A Guide to Vaccinating Patients with Cirrhosis and IBD

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Timeline for vaccine development and Licensure

Nable GJ. NEJM 2013;368(6):551
History of Vaccine Development

- More than 70 vaccines licensed since 1923 against 30 microbes (starting with diphtheria)
- Hep B (plasma-derived 1981, recombinant 1986);
- Hep A inactivated vaccine 1996
- Major targets still unfulfilled: HIV, malaria, hepatitis C  \textit{(as no natural immunity to infection exists for a vaccine to mimic)}

\textit{Nabel NEJM 2013;368:551}

Vaccination Guidelines

- CDC Advisory Committee on Immunization Practices (ACIP) \[Ann Intern Med 2013; 158 (3; Feb 5): 191\]
- World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) \[www.who.int/immunization/sage/en/\]
- AASLD \[Hepatology 2009; 49 (4): 1335 \]
- American Society of Transplantation (AST) Infectious Diseases Community of Practice - guidelines for vaccination of solid organ transplant candidates and recipients \[Am J Transplant 2009;9(suppl 4):S258\]
Challenges and Concerns Regarding Vaccinating Patients with Cirrhosis or IBD

- Use of live virus vs inactivated vaccines in immunosuppressed patients
- Reduced response rates in cirrhosis, renal failure, HIV and IBD
- Is HAV vax in HCV cost-effective
- QI and CMS recommendations and utilization reviews for vaccinations
- Morbidity of failure to vaccinate
2013 CDC Vaccination Recommendations - Main Messages

- Live vaccines (Varicella, Zoster, MMR): **contraindicated** in pregnancy, immunocompromised, HIV CD4<200
- Chronic liver disease: **no contraindications** for any vaccine (except for live virus influenza)
- IBD on long-term steroids, biologics: **considered immunosuppressed**

Recommended Adult Vaccines

For Chronic liver disease patients

- For all persons lacking immunity and meeting age requirements: influenza, tetanus/diphtheria/pertussis; varicella, HPV, zoster, measles/mumps/rubella(MMR), pneumococcal, Hep A, Hep B
- **Contraindicated**: none
- Recommended only if a risk factor is present: meningococcal
Recommended Adult Vaccines

For immunocompromising conditions
(excluding HIV)
- For all persons lacking immunity and meeting age requirements: influenza, tetanus/diphtheria/pertussis; HPV, pneumococcal
- **Contraindicated**: varicella, zoster, measles/mumps/rubella (MMR)
- Recommended only if a risk factor is present: Hep A, Hep B, meningococcal

Recommended Adult Vaccines

For health care personnel; diabetics; renal failure and dialysis patients
- For all persons lacking immunity and meeting age requirements: influenza, tetanus/diphtheria/pertussis; varicella, HPV, zoster, measles/mumps/rubella (MMR), hepatitis B
- **Contraindicated**: none
- Recommended only if a risk factor is present: pneumococcal, meningococcal, hepatitis A
2013 CDC Recommendations for Hepatitis A and B Vaccination in non-Chronic Liver Disease Groups

- Pregnant or meets definition of immunocompromised: give if a risk factor is present for either A and/or B
- HIV: HAV only if risk factors present; HBV for all persons regardless of CD4 count
- MSM: both A and B for all persons
- Heart disease, COPD, chronic alcoholism, asplenia or complement deficiencies: give if risk factors present for A and/or B
- CKD on HD, diabetics: A only if risk factors; B for all persons

Recommended Adult Vaccines

**Influenza**

- Inactivated influenza vaccine (IIV) recommended annually from age 6 months
- IM or intradermal IIV can be used for adults 18-64
- Intranasal live attenuated influenza vaccine (LAIV) for healthy nonpregnant persons aged 2-49
- Health care personnel who care for severely immunocompromized persons should avoid LAIV
- Adults >65 can receive standard or high-dose IIV (Fluzone high-dose)
Vaccination of Hepatitis C Patients

- **AASLD Recommendation #63.** 
  "All persons with chronic HCV infection who lack antibodies to hepatitis A and B should be offered vaccination against these two viral infections (Class IIa, Level C)."

_Ghany et al._ Hepatology 2009; 49 (4): 1335

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Prospects for a HCV Vaccine

- Infectious cell culture system not developed until 2005 - limited understanding of immune evasion of HCV
- Chimps remain the only in vivo model - limited by ethical and cost concerns
- Large genetic diversity of the virus
  - 30-35% dissimilarity across 7 genotypes; multiple quasispecies
  - Positive sense single stranded RNA replicates its genome through a highly error-prone polymerase
- Likelihood of escape mutants is high for any vaccine designed against a limited number of epitopes
Hep A Vaccine in Cirrhosis

- Recommended by AASLD guidelines for HCV and HBV (to reduce the >20-fold increase in mortality from acute HAV superinfection)
- Recommendation of the 2013 US Advisory Committee on Immunization Practices for pts with CLD
  *(Ann Intern Med 29 Jan 2013)*

Hepatitis A and B vaccination in CLD: How Often is it Done?

- A and B recognized as quality of care indicator by CMS
- Frequency of administration remains below accepted standards:
  - only 32-42% receive B vax
    *(NHANES, VAMC databases)*
  - only 20-38% receive A vax for CHCV

*Leise & Talwalker Curr Gastro Rep 2013;15:300*
Immunogenicity of HAV Vaccine in cirrhosis

- Seroconversion rates:
  - Child A = 71%; 98% after booster
  - Child B or C = 37%; 66% after booster
  - Serum antibody concentrations significantly lower in decompensated groups (*Hepatology* 2011;34:28)

Cost-effectiveness of Hep A Vaccine in CLD

- High background seropositivity rates reduce the cost-utility of universal vaccination strategy
- Younger patients have lower baseline immunity rates
- Targeted strategy for anti-HAV negative pts had cost of $51K per QALY vs $3.9 million for universal vaccination (reducing infections from 67 to 5 per 100K vs preventing only 1 additional infection in the universal group)  
  \[Am J Gastro 2002;97:721\]
- Not cost-effective under any circumstances in HCV pts in a recent study  
  \[Vaccine 2010;28:1726\]
Recommendations for HAV Vaccine in CLD: Summary

- Cost-utility remains unproven
- Decompensated cirrhotics have low seroconversion rates but benefit the most from vaccination and post-vaccination testing
- Post-vaccination testing not recommended for CLD pts with mild disease
- Combined A and B vax (Twinrix, et al) offers convenience and 4-dose accelerated schedule (0,7,21-30 days and booster at 12 mo) and may produce earlier seroprotection

Leise & Talwalker Curr Gastro Rep 2013;15:300

Immunogenicity of Hep B Vax in cirrhosis/OLT is very low

- Standard dose response rates 16-20% in pre-transplant setting
- Post-transplant response rate 32%
- Persistence of anti-HBs positivity post-transplant in only 12% at year 1 and 8% at year 2
Recommendations for HBV Vaccination in cirrhotic and post-transplant patients

- Pre-cirrhotic can receive standard series
- Compensated cirrhotic may benefit from high-dose (40 ug) regimen at standard intervals
- Accelerated schedules generally result in seroprotection <50%
- Post-LTx use double-dose when on stable immunosuppression (generally at 4-6 mo)
- Pt with persistent +anti-core (with neg HBV-DNA) should receive 1st dose of vax to determine amnestic response

Leise & Talwalker Curr Gastro Rep 2013;15:300

Improving response rates to HBV vaccine in cirrhosis

- Double-dose (40 ug) at 0, 1, 6 mo achieved 68% response in pts on transplant list (Am J Med Sci 1999;318:304)
- Accelerated dosing schedule at 0, 1 and 2 mo. with double-dose produced 44% response (anti-HBs >10 mIU/ml); and a 2nd course achieved response in 60% of initial non-responders in Brazil (Liver Transplantation 2000;6:440)
- Double-dose at 0, 7 and 21 days in pts awaiting transplant produced a response of 26% (Eur J Gastroenterol Hepatol 2001;13:363)
- High-dose accelerated schedule at 0, 1, 2 mo with additional booster produced seroprotection in 42-55% (Am J Gastro 2002;97:435; J Viral Hepat 2001;8:372)
Influenza Vaccine in Cirrhosis

- Seroconversion rates are largely unaffected by cirrhosis vs controls using inactivated vaccine
- Not affected by antiviral or immunosuppressive therapies
- Reduced incidence of influenza (14% vs 23%) and risk of hepatic decompensation in vaccinated vs unvaccinated cirrhotics [Song et al. J Clinic Virolog 2007;39:159]
- Safe and effective in transplant pts, but higher seroconversion rates (56-89%) occur on stable immunosuppression (generally after 4-6mo) compared to earlier (14-43%) [Am J Transplant 2004;4:1805; Liver Transplant 2001;7:311]

**avoid live virus vax in CLD and post-LTx pts**

Vaccinations in solid organ transplant recipients: General Principles

- Vaccinations prior to transplant are preferred:
  - while vaccine responses pre-transplant are often low, antibody responses post-transplant are even more attenuated
  - live virus vaccines (measles, mumps, rubella, varicella, intranasal influenza) should be avoided post-transplant due to risk of allograft rejection and infection (and there should be at least 4 weeks between live vaccine and transplant)
IBD patients are at risk for vaccine-preventable disease

- Survey of 169 IBD patients at Cedars-Sinai Med Center, Los Angeles (mean age 35yr)
- Recall or documentation of:
  - Tetanus w/i 10 yrs 45%
  - Flu shots 28%
  - Pneumococcal vaccine 9%
  - Hep B 28% (among the 44% at risk)
- Main reasons for not receiving vaccines:
  - lack of awareness (49%)
  - concern for side effects (18%)

*Melmed et al. AJG 2006;101:1834*

Definitions of Immunosuppression in IBD

1. Treatment with glucocorticoids:
   - prednisone >/=20 mg /day or its equivalent for 2 weeks or more; and within 3 months of stopping
2. Ongoing treatment with effective doses of 6-MP / azathioprine; or its recent discontinuation within the previous 3 months
3. Treatment with methotrexate or its recent discontinuation within the previous 3 months
4. Treatment with infliximab* or its recent discontinuation within the previous 3 months
5. Significant protein-calorie malnutrition

*Adalimumab, certolizumab, and natalizumab should also be included in the definition above with the same window after discontinuation.*


Live Vaccines and Immunosuppressed IBD Patients

- the use of live vaccines (MMR, oral poliomyelitis vaccine, yellow fever and varicella zoster) is contraindicated in immunosuppressed IBD patients under immunotherapy
- Immunosuppressed individuals are not capable of mounting an adequate immune response towards the vaccine virus and have an increased risk of enhanced virus replication, possibly leading to persistence of the virus or even to overt vaccine-associated disease.

Response to Vaccinations in IBD

- Only limited data available
- No flare in IBD is to be expected
- Influenza vaccine: immunomodulators (IMs) and anti-TNF agents may cause slightly diminished immune response but most patients develop protective antibodies
- Pneumococcal vaccine: diminished response to PPV23 by IMs and anti-TNFs
- Hep B vaccine: reduced immunogenicity whether or not taking IMs or anti-TNFs
General principles to Vaccinating the Patient with IBD

- Killed inactivated vaccines are well-tolerated
- Live attenuated vaccines are contraindicated if already on immunomodulators or biologics (or if starting within 1-3 months of giving MMR, varicella or zoster)
- Recommended to check titers for immunity prior to vaccinating for MMR, varicella, HBV, HAV
- Inactivated influenza given intramuscularly should be used rather than the intranasal live attenuated vaccine (FluMist) if immunosuppressive therapy being used

*Always best to initiate vaccinations prior to having to start immunosuppressive therapies

Response to HBV Vaccine in IBD: results at a Spanish center

- Overall 59% of pts had anti-HBs titer >10 IU/L
- 39% had a titer > 100 IU/L (the new level of seroprotection defined by WHO [Vaccine 2009;28:589]
- Responders were younger (age 41 vs 49); and fewer were on anti-TNF (15 vs 26%)
- For patients not on immunosuppressive or anti-TNF, response rate was 63% (>10) and 39% for >100 IU/L
- 95 of 148 pts not responding to the first series of HB vax (anti-HBs <100) were re-vaccinated and 42% responded (higher likelihood when an initial titer was seen)

Live Vaccines and Household Contacts of Immunosuppressed Patients

- Severely immunocompromized individuals may be at risk of developing infectious disease from some live vaccine viruses given to household contacts.
- Spreading of vaccine virus has been described after oral poliomyelitis or rotavirus vaccination which are contraindicated in this setting.
- MMR, varicella, zoster and BCG vaccination are not contraindicated for household contacts of immunosuppressed patients.

Vaccinations for Travelers with IBD on Immunosuppressives

- Avoid live attenuated vaccines (yellow fever, MMR, oral polio, oral typhoid, intranasal influenza, BCG)
- Inactivated vaccines permitted: Japanese encephalitis, rabies, injectable typhoid, injectable polio, Hep A, Hep B, HPV, meningococcal, tetanus, diphtheria,

*May be best to avoid travel to endemic areas when vaccination is not possible

Wasan et al. AJG 2010;105:1231
When in Doubt about Vaccine Safety or Indications – Call the CDC

- For vaccine & immunization information:
  1-800-232-4636 (1-800-CDC-INFO)

- For information on international travel:
  1-877-394-8747
  information pertaining to international travel including geographic recommendations, health precautions and reported outbreaks.
  http://wwwnc.cdc.gov/travel/