Hepatobiliary complications of alveolar echinococcosis: A long-term follow-up study

Tilmann Graeter, Franziska Ehing, Suemeyra Oeztuerk, Richard Andrew Mason, Mark Martin Haenle, Wolfgang Kratzer, Thomas Seufferlein, Beate Gruener

Abstract

AIM: To determine the long-term hepatobiliary complications of alveolar echinococcosis (AE) and treatment options using interventional methods.

METHODS: Included in the study were 35 patients with AE enrolled in the Echinococcus Multilocularis Data Bank of the University Hospital of Ulm. Patients underwent endoscopic intervention for treatment of hepatobiliary complications between 1979 and 2012. Patients’ epidemiologic data, clinical symptoms, and indications for the intervention, the type of intervention and any additional procedures, hepatic laboratory parameters (pre- and post-intervention), medication and surgical treatment (pre- and post-intervention), as well as complications associated with the intervention and patients’ subsequent clinical courses were analyzed. In order to compare patients with AE with and without hepatobiliary complications and had not undergone endoscopic intervention were retrieved and analyzed.

RESULTS: Included in the study were 22 male and 13 female patients whose average age at first diagnosis was 48.1 years and 52.7 years at the time of intervention. The average time elapsed between first diagnosis and onset of hepatobiliary complications was 3.7 years. The most common symptoms were jaundice, abdominal pains, and weight loss. The
number of interventions per patient ranged from one to ten. Endoscopic retrograde cholangiopancreatography (ERCP) was most frequently performed in combination with stent placement (82.9%), followed by percutaneous transhepatic cholangiodrainage (31.4%) and ERCP without stent placement (22.9%). In 14.3% of cases, magnetic resonance cholangiopancreatography was performed. A total of eight patients received a biliary stent. A comparison of biochemical hepatic function parameters at first diagnosis between patients who had or had not undergone intervention revealed that these were significantly elevated in six patients who had undergone intervention. Complications (cholangitis, pancreatitis) occurred in six patients during and in 12 patients following the intervention. The average survival following onset of hepatobiliary complications was 8.8 years.

CONCLUSION: Hepatobiliary complications occur in about 10% of patients. A significant increase in hepatic transaminase concentrations facilitates the diagnosis. Interventional methods represent viable management options.

Key words: Alveolar echinococcosis; Endoscopic retrograde cholangiopancreatography; Hepatobiliary complication; Magnetic resonance cholangiopancreatography; Percutaneous transhepatic cholangiodrainage; Stent placement; Treatment

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Approximately 10% of patients with alveolar echinococcosis experience hepatobiliary complications that occur on average 3.7 years (range: 0-41 years) following first diagnosis. Elevated hepatic transaminases in association with jaundice, abdominal pain, and weight loss are typical symptoms facilitating the diagnosis. Interventional endoscopic methods represent important options in these patients’ management. Even in cases of repeated interventions, the rates of complications and treatment-associated mortality are low. The average survival following onset of hepatobiliary complications and interventional treatment stands at 8.8 years.

INTRODUCTION

Alveolar echinococcosis (AE) is a rare but potentially life-threatening parasitic disease that results from infection with the larval stage of Echinococcus multilocularis. Worldwide, the range of the parasite is limited to cold and temperate regions of the northern hemisphere. Although its incidence in endemic regions is generally low (0.03-1.20 per 100000 persons), more recent studies suggest that the endemic regions of E. multilocularis are larger than previously believed. In addition, increased fox (Vulpes vulpes) populations, including in urban areas, have been reported with an associated increased infection risk for humans. Despite abundant clinical resources and technical advances, the diagnosis of AE in infected individuals, especially among inexperienced clinicians, remains challenging. With delayed diagnosis, therapy often begins in a late stage of the disease, which significantly limits treatment options. A characteristic feature of AE is its tumor-like growth, which may lead to infiltration of neighboring organs. The liver is the first organ to be affected by larval infestation. Hepatic lesions are localized to the right hepatic lobe in seven of ten cases, while in 40%, the liver hilus is additionally affected. Only in two of ten cases are both hepatic lobes infested. Patients are typically asymptomatic during the initial phase of the infection. The first symptoms may include upper abdominal pain and cholestatic jaundice. The incubation time ranges from five to fifteen years. Radical resection of the echinococcal lesion is the only curative therapy. Untreated patients experience a mortality rate of 95% within ten years of first diagnosis. Only early detection serves to increase the rate of curative resection, which is confirmed on the basis of imaging methods and serologic markers. Complications such as biliary obstruction, portal hypertension, and bleeding esophageal varices have been described in advanced disease stages and are ascribed to the invasive growth of the E. multilocularis lesion in the liver.

Biliary complications such as intrabiliary rupture in combination with obstructive jaundice in cystic echinococcosis, which is caused by E. granulosus, has an incidence of 1%-25% and, in cases of biliary fistulae, can often be effectively treated using endoscopic retrograde cholangiopancreatography (ERCP). By contrast, a search of the literature with respect to the use of interventional methods such as ERCP in the treatment of hepatobiliary complications of AE reveals no prospective studies and only a few case studies and reports of experience with small numbers of patients. A recently published study with 26 cases represents the largest currently available study of patients with hepatobiliary complications in AE. The authors postulate that surgical interventions represent risk factors for the occurrence of such complications. The incidence of biliary complications was reported to be about 30% with an average survival of three years following hepatobiliary complications. The studies by Ozturk et al and Sezgin et al with 13 and 12 patients, respectively, primarily address the main clinical symptoms and changes in laboratory
parameters associated with biliary complications. Hilmioglu et al.\textsuperscript{[23]} report on six patients and their ERCP results, which they discuss in terms of characteristic cholangiographic findings. Other authors report single cases, such as Gschwantler et al.\textsuperscript{[24]} who report on a combined endoscopic and pharmacetic approach in a patient with rupture of an AE lesion into the bile duct, Koroglu et al.\textsuperscript{[25]}, who describe the complete disappearance of AE following percutaneous drainage, and Rosenfeld et al.\textsuperscript{[26]}, who discuss the onset of painless jaundice and the subsequent therapy. Finally, a few authors mention endoscopic and percutaneous interventions as treatment options for patients in whom the risks of surgery are unacceptably high or in whom the total resection of the AE lesion cannot be guaranteed.\textsuperscript{[22-24]}

The objective of the study was to describe the clinical and biochemical outcomes of patients with hepatobiliary complications of AE and to determine treatment options using interventional methods.

**MATERIALS AND METHODS**

Between 1979 and 2012, AE was diagnosed in 357 patients presenting to the Echinococcosis Specialty Clinic of the University of Ulm. In the present study, we report on 35 patients examined and treated for hepatobiliary complications of AE with interventional methods including ERCP, with or without stent placement, percutaneous transhepatic cholangiopancreatography (PTCD), and magnetic resonance cholangiopancreatography (MRCP). Criteria for inclusion in the study included confirmed diagnosis of AE, use of at least one of the above-mentioned methods for treatment of hepatobiliary complications, and availability of preand post-procedure data on laboratory findings, medication, and surgery. Not all patients were diagnosed and treated in our clinic; patients’ records, however, contained reports and discharge summaries from outside institutions. Patient data was derived retrospectively from the Echinococcus Multilocularis Data Bank of the University Hospital of Ulm. Patients’ epidemiologic data, clinical symptoms, and indications for the intervention, the type of intervention and any additional procedures, hepatic laboratory parameters (pre-and post-intervention), medication and surgical treatment (pre-and post-intervention), as well as complications associated with the intervention and patients’ subsequent clinical courses were recorded.

In addition, available discharge summaries, digital patient records, and reports from outside institutions were reviewed with retrospective compilation of information regarding the indication for the intervention, biochemical hepatic function parameters before and after the intervention, type of intervention, and prior treatment and medication. The subsequent clinical courses of these patients through the end of 2012 were analyzed. All data were then compared with the clinical courses of 322 patients without history of hepatobiliary complications and, thus, without intervention with respect to prior treatment (surgery, medication) and laboratory parameters including hepatic function tests. Prior to analysis, all patient data were anonymized.

The study was conducted in conformity to the basic principles of Helsinki Declaration. It was approved by the local ethics committee. We declare that none of the authors of the present study has any competing commercial, personal, political, intellectual or religious interest with respect to the present study.

**Statistical analysis**

Data were analyzed using the SAS 9.2 statistical software package (SAS Institute, Cary, NC, United States). Data were first analyzed descriptively. For quantitative variables, mean, standard deviation, and minimum and maximum values were derived. For qualitative variables, absolute and relative values are given. In order to identify differences between patients with hepatobiliary complications and those without hepatobiliary complications and without intervention, the Wilcoxon rank-sum test was used for quantitative variables; for qualitative variables, the $\chi^2$ test or, when the number of cases was too small, Fisher’s exact test was used. All tests were two-sided. Statistical significance was established at $P < 0.05$. The statistical methods of this study were reviewed by Suemeyra Oeztuerk (BSc) from Department of Internal Medicine 1, University Hospital Ulm.

**RESULTS**

Included in the present study were 35 patients (22 male, 13 female), whose average age at the time of intervention was 52.7 years (range: 18-82 years). Age distribution at the time of intervention showed two peaks, at 70-79 years (25.7%) and 40-49 years (22.9%), with fewer interventions in patients over the age of 80 years (5.7%) and under 20 years (2.9%). The time from first diagnosis to the onset of hepatobiliary complications showed high variability (0-41 years), with an average of 3.7 years. In 65%, this period was less than one year (Figure 1).

The most frequent symptom of hepatobiliary complications was jaundice (54.3%) (Table 1). The total number of interventions performed in any individual case ranged from one to ten; more than one method could have been employed in patients undergoing multiple interventions. ERCP was most frequently performed in combination with stent placement (82.9%). In addition to the intervention, 16 patients underwent additional procedures. A stent was placed in 74.3% of patients ($n = 26$). Twenty-five patients underwent stent exchange at some point in their clinical course, with only one patient not undergoing exchange. The most frequent reason
prior to onset of hepatobiliary complications, including albendazole (n = 14), mebendazole (n = 8), and amphotericin B (n = 1). Eleven patients underwent further treatment following the first intervention, including partial liver resection (n = 1), curative hemihepatectomy (n = 1), and pharmacotherapy with albendazole (n = 9).

In the group of patients who had not experienced hepatobiliary complications, 46.3% (149/322) had undergone surgery, whereas 50.9% (164/322) had not. In the remaining 2.8% of patients (n = 9), it was not possible on the basis of the available records to retrospectively determine whether or not they had undergone surgery. In the group of patients who had undergone a single intervention, 14/35 (40%) also required surgical treatment, whereas 21/35 (60%) patients did not undergo surgery. There was no significant difference in the rate of surgery between the groups with and without hepatobiliary complications.

Non-resectable AE was diagnosed in 63.0% (225/357) of patients, and hepatobiliary complications were reported in 10.7% (24/225) of these. Patients were considered to have non-resectable AE if they were deemed unsuitable for operation or if curative surgery was unfeasible.

A comparison of biochemical hepatic function parameters at the time of first diagnosis, intervention, and post-intervention in six patients revealed that all parameters increased from the point of first diagnosis to intervention and then declined following intervention. In fact, aspartate transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, and total bilirubin concentrations fell to levels below those documented at first diagnosis (Table 2).

There was a statistically significant difference in biochemical hepatic function parameters between the group of patients with hepatobiliary complications and subsequent intervention and those who did not experience complications (P < 0.05). The same

![Figure 1](https://example.com/figure1.png)
Hepatobiliary complications of alveolar echinococcosis

Table 2 Hepatic function parameters in six patients with alveolar echinococcosis with hepatobiliary complications and intervention

| Parameter | First diagnosis | Intervention | Post-intervention |
|-----------|----------------|--------------|-------------------|
| ALT, U/L  | 109.0 ± 64.3   | 169.0 ± 87.4 | 118.5 ± 154.9     |
| AST, U/L  | 72.7 ± 50.0    | 108.7 ± 41.9 | 66.7 ± 50.0       |
| GGT, U/L  | 301.3 ± 237.3  | 393.3 ± 242.3| 227.3 ± 117.7     |
| AP, U/L   | 272.3 ± 134.8  | 300.3 ± 75.5 | 246.5 ± 95.5      |
| Bilirubin, mmol/L | 101.3 ± 164.8 | 147.1 ± 154.2| 83.6 ± 89.8       |

ALT: Alanine transaminase; AP: Alkaline phosphatase; AST: Aspartate transaminase; GGT: Gamma-glutamyl transpeptidase.

Table 3 Hepatic function parameters in patients with and without hepatobiliary complications of alveolar echinococcosis and subsequent intervention at time of first diagnosis

| Parameter | Hepatobiliary complications | P value |
|-----------|-----------------------------|---------|
| No (n = 148) | Yes (n = 24) |         |
| ALT, U/L  | 43.2 ± 73.6                | 59.8 ± 48.7 | 0.0035 |
| AST, U/L  | 29.3 ± 35.4                | 41.4 ± 35.5 | 0.0431 |
| GGT, U/L  | 94.4 ± 133.2               | 186.4 ± 194.1 | 0.0005 |
| AP, U/L   | 123.8 ± 88.6               | 200.3 ± 125.3 | 0.0016 |
| Bilirubin, mmol/L | 9.8 ± 6.2             | 36.5 ± 86.7 | 0.0148 |

ALT: Alanine transaminase; AP: Alkaline phosphatase; AST: Aspartate transaminase; GGT: Gamma-glutamyl transpeptidase.

parameters were significantly higher in patients with hepatobiliary complication compared to the group of patients who had not undergone intervention (Table 3).

Six patients (17.1%) experienced complications during the first intervention (Table 4). Complications occurred in three patients undergoing ERCP and stent placement (8.6%), in two patients undergoing only ERCP (5.7%), and in one patient with PTCD (2.9%). Within the first week after the intervention, an additional 34.4% of patients (n = 12) experienced complications.

Antibiotic treatment was administered in ten patients following intervention, with metronidazole and amoxicillin being the two more frequently administered agents (in two patients each).

During follow-up through December 2012, a total of 11 (31.4%) patients died, whereas 23 (65.7%) patients remained alive (Figure 2). The average age at time of death was 75.6 years (range: 18-91 years), whereas the average time from onset of hepatobiliary complications to death was 7.2 years (range: 4 d to 15 years). The average age at the conclusion of the follow-up period of the 23 patients who remained alive was 55.4 years (range: 26-86 years), whereas the average time from onset of hepatobiliary complications to conclusion of follow-up was 9.2 years (range: 3 mo to 34 years). For the entire collective of patients (living and deceased), the average period following onset of hepatobiliary complications was 8.8 years.

### Discussion

To date, only a few studies have investigated the biliary complications of AE. In addition to rare vascular, cerebral, and musculoskeletal complications, AE is associated with hepatobiliary complications, for which the incidence and treatment have been reported in only a few studies with small numbers of patients[13-16,23] and case reports[17-20]. Vascular complications include the Budd-Chiari[25,26] and Vena-cava syndrome[27,28], which are caused by occlusions of the hepatic veins[25] or inferior vena cava[27], respectively. Cerebral involvement is associated with immunosuppression and occurs in 1%-5% of cases[29,30], whereas musculoskeletal manifestation resembles a type of spondylitis when the spinal column is impacted, or an abscess in soft tissue[31,32]. Hepatobiliary complications manifest as cholestatic jaundice, cholangitis, biliary colic, and fever[1,5]. The rate of biliary invasion is given at 11.4%[16]. In our overall collective, hepatobiliary complications occurred in 35 of a total 357 patients. The resulting complication rate of 9.8% is comparable to findings published by Ozturk et al[16]. A recent study by Frei et al[21] reports a complication rate of 30% in patients with non-resectable AE. In the present study, 24/322 patients with non-resectable AE experienced hepatobiliary complications, corresponding to a rate of 7.0%.

The main symptoms reported by patients in our collective included jaundice, abdominal complaints, and weight loss, which correspond to symptoms reported in other studies[13]. Similarly, the predominant indications of intervention in our study were obstructive jaundice and cholangitis, which agrees with the results of other studies[16,17]. Other indications for intervention reported in the literature, such as biliary fistula[16], portal vein thrombosis, and esophageal varices[22], were not observed in our collective. On average, hepatobiliary complications occurred 3.7 years following first

### Table 4 Type of complications

| Complication | Frequency |
|--------------|-----------|
| During first intervention | | |
| Failure visualize bile ducts | 66.7% |
| Bleeding at the papilla of vater | 16.7% |
| Bile leakage | 16.7% |
| Within first week after intervention | | |
| Panreatitis | 41.7% |
| Cholangitis | 33.3% |
| Hemorrhage | 8.3% |
| Wound infection | 8.3% |
| Fistula formation | 8.3% |
| Bacteremia | 8.3% |
| Abdominal pain | 8.3% |
| Abscess information | 8.3% |
| Pneumoperitoneum | 8.3% |

1Multiple indications possible.
not able to identify any difference in the rate of surgery between patients with and without hepatobiliary complications. Our data also confirm that prior liver resection does not represent a risk factor for the development of hepatobiliary complications[21].

To date, only one study by Frei et al[21] has investigated survival following onset of hepatobiliary complications. They report a survival of only three years following onset of complications, which, in their series, occurred in about 30% of patients. By contrast, data in the present study show an average survival of 8.8 years following onset of complications. On average, Frei et al[21] also report the onset of hepatobiliary complications 15.0 years following first diagnosis of AE compared with the average of 3.7 years in the present study.

The main limitation of this study is its retrospective design. As a result, it was not possible to retrieve more detailed information about the complications occurring in these patients.

The data of the present study allow us to conclude that hepatobiliary complications requiring treatment occur in about 10% of patients with AE. Significant increases in biochemical hepatic function parameters are already present at the time of first diagnosis. On average, hepatobiliary complications occurred 3.7 years following first diagnosis of AE, but this time to occurrence is subject to high variability (0-41 years). Despite the fact that many patients will require multiple treatments, endoscopic interventional methods offer a well-established treatment procedure with a tolerable rate of complications and treatment-associated mortality and an average survival of 8.8 years.

**COMMENTS**

**Background**

Despite abundant clinical resources and technical advances, the diagnosis of alveolar echinococcosis in infected individuals, especially among inexperienced clinicians, remains challenging. With delayed diagnosis, therapy often begins in a late stage of the disease, which significantly limits treatment options.

**Research frontiers**

The liver is the first organ to be affected by larval infestation. Hepatic lesions are localized to the right hepatic lobe in seven of ten cases, whereas in 40%, the liver hilus is additionally affected. Only in two of ten cases are both hepatic lobes infested.

**Innovations and breakthroughs**

Hepatobiliary complications occur in about 10% of patients. A significant increase in hepatic transaminase concentrations facilitates the diagnosis. Interventional methods represent viable management options.

**Applications**

Many patients will require multiple treatments, and endoscopic interventional methods offer a well-established treatment procedure with a tolerable rate of complications and treatment-associated mortality and an average survival of 8.8 years.

**Peer-review**

In this paper, the authors systemically described their own long-term clinical data on alveolar echinococcosis. How to effectively manage post-operative complications was still a challenging problem for the surgeons. This paper was well organized and informative.
REFERENCES

1. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 2004; 17: 107-135 [PMID: 14726458 DOI: 10.1128/CMR.17.1.107-135.2004]

2. Miguet JP, Bresson-Hadni S. Alveolar echinococcosis of the liver. J Hepatol 1989; 8: 373-379 [PMID: 2567298 DOI: 10.1016/1016-827 8(89)90037-8]

3. Nunnari G, Pinzone MR, Gruttadamia S, Celesia BM, Madeddu G, Malaguarnera G, Pavone P, Cappellani A, Cacepardo B. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol 2012; 18: 1448-1458 [PMID: 22509076 DOI: 10.3748/wjg.v18.i13.1448]

4. Romig T. Epidemiology of echinococcosis. Langenbecks Arch Surg 2003; 388: 209-217 [PMID: 12937989 DOI: 10.1007/s00423-003-0413-3]

5. Ammann RW, Eckert J. Cestodes. Echinococcus. Gastroenterol Clin North Am 1996; 25: 655-689 [PMID: 8863045 DOI: 10.1016/S0042-3372(05)00268-5]

6. Atanasov G, Benckert C, Thelen A, Tappe D, Frosch M, Teichmann D, Barth TF, Witekind C, Schubert S, Jonas S. Alveolar echinococcosis-spreading disease challenging clinicians: a case report and literature review. World J Gastroenterol 2013; 19: 4257-4261 [PMID: 23864792 DOI: 10.3748/wjg.v19.i26.4257]

7. Davidson RK, Romig T, Jenkins E, Tryland M, Robertson LJ. The impact of globalisation on the distribution of Echinococcus multilocularis. Cestodes. Echinococcus. Parasitology 2000; 120: 1-7 [PMID: 10831683 DOI: 10.1017/S0031182000007967]

8. Schweiger A, Ammann RW, Candinas D, Clavien PA, Eckert J, Gottstein B, Halkic N, Muellerb H, Prinz BM, Richen J, Tarr PE, Torgerson PR, Deplazes P. Human alveolar echinococcosis after fox population increase, Switzerland. Emerg Infect Dis 2007; 13: 878-882 [PMID: 17553227 DOI: 10.3201/eid1306.061074]

9. Heyd B, Weise L, Betschert V, Gillet M. Surgical treatment of hepatic alveolar echinococcosis. Chirurg 2000; 71: 16-20 [PMID: 10662925 DOI: 10.1007/s001040051007]

10. Craig P. Echinococcus multilocularis. Curr Opin Infect Dis 2003; 16: 437-444 [PMID: 14501996 DOI: 10.1097/00010432-200310000-00010]

11. Buttenschon K, Carl Buttenschon D, Gruner B, Kern P, Beger HG, Henne-Bruns D, Reuter S. long-term experience on surgical treatment of alveolar echinococcosis. Langenbecks Arch Surg 2009; 394: 689-698 [PMID: 18651165 DOI: 10.1007/s00423-008-0392-5]

12. Kern P, Kratzer W, Reuter S. Alveolar echinococcosis: diagnosis. Dtsch Med Wochenschr 2000; 125: 59-62 [DOI: 10.1055/s-2007-1023007]

13. Sezgin O, Altintaş E, Saritas U, Sahin B. Hepatic alveolar echinococcosis: clinical and radiologic features and endoscopic management. J Clin Gastroenterol 2005; 39: 160-167 [PMID: 156819144]

14. Erzurumlu K, Dervisoglu A, Polat C, Senyurek G, Yetim I, Hokelek M. Intrabiliary rupture: an algorithm in the treatment of controversial complication of hepatic hydatidosis. World J Gastroenterol 2005; 11: 2472-2476 [PMID: 15832420]

15. Sharma BC, Reddy RS, Garg V. Endoscopic management of hepatic hydatid cyst with biliary communication. Dig Endosc 2012; 24: 267-270 [PMID: 22725113 DOI: 10.1055/s-0032-1273992]

16. Ozturk G, Polat KY, Yildirgan MI, Aydinni B, Atamanalp SS, Aydin U. Endoscopic retrograde cholangiopancreatography in hepatic alveolar echinococcosis. J Gastroenterol Hepatol 2009; 24: 1365-1369 [PMID: 19702904 DOI: 10.1111/j.1440-1746.2009.05877.x]

17. Hilmiglobu F, Dalay R, Caner ME, Boyacioglu S, Cumhur T, Sahin B. ERCP findings in hepatic echinococcosis. Gastrointest Endosc 1991; 37: 470-473 [PMID: 1916171 DOI: 10.1016/S0036-7293(91)70783-9]

18. Gschwantler M, Brownstone E, Erben WD, Auer H, Weiss W. Combined endoscopic and pharmaceutical treatment of alveolar echinococcosis with rupture into the biliary tree. Gastrointest Endosc 1994; 40: 238-241 [PMID: 8013833 DOI: 10.1016/S0016-5107(94)07178-4]
Graeter T et al. Hepatobiliary complications of alveolar echinococcosis

bile ducts. Dig Surg 2013; 30: 444-450 [PMID: 24434644 DOI: 10.1159/000356711]

36 Hossary SH, Zytoon AA, Eid M, Hamed A, Shanaan M, Ebrahim AA. MR cholangiopancreatography of the pancreas and biliary system: a review of the current applications. Curr Probl Diagn Radiol 2014;

37 Draganov P, Hoffman B, Marsh W, Cotton P, Cunningham J. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. Gastrointest Endosc 2002; 55: 680-686 [PMID: 11979250]

P- Reviewer: Atanasov G, Bottcher D, Hatipoglu S, Jovanovic P, Wen H
S- Editor: Qi Y  L- Editor: AmEditor  E- Editor: Wang CH
