in one state (e.g., Uttar Pradesh with an estimated population of 150 million) would mean staggering costs and unmanageable logistics. The expected 0.2–0.4% incidence of bile duct injury (BDI) in laparoscopic cholecystectomy to these numbers adds another dimension that cannot be ignored [52].

No prospective studies for natural history of AsGS are available from regions with high prevalence of GBC such as northern India. Data to make quantitative estimates of risk of developing GBC are not available and clear identification of high-risk sub-groups (molecular markers, stone characteristics, etc.) not yet possible.

## AsGS Treatment

### Open Cholecystectomy

Open cholecystectomy (OC) was the gold standard treatment of GS for more than a century before this status was rapidly taken over by laparoscopic cholecystectomy. Large studies with no or extremely low mortality were commonly reported. Roslyn et al. [53] in a large population-based study of 42,474 patients, reported an extremely low mortality (overall – 0.17%, 0.03% in patients <65 year and 0.5% in patients >65 years). The rate of BDI was as low as 0.2%.

### Laparoscopic Cholecystectomy

The charm of laparoscopic cholecystectomy (LC) is related to reduced pain, better cosmesis, early recovery and early return to work; it has become the gold standard treatment of GS without going through the rigors of randomized controlled trials, which most new surgical procedures are usually expected to face. The overall morbidity and mortality are comparable to OC; however, disconcertingly, even after more than two decades of experience, the rates of BDI after LC are definitely and significantly higher than those after OC [54–61] (Table 4).

**Table 4** Incidence of BDI after laparoscopic cholecystectomy

| Country | Incidence of BDI | Series |
|---|---|---|
| USA | 0.5% | Flum et al. [54] |
| Sweden | 0.4% | Waage and Nilsson [55] |
| Finland | 0.9% | Karvonen et al. [56] |
| Netherlands | 1.09% | Gouma and Go [57] |
| Italy | 0.4% | Nuzzo et al. [58] |
| India: | | |
| Kolkata | 0.39% | Tantia et al. [59] |
| Chandigarh | 0.64% | Kaushik et al. [60] |
| Lucknow (SGPGIMS) | 1% | Pottakkat et al. [61] |

*BDI* bile duct injury

The most noticeable aspect of the rates of BDI after LC, apart from the fact that they are more than double the rates after OC, is that they do not seem to be related to the 'learning curve' of the surgeons. In the USA, one-third of 1,600 surgeons experienced a BDI during LC. One-third of the 704 injuries occurred after the surgeon's first 200 cholecystectomies [62]. In Canada, 50% of surgeons, including those with enough experience and those working in large volume centres, experienced a BDI after LC [63].

The cost of BDI is enormous, both in terms of money and the physical and psychological trauma to the patient and the family. The effects can range from markedly increased morbidity from intra-abdominal bile collections, biliary fistulae and bile duct strictures to liver failure and portal hypertension requiring liver transplantation and even death. The mortality after BDI has ranged from 4% to 9% [57, 61, 64, 65]. The need for multiple interventions and increased hospital stay leads to a spiralling of expenses that leave most patients financially drained. These patients, most of whom are otherwise healthy, young adults, need life-long follow-up and face a life-time increased risk of death; the loss of life years is in the most productive years of life. Not surprisingly, it has been reported that the quality of life of patients operated on for BDI has been reported to be compromised even after successful repair of postcholecystectomy bile duct strictures [66–68]. The personal, family and social implications of a BDI sustained at cholecystectomy are usually not addressed in medical literature [69, 70]. That they should often lead to malpractice claims and litigation would not be a surprise to anyone. A recent study from England, which looked into the prevalence and outcome of litigation claims to the NHS Litigation Authority, reported that common bile duct injury is the most common claim to the NHSLA after laparoscopic cholecystectomy, and results in the highest proportion of successful claims and the largest sums paid to the claimant [71].

### What Should We Do Then?

Taking into consideration the fact that the natural history of AsGS is by and large benign, the incidence of complications is low and one or more episodes of biliary colic usually precede development of serious complications (and thus warn about transition from asymptomatic to the symptomatic stage when treatment is warranted), management of AsGS should be selective cholecystectomy in only high-risk subgroups (*vide supra*). In the absence of any data from our part of the world, this recommendation is necessarily based on data from studies done in the West.

There is, however, an urgent need to explore the geographic/ethnic differences in the natural history of AsGS and to more specifically identify high-risk sub-

groups of patients. In the northern Indian context, the issue of GBC (especially because of its dismal prognosis) is especially important and we need to generate our own data on the basis of long-term studies, specifically looking at the rate of development of symptoms, complications and GBC in our population. Hard data from such studies would tell us if it is correct to extrapolate results from one population to another.

Till such data and evidence are available, surgeons and patients together would take a decision depending on their assessment of individual risks and choices. Patients definitely have to be cognizant partners in the decision after being explained the risks of waiting and an intervention that will not have any perceptible, immediate benefit, but has a definite risk of harm. There ***MAY*** be a case for suggesting preventive (for GBC) cholecystectomy in a young (20s or 30s) patient with a large GS in northern India but, as of today, there is no data or evidence to support it.

A recent Cochrane Database Systematic Review [72] (2007) observed the following:

- There are no randomized trials comparing cholecystectomy versus no cholecystectomy in patients with silent (asymptomatic) GS.
- Further evaluation of observational studies, which measures outcomes such as obstructive jaundice, GS-associated pancreatitis and/or GBC for sufficient duration of follow-up, is necessary before randomized trials are designed in order to evaluate whether cholecystectomy or no cholecystectomy is better for asymptomatic GS.

'*The availability of laparoscopic cholecystectomy should not expand the indications for gall bladder removal*'.
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