

# Conservative Treatment for Acute Cholecystitis: Clinical and Radiographic Predictors of Failure

Orly Barak MD<sup>1</sup>, Ram Elazary MD<sup>1</sup>, Liat Appelbaum MD<sup>2</sup>, Avraham Rivkind MD FACS<sup>1</sup> and Gidon Almog MD<sup>1</sup>

Departments of <sup>1</sup>General Surgery and <sup>2</sup>Radiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

**ABSTRACT:** **Background:** Current treatment options for acute calculous cholecystitis include either early cholecystectomy, or conservative treatment consisting of intravenous antibiotics and an interval cholecystectomy several weeks later. Percutaneous drainage is reserved for patients in whom conservative therapy failed or as a salvage procedure for high risk patients.

**Objective:** To identify clinical and radiographic factors leading to failure of conservative treatment.

**Methods:** We prospectively collected data on consecutive patients admitted with the diagnosis of acute cholecystitis. Parameters were compared between patients who were successfully treated conservatively and those who required percutaneous cholecystostomy. Logistic regression analysis was performed to identify predictors for failure of conservative treatment.

**Results:** The study population comprised 103 patients with a median age of 60 who were treated for acute cholecystitis. Twenty-seven patients (26.2%) required PC. On univariate analysis, age above 70 years, diabetes, elevated white blood cell count, tachycardia ( $> 100$  beats/min) at admission, and a distended gallbladder ( $> 5$  cm transverse diameter) were found to be significantly more common in the PC group ( $P < 0.001$ ). WBC was higher in the PC group throughout the initial 48 hours. On multivariate analysis, age above 70 (odds ratio 3.6), diabetes (OR 9.4), tachycardia at admission (OR 5.6), and a distended gallbladder (OR 8.5) were predictors for cholecystostomy ( $P < 0.001$ ). Age above 70 (OR 5.2) and WBC  $> 15,000$  (OR 13.7) were predictors for failure of conservative treatment after 24 and 48 hours ( $P < 0.001$ ).

**Conclusions:** Age above 70, diabetes, and a distended gallbladder are predictors for failure of conservative treatment and such patients should be considered for early cholecystostomy. Persistently elevated WBC ( $> 15,000$ ) suggests refractory disease and should play a central role in the clinical follow-up and decision-making process for elderly patients with acute cholecystitis.

IMAJ 2009; 11: 739–743

**KEY WORDS:** acute cholecystitis, percutaneous cholecystostomy, high risk patients, elderly

Every year more than 500,000 cholecystectomies are performed in the United States alone. In the majority of cases the etiology is related to gallbladder stones. The prevalence of gallstones increases throughout life, and in the western world almost 10% of the elderly population has gallbladder stones. Other risk factors for gallbladder stones are female gender, obesity, rapid weight loss, pregnancy, exogenous estrogens, hemolytic disease, biliary tree infections, hypercholesterolemia and hepatic cirrhosis [1]. Roughly 10% of patients with gallstones will develop biliary symptoms within 5 years after diagnosis, and, according to the Group of Epidemiology and Prevention of Cholelithiasis, one-fourth will eventually undergo surgery [2,3].

The pathophysiology of acute cholecystitis is cystic duct obstruction, which causes an acute sterile inflammation. Secondary infection of the gallbladder space by bacteria follows [4]. Right upper quadrant abdominal pain and tenderness, nausea, vomiting and fever are the most common symptoms and signs. An elevated white blood cell count is usually also noted. Diagnosis is supported by findings on abdominal sonography.

Treatment options include early cholecystectomy and conservative treatment with antibiotics and interval cholecystectomy for 6–8 weeks [5]. Patients who fail to improve under conservative treatment are referred to either surgery or percutaneous cholecystostomy. PC is an indispensable option for elderly patients and for high risk patients with severe co-morbidities such as ischemic heart disease, chronic obstructive pulmonary disease, and uncontrolled diabetes mellitus [6–9]. DM and an elevated WBC were shown to be prognostic factors for the development of complications such as gangrenous cholecystitis [10].

The goal of the present study was to identify factors that predict failure of conservative treatment. Early identification of such patients will possibly shorten hospitalization, minimize septic complications, improve overall outcome, and facilitate interval laparoscopic cholecystectomy several weeks later.

PC = percutaneous cholecystostomy  
WBC = white blood cells  
OR = odds ratio

DM = diabetes mellitus

## PATIENTS AND METHODS

We established a prospective database for patients admitted with the diagnosis of acute cholecystitis to the Department of Surgery at the Hadassah University Hospital in Jerusalem. All consecutive patients admitted during the period 1 January 2005 to 30 June 2006 were enrolled in the study. We established a worksheet listing current illness, vital signs, laboratory results, imaging studies and medical history. Parameters were recorded at admission and at 24 and 48 hours follow-up. The time between admission and PC was also registered.

The diagnosis of acute cholecystitis was based on well-described clinical parameters such as the presence of right upper quadrant or epigastric pain and tenderness, nausea, vomiting, fever and elevated WBC. Abdominal pain was graded by the attending physicians according to their clinical experience as mild, moderate, or severe. All patients were evaluated by either ultrasound or computed tomography. Imaging criteria suggestive of acute calculous cholecystitis on ultrasound included the presence of gallstones, distended gallbladder (> 5 cm transverse diameter), thickened walls (> 3 mm) and peri-cholecystic fluid. Patients with acalculous cholecystitis, patients with uncertain diagnosis, and patients with active hematological disease affecting blood counts were excluded from the study.

Relevant medical history included the presence of DM defined as hyperglycemia requiring oral hypoglycemics or insulin injections; a history of IHD was defined as unstable angina pectoris or previous episode/s of acute coronary syndrome; and heavy smoking was defined as currently smoking more than 10 cigarettes per day.

The protocol at Hadassah University Hospital for treating patients with acute calculous cholecystitis includes bowel rest and administration of broad-spectrum antibiotics (usually ampicillin and an aminoglycoside) and intravenous fluids. There were no specific guidelines defining failure of conservative treatment. Failure of conservative treatment was defined at the discretion of the attending surgeons based on subjective findings such as lack of improvement, or objective findings such as worsening clinical signs and laboratory results. Failure of conservative treatment prompted percutaneous drainage. Patients were divided into two groups: those who were treated conservatively and whose condition improved were defined as the "conservative group." Those who required gallbladder drainage due to failure of conservative treatment were defined as the "percutaneous cholecystostomy group." PC was performed under either ultrasound or CT guidance at the discretion of an interventional radiologist.

The chi-square test and Fisher's exact test were used to compare proportions, and the *t*-test to compare continuous

variables. Multivariate logistic regression analysis was performed to analyze predictors of failure of conservative treatment. The odds ratio as well as its 95% confidence interval was calculated for each of the independent variables. A *P* value of 0.05 or less was considered statistically significant. Statistical analysis was performed using the SPSS version 11.5 (Statistical Package for Social Science, Chicago, IL, USA).

## RESULTS

### PATIENT POPULATION

During the study period 109 patients suffering from acute cholecystitis were treated in our department. Six patients with acalculous cholecystitis, unclear diagnosis, or active hematological disease (affecting blood counts) were excluded. The study population consisted of 59 females (57.3%) and 44 males (42.7%) with a median age of 60 (range 18–97 years). Twenty-seven patients (26.2%) required gallbladder drainage (PC group) [Table 1]. Two-thirds of the procedures (18/27) were performed within 48 hours of admission (one at admission, 10 within 24 hours, 7 within 48 hours, and 9 later than 48 hours). On univariate analysis, patients in the PC group were older and had a higher prevalence of DM than patients treated conservatively (*P* < 0.001). Patients in the PC group were also more likely to suffer from IHD, but this difference was not statistically significant [Table 1].

### ADMISSION PARAMETERS

Average duration of abdominal pain prior to admission and the overall degree of abdominal tenderness were not different between the groups [Table 2]. However, the need for percutaneous drainage was higher, albeit not statistically significant, among patients with severe abdominal tenderness (*P* = 0.08). Patients in the PC group had a statistically higher pulse rate and WBC upon admission compared to patients in the conserva-

**Table 1.** Demographic data of all patients admitted to the Hadassah University Hospital with acute calculous cholecystitis, 1 January 2005 to 30 June 2006

	PC group (n=27)	Conservative group (n=76)	<i>P</i> value
Gender (male:female)	13:14	31:45	0.51*
Age (yrs)†	73 (53–94)	58 (18–97)	< 0.001**
Age > 70 yrs	15 (55%)	20 (26%)	0.01*
DM	10 (37%)	9 (12%)	< 0.001*
IHD	10 (37%)	16 (21%)	0.10*
Heavy smoking	6 (22%)	16 (21%)	0.90*

\*Chi-square test, \*\* *t*-test

† Median (and interquartile range)

PC = percutaneous cholecystostomy, DM = diabetes mellitus, IHD = ischemic heart disease

IHD = ischemic heart disease

tive group ( $P < 0.001$ ). The proportion of patients with a WBC  $> 15,000$  cell/ $\mu\text{l}$  was 48% in the PC group compared to 17% of patients in the conservative group ( $P < 0.001$ ). Liver function tests were not different between the two groups [Table 2].

**Table 2.** Clinical parameters and laboratory results at admission

	PC group (n=27)	Conservative group (n=76)	P value
Duration of pain (days)*	1.8 (0.3–7)	2.5 (0.25–30)	0.17**
Mild abdominal tenderness	5 (18%)	23 (30%)	0.24†
Moderate abdominal tenderness	14 (52%)	42 (55%)	0.76†
Severe abdominal tenderness	8 (30%)	11 (15%)	0.08†
Heart rate (beats/min)*	94 (54–132)	78 (40–115)	$< 0.001^{**}$
Systolic blood pressure (mmHg)*	130 (87–199)	135 (90–189)	0.30**
Diastolic blood pressure (mmHg)*	69 (50–97)	76 (44–116)	0.01**
Body temperature ( $^{\circ}\text{C}$ )*	37.1 (35.5–38.5)	36.8 (35.5–39.5)	0.16**
WBC ( $10^3$ cells/ $\mu\text{l}$ )*	13.3 (7.1–23.4)	9.1 (2.5–20.9)	$< 0.001^{**}$
WBC $> 15,000$ cells/ $\mu\text{l}$	13 (48%)	13 (17%)	$< 0.001^{\ddagger}$
ALT IU/l †	30 (3–349)	27 (4–884)	0.25**
AST IU/l †	50 (14–286)	35 (17–521)	0.71**
ALK P IU/l †	96 (11–923)	93 (42–464)	0.44**
GGT IU/l †	50 (18–1195)	44 (9–1257)	0.30**
Amylase IU/l †	48 (30–1620)	57 (30–2521)	0.44**
Total bilirubin mg/dl †	18 (2–76)	13 (2–422)	0.82**

\*Average (and interquartile range), † Median (and interquartile range), \*\* t-test, ‡ Chi-square test.

PC = percutaneous cholecystostomy, WBC = white blood cell count, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALK-P = alkaline phosphatase, GGT = gamma-glutamyl transferase

**Table 3.** Findings on imaging studies at admission

	PC group	Conservative group	P value*
<b>Abdominal sonography</b>	(n=25)	(n=73)	
Small gallstones	12 (48%)	48 (65%)	0.15
Single gallstone	7 (28%)	18 (25%)	0.79
Sludge	5 (20%)	16 (22%)	1.0
Impacted stone	8 (32%)	20 (27%)	0.80
Distended gallbladder ( $> 5$ cm in diameter)	20 (80%)	25 (34%)	0.001
Thickened gallbladder wall ( $> 3$ mm)	19 (76%)	60 (82%)	0.56
Peri-cholecystic fluid	7 (28%)	11 (15%)	0.23
<b>Computed tomography</b>	(n=14)	(n=8)	
Thickened gallbladder wall	14 (100%)	6 (75%)	0.12
Peri-cholecystic fluid	10 (71%)	8 (100%)	0.25

\* Chi-square test

Abdominal sonography was performed in 98 patients (95.15%). On univariate analysis, patients in the PC group were more likely to have a distended gallbladder on sonography than patients in the conservative group ( $P < 0.001$ ) [Table 3]. Other sonographic findings, such as the size and number of gallstones, thickened gallbladder wall, the presence of an impacted stone, and the presence of peri-cholecystic fluid, were not shown to be different between the groups [Table 3]. CT was performed in 22 patients (21.4 %) and did not differ between the groups.

**PARAMETERS AT FOLLOW-UP**

At 24 and 48 hours follow-up, heart rate, absolute WBC and the proportion of patients with WBC  $> 15,000$  cell/ $\mu\text{l}$  were all significantly higher in the PC group than in the conservative group ( $P < 0.001$ ) [Table 4]. The absolute WBC, the proportion of patients with WBC  $> 15,000$  cell/ $\mu\text{l}$ , and a higher heart rate were the most consistent parameters characterizing the PC group throughout the initial 48 hours [Tables 2 and 4]. Average body temperature at 24 hours was higher in the PC group than in the conservative group, but this difference lacks clinical relevance ( $37.6^{\circ}\text{C}$  vs.  $37^{\circ}\text{C}$ , respectively;  $P < 0.001$ ).

**PREDICTORS OF FAILURE**

Multivariate logistic regression analysis was performed to identify predictors of failure of conservative treatment. Separate analyses were performed for three time periods: admission, 24 hours, and 48 hours. Admission parameters included in the analysis were gender, age above 70, diabetes, ischemic heart disease, severe abdominal tenderness, WBC  $> 15,000$  cell/ $\mu\text{l}$ , and distended gallbladder. Age above 70 (OR 3.55, CI 1.05–11.9,  $P = 0.04$ ), diabetes (OR 9.43, CI 2.2–40,  $P = 0.002$ ), tachycardia (OR 5.55, CI 1.5–21.3,  $P = 0.012$ ) and a distended gallbladder (OR 8.54, CI 2.2–33.3,  $P = 0.002$ )

CI = confidence interval

**Table 4.** Temperature, heart rate and white blood cell count throughout the initial 48 hours

	PC group (n=27)	Conservative group (n=76)	P value
<b>24 hrs from admission</b>			
WBC ( $10^3$ cells/ $\mu\text{l}$ )*	15.3 (2.9–23.7)	9.4 (3.9–21.9)	$< 0.001^{**}$
WBC $> 15,000$ cells/ $\mu\text{l}$	15 (55%)	4 (5%)	$< 0.001^{***}$
Body temperature ( $^{\circ}\text{C}$ )*	37.6 (36–39.2)	37.0 (35.5–38.5)	$< 0.001^{**}$
Heart rate (beats/min)*	90 (53–113)	79 (50–115)	$< 0.001^{**}$
<b>48 hrs from admission</b>			
WBC ( $10^3$ cells/ $\mu\text{l}$ )*	13.3 (7.1–23.4)	9.1 (2.5–20.9)	$< 0.001^{**}$
WBC $> 15,000$ cells/ $\mu\text{l}$	11 (40%)	5 (6.5%)	$< 0.001^{***}$
Body temperature ( $^{\circ}\text{C}$ )*	37.0 (35.8–38.5)	37.0 (36–38.4)	0.89**
Heart rate (beats/min)*	87 (60–110)	77 (49–120)	$< 0.001^{**}$

\* Average (and interquartile range), \*\* t-test, \*\*\* Chi-square test.

were found to be predictors for the failure of conservative treatment at admission.

Parameters entered into the analysis of the follow-up period were gender, age above 70, tachycardia and WBC > 15,000 cell/ $\mu$ l. Although the absolute heart rate was statistically different between groups, the proportion of patients with tachycardia was entered into the analysis in order to grant the results clinical relevance. Likewise, the proportion of patients with WBC > 15,000 cells/ $\mu$ l was entered instead of the absolute WBC. Age above 70 (OR 5.2, CI 1.5–18.2,  $P = 0.01$ ), WBC > 15,000 cell/ $\mu$ l (OR 13.7, CI 10–58.8,  $P = 0.02$ ) and an elevated temperature (OR 2.8, CI 1.2–6.4,  $P = 0.017$ ) were found to be predictors for the failure of conservative treatment at 24 and 48 hours follow-up.

## DISCUSSION

Acute calculous cholecystitis is a common disease affecting 10–20% of the 20 million patients suffering from gallstone disease in the United States. It has been repeatedly shown that early laparoscopic cholecystectomy is safe and feasible in the majority of cases. Accordingly, early cholecystectomy is the procedure of choice in most medical centers [11]. Due to largely logistic and administrative considerations, in many medical centers patients are treated "conservatively." This approach includes broad-spectrum antibiotics, bowel rest and interval cholecystectomy 6–8 weeks later. High risk patients who are considered poor surgical candidates are also treated conservatively. Unfortunately, a significant portion of patients will not respond to conservative treatment and will need an urgent drainage procedure. Muira et al. [12] have suggested a treatment algorithm that differentiates acute cholecystitis into mild, moderate and severe disease. However, the parameters used to define disease status into those categories were not defined and remain unclear. Hence, the decision is made by surgeons upon clinical assessment and is not based on well-established guidelines.

Our study deals with results obtained from demographic and clinical data of 103 patients diagnosed with acute calculous cholecystitis. The cardinal finding of this study is that patients more likely to fail conservative treatment can be identified at an early stage of their hospital course by clinical, laboratory or imaging findings. It is possible that early recognition and drainage shortens the hospital course, avoids septic complications associated with prolonged disease, improves overall outcome, and perhaps facilitates interval laparoscopic cholecystectomy several weeks later.

Early cholecystectomy is advocated for elderly patients with gallstone disease. Leandros and colleagues [13] reported on 92 octogenarian patients with complicated ( $n=51$ ) and uncomplicated ( $n=41$ ) gallstone disease. For patients with complicated disease, this approach was associated with a longer operative time, longer hospital stay and a 27.3% complication rate, all significantly different from same-age patients with uncom-

plicated disease. Lyass et al. [7] demonstrated that the most important risk factor for postoperative morbidity and mortality is advanced age. Macri and co-authors [6] have shown that early PC (performed < 12 hours from admission) improved prognosis in patients 70 years and older. Our results show that the mean age of patients who underwent PC was 73 years compared with a mean age of 58 years in the conservative group ( $P < 0.001$ ). On multivariable regression analysis, age above 70 was the most consistent predictor of the need for PC at admission and throughout the follow-up period. Thus, our results combined with the high complication rate associated with cholecystectomy for complicated gallstone disease in elderly patients may suggest that the treatment of choice for elderly patients with acute cholecystitis as well as diabetes, tachycardia and a distended gallbladder should be early PC.

A number of studies recently concluded that the prevalence of cholelithiasis is significantly increased in diabetic patients, especially those with type II diabetes [14–16]. Increased age, increased body mass index, and family history of cholelithiasis are additional risk factors for cholelithiasis in diabetic patients [14]. The apparent conclusion that increased cholelithiasis in diabetics will cause an increase in the incidence of acute cholecystitis has not been proven [17]. Our results show that diabetes mellitus is associated with failure of conservative treatment and the need for early PC (37% in the PC group compared to 12% in the conservative group,  $P < 0.001$ ). On multivariate regression analysis, diabetes mellitus was found to be an independent predictor that increases the risk for the need for PC almost tenfold (95% CI 2–40,  $P = 0.002$ ). This supports data in the literature that diabetes mellitus is a major factor for the development of complications in acute cholecystitis [10].

Tachycardia, increased fever and elevated WBC are well-known markers of inflammatory disease. Among the initial admission parameters only tachycardia (defined as pulse over 100/min) was found to be a predictor for failure of conservative treatment and the need for PC. WBC count above 15,000 cells/ $\mu$ l was found to be a reliable, strong and persistent predictor of the need for PC throughout the initial 48 hours of follow-up, but not at admission. A possible explanation for this finding is that a persistently elevated WBC may indicate none or incomplete resolution of the inflammatory process, as observed in the PC group compared with the conservative group. Elevated temperature was higher in the PC group, but the temperature levels themselves lacked clinical significance since the mean temperature in the PC group was 37.6°C compared with 37°C in the conservative group.

As physicians we are trained to rely on our clinical judgment. Surgeons rely on the duration of abdominal pain and the degree of abdominal tenderness to make clinical decisions about patient management. Since abdominal tenderness is influenced by subjective factors such as physician experience and capability and inter-examiner variation among physi-

cians, our ability to discern mild from moderate tenderness may be diminished. Our results show that the duration of abdominal pain and level of abdominal tenderness on admission were not different between the groups. Patients in the PC group, however, tended to have more severe abdominal tenderness than the conservative group ( $P = 0.08$ ). These findings may indicate that severe abdominal tenderness is a reliable sign of the need for early PC. The relatively small sample size in each subgroup may be the source for the lack of statistical significance in this group of patients.

Sonography of the gallbladder is the modality of choice for assessment of acute cholecystitis. Sonographic criteria for diagnosing acute cholecystitis include thickening of gallbladder walls above 3 mm, "railway" signs on the gallbladder wall, sonographic Murphy's sign, and distension of the gallbladder above 5 cm on its transversal diameter [18]. Ultrasonography is highly accurate for evaluation of the presence of gallstones, and their size and mobility. Ultrasound imaging is the procedure of choice and was performed in 95% of our patients. Our results show that a distended gallbladder is the only sonographic parameter that predicted failure of conservative treatment. On multivariate regression analysis this parameter increased the risk for failure of conservative treatment almost ninefold ( $P = 0.002$ , 95% CI 2.2–33.3).

Due to the exceptional sensitivity and specificity of ultrasonography in detecting acute cholecystitis, CT is not widely used for this indication. However, when complications of cholecystitis such as gangrenous cholecystitis or abscess formation are suspected, CT discrimination is more accurate [18]. CT was performed in 21% of the patients either because of equivocal clinical presentation or equivocal findings on ultrasound. According to our results, CT confirmed the diagnosis of acute cholecystitis but had no role in predicting the need for drainage.

## CONCLUSIONS

Age above 70 years old, diabetes mellitus, tachycardia at admission, and a distended gallbladder were found to predict failure of conservative treatment for acute calculous cholecystitis. We suggest that these parameters be used as indications for early percutaneous cholecystostomy in elderly patients, thus preventing complications and shortening hospitalization. White blood cell count above 15,000 cells/ $\mu$ l reflects a non-resolving inflammatory process and is a strong predictor of treatment failure after 24 and 48 hours of observation.

## Correspondence:

**Dr. G. Almogy**

Dept. of General Surgery, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel

**Phone:** (972-2) 677-8800

**Fax:** (972-2) 644-9412

**email:** galmogy@hadassah.org.il

## References

- Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. *J Long Term Eff Med Implants* 2005; 15(3): 329-38.
- NIH Consensus Statement. Gallstones and laparoscopic cholecystectomy. NIH Consensus Statement 1992; 10: 1-28.
- Attili AF, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. *Hepatology* 1995; 21: 655-60.
- Csendes A, Burdiles P, Maluenda F, Diaz JC, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common bile duct in control subjects and patients with gallstones and common duct stones. *Arch Surg* 1996; 131: 389-94.
- Papi C, D'Ambrosio L, Capurso L. Timing of cholecystectomy for acute calculous cholecystitis: a meta-analysis. *Am J Gastroenterol* 2004; 99: 147-55.
- Macri A, Scuderi G, Saladino G, et al. Acute gallstone cholecystitis in the elderly – treatment with emergency ultrasonographic percutaneous cholecystostomy and interval laparoscopic cholecystectomy. *Surg Endosc* 2006; 20: 88-91.
- Lyass S, Perry Y, Venturero M, et al. Laparoscopic cholecystectomy: what does affect the outcome? A retrospective multifactorial regression analysis. *Surg Endosc* 2000; 14: 661-5.
- Teoh WM, Cade RJ, Banting SW, Mackay S, Hassen AS. Percutaneous cholecystostomy in the management of acute cholecystitis. *ANZ J Surg* 2005; 75: 396-8.
- Welschbillig-Meunier K, Pessaux P, Lebigot J, et al. Percutaneous cholecystostomy for high-risk patients with acute cholecystitis. *Surg Endosc* 2005; 19: 1256-9.
- Fagan SP, Awad SS, Rahwan K, et al. Prognostic factors for the development of gangrenous cholecystitis. *Am J Surg* 2003; 186: 481-5.
- Knight JS, Mercer SJ, Somers SS, Walters AM, Sadek SA, Toh SK. Timing of urgent laparoscopic cholecystectomy does not influence conversion rate. *Br J Surg* 2004; 91: 601-4.
- Miura F, Takada T, Kawarada Y, et al. Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 2007; 14: 27-34.
- Leandros E, Alexakis N, Archontovasilis F, et al. Outcome analysis of laparoscopic cholecystectomy in patients aged 80 years old and older with complicated gallstone disease. *J Laparoendosc Adv Surg Tech A* 2007; 17: 731-5.
- Pagliarulo M, Fornari F, Fraquelli M, et al. Gallstone disease and related risk factors in a large cohort of diabetic patients. *Dig Liver Dis* 2004; 36: 130-4.
- Liu CM, Tung TH, Liu JH, Lee WL, Chou P. A community-based epidemiologic study on gallstone disease among type 2 diabetics in kinmen, Taiwan. *Dig Dis* 2004; 22: 87-91.
- Tolman KG, Fonseca V, Tan MH, Dalpiaz A. Narrative Review: Hepatobiliary disease in type 2 diabetes mellitus. *Ann Intern Med* 2004; 141: 946-56.
- Bell DS, Allbright E. The multifaceted associations of hepatobiliary disease and diabetes. *Endocr Pract* 2007; 13: 300-12.
- De Vargas Macchiucca M, Lanciotti S, De Cicco ML, Coniglio M, Gualdi GF. Ultrasonographic and spiral CT evaluation of simple and complicated acute cholecystitis: diagnostic protocol assessment based on personal experience and review of the literature. *Radiol Med* 2006; 111: 167-80.

**“Every one is a moon, and has a dark side which he never shows to anybody”**

Mark Twain (1835-1910) U.S. author and humorist, best known for his books *The Adventures of Tom Sawyer* and *The Adventures of Huckleberry Finn*. During his lifetime, he became a friend to presidents, artists, industrialists and European royalty. He enjoyed immense public popularity. His keen wit and incisive satire earned him praise from both critics and peers.