SAFETY AND EFFICACY OF IMMUNIZATIONS IN CHILDREN WITH IBD

Eric Benchimol, MD, PhD, FRCPC
Assistant Professor, Departments of Pediatrics, and Epidemiology and Community Medicine, University of Ottawa
Division of Gastroenterology, Hepatology & Nutrition
Children’s Hospital of Eastern Ontario

www.cheo-ibd.ca
@CHEOibd
DISCLOSURES

• No conflicts of interest to disclose.
CDDW/CASL Meeting Session: Safety and Efficacy of Vaccinations in Children with IBD

**CanMEDS Roles Covered in this Session:**

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
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<tr>
<td><strong>Collaborator</strong></td>
<td>(as Collaborators, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
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<tr>
<td><strong>Manager</strong></td>
<td>(as Managers, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
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<tr>
<td><strong>Health Advocate</strong></td>
<td>(as Health Advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
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<tr>
<td><strong>Professional</strong></td>
<td>(as Professionals, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
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OBJECTIVES

1) Review recommendations for indications and contraindications of vaccines in children with IBD.

2) Discuss the safety of immunizations in immunosuppressed children with IBD.

3) Understand the efficacy and immunogenicity of immunizations in immunosuppressed children with IBD.

4) Assess the risk of vaccine-preventable infections in children with IBD.
“IMMUNO-COMPROMISED”

• Alteration in
  
  • Immune Function
    • Phagocytic Immunity
    • Cellular Immunity
    • Humoral Immunity
  
  • Barrier Function
    • Skin barrier
    • Mucosal Defence Barrier

*Increasing the risk of an infectious complication or an opportunistic process.*
THE IBD PATIENT AS “IMMUNOCOMPROMISED”?

• Evidence of defective mucosal immunity
• Proof of a systemic immune defect
• Risk factors for opportunistic infection
  • “Inherent”
    • Age
    • Co-morbidity
    • Malnutrition
  • “Acquired”
    • Immunomodulator therapy
    • Pathogen exposure
    • Geographic clustering
ACQUIRED IMMUNOSUPPRESSION

• Immunomodulator Therapy
  – Includes
    • Corticosteroids >0.5mg/kg or >10 mg/day for >2 wks
    • Thiopurines
    • Methotrexate
    • Calcineurin Inhibitors
    • Anti-TNF and other Biologic Agents

  – No strict relationship between drug and infection type
    • Steroids with Fungal
    • Azathioprine with Viral
    • Anti-TNF with Fungal or mycobacterial

Toruner et al, Gastro 2008;134:929-36
COMPLETION OF VACCINE SERIES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Complete series</th>
<th>Complete series for age</th>
<th>Partial series</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>92%</td>
<td>94%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>75%</td>
<td>76%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>DPTPHib/dTap</td>
<td>48%</td>
<td>51%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

deBruyn J et al., Inflamm Bowel Dis 2012; 18(Suppl 1): S4-S5
SEROLOGIC PROTECTION IN CHILDREN WITH IBD

Approximately 20-40% of children lack serologic protection in spite of complete vaccine series.
Predictors of serologic protection among children with complete series

- **Varicella**
  - Older age at diagnosis & at enrolment
  - ↑ frequency of natural infection in older children
  - ↑ frequency of serologic protection among naturally-infected children

- **No association for measles, mumps, rubella, HBV**
  - IBD type, immunosuppressive therapy
  - Age at and time from diagnosis
  - Age at enrolment, time from vaccine completion

deBruyn J et al., Inflamm Bowel Dis 2012; 18(Suppl 1): S4-S5
CONCLUSION

• Strong adherence to vaccine schedules
  • 75-95% with age-appropriate complete vaccine series

• However in spite of complete vaccine series
  • Lack of serologic protection is common (~20-40%)

• Implications
  • Avoid making assumptions of serologic protection based on vaccine status
  • Monitor response to vaccinations

deBruyn J et al., Inflamm Bowel Dis 2012; 18(Suppl 1): S4-S5
INITIAL SCREENING

• At diagnosis, we check for:
  • Tuberculosis (Mantoux skin test, chest x-ray)
  • Varicella and zoster immunity (VZV IgG)
  • Hepatitis A serology
  • Hepatitis B serology (check anti-HBsAg for immunity)
  • Hepatitis C serology
  • CMV IgG + IgM
  • EBV IgG + IgM
LIVE VACCINE IMMUNIZATION

"I'm right there in the room, and no one even acknowledges me."

The New Yorker, 9/18/06
LIVE VACCINES

• Examples of live attenuated vaccines:
  • MMR
  • Varicella (chickenpox and shingles)
  • Rotavirus
  • Yellow Fever
  • Oral Polio virus
  • Smallpox
  • Live-attenuated influenza vaccine (LAIV)
TIMING OF LIVE VACCINES

• ECCO Guidelines:
  – “If the medical history of chickenpox, shingles and VZV vaccination is negative, immunisation with VZV vaccine should be performed at least 3 weeks before onset of immunomodulator therapy, and preferably at diagnosis of IBD [EL5, RG D].”
  – Immunosuppression includes high-dose prednisone (2 mg/kg/day or >20 mg/day in patients >10 kg)
  – Discontinue immunosuppression >3 months prior to live-virus vaccine

TIMING OF LIVE VACCINES

• RED BOOK:
  – Live-virus vaccines withheld for ≥3 months after immunosuppression discontinued
  – “Immunodeficiency that follows use of recombinant human proteins with anti-inflammatory properties… appears to be prolonged.”
  – “Therefore, it often is not possible to make a definitive recommendation for an interval after cessation of immunosuppressive therapy.”
  – “If there is an available test for a known antibody correlate of protection, specific postimmunization serum antibody titers can be determined 4 to 6 weeks after immunization to assess immune response and guide further immunization and management of future exposures.”

VARICELLA ZOSTER (VZV)

• Unlike other herpes viruses, primary infection with VZV is nearly always symptomatic.

• Risk of IM
  • Increases risk of dissemination and complications such as pneumonia, hepatitis and encephalitis.

• Exposure and/or Infection during IM
  • If seronegative,
    • VZIG should be given within 96 hours of suspected exposure
    • 125 units (1 vial) per 10kg body weight up to 625 units
    • Observe for 28 days, in the event of clinical symptoms commence immediate anti-viral therapy
  • Disseminated VZV = medical emergency
    • 3 reported fatal cases despite intravenous acyclovir therapy
    • IM may be restarted once clinical symptoms resolved
VACCINES: THE HEAVY HITTERS
Biologic response modifiers to decrease inflammation: Focus on infection risks

N Le Saux; Canadian Paediatric Society
Infectious Diseases and Immunization Committee
Paediatr Child Health 2012;17(3):147-50
INFLUENZA IMMUNIZATION

THE TWO STAGES OF WINTER

DECEMBER: A MAGICAL WONDERLAND OF LIGHTS!

JANUARY—SPRING: A COLD, GRAY, BUCKET OF SUCK.
INFLUENZA VIRUS

• Risk of IM
  • Minimal data exist on the incidence of influenza infection in IBD, but IM therapy is generally considered to enhance the risk of infection.
  • Suggestion that incidence of ‘benign URTIs’ was unaffected by IM therapy

Seksik et al, Aliment Pharmacol Ther 2009;29:1106-1113

• Infection during IM
  • No data available on the use of antiviral drugs for influenza in IBD (+/- IM).
  • ??During an epidemic, maybe start antiviral Rx within 36 hours.
INFLUENZA IMMUNIZATION

• International clinical IBD guidelines and PHAC recommend influenza immunization

• Low uptake of influenza vaccine noted in IBD
  • 28% of American adults ever vaccinated
    Melmed et al., Am J Gastroenterol 2006; 101:1834-40.
  • 50% of Alberta children ever vaccinated
    deBruyn et al., Inflamm Bowel Dis 2012; 18:25-33.
  • 28% of German adults vaccinated in 2008
    Teich et al., Dtsch Arztebl Int 2011; 108:105-11.
INFLUENZA IMMUNIZATION AND IBD FLARES

• Case reports of IBD flare after influenza immunization
  Fields et al., Inflamm Bowel Dis 2009; 15:649-51
  Kwon et al., Korean J Gastroenterol 2007; 49: 327-30
  Luca et al., Allergy 2004; 59: 367.

• 8-33% of patients don’t get immunized due to concern over adverse effects
  Melmed et al., Am J Gastroenterol 2006; 101:1834-40.
  deBruyn et al., Inflamm Bowel Dis 2012; 18:25-33.
  Teich et al., Dtsch Arztebl Int 2011; 108:105-11.

• Bruce Sands:
  • “Additional rigorous epidemiologic studies and randomized controlled trials are needed to determine the efficacy and risks of immunization in patients with IBD.”
Safety and Utilization of Influenza Immunization in Children With Inflammatory Bowel Disease

**A U T H O R S:** Eric I. Benchimol, Steven Hawken, Jeffrey C. Kwong, and Kumanan Wilson

**WHAT’S KNOWN ON THIS SUBJECT:** Yearly influenza immunization is recommended in patients with inflammatory bowel disease (IBD). However, concern regarding vaccine-related adverse events may limit uptake, and case reports in the literature detail disease flares after immunization.

**WHAT THIS STUDY ADDS:** Influenza immunization rates in children with IBD are low but immunization did not result in increased outpatient visits, hospitalizations or emergency visits. Immunization was associated with fewer IBD-related visits in the post-vaccine period, which may indicate protection against IBD symptoms.

**K E Y W O R D S**
epidemiology, health administrative data, inflammatory bowel diseases, influenza vaccines, pediatrics, seasonal influenza,

PEDIATRICS Volume 131, Number 6, June 2013
INFLUENZA IMMUNIZATION AND IBD FLARES

- Children with IBD <19 years old diagnosed between 1999-2010 identified from the Ontario Crohn’s and Colitis Cohort
- Each IBD case matched to 5 non-IBD controls by date of birth (±30 days), sex, region
- Longitudinal follow-up starting with date of IBD diagnosis (same date in matched controls)
- Self-controlled case series analysis (SCCS)
  - Compares rates of events in a risk period (post-immunization) to events in a no-risk period (before or remote to immunization)
INFLUENZA IMMUNIZATION AND IBD FLARES

Observation Period

- Control
- Washout + Risk
- Control
- Washout + Risk
- Control
- Washout + Risk
- Control

Birth
IBD Diagnosis
Flu Vaccination
Flu Vaccination
Flu Vaccination
Flu Vaccination
19th Birthday

Control (unexposed) Period
Washout Period
Risk (exposed) Periods
Flu Vaccination
Control (unexposed) Period

-30-2
3-14
15-30
31-45
46-60
61-75
76-90
91-180
INFLUENZA IMMUNIZATION – ADVERSE EVENTS IBD-RELATED

DAYS 3-14
DAYS 15-30
DAYS 15-30
RI 0.45, 95% CI 0.26 to 0.80
DAYS 31-45
DAYS 46-60
DAYS 61-75
DAYS 76-90
DAYS 91-180
POOLED DAYS 3-180
POOLED DAYS 15-180
RI 0.81, 95% CI 0.68 to 0.96
RI 0.78, 95% CI 0.66 to 0.94

INFLUENZA IMMUNIZATION - IMMUNOGENICITY

• No difference in immunogenic response or protection to A/Brisbane/10/2007 (H3N2) or A/Brisbane/59/2007 (H1N1)
• Maybe lower response and protection rates against B/Florida/4/2006
• No difference if immunosuppressed
• 1/60 IBD patients had adverse event – pancreatitis (temporally related but not associated with vaccine)

INFLUENZA IMMUNIZATION - IMMUNOGENICITY

• Other studies showed adequate response in children with IBD

• But may have lower response to:
  – B/Hong Kong/330/2001

  – B/Malaysia/2506/2004
    Lu et al., Am J Gastroenterol 2009; 104: 444-53.
INFLUENZA IMMUNIZATION - TIMING

• What is the timing of influenza immunization for a patient on a biologic?


• Patients on infliximab 3 mg/kg every 6-8 weeks

• Randomized: 22 vaccinated on day of IFX, 16 vaccinated 3 weeks after IFX
“Unexpectedly, we found a trend toward unexplained lower immunity in the group vaccinated 3 weeks after infusion with infliximab. Our results demonstrate that for most of the groups, the timing did not influence the response, further confirming the lack of significant effect of infliximab on the humoral response to influenza vaccine.”

INFLUENZA IMMUNIZATION - CONCLUSIONS

- Influenza Immunization is under-utilized
- Influenza immunization is safe
- Influenza immunization *may be protective* against IBD-related health services visits, and therefore may reduce cost of care
- Immunogenicity is probably good
- Timing related to IFX infusions uncertain
OTHER HEAVY HITTERS:
PNEUMOCOCCUS
MENINGOCOCCUS
HPV
HEPATITIS A
HEPATITIS B
STREP PNEUMONIAE

• **Epi:**
  - IBD patients on IM are considered high-risk for invasive pneumococcal disease
  - Bacterial pneumonia is one of the most prevalent infections in IBD patients on IM*.

*Colombel et al, Gastro, 2004;126:19-31
Blonski et al, IBD, 2007; 13:769-96

• **Risk of IM**
  - Host defence depends on both humoral and cellular immunity.

• **Infection during IM**
  - In the setting of IM, AB Rx should always cover *S. pneumoniae*. IM should be withheld until resolution of infection.
STREP PNEUMONIAE

• Children <60 months:
  • Complete primary series of pneumococcal conjugate vaccine
  • Pneumococcal polysaccharide 8 weeks after last conjugate vaccine (>24 months)

• Children ≥60 months:
  • If hasn’t completed course of conjugate, give either conjugate/polysaccharide, with the other 8 weeks later

References:
CPS Practice Point, Paediatr Child Health 2012; 17(3):147-50.
MENINGOCOCCUS

- Meningococcus polysaccharide
  - Against meningitis, meningococcemia
  - Serogroup C now almost completely gone
  - Serogroup B now >80% of cases

References:
HUMAN PAPILLOMA VIRUS (HPV)

• Risk of IM
  • Increased occurrence of both genital and cutaneous warts has been documented.

  Seksik et al, Aliment Pharmacol Ther 2009;29:1106-1113

• Infection during IM
  • Appears to be a higher prevalence of abnormal cervical smears in women with IBD cf general population.
  • Risk of an abnormal cervical smear reported to be higher in subjects on IM
  • Reports of increased cutaneous warts in patients on IM and suggestion that incidence of SCC is higher

HPV VACCINE – A FEW NOTES

• HPV Vaccine (Ceravix or Gardasil) recommended for all women 9-26 years old
• HPV Vaccine (Gardasil) recommended for all boys 9-26 years old

Note: HPV also causes 25% of oral cancers, 35% head and neck cancers

PHAC National Advisory Committee on Immunization, 2012 update.
HEPATITIS B

• Epi
  • In Canada, ~1/3 of cases have no identified risk factor

• Risk of IM
  • Reactivation of HBV replication occurs in 20-50% of Hep B carriers with IM.
  • Their effect on the course of HBV in IBD has not been studied prospectively.

• Infection during IM
  • Generally recommended IM should be delayed until resolution of acute infection.
  • Greater risk of becoming chronic carriers
HEPATITIS A/B

• Recommendations:
  • Full regular course of Hepatitis B vaccine
  • Give Hepatitis A/B vaccine if intends to travel to Hepatitis A endemic areas
  • Check Hepatitis A IgG and Hepatitis B titres
  • Consider booster if non-immune
TRAVEL VACCINES
Travel and Immunomodulators

• The “Live Travel Vaccines” are
  • 1) Yellow Fever
  • 2) Oral Typhoid
  • 3) BCG

• Japanese Encephalitis, Rabies and Injectable Typhoid are all inactivated.
Vaccination and Immunomodulators

• IBD patients are considered immunosuppressed if taking
  • Steroids for > 2 weeks
  • Azathioprine/6-MP
  • Methotrexate
  • Biologic Agents

• Time interval to allow for immune recovery
  • 3 months
  • Lymphocyte count $\geq 1.2 \times 10^9$/$L
Vaccination and Immunomodulators

• Recommended time interval to allow for clearance of live viral particles from last dose of vaccine prior to the initiation of immune suppression
  – 4 to 6 weeks

Given you must wait 10 days post yellow-fever vaccine to fly, having been away for 3 weeks, the patient should be fine to restart therapy immediately
CONCLUSIONS

• At Diagnosis
  • Document vaccination history
    • Confirm completion of all scheduled doses
    • Record any missed or additional immunizations
  • Review and address nutritional status
  • Confirm seroconversion - VZV, HBV

• Advise updated vaccination schedule as appropriate (including household contacts)
  • VZV (live vaccine)
  • HPV (boys and girls)
  • Influenza (yearly)
  • Pneumococcal conjugate/polysaccharide
  • HAV, HBV
  • Travel vaccines
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