

## Acute cholecystitis - Predictors of severity

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**ABSTRACT:** Our purpose was to determine factors influencing the severity of acute cholecystitis, and to assess their prognostic significance. During the period 1995-2003, we operated urgently on 149 patients with the disease. The following parameters were prospectively recorded; Age, sex, presence of diabetes mellitus, blood white cell count, serum amylase and alkaline phosphatase levels at diagnosis, as well as radiological findings of peri-cholecystic fluid collection and presence of gas in the gallbladder wall. Operative records and histology findings were also included in the examined data. Histological diagnosis of gangrenous cholecystitis was established in 40 (26.8%) patients, with gallbladder perforation present in seven (17.5%) of them at laparotomy, and hepatic abscess development in one. Peri-cholecystic collection was present in 44(29.5%) patients. Analysis of our findings suggests that diabetes, a white cell count more than 15000/ml at diagnosis, and presence of peri-cholecystic fluid collection, could be useful prognostics of gangrenous cholecystitis.

*Key Words: Acute cholecystitis, Gangrenous cholecystitis, Early cholecystectomy, Laparoscopic cholecystectomy.*

### INTRODUCTION

Acute cholecystitis usually results from gallstones (90%), while an acalculus type is also recognised but less frequently encountered. The development of gangrene of the gallbladder wall represents an extreme form of acute cholecystitis occurring in up to 30% of patients and associated with increased morbidity and mortality<sup>1,2</sup>.

Treatment of acute cholecystitis traditionally consisted of conservative management at first, allowing for the initial attack to subside, before cholecystectomy could be performed at a later, elective manner. During the last decade, many researchers advocated surgery (mainly laparoscopic) in the original setting, claiming that it affords a shorter hospital stay for the patient, with a reduction in the number of operative and late complications<sup>3,4</sup>. In everyday practice however, most patients with acute cholecystitis are still nursed in medical wards, prior to laparoscopic cholecystectomy at a future admission.

It therefore becomes apparent, that prompt sur-

gery after early recognition of gangrenous cholecystitis could help reduce the morbidity and mortality associated with this condition, while establishing a strong indication for emergency - «early» cholecystectomy<sup>5</sup>.

In this context, it would be beneficial to diagnose gangrenous cholecystitis early. Attempts made so far to define prognostic factors, led to the conclusion that there is always a subset of patients where diagnosis cannot be established early in the course of the disease<sup>6,7</sup>. Below, we would like to report our experience with this serious clinical problem.

### PATIENTS AND METHODS

During the period 1995 to 2003, we operated urgently (within 48 hours from admission) on 149 patients with acute cholecystitis (61 men and 88 women, mean age 57.8 years, range 26-80). Pre-operative diagnosis was based on clinical, laboratory and radiology findings. Most of the patients presented with fever and a positive Murphy's sign, some with acute abdomen

and signs of generalized peritonitis, and only a few showed signs of generalized sepsis, necessitating admission to the intensive care unit (ICU). The most common radiological investigation performed was abdominal ultrasound, followed by computerized tomography. Characteristics sought were gallbladder wall thickening, peri-cholecystic fluid collection and intraluminal or intramural gas.

### STATISTIC ANALYSIS

The mean value and standard deviation were calculated for continuous variables, while categorical variables were analysed to estimate their frequency and proportion. Comparisons between groups was performed using Chi-square test for categorical variables (confidence interval - CI=95%). Comparison of continuous variables were performed using Student's t-test for independent values, after testing for normal distribution and using Levene's test to assess homogeneity of variances. A two sided P value <0.05 was accepted as statistically significant. Variables identified as significant, were entered in multivariate logistic regression analysis to determine their independent prognostic value.

### RESULTS

During the study period, 149 patients (61 men and 88 women, mean age  $57.7 \pm 11.9$  years, range 26-80) underwent urgent surgery for acute cholecystitis. Forty

of them (26.8%) were found to have gallbladder gangrene. Overall, 14.8% of patients were diabetics and 2% suffered from chronic renal failure. Criteria used to decide early operation were persistence of symptoms and a deteriorating general condition despite systemic therapy. Operative records and histology reports were reviewed to identify the group of patients with gangrenous cholecystitis. Patient demographics and co-morbid conditions are listed in Table 1. Univariate analysis performed using Chi-square and t-test as appropriate, identified nine variables significantly associated with the development of gangrenous cholecystitis. These included the presence of raised white cell count (WBC>15000/ml), pyrexia ( $T>38.5^{\circ}\text{C}$ ), increased serum levels of SGOT, and amylase, as well as the presence of diabetes, chronic renal failure and radiological detection of peri-cholecystic collection or free gas in the gallbladder lumen/wall. Patient sex was not significantly associated with the development of gallbladder gangrene, Table 2. The presence of diabetes, peri-cholecystic fluid collection, a raised WBC and pyrexia were further entered in multivariate logistic regression analysis to prove their independent predictive status, Table 3. The presence of chronic renal failure was excluded from multivariate analysis because of the small number of patients (three) in the study. Interestingly, diabetes was not found to have independent predictive value for the development of gangrenous cholecystitis.

**Table 1.** Patient demographics and presence of gangrenous cholecystitis.

		Gangrenous cholecystitis	
Sex	Male	61 (40.9%)	15 (24.6%)
	Female	88 (59.1%)	25 (28.4%)
Diabetes	Yes	22 (14.8%)	14 (63.6%)
	No	127 (85.2%)	26 (20.47%)
Chronic renal failure	Yes	3 (2%)	3 (100%)
	No	146 (98%)	37 (25.3%)
Total Patients		149 (100%)	40 (26.8%)

**Table 2.** Univariate analysis of variables associated with gallbladder gangrene.

Variable	Test used	P value
Sex	Pearson Chi-square	0.605
Diabetes mellitus	Pearson Chi-square	0.000
Chronic renal failure	Pearson Chi-square	0.004
Peri-cholecystic collection	Pearson Chi-square	0.000
Intra-mural/luminal gas	Pearson Chi-square	0.000
WBC>15000/ml	Pearson Chi-square	0.000
Fever>38.5 °C	Pearson Chi-square	0.000
Raised amylase	Students' t-test	0.000
Raised SGOT	Students' t-test	0.000
Raised WBC	Students' t-test	0.000
Pyrexia	Students' t-test	0.000

**Table 3.** Multivariate logistic regression analysis.

Variable	Odds ratio	P value
Diabetes mellitus	0.908	0.514
Peri-cholecystic collection	0.675	0.036
WBC>15000/ml	0.642	0.000
Fever>38.5 °C	0.909	0.020

## DISCUSSION

Acute cholecystitis is usually caused by gallstones (90%), or by a variety of other reasons encountered in its acalculus form<sup>8,9</sup>. In the presence of asymptomatic gallstones, its incidence is estimated to be 1-3% annually<sup>10</sup>.

The disease evolves as gallstones impact and block Hartmann's pouch or the cystic duct, causing bile retention and secondary bacterial infection, usually from enteric organisms (commonly *E. coli*, *Klebsiella* and *Streptococcus Faecalis*). Raised endoluminal pressure can lead to ischaemic necrosis and perforation of the gallbladder wall.

Acalculus cholecystitis is associated with sepsis and hospitalisation in the ICU<sup>11</sup>. Its pathogenesis is related to severe disturbances to local tissue perfusion (as demonstrated by micro-angiography studies), caused by direct endotoxin damage or dysfunction of tissue perfusion regulatory mechanisms (i.e. prostaglandin activity), being responsible for the development of gallbladder gangrene<sup>12,13</sup>.

Gangrenous cholecystitis compared to its milder counterpart, acute cholecystitis, is characterised by increased morbidity and mortality that seems to drop after emergency cholecystectomy. The observed reduction in complications and mortality observed when early cholecystectomy was performed<sup>14</sup>, led to an increase in the efforts to identify reliable prognostic indicators, which could establish the diagnosis early in the course of the disease<sup>15</sup>.

In the present study, diabetes mellitus was identified as a pre-operative risk factor for the development of gangrenous cholecystitis. The increased incidence of gangrenous cholecystitis observed in diabetic patients, could be related to the existing micro-angiopathy of the disease and/or the presence of atheromatous stenosis of the cystic artery, both contributing to susceptibility to ischaemic complications. Furthermore, the experimentally demonstrated increased incidence of severe cholecystitis with sympathetic denervation of the gallbladder<sup>16</sup>, brings the hypothesis forward, that diabetic neuropathy may represent an individual predisposing factor.

Despite the observed in our study tendency of patients with gangrenous cholecystitis to be of older age compared to those with acute disease, this difference did not reach statistical significance. This observation is not in agreement with the traditional belief that old age is a predisposing factor to gangrenous cholecystitis<sup>17</sup>. Likewise, our findings did not identify pyrexia and sex as significant prognostic indicators.

Evaluating the results of laboratory investigations, the presence of a raised white cell count ( $>15000/\text{ml}$ ) was identified as a significant prognostic factor. This association could be explained by the increased inflammation observed with gangrene of the gallbladder wall. This observation is in agreement with other studies where the likelihood of development of gangrenous cholecystitis was demonstrated to be proportional to the white cell count at diagnosis<sup>6</sup>.

In addition, the observed high values of serum liver enzymes, could be explained by the extension of inflammation and tissue necrosis in the hepatic parenchyma surrounding a gangrenous gallbladder. This hypothesis is accredited by the results of radio-nuclide imaging studies, where a characteristic rim around the gallbladder is a strong indicator of gangrene<sup>18</sup>.

Demonstration of a peri-cholecystic fluid collection and/or presence of gas in the gallbladder wall or lumen by means of ultrasonography or computerised tomography, were also associated with gallbladder wall gangrene. Of them, the presence of a fluid collection was more frequent but showed moderate specificity, while the demonstration of intramural or intraluminal gas was pathognomonic of gallbladder gangrene, albeit of decreased sensitivity.

### CONCLUSIONS

Gangrenous cholecystitis - a severe form of the acute - is characterised by increased complications, largely preventable by «early», emergency cholecystectomy.

The ability to establish an early diagnosis using common clinical, laboratory and radiological criteria, calls for the practice of early cholecystectomy, even by those who do not generally support its value in the setting of acute cholecystitis. Pre-operative factors that are strongly associated with the development of gangrenous cholecystitis are a raised white cell

count ( $>15000/\text{ml}$ ), demonstration of a peri-cholecystic fluid collection by means of modern radiology and presence of diabetes. Presence of these findings - alone or in combination, should constitute strong indications for emergency, potentially life saving cholecystectomy.

## Προγνωστικοί παράγοντες της βαρύτητας της οξείας χολοκυστίτις

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**ΠΕΡΙΛΗΨΗ:** Σκοπός της προοπτικής αυτής μελέτης αποτελεί ο προσδιορισμός των παραγόντων οι οποίοι επηρεάζουν τη βαρύτητα της οξείας χολοκυστίτιδας και μπορεί να χαρακτηριστούν ως προγνωστικοί παράγοντες.

**Υλικό-Μέθοδος:** Κατά το χρονικό διάστημα 1995-2003 αντιμετωπίστηκαν 149 περιπτώσεις ασθενών με οξεία χολοκυστίτιδα. Προεγχειρητικά εκτιμήθηκαν οι ακόλουθοι παράμετροι: η ηλικία καθώς και το φύλο των ασθενών, το ιστορικό σακχαρώδους διαβήτη ο αριθμός των λευκών αιμοσφαιρίων, οι τιμές των τρανσαμινασών, της αμιλάσης και της αλκαλικής φωσφατάσης, η περι-χολοκυστική συλλογή υγρού, καθώς και η απεικόνιση αέρα στο τοίχωμα της χοληδόχου κύστεως.

**Αποτελέσματα:** Τα διεγχειρητικά ευρήματα καθώς και ο ιστολογικός έλεγχος κατέδειξαν γαγγραινώδη χολοκυστίτιδα σε 40 ασθενείς (26.6%), ενώ σε 7 περιπτώσεις (17.5%), διαπιστώθηκε ρήξη της χοληδόχου κύστεως και περι-χολοκυστική συλλογή. Σε μία περίπτωση διαπιστώθηκε σχηματισμός ηπατικού αποστήματος.

**Συμπεράσματα:** Από το συσχετισμό των προεγχειρητικών παραμέτρων με τα εγχειρητικά και ιστολογικά ευρήματα, προκύπτει ότι ο αριθμός των λευκών αιμοσφαιρίων (>15000/ml), η ύπαρξη περι-χολοκυστικής συλλογής υγρού, καθώς και το ιστορικό σακχαρώδους διαβήτη, αποτελούν τους κυριότερους προγνωστικούς παράγοντες για την ύπαρξη γαγγραινώδους χολοκυστίτιδας.

**Λέξεις Κλειδιά:** Οξεία χολοκυστίτις, Γαγγραινώδης χολοκυστίτις, Επείγουσα χολοκυστεκτομή, Λαπαροσκοπική χολοκυστεκτομή.

## REFERENCES

- Gangrene of the gallbladder. *Am Surg* 1983; 49: 155-158.
- Wilson AK, Koszol RA, Salwen WA et al. Gangrenous cholecystitis in an urban VA hospital. *J Surg Res* 1994; 56: 402-404.
- Pessaud P, Touech JJ, Rouge C et al. Laparoscopic cholecystectomy in acute cholecystitis. A prospective comparative study in patients with acute vs. chronic cholecystitis. *Surg Endosc* 2000; 14: 358-361.
- Cox MR, Wilson TG, Luck AJ et al. Laparoscopic cholecystectomy for acute inflammation of the gallbladder. *Ann Surg* 1993; 218: 630-634.
- Eldar S, Eitan A, Bickel A et al. The impact of patient delay and physician delay on the outcome of laparoscopic cholecystectomy for acute cholecystitis. *Am J Surg* 1999; 178: 303-307.
- Fagan SP, Awad SS, Rahwan KR et al. Prognostic factors for the development of gangrenous cholecystitis. *Am J Surg* 2003; 186: 481-485.
- Decker G, Goergen M, Philipart P et al. Laparoscopic cholecystectomy for acute cholecystitis in geriatric patients. *Acta Chir Belg* 2001; 101: 294-299.
- Kalliafas S, Ziegler DW, Flancbaum L et al. Acute acalculous cholecystitis: incidence, risk factors, diagnosis and outcome. *Am Surg* 1998; 64: 471-475.
- Sessions S, Scoma RS, Sheikh SA et al. Acute acalculous cholecystitis following open heart surgery. *Am Surg* 1993; 59: 74-77.
- Friedman GD. Natural history of asymptomatic and symptomatic gallstones. *Am J Surg* 1993; 165: 399-404.
- Moseley R. Sepsis associated cholestasis. *Gastroenterology* 1997; 112: 302-306.
- Warren BL. Small vessel occlusion in acute acalculous cholecystitis. *Surgery* 1992; 111: 163-168.
- Hakala T, Nuntonen PJO, Rukonen ET et al. Microangiopathy in acute acalculous cholecystitis. *Br J Surg* 1999; 84: 1249-1252.
- Eldar S, Sabo E, Nash E et al. Laparoscopic cholecystectomy for acute cholecystitis: prospective trial. *World J Surg* 1997; 21: 540-545.
- Nguyen L, Fagan SP, Lee TC et al. Use of a predictive equation for the diagnosis of acute gangrenous cholecystitis. *Am J Surg* 2004; 188: 463-466.
- Tabata M. Experimental study of the pathogenesis of acute acalculous cholecystitis: role of autonomic denervation. *J Gastroenterol* 1994; 29: 320-331.
- Morfin E, Ponka JL, Brush BE. Gangrenous cholecystitis. *Arch Surg* 1968; 96: 567-572.
- Bohdiewicz PJ. The diagnostic value of grading hyperperfusion and the rim sign in cholecintigraphy. *Clin Nucl Med* 1993; 18: 867-871.