

**Gut parasites in general practice**  
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Parasitic infections are easily forgotten by clinicians working in developed countries. They are often regarded as mild, unimportant, and above all, rarely seen in clinical practice. However, parasites remain some of the commonest causes of morbidity and mortality in many parts of the world. With increasing ease of international travel and increasing number of immunocompromised hosts, one might expect to see exotic or unusual parasitic infections anywhere in the world.

**Parasitism and parasites**

Parasitism refers to any reciprocal association in which a species depends upon another for its existence. A parasite is therefore the species that derives all the benefit from the association. The species harbouring the parasite is termed the host, and there may be more than one host involved in the life cycle of the parasite (definitive and intermediate hosts). Although many pathogenic bacteria, fungi, and viruses may also be considered as parasites in the broadest sense, medical parasitology is generally restricted to the study of the following groups of organisms: protozoa, helminths (consisting of nematodes, trematodes, and cestodes), and various medically important arthropods (insects and arachnids). The epidemiology of parasitic infections is determined very much by the interaction between the parasite, the host, the vector, and the environment. Understanding these interactions is the first step to effective prevention and control of parasitic diseases.

**Changing epidemiology of parasitic infections in Hong Kong**

There were few published data on the prevalence of parasitic infections in Hong Kong. Much of the information from older series were retrospective hospital-based studies. Comparisons on the prevalence of parasitic infections from the 1960's to the early 1990's showed that *Clonorchis sinensis* is still the commonest gut parasite encountered in Hong Kong, although the percentage has been decreasing in the past decades (1). Most notably, there has been a dramatic drop in the

prevalence of geohelminth infections (*Ascaris lumbricoides*, hookworms, and *Trichuris trichiura*). A recent review of the data in Queen Mary Hospital (2002 to the first half of 2003) also showed similar findings, with a predominance of *Clonorchis sinensis*. Geohelminths, *Enterobius vermicularis*, *Entamoeba histolytica*, and *Giardia lamblia* are only occasionally seen in the hospital setting. However, a worrying finding is that strongyloidiasis has assumed greater significance in recent years. The findings are completely reconcilable. The predominance of clonorchiasis partly reflects the culinary habits of southern Chinese and partly reflects the long-standing nature of some helminthic infections. (The adult worm of *Clonorchis sinensis* has an average life span of 20-25 years.) *Enterobius vermicularis*, a cosmopolitan infection even in developed countries, is still occasionally encountered in hospital practice, although one would expect to see more cases of pinworm infection in the primary care setting. Geohelminths require part of their life cycles spent in the soil; they are typically commoner in agricultural societies and places where sanitation is poor. With improvements in hygiene and increasing urbanization in Hong Kong over the decades, geohelminth infection is becoming less prevalent in the community. One important exception to this phenomenon is *Strongyloides stercoralis*, which now accounts for 5.4% of all gut parasites identified in our hospital. Once infected, *Strongyloides* persists in the body even without re-exposure to the parasite in the environment because of the unique capability of autoinfection. With an aging population and an increasing number of immunocompromised patients (especially those receiving corticosteroid therapy), reactivation of strongyloidiasis later in life becomes an important opportunistic infection.

### **Recognising parasitic infection in general practice**

Parasitic infections can present with protean manifestations (3). Symptoms and signs may be referable to the gastrointestinal tract (e.g. diarrhoea, dysentery, other abdominal symptoms, pruritus ani, malabsorption, cholangitis, pancreatitis, intestinal obstruction, and appendicitis) or there may be systemic manifestations (e.g. eosinophilia, pneumonitis, and anaemia). Long-standing infections, for example, of the biliary tree, has been linked to the development of malignancies (e.g. cholangiocarcinoma). A few key points are noteworthy. Firstly, it

must be realized that the occurrence of many of the "classical" signs and symptoms depends very much on the parasite load and underlying health condition of the patients. For example, while anaemia is the most typical feature of geohelminth infections (e.g. hookworms and *Trichuris*), it is more often seen in those with heavy infections, mixed infections, and patients suffering from malnutrition. Light infection in an otherwise healthy and well-nourished person is most often asymptomatic. Secondly, patients who are found to have peripheral eosinophilia are often worked up for possible parasitic infections. While this is a reasonable and important step in the investigations, eosinophilia is generally not a feature of protozoal infections. It is generally the helminths that give rise to eosinophilia, especially those with a migratory larval stage and those which cause systemic infections. Typical examples include loiasis, schistosomiasis, filariasis, trichinosis, hookworm infection, cutaneous and visceral larva migrans, fascioliasis, and ascariasis. Thirdly, a competent laboratory service is essential for the definitive diagnosis of most parasitic infections. Although a number of antigen detection assays and serological tests are available nowadays, their value in routine clinical diagnosis is sometimes limited by the cost, sensitivity and specificity of the tests, and in areas of low disease prevalence, poor positive predictive value. Microscopic examination of a relevant clinical specimen remains the most reliable diagnostic method in most circumstances. Lastly, one must consider parasites as opportunistic pathogens in immunocompromised patients. In AIDS patients, opportunistic infections due to gut protozoa are important causes of morbidity and occasionally mortality. Examples include *Cryptosporidium parvum*, *Cyclospora cayatanensis*, *Isospora belli*, microsporidia, and sometimes *Strongyloides stercoralis*. In elderly people and especially those who had received therapeutic doses of corticosteroids, disseminated strongyloidiasis is an uncommon but potentially fatal complication. It may present with diarrhoea, Gram negative bacteraemia and sepsis, fleeting shadows on chest radiographs, transient urticarial skin lesions especially over the buttocks and trunk (larva currens), and even pyogenic meningitis or brain abscess due to gut flora. Early recognition of disseminated strongyloidiasis with appropriate antiparasitic treatment is essential for the management of these patients.

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## **Viral gastroenteritis**

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Viral gastroenteritis constitutes a major health problem for the individual as well as the community as a whole. This presentation covers the essential information obtained from three local studies. The first study was conducted at the Government Virus Unit, Department of Health to retrospectively review laboratory data collected from 1987 to 1992. The uniqueness of this study was that electron microscopy was applied on investigating all 27,618 stool specimens collected from public hospitals during the study period. Although electron microscopy lacks sensitivity, it provides a comparison on the relative prevalence of various viruses associated with diarrhoea. Of the 4,614 positive stool samples, rotavirus was most commonly detected (84.4%), followed by adenovirus (9.0%), astrovirus (4.3%), Norwalk-like viruses (1.9%), and calicivirus (0.4%). Winter (December and January) predominance was consistently observed for rotavirus and astrovirus. A male predominance was also observed for rotavirus but not the others. Samples with rotavirus detected by electron microscopy but not by the more sensitive enzyme immunoassay was rare (5/3,894) in Hong Kong, suggesting non-group A rotavirus is not common in this locality. It should be noted that the prevalence data generated from this study could only be applied to infants and young children, which constituted 75% of the studied subjects. The prevalence of Norwalk-like viruses was likely to be underestimated, as this virus is known to associate with food- and water-borne outbreaks in adults. The second study was conducted at the Prince of Wales Hospital to retrospectively review laboratory data of 1987-1996. In this 10-year survey of rotavirus gastroenteritis, 2281 cases were detected of which 2213 (97%) occurred in children <5 years old. A consistent epidemic was also observed at each winter during the months of December and January. Of all laboratory-confirmed cases, 78% were community-acquired with a mean hospital stay of 4.7 days. The estimated incidence of rotavirus-attributed hospitalization was 2/1000 children <5 years old. Over the 10 years, rotavirus was responsible for one death, and contributory to 3 other deaths. On average each year, 195 children <5 years old were hospitalised for a total of 917 days in Prince of Wales Hospital, accounting for an estimated expenditure of

HK\$2.8 (~US\$0.4) million on hospitalisation costs. The annual financial burden for rotavirus gastroenteritis for the whole of Hong Kong could be in excess of HK\$9.6 (~US\$1.2) million. The third study addresses the current topic of severe acute respiratory syndrome (SARS). SARS is a recently emerged infection due to a novel coronavirus (SARS-CoV). Apart from fever and respiratory complications, gastrointestinal symptoms are frequently observed in SARS patients. This study retrospectively analysed the gastrointestinal symptoms of the first 138 confirmed SARS patients admitted to the Prince of Wales Hospital during a major outbreak in Hong Kong in March 2003. Among these 138 SARS patients, 27 (19.6%) presented with watery diarrhoea and up to 36.2% patients had diarrhoea symptoms during the course of illness. Diarrhoea was more frequently observed during initial few days and towards the end of second week, which paralleled their temperature changes. Most diarrhoea episodes were self-limiting and last for a mean of  $2.2 \pm 2.4$  days. Intestinal biopsies obtained from a patient while having diarrhoea showed minimal architectural disruption but presence of active viral replication within both small and large intestine. The histological features were consistent with rotavirus-associated diarrhoea. Coronavirus was isolated from the biopsies, suggesting diarrhoea may be a direct result of local mucosal infection. In addition, SARS-CoV RNA can be detected in stool of patients for more than 10 weeks after symptom onset. Fever and diarrhoea is an atypical but common presenting symptom of SARS. The intestinal tropism of the SARS-CoV has major implications on clinical presentation and the route of viral transmission.

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## **Highlights from conference**

### **A breakthrough in the management of HIV: fusion inhibitor (From the Second International AIDS Society Conference on HIV Pathogenesis and Treatment held in Paris July 2003)**

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The Conference was held in Paris from 13 to 16 July 2003, 20 years after the publication of the first isolation of HIV from a clinical specimen by a French scientist F. Barre-Sinoussi. This conference has laid emphases on a variety of topics including the latest FDA approved treatments, namely atazanavir, enfuvirtide and emtricitabine. Of special note, enfuvirtide became the main theme of discussion, not only because of its novel mechanism of HIV treatment, but also as a result of its remarkable efficacy in the management of HIV in a group of heavily treatment-experienced individuals.

Mechanism of HIV entry includes three major steps. The first step involves the binding of the glycoprotein subunit (gp) 120 of HIV and the CD4 receptor on the surface of T cells. The chemokine receptors CXCR4 and CCR5 are the necessary co-receptors used by HIV for T cell attachment. The binding of the gp 120 to CD4 will induce a conformational change in another transmembrane protein gp 41, allowing it to insert its hydrophobic NH<sub>2</sub>-terminal into the T cell membrane, mediating the fusion of the viral envelope and the cell membrane. Enfuvirtide is the first synthetic peptide that can bind onto gp 41 and stop the fusion process.

TORO 1 (T-20 versus optimised regimen only study) enrolled 491 patients in North America and Brazil. Almost all patients were heavily pre-treated and harboured multiresistant viruses at entry. They were randomised to receive either 90mg twice-daily subcutaneous injection of T-20 or none, while they were given an optimised highly active anti-retroviral treatment (HAART) regime. At 24 weeks, the reduction of viral load was 1.7 log in the T-20 group, compared to 0.76 log in the control ( $p < 0.0001$ ) (1). In TORO 2, the same design was tested in 504 patients in Europe and Australia. The result was again astounding (1.43 versus 0.65 log reduction in viral load at 24 weeks ( $p < 0.0001$ )) (2).

Doctor David Cooper presented the 48 weeks results of the TORO studies in the meeting. Pooling together, 661 patients on T-20 and 334 others who were on optimised HAART only were compared. The reduction of viral load was 1.48 log in the T-20 group, compared to 0.63 log in the control ( $p < 0.0001$ ). The elevation in CD4 cells/mm<sup>3</sup> was 91 versus 45 respectively ( $p < 0.0001$ ). Side effect of the T-20 treatment was minimal. The rate of bacterial pneumonia in the T-20 group was higher (6.6 versus 0.6 events per 100 patients-years). He concluded that current data supported the efficacy and safety of enfuvirtide and substantiated the utility, tolerability and feasibility of long-term enfuvirtide therapy.

However, despite the enthusiasm of enfuvirtide therapy, study showed that clinical resistance could develop as short as 14 days after its use. This resistance could be attributed to the mutations involving G36D and other residues within the HR1 domain of the HIV genome. (3)

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**HIV treatment interruption - still a controversy**  
**(From the Second International AIDS Society Conference on HIV**  
**Pathogenesis and Treatment held in Paris, July 2003)**

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Treatment interruption of highly active antiretroviral therapy (HAART) for HIV patients has been a hot topic for several years. Previous study showed that almost all HIV patients stopping HAART therapy would have a rebound in the viral load within a few weeks, even in patients with undetectable HIV levels over several years. The sharp increase in viral load may lead to a retroviral syndrome which is similar to acute HIV infection. Patients with this syndrome may have lymphadenopathy, fever, asthenia and malaise. Treatment interruption can lead to severe immunological consequence, e.g. CD4 lymphocyte counts can fall within a short time to pretreatment levels. Treatment interruption may also lead to increased risk of transmission while off therapy and a reluctance to restart therapy when needed.

Some researchers supporting treatment interruption proposed that the temporary viral rebound would strengthen the HIV-specific immune responses, which may decline with increasing viral suppression on HAART. Dr. Mark Dybul of the National Institute for Allergy and Infectious Diseases presented a pilot study on scheduled intermittent therapy with once-daily efavirenz, lamivudine and didanosine. In this study, all of the seven patients were able to maintain undetectable viral loads for 48-68 weeks by taking medications only every other week. No resistance was detected in proviral DNA specimens. However, the Swiss-Spanish Intermittent Therapy Trial (SSITT) led by Dr. Bernard Hirschel of Geneva University Hospital gave another finding. In this study, 133 patients were monitored throughout four 10-week cycles, each of eight weeks HAART and two weeks of treatment interruption. After 40 weeks, HAART was permanently interrupted. Treatment success, defined by a viral load of < 5000 copies/ml without HAART after week 52, only occurred in 21/99 patients. None of the 32 patients with a pre-HAART viral load > 60000 copies/ml achieved a viral load of < 5000 copies/ml. Improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection.

Some clinicians believed that treatment interruption could be beneficial for salvage strategies. The rationale behind is that for most HIV patients with multidrug resistance, treatment interruption can lead to a gradual shift back to wild-type virus and loss of resistance. The GIGAHAART study, led by Dr. Christine Katlama of Hospital Pitie-Salpetriere in Paris, showed that treatment interruption could confer benefit for some patients needing salvage therapy. In her study, patients who had interrupted treatment before starting a salvage regimen had a significantly greater decrease in viral load after 24 weeks (1.08 versus 0.29 log in the control group). Contrary to Dr. Katlama's finding, Dr. Jody Lawrence from the University of California at San Francisco reported that patients with treatment interruption had worse mean CD4 lymphocyte count response than those without a break in treatment. In Dr. Lawrence's study known as CPCRA 064, 270 patients with HIV RNA greater than 5000 viral copies/ml were randomized to have 4-month treatment interruption or no interruption prior to changing therapy. During a follow up period of 12 months, Dr. Lawrence did not notice any benefit in the group with treatment interruption. Subgroup analysis by baseline CD4 lymphocyte count and phenotypic sensitivity score showed similar results as the full cohort. These findings suggest that structured treatment interruption do not confer any immunological or virological benefit. Whether the duration of treatment interruption contributes to the overall outcome is still unknown.

Treatment interruption will continue to be a topic for much debate. Further study will give new insight which could fundamentally change our current approach to lifelong HAART.

**Molecular epidemiology of norovirus infections in sporadic cases and outbreaks of gastroenteritis in Hong Kong**  
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Viruses are thought to be responsible for three-quarters of all cases of infective diarrhoea. Previously, rotaviruses were thought to be involved in the majority of cases of viral gastroenteritis. However, recent data obtained using more sensitive diagnostic methods suggest that noroviruses are the most important cause. In this study, the molecular epidemiology of noroviruses in sporadic and outbreak cases of acute gastroenteritis in Hong Kong was examined over a 12-month period from July 2001 to June 2002. Specimens from 3 groups of patients were used in this study (1) 987 specimens from patients enrolled in the Acute Diarrhoeal Diseases Surveillance Programme of the Department of Health, Hong Kong Government. (2) 735 clinical specimens from hospital patients with acute gastroenteritis, and (3) 122 specimens from 44 norovirus outbreaks. Reverse Transcription Polymerase Chain Reaction (RT-PCR) was carried out using primers directed against the RNA polymerase region of noroviruses. PCR products were then sequenced and compared to known norovirus strains in GENBANK.

Ninety-eight (9.9%) surveillance specimens were positive for norovirus-RNA by RT-PCR compared to 123 (16.7%) clinical specimens. Of the 44 norovirus outbreaks in the study, 20 were from kindergartens or nurseries, 5 were from schools, 1 was from a nursing home, 13 involved catered meals consumed at hotels, restaurants or food stalls, and 5 involved meals taken at home. One hundred and one (82.8%) outbreak specimens were positive by RT-PCR. The majority of outbreaks (29 outbreaks, 65.9%) occurred in the 6-month period between July and December 2001 with 90 (73.8%) of specimens involved. For the first six months of the study period, the predominant strain was the Bristol strain that belonged to genogroup II. In the later six months of the study, genogroup I and strains belonging to other clusters of genogroup II were more commonly seen. The vast majority of strains belonging to the Bristol virus cluster were highly related to the 95/96-US subset that was associated with pandemic infection from 1995 onwards. Therefore

Hong Kong was at the tail-end of the pandemic caused by the 95/96-US subset in the last six months of 2001, but this has since died down. This study clearly establishes the importance of noroviruses as a cause of acute gastroenteritis in Hong Kong.

## **The relationship between cytomegalovirus infection and graft rejection in renal transplantation**

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One of the controversial issues regarding the development of acute rejection and chronic graft loss in renal transplantation is the role of cytomegalovirus (CMV) infection. CMV infection can result in upregulation of adhesion molecules, thereby facilitating the inflammatory process. Infection with CMV is also associated with an increased expression of MHC class II on multiple cell types, thereby contributing to graft failure. Lastly, CMV infection has been implicated in the induction of smooth muscle proliferation and intimal thickening, which are the hallmarks of transplant atherosclerosis<sup>1</sup>. CMV infection was therefore proposed as an important risk factor for the development of rejection and subsequent graft loss. Various clinical and experimental organ transplant studies have been done to examine this relationship, however, the results were conflicting.

In a study performed by Claire Pouteil-Noble et al, they prospectively followed up 242 renal transplant patients for CMV infection<sup>2</sup>. Infected and noninfected patients were randomly paired off and they could find 85 pairs. They found that the incidence of "rejection after" the diagnosis of CMV infection was significantly higher in the group of patients with CMV infection: 45% among infected (38/85) versus 10.6% among noninfected (9/85) ( $P < 0.0001$ ). Even after taking into account some significant confounding factors, the significance of the result did not change. The author concluded that CMV infection is a risk factor of subsequent rejection episodes.

Olivier Toupance et al performed a historical cohort study with case-control analysis involving 192 renal transplant patients<sup>3</sup>. The patients were divided into 3 groups. Group 1 consisted of 64 patients who had neither clinical signs of CMV disease nor CMV serological changes after transplantation. Group 2 consisted of 77 seropositive patients with asymptomatic viraemia. Group 3 consisted of 51 seropositive patients with clinical CMV disease. Groups 2 and 3 patients were paired with Group 1. They found that transplant patients

with CMV disease, had a significant likelihood of developing acute rejection after CMV infection or reactivation (10/51 in CMV disease group versus 2/51 in control group  $P < 0.01$ ). The odds ratio for developing rejection was 5.98. However, such a link was not documented for recipients with asymptomatic CMV infection (4/64 in asymptomatic CMV infection group versus 3/64 in control group). They concluded that CMV disease, but not asymptomatic viraemia, is a risk factor of acute rejection.

In a prospective study done by Michael J. Dickenmann et al, 48 renal transplant recipients at risk for CMV infection (donor and/or recipient CMV seropositive) and a control group of 36 CMV seronegative recipients of CMV seronegative kidney donors were followed up<sup>4</sup>. CMV infection developed in 83% (40/48) of patients of the CMV risk group within 4 months post transplant. A total of 18 patients in the CMV risk group experienced an acute rejection episode (control group 16/36;  $P = 0.65$ ). Out of the 18 patients with acute rejection, 12 occurred before a CMV infection episode, 3 occurred after while 3 patients remained CMV antigenaemia negative. At five years followed up, there were no significant difference in patient survival, graft survival, number of patients with at least one acute rejection episode, serum creatinine and proteinuria observed between CMV risk group and control group. The author concluded that CMV infection within 4 months post transplant was not a risk factor for acute rejection or chronic graft dysfunction at 5 years.

### **Local study**

In a local study done by Lee et al, 459 renal transplant patients record were reviewed<sup>5</sup>. Patients with CMV disease were identified and they were compared with the matched control group with no CMV disease.

Forty-eight patients were identified to have CMV disease. 20 of them had acute rejection within first six months post transplantation. Out of these 20 patients, 13 patients had CMV disease after receiving treatment for acute rejection. The remaining 7 patients had acute rejection within 3 months post CMV disease.

When these 48 patients with CMV disease were compared with the

control group (N = 50), there was no significant differences in the number of biopsy proven acute rejection episode within first 6 months noted (20/48 versus 13/50). Moreover, there were no significant differences in serum creatinine, degree of proteinuria, patient survival and graft survival at one-year post transplantation.

Sub-group analysis was also performed for those patients with at least 5 years follow-up. There were no significant differences in serum creatinine, degree of proteinuria, and patient survival at 5 years post transplantation. The 5-year graft survivals were 79% and 100% for the CMV group and control group respectively ( $p < 0.05$ ). Four grafts were lost in the CMV group; 3 due to patient's death and 1 due to recurrent IgA nephropathy.

With the above findings, the author concluded that CMV infection was not shown to be a risk factor for acute rejection or chronic graft dysfunction at 1 and 5 years.

## **Discussion**

CMV infection is an important complication in renal transplant patients and may have serious consequences. It can directly result in CMV disease with fever, leucopenia, or even pneumonitis, hepatitis, gastrointestinal tract involvement, retinitis and central nervous system involvement. Otherwise, it has been postulated to be an important cause of acute rejection and chronic allograft nephropathy. Acute rejection can directly cause graft injury, or even graft loss and it can increase the incidence of chronic allograft nephropathy. Moreover, intensified immunosuppressive regimen used during an acute rejection episode renders the recipient susceptible to the complications of intensified immunosuppression. These include more infection episodes, increased risk of malignancy later and also the various side effects of the drugs used. Chronic allograft nephropathy is second only to death with a functioning kidney as the most common cause of late graft failure. Therefore, prevention of acute rejection and chronic allograft nephropathy is important to the clinical well being of the patient and the long term outcome of the graft. There are various protocols proposed for CMV prophylaxis in post renal transplant patients. These include monotherapy

with antiviral agents such as acyclovir or ganciclovir, monotherapy with CMV immune globulin or hyperimmune serum, or a combination of antiviral agents and CMV immune globulin. If the role of CMV infection in acute rejection and chronic allograft nephropathy can be definitely established, it may lead to a revision in CMV prophylaxis protocol for post renal transplant patients. However, the theoretical plausibility of the relationship between CMV infection and acute rejection and chronic allograft nephropathy has not been perfectly verified by clinical studies. It seems that further effort in basic science research and clinical studies are required to further elucidate the relationship.

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