

OVERVIEW

CURRENT STATUS OF INFECTION-RELATED GASTROINTESTINAL AND HEPATOBILIARY DISEASES IN THAILAND

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Abstract. The objective of this overview is to assess the present situation with regards to gastrointestinal and hepatobiliary diseases prevailing in Thailand. In that context, special emphasis has been put on those forms of viral hepatitis prevalent in the region, namely, hepatitis A the frequency of which has undergone a change from hyper- to hypoendemic with a resulting decline in naturally acquired immunity; hepatitis B with its tendency to cause chronic liver disease mainly due to asymptomatic infections during early childhood and the impact of mass vaccination programs on its endemicity; hepatitis C which can also lead to chronicity; hepatitis D solely found as a coinfection with hepatitis B; hepatitis E acute cases of which can sporadically be found; hepatitis G encountered in healthy subjects at a prevalence similar to that seen in patients with chronic liver disease and rather more prevalent among people at risk for contracting blood borne agents; finally the novel hepatitis TT virus with a distribution comparable to that of hepatitis G virus and a similarly unclear role as to the etiology of serious liver disease. Particularly in connection with hepatitis B we have examined the situation regarding hepatocellular carcinoma which represents one of the most common malignancies among the Thai population. Cholangiocarcinoma caused by the liver fluke *Opisthorchis viverrini* is the most common form of liver cancer in the northeastern part of Thailand where an estimated 70 % of the population are infested with the parasite. Peptic ulcer caused by *Helicobacter pylori* constitutes another common gastrointestinal affliction with the overall prevalence of antibodies to the agent amounting to 63 to 74 % in patients exhibiting gastroduodenal symptoms. The final part of the paper deals with HIV-related gastrointestinal and liver disease and with amebic and pyogenic liver abscesses.

INTRODUCTION

Gastrointestinal and hepatobiliary diseases remain a major public health burden in Thailand (Kullavanijaya, 1997). As it is a developing country with tropical climate, several gastrointestinal and hepatobiliary disorders related directly and indirectly to infectious agents in this region are still common, for example, hepatitis viruses, intestinal and hepatic parasites and *Mycobacterium tuberculosis*. The various infections encountered are particularly concentrated in certain regions of the country, for example, in most of the northeast liver fluke with subsequent cholangiocarcinoma is endemic, as well as melioidosis caused by *Burkholderia pseudomallei*, whereas infection with the fungus *Penicillium marneffe* is

prevalent among individuals harboring the human immunodeficiency virus (HIV) in some northern areas. The magnitude of the problem is particularly evident in rural areas where poor sanitation and hygiene, as well as lack of adequate health services are common. Furthermore, the current health problems in urban areas are not only limited to tropical diseases, but also resemble those of developed countries. In addition, the wide-spread HIV infection in recent years has contributed to a large number of AIDS-related opportunistic infections and now has a major impact on public health and becomes a social impediment.

Our objective is to review the present situation regarding gastrointestinal and hepatobiliary diseases prevailing in Thailand, with special emphasis on six afflictions that are particularly common. These are viral hepatitis, hepatocellular carcinoma, liver fluke and cholangiocarcinoma, *Helicobacter pylori* and peptic ulcer, HIV-related gastrointestinal and hepatobiliary diseases, and liver abscesses.

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VIRAL HEPATITIS

Hepatitis A

Epidemiological studies have shown its prevalence in Thailand having undergone a profound change from hyperendemic through an intermediate state to hypoendemic due to improvements in sanitation and hygiene (Poovorawan *et al*, 1993; Kosuwon *et al*, 1996; Poovorawan *et al*, 1996c; Poovorawan *et al*, 1997). These circumstances might favor an outbreak, since infection with HAV has been postponed from childhood towards adolescence and early adulthood. Consequently, the majority of the Thai population have not acquired protective immunity during childhood when HAV infections are usually asymptomatic. Yet, even among patients devoid of previously acquired immunity to HAV infection during adulthood is rarely fatal and progression towards fulminant hepatic failure rather represents a rare exception, whereas development to HCC has never been reported.

Preventive measures are essential in reducing the infection rate. These include improvement of personal hygiene, health education, hepatitis A surveillance, and control of outbreaks. Immunoprophylaxis is another promising preventive measure, particularly during an epidemic (Poovorawan *et al*, 1994, 1995, 1996a).

Hepatitis B

In Thailand, similar to other countries in Southeast Asia where HBV infection is hyperendemic, carriage of the virus is encountered at an especially high frequency. More than half of the population in this area have been infected with the virus at some time in their lives, the result of either vertical (perinatal) transmission or horizontal transmission among the members of extended families or among children at preschooling age (Lee, 1997). Hence, the epidemiology of infection differs from areas of low endemicity such as North America and other Western countries where as a consequence of sexual activity, intravenous drug abuse or occupational exposure adults are at greatest risk of infection (Alter and Mast, 1994). Infection of infants and children results in persistent HBV carriage with a significant risk for the development of chronic active hepatitis, cirrhosis and its fatal complication, hepatocellular carcinoma (HCC) (Beasley *et al*, 1981). In a case-control study, the relative risk of HCC associated with HBsAg in Thailand has been determined at approximately 15.2, comparable to data obtained from other countries where HBV is prevalent (Srivatanakul *et al*, 1991a).

Chronic HBV infection constitutes the most important etiologic cause of chronic liver disease in Thailand, amounting to approximately 66-70% of cases diagnosed, and exceeding those caused by chronic HCV infection by three-to four fold (Pramoolsinsap *et al*, 1992; Tangkijvanich *et al*, 1999). Up to now, alfa-interferon (IFN- α) has been the only therapy licensed for the treatment of chronic hepatitis B in Thailand. In our experience, the therapeutic efficiency of IFN, given at a dose of 3-10 mU thrice weekly for 4-6 months, has been disappointing. Complete response with loss of HBsAg, HBeAg and normalization of ALT during the follow-up period of 30 months (8-58 months) can be achieved with less than 5 % of cases. Partial response with loss of HBeAg and normal ALT is found less than 30%. This low response rate can probably be explained by the fact that most Thai patients have acquired the infection already for a long time. More recent medications such as nucleoside analogues, lamivudine and adefovir, are currently undergoing clinical trials.

In order to combat HBV infection and subsequent carriage, most East Asian and Southeast Asian countries have introduced mass vaccination programs during the late eighties to mid nineties, which have resulted in a drastic decline of the HBV carrier rate and the number of hepatocellular carcinoma patients. Recent data on the immunization program against hepatitis B in Taiwan have demonstrated a reduction in the rate of HBV carriage in six-year-old children from about 10% during the period of 1981 to 1986 to 0.8-0.9% between 1990 and 1994 (Chang *et al*, 1997). Likewise, the incidence of HBV carriers among the Thai population has been steadily declining during the period from 1981 to 1991. For example, the prevalence of HBV carriers among blood donors and students decreased from 8.23 and 6.6%, respectively, in 1987 to 6.45 and 5.2%, respectively, in 1991 (Tanprasert and Somjitt, 1993). Current data from an epidemiological survey in Songkhla Province in the south of Thailand has demonstrated the overall prevalence of the HBV carrier rate established at 0.55% among children under 15 years of age (Chub-uppakarn *et al*, 1998). It has been clearly shown that hepatitis B immunization as part of the national Expanded Program on Immunization (EPI) is highly efficient in protecting newborns from infection.

Hepatitis C

The prevalence of anti-HCV among the Thai adult population is about 1.5% in Bangkok, comparable to data from other Asian countries non-endemic for HCV (Chainuvati *et al*, 1991; Suwanagool *et al*, 1995). However, in the northeast the preva-

lence reaches as high as 5% (Songsivilai *et al*, 1997). HCV genotype 3a is the most common genotype, accounting for about 40-70% of Thai HCV cases, followed by genotype 1b (12-20%) and genotype 6 (18%) (Luengrojanakul *et al*, 1994; Theamboonlers *et al*, 1995; Kanistanon *et al*, 1997). The distribution of HCV genotypes in Thailand is different from that found in other countries in Southeast Asia including Singapore, Indonesia and the Philippines, but may be similar to that in Lao PDR and Vietnam. In addition, the HCV genotype prevalent among HCC patients is similar to that in the general population and no specific association between genotype 1b and HCC has been observed, in contrast to previous reports from western countries. (Songsivilai *et al*, 1996).

Hepatitis C is responsible for approximately 20% of chronic liver disease cases (Luengrojanakul *et al*, 1994). Once infected with HCV, progression towards chronicity is the most outstanding characteristic, occurring among more than 85% of patients with acute infection. Cirrhosis can develop rapidly within a few years after exposure, or slowly within 20-30 years. (Hoofnagle, 1997). Typically, patients with chronic hepatitis C have few symptoms, and these are usually nonspecific, intermittent, and mild. Extrahepatic manifestations of hepatitis C, for example essential mixed cryoglobulinemia (EMC), are uncommon in Thai patients. (Kheawsreekul *et al*, 1997).

Alfa-interferon therapy in chronic hepatitis C at a dose of 3 mU thrice weekly for 6 months on average can induce a complete response, defined by normal ALT and lack of HCV RNA in serum throughout the follow-up period in approximately 17% of the patients, but relapse is common (>70%) among those showing an initial response (Tanwandee *et al*, 1997). The data suggests a six-month regimen is probably insufficient and a more extended therapy might be required in order to induce long-term remission. Combination therapy of IFN and ribavirin, proposed to be superior to therapy with IFN alone, is currently undergoing clinical trials.

Hepatitis D

As hepatitis delta virus requires a helper virus for replication its transmission depends on either coinfection with HBV or superinfection in individuals who are HBV carriers. In Thailand, HDV has been found only among IVDUs as a coinfection with HBV (Poovorawan *et al*, 1989).

Hepatitis E

HEV infection does not constitute a problem in

Thailand. We have detected only a low prevalence of HEV IgG among the Thai population. However, sporadically acute cases of HEV infection can be encountered (Poovorawan *et al*, 1996b).

Hepatitis G

The newly discovered hepatitis G virus (HGV/GBV-C) has a worldwide distribution and is rather commonly found in healthy people. The prevalence of HGV infection among the healthy Thai population amounts to 1-5%, similar to that in patients with chronic liver disease and HCC, but is much lower than among individuals at risk for contracting blood-borne viruses such as thalassemic children and IVDU (Poovorawan *et al*, 1998a; Tangkijvanich *et al*, 1999). The association of HGV with liver disease has not been clearly established. It appears to be innocuous or relatively harmless to the liver and has not been identified as the etiological agent in the majority of cryptogenic fulminant hepatitis and chronic liver disease (Okuda, 1998). Moreover, the response of chronic hepatitis C to interferon is not altered by coinfection with HGV (Pramoosinsap *et al*, 1998).

Hepatitis TT

Hepatitis TT virus (TTV) represents a novel hepatitis virus which had first been isolated by representational difference analysis (RDA) (Lisitsyn *et al*, 1993) as a clone of 500 nucleotides from the serum of a patient with post-transfusion hepatitis of unknown etiology, who exhibited elevated ALT levels indicating liver inflammation (Nishizawa *et al*, 1997). Subsequently, the same team of researchers has molecularly cloned and characterized the agent as a non-enveloped, single-stranded DNA virus. By now, approximately 3.7 kb of its genome harboring two potential open reading frames have been sequenced. Upon subjecting the nucleotide sequence of the 3.7 kb clone to homology search, no nucleotide sequences showing a significantly high sequence homology to it could be detected (Okamoto *et al*, 1998). To date, five different genotypes of TTV, each displaying the second open reading frame particularly rich in arginine, have been isolated from serum of infected individuals in Japan where the virus has been found highly prevalent in patients at risk for contracting blood borne viruses, such as hemophilia and hemodialysis patients, or intravenous drug users (IVDU). Likewise, TTV was detected among patients with non-A-to-G fulminant hepatitis and chronic liver disease at a frequency amounting to almost 50% (Okamoto *et al*, 1998).

In Thailand, the prevalence of TTV was established 7 % (14/200) and 6.8 % (7/103) in voluntary

blood donors and pregnant women, respectively. Contrasting that, among members of groups at high risk for contracting blood-borne viruses TTV DNA was detected at frequencies amounting to 18 % in patients with chronic non-A-to-G liver disease (9/50), 9.2 % in hepatocellular carcinoma (9/98), 32.7 % in intravenous drug users (17/52), 18.8 % in thalassemia patients with multiple blood transfusions (15/80) and 9.7 % in prostitutes (3/31), respectively (Poovorawan *et al*, 1998b).

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) represents one of the most common malignancies among Thai people: the most common in males, 16.3%, and the third most common in females, 5.5% (Srivatanakul *et al*, 1988). Its prevalence peaks in the age group of between 51 and 70 years (Kanistanon *et al*, 1997; Tangkijvanich *et al*, 1999). The majority of patients have underlying liver cirrhosis caused by viral hepatitis B or C, alcohol abuse, or of unknown etiology. Among these, HBV infection by far ranks the highest as an etiologic factor, is found at a frequency surpassing 60% of HCC cases. However, in those seronegative for HBsAg HCV plays an important part (Tangkijvanich *et al*, 1999; Kanistanon *et al*, 1997). In a long term study lasting for more than 5 years, about 16% of chronic HCV infection developed HCC associated with cirrhosis, which is much higher percentage than that observed with chronic HBV patients (<1%) (Punyagupta *et al*, 1999). In addition, due to the hot and humid climate in Thailand, contamination of food by aflatoxin B₁ (AFB₁), may constitute another etiologic agent (Hollstein *et al*, 1993).

Theoretically, regular follow-up of cirrhotic patients with ultrasonography and serial determinations of alpha-fetoprotein (AFP) concentrations is essential for early detection and treatment. Unfortunately, early diagnosis is not possible for most high-risk Thai patients because of the high cost of the imaging procedure and shortage of available resources, particularly in rural areas. Moreover, the screening programs are still limited to some central hospitals and hence, almost inaccessible from the more remote rural areas.

The prognosis of most Thai HCC patients is rather poor due to the advanced stage at presentation and rapid clinical deterioration. In general, hepatic resection is usually performed too late to be effective and liver transplantation, the "ideal" therapeutic

modality, can only be awarded to a very few patients. Therefore, the majority of patients are not amenable to curative therapy. The palliative treatments currently available in Thailand are arterial chemoembolization, and to a lesser extent, percutaneous ethanol injection. The therapy outcome tends to be variable, depending not only on the characteristics of the tumor but also on the severity of the underlying liver disease. In a study on chemoembolization in unresectable HCC, the data has shown it to be an effective treatment, particularly for Okuda stage II tumors. Furthermore, it may enhance the chances for survival in some cases and is sometimes performed before curative surgical resection (Phornphutkul *et al*, 1992). For untreated patients, the overall median duration of survival from the time of diagnosis is only 8.7 weeks and the median survival ranges for Okuda II and III patients are 10.7 and 7.3 weeks, respectively. Common causes of death are upper gastrointestinal hemorrhage, cancer-related causes (cachexia, HCC rupture, metastatic disease) and liver failure (Pawarode *et al*, 1998).

LIVER FLUKE AND CHOLANGIOPHILIC CARCINOMA

Cholangiocarcinoma (CCA) is the most common liver cancer in the northeastern part of Thailand where the liver fluke, *Opisthorchis viverrini*, is hyperendemic. It is estimated that 70% of the population in this region are infected with the fluke and the incidence of CCA is believed to be at least 50 times that of Western countries (Upatham *et al*, 1983). In Khon Kaen Province, for example, the age standardized incidence rate of CCA is estimated at 84.6 and 36.8 per 100,000 males and females, respectively, at least 30-times that reported from other regions in Thailand where the prevalence of fluke infection is low (Vatanasapt *et al*, 1993). The evidence gathered thus far hints at liver fluke infestation due to ingestion of uncooked fish, as well as a high content of nitrosamine compounds in fermented salted fish, the predominant diet in this region, as the two factors predisposing to a high incidence of CCA (Srivatanakul *et al*, 1991b).

Compared to HCC, CCA is usually not associated with cirrhosis. Males are four to five times more likely to be affected than females, with presentations peaking within the age group of 45 to 65 years. There are two main types of clinical presentation, namely, the jaundiced and the jaundice-free patients. The most common by far is jaundice due

to a malignant tumor obstructing the hilum or common bile duct (70%). The remaining patients present with right upper quadrant pain caused by liver mass (14%), hydrops of the gallbladder (6.7%) or acalculous cholecystitis (7%). However, in recent years the percentage of jaundice-free patients appears to be on the increase (Uttaravichen *et al*, 1996).

The most useful diagnostic tool applied to the management of CCA in the endemic area is ultrasonography. It is used both for screening and as a pre-operative assessment guide to demonstrate the characteristic ductal dilatations and the sites and extent of tumor obstruction. Serologically, almost none of the CCA patients is alpha-fetoprotein (AFP) positive. Performing combined tests for CA125 and CA19-9 reveals an increase in sensitivity and specificity up to 85.7% and 98.1%, respectively (Pungpak *et al*, 1991). It has been suggested that these two markers might be useful for early detection of opisthorchiasis-associated CCA.

As a result of advanced disease at presentation, treatment is usually palliative and the prognosis is poor. Most of the surgical procedures are carried out in order to relieve the obstruction by various types of by-pass or to remove the mass if that is altogether possible. The resectability rate for hilar tumor is approximately 17% (Bhudhisawasdi, 1997). For jaundiced cases, the one-year and five-year survival rate is 15% and 1-2%, respectively. On the other hand, the results for jaundice-free cases are better, with one-year and five-year survival rates of 75% and 15%, respectively (Bhudhisawasdi, 1997 ; Uttaravichen, 1994). Palliative radiological intervention aimed at establishing percutaneous biliary drainage has also proven useful in cases with inoperable obstructive tumors. However, due to its high cost and lack of trained personnel this technic is not widely used in Thailand.

As regards the enormous impact of CCA on public health, during the last few years the Ministry of Public Health has justifiably supported the campaign against eating raw fish and fermented salted fish. Since 1984, upon intensive health education and mass treatment for liver fluke with praziquantel, the prevalence of the fluke in northeastern Thailand has continuously declined from nearly 80% in 1984 to approximately 20% in 1994. Health related behavior patterns, particularly frequent consumption of uncooked fish dishes, have shown a declining trend from 14% in 1990 to 7% in 1994, whereas occasional consumption has remained as high as 42% (Jonsuksuntigul and Imsomboon, 1997). The effectiveness of this preventive and control program

geared at reducing the prevalence of CCA ought to be re-evaluated in the future.

HELICOBACTER PYLORI AND PEPTIC ULCER

Peptic ulcers are common in all regions of Thailand, however, the actual prevalence among the population can never be accurately assessed. National data compiled from official annual reports from provincial hospitals, as well as hospital-based data are at best selective and subject to several drawbacks in the process of data collection. Between 1981 and 1988, the hospitalization rate for peptic ulcer cases throughout the country remained constant at around 110 to 120 per 100,000 population. The proportions between gastric ulcers and duodenal ulcers were comparable, with gastric ulcers more frequently encountered among females than males (Wilairatana *et al*, 1991).

As to *Helicobacter pylori* (*H. pylori*), a serologic study has shown the seroprevalence of the infection in Thailand to be higher than in industrialized countries. In the Thai community, formation of *H. pylori* antibodies is initiated early (17.5% of children 5-9 years old), increases to 55% during the third decade of life, and peaks within the age group between 30 and 50 years (Perez-Perez *et al*, 1990). The overall prevalence in patients exhibiting gastroduodenal symptoms amounts to approximately 63-74%. Among these patients, duodenal ulcer (DU) is found most frequently (66-77%), followed by gastric ulcer (GU) and non-ulcer dyspepsia (NUD) at 52-55% and 44%, respectively (Kachintorn *et al*, 1992; Chinprasatsak *et al*, 1993). Hence, association of the bacterium with DU and GU in Thailand is less pronounced than in Western countries where the prevalence of *H. pylori*-associated DU and GU amounts to 90-95% and 70-80%, respectively (Hunt and Lam, 1998). If this is confirmed, the etiology of peptic ulcer in Thailand may be due to other causes, for example, NSAIDs usage known to account for at least 25% of cases (Chinprasatsak *et al*, 1993)

Until now, the bacterial virulence factors of *H. pylori*, such as the cytotoxin associated gene A (CagA) and the vacuolating cytotoxin gene A (VacA), have been extensively studied. Data from Western countries have demonstrated infection with CagA-positive strains to be associated with more severe gastritis and a higher prevalence of peptic ulceration and gastric carcinoma (Weel *et al*, 1996; Parsonnet *et al*, 1997). However, studies performed in Thai patients have revealed an equally high

seroprevalence of CagA-positive strains amounting to approximately 70-90% in peptic ulcer, gastric cancer and non-ulcer dyspepsia (Mahachai *et al*, 1999, *in press*). This finding indicates that the strain is common among the Thai population comparable to other Asian countries, such as China and Japan (Shimoyama *et al*, 1997; Pan *et al*, 1997). Therefore, anti-CagA antibody is not a reliable marker for screening severe gastroduodenal disease in the Thai population.

The management of *H. pylori* infection in Thailand is similar to that in the Asian Pacific region where there is a high background prevalence of infection, a high incidence of gastric cancer, along with limited resources. According to the consensus reached at the 1997 Asia Pacific conference (Lam and Talley, 1998) for example, the diagnostic method of choice for detection of *H. pylori* after endoscopy is a biopsy urease test (CLO test), with histology recommended only if the former yields a negative result. All DU and GU patients infected with the bacterium should be treated irrespective of the ulcer being active or in remission. It has also been agreed that for ulcer-free dyspeptic patients with documented infection to treat or not will depend on a case-by-case decision after informing them about potential risks and benefits. Treatment regimens include proton pump inhibitors (PPI), or ranitidine bismute citrate (RBC), combined with two antibiotics administered for seven days. In Thailand, with metronidazole resistance strain found in about 50% of the population (Phaosawasdi *et al*, 1995) amoxicillin-containing combinations are recommended over those containing metronidazole.

HIV-RELATED GASTROINTESTINAL AND LIVER DISEASES

Thailand's human immunodeficiency virus (HIV) epidemic is one of the most extensively documented for any developing country. It has been estimated that the total number of people in Thailand with HIV infection will exceed 1 million by the year 2000 (Surasiengsunk *et al*, 1998). Despite the declining trend of HIV infection in the general population as a consequence of successful prevention programs during the past few years, the number of AIDS-related deaths is expected to increase rapidly to around 70,000 cases per year in 2000 before declining slowly in the course of the next decade (Phoolcharoen, 1998). Hence, the health burden in terms of HIV-related gastrointestinal and liver diseases may increase as these symptoms are among the

most frequent complaints of AIDS patients.

Diarrhea is a major complication of HIV infection and has a severe impact on health care costs, quality of life, and survival of patients. In chronic diarrhea, the attempt to identify the etiologic agents is challenging but is not a common practice. Therefore, the data available are very limited, particularly in developing countries. A prospective study conducted to investigate the causes of chronic diarrhea in 45 HIV-infected Thai patients (Manatsathit *et al*, 1996) revealed etiologic pathogens in approximately 65%. This figure is higher than that reported from African countries but lower than the results from developed countries, where more thorough and extensive investigative methodology is applied. The most commonly found enteric pathogen is *Cryptosporidium parvum* (20%), followed by *Mycobacterium tuberculosis* (17.8%), *Salmonella* spp (15.5%), *Cytomegalovirus* (11.1%), *Mycobacterium avium* complex (6.6%), *Strongyloides stercoralis* (4.4%) and *Giardia intestinalis* (4.4%). This finding differs from reports in most African countries, where *Isospora* is the second most common cause of AIDS-related diarrhea. Another retrospective study on stool samples of 22 HIV-infected patients has shown about 50% of the cases to be infected with protozoa. These include *Microsporidium* (27%), *Cryptosporidium* (9%), *Giardia intestinalis* cysts (9%) and *Isospora belli* (4.5%) (Punpoowong *et al*, 1998). The discrepancy between etiologic pathogens apparent from these two studies may be explained by differences in study design.

Hepatomegaly with or without jaundice, accompanied by one or more liver function test abnormalities, is a frequent finding in AIDS patients. A prospective study conducted in Bangkok to identify etiologies of prolonged fever among patients with advanced HIV infection has shown the leading candidates among pathogens to be mycobacteria and fungi (Suwanagool *et al*, 1998). Of these, *Mycobacterium avium* complex (MAC) is the most common blood isolate in 24% of the patients, followed by *Mycobacterium tuberculosis* in 20%, *Cryptococcus neoformans* and *Penicillium marneffeii* in about 6% each. In these patients, except those infected with *Cryptococcus*, diarrhea, abdominal pain, hepatomegaly, splenomegaly and high alkaline phosphatase are among the most frequent findings of systemic involvement, accounting for more than 50% of the cases.

Although involvement of the liver, particularly in disseminated cases, is not uncommon, tuberculosis (TB) exclusively involving the liver is found to

a lesser extent. However, in the era of AIDS, unusual forms of hepatic TB may be seen more frequently (Pottipati *et al*, 1991). In our experience, there have been many cases of tuberculous hepatitis and tuberculous liver abscess among HIV-infected patients. The former present with unexplained fever, hepatomegaly, mild jaundice, which, on liver biopsy shows caseating granuloma and positive AFB staining. More interestingly, in the latter form, ultrasonography of the liver shows hypo-echoic lesions and complex masses similarly to those of either pyogenic liver abscess or liver malignancy. In these cases, ultrasonography guided liver aspiration can confirm the diagnosis by conventional methods (AFB stain or culture). Treatment of hepatic or disseminated TB in HIV-infected patients does not differ from that of TB in general. However, in the central region of Thailand the percentage of multidrug-resistant tuberculosis (MDR-TB) has increased to 4.2% among new patients and 25.2% of previously treated cases (Riantawan *et al*, 1998). The spread of drug resistant strains has serious implications for TB control in HIV-infected patients, as well as in HIV-seronegative cases.

Penicillium marneffei infection is very common among individuals with advanced HIV infection in northern Thailand. The usual presentations are fever, anemia, weight loss, skin lesions commonly in the form of papules with central umbilication, generalized lymphadenopathy and hepatomegaly. The diagnosis of penicilliosis is easily arrived at when typical skin lesions appear but is frequently missed in their absence and the mortality rate is high among undiagnosed cases (Supparatpinyo *et al*, 1994). Penicilliosis primarily involving the liver without skin lesions has been reported in endemic areas (Kantipong *et al*, 1998). The clinical indications leading to diagnosis are fever of short duration, hepatomegaly and markedly elevated serum alkaline phosphatase levels. The definite diagnosis should be confirmed by demonstrating the causative agent in the liver or in the blood. The fungus is sensitive to amphotericin B, itraconazole and ketoconazole.

AMEBIC AND PYOGENIC LIVER ABSCESSSES

Liver abscess remains a common disease in the tropics. The incidence rate in Thailand is not exactly known as reliable statistics are not available. Nearly all liver abscesses encountered in Thai people are either of amebic or pyogenic origin. Data obtained from three combined studies involving more than

500 cases in Bangkok have shown that amebic outnumber pyogenic abscesses by more than 3 to 1, with 61.8% amebic, 21.7% pyogenic, 5.6% amebic with secondary bacterial infection, and the remaining 10.9% of undetermined etiology (Kurathong, 1982; Kladcharoen *et al*, 1989; Thanmlikitkul and Yamwong, 1990). Neither symptoms and signs nor laboratory tests can assist in differentiating the two types of liver abscess, although diarrhea tends to be more common in amebic cases. Serological tests may be valuable in the diagnosis of amebic liver abscess. The tests show positive results in more than 95% of cases, however, false positives are not uncommon, particularly in pyogenic abscess with underlying intestinal amebiasis (Boonyapisit *et al*, 1993). Liver aspiration under ultrasonography guidance is recommended for both diagnostic and therapeutic purposes. Major complications in both the amebic and pyogenic groups are similar and in most cases are related to rupture and associated sepsis. Abscess rupture occurs in 20% of cases and is rather more frequent in the pyogenic (24%) compared with the amebic group (15%) (Kladcharoen, 1990; Boonyapisit *et al*, 1993).

With amebic abscess, medical treatment with metronidazole (or other 5-nitroimidazoles) alone is usually effective. However, therapeutic aspiration of large abscesses is thought to shorten the hospital stay and to accelerate the recovery of the patients. Surgical drainage is reserved only for cases with potential or ongoing serious complications. With pyogenic abscess, repeated aspiration helps to remove heavily infected material, facilitating and thereby enhancing the effect of antibiotics administered. Patients not responding to such measures, or in whom abscesses are technically hazardous to approach, may be considered for percutaneous catheter or surgical drainage (Kladcharoen, 1990; Boonyapisit *et al*, 1993).

In northeastern Thailand, melioidosis caused by the gram-negative bacillus *Burkholderia (Pseudomonas) pseudomallei* is highly endemic. The clinical manifestations of melioidosis are protean and range from localized infection to fulminant septicemia. Visceral abscesses, including liver abscess, are common in disseminated form and are associated with a high mortality rate. Moreover, it has been regarded by some as contraindicated to perform liver aspiration in melioidosis due to the risk of precipitating septic shock (Leelarasamee and Bovorn kitti, 1989). Data obtained from a retrospective study (Vatcharapreechasakul *et al*, 1992) suggests melioidosis liver abscess to be more frequently associated with jaundice, right upper quadrant pain,

anemia, and underlying diabetes or renal disease when compared with other pyogenic liver abscesses. Furthermore, multiple hypoechoic areas in the liver and associated splenic abscess are often found on ultrasonography in melioidosis. However, the serological assay for antibodies to *B. pseudomallei* is of limited use in differentiating the two types of abscess. Therefore, in an area where melioidosis is common, patients with characteristic ultrasonography findings should be considered for treatment with appropriate antibiotics, for example ceftazidime and co-trimoxazole.

SUMMARY AND FUTURE PERSPECTIVES

Infectious diseases are still common in Thailand particularly tuberculosis, AIDS, dysenteries, parasites, and viral hepatitis. Hepatocellular carcinoma is also common due to viral hepatitis B, C and alcohol. Cholangiocarcinoma is common and seems to be confined to the northeastern region of Thailand where the habit of eating raw fish infected with liver fluke is wide spread. Peptic ulcer is also commonly seen and is associated with *Helicobacter pylori* infection although not as much as in the West which is somewhat surprising. This is possibly explained by the fact that NSAID is commonly used in Thailand and antibiotics are freely available over the counter thus accounting also for the high metronidazole resistance rate. Thankfully, Crohn's disease and ulcerative colitis are rare, especially the former. Hiatus hernia and gastroesophageal reflux diseases (GERD) are also rare but we think as civilization and globalization occur these will become more common.

Many of these infectious diseases will disappear as they are somewhat iatrogenic or man made or preventable. By vaccination and not eating raw fish we can prevent hepatitis B, its complications and cholangiocarcinoma. By living a simple, hygienic life we can prevent AIDS, hepatitis C and many other infectious diseases. However, before the calm sea we will certainly have a big storm in the form of AIDS. *H. pylori* will certainly become less but gastropathy from NSAID will surely increase.

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