

Should Deep Remission Be A Treatment Goal?

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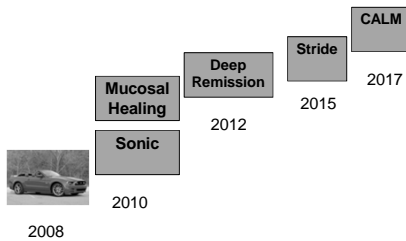


Should Deep Remission Be A Treatment Goal?

- No, not until we have convincing data that it makes a difference.



Deep Remission: Cohn's Disease Evolution



Top Down versus Step Up Therapy for Crohn's Disease



2008



Top-Down vs Step-Up Treatment for Crohn's: Final Data

- Top Down 59 pt
- Step Up 60 pt
- 16 semester follow-up past the original 2 yr study
- At 2 years:

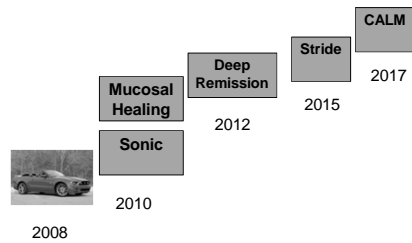
| | Top Down | Step Up |
|-----|----------|---------|
| AZA | 60% | 51% |
| MTX | 22% | 11% |
| IFX | 20% | 15% |

| | Top Down | Step Up | P |
|-------------------------------------|----------|---------|-------|
| Time in remission | 67% | 68% | NS |
| # of flares | 13% | 20% | <0.01 |
| Time to Hospitalization (semesters) | 14 | 13 | NS |
| Time to Surgery (semesters) | 15 | 14 | NS |
| No ulcers at endoscopy | 64% | 56% | NS |

Hoekman DR *et al.* Amsterdam, Leuven DDW 2015
 Abstract # 924



Deep Remission: Cohn's Disease Evolution



Mucosal Healing in Crohn's Predictor of Sustained Remission?

- Subgroup analysis
 - Top-Down vs Step-Up study 133 pt
- Colonoscopy at 2 years
 - 46 patients
 - Mucosal healing +
 - SES = 0
 - Mucosal healing -
 - SES 1-9
- Reassessed at 3-4 years

Proportion of patients in remission

| Group | Patients in Remission |
|-------|-----------------------|
| MH+ | 17/24pt |
| MH- | 6/22pt |

Colonoscopy at 2 yrs

Baert F et al Gastro 2010; 138:463-68

Crohn's Disease: SONIC Infliximab, Azathioprine, or Combination

Background

- Crohn's 169 pt
 - Infliximab
 - Azathioprine
 - Infliximab + Azathioprine
- 26 wk
- CDAI <150 off steroids

Clinical Remission

| Treatment | Clinical Remission (%) |
|---------------------------|------------------------|
| INFLIXIMAB | ~55 |
| AZATHIOPRINE | ~30 |
| INFLIXIMAB + AZATHIOPRINE | ~65 |

Colombel JF NEJM April 2010; 362(15): 1383-95

Higher Levels of Infliximab May Alleviate the Need of Azathioprine Co-medication for Crohn's Disease: A Sonic Post-Hoc Analysis

- Sonic Study 2010 post hoc
- 206 patients with Crohn's
 - 97 IFX only
 - 109 IFX + Azathioprine
- Serum Infliximab concentration
- Clinical steroid-free remission at week 26
- Conclusion: Benefit of combination Rx only with low IFX concentrations

Steroid-free Remission at 26 wk

| IFX Concentration | IFX AZA (%) | IFX (%) |
|-------------------|-------------|---------|
| Q1 | ~65 | ~35 |
| Q2 | ~75 | ~65 |
| Q3 | ~70 | ~70 |
| Q4 | ~80 | ~70 |

IFX Concentrations

Colombel JF et al Mt Sinai NYC DDW 2017 oral # 134

Deep Remission: Cohn's Disease Evolution

2008 2010 2012 2015 2017

Deep Remission

- Definition: A state with little or no risk of disease progression

| Criteria | |
|---|---|
| Crohn's Disease | Ulcerative Colitis |
| 1. Resolution of inflammation by endoscopy, imaging, or markers | 1. Clinical remission |
| 2. Resolution of symptoms | "No data that endoscopic remission yields a better long-term outcome" |

Colombel JF et al Digestive Dis 2012 sup 3: 107-11

Deep Remission: Cohn's Disease Evolution

2008 2010 2012 2015 2017

Selecting Therapeutic Targets in IBD Stride

- Treat to Target
- 28 IBD Experts, 75% of those who voted

| Criteria | |
|--|--|
| Crohn's Disease | Ulcerative Colitis |
| 1. Resolution of pain and diarrhea | 1. Resolution of bleeding and diarrhea |
| 2. Endoscopic (no ulcers) or imaging remission | 2. Mayo Score 0-1 |

Peyrin-Biroulet L *et al* Amer J Gastro 2015;110:1324-38



Selecting Therapeutic Targets in IBD Stride

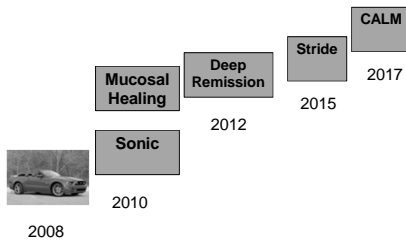
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| Not Criteria | |
|--|--|
| Crohn's Disease | Ulcerative Colitis |
| • Biomarker remission CrP, Fecal Calprotectin | • Biomarker remission CrP, Fecal Calprotectin |
| • Histologic remission | • Histologic remission |

Peyrin-Biroulet L *et al* Amer J Gastro 2015;110:1324-38



Deep Remission: Cohn's Disease Evolution



CALM Study Tight Control Management of Crohn's

- 244 patients, multi-national, Open-label
- Entry Criteria
 - CDAI 200-450
 - CDEIS >6 with ulcers in ≥ 1 segment
 - High CrP and/or Fecal Calprotectin
- Primary Endpoint
 - CDEIS < 4 and no deep ulcers at 48 weeks

Colombel JF *et al* The Lancet 2017; 390: 2779-2789



CALM Study Design

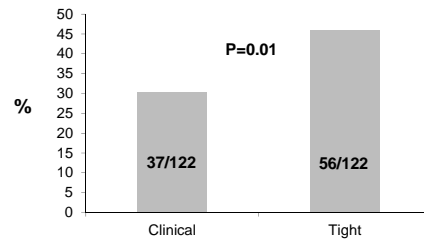
Baseline: Prednisone ≤ 40 mg daily tapered over 9 weeks, time shortened at treating physician's discretion

| Clinical Management | Tight Control |
|--|---|
| Treatment escalated at 12, 24, 36 wk if: CDAI decreased <100 pt or CDAI ≥ 200 Still on prednisone | Treatment escalated at 12, 24, 36 wk if: CDAI ≥ 150 CRP high Fecal calprotectin high Still on prednisone |

Colombel JF *et al* The Lancet 2017; 390: 2779-2789

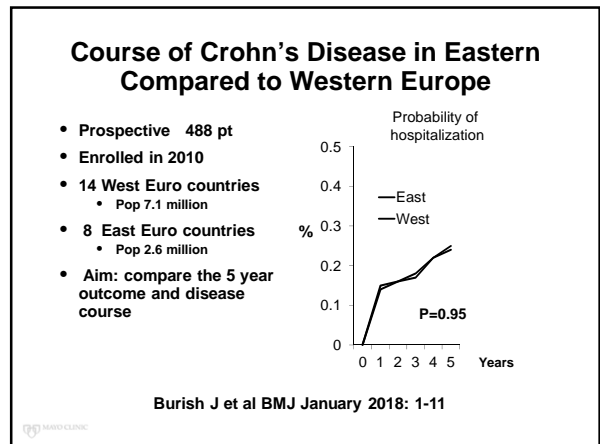
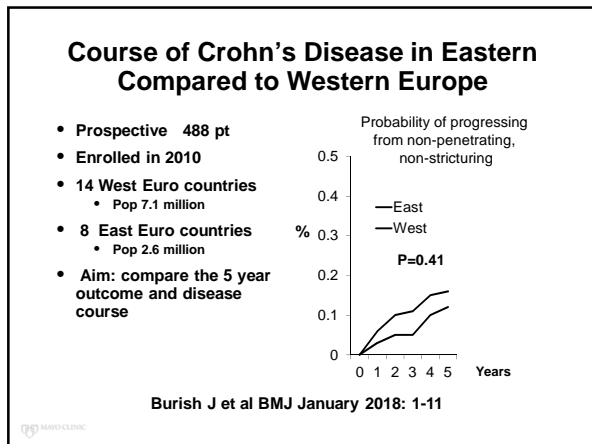
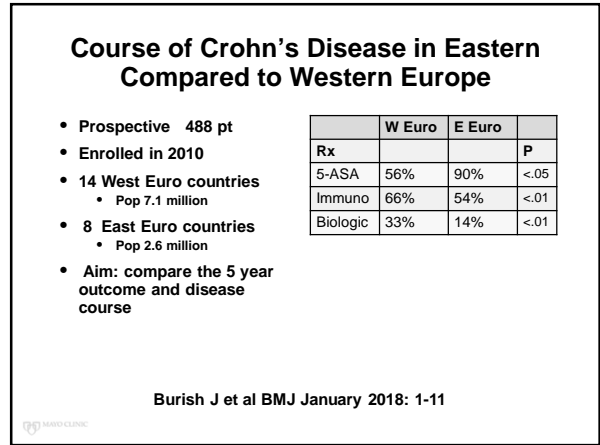
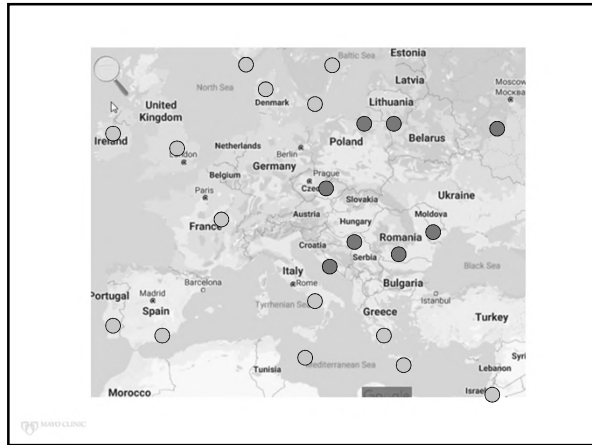
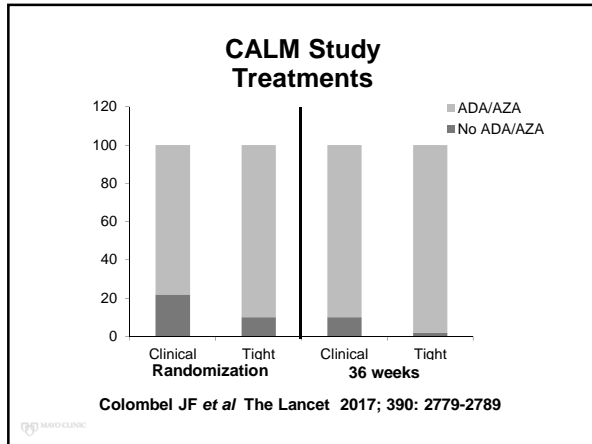


CALM Study Primary Endpoint Achieved: 48 wks



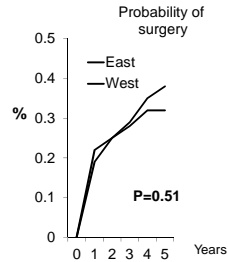
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Course of Crohn's Disease in Eastern Compared to Western Europe

- Prospective 488 pt
- Enrolled in 2010
- 14 West Euro countries
 - Pop 7.1 million
- 8 East Euro countries
 - Pop 2.6 million
- Aim: compare the 5 year outcome and disease course

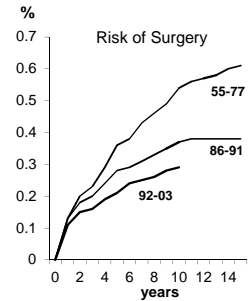


Burish J et al BMJ January 2018: 1-11



Surgery for Crohn's Disease Declining Rates Prior to Biologic Use

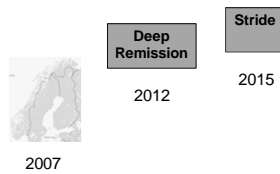
- Published data from:
 - Europe
 - Canada
 - U.S.
 - Korea
 - Japan
 - Hong Kong



Bernstein CN et al GUT 2012; 61: 622-9

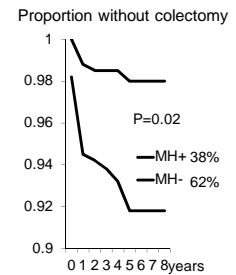


Deep Remission: Ulcerative Colitis Evolution



Mucosal Healing Ulcerative Colitis

- Norway
- Diagnosis 1990-94
- 353 UC pts
 - Endoscopy within 0.5 and 2 yrs after diagnosis
- 150 patients
 - Endoscopy 5 yrs after diagnosis
- Colectomy
 - MH+ 3pts
 - MH- 13pts



Frøslie KF et al Gastro 2007;133: 412-22



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| Predictors of Mucosal Healing | |
|--------------------------------|---------|
| Education longer than 12 years | p=0.004 |
| Extensive disease at diagnosis | P=0.02 |

Frøslie KF et al Gastro 2007;133: 412-22



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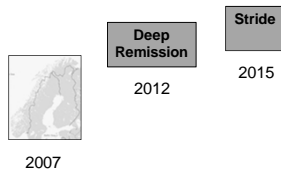
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Is this data relevant in the biologic era?

Frøslie KF et al Gastro 2007;133: 412-22



Deep Remission: Ulcerative Colitis Evolution



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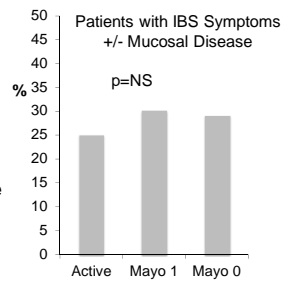
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IBS in UC Patients in Deep Remission

- Southeast Norway
- 260 UC patients for ≥ 20 years
- Colonoscopy and/or fecal calprotectin
- Prospective assessment of Rome III criteria
- Comparison: % IBS symptoms



Henriksen M *et al* J Crohn's Colitis 2017: 1-5

MAIO CLINIC

Deep Remission Conclusions

- Deep Remission—relief of symptoms and endoscopic healing—makes sense
- Evidence that achievement of Deep Remission changes the natural history of disease is lacking for Crohn's Disease and Ulcerative Colitis
- Deep remission isn't a mandatory goal until we have convincing data that it makes a difference.

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