Immunogenicity From The Perspective Of A Practicing Pediatric Gastroenterologist

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Perhaps A Better Title For This Talk

The Barriers To Practicing What I Preach

Disclosures

- None

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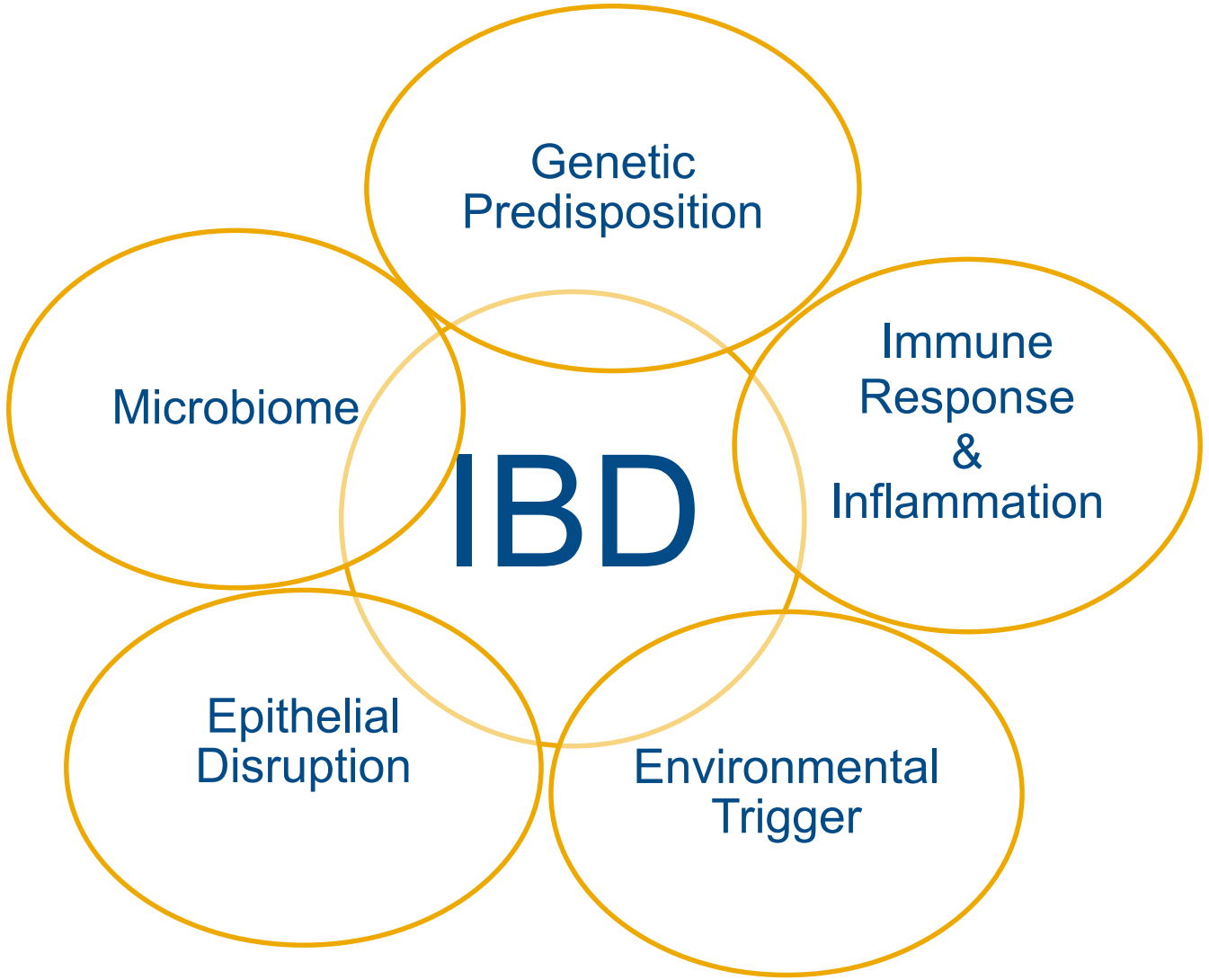
Objectives

- Discuss what anti-drug antibodies (ADA's) mean to our patients
  - Inflammatory Bowel Disease (IBD) as an example
  - Focus on infliximab (IFX)
- Review practical strategies for avoiding and/or overriding ADA's
- Evaluate what we can do vs. what we want to do about ADA's
  - Patient Case

Inflammatory Bowel Disease



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IBD Disease Burden

- Prevalence: 568 per 100,000 in U.S.
- Onset: adolescence & young adulthood
  - 20% pediatric
    - More aggressive phenotype
- Anti-TNF-α revolutionized IBD tx in early 2000's
  - Steroid-free remission
  - Lots of time for ADA's to develop

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Moledecky et al. Gastroenterol 2012
bpca.nichd.nih.gov/about; last accessed Nov. 13, 2015

Why Do ADA's Form?

- Nature of biologics
  - 0.3-65% in IBD (122 pubs rev)
  - Neutralizing vs. non-neutralizing ADA
- Inflammation
- Low albumin
- Low drug concentrations
  - Monitor troughs

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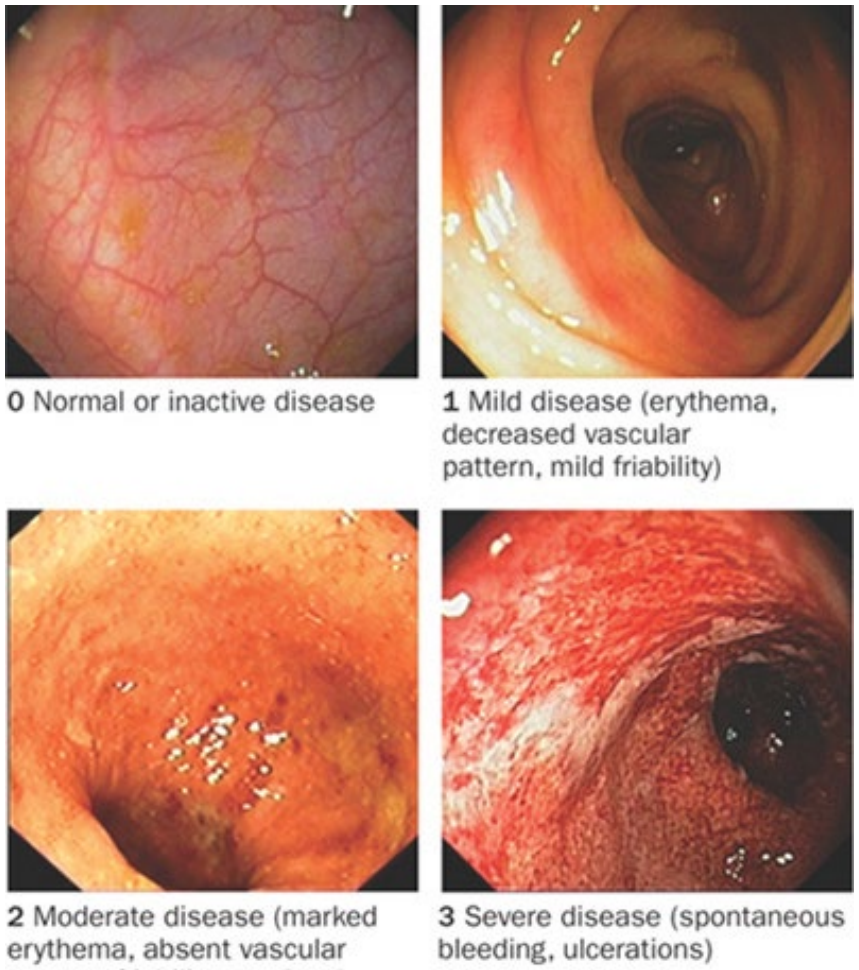
Vermiere et al. Ther Adv Gastroenterol 2018
Strand et al. BioDrugs 2017
Mould. Dig Dis 2015

IBD Is A Set-up For ADA Formation

- Inflammation
  - Disease flares expected
- Protein losing enteropathy
  - Low albumin
  - Spill drug



0 Normal or inactive disease

1 Mild disease (erythema, decreased vascular pattern, mild friability)

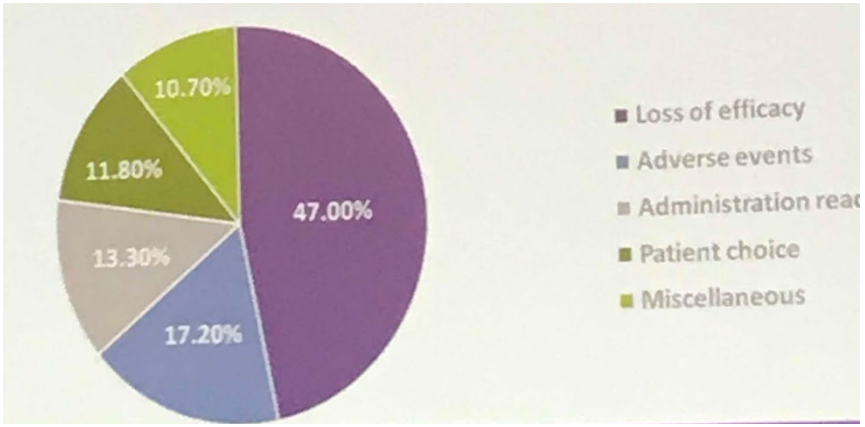
2 Moderate disease (marked erythema, absent vascular

3 Severe disease (spontaneous bleeding, ulcerations)

http://www.nature.com/nrgastro/journal/v7/n1/images/nrgastro.2009.203-f1.jpg; last accessed Dec. 1, 2016

ADA's → Loss of Response

- DEVELOP: international, multicenter, prospective, observational, pediatric IBD registry (2007-2017)
  - n=6,070
  - median age 13 yrs
- 27.3% discontinued IFX
  - 47% due to loss of response
  - 13% due to infusion reaction



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Coletti et al. CCFC. Feb, 2019; Las Vegas, NV

Preventing ADA's and LOR

- Increase dose
- Shorten interval
- Combo therapy with immunomodulators ~~or steroids~~

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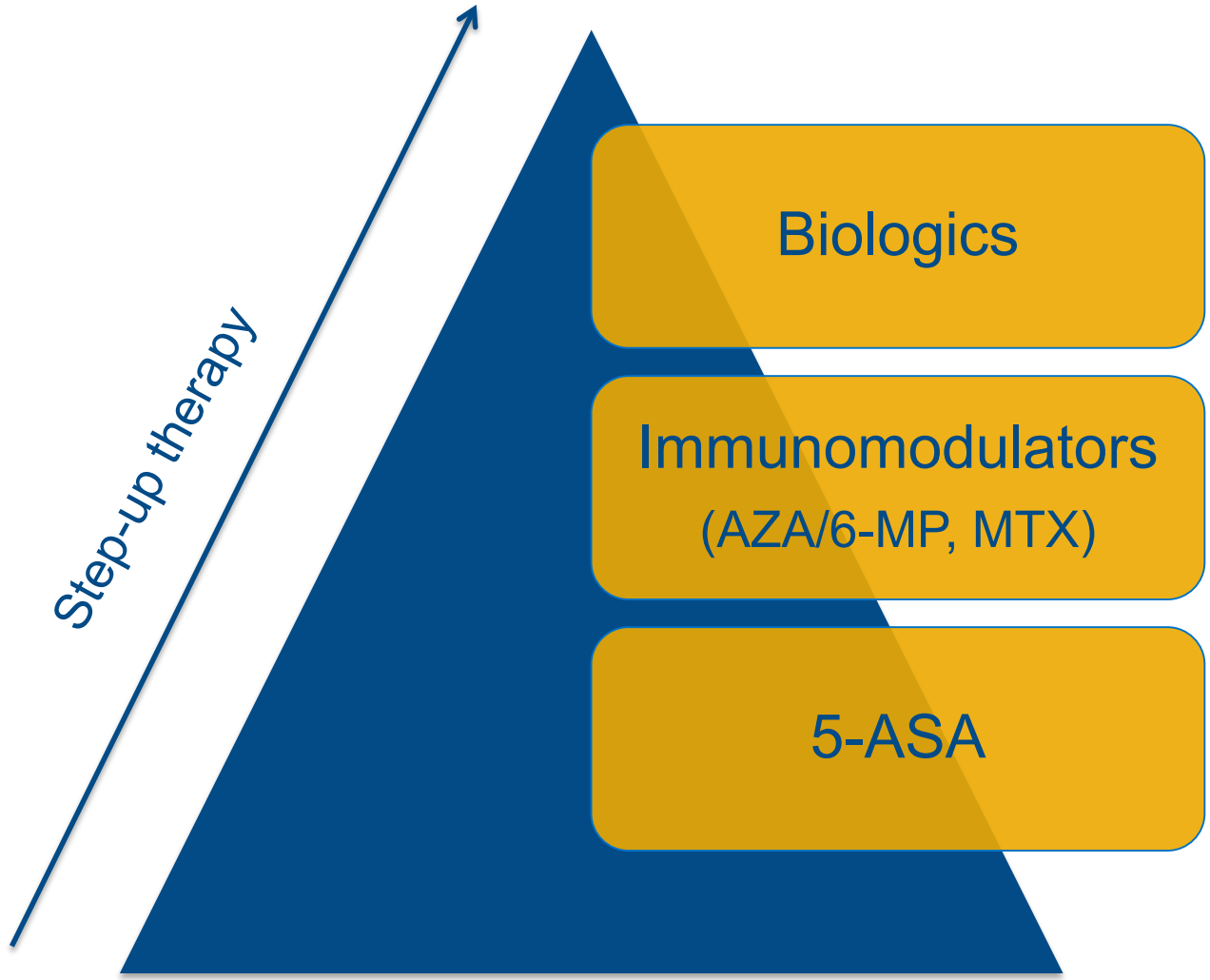
Chi et al. Inflamm Bowel Dis 2018
Lega et al. Inflamm Bowel Dis 2019

Ptient Case: It's 2013



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Aloi et al. Nature Reviews Gastroenterol & Hepatol 2014

You Make The Diagnosis

- 9yof dx with Crohn's → steroids & 5-ASA
  - start AZA
- 4 months post-dx, therapeutic 6-TGN, but active disease
  - symptomatic, anemic (Hgb 10.4), ESR 54, CRP 3.5→steroid burst & start IFX
- IFX induction, followed by 5 mg/kg Q8 weeks→8.2mg/kg Q6 weeks
  - no sx, no anemia, ESR 13, CRP 0.9→ remission at 20mo

Disease Flare

- IFX weaned down
  - 18 months later, at “standard” 5 mg/kg Q8 weeks
- She gradually gets worse
  - Hgb 10.1, ESR 48, CRP 3.1, albumin 3.1
  - IFX levels undetectable
  - IFX ADA 1:164

What do YOU want to do?

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Bots et al. Inflamm Bowel Dis 2018

What you CAN do…

- Insurance denies shorter interval
- Insurance approves dose increase to 6.8mg/kg (400mg) Q8wks
- 3 months later, she feels well & labs improved
  - Order IFX level & ADA

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WAIT!!! WHAT?! WHY?!

- In 2017, BCBS denies “experimental lab tests”

Improved Long-Term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab

Konstantinos Papamichael,[*] Karen A. Chachu,[‡] Ravy Vajravelu,[§] Byron P. Vaughn,[||] Josephine Ni,[§] Mark T. Osterman,[§] and Adam S. Cheifetz[*]

- 43% of our IBD population (n=260) have BCBS
  - 18% Medicaid
  - Appeal denied
  - Peer-to-peer courtesy, not right

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Papamichael et al. Clin Gastroenterol Hepatol 2017
Vaughn et al. Inflamm Bowel Dis 2014

You're Resourceful

- Different assay used
  - IFX levels undetectable
  - IFX ADA >200
  - She feels well

What do YOU want to do Now?

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Add Immunomodulator

- Add AZA
  - AZA vs. MTX
- 4 months later:
  - IFX ADA down to 57
- Request to increase IFX dose/interval

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Abandon IFX

- 4 months later, bad disease flare→ steroids, switched to adalimumab
- Combo vs. mono therapy?

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Combo Pro's

- Higher IFX levels, lower ADA tendency
- Can override ADA's
- CMKC data over 2 yrs for IFX
  - ARUP: 370 kids tested→35 (9.5%) ADA +
    - 10 cleared ADA's, 1 redeveloped ADA's
  - INFORM: 242 kids tested→6 (2.4%) ADA +
    - 4 cleared ADA's

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Chi et al, Inflamm Bowel Dis 2018

Combo Con's

- 2 side-effect profiles instead of 1
  - Immunomodulators not benign
- Additive immunosuppression
  - No evidence for 6-MP vs. MTX
- Hepatosplenic T-cell lymphoma (HSTCL)

HSTCL

- Universally fatal cancer
- 37 cases in IBD (all Crohn's)
  - 86% young males
  - 1st case reports came out in early 2000, around the time biologics hit the market for IBD
- GI community is split on whether it's biologics or immunomodulators or a combination of the two

Mekelburg et al, J Inflamm Bowel Dis & Disord 2016
Thayu et al, J Pediatr Gastroenterol Nutr 2005
Subramaniam et al, Intern Med J 2005
Kotlar et al, Gastroenterology 2009
Diamnond et al, Clin Gastroenterol Hepatol 2011
Deepak et al, Am J Gastroenterol 20013
Brensenger et al, Clin Gastroenterol Hepatol 2016

Conclusions

- ADA's are bad for patients
- 3 strategies to prevent ADA's
  - Choice is yours (sort of)
    - Increase dose
    - Decrease interval
    - Add immunomodulator
- Future: treat to target
  - Agree on target

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Acknowledgements

- Rachel Hasenkamp, RN

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