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FACULTY OF MEDICINE
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ATIC newsletter

VOLUME : 6 ISSUE : 6 NOVEMBER 2009

INFECTIOUS DISEASES INSTITUTE

Quarterly Newsletter of the AIDS treatment information centre, Infectious Diseases Institute, Makerere University, Kampala

Viral hepatitis B in Uganda:
What the Health Care Worker needs to know

By Ponsiano Ocama, Emmanuel Seremba, Christopher K. Opio
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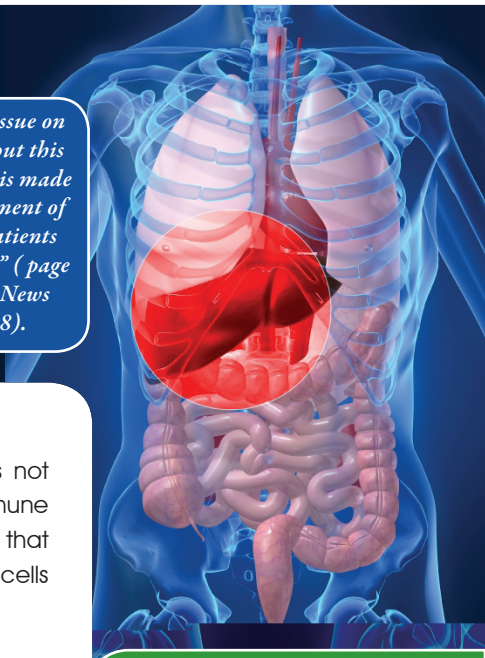
We welcome you to yet another issue on Hepatitis B infection. Throughout this article please note that reference is made to the article on entitled "Treatment of hepatitis B virus infection in patients co-infected with HIV in Uganda" (page 7 of Vol 4 Issue 3 of the ATIC News published in September 2008).



Introduction

Close to 2 billion people worldwide have been exposed to hepatitis B virus (HBV) with 400 million having chronic hepatitis B infection.

In Uganda, chronic hepatitis B infection, defined as persistence of hepatitis B surface antigen for more than 6 months has been demonstrated in 10% of the population.

There is a varying distribution of the virus in Uganda with the northern and northeastern ranging from 13% to 23%, 3% in the west, 3 – 5% in the south and 10% in the east. Reasons for this wide variation of distribution of hepatitis-B in Uganda are not yet known.

Because chronic HBV is the commonest cause of cirrhosis and hepatocellular carcinoma (HCC), most of the patients with HCC seen in the National Referral Hospital Mulago, come from the north and northeast of the country.

Transmission

Hepatitis B virus transmission is similar to that of human immune deficiency syndrome virus (HIV). Therefore, transmission will occur through transfusion with blood and blood products, sexual intercourse, mother- to- child, and use of infected needles.

HBV transmission is also presumed to occur among children between 1-5 years during fights, injuries and bites sustained when they are playing. This occurs in areas where hepatitis B is highly endemic.

Immune pathogenesis

In most cases the Hepatitis-B virus does not directly cause liver damage. It is the immune system (both cellular and humeral) that damages the liver by targeting liver cells infected with the virus.

However, in situations of suppressed immunity such as HIV infection and after organ transplants, the ability of the immune system to attack and destroy the infected cells is lost. In this case the virus then multiplies to high levels and directly attacks the liver cells causing fibrosing cholestatic hepatitis (FCH).

NATURAL HISTORY OF HEPATITIS B INFECTION

Hepatitis B infection can be influenced by many factors such as host immune status, age at infection, and level of viral replication. Age at the time of infection is a strong determinant of chronicity, the earlier the acquisition of infection, the higher probability of developing chronic infection.

There are four Phases of infection.

Phase 1: Immune tolerant

During this phase the virus multiplies in the hepatocytes but there is no damage done to the liver. There is no recognition of the infection by the body's immune system and there are no signs and symptoms of the infection. Detection of infection is by deliberate testing which is in most cases incidental.

INSIDE stories

EDITORIAL...

Infectious diseases are caused by pathogenic microorganisms such as bacteria, viruses, parasites, fungi, and protozoa. The diseases (also called communicable or contagious diseases) can easily be spread, directly or indirectly, from one person to another.

These diseases are a major cause of death, disability, social and economic disruption for millions of people. This is because they directly impact on families and communities because of lost productivity, missed educational opportunities due to poor health and high health-care costs.

Children are particularly vulnerable to infectious diseases. It is true that pneumonia, diarrhoea and malaria are leading causes of death among children under 5 years worldwide.

The adverse impact of infectious diseases is most severe among the poorest people, who have limited resources to draw from and limited or no access to preventive and treatment care,

In developing countries where the burden of infectious diseases is highest, co-infection is also a very common feature. Co-infection is when a person infected with one infectious disease becomes more susceptible to another. For example, HIV/AIDS co-infection with hepatitis B or HIV/AIDS co-infection with TB. In general co-infection tends to make both diseases more severe, harder to treat and also leads to higher mortality.

Illness and death from infectious diseases is particularly tragic because they are preventable and treatable. The sixth Millennium Development Goal (MDG) focuses on stopping and reversing the spread of infectious diseases by 2015. This can only be achieved if there are strong health care systems in place and if people are empowered with as much knowledge about infectious diseases as possible.

Increased funding to health sector for research, vaccines and drug treatments could help eradicate and control diseases thereby saving millions and improving the lives of many more.

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In Uganda, most patients come to know they are infected when they take a Hepatitis B test due to travel or employment demands. Majority are young people with no symptoms at all.

In this phase,

- Hepatitis B s antigen (HBsAg) is positive,
- Hepatitis B viral load (HBV DNA) is very high
- The alanine aminotransferase (ALT) is normal,
- Hepatitis B e antigen (HBeAg) is positive,
- Hepatitis B antibody (HBeAb) is negative
- Liver histology is normal.

The duration of the immuno tolerant phase usually depends on the age of acquisition of the infection. Earlier age at acquisition leads to longer immune tolerant periods (lasting 10-30 years) but unfortunately also leads to higher rates of progression form acute to chronic illness.

Phase 2: Immune clearance

This is the period in which liver damage becomes evident. The immune system begins to destroy liver cells that are infected by hepatitis B virus. As a result the patient may present with signs of liver disease like: fever, yellow eyes, easy fatigability, nausea, vomiting and loss of appetite. During this time,

- The viral load drops but may be fluctuating ,
- Hepatitis B e antigen is lost,
- Liver enzymes are elevated or may be fluctuating
- Liver histology shows chronic inflammation/fibrosis.

In people who acquire hepatitis B as adults, this period results in viral clearance in more than 95% of cases. If the immune response is very brisk, this may lead to massive hepatic necrosis and death. In other words the chance that hepatitis B becomes chronic in a person that gets infection as an adult, for example sexually, is lower than 5%. In Uganda, most patients presenting with chronic HBV have been infected in early childhood.

Phase 3: Inactive carrier

- During this time, the patient has cleared the infection,
- Viral load is undetectable,
- HBeAg is lost,
- HBeAb is gained,
- Liver enzymes are normal or near normal.
- Histology is normal or near normal

In fact the immune system has suppressed the virus. This period may last for long but in some cases the infection enters another phase- the phase of reactivation.

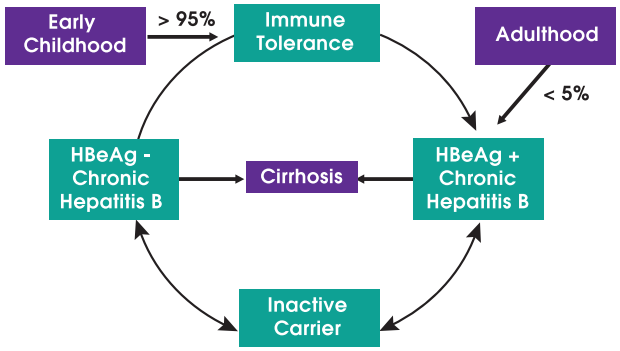
Phase 4: Reactivation

The virus becomes active again, with

- Viral load rising to detectable levels
- Liver enzymes rising to high levels or fluctuating.
- HBeAg is negative,
- Anti HBe antibody is positive.

Characteristically the viral loads are not as high as those with positive HBeAg. This is the HBeAg negative chronic hepatitis B virus infection.

Summary of the natural of hepatitis B



Courtesy of W. Ray Kim, MD.
Chen DS, et al. J Gastroenterol Hep. 1993;8:470-475.
Seeff L, et al. N Engl J Med. 1987;316:965-970.

Treatment of hepatitis B virus

The primary goal of treating hepatitis B is to prevent progression to cirrhosis and hepatocellular carcinoma which is a function of high viral loads. This goal is therefore achieved by suppression of viral loads.

Following the phases described above, the main question with hepatitis B infection is therefore not who to treat but when should treatment be administered. Please refer to treatment algorithm on page .....

Several drugs have been approved by FDA for treatment of hepatitis B including the injectable alpha interferons (short acting or pegylated) or the orally administered lamivudine, adefovir, entecavir, telbivudine and tenofovir.

Indications for treatment and eventually treatment monitoring will depend on HBeAg status, as shown below

Hepatitis B e antigen positive	Hepatitis B e antigen negative
• HBV DNA >20,000 IU/ml • ALT >2 ULN • Significant Liver disease with fibrosis/inflammation	• HBV DNA >2,000 IU/ml • ALT >1 ULN • Significant Liver disease with fibrosis/inflammation

Note: The above criteria for HBV DNA, ALT and disease stage must all be met

- If not, guidelines recommend monitoring and consideration of treatment based on individual's age, health status, and stage of infection/disease.

Some HBV infected populations that require treatment regardless of HBV DNA and ALT levels include:

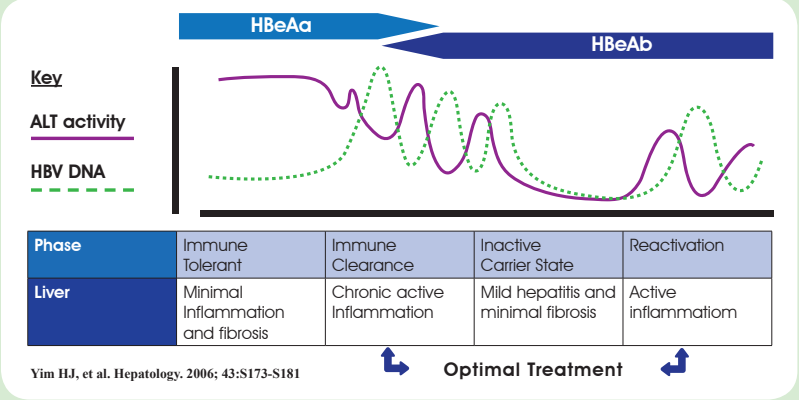
- Patients with rapid deterioration of liver function
- Patients with compensated cirrhosis
- If DNA > 2,000 IU/mL, regardless of ALT
- Patients with decompensated cirrhosis (IFN contraindicated)
- Recurrent HBV infection post liver transplantation
- HBV carriers undergoing immunosuppressive or cytotoxic chemotherapy.
- HIV co-infected who require treatment for HBV even if there was no indication for treating the hepatitis B at that time. In the above case treatment has to include combination antiretroviral therapy with drugs effective against both HIV and HBV.

Patients who require treatment for hepatitis B without treating HIV should be treated with drugs that have no effect on HIV such as the interferon, telbuvidine and adefovir.

All hepatitis B infected patients must be tested for HIV before treatment initiation. On the other hand HIV infected patients should also be tested for HBV before ART so that appropriate treatment combination of drugs can be used.

Summary of 4 phases of chronic HBV infection.

Treatment is indicated during the immune clearance and the reactivation phases



Yim HJ, et al. Hepatology. 2006; 43:S173-S181

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Monitoring of Treatment

While on treatment the HBV viral loads, liver enzymes, HBeAg and antibody (for those who are HBeAg positive at the beginning) should be monitored every 3-6 months.

Response is defined as:

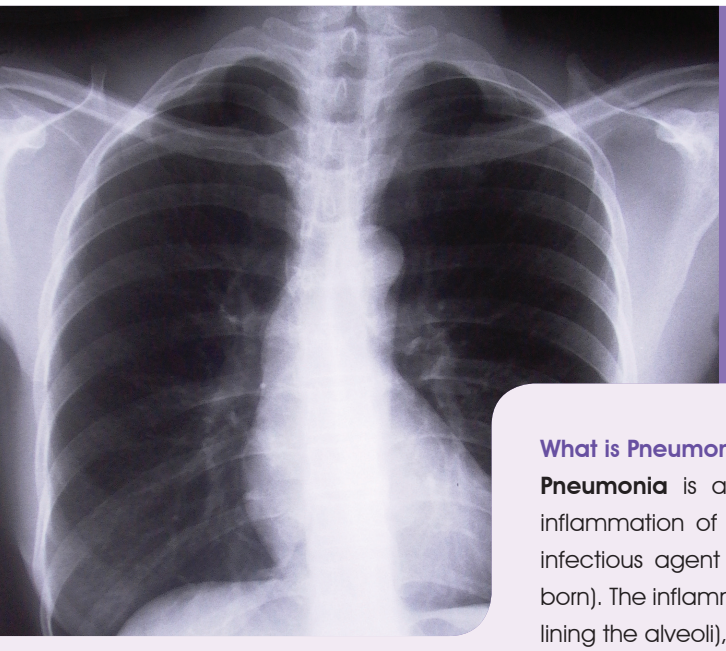
- HBeAg loss
- Gain in HBeAb
- Undetectable viral loads
- Normalization of liver enzymes.
- A few patients will in addition lose HBsAg and gain HBsAb.

However, since HBsAg tends to stay lifelong in the majority of patients it is not frequently used as a marker of response.

In Hepatitis B mono-infected patients, when response occurs as above, treatment with the oral agents may be stopped 6-12 months from the time it occurs if no relapse is noted.

In conclusion

- Not all patients who test HBsAg positive should be treated without further analysis of the patient's hepatitis B and health status.
- Only patients in the immune clearance stage and those with reactivation should be treated as well as those in the special populations listed above.
- While treatment with interferon will last about 1 year, the nucleos(t)ide analogs (oral medications) will require to be administered for 1 or more years depending on when treatment end point occurs. Cirrhotic patients may be treated for a much longer duration of time.
- Patients in other stages of the infection should be monitored and only treated if treatment is indicated.



Pneumonia in children

By Dr Jonathan Mayito and Dr Lillian Mukisa Nabukeera

Pneumonia accounts for one in five deaths occurring in children under 5 years of age.

What is Pneumonia?

Pneumonia is an inflammatory illness of the lung tissue. It is characterized by inflammation of the alveoli and terminal airspaces in response to invasion by an infectious agent introduced into the lungs through blood spread or inhalation (air born). The inflammation triggers the leakage of plasma and the loss of surfactant (fluid lining the alveoli), resulting in loss of air and consolidation.

Why is Pneumonia so dangerous?

More than 2 million children world wide die annually of pneumonia accounting for one in five deaths in children under 5 years. 98% of pneumonia deaths occur in Sub Sahara Africa. The following factors increase the risk of fatal pneumonia in children:

1. Poverty (poor socioeconomic status),
2. Poor immunity (incomplete immunization schemes),
3. Malnutrition,
4. Late care seeking and inadequate treatment.

In Uganda alone, roughly 27,000 children die of pneumonia annually mainly due to a delay in recognising the disease by patients and care givers, as well as mistreatment of the disease with anti malarias.

Unless pneumonia is diagnosed quickly and treated appropriately, death can occur in a period as short as 3 days and the Case Fatality Rate can reach as high as 20%.

In infants/children with fever lethargy in whom a malaria smear is negative, consider sepsis with a respiratory source and early antibacterial treatment may make a difference.

To reduce the case fatality control measures should focus on:

- Improvement in vaccine coverage for measles, haemophilus influenzae type B and whooping cough.
- Community education,
- Improved nutrition,
- Training of health providers in diagnostic and treatment algorithms, use of effective antibiotics, and timely referral of severely ill children.

The most common causes of severe pneumonia in children under 5 years in the developing world are ***Strep. pneumoniae*** and ***Hemophilus influenza.*** Plans for the introduction of the 10 - valent pneumococco vaccine are under way in Uganda.

Clinical Features

How does a child with Pneumonia Present?

The signs and symptoms of pneumonia are often nonspecific and widely vary based on the patient's age and the infectious organisms involved.

- Newborns/neonates with pneumonia rarely cough; they more commonly present with tachypnea, chest indrawing, grunting, and cyanosis (bluing of the mouth and tongue)
- Infants, toddlers and preschoolers present with a persistent cough, which may be wet or dry, accompanied by fever, tachypnea and chest indrawing. Grunting is present in these children too and is a sign of sever pneumonia. They are also irritable and have decreased feeding.
- Older children and adolescents will also present with fever, cough (productive or nonproductive), congestion, chest pain, dehydration, and lethargy.
- Extrapulmonary signs and symptoms which may be present in all children include:
- abdominal pain or ileus accompanied by vomiting in patients with lower lobe pneumonia,
- neck rigidity in patients with right upper lobe pneumonia, or
- a rub caused by pericardial effusion in patients with lower lobe pneumonia due to Haemophilus influenzae infection.

DIAGNOSIS

Diagnosis of pneumonia is mainly done on clinically grounds. A child who presents with any of these symptoms listed above should be suspected of having Pneumonia. On listening to the child's lungs, the clinician may find the following:

- Rales (crackling sounds), wheezing, diminished breath sounds, tubular breath sounds, or pleural friction rub.
- The affected lung field may be dull to percussion i.e. may sound like hitting against a wall.
- Increased chest resonance to touch or on auscultation with the stethoscope (tactile and vocal fremitus, may be heard and felt over the area of pneumonia.
- With pulse oximetry if available, persistent hypoxia (i.e. Oxygen Saturation <90%)

Age as a guide to diagnosis

Because basic laboratory and radiologic testing is often not helpful in understanding the etiology of pneumonia, clinicians often use epidemiological trends e.g. seasonal trends, age group trends, hospital or community acquired trends to decide the most likely cause of pneumonia in a specific patient.

The classification below is an age related guide to the diagnosis of pneumonia.

- Newborns/Neonates ***(age 0-2months)***
  - Infections with group B ***Streptococcus,*** Listeria monocytogenes, or gram-negative rods (e.g. Escherichia coli, Klebsiella pneumoniae) are a common cause of bacterial pneumonia. These pathogens can be acquired in utero, via aspiration of organisms present in the birth canal, or by postnatal contact with other people or contaminated equipment.
  - Community-acquired viral infections may occur in newborns but mostly occur in premature infants who may not have benefited from sufficient transfer of transplacental immunoglobulin G from their mothers.
- Infants and toddlers
  - In developed countries , viruses are the commonest cause of infection in this age group but in developing countries, bacterial infections are the most common cause and are attributable to Streptococcus pneumoniae, H influenzae type B (less common in immunized children), or Staphylococcus aureus . Whooping cough caused by Bordetella Pertusis can be a cause especially if a child has not finished their immunization schedule
- Preschool children (2-5 years)
  - Children enrolled in daycare, or those with frequent ear infections are at increased risk for invasive pneumococcal disease and infection with resistant pneumococcal strains.
  - ***If an infant is HIV positive, Pneumocystis Pneumonia (PCP) caused by a fungus called Pneumocystis jiroveci***

continues on page 6

(formerly called pneumocystis carinii) can be a major cause of severe pneumonia (15 – 30%) and death (30-50%) The infants are usually in good nutritional state and may not have other signs and symptoms of HIV. The incidence of PCP is highest in the first year of life and usually peaks at 3 to 6 months of age. It occurs with decreasing frequency after one year of age

If PCP is suspected especially in a child presenting with severe pneumonia, obtain an HIV test on the mother is possible. If positive consider High dose Septrin (TMP / SMX 120mg/kg in 2-4 divided dose for 14 days).

- School-aged children and adolescents:
  - Bacterial pneumonia (10%) is common, and these children are often febrile and appear ill.
  - Atypical Pneumonias are also common in this age group and are caused by mycoplasma pneumoniae and Chl. Pneumoniae

PS: Tuberculosis (TB) can be a cause of pneumonia in all children and warrants special mention. Children with TB usually do not present with symptoms until 1-3 months after primary infection. Infants and post pubertal adolescents are at increased risk of disease progression. A history of exposure to possible sources should be obtained

Lab Investigations:

Lab investigations may include:

1. CBC : which will show Increased white blood cell counts with neutrophilia,
2. Blood Culture: which may" grow" the causative organism but only in <30%of all cases
3. CXR : if available, should ALWAYS be done in suspected pneumonia.
4. Because symptoms of malaria and pneumonia overlap, a blood slide for malaria parasites should be done.

MANAGEMENT

According to Integrated Management of Childhood Illnesses (IMCI), presence of cough and fever is graded as No Pneumonia, Severe Pneumonia or Very Severe Pneumonia depending on the clinical presentation of the child.

Severe or very severe pneumonia in a child is graded as cough and fever with the following signs:

- Chest indrawing
- Grunting
- Nasal flaring
- Cyanosis

- **Mild Pneumonia**

  Management should generally follow the IMCI guidelines:

For Cough and Fever Classified as No Pneumonia:

Oral amoxicillin or penicillin is the first line treatment. Cotrimoxazole is no longer used as first line treatment for out patient pneumonia due to extensive drug resistance.

If the child is on cotrimoxazole prophylaxis, as in HIV, no cotrimoxazole should be given except if PCP is suspected (i.e. high dose cotrimoxazole)

Analgesics (paracetamol) for fever and pain

Recurrent pneumonias (i.e. >3times in a year), investigate the child to rule out TB, foreign body or a chronic lung disease.

- **Severe Pneumonia**

  Management should be in a hospital or inpatient facility, to include both supportive and specific therapy.

  Supportive Therapy would include:

- Supplemental Oxygen
- Correction of severe anemia (HB <5 g/dl) by transfusion with packed red blood cells.
- Adequate oral rehydration and monitoring fluid input and output. If the child is vomiting, IV fluids can be used with precaution.
- If respiratory distress is severe, pass a nasogastric tube and give food in small volumes to avoid aspirations.
- Analgesics (paracetamol) can be used for fever and pain.
- Vitamin A and Zinc supplementation if the child has not received Vit. A in the last three months.

MANAGEMENT STRATEGY

The key strategies for pneumonia control in the context of child survival strategies:

1. Case management with IMCI at all levels
2. Vaccination
3. Improvement of nutrition/low birth weight.
4. Control of indoor pollution.
5. Prevention and management of HIV infections.

Treatment of bacterial pneumonia in children;

Neonates (0-2 months)

1st Line: Amoxicillin 75mg/kg/Day divided in 3 doses

2nd Line: Gentamicin (3-5mg/kg as od x 5-7 Days) with Ampicillin 75mg/kg/Day divided in 2/3 doses x 5-7 days.

3rd Line: Cefriaxone 50mg/kg/Day x 5 days.

For children 2 months - 5 years

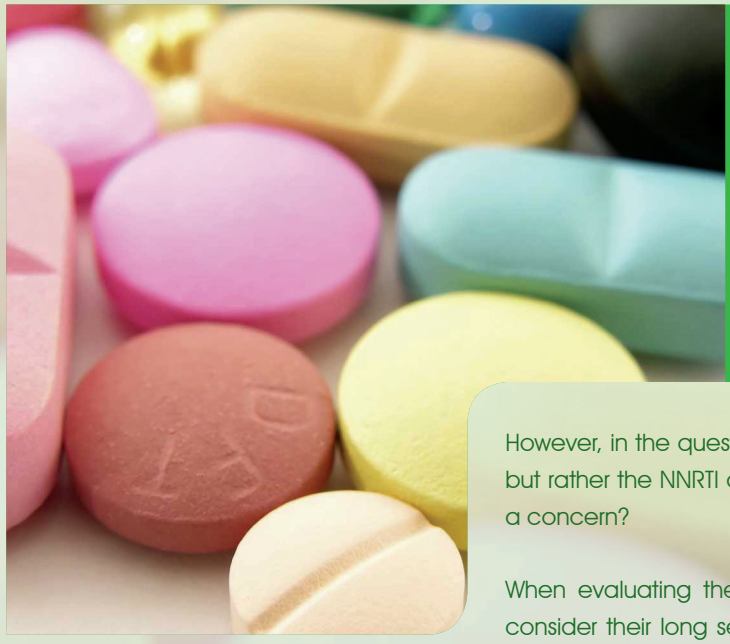
1st line: Amoxicillin or a penicillin or a macrolide derivative in patients allegic to penicillin.

2nd line: I.V Chloramphenicol 75mg - 100mg/kg/Day in 3/4 doses.

3rd line: I.V Cefriaxone 50mg/kg/Day

For children aged 6 years and above:

Follow treatment guidelines above (2 months - 5 years) calculate appropriate dose according to weight.



Pharmacokinetic Considerations when Switching from NNRTI-Based to PI-Based Antiretroviral Therapy

Kristin M. Hurt, PharmD, BCPS

Often in clinical practice, HIV-infected patients receiving antiretroviral therapy containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) require a switch to a protease inhibitor (PI)-based regimen. The most common example of this scenario occurs when a patient failing nevirapine (NVP)- or efavirenz (EFV)-based first-line therapy switches to a second-line regimen containing lopinavir/ritonavir (LPV/r). When this switch occurs, a commonly raised question is if special consideration needs to be given to the LPV/r dose, that is – Does the LPV/r dose need to initially be increased when switching from NNRTI-based therapy? This article evaluates the question further.

The pharmacokinetic basis for this question is that when an NNRTI is co-administered with a PI, the levels of the PI may be significantly decreased. The extent of this drug interaction is multifactorial, not limited to host factors, the specific PI and NNRTI, and if the PI is boosted with ritonavir (RTV). For example, when NVP and LPV/r are given concomitantly, LPV/r systemic exposure is decreased by approximately 27% and trough concentrations (Cmin) by 39-55%.1,2 This interaction results from induction of the cytochrome (CYP) enzyme system by NVP, specifically CYP3A4, which metabolizes LPV/r. If co-administered, most experts would recommend increasing the LPV/r dose to overcome this interaction.

However, in the question at hand, the PI and NNRTI are not being co-administered, but rather the NNRTI discontinued and the PI initiated. So, is the drug interaction still a concern?

When evaluating the drug interaction potential of the NNRTIs, it is necessary to consider their long serum half-life (t ½). With repeated dosing, the NVP serum t ½ is 25-30 hours, while that of EFV is 40-55 hours.1,3 Thus, therapeutic levels may persist for several days to weeks after discontinuation. Enzyme induction itself also persists for some time after drug discontinuation, generally 1-2 weeks. Therefore, an interaction may ensue even though the drug is no longer administered. This effect has been documented in a pharmacokinetic study of 12 patients switching from EFV to NVP.4 In patients who initiated NVP using the lead-in dose (200mg once daily) immediately following EFV discontinuation, mean NVP trough levels fell below the recommended target until day 15. Therapeutic EFV levels were no longer detected by day 8; however, enzyme induction persisted even longer, resulting in lower than expected NVP levels.

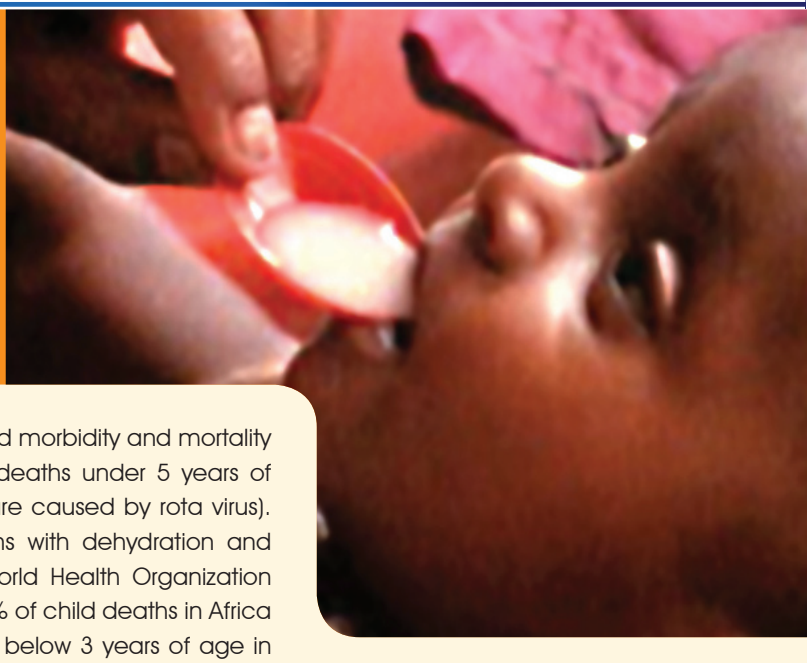
To summarize, we know that (a) NNRTIs have a long t ½ and therapeutic concentrations may persist after discontinuation; (b) enzyme induction also persists after drug discontinuation; (c) for both of these reasons, drug interactions may occur even after NNRTI discontinuation; and (d) NNRTIs induce CYP3A4, which can significantly decrease PI concentrations.

The final piece to consider is the clinical significance of 1 to 2 weeks of decreased LPV/r levels, which may occur while enzyme induction ceases. According to US treatment guidelines, the suggested minimum target LPV/r trough concentration for a patient with wild-type virus is 1000 ng/mL.5 In one study of 25 patients receiving standard dose LPV/r (400/100 mg twice daily) plus NVP (n=9) or EFV (n=16), the mean LPV/r Cmin was 3555 ± 2646 ng/mL.2 Despite the interaction, mean levels still remained above the minimum target, though high interindividual variability was noted. Although the target concentration may be higher for a patient with existing PI mutations, the presence of such mutations is rare for PI-naïve patients and LPV/r is known to have a relatively high barrier to resistance. Thus, the brief time in which a patient may experience decreased LPV/r levels is not of clinical significance and standard dose LPV/r may be commenced. A notable exception is patients commencing an unboosted PI, such as indinavir (IDV). In this case, ongoing enzyme induction would likely decrease IDV levels below the suggested minimum target; therefore, RTV-boosting the IDV would be recommended.5,7

In conclusion, standard dosing of LPV/r may be commenced following discontinuation of an NNRTI. Although a decrease in the LPV/r concentration may be noted while NNRTI-related enzyme induction ceases, this decrease is likely not clinically significant.

LOW OSMOLARITY ORAL REHYDRATION SALTS IN COMBINATION WITH ZINC IN THE MANAGEMENT OF DAIRRHOEA

By Robinah.N.Lukwago BPharm, MPH, MPS.



Diarrhoeal diseases are one of the leading causes of childhood morbidity and mortality in developing countries. Diarrhoea accounts for 21% of all deaths under 5 years of age and causes 2.5 million deaths per year (20% of which are caused by rota virus). Diarrhoeal diseases are associated with many complications with dehydration and malnutrition being the major concerns. According to the World Health Organization report on World Health Statistics 2007, it was estimated that 17% of child deaths in Africa were attributed to diarrhoeal diseases. On average, children below 3 years of age in developing countries experience three episodes of diarrhoea each year. The majority of diarrhoeal episodes in children have an infectious cause. Research laboratories can now identify a microbial cause in over three quarters of children presenting at health facilities with diarrhoea. Some of the most important diarrhea-causing pathogens include;

1. Viruses- Rotavirus
2. Bacteria- E.coli, Shigella
3. Protozoa- Gardia duodenalis, Entamoeba histolytica
4. Fungal – Cryptosporidia species

Diarrhoea accounts for 21% of all deaths in children under 5 years of age and causes 2.5 million deaths per year (20% of which are caused by rota virus).

What is Diarrhoea?

Diarrhoea is defined as the passage of unusually loose or watery stools, at least three times or more in a 24 hour period. In diarrhoea, stools contain more water than normal and they usually take the shape of the container. Acute diarrhoea is defined as diarrhoea lasting for fourteen days while persistent diarrhoea is diarrhoea lasting for more than fourteen days. In some cases the stool may also contain blood, in which case the diarrhoea is called dysentery.

The number of stools normally passed in a day varies with the diet and the age of the child. For example babies fed only breast milk often pass loose, "pasty" stools; this is not diarrhoea. Diarrhoea is most common in children aged between 6 months and 2 years of age. However it's not uncommon in babies less than 6 months who are drinking cow's milk or infant feeding formulas.

Why is diarrhea dangerous?

Two main dangers of diarrhoea are dehydration and malnutrition. Death from acute diarrhoea is most often caused by loss of a large amount of water and salt from the body resulting in dehydration. The dehydration is further complicated by electrolyte imbalances. These electrolyte imbalances are known to be worse in children with malnutrition.

Dehydration

During diarrhoea there is an increased loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate) in the liquid stool. Water and electrolytes are also lost through vomit, sweat, urine and breathing and this is worsened by reduced fluid intake by the child. Dehydration occurs when these losses are not replaced adequately and a deficit of water and electrolytes develops. The volume of fluid lost through the stools in 24 hours can vary from 5 ml/kg (near normal) to 200 ml/kg, or more. The concentrations and amounts of electrolytes lost also vary. The total body sodium deficit in young children with severe dehydration due to diarrhoea is usually about 70-110 millimoles per litre of water deficit. Potassium and chloride losses are in a similar range. Deficits of this magnitude can occur with acute diarrhoea of any aetiology.

The degree of dehydration is graded according to signs and symptoms that reflect the amount of body fluid lost:

- In the early stages of dehydration, there are no signs or symptoms.
- As dehydration increases, signs and symptoms develop. Initially these include: thirst, restless or irritable behaviour, decreased skin turgor, sunken eyes, and sunken fontanelle (in infants). At this stage usually there's been a loss of 5-10% of total body water.
- In severe dehydration, these effects become more pronounced and the patient may develop evidence of hypovolaemic shock, including: diminished consciousness, lack of urine output, cool moist extremities, a rapid and feeble pulse (the radial pulse may be undetectable), low or

undetectable blood pressure, and peripheral cyanosis. Death follows soon if rehydration is not started quickly.

Malnutrition

During diarrhoea, decreased food intake, decreased nutrient absorption, and increased nutrient requirements often combine to cause weight loss and failure to grow. The child's nutritional status declines and any pre-existing malnutrition is made worse. Malnutrition is usually a complication of persistent diarrhea but may occur in acute diarrhea.

Diarrhoea in malnourished children may be further complicated by secondary bacterial infections and many electrolyte imbalances. Dehydration in this special group may be harder to recognize using the usual signs of dehydration and correction of water losses is also done more cautiously. Malnutrition may be prevented by continuing to give a nutritious diet, appropriate for the child's age.

Management of Diarrhoea

A child with diarrhoea should be assessed for dehydration, bloody diarrhoea, persistent diarrhoea, malnutrition and serious non-intestinal infections, so that an appropriate treatment plan can be developed and implemented without delay. The treatment plan should be based on a thorough assessment of the child. This can be done by;

a) Taking history by asking the mother or other caretaker several questions such as the duration of the diarrhoea, the number of watery stools per day, presence of fever, cough or other important problems (e.g. recent measles) etc.

b) The clinician should then do a physical examination of the child. Points to consider are the general condition of the child, the skin turgor, the child's temperature and observation of whether the eyes are normal or sunken.

c) After doing the physical exam, the clinician should determine the degree of dehydration and treat the child based on the degree of dehydration.

The treatment plan will range from treating the child at home to prevent dehydration and malnutrition when there are no signs of dehydration to intravenous rehydration for those with severe dehydration. The main stay of management of diarrhoea with oral therapy is the use of oral rehydration salts and zinc supplements.

Oral rehydration using Oral Rehydration Salts (ORS) can be safely and effectively used in the prevention and treatment of dehydration from diarrhoea of any aetiology and at any age, except when the dehydration is severe. ORS is a mixture of glucose and several salts which are dissolved in water to form a solution. ORS solution is absorbed in the small intestine even during copious diarrhoea, thus replacing the water and electrolytes lost in the faeces.

After over 20 years of research, an improved ORS solution has been developed. Called reduced (low) osmolarity ORS solution, this new ORS solution reduces by 33% the need for supplemental IV fluid therapy after initial rehydration when compared to the previous standard WHO ORS solution. The new ORS solution also reduces the incidence of vomiting by 30% and stool volume by 20%. This new reduced (low) osmolarity ORS solution, containing 75 mEq/l of sodium and 75 mmol/l of glucose, is now the ORS formulation officially recommended by WHO and UNICEF.

In addition, numerous studies have now shown that zinc supplementation (10-20 mg per day until cessation of diarrhoea) significantly reduces the severity and duration of diarrhoea in children less than 5 years of age. Additional studies have shown that short course supplementation with zinc (10-20 mg per day for 10 to 14 days) reduces the incidence of diarrhoea for 2 to 3 months. Based on these studies, it is now recommended that zinc (10-20 mg/day) be given for 10 to 14 days to all children with diarrhoea. This supplement is packaged in both syrup and dispersible tablet formulations.

Appropriate identification and treatment of dehydration is the most important component of care for patients with diarrhoea. Rotavirus infection remains the most common cause of severe, dehydrating diarrhoea among children worldwide. Therefore antimicrobials should not be used routinely. Antimicrobials are reliably helpful only for children with bloody diarrhoea with infectious cause (probable shigellosis), cholera, and serious non-intestinal infections such as pneumonia. Anti-protozoal drugs are rarely indicated. "Antidiarrhoeal" drugs and anti-emetics have no practical benefits for children with acute or persistent diarrhoea. Antidiarrhoeal medications should not be used to treat acute diarrhoea in young children because of their side effects such as lethargy, seizure, ileus and respiratory depression.

Public Health perspective

Before the introduction of this low osmolarity ORS, caretakers were being given estimates used to prepare ORS at home using salt and sugar. However these estimates are now discouraged as they produce a solution similar to the high osmolarity ORS. Caretakers are now encouraged to use the pre-packaged low osmolarity ORS. Low osmolarity ORS and zinc are inexpensive, safe and easy to use. On the Ugandan market a sachet of this new low osmolarity ORS can be obtained for as low as 150 Ugshs in the private sector. They can also be obtained free of charge from public health facilities.

However the challenge remains access to these life saving formulations. As the countdown continues to the year 2015 for meeting the Millennium Development

Goal (MDG) 4 for reducing child mortality by two-thirds, median coverage rates for oral rehydration therapy (ORT) hover at 38% of episodes among the 68 UNICEF priority countries with an increase in use of only 2 percentage points reported from 2000 to 2006. Policy makers, governments, donors and agencies need to increase efforts to finance the availability and access to these new formulations. Health care workers should receive quality training to accelerate uptake, ensure zinc is used correctly, increase ORS use, decrease unnecessary antibiotic use and increase timely referral. Health workers and the village health teams should also work together to increase awareness among caretakers in their communities about the new low osmolarity ORS and zinc formulations and the benefits of early management of diarrhoea. They must also work to promote positive cultural practices used in the management of diarrhoea and discourage negative practices such as not feeding a child that has diarrhoea.

Hepatitis B vaccine:

By Dr Ponsiano Ocama

Hepatitis B is a vaccine preventable infection. The vaccine that is used contains the hepatitis B surface antigen (HBsAg).

Indication:

The vaccine is indicated in all persons that are at risk of acquiring hepatitis B and these include;

- Sexual and household contacts of hepatitis B carriers
- Sexually active individuals with multiple sex partners
- HIV positive people and those with history of Sexually transmitted infections
- Injection drug users
- Hemodialysis patients
- Recipients of clotting factor concentrates
- Health care and public safety workers with occupational risks
- Persons in institutions for the developmentally disabled or in long-term correctional facilities
- Travelers to countries endemic for hepatitis B who plan to stay >6 months
- Transplant candidates before transplantation
- Patients with chronic liver disease if the liver disease is not caused by hepatitis B

Dosage

A 20 microgram dose (in 1.0 ml suspension) is used to vaccinate individuals who are 20 years or older

A 10 microgram dose (in 0.5ml suspension) is used to vaccinate neonates, infants and children up to and including 19 years

Administration:

A series of three intramuscular injections is required to achieve maximum protection.

The injections are given in the deltoid region in adults and adolescents and in the anterolateral thigh in neonates and infants

There are 2 recommended schedules for immunization,

- A 3 dose schedule where the 1st dose is given at 0 months, the second dose is given 1 month after the 1st dose and the third dose 6 months after the 1st dose .

Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Date of month e.g. 10th of Feb	Date of Month 10th of March					Date of month e.g. 10th of Aug.
Dose 1	Dose 2	-	-	-	-	Dose 3

- An alternative 4 dose schedule where the 1st dose is given at 0 months, the second 1 month after the 1st and the third 2 months after the 1st dose. In this case the fourth dose is given as a booster given at 12months.

Month 0	Month 1	Month 2	Month 3-11	Month 12
Date of month e.g. 10th of Feb	Date of Month 10th of March	Date of month e.g. 10th of April	No vaccination	Date of month e.g. 10 of Feb
Dose 1	Dose 2	Dose 3	-	Dose 4 (Booster Dose)

- In exceptional circumstances and ONLY in adults above 18 years, when a more rapid induction of protection is required e.g. someone soon travelling abroad, or new to prison or sharing a needle to inject drugs., a schedule of 3 injection given, the 1st dose on Day 0, the second on Day 7 and the third dose is given on Day 21. When this schedule is used, a booster dose is required at 12months.

Day 0	Day 7	day 21	Day 22 - Month 11 No vaccination	Month 12
Date of month e.g. 10th of March	Date of Month 17th of March	Date of month e.g. 31st of March		Date of month e.g. 10 of March
Dose 1	Dose 2	Dose 3	-	Dose 4 (Booster Dose)

Response to the vaccination

When the HBsAg particles are introduced into the body, the immune system recognizes the antigens and produces antibodies against them known as the anti Hepatitis B surface antibody (anti-HBsAb.)

The immune system's "memory" also retains the capacity to produce more antibodies to the Hepatitis B virus should the need arise e.g. in the event of an acute infection with Hepatitis B virus.

The antibodies produced and immune system "memory" then provide immunity to hepatitis B infection.
Sufficient immunity is said to have been achieved when the body produces (anti-HBsAb) levels above 100mIU/ml. Such a full response occurs in about 85-90% of individuals and can be tested from blood samples taken from an individual 1-4 months after the full course of vaccination

Sometimes an individual's body does not produce sufficient response to the vaccine. An insufficient response is described as an antibody level between 10 and 100 mIU/ml, 1-4 months after the full course of vaccination.
These people are then given a single booster vaccination at this time, but do not need further retesting.
Some individuals fail to respond to the vaccine. Failure to respond is described as anti-HBsAb levels below 10 mIU/ml.

These individuals should be tested to exclude current or past Hepatitis B infection, and given a repeat course of 3 vaccinations, followed by further retesting 1–4 months after the second course.

Those who still do not respond to a second course of vaccination may respond to a high doses of vaccine ,to intradermal administration or may require hepatitis B immunoglobulin if later exposed to the hepatitis B virus.

Poor responses tend to occur in persons above 40 years, in obesity, smokers and alcoholics, especially if with advanced liver disease.

Patients who are immuno suppressed or on renal dialysis may respond less well and may require larger or more frequent doses of vaccine.

Side Effects

Side effects to the vaccine are usually mild and confined to the 1st few days after the injection. When they occur, they can be effectively treated with simple analgesics like oral paracetamol or diclofenac

These include person may have redness, pain and swelling at the site of the injection, occasionally fever, malaise, headache and influenza like symptoms.

Duration of Protection

Hepatitis B vaccine provides long term immunity. This is due to immunological memory which persists longer than the loss of antibody levels. In immune competent individuals subsequent testing and administration of booster doses is not required in those who have been successfully vaccinated.

Hence with the passage of time and longer experience, protection has been shown for at least 25 years in those who showed an adequate initial response to the primary course of vaccinations, and UK guidelines now suggest that for initial responders who require ongoing protection, such as for healthcare workers, only a single booster is advocated at 5 years.

Postexposure prophylaxis:

If a person who has not been vaccinated gets exposed to hepatitis B, e.g. babies born to mothers with active hepatitis B infections, uninfected persons exposed to blood/blood products of an infected person post exposure prophylaxis should be given within 48hours or as soon as possible and should include hepatitis B immune globulin (HBIG) together with first dose of hepatitis B vaccine.

Vaccination status

Many countries now routinely vaccinate infants against hepatitis B. In Uganda, routine Hepatitis B vaccination was introduced in 2002 as the pentavalent vaccine given at 6 weeks, 10 weeks and 14 weeks after birth.

ASK ATIC:

By Stella Zawedde-Muyanja, MB ChB

Question:

We have a 43 year old man who presented to our facility 2 months ago with a month's history of evening fevers and night sweats. He also had firm, non tender cervical hymphadenopathy. Fine Needle Aspiration of the lymph nodes yielded AAFBs on ZN stain. He was started on the anti-TB regimen 2HRZE/6EH. He improved in the first 2-3 weeks with reduction of his constitutional signs and size of lymph nodes. However, after that, his lymph nodes started to get bigger and bigger. He is now in his last week of the Intensive Phase but the Lymph nodes are still present and quite large. Is this patient improving or is he getting worse?

Response:

This patient has got a paradoxical worsening of the symptoms of his disease.

Definition:

Paradoxical reaction during anti-tuberculosis therapy is defined as the clinical or radiological worsening of pre-existing tuberculosis lesions or development of new lesions in a patient who initially improves with anti-tuberculosis therapy, in the absence of disease relapse.

Diagnosis:

Because enlargement of pre-existing lymph nodes and appearance of new enlarged lymph nodes in other areas could suggest a number of differential diagnoses including concomitant bacterial infection or inadequate anti-tubercular treatment due to drug resistance or poor drug compliance, diagnosis is made by exclusion.

- First, the patient should show initial clinical improvement with improved appetite, weight gain and minimal constitutional symptoms e.g. evening fevers and night sweats

- Then assess treatment response to make sure that there is no resistance to the anti-TB treatment. A quick way to assess treatment response is to repeat FNA of the enlarged lymph node for Ziehl-Neelsen staining to look for AFB. Clearing up of AFB in smear indicates positive treatment response. On the contrary, demonstration of AFB does not necessarily mean treatment failure since the organisms may only represent dead AAFBs. A more accurate way of detection of treatment would be to do a culture and sensitivity the aspirate.

- A thorough physical examination should be done to look for other causes of lymphadenopathy, e.g. focus of infection: pyogenic lymphadenitis should be hot and tender whereas suppurative tuberculous lymphadenitis gives rise to cold abscess.

- Do a CXR to rule out malignancy and to study the extent of disease because mediastinum and pleura are a common site of paradoxical involvement

- Ask for counselling evaluation and support to rule out poor adherence to treatment

- Elevation of total white cell count and inflammatory markers like erythrocyte-sediment rate (ESR) and C-reactive protein are non-specific because their elevation can be contributed by both secondary infection and paradoxical reaction.

Management:

Mild paradoxical reaction like recurrence of fever and enlargement of superficial lymph nodes does not require specific treatment and no alternation in the anti-tuberculosis regimen is needed.

For severe paradoxical reaction such as massive pleural effusion and development of deep seated abscesses, a combination of anti-tuberculosis & steroid therapies and surgical treatment should be considered.

The use of systemic steroids is controversial as there is no consensus on dosage and duration of systemic corticosteroids for treating paradoxical reaction .Some clinicians recommend a dose of 1mg/kg tapered over 3 months.

Conclusion:

It is useful to discuss with patients at time of initial diagnosis that there is about 11-15% possibility of paradoxical deterioration despite effective treatment. This helps to relieve doubt and worry when there is deterioration after an apparent clinical improvement.

References for articles in this Issue are available on request.