Since the launching of sildenafil citrate, ED has become a hot topic in the mass media. As a clinician, it is hard to avoid patients asking questions about ED.

Definition of ED (First International Consultation of Erectile Dysfunction, Paris 1999)
ED is the consistent or recurrent inability of a man to attain and/or maintain penile erection sufficient for sexual performance.

Prevalence of ED
Although ED is not a life-threatening disorder, it affects the patient’s quality of life, his social interaction and his own feeling of well-being. Accurate estimation of the prevalence worldwide is still difficult and there are a lot of variations according to population studied. The following studies can be used as references:

1. Massachusetts Male Aging Study (MMAS) of 1994 involved 1,290 men (40-70 years) and found that 52% of men had some degree of ED (complete, moderate, minimal).

2. Japanese study by Sato et al. in 1995
   - 20 – 44 years <2.5%
   - 45 – 59 years 10%
   - 60 – 64 years 23%
   - 65 – 69 years 30.4%
   - ≥70 years >44.3%

Perhaps it is interesting to look at a Chinese study done by Wang et al. in Shanghai in 1997 which showed a much higher incidence in similar age groups than the Japanese study:
- 1,582 non-institutionalized men >40 years
  - 40 – 49 years 32.8%
  - 50 – 59 years 36.4%
  - 60 – 69 years 74.2%
  - ≥70 years 86.3%

By knowing the incidence, clinician can get an idea of how big the problem is. It is also important to investigate further those who do not fall into typical age group and to look for correctable factors or factors that may indicate severe underlying physical, psychological, social and familial problems. On the other hand, patients regard ED as a very private problem that they do not want to talk about. They do not want people to think that their bodies are especially “weaker” than others. Appropriate prevalence survey discloses the real incidence that can help clinician to plan the service and to encourage the patients to come forth to seek treatment.

Differential Diagnosis
ED should be differentiated from ejaculatory disorder which may be presented alone or in combination with ED. Patient of premature ejaculation (PME) often complain of flaccidity during intercourse (after they have prematurely ejaculated) instead of problem of ejaculation itself. ED due to penile deformity like Peyronie’s Disease and hypospadias that needs surgical correction should be obvious during physical examination.

Normal Erection Process
Penile erection is an integrated response. According to current understanding, the process can be simply summarized in the following steps:

Proerectile stimuli (imagination, audiovisual, tactile) and inhibitory stimuli (depression, anxiety, fear) are transmitted from the cerebral cortex to the paraventricular nucleus of the hypothalamus leads to the release of dopamine.

Erectile signal transmitted down the appropriate pathway of the spinal cord and to the peripheral nerves that innervate the penile smooth muscle. Autonomic nervous system is involved. Relaxation of smooth muscle of the corpora cavernosa and corpus
spongiosum of the penis causes increase in blood flow into their sinusoids.

A tough fibrous layer, the tunica albuginea surrounds each corpus cavernosum and allows a finite degree of penile expansion. The resulting compression compresses the subtunical venous plexus against the tunica albuginea, resulting in venous occlusion which maintains the erection.

In this process, the generation of nitric oxide (NO) in penile tissue is crucial. It activates guanylate cyclase which in turn catalyzes cGMP formation. The substance sildenafil citrate can inhibit phosphodiesterase isoenzymes resulting in reduced degradation of cGMP and augmentation and prolongation of penile erection. On the other hand, apomorphine acts on dopamine receptors (especially D2) resulting in enhancement of erectile signals present during sexual stimulation. Both substances have been marketed as therapeutic agents for treatment of ED.

Risk Factors of ED
Most Important Risk Factors:
Age, cardiovascular disease, hyperlipidaemia, diabetes mellitus, side-effects of drug, smoking.

Drugs that may cause ED include: antihypertensives, cardiac-active agents like digoxin, disopyramide, diuretics (thiazides, spironolactone), cimetidine and ranitidine, hormones (steroids, GnRH agonists), clofibrate and simfibrate, psychotherapeutic agents.

Additional Risk Factors:
Psychological, relationship issues, sexual technique, trauma, pelvic surgery, pelvic irradiation, neurological disorders, hormonal disorders, excessive alcohol.

Patient Evaluation and Diagnosis
Management of ED has been simplified by availability of first line oral medication. However, it has to be remembered that more in depth investigations have to be considered at least in the following conditions:

1. Patient not within the typical age group;
2. There is a high likelihood of modifiable factors;
3. Possibility of serious underlying problem that may be life threatening;
4. The patients want to know.

Detail medical, sexual and psychological history taking should be concentrated at those risk factors and should include the use of one of those erectile dysfunction questionnaires like the IIEF (International Index of Erectile Function). Sexual history assessment should include aspects of erectile insufficiency, altered sexual desire, ejaculation, orgasm, sexually induced genital pain, partner sexual function, lifestyle factors. Physical examination includes the body habitus (secondary sexual characteristics), cardiovascular system, genitourinary system and focused neurological examination. Recommended diagnostic tests include fasting glucose or glycosylated haemoglobin (Hb A1c), lipid profile and serum testosterone level. Optional diagnostic tests include serum prolactin (inhibitory effect to paraventricular nucleus), luteinising hormone, thyroid-stimulating hormone, complete blood count. Psychological consultation is indicated in some cases.

ED has been associated with neurotic tendency, anxiety tendency and may be a sign of depression.

According to etiology, ED is often classified as:
1. Organic
2. Psychogenic/functional (including sex skill)
3. Mixed

More and more, ED is found to be organic instead of purely psychogenic. Psychogenic / functional factors however can be present as contributory or secondary factors and should not be ignored.

Organic factors include:
1. Vascular
2. Neurological
3. Penile tissue

Specialized Tests of ED
Lots of special tests have been designed to test the various etiology of ED. Some more useful ones are quoted here.

1. **Audiovisual Sexual Stimulation (AVSS) Loading Test**
   A RigidScan is used to measure the penile erection while the patient is under audiovisual erotic stimuli. This is used to differentiate whether the ED is organic in nature or not.

2. **Nocturnal Penile Tumescence (NPT)**
   Spontaneous penile erection is measured during
sleep. Preferably done in a sleep laboratory where the presence of REM sleep can be observed.

3. **Erection Induction Using Intracavernosal Injection**
   Pharmacological agent (like prostaglandin E1) is injected into the corpora in order to check the vascular integrity of the penis.

4. **Color Doppler of Penile Artery after Intracavernosal Injection**
   Rate of penile arterial flow is measured to look for presence of arterial insufficiency and venous leakage problem.

5. **Selective Pudendal Arteriography**
   Indicated in selected cases only especially when correctable factor is suspected like congenital AV malformation, post-traumatic arterial damage. In general, the cure for arteriosclerosis disease is low and the test is not routinely indicated in this situation.

6. **Test of Venous System**
   This is indicated when mainly venous leakage problem is suspected and the clinician is considering surgery. Dynamic Infusion Cavernosometry involves putting one needle into one cavernosus to measure its pressure while another needle is put into another cavernosus to infuse normal saline solution as preset rate. Penile erection is then observed. If venous leakage is suspected, radiological contrast is infused and X-ray films are taken to locate the site of leakage. The leaking venous channels may be then surgically ligated.

7. **Penile Nerves Tests**
   Since not only somatic sensory nerves are involved but the autonomic nervous system as well, it is not easy to design reliable tests to test the penile nerves. Investigations like checking the bulbocavernous reflex time, vibration threshold of the glans, dorsal nerve conduction test are not easily available to usual clinician. Recently, cavernosal biopsy and staining for nitric oxide syntase (NOS) is gaining popularity.

### Limitations of Special Tests

These tests suffer certain problems:

1. Many of them are not easily available (both equipment and expertise);
2. There are a lot of grey areas in their interpretation making them very inconclusive in many instances;
3. The underlying problem may not be correctable even if it is found e.g. arteriosclerotic diseases.

Therefore in recent years, a so called target oriented approach has been recommended in most patients and that is the clinician just try to find out which method would satisfied the patient’s need after some more simple basic evaluation. Further testing is reserved to some people only (see “Patient evaluation and diagnosis”).

### Conclusion

The last 20 years have seen a lot of advances in ED evaluation and treatment. The substance nitric oxide (NO) was identified in 1987 and earned its discoverer a Nobel Prize. Recently, pharmaceutical industry has developed rather effective and convenient drug for the treatment. Many more drugs are still in the pipeline which will very soon be available. Each is carrying its own special advantage. Like treatment of many other illnesses, the future may lie on gene therapy. If we can modified the cells of the corpus cavernosum and make them to produce more NO in response to natural stimuli, the patient may not need to take the drug constantly for at least a period of time. The future however may looked very near and yet is still very far. For the time being, there is nothing which can replace the very considerate and understanding attitude of a knowledgeable clinician.
Erectile Dysfunction: Treatment Options
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Specialty Editor, HKMD

Introduction
With modern technology, an erection could be achieved almost in any living man. However, management of erectile dysfunction (ED) is not simply getting a penis erected. The clinician should try to help his patient in the following aspects:

1. Is the ED part of the symptoms of significant medical conditions that need to be managed? e.g. diabetes mellitus.
2. Are there specific causes of the ED that could be treated?
3. Are there reversible factors that may be detrimental to his erectile function?
4. How and how far should we go with symptomatic treatment of the ED for this patient (& his partner)?

ED as Part of a Systemic Disease
The penis represents a good sample of vascular tissue of the body. Not surprisingly, ED can be part of the symptoms of conditions that affects cardiovascular system of the body. ED is associated with coronary, cerebral and peripheral vascular diseases. Hypertension and dyslipidemia increase risk of ED. ED can sometimes even be the presenting symptom for diabetes mellitus. Obviously, these systemic problems need to be addressed before dealing with the symptom of ED itself.

Specific Causes of ED
In a small proportion of patients, specific cause for the ED could be identified. Some of these are amenable to specific treatments. There are certain clues suggesting specific causes:

1. Psychological: significant psychological issues identified may need help of psychotherapist. Symptomatic treatment (discussed later) can still be a useful adjunct in these patients.
2. Vascular: young patients with pelvic trauma may have a vascular cause that may benefit from revascularization operation. Proven venous leakage in young patients may be helped by venous ligation operation.
3. Penile: structural problem of the penis such as Peyronie's disease will be evident on physical examination and will need specific treatment.
4. Hormonal: androgen deficiency may be suggested by a decrease in libido. The help of an endocrinologist may need to be enlisted. Testosterone replacement therapy should be reserved only for cases with proven testosterone deficiency. Depot formulation of long acting esters of testosterone could be given by injection every 2-3 weeks. Oral preparations are less predictable in serum levels and also carry a risk of liver toxicity. Transdermal administration has been developed. Patches could be applied daily. Prior to starting testosterone replacement, digital rectal examination and serum prostatic specific antigen (PSA) test should be performed. Patients should be monitored regularly while on replacement. It should be mentioned that this treatment is not always effective in managing ED associated with hypogonadism.

Reversible Factors
Factors that may affect erectile function should be removed if possible. These include:

Lifestyle Factors:
1. Smoking: smoking contribute to probability of ED development. Those who quit smoking had a lower ED risk than those who continue smoking.
2. Alcohol: chronic alcoholism is significant in the development of ED.

Drugs that May Affect Erectile Function:
1. Antihypertensives: beta-blockers and thiazide are known to be associated with ED. The physician should be informed to modify the antihypertensive medication. Alpha-blockers may be used.
2. Psychotherapeutic agents, cimetidine, digoxin, and estrogens can cause ED. Modification may not be possible.
Symptomatic Treatment for ED
When no specific cause is identified, or when after managing any adverse factors the ED is not resolved, a strategic approach should be adopted to give symptomatic treatment for ED.

The patient and his partner, when possible, should be informed of the options available. It should be emphasized to the patient that sexual intercourse is a form of physical exertion and the patient should be fit for such activity before symptomatic treatment is suggested. According to the degree of invasiveness, there are 3 lines of therapy available:

1. First-line Therapy
   Oral Therapy:
   Sildenafil (Viagra) is a potent and selective inhibitor of cGMP dependent PDE5 (phosphodiesterase 5). During sexual stimulation, nerves in the penis release NO (Nitric Oxide) which in turn causes an increase of cGMP. Elevated cGMP is responsible for smooth muscle relaxation which produces erection. Taken orally sildenafil is effective after 60 minutes in the presence of sexual stimulation. The most common side effects include headaches, flushing, dyspepsia and nasal congestion. Sildenafil is a weak inhibitor of PDE6 and hence transient visual disturbance has been noted in a small number of patients. Sildenafil will augment the response of exogenous nitrates, resulting in profound hypotension. Therefore, its use is absolutely contraindicated in patient using nitrate drugs in any form. It may be hazardous to prescribe sildenafil in patients with active coronary ischemia, congestive heart failure, or in patient who is on a complicated multi-drug anti-hypertensive regime or on drugs that may prolong the half life of sildenafil (e.g. erythromycin, ketaconazole, cimetidine). Cardiac patients at low risk according to a recent consensus meeting at Princeton University can, however, be safely advised to receive treatment and resume sexual activity provided that they are not on nitrates. The staring dose is 50 mg. Patients who are old, with renal or hepatic impairment should receive a lower dose of 25 mg. Doses can be adjusted according to response and no additional benefit could be expected for doses above 100 mg.

   Apomorphine sublingual (Uprima) has just been marketed in Hong Kong (February 2002). It is a dopamine D2 receptor agonist that acts centrally to initiate erection. At a starting dose of 2 mg and subsequent doses of 3 mg taken sublingually on demand, it can produce erection in 10-20 minutes. There have been no drug related myocardial infarct or priapism. The most common adverse effect is nausea. The most severe reaction is vasovagal syncpe, which is fortunately rare.

   Other new oral agents for ED, including oral phenotolamine (Vasomax), and other phosphodiesterase inhibitors including cialis and vardenalfil are still under investigation. Yohimbine, trazodone and L-arginine have been used to improve erection but their effectiveness has not been substantiated by control trials.

Vacuum Device:
Vacuum devices could be used by patients with very understanding partners. They are better accepted by couples in stable relationship and by older patients. The device works by applying a negative pressure on the penis, which draws venous blood into the penis to produce an engorgement. The blood is retained in the penis by a constriction ring placed at its base. It takes 2-3 minutes pumping to achieve an erection and the ring should not be left in situ for over 30 minutes. The engorgement is far from natural: the penis is numb, cyanotic, cold, dangling and there is also problem with ejaculation with the constriction band. Not many patients can persist with its use. Patients with fibrosis of erectile tissue, Peyronie’s disease or bleeding tendency should not use such device.

2. Second-line Therapy
Various drugs have been proposed for intracavernosal injection, alone or in combination. The most widely used agent is prostaglandin E1 or alprostadil (Caverject), which modulates adenyl cyclase to increase cAMP concentration and causes smooth muscle relaxation. The injection requires manual dexterity of the patient or his partner. The dose could be titrated from 2.5 mcg. The erection appears in 5-15 minutes. Duration of erection varies with the dose. If the erection persist for over 4 hours, patients are advised to consult the doctor to avoid any damage to the erectile tissues. Papaverine intracavernosal injection is now seldom used because of the risk of inducing tissue fibrosis after long term use.

Prostaglandin E1 may be administered intraurethrally (MUSE) in the form of a semi-solid pellet. The dose is
much higher than that used in injection and starts from 250 mcg. Such administration may appear less frightening compared to injection but there can be penile pain and hypotension, and the clinical success rate is less than injection.

3. Third-line Therapy

Prosthesis
For patients who failed pharmacological therapy or who prefer a permanent solution to their problem, surgical implantation of a penile prosthesis could be suggested. Two basic types of implants are available: malleable (semi-rigid) or inflatable. The inflatable device produces a more cosmetic and satisfying erection, but the device is more expensive, and is associated with an increase rate of mechanical failure and complications. Insertion of a penile prosthesis should be considered an irreversible step as erectile tissues are damaged and there is no going back to less invasive treatments for ED. It should only be performed for patients with proven organic cause. The patient should be aware of the complications that may occur. Infection of a penile prosthesis would be disastrous and usually requires its removal. It is not uncommon in diabetics. Mechanical malfunction may also necessitate prosthesis replacement. The risk can be as high as 5-10% in 5 years.

Conclusion
The clinician should look for and deal with underlying conditions and specific causes in a patient with ED. Treating ED is also a good chance to steer a patient into a healthier lifestyle. Effective oral treatment has revolutionized ED management and newer drugs are coming up. We have more invasive methods in our armamentarium for symptomatic treatment of ED in case oral agents fail. However, use of such methods has to be discussed carefully with the patient as their expectation and acceptance would be crucial. All in all, treatment of ED is a very personal matter and every case needs to be individualized.
Epidemiology and Clinical Significance of HBV Genotypes

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HBV can be classified into 7 genotypes (A-G) based on an inter-group divergence of 8% or more in the complete nucleotide sequence. Table 1 summarizes the geographical distribution of these 7 HBV genotypes. Several methods have been used for HBV genotyping: direct sequencing, restriction fragment length polymorphism (RFLP), line probe assay and enzyme-linked immunoassay.

Several studies suggest that HBV genotypes may be related to rate of recovery after acute HBV infection, and progression of liver disease in patients with chronic HBV infection. These studies suggest that genotype C is associated with more active/progressive liver disease than genotype B. However, all the studies were based on retrospective analysis with the potential for selection bias. All except one study was performed on Asian patients.

Recent studies, all in Asian patients, found that the prevalence of HBeAg was higher in patients with genotype C than those with genotype B suggesting that genotype B may be associated with higher rates of HBeAg seroconversion. It is conceivable that the correlation between HBV genotypes and liver disease may at least in part be explained by differences in duration of active virus replication. A few studies reported that HBV genotype plays a role in response to interferon therapy. The role of HBV genotype in response to lamivudine treatment has not been studied.

Mutations in the precore region of the HBV genome have been reported in many HBeAg-negative patients who have persistent viraemia and active liver disease. The predominant mutation involves a G-A change at nucleotide 1896 (G1896A), which creates a premature stop codon (eW28X). This mutation prevents translation of the precore protein and completely abolishes the production of HBeAg. Current evidence suggests that selection of the G1896A mutation is genotype-dependent, being more common in HBV genotypes B, C and D and rare in genotype A. This accounts for the high prevalence of HBeAg negative chronic hepatitis and G1896A variant in Asia and the Mediterranean basin.

Mutations in the core promoter region downregulate precore mRNA transcription and HBeAg synthesis. The most common core promoter variant involves a 2-nucleotide substitution: A to T at nucleotide 1762 and G to A at nucleotide 1764 (A1762T, G1764A). There is growing evidence that the prevalence of the core promoter variant varies among different HBV genotypes. Several studies found that the core promoter variant is more often detected in patients with HBV genotype C and genotypes that preclude the selection of the G1896A precore variant.

Table 1. Geographic distribution of HBV genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>North-west Europe, North America, Central Africa</td>
</tr>
<tr>
<td>B</td>
<td>Indonesia, China, Vietnam</td>
</tr>
<tr>
<td>C</td>
<td>East Asia, Korea, China, Japan, Polynesia, Vietnam</td>
</tr>
<tr>
<td>D</td>
<td>Mediterranean area, Middle East, India</td>
</tr>
<tr>
<td>E</td>
<td>Africa</td>
</tr>
<tr>
<td>F</td>
<td>American natives, Polynesia</td>
</tr>
<tr>
<td>G</td>
<td>United States, France</td>
</tr>
</tbody>
</table>

Outcome of Acute Reactivation

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Exacerbation of chronic hepatitis B virus (HBV) infection is a common event and is estimated to occur in around 40-50% and 15-30% in HBeAg positive and anti-HBe positive patients respectively. Severe exacerbation
leading to hepatic decompensation is reported to occur in less than 1%. Prognostic factors for severe exacerbation of HBV are not known. Forty-seven HBV patients (23 HBeAg positive, 24 anti-HBe positive) who were admitted to Queen Mary Hospital with symptomatic HBV exacerbation were studied. Liver biochemistry, HBV serology, prothrombin time (PT), renal function and clinical progress were monitored. Seventeen patients (36.2%) died (n=15) or had liver transplant (n=2). Using multiple regression analysis, the following are the independent factors associated with high mortality/transplantation rate: low albumin levels on admission (p=0.001), high bilirubin levels on admission (p<0.0001), prolonged PT on admission (p<0.0001), low platelet count on admission (p=0.015), high subsequent peak bilirubin levels (p<0.0001), prolonged subsequent peak PT (p<0.0001), longer time of reaching peak PT (p=0.021), presence of encephalopathy (p<0.0001) and presence of ascites (p=0.003).

Upon admission for patients with albumin levels of <35 g/L, bilirubin levels of >200 µmol/L, and PT of >30 seconds, the mortality/transplantation rate was 92.3% (12/13) compared to only 14.7% (5/34) in patients who did not have ALL three adverse factors (p<0.0001). The sensitivity and specificity for predicting poor outcome using a combination of these 4 adverse factors were 0.71 and 0.97 respectively. The positive and negative predictive values were 0.92 and 0.85 respectively. There was no difference in the HBV DNA levels on admission between patients who survived (median 0.46 Meq/ml, range <0.14-1392 Meq/ml) and patients who died/ were transplanted (median 6.67 Meq/ml, range <0.14-70 Meq/ml, p=NS).

Upon subsequent monitoring in patients with early peaking of bilirubin and PT, and patients with peak of bilirubin levels of <200 µmol/L or peak of PT of <33 seconds, the mortality rate was zero. There were no significant differences in the peak ALT levels and the time to reach the peak ALT levels between patients who survived and patients who died/ were transplanted.

Conclusions
Albumin levels, bilirubin levels, PT and platelet count on admission, the subsequent peak and time of bilirubin and PT, presence of encephalopathy and/ or ascites had prognostic significance for HBV exacerbation. According to these parameters, patients could be categorized into high-risk group in whom liver transplantation is necessary. ALT levels however were not of prognostic significance.

Hepatitis C: Re-Treatment of Non-Responders
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Significant advances have been made in the treatment of hepatitis C in the last decade. Sustained virologic response, defined as undetectable hepatitis C virus RNA 6 months after stopping treatment, has improved from 10-15% with interferon therapy alone to approximately 35-40% with combination therapy of interferon and ribavirin and more recently to 50-55% with combination of pegylated interferon and ribavirin. Nevertheless, approximately 50% patients will not achieve a sustained response and 10-20% patients will develop breakthrough infection during treatment or relapse after cessation of therapy.

In general, patients who relapse after initial response may achieve sustained response if re-treated for a longer duration. The management of non-responders is more difficult, and data from large-scale studies are not available. The first question in the management of non-responders is whether re-treatment is worthwhile. A complete assessment of the patient including age, other concurrent medical problems, severity of liver damage, likelihood of response to re-treatment, and tolerance to previous therapy should be performed before a decision is made. It must be realized that while hepatitis C is in general a progressive liver disease, the rate of progression is highly variable and some patients may not develop cirrhosis or complications of liver disease in their life-time. Thus, decision on re-treatment must be tailored to the individual patient.

Once a decision to re-treat is made, the options include:
1. Re-treatment with newer and more effective treatment – Unfortunately, current data suggest that only 10-15% of patients who failed to respond to previous therapy will have a long-lasting response to any of the new treatment that will be available now or in the foreseeable future.
2. Long-term suppressive therapy – because the
likelihood of a cure with re-treatment is low, another approach is to use long-term therapy to slow down disease progression. There is some evidence to suggest that long-term interferon therapy may decrease inflammation and fibrosis and the risk of liver cancer. The problems with this approach are the costs of treatment and the side effects. This approach is being evaluated in several ongoing studies.

3. Experimental therapies – in addition to pegylated interferons, many experimental therapies including ribozymes and HCV polymerase inhibitors are being evaluated. Most of these new agents are in their early phase of development and their success rates are unknown.

Patients who decide not to be re-treated should be regularly monitored to determine if there are any signs of progression and to determine if they may benefit from re-treatment at a later date as new treatment become available. For patients with cirrhosis, surveillance for liver cancer should be considered and close monitoring for early signs of liver failure should be performed so referral for liver transplantation can be initiated in a timely manner.

The goals of antiviral therapy are to prevent HCC and liver failure, and to improve quality of life. It is now agreed that the desired endpoint of treatment is sustained virologic response (SVR) - HCV RNA not detected (by the most sensitive method) 6 months after treatment. The benefits of SVR include 90% reduction of HCC among those at highest risk, improved liver function, and significant fibrotic regression. Some types of non-SVR (e.g. response-relapse; normalisation of ALT) may delay or slightly reduce HCC risk. The central place of combination IFN/ribavirin as first treatment is now established. Practical details include delivering the optimal dose of both agents, and modifying the course according to genotype (6 mo for types 2 and 3; 12 mo for types 1, 4 and probably 5/6) and viral load (6 mo for <800 000 IU/mL if type 1). Psychological side-effects are the usual reason for discontinuing therapy; standards of care need to be established (such as <5% dropout for 6 mo; <10% dropout for 12 mo) and audited, while optimal treatment requires support services (nurse education, counselling by clinical psychologists, self-help groups) to optimise outcomes. Because the teratogenicity of ribavirin, continued conception (both partners) is mandated until 6 mo after therapy. The significance and management of haematologic changes is now standard care; colony stimulating factors are being tried for those
with severe neutropenia associated with cirrhosis and PEG-IFN.

Peglated interferons (PEG-IFN) show efficacy that is between 2 and 5 times better than conventional IFN monotherapy; the most impressive results are in difficult-to-treat cases. Relapse remains a problem, so overall results are inferior to conventional combination therapy. PEG-IFN/ribavirin combination generally gives the best SVR in all categories, but comparative data between studies and products are difficult to interpret. Modifying treatment choice for individuals now needs to be considered, particularly in light of safety and tolerance, but also the high cost of these products. PEG-IFN/ribavirin may be the ideal treatment for less responsive cases (cirrhosis; genotypes 1, 4, 5, 6; high viral load), but more data are needed to know whether this is always required in highly responsive cases (less fibrosis; genotypes 2,3; low viral load). The place of triple therapy with amantidine continues to be debated, but scientific rationale and the weight of evidence are against it. For persons who elect not to have antiviral therapy at the time of assessment, therapies directed at fibrosis and HCC risk caused by more severe types of chronic hepatitis (especially herbal medicines, anti-oxidants) should be subjected to more rigorous and prolonged studies.

Natural History of HBeAg-Negative Chronic Hepatitis B
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In Southeast Asia including Hong Kong, most chronic hepatitis B virus (HBV) infected patients acquire the infection via perinatal route. These patients are usually HBeAg-positive initially, and undergo immune clearance to negative HBeAg at the age of 20-30. Although the loss of HBeAg is believed to reflect quiescent disease, there is increasing evidence that some patients still have disease progression to cirrhosis or hepatocellular carcinoma in the absence of HBeAg.

To study the natural history of HBeAg-negative chronic hepatitis B is never easy. Patients with active liver disease as signified by active liver histology and elevation of transaminases have been shown to associate with poorer survival. However, liver histology and transaminases may fluctuate with time and liver damage before HBeAg seroconversion may confound the interpretation of liver histology in the HBeAg-negative phase. Longitudinal follow-up for the development of hepatic decompensation and liver-related mortality is more informative, but the follow-up duration of most studies are not long enough for the assessment of these clinical endpoints.

Among asymptomatic blood donors, HBeAg-negative chronic hepatitis B is associated with <1% liver-related mortality in over 10 years of follow-up. On the contrary, HBeAg-negative patients with active disease in tertiary referral centers have approximately 10% liver-related mortality in 6-7 years. This wide discrepancy reflects a poorer prognosis among HBeAg-negative patients who have active liver disease. Various studies have demonstrated the association of elevated HBV DNA and active liver disease, whereas normal alanine transaminase (ALT) is a good predictor of inactive liver disease. More active liver disease has been found to associate with genotype C HBV in some preliminary studies but not with HBeAg-negative HBV mutants (precore stop codon mutant and core promoter mutants).

Therefore, we recommend that HBeAg-negative patients with normal ALT levels have a lower risk of disease progression and can be followed up in the primary sector. On the other hand, HBV DNA should be checked in those patients with elevated ALT levels, and patients with elevated HBV DNA should be referred to tertiary centers for closer observation and consideration of anti-viral therapy.

New Vaccine Against Hepatitis B Virus
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Over 120 countries have already adopted the recommendation of the WHO to start universal vaccination against HBV to neonates into their EPI programs. To date, several hundred million doses of first and second generation hepatitis B vaccines produced from plasma or in yeast were administered worldwide. Efficacy of such vaccines has been demonstrated unequivocally as reflected in the reduction of HBsAg
carrier rates and hepatocellular carcinoma, especially in countries in Asia and in Africa who were among the first to implement the WHO recommendation. The safety and tolerability record of such vaccines is excellent. New generations of HBV vaccines expressed in mammalian cells containing Pre-S/S epitopes and DNA vaccines have been developed. Such vaccines may be useful in special risk groups such as non-responders to conventional HBV vaccines including older adults, obese people at risk, healthcare workers, patients on renal dialysis, transplant patients, patients with non-HBV chronic hepatitis and even patients with persistent HBV in vaccines who need immediate protection i.e. pending travel or elective surgery. The future of such vaccines depends on their immunogenicity cost and safety profile. Pre-S/S hepatitis B vaccines produced in mammalian cells have been shown to induce faster and higher seroprotection rates against HBV, using fewer doses as compared to conventional yeast derived vaccines. In addition higher anti-HBs titers following each dose may be induced by the mammalian derived Pre-S/S hepatitis B vaccines. Recently, it has been suggested that vaccines against HBV might be efficacious not only for prevention of hepatitis B but also for intervention in persistent HBV infection. Preliminary data obtained in limited clinical trials conducted in Europe and East Asia suggest that some mammalian cell derived HBV vaccines may suppress HBV replication when administered repeatedly over a prolonged period of time to patients with persistent HBV infection and hepatocellular injury. Optimal protocols and efficacy of such an intervention, intended to bypass immune tolerance to HBV, remain to be explored. Introduction of new adjuvants instead of alum may improve the induction of cytotoxic T-cells responses in vaccines persistently infected with HBV. Future avenues of research include evaluation of Pre-S/S vaccines in treatment of persistent HBV infection in combination with nucleoside analogues or other new anti-viral agents as well as design of an efficacious DNA vaccine. The new vaccines should induce cellular and humoral immune responses designed to bypass immune tolerance to HBV.

Antiviral Therapy of Chronic Hepatitis B
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The main aim of treatment of chronic hepatitis B is to suppress hepatitis B virus (HBV) replication before there is irreversible liver damage. Interferon alfa (IFNα) and lamivudine (Epivir™-HBV) are the only approved treatment for chronic hepatitis B.

Interferon-alfa (IFNα)
IFNα is effective in suppressing HBV replication in patients with chronic hepatitis B but HBeAg clearance is achieved in only 20-30% of treated patients. However, IFNα has very low efficacy in HBeAg positive patients who are in the immune tolerant phase, a condition which is very common among young Chinese patients with chronic HBV infection, and hazardous in patients with decompensated cirrhosis. IFNα has also been shown to be beneficial in patients with HBeAg negative chronic hepatitis B but post-treatment relapse is common especially after short (≤6 months) courses of therapy. IFNα is also very expensive and associated with many side effects.

Lamivudine (3TC, Epivir-HBV)
Lamivudine induces a rapid 2-3 log decrease in serum HBV DNA levels in patients with chronic hepatitis B. Several randomized controlled trials of a 1-year course of lamivudine demonstrated that lamivudine can induce HBeAg seroconversion (HBeAg loss, detection of anti-HBe and undetectable HBV DNA) in 16-18% of treated patients compared to 4-6% of placebo controls. Follow-up reports of the multi-center Asian study showed that HBeAg seroconversion rates increased with the duration of treatment from 17% at 1 year to 27%, 33% and 47% at 2, 3 and 4 years, respectively. Preliminary data suggest that 70-80% patients who achieve HBeAg seroconversion and who have completed one year of treatment have a durable response. Pretreatment ALT is the strongest predictor of response.
Studies comparing lamivudine and IFNα monotherapy and combination therapy of the two agents showed that antiviral response after a 1-year course of lamivudine was comparable to that of a 16-week course of IFNα. Combination therapy may provide added benefit compared to monotherapy with either agent but the appropriate regimen remains to be determined.

Lamivudine is also effective in inhibiting HBV replication in patients with HBeAg- chronic hepatitis B. Response has been reported in 60-70% patients after one year of therapy but 90% patients relapse after treatment is stopped.

Lamivudine is well tolerated and results in clinical improvement in some patients with decompensated cirrhosis. Because of the delay in clinical benefit and the potential for resistance with long-term therapy, the optimal timing to initiate lamivudine treatment in patients with decompensated cirrhosis, especially those who are candidates for liver transplantation, is still debated.

The major drawback of lamivudine treatment is the selection of resistant mutants. The M204I/V mutation is the most important and has been reported in 15-30% patients who have received lamivudine for one year increasing to 65% in patients who have been treated for four years. The development of resistance should be suspected in patients with breakthrough infection. In many patients with lamivudine resistance, serum HBV DNA and ALT levels remain lower than pre-treatment values. However severe hepatitis and hepatic decompensation have been reported.

The optimal duration of lamivudine treatment is uncertain. For patients with HBeAg+ chronic hepatitis B, treatment should be for one year. Treatment may be discontinued in patients who have sustained HBeAg seroconversion. Treatment may be continued beyond one year in patients who have not achieved HBeAg seroconversion in the hope that delayed HBeAg seroconversion may occur but the benefits of extended treatment must be balanced against the increased risk of antiviral resistance. Treatment may be continued in patients who have developed breakthrough infection as long as clinical benefit is maintained. Patients with breakthrough infection and worsening liver disease should be referred for rescue therapy. For patients with HBeAg- chronic hepatitis B, the end-point and optimal duration of treatment have not been established.

Other Treatment

Famciclovir – the antiviral effect is weak and require three times a day administration.

Emtricitabine/Coviracil (FTC) – Phase I and II clinical studies showed that it is well tolerated and has similar efficacy to lamivudine but cross-resistance with lamivudine is anticipated.

Adefovir – Phase III placebo-controlled trial showed that a 52-week course of adefovir 10 mg/d is safe, associated with significantly higher HBeAg seroconversion rate and no evidence of drug resistance. In addition, in vitro and in vivo data showed that adefovir can suppress replication of lamivudine resistant HBV mutants.

Entecavir – Phase I and II trials showed that entecavir can decrease serum HBV DNA levels. In vitro and in vivo studies found that high doses of entecavir is effective against lamivudine resistant HBV.

Clevudine (L-FMAU) and β-L-thymidine (L-dT) have also been shown to have potent antiviral activity against HBV in preliminary clinical studies.

Summary

Significant advances have been made in the treatment of chronic hepatitis B. Recommendations for treatment have to take into consideration the replicative status of the virus, activity of liver disease and other host factors such as age and comorbid conditions. As more therapeutic agents become available, combination therapy has to be examined. Ideally, combination therapy should have additive or synergistic antiviral effect, decrease risk of resistance, no added toxicity or cost, and no untoward drug interactions.
• 1989 hepatitis C virus (HCV) was identified; 6 major genotypes.
• Anti-HCV prevalence in Hong Kong is <1%; genotype 1b predominates over 2, 3 and 6.
• Transmission is mainly from blood transfusion, contaminated medical procedures, and injections. Transmission form sexual & vertical route is rare. Vaccine is not available; universal precaution is mandatory.
• Chronic hepatitis C (CHC) occurs in 80%; mostly asymptomatic but progressive disease except in those with persistently normal ALT.
• CHC leads to cirrhosis (=10-20% in 10 years) and hepatocellular carcinoma after 30 years, or 1-4% per year among the patients with cirrhosis.
• Host factors (male gender, infected at older age, alcohol abuse, co-infection with HIV and HBV) are associated with disease severity.
• Renal and skin manifestations; mixed cryoglobulinaemia syndromes may occur.
• Viral genotype and serum HCV-RNA should be determined prior therapy.
• Liver biopsy before therapy is recommended for patients with abnormal ALT.
• Hepatitis A and B vaccination is recommended for patients with CHC.

**Milestones in the Therapy of Chronic Hepatitis C**

♦ Therapy for CHC has major advances in the past decade.
♦ Therapeutic endpoint is sustained viral and ALT response (SR).
♦ Interferon monotherapy (SR =15%) has been superseded by interferon-ribavirin combination (SR =45%).

♦ Pegylated interferon has become available this year. It has improved efficacy compared to standard interferon. Further enhanced efficacy is found in combination with ribavirin (SR =60%).

1997 NIH Health consensus on "The Management of Hepatitis C" recommended 12 months interferon alpha 3 MU TIW for CHC patients with persistently abnormal ALT (>6 months), positive HCV-RNA, and liver biopsy evidence of septal fibrosis and/or moderate to severe necroinflammatory changes. Predictors of response are young age; absence of cirrhosis; low pre-treatment serum HCV-RNA, genotypes 2 and 3 and low hepatic iron. Reports of improved survival are pending confirmation form "HALT-C" study by NIH in USA.

1999 EASL International Consensus and Asia-Pacific consensus recommended combination therapy for patients with fibrosis stage F2 and F3, and compensated Child's A cirrhosis. Duration of therapy is 6 months for genotypes 2 and 3; and genotype 1 with HCV-RNA <2 million copies/ml; 1 year for high viral level in genotype 1. Interferon dosage is 3 MU TIW and ribavirin 800-1200 mg daily, based on body weight. Combination therapy significantly increases response and reduces relapse, increasing SR to 30-40%. Patients with cirrhosis also showed significant response. However, ribavirin can cause significant haemolytic anaemia. No therapy is indicated if ALT is normal or minimal fibrosis on biopsy unless activity score is high or that the patient has associated disabling symptoms. Patients who relapse after interferon monotherapy can expect SR of ≈20%. Interferon priming or daily dosing regimens showed no added benefit.
Pegylated interferon (PIFN), a long acting weekly injection formula, has been shown to have higher efficacy than standard interferon in the treatment of chronic hepatitis C. Sustained response of 60% was achieved in initial controlled trials of PIFN-ribavirin combination. Improved response in patients with severe bridging necrosis and cirrhosis, and genotype 1 was observed.

Pegylated Interferon
Initial studies showed PIFN was superior to standard IFN in SR. 30-39% vs 8-19%, and p <0.001 Significant ALT normalization and improvement in histology were observed with PIFN. SR in genotype 1 patients was 28% marked improvement from IFN monotherapy which has below 10% SR.

PIFN was well tolerated. Discontinuation due to side-effects and laboratory abnormalities was similar to IFN monotherapy (23-27%). Similarly, dosage modification was required in a third of the patients.

Pegylated Interferon and Ribavirin Combination
Preliminary results showed an overall SR of 61% with PIFN+RIB combination (compared with 47% with IFN+RIB combination). SR in genotype 1 is markedly enhanced to 48% (34% with IFN+RIB). Adjusting dosage according to body weight will maximize response - PIFN 1.5 mcg/kg and ribavirin ≥10.6 mg/kg. This is especially important for patients with genotype 1.

- Contraindications for PIFN and IFN therapy are history of major depressive illness, cytopenia, active alcohol use or illicit drug use, hyperthyroidism, renal transplantation, or auto-immune disease.
- Absolute contraindications for ribavirin are endstage renal failure, anaemia (Hb <10 g/l), haemoglobinopathies, severe heart disease, pregnancy, and unreliable contraception (teratogenicity). Relative contraindications are old age and arterial hypertension.
- Therapy should not be limited by mode of acquisition, risk group, HIV status, viral levels or genotypes.

- Management for patients with CHC in certain situations is not well defined due to insufficient data for general guidelines. These include renal failure and transplantation, children with haemolytic anaemia, pregnancy, co-infection with HBV and HIV. Specialist assessment is recommended. There is increasing evidence that interferon therapy can reduce chronicity in acute hepatitis C.

References