Post Exposure Prophylaxis: What To Do Before It's Too Late

Jason Lancaster, PharmD
Assistant Clinical Professor
Northeastern University

Objectives

- Differentiate events and exposures that require post exposure prophylaxis from those that do not
- Outline the use of vaccines in adults to eradicate certain diseases
- Evaluate the need for the administration of newer vaccines
- Given a patient case, determine appropriate vaccine and/or hyperimmune therapy

Topics to be Reviewed

- Review of immunization modalities:
  - Vaccines, toxoids, immune globulin
- Review of active and passive immunization
- Focus on common exposures:
  - Rabies
  - Tetanus/Tdap
  - Hepatitis A/B

Patient Case 1

- AS is a 38 yo man who presents to your pharmacy counter with triple antibiotic ointment and bandages
- AS states that while opening up his summer home in Maine he discovered a family of bats living in the attic.
- While trying to "encourage" the bats to leave with a broom, AS was bitten by a bat on his left arm approximately 4 hours ago. Subsequent to the bite, the bat then flew out the window.

Appropriate Options

Which one of the counseling points should we recommend to AS?

A. AS should wash the wound with soap and water before using the triple antibiotic ointment
B. AS should use the triple antibiotic cream, rather than the ointment, as the cream is more effective
C. AS should get some isopropyl alcohol to wash the wound and then go to the emergency room
D. AS should get some povidone iodine to wash the wound and then go to the emergency room

Immunization Modalities

- Vaccines:
  - Derived from the infecting organism
  - Stimulates an immune response via immunogen
- Toxoids:
  - Inactivated bacterial toxins that stimulate the formation of antitoxin
- Immune Sera:
  - Antibody derived from human sources

Vaccines

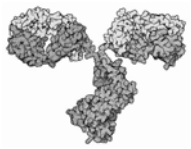
- Viral or Bacterial:
  - Live attenuated:
    - Live particles with minimal virulence
  - Killed:
    - Virus particles are grown and killed in a controlled environment
    - May require booster dose(s)
  - Subunit:
    - Purified virus or viral antigens
- All vaccines produce active immunity

Toxoids

- Bacterial toxin that is weakened or suppressed and non-toxic
- Immunogenicity is retained and produces active immunity via antitoxins (antibodies)
- Examples include:
  - Botulinim, tetanus, and diphtheria

Immune Globulin

- Antibody derived from B lymphocytes:
  - IgG subclass 1 (IgG1) is the major component
  - Non-specific (IVIG, IMIG)
  - Disease-specific (rabies, tetanus, hepatitis B)
  - Produces passive immunity



Active vs. Passive

Active Immunity

- May take 7-10 days to detect antibodies
- Most often permanent
- May be inhibited by passive immunization (e.g. MMR with IVIG or maternal antibodies)
- Caution administration in immunocompromised hosts

Passive Immunity

- Acts immediately
- Temporary (days-weeks)
- Human immune serum globulin (IVIG, IMIG)
- Specific immune globulins targeted at a specific agent
- Animal sera/antitoxins

Rabies

- Rabies is a potentially fatal viral disease acquired from exposure or bite from a rabid animal
  - Lyssavirus family
- How common is it:
  - In 2006:
    - 7,000 cases in animals and 3 in humans
  - Since 2000, 24 reported human cases
    - Of which, 23 died subsequent to infection

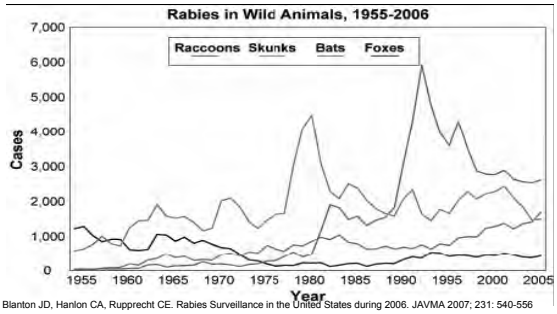
Blanton JD, Hanlon CA, Rupprecht CE. JAVMA 2007; 231: 540-556

Krebs, JW et al J Am Vet Med Assoc 1997: 1025

The where and how of rabies

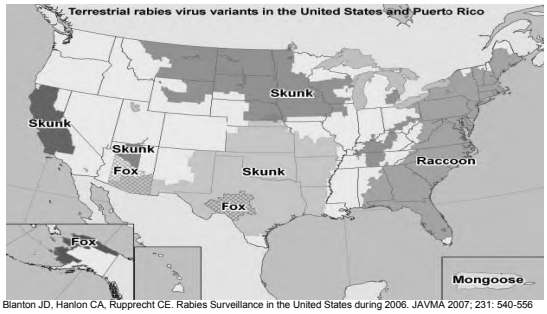
- Where:
  - Largely unknown
  - Documented as far back as 3000 years ago
    - Sanskrit describe a rabies-like disease in 3000 BC
- How:
  - Theorized to have reached the U.S. via pack/sled animals from early settlers
  - Transmitted in warm-blooded mammals via saliva
  - “Rabies-free” countries/continents do exist
    - Australia, France, Ireland, Sweden and the UK

Rabies in the Wild



Blanton JD, Hanlon CA, Rupprecht CE. Rabies Surveillance in the United States during 2006. JAVMA 2007; 231: 540-556

Wildlife Carriers



Blanton JD, Hanlon CA, Rupprecht CE. Rabies Surveillance in the United States during 2006. JAVMA 2007; 231: 540-556

Assessment of Risk

- Type of Exposure:
  - Bite:
    - Risk increases with the number of bites and bites closer to the CNS
  - Non-bite exposure (two conditions must be met):
    1. Exposure must be to the mucus membranes or open wounds
    2. Animal tissues making contact must be potentially infectious (i.e. saliva, neural tissue)
    - Blood/feces don't count
- Provoked vs. Unprovoked
- Type of animal

Urgency Versus Emergency

- Wound care:
  - Thorough washing with an virucidal agent (povidone iodine)
    - Iodine is also bactericidal, fungicidal, tuberculocidal and sporicidal
    - Alcohol is not sporicidal and can form a coagulum where bacteria can become trapped and proliferate
- Isolation of the animal
  - Testing of neural tissue, results may take 1-4 days
  - Watching of domestic animal for 10 days
- Timing of prophylaxis:
  - Administer as soon as possible
  - Latency periods of 1-2 months have been reported

McDonnell G, Russell AD. Clin Microbiol Rev. 1999;12:147–79

Post-exposure Agents

- Utilization of post-exposure agents:
  - 16,000-39,000 people in the U.S. receive rabies post-exposure prophylaxis annually
  - Cost of therapy is $1500 for biologics alone

To Give or Not To Give

- Inappropriate in 40% of patients to whom it was given
  - Most common mistake was that an available animal for testing was not tested
- Inappropriately withheld in 6.3% of patients
  - Most common mistake was exposure in high endemic areas from an animal unavailable for testing

Moran G, et al: JAMA 2000;284: 1001-1007

Who Should Receive Prophylaxis?

- Two very clear groups:
  - Those with an exposure from a rabies positive animal
  - Those with an exposure from an unavailable animal in a highly endemic area
- What about all others?
  - CDC recommends that those who are unable to/poor historians receive prophylaxis
  - For those who do not fit this criteria, best clinical judgment is advised

Post Exposure Prophylaxis

- Patients not previously vaccinated:
  - 5 doses of rabies vaccine: days (0,3,7,14,28)
    - Give in deltoid in adults, anterolateral thigh in children
  - Rabies Immune Globulin:
    - 20 IU/kg x 1 dose
    - Infiltrate in and around the wound as much as possible, then administer the remainder IM at a site distant from vaccine administration.
    - Do not give if exposure >7 days prior
    - Do not give other live vaccines within 3 months (MMR)

Post Exposure Prophylaxis

- Patients with previous rabies vaccination:
  - Two doses rabies of vaccine: days 0 and 3
  - Rabies immune globulin should not be administered



Why the current shortage?

- July 2007-Sanofi Pasteur began a renovation of French facilities
  - A stockpile of rabies vaccine was created based on historical usage
  - Facility will continue improvements until mid-2009
- 2008-Novartis was unable to meet US market demands
  - Providing vaccine for post-exposure only
- August 29th, 2008-Sanofi began providing rabies vaccine on a limited basis only

Patient Case Revisited

- AS, 38 yo man presents to the pharmacy:
  - AS was bitten by a bat on his left arm approximately 4 hours ago
  - Bat then flew away

- What question(s) do we need to ask before making any recommendations?

Recommendation for AS

At your tables please devise one recommendation for AS, giving consideration to the information provided

Recommendation for AS

Which one of the recommendations listed is the most appropriate for AS, giving consideration to the information provided?

A. Recommend nothing as the bat is available for testing and was determined not to be rabid
B. Recommend AS receive a 5-dose course of the rabies vaccine
C. Recommend AS receive a 5-dose course of rabies vaccine + rabies immune globulin
D. Recommend AS receive a 2-dose course of rabies vaccine
E. Recommend AS receive a 2-dose course of rabies vaccine + rabies immune globuin

Real-life Tragedy

- In 2004 Jenna Giese, a 15 yo student was bitten by a bat while at church
- Mother treated her bite with hydrogen peroxide and decided against further medical attention
- 37 days later Jenna was admitted to a hospital with tremors and mobility impairment

Jenna Giese's story

- After almost 80 days in the hospital and $600,000 in medical bills Jenna did leave the hospital and was dubbed the "first non-vaccinated rabies survivor" and became only the 6th recorded rabies survivor
- After a year of rehab, Jenna was able to walk on her own, and in 2007 graduated from high school

Tragedy Turned Reality

What is the most tragic part of Jenna's ordeal and story?

That this was all entirely preventable had she received appropriate and early medical intervention

Tetanus

- Neurologic disorder characterized by increased muscle tone
- Caused by a protein (tetanospasmin) elaborated by *Clostridium tetani*
- Usually acquired through puncture wounds, lacerations, or abrasions
  - *C. tetani* is found in the soil

High-risk populations

- Elderly patients:
  - Age related decline in protection against tetanus (<30% in adults older than 70 yrs)
  - Patients older than 60 account for 60% of all cases of tetanus
- Those born outside of the United States:
  - Mexican Americans: <60% immunity rate
  - Korean Americans: <20% immunity rate

Gergen PT, McQuillan GM, Kiely M, et al. NEJM 1995;332:761-6
Alagappan K, Park R, Naderi S, et al. J Immigr Minor Health 2008;Mar 18.doc
Blake, PA et al. JAMA 1976; 235:42
Fedson DS, JAMA 1994;272:1133-7

Vaccination and Prophylaxis

- Primary vaccination series (adults):
  - 3 doses: 0,1 and 12 months
  - Booster doses are given every 10 years
- Prophylaxis therapy is dependant on the vaccination status of the patient:
  - Primary series
  - Uncertain or incomplete primary series
  - Puncture wounds are highest risk, followed by deep lacerations

Prophylaxis

History of previous tetanus immunization	Clean, minor wounds	All other wounds (wounds contaminated with dirt, feces, soil and saliva, puncture, crushing, burns and frostbite wounds)
Uncertain or fewer than 3 doses	Give vaccine only	Give vaccine and tetanus immune globulin
3 or more previous doses	No need to vaccinate, unless ≥10 years since last dose	Give vaccine if ≥5 years since last dose

American College of Physicians Task Force on Adult Immunization and IDSA. Guide for Adult Immunization. 1994

Tetanus Immune Globulin

- Given to patients with questionable immunization history with high risk wounds
- Dose:
  - 250 units IM x 1 dose (prophylactic dose)
  - 3000-6000 units x 1 dose (treatment dose)
    - Dose varies based on severity of infection
- Administer in a different syringe at a different site from vaccine

Patient Scenario 2

- JL an 8 yo screaming and crying boy is brought to urgent care by his parents. JL and his brother were building a tree fort at their house, and upon examination the following is found:

JL continued

- All of JL's childhood vaccines are up to date
- At your tables please formulate one recommendation for JL giving consideration to the information provided

Treatment recommendations

Which one of the following is the best recommendation for JL?

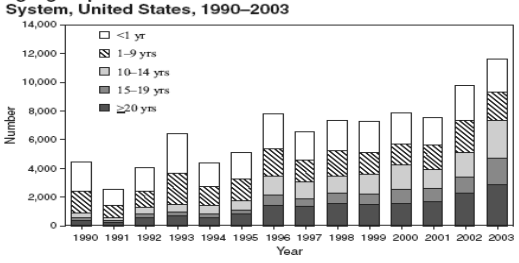
A. Remove the nail and bandage toe, but JL doesn't need a tetanus vaccine
B. Remove the nail and bandage the toe and administer a tetanus vaccine
C. Remove the nail and bandage the toe and administer a tetanus vaccine + immune globulin
D. Remove the nail and bandage the toe and administer immune globulin

Pertussis (Whooping Cough)

- Acute, infectious cough due to a gram negative organism (*B. pertussis*)
- Immunity wanes 5-10 years post vaccination
- Vaccinations:
  - Pediatric: DTap
  - Adolescent and Adult: Tdap

Pertussis in the U.S., 1990-2003

FIGURE 1. Number of reported pertussis cases,* by year and age group — National Notifiable Diseases Surveillance System, United States, 1990–2003



* Confirmed and probable.

MMWR December 23, 2005 / 54(50);1283-1286

Who should be receiving Tdap?

- Adults 19-64 for their next tetanus booster
- Adults with close infant contact
- Prenatal women
- Postpartum women:
  - Who received Tdap ≥10 years ago
  - Who have never received Tdap
- Healthcare workers with patient contact

MMWR Dec 15, 2006/55(RR17) 1-33

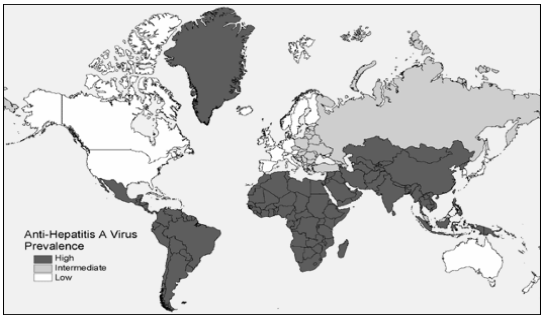
Hepatitis A

- RNA Picornavirus:
  - Produces asymptomatic or symptomatic infection
    - Jaundice , fatigue, nausea, diarrhea, fever
    - CDC reports case fatality is 0.3%
- No chronic (long term) infection
  - Once resolved, lifelong immunity is conferred
- Largely spread via fecal-oral route
  - Found in the stool of persons with hepatitis A

Those at Greatest Risk

- Those living in and traveling to areas with high rates of hepatitis A
- Household contacts of infected persons
- Sexual contacts of infected persons
- Men who have sex with men
- Injecting and non-injecting drug users

Geographic Prevalence of Hepatitis A



http://www.medic8.com/travel/viral-hepatitis-a.htm

Hepatitis A Vaccine

- Two formulations:
  - Both are inactivated viral vaccines
  - May be interchanged if necessary
- Dosing schedule:
  - Two doses: 0 and 6-12 months
- Sero-protection:
  - Achieved within ~4 weeks after first dose
    - 94-100% will have protective antibody titers
  - 2nd dose given to ensure long-term immunity

Use of Immune Globulin (IMIG)

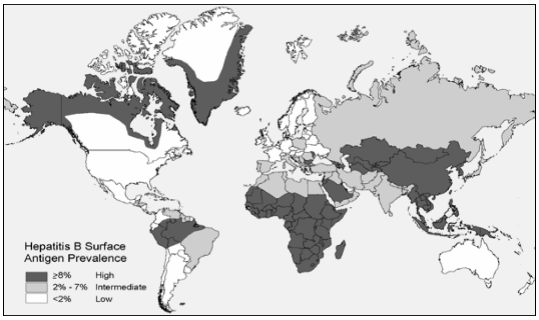
- Given to those exposed to a documented source of hepatitis A:
  - Wolfgang Pucks' Sports Illustrated Swimsuit party
  - Taco Bell®
  - Dose:
    - 0.02 mL/kg x 1 dose
      - Will provide protection in up to 85% of patients
    - The earlier the administration, the better
    - Do not use if exposure >2 weeks prior
  - Caution co-administration with other live vaccines
    - Must wait ≥3 months for MMR and ≥5 months for Varicella

Hepatitis B

- Double stranded DNA Hepadnavirus:
  - Replicates in the liver
  - May cause acute and chronic hepatitis
  - Highest concentration in the blood, but also in serum derived body fluids
  - Incubation period: 45-160 days
- 360 million HBV carriers in the world:
  - 1.5 million in the U.S.
  - 400,000 new cases each year

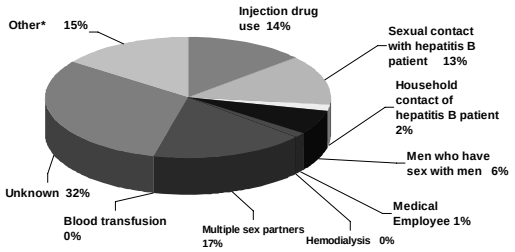
VPD Surveillance Manual 3rd ed. 2002
Maynard, JE Vaccine 1990; 8(Suppl): S18
Wasley A, et al. MMWR. 2007;56.SS-3.

Geographic Prevalence of Hepatitis B



http://www.medic8.com/travel/viral-hepatitis-b.htm

Risk Factors for HBV



*Other: Surgery, dental surgery, acupuncture, tattoo, other percutaneous injury
http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm
Hollinger, FB Gut 1966; 38:24S
Gerberding JL NEJM 1996; 334:594

Risk of Infection

- Adults with normal immune status:
  - 94-98% will recover completely from newly acquired Hepatitis B infections, eliminating virus from blood and producing antibodies

Infants
Young Children
Immunosuppressed

⇒ Newly acquired Hep B virus more likely to result in chronic infection

VPD Surveillance Manual 3rd ed. 2002

Newer Considerations

- Immigrants to the U.S.:
  - Higher prevalence than those born in the U.S.
- Pregnancy:
  - Prevention of perinatal transmission
- Routine vaccination:
  - All children born in the U.S.
  - Vaccinating adults in high risk groups
    - IVDA, etc

MMWR June 29, 2001, Vol 50, RR-11
MMWR May 12, 2006/ 55(18);505-509

Hepatitis B Vaccine

- Adult schedule:
  - Three doses: 0,1, and 6 months
  - First dose should be administered within 12 hours of exposure
- Check antibody titer 1-2 months after series
  - Not routinely done, only to be done for certain patient populations
    - Responder: >10mIU/mL anti-HepB surface antigen (anti-HBs)
    - Non-Responder: <10mIU/mL anti-HBs
- Risk factors for failure to respond:
  - Obesity
  - Smoking
  - Age >50
  - Immunosuppressed

Hepatitis B Immune Globulin (HBIG)

- Dose:
  - 0.06 mL/kg IM x 1 dose
- Indications for use:
  - Dependant on prior history of immunization and documented response of exposed person
  - Perinatal to prevent maternal transmission to infant
- Efficacy:
  - Greatest when administered <7 days post exposure

Hep B Prophylaxis

Vaccination history and antibody response of exposed person	Source is HBsAG+ (indicates active hep B)	Source is HBsAG-	Source not tested or unknown status
Unknown vaccination	HBIG + vaccine series	Vaccine series	Vaccine series
Previously vaccinated	No treatment necessary	No treatment necessary	No treatment necessary
Known responder	No treatment necessary	No treatment necessary	No treatment necessary
Known non-responder	HBIG + vaccine series	No treatment necessary	If high risk source, treat like HBsAG+
Unknown antibody response	Test exposed person and follow above	No treatment necessary	Test exposed person and follow above

American College of Physicians Task Force on Adult Immunization and IDSA. Guide for Adult Immunization. 1994

Hepatitis Patient Case

- ME is a 34 year old outpatient nurse who presents to the employee health department of the hospital after an accidental needle stick.
- ME states that the needle stick occurred after she was checking the patients blood glucose and the lancet slipped while removing it from the device, causing the lancet to stick in her right index finger.

Hepatitis case cont.

- The patient is a known hepatitis B carrier (HBsAG+).
- The nurse has received the primary hepatitis B vaccination series, and a titer preformed 2 months after her series was found to be 5 mIU/mL anti HBs.
- ME also had a tetanus booster 3 years prior

Options for ME

Which one of the options below is the best recommendation for ME?

A. ME was previously vaccinated and no treatment is necessary
B. ME was previously vaccinated but she needs immune globulin
C. ME was previously vaccinated but needs to be re-vaccinated
D. ME was previously vaccinated but needs to be re-vaccinated and receive immune globulin

Points to Remember

- Many times post exposure prophylaxis does not require the administration of passive immunity
- Certain patient populations (elderly, children, immunosuppressed) are at greater risk and should be given special consideration
- When administering passive and active immunity, give injections at different sites

QUESTIONS?

Email: J.Lancaster@NEU.EDU
Tel: 617-373-2655

References

- Blanton JD, Hanlon CA, Rupprecht CE. Rabies Surveillance in the United States during 2006. JAVMA 2007; 231: 540-556
- Krebs, JW et al J Am Vet Med Assoc 1997: 1025
- McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev. 1999;12:147–79
- Moran G, et al: JAMA 2000;284: 1001-1007
- Gergen PT, McQuillan GM, Kiely M, et al. A pop-based serologic survey of immunity to tetanus in the US. NEJM 1995;332;761-6
- Alagappan K, Park R, Naderi S, et al. Eval for tetanus antibodies in korean-americans living in the NY area. J Immigr Minor Health 2008;Mar 18
- Blake, PA et al. JAMA 1976; 235:42
- Fedson DS, JAMA 1994;272:1133-7
- American College of Physicians Task Force on Adult Immunization and IDSA. Guide for Adult Immunization. 1994
- MMWR December 23, 2005 / 54(50);1283-1286
- MMWR Dec 15, 2006/55(RR17) 1-33

References cont.

- http://www.medic8.com/travel/viral-hepatitis-a.htm
- VPD Surveillance Manual 3rd ed. 2002
- Maynard, JE Vaccine 1990; 8(Suppl): S18
- Wasley A, et al. MMWR. 2007;56.SS-3
- http://www.medic8.com/travel/viral-hepatitis-b.htm
- http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm
- Hollinger, FB Gut 1966; 38:24S
- Gerberding JL NEJM 1996; 334:594
- MMWR June 29, 2001, Vol 50, RR-11
- MMWR May 12, 2006/ 55(18);505-509