



**IBD of the Elderly:  
 A “Wake-up” Call**

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**IBD – Age/Gender Distributions**

	M10-20	F10-20	M21-30	F21-30	M31-40	F31-40	M41-50	F41-50	M51-60	F51-60
Ileitis	4	3	19	19	6	20	7	23	19	19
Colitis	1	1	9	10	10	11	9	16	14	16
Ileocolitis	5	0	22	17	12	19	23	20	28	19
Crohn's (unspecified)	0	1	1	0	0	0	0	2	3	0
Ulcerative										
Enterocolitis	0	2	2	4	0	0	0	3	0	4
Ulcerative Proctitis	1	0	0	2	1	6	0	5	1	3
Ulcerative										
Proctosigmoiditis	0	0	1	0	3	2	2	4	1	3
Pseudopolyposis										
of Colon	0	0	0	1	0	0	0	0	0	0
L sided U.C.	1	1	5	3	3	2	3	1	7	8
Pancolitis	0	4	13	6	7	4	9	3	16	13
U.C. (unspecified)	0	2	4	3	6	3	9	9	6	5
TOTAL	12	14	76	65	48	67	62	86	95	90

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**IBD – Age/Gender Distributions**

	M61-70	F61-70	M71-80	F71-80	M 81&OVER	F 81&OVER
Ileitis	18	11	6	9	3	4
Colitis	7	14	17	14	3	3
Ileocolitis	16	19	9	14	5	5
Crohn's (unspecified)	0	0	1	2	0	0
Ulcerative Enterocolitis	0	4	4	2	1	2
Ulcerative Proctitis	1	0	0	1	0	2
Ulcerative Proctosigmoiditis	1	3	5	2	1	2
Pseudopolyposis of colon	0	0	0	0	0	0
L sided U.C.	3	8	1	8	0	2
Pancolitis	6	13	13	8	5	4
U.C. (unspecified)	3	9	5	6	2	2
TOTAL	55	81	61	66	20	26

TOTAL	929	
TOTAL OVER 61	315	33%

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### Epidemiology

#### Incidence

C.D. > 60 = 4/100,000 patient years

U.C. > 60 = 6 to 8/100,000 patient years

Generally: ¼ newly diagnosed CD occurs in Elderly. F:M = 2:1

60% initially misdiagnosed vs. 15% younger CD

Greater delay in diagnosing IBD elderly (6 years vs. 2 years)

Conclude: Clinicians have great difficulty diagnosing IBD in elderly

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### Differences Clinical Presentation/Course in Elderly

Less likely: Abdominal pain, diarrhea, anemia

More frequent: weight loss, bleeding, fever, (Paradoxical) constipation

Distal U.C. more common than pancolitis

Colonic CD: more common; fewer strictures

Less family history IBD

Greater osteoporosis but similar E.I.M

Disparity: Reports of no difference in disease location

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### Surprise! Fewer Crohn's Disease (CD) complications in elderly IBD patients

- Of the 141 patients ( Mayo-Jacksonville), 4.1% > 40 y.o. fistulae/strictures vs. 32.9% < 40 y.o.
- Comment: > 40 y.o. CD patients had 90% decreased risk of complications .

Picco et al. ACG Poster 1137

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### DDX

Infectious colitides: (38%) vs. IBD. (41%) of bloody mucoid diarrhea: (*C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *Giardia*, *E. Coli* O157:H7, *Yersinia*)

- Ischemia
- Segmental colitis of diverticulitis
- Microscopic colitis (collagenous, Lymphocytic)
- R.T.
- Drug: NSAIDS, estrogen, digitalis, Gold, NaP enema, Methyldopa

(Key to DX: Colonoscopic biopsy)

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### Course

- Similar indications for Med/Surgical interventions
- 1<sup>st</sup> attack: Severe, may require surgery. Yet overall less severe course, fewer relapses and hospitalizations : lower surgical rate in elderly; Higher mortality after severe attack
- 80% respond to medical therapy
- Fear of steroid (GCS) A/E – but may lessen speed of response

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### Course (contd.)

- ♦ Greater comorbidities alter prognosis
- ♦ Lower recurrence rate C.D.
- ♦ Greater mortality, F>M, after 25 years (or if older than 40 when first diagnosed)

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### Pharmacokinetics of IBD Drugs in Elderly

#### Glucocorticosteroids (GCS)

- Prednisolone = pharmacologically active form (Prednisone and Prednisolone = metabolically interconvertible).
- 37 % decreased drug clearance (unbound) with decreased renal/non-renal factors
- Budesonide: undergoes presystemic CYP3A4-mediated metabolism in liver and intestinal wall; Result: only 10-15% bioavailability

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### Pharmacokinetics of IBD Drugs in Elderly (contd.)

- Unknown if altered GCS  $t_{1/2}$  (2.8 h.) and clearance in elderly; Possible high clearance (dependant on hepatic blood flow) may yield greater bioavailability and greater A/E (osteoporosis, mental status changes e.g., confusion)



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### 5-ASA

- $T_{1/2}$  = 0.5 to 2 h., clearance range 300-610 cc/min dependent on intestinal wall and hepatic acetylation
- Elderly: Slower sulfasalazine elimination ( $t_{1/2}$  = 13.7% h)
- Decreased GFR and renal clearance of acetylated 5-ASA; 50% greater inactive acetylated metabolites (plasma steady state levels)
- Potential nephrotoxicity (interstitial nephritis) if decreased renal function.

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### Renal "Safety" with 5-ASA in Ulcerative Colitis

- No significant creatinine clearance (CrCl) change in 1461 U.C. patients over 8 years with dosage range 0.4 gm to 7.2 gm ages 9 to 99.

[Katz S, et al. DDW 2007]

- No CrCl changes over 6 weeks with 2.4 gm/day (187) or 4.8 gm (183 patients) from baseline.

[Sandborn WJ, Yeh C, Magowan S. DDW 2007]

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### 5-ASA (contd.)

- Overall: "Fit" Elderly – no greater decreased CrCl than expected with age.
- Reduces Digoxin bioavailability. Increased 6MP metabolites
- Topical therapy only effective if intact anal sphincter, manual coordination and functional status

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### 6MP / AZA

Allopurinol, 5 ASA increases 6 TGN metabolites but no data in elderly

MTX:

Increased mortality if coexistent cardiac disease; Renal excretion reflects diminished GFR

CSA:

- Metabolized by CYP3A4; No age differences in peak plasma conc. Or  $t_{1/2}$  (10.7 – 12.7 h)
- Avoid K+ Sparing Diuretics, Live Vaccines

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**Safety of 6-MP Use in the Elderly Inflammatory  
Bowel Disease Population**

- 29 patients ( mean age 70.3 yrs, 20 women, 9 men; 14 CD, 15 UC)
- 6-MP dosage: 50 to 150 mg; average duration 44 months
  - 11 with 1 A/E, 5 > 1 A/E, 13 none
  - Anemia 34% if > 50mg in 70% patients
  - Low WBC, High LFT's – none required D/C 6-MP
- Comment: 6-MP well tolerated in elderly IBD patients.

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**Anti-TNF Therapy**

Anti-TNF:

- Distributed in vascular compartment – very slow t  $\frac{1}{2}$  9 – 14 days
- No age effect known
- Anticipate greater A/E: CHF, Hepatitis, Infection, BM depression

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**Biologic Therapy in Older IBD Patients.**

- 50 patients ( 60 to 86 y.o.) 42 Crohn's disease and 8 ulcerative colitis were given median median of 10 doses, follow up in 17.2 months.  
Concomitant meds: GCS: 26%, IMD 34%, Both GCS and IMD 35%
- 42% adverse effects (3 IFX reactions, 1 delayed hypersensitivity reaction): 26% with serious adverse effects.
- 13 infections: ( 1 fatal pneumonia, 3 surgically treated abscesses, 1 cholangitis, 1 c.diff, 4 viral ( 1 rotavirus, 1 CMV), 3 fungal ( 2 candida, 1 histoplasmosis).  
Malignancies: 1 lung cancer, 1 rectal cancer, 2 squamous cell skin cancer, 20% ( 10 patients) discontinued biologic due to adverse effects.
- Comment: Older IBD patients require more intuitive vigilance for serious adverse effects.

Bhushban A, Parodi D, Loftus E, et al. ACG 2009, Poster 1136

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Biologic therapy adverse events versus efficacy	Age Score card
Harrison MJ, Salliot C: Age is a predictor of serious infection especially TBC	+
Fleischmann RM: 1128 etanercept (17% >65 years) patients experienced no Difference in SAE	=
Fleischmann RM: 4000 psoriasis patients on etanercept: (13.8% >65 years) A/E no differences: higher in young patients vs. SI in elderly	=
Bathon JM: Etanercept in RA patients >65 years (4 RCT, 2 open label trials) showed similar adverse events with PBO	=
Genevay S: 19 of 58 Swiss patients >65 years showed no safety differences between age groups	=
Harrison MJ: 49 women >70 years vs. 49 younger women: A/E and lack of efficacy: 12 and 24% in elderly vs. 7 and 21% in younger women	=
Salliot C: 623 RA patients: age not a risk for infection. 35 episodes seen in ± 67 of 100 patients (elderly) vs. 39 ± 67 of 100 patients (younger population)	=

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Biologic therapy adverse events versus efficacy	Age Score card
Chevillotte-Maillard E: 83 French RA patients: greater serious infection in elderly (18.2%) vs. younger RA patients (2.8%)	+
Davas EM: 73 of 269 RA (Greece) patients: 17 serious anti-TNF DMARDs. Age ± risk. AODM and interstitial lung disease	?
Koeller MD: MTX alone vs. MTX and BO: Not less effective in elderly	=
Schneeweiss S: GCS double the SI rate in patients >65 years (mean 76.5) with BO/DMARDs especially at higher GCS dosage	+
Remicade prescribing information: 181 RA vs. 75 psoriasis patients: no age difference efficacy but SAE increased in patients >65 years	=
Massara A: 19 elderly RA vs. 82 younger RA patients on B.O. and DMARDs: SAEs in 13 of 19 elderly (68.4%); 32 of 82 younger (39%). Elderly SAE: CV (35.7%), infusion reaction (28.5%), and infections (21.4%)	+

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**Summary: Biologic therapy adverse events versus efficacy**

10 of 14 studies showed no difference in efficacy or safety in the elderly versus the younger IBD population

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**Discontinuation of Patients on  
Anti-TNF**

- a. 26 elderly (>65 years old) rheumatoid arthritis (R.A.) patients vs. 98 young R.A. patients revealed:
- b. Allergic reactions were more often a cause in young patients (22% vs. 3.8% in the elderly).
- c. Cancer as anticipated was a more frequent finding in the elderly (15.4%) vs. young patients with rheumatoid arthritis (4%  $p = <0.05$ ).

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**Safety and Efficacy in Elderly  
(continued)**

- 1. 1768 patients (ages 18-83): no age or gender influence on drug pharmacokinetics.
- 2. No difference in efficacy based on age (>65).
- 3. Actually better 'probability' by 15% of remaining in response in elderly 65 years old patients over younger rheumatoid arthritis patients.
- 4. Pharmacokinetics in Crohn's disease patients was not influenced by age, gender, creatinine clearance or WBC.

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**RCT (Randomized Controlled Trials)**

- 1. Although RCTs are held to be the highest standard ("the Holy Grail"), concerns: relevancy strict inclusion/exclusion criteria do not relate to clinical practice, i.e. real world patients with multiple co-morbidities that would never be accepted into a RCT.
- 2. Limited goals, i.e. primary and secondary end points do not address the global patient concerns seen in practice.
- 3. RCT population is often healthier due to restrictive entry criteria, not representative; result: caution about safety of particular formulations unstudied particularly in the elderly.<sup>96</sup>

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**RCT (Randomized Controlled Trials)  
(contd.)**

4. Observational studies often rank lower than RCT (lesser degree of supportive evidence based literature). But useful regarding safety issues often are not dealt with in restricted RCTs (true in the elderly).

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**Extrapolating Study Results in Elderly**

1. Most studies not crafted to test criteria in the elderly.
2. Study designs/definitions of just of the 'elderly' employ methods of data collection and statistical analysis that are highly variable and more often than not, neglect co-morbidities.
3. With the exception of etanercept, most anti-TNF alpha studies lack sufficient number of elderly patients for adequate statistical power.

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**Extrapolating Study Results in Elderly  
(contd.)**

4. Physician and RCT bias using anti-TNF alpha therapy too cautiously in the elderly which selects out the healthier (i.e. the 'fit' elderly) with lesser risk factors.
5. Further sub-group analyses are awaiting study (i.e. >60, >70, and >80 year old patients).

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### Prescribing For Elderly

- Basic Principles: Drug elimination patterns (enzymes in drug metabolism, )
- Most drugs require metabolic processing before elimination – therefore must know route
  - a. Hepatic elimination – usually normal in “Fit Elderly”
  - b. Renal elimination – Age dependent decreased GFR but less so in “Fit Elderly”

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### Prescribing For Elderly (Contd.)

- Caution Re: Anti-diarrheals, analgesics, opiates less effective in elderly due to higher endogenous opioid levels. Tendency to “push” dosage: A/E: confusion, Ileus, impactions
- Anti-cholinergics (including anti-depressants) A/E: urinary retention, glaucoma, confusion, arrhythmia

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### Surgery in Elderly

U.C.:



- Higher rate earlier surgery for severe pancolitis yet surgical rate is less after 5 years disease (> 5 years)
- Predictors poor outcome: “urgent” surgery, hypoalbuminemia yet age, sex, disease extent : no influence on surgical outcome
- Successful Ileal pouch surgery provided anal sphincter function retained

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### CD Surgery

- Less frequent with "Late onset in life" disease
- Ileocolitis 2x greater likelihood than limited ileal or colonic disease; greater recurrence rate
- Elderly CD higher surgical mortality and perioperative problems
- Disparate literature: 5x greater recurrence rate vs. no difference from younger patients

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### Surgery

- IPAA pouch failure rate surprisingly no different
- Anal rectal incontinence = contraindicates IPAA
- Dysplasia more common an indication for colectomy in U.C.
- Toxic megacolon much less common
- Overall surgical mortality/morbidity less frequent
- Similar anastomatic leak rates

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### Diet and Lifestyle in Elderly IBD

- Lesser caloric requirement
- Restrictive diets with comorbidities (Low salt, sugar, fat)
- Low residue diet effects with inflammatory/fibrostenotic
- Enteral nutrition – limited use! TPN not effective primary therapy U.C. or fistulizing CD
- Supplements required: Vitamin D 1000 u, Calcium



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## Osteoporosis

- Higher fracture rate (additive drug effect GCS, MTX, CSA; disease associated inflammatory cytokines; coexistent malabsorption (Vitamin D and Calcium); malnutrition of elderly = often overlooked ... 85% hospitalized elderly protein malnourished.




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## Denosumab: Prevention of Fractures in Postmenopausal Women

Reduction of:	Denosumab (3902 patients)	PBO (3906 patients)	Relative Decrease
Vertebral fractures to:	2.3%	7.2% (Risk ratio: 0.32, 95% CI: 0.26-0.41, P<0.0001)	68%
Hip Fracture to:	0.7%	1.2% (Hazard ratio: 0.60, 95% CI: 0.37-0.97, P=0.04)	40%
Non-vertebral fracture to:	6.5%	8.0% (Hazard ratio: 0.80, 95% CI: 0.67-0.95, P=0.01)	20%

Comment: Impressive s.q. twice yearly program results of 36 months f/u.

*Cummings et al: N Engl J Med 2009; 361:756-65.*

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## Conclusion

- ❖ Recognize "BBB" = Burden of baby boomers on health care – create new standards for allocation of available resources
- ❖ Challenge present concepts of immutability of genetic predisposition of disease by ageing effect. "Does it change in time with disease". (e.g. UC conversion to CD, altered severity "with ageing")
- ❖ Distinguish between "fit elderly" and "frail elderly" in designing clinical trials, pharmacokinetics, or evaluating data

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**Conclusion (cont'd)**

- ❖ Establish cadre clinician – investigators skilled in biology of ageing (i.e. drug interactions, comorbid disease) impact. goal: “save lives ... as well as save money”
- ❖ Drug therapy in elderly (“Start Low – Go Slow”) - Reassess candidacy for more aggressive therapy (biologics, apheresis, surgery) – don’t Rx or exclude on basis of age alone

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