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Calling the shots – post-exposure prophylaxis against viruses

How effective is post-exposure prophylaxis against viruses? This article addresses this issue and offers a rational approach.

Questions about encounters with viral disease and post-exposure prophylaxis (PEP) are very common in general practice, and are frequently referred to us for a specialist opinion. This article is intended to provide a quick guide to the action that can be taken (if any) when a patient has been exposed to a viral disease, whether in the community or hospital setting.

It is worth bearing in mind that many of the following diseases can cause asymptomatic infection and exposed individuals may unknowingly already be immune. So it is often worth while to send a blood sample to the laboratory to check for pre-existing immunity before starting prophylaxis since results can usually be obtained within a few hours.

Recipients of PEP may be infectious and can themselves pose a risk of transmitting infection to other susceptible contacts.

Preventing viral infection relies on three modalities: passive immunisation (immune globulins), vaccination or antiviral therapy. PEP strategies are all summarised in Table I.

A common concern that can be addressed at the outset, relates to uncertainty regarding the safety of immune globulin

preparations, particularly with regard to the possibility of HIV infection. The manufacturing processes used in immune globulin preparation are geared to inactivate viruses and other organisms, and the preparations licensed in South Africa are very safe. Similarly, modern viral vaccines have a good safety profile although possible side-effects of the individual vaccines should be conveyed to patients.

A final general point to consider is that while post-exposure measures may avert clinical disease, in many cases sub-clinical infection will occur. This means that recipients of PEP may be infectious after the usual incubation period, and can themselves pose a risk of transmitting infection to other susceptible contacts.

MEASLES

Measles is highly infectious. The virus is shed in respiratory secretions and has an attack rate of more than 90% in susceptible household contacts. The disease has a high morbidity especially in children less than 1 year of age. In South Africa, outbreaks occur from time to time among unvaccinated individuals or vaccinated individuals with waning immunity. Both human normal immunoglobulin (HNIG) and measles vaccine (given within 72 hours of exposure) can be used to prevent or attenuate an attack in exposed individuals. Immunoglobulin is preferred for babies less than 6 months of age and for severely immunocompromised individuals.

Table 1. Summary of post-exposure measures for common viral diseases

Virus	Period of infectivity	Context	PEP	Dose	Efficacy	Comments
Hepatitis A	14 days before onset of jaundice until 7 days after	Household or community contacts If immuno-compromised or pre-existing liver disease	HNIG/ hepatitis A immune globulin (200 IU/2 ml) or vaccine (< 2 weeks post exposure)	0.02 -0.04 ml/ kg 2 doses a month apart As above	HNIG alone: 47 - 87% Vaccine alone: 79 - 95%	Vaccine favoured unless > 2 weeks since contact. In this case vaccine + immune globulin is recommended Vaccine and immune globulin should be given at different sites if given simultaneously
Hepatitis C	Consider infectious if HCV antibody or HCV RNA-positive	Percutaneous or mucocutaneous exposure to blood, body fluids	No effective prophylaxis			Follow-up testing advised at 6, 12 and 24 weeks
Hepatitis B	Infectious if hepatitis B surface antigen-positive	Mucocutaneous exposure to blood, body fluids	Hepatitis B immune globulin (200 IU/2 ml) and vaccine	< 5 years: 200 IU 5-9 years: 300 IU >10 years: 500 IU 3 doses at monthly intervals	HBIG alone or vaccine alone: 75%	Vaccine and immune globulin should be given at different sites if given simultaneously History of complete immunisation and previous laboratory confirmation of immunity, regard patient as immune (no action necessary) History of complete immunisation, but no laboratory confirmation of immunity, check hepatitis B surface antibody. If >20 IU/ml, no further action. If <10 IU /ml, regard as non-immune
		Institutional or household contacts (no defined exposure)	Vaccine	3 doses at monthly intervals		
		Newborns of hepatitis B surface antigen-positive mothers	Mother eAg-positive: hepatitis B immune globulin and vaccine, 1st dose at birth Mother eAg negative: vaccine only, 1st dose at birth	Immune globulin 200 IU 3 doses vaccine at monthly intervals	HBIG + vaccine: 85 - 95%	Treatment should be commenced < 72 hours post delivery Vaccine and immunoglobulin should be given at different sites if given simultaneously

Virus	Period of infectivity	Context	PEP	Dose	Efficacy	Comments
HIV	HIV antibody-positive or antibody-negative but p24 antigen/PCR-positive	Mucocutaneous or percutaneous exposure (incl. sexual exposure)	Low-risk exposure – small volume of blood/body fluids, source patient asymptomatic, superficial injury, mucocutaneous exposure: 2-drug regimen High-risk exposure – large volume of blood, source patient with high viral load, visible blood on needle, hollow bore needle, deep puncture: 3-drug regimen	AZT 200 mg tds 3TC 150 mg bd for 4 weeks as above + protease inhibitor: indinavir 800 mg tds or Kaletra® 400/100 mg bd	79% for AZT alone	If source virus suspected to be resistant, seek expert advice on suitable drug combinations Drug toxicity monitoring required, drug substitutions possible if toxicity/side-effects (see text) HIV exposure in pregnancy: If < 14 weeks, consider using AZT alone Follow up testing advised at 6, 12 and 24 weeks.
Influenza	From onset of symptoms until 5 days later	To control an outbreak in an institution, or to prevent secondary cases in a family	Amantadine or Zanamivir	> 10 years: 100 mg bd < 10 years: 5 mg/kg/day in 2 divided doses 10 mg daily (inhaled) for 10 days 1 dose if > 1 year if < 1 year, repeat at 15 months 0.2 - 0.25 ml/kg (max 15 ml)	70 - 90% 84%	Give prophylaxis to all inmates (including those who have been vaccinated) for 2 weeks or until 1 week after last case Effective only against influenza A Neurological side-effects common in the elderly Give therapeutic dose to index case to decrease period of shedding: zanamivir 10 mg bd x 5 days Vaccine not suitable for contacts < 6 months old Immune globulin recommended for immunocompromised contacts
Measles	3 days before onset of rash to 5 days after	Household or community contacts	Vaccine (< 72 hours post exposure) or Normal immunoglobulin		Not accurately quantified	
Mumps	6 days before swelling to 9 days after		No effective prophylaxis			
Rubella	7 days before to 10 days after onset of rash	Pregnant women	No effective prophylaxis			See text
Rabies	Consider infectious from 1 week before the animal displays abnormal behaviour	Exposure to saliva of rabid animal, or possibly rabid animal (see text)	Low-risk exposure – superficial scratch, licking of unbroken skin: vaccine only	Vaccine on days 0, 3, 7, 14, 28 into deltoid (adults) or antero-lateral thigh (infants)	> 99% for all categories of exposure if timeous and correctly administered	Thorough cleaning of the wound is paramount If treatment initiated > 48 hours post exposure, or if subject is immunocompromised, double dose of vaccine should be given on day 0

Virus	Period of infectivity	Context	PEP	Dose	Efficacy	Comments
			High risk exposure – bites/scratches which penetrate the skin, licking of broken skin/mucous membranes; rabies immune globulin on day 0 (300 IU/2 ml) and	20 IU/kg infiltrate around the wound, remainder into buttock		Although no case of human to human transmission has been recorded, medical personnel caring for a rabies victim should receive a course of vaccination, as for a low-risk exposure
Varicella	2 days before onset of rash until all the lesions have scabbed (usually 6 days after onset of rash)	Neonates Immuno-compromised	vaccine ZIG (200 IU/2ml) (preferred) or	vaccine as above 0-5 years: 2 ml 6-10 years: 4 ml 11-14 years: 5 ml > 15 years: 6 ml	Efficacy of ZIG alone not quantified in any context	Neonates exposed in utero: ZIG does not reduce attack rate, but ameliorates disease and reduces mortality
		Pregnant women	Aciclovir from day 7-21	Adults: 800 mg 5 x daily Children 40 mg/kg/day in 4 divided doses	84%	Vaccine is safe for children with haematological malignancies who are in remission and also HIV-positive children with CD4 counts > 250, but its efficacy for PEP in these groups is not known
		Healthy non-immune contacts	Vaccine (< 72 hours post exposure) or aciclovir from day 7 - 21 post exposure	< 13 years: 1 dose >13 years: 2 doses 4 weeks apart 800 mg 5 x per day	< 13 years: 1 dose 90% >13 years: 2 doses 4 weeks apart	PEP in pregnancy not proven to prevent fetal infection/congenital varicella syndrome

MUMPS

Mumps virus circulates freely in South Africa because there is no national childhood vaccination policy. There is no evidence that post-exposure administration of either normal immunoglobulin or mumps vaccine will protect an individual from clinical disease. Fortunately, serious complications are rare.

RUBELLA

Like mumps, rubella circulates freely in South Africa. It is rarely associated with significant complications other than in instances of fetal infection. Infection in the first trimester of pregnancy is associated with serious congenital abnormalities in approximately 80% of cases. If infection occurs beyond 18 weeks of gestation, rubella no longer poses a risk to the fetus.

There is no form of PEP that is of proven efficacy for preventing fetal infection and fetal abnormalities. For women for whom termination of pregnancy is not an option, the administration of a high dose of human normal immune globulin (750 mg) intramuscularly as soon as possible post exposure is advised. This does not prevent infection, but it may reduce the viraemia, attenuate the clinical disease, and reduce the risk to the fetus.

INFLUENZA

Influenza is highly infectious and has a significant morbidity and mortality in the very young and the elderly. Annual vaccination remains the most effective way of preventing influenza. However, prophylaxis with certain anti-influenza drugs is also effective in protecting against disease when vaccination has been neglected. As the incubation period for influenza is short (48 hours), prophylaxis needs to be given very promptly.

There are two contexts where PEP for influenza has been used:

- to control an outbreak in an institution
- to prevent secondary cases within a family.

Prophylaxis may be requested in other contexts, for example by leading sports people taking part in a competitive event during a period of recognised influenza activity (such as occurred during the Olympic games in Sydney in 2000).

In South Africa two antiviral agents are available for treatment and prophylaxis of influenza. Amantadine has been available for many years, but it has activity against influenza A only, and has significant side-effects. The newer neuraminidase inhibitors, zanamivir (administered by inhalation) and oseltamivir (orally) have activity against both influenza A and B and have few side-effects. Only zanamivir is currently licensed in South Africa. The use of these drugs for influenza prophylaxis is described in Table I.

VARICELLA

Chicken pox is highly infectious, with an attack rate of 90% in susceptible household contacts. Transmission occurs through respiratory secretions as well as contact with skin lesions, including the skin lesions of shingles. Note that patients with shingles may be a source of chicken pox infection, but the converse is not true; contact with chicken pox does not lead to shingles!

Three agents can be used as PEP to prevent clinical chicken pox or reduce disease severity:

- Zoster immune globulin (ZIG) is a high-titre preparation of human antibody against varicella zoster virus (VZV), prepared from the serum of people who

have recently had shingles. It contains a defined quantity of anti-VZV antibodies, expressed in international units (IU). ZIG is in relatively short supply and should be reserved for patients who are at the highest risk of serious complications (see below).

- Varicella live attenuated vaccine was licensed for use in South Africa in 2002.
- Aciclovir and related drugs (valaciclovir, famciclovir) have specific activity against herpes simplex and varicella zoster virus, but the effective oral dose for varicella zoster is four times higher.

The recommended form of PEP following VZV exposure depends on the context:

- **Healthy non-immune contacts**. Either vaccine (if given < 72 hours post exposure) or prophylactic aciclovir (from day 7 to 21 post-exposure) is suitable.
- **Pregnant women**. Varicella may cause more severe disease in pregnant women, especially in the third trimester. If infection occurs in the first 20 weeks of pregnancy, there is a small risk (2%) of congenital varicella syndrome. Thus a seronegative woman who has been exposed to chicken pox at any stage of pregnancy should receive ZIG. If ZIG is not available, aciclovir is regarded as a safe second option in pregnancy.
- **Neonates**. The risk of severe chicken pox in neonates and pre-term infants is greatest (30% mortality) when the infant lacks protective maternal anti-varicella antibodies. The usual scenario is when the mother develops chicken pox during the final days of her pregnancy. If the mother's rash emerges 7 or more days before delivery, the baby will be protected by mater-

nal antibody at birth and is not at risk. If, however, the disease erupts *within* 7 days of delivery and up to 28 days post delivery, the baby is unprotected and should be given prophylaxis in the form of ZIG. Eruption of shingles in the mother during pregnancy or in the perinatal period is not regarded as a serious risk to the baby as it will be protected by maternal antibody.

Note that babies of varicella-immune mothers are protected by maternal antibody in the neonatal period, but this immunity soon wanes, rendering the infant susceptible by 2 - 3 months of age. Effectively, post-exposure ZIG is probably advisable for any infant up to the age of 6 months.

- **Immunocompromised patients** . In this group, children with haematological malignancies are particularly at risk. Although varicella causes a higher rate of complications in those infected with HIV, it does not usually result in fulminant disease. Nevertheless, post-exposure prophylaxis is still advised. The varicella vaccine has been shown to be safe and effective for most categories of immunocompromised patients. However, the protective efficacy of *post-exposure* vaccine may be lower than in healthy recipients, and ZIG is advised in this context.

HEPATITIS A

Hepatitis A virus (HAV) has a significant morbidity in adults and may (rarely) be fatal at any age. The prevalence is high in South Africa, but varies in different communities. In poorer communities, most people are infected in childhood, but in more affluent communities, up to 50% of adults will have no immunity. The hepatitis

A virus is shed in the stool and is acquired by ingestion.

There are two approaches to protecting non-immune individuals following hepatitis A exposure, namely passive immunisation by administration of antibody or active immunisation with a vaccine:

- Human normal immunoglobulin (HNIG) contains a defined amount of anti-HAV antibody that provides short-lived protection. With the advent of an effective vaccine, the use of HNIG for hepatitis A prophylaxis is declining.
- Hepatitis A vaccine is a cell culture-derived, formalin-inactivated vaccine. Either HNIG or the vaccine, or both, can be used for hepatitis A prophylaxis. The recommendations are given in Table I.

HEPATITIS B

In the medical setting, hepatitis B virus (HBV) is mainly spread by percutaneous exposure to blood and body fluids of infected individuals, with the risk of transmission as high as 60% when the source is e antigen-positive (Fig. 1). However, in the community, transmission occurs more commonly through sex or close personal contact, and the disease prevalence peaks in toddlers and again in young adults. About 5% of adults and a greater percentage of children will go on to be chronically infected. Childhood vaccination against hepatitis B, initiated in South Africa in 1995, should reduce the disease prevalence within two decades. Post exposure, infection can be prevented in non-immune individuals with the use of immune globulin or vaccine.

- Hepatitis B immune globulin (HBIG) is prepared from serum of immune individuals. It contains a defined amount of anti-

body to the surface protein of hepatitis B (surface antibody).

- Hepatitis B vaccine consists of purified hepatitis B surface protein (surface antigen). The serum-derived vaccine is prepared from the serum of hepatitis B carriers and the recombinant vaccine is synthesised in yeast through recombinant DNA technology. They are equally safe and effective. Vaccine alone, or HBIG and vaccine in combination, are used prophylactically, depending on the context:
- **Household/institutional exposure.** Sexual partners, children and individuals in the same household as a (newly identified) HBV-infected individual are at risk of infection and should be vaccinated, if they are not already immune.
- **Non-immune contact with definite exposure.** In instances such as occupational exposure to a HBV-positive source, or perinatal exposure when the mother is an HBV carrier, both HBIG and initiation of vaccination are indicated, within 72 hours (see Table I).
- **Vaccinated contacts with definite exposure.** See Table I for guidelines.

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- **Rape.** The prevalence of hepatitis B in South Africa and the highly infectious nature of the virus are reasons for routine hepatitis B vaccination following rape. In the unusual circumstance that the perpetrator is *known* to be a hepatitis B carrier, HBIG is indicated as well.

HEPATITIS C

Hepatitis C virus (HCV) is another parenterally transmitted cause of hepatitis, with the risk after percutaneous exposure estimated to be around 2%. Infection is also transmitted vertically (mother to child) and through sexual contact, but the risk is low. Up to 80% of infected patients fail to clear the virus and are at risk of chronic liver disease. There is no effective PEP for hepatitis C. Health care workers who are exposed to infected blood should be monitored, as early treatment of hepatitis C infection is more effective than if it is delayed.

The exposed person should be tested for HCV RNA at 6 and 12 weeks after exposure and for HCV antibody at 12 and 24 weeks.

RABIES

A detailed description of rabies PEP is not feasible in this article. Readers are referred to the Department of Health website for comprehensive information and contact details and state sources of vaccine and rabies immunoglobulin (available on the internet at <http://www.nbi-kzn.org.za/inter-est/contrabi.htm>). What follows is an outline of the DOH guidelines.

In South Africa dog bites are the cause of most of the 20 - 30 annual human cases of rabies and geographically most of these cases occur in KwaZulu-Natal. The risk of contracting rabies following a bite by a rabid animal varies according to the site and severity of

the bite(s), but overall the figure is around 50%. Rabies carries a 100% mortality in humans. The decision to embark on prophylaxis depends on an assessment of the likelihood that the attacking animal was rabid. Should there be a possibility that the animal was rabid, the extent of the prophylactic measures depends on the severity of the exposure (bite versus superficial scratch or licking of broken skin).

An evaluation of the risk of rabies in the animal can be based on 5 questions:

- Is rabies prevalent in the area?
- Was the animal abnormal in any way?
- Was the attack unprovoked?
- Is the animal known to have been exposed to rabies?
- Was the animal immunised against rabies?

If the answer to any of the first four questions is yes (or don't know) or the answer to question 5 is no (or

don't know), prophylaxis should be initiated. Under no circumstances should prophylaxis be delayed awaiting confirmation of the diagnosis in the animal.

In many instances it is difficult to rule out the possibility of exposure and if a query remains, a 'better safe than sorry' approach should prevail. Even late reporting of possible rabies exposure must be assessed and treated. There is no cut-off time for starting rabies PEP. Rabies prophylaxis involves the use of a combination of vaccine and immunoglobulin:

- Human anti-rabies immunoglobulin is prepared from the serum of rabies vaccine recipients. Since the purpose of the immune globulin is to neutralise the virus, as much globulin as possible should be infiltrated around the wound.
- The rabies vaccine used in

South Africa is an inactivated, cell culture-derived vaccine which is completely safe. Bite victims who have been previously immunised should receive 2 booster doses of vaccine (immunoglobulin is not indicated).

Note that the sites of injection of rabies vaccine and immune globulin are critical (see Table I.)

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The general practitioner is often faced with a situation where there is a definite risk of HIV infection and PEP is clearly indicated; for example after occupational exposure or rape. However, cases may arise where the appropriate intervention is less clear cut, for example, an injudicious sexual encounter ('one night stand'), a good Samaritan helping at an accident

site, or highly anxious individuals presenting with a wide range of possible exposure situations from the feasible to the highly improbable. In these contexts common sense and compassion must be exercised, and PEP may or may not be necessary.

Occupational exposure

In the health care setting, HIV is spread by percutaneous or mucocutaneous (typically a splash in the eye) exposure to infected blood or body fluids. The average risk of transmission is 0.3% and 0.1% respectively. Used as PEP, anti-retroviral drugs selectively block steps in the virus replication cycle and prevent establishment of an infection. Animal studies and follow-up studies of occupational exposures have confirmed that these drugs are indeed effective.

International recommendations are for a two- or three-drug PEP regi-

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men, where three drugs are given for higher risk exposures (see Table I), although there are no direct data supporting the use of the 2nd and 3rd drugs. The two-drug regimen consists of two nucleoside reverse transcriptase inhibitors. If the usual combination of zidovudine (AZT) and lamivudine (3TC) is poorly tolerated, AZT can be replaced by stavudine (D4T). Alternatively, a combination of D4T and didanosine (ddI) can be used. For the three-drug regimen, a protease inhibitor is added, usually indinavir, although Kaletra (lopinavir/ritonavir) may be a better choice due to the lower potential for toxicity (Gary Maartens, personal communication). Although nevirapine would seem to be ideal for PEP, it is precluded from the recommendations because of a few cases of severe (fatal) hepatitis occurring during 28-day prophylactic therapy.

If there is reason to suspect that the source virus is drug-resistant, the prophylactic regimen would need to be devised accordingly, usually with a three-drug regimen.

Since the potential benefits of HIV PEP usually outweigh the risks, PEP is recommended for exposed pregnant women, although the safety of none of the antiretroviral drugs in pregnancy is certain. Most safety data exist for the use of AZT, and prophylaxis with AZT as a single agent is advised for women who have been exposed in the first 14 weeks of pregnancy.

It is imperative that the drugs be given as soon as possible after exposure (preferably within 1 hour), but they may still be effective if given up to 72 hours post exposure. The longer the delay, the higher is the risk of failure. Animal studies support the efficacy of a 4-week regimen. There are no data on whether a shorter course of therapy would be as effective.

Most antiretroviral drugs have side-effects and may be poorly tolerated. PEP recipients should be forewarned; symptoms may be manageable with additional medications such as an antiemetic, and analgesia for headache. Toxicity monitoring depends on the toxicity profile of the drugs used as prophylaxis. For the standard AZT/3TC combination, a full blood count and liver function tests should be done at the beginning of therapy and repeated 2 - 4 weeks later.

Prophylaxis recipients should be counselled and advised to practise safe sex until the three-month follow-up test.

Rape or injudicious sexual encounter

The risk of HIV transmission through sexual contact is approximately 0.1 - 1% per sexual encounter (somewhat higher for receptive anal sex), but is presumed to be increased in the case of rape. Usually the HIV status of the assailant/partner is unknown. Rape victims should therefore be offered antiretroviral prophylaxis, which should be initiated along with prophylactic measures against other STDs, within 72 hours of the assault. The same regimens used for occupational exposures are appropriate.

Mother-to-child transmission

Prophylaxis in the context of mother-to-child transmission is not strictly PEP and is beyond the scope of this article. However, if a neonate has been exposed to HIV during delivery and the mother's status is only discovered afterwards, the baby should be given prophylaxis with AZT (2 mg/kg 6 hourly) for 6 weeks. Ideally, therapy should be started within 72 hours of birth.

FURTHER READING

British Public Health Laboratory Service Immunoglobulin Handbook:

http://www.phls.org.uk/topics_az/immunoglobulin/immunoglobulinHandbook.pdf

Gibbon C.J. *South African Medicines Formulary*, 5th ed. Cape Town: South African Medical Association Publishing Group, 2000.

MMWR Recommendations and reports, June 29, 2001/50 (RR11):1-41:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm>

South African Department of Health guidelines on rabies prophylaxis:

<http://www.nbi-kzn.org.za/interest/contrabi.htm>

Updated US Public Health Service guidelines for the management of occupational exposures to HBV, HCV and HIV and recommendations for post-exposure prophylaxis.

US Department of Health and Social Services guidelines on post-exposure prophylaxis for HIV and prevention of mother to child transmission:

<http://www.aidsinfo.nih.gov/guidelines/>

IN A NUTSHELL

Certain viral infections can be prevented in susceptible contacts with the timely use of vaccines, immunoglobulin or antiviral drugs.

Active immunisation post exposure is usually the most effective means of preventing infection with hepatitis A, B, measles, rabies and varicella.

If PEP is delayed, or the patient has had a high-risk exposure, a combination of immunoglobulin and vaccine is advised.

Live attenuated vaccines are contraindicated in immunocompromised patients, very young babies and pregnant women, and these individuals should receive immuno-globulin only, for example following exposure to varicella or measles.

Specific antiviral drugs can be used to prevent HIV, influenza or varicella.

Where no reliable prophylaxis is available, careful follow-up and early intervention are essential, for example after rubella exposure in pregnancy and hepatitis C exposure in health care workers.