Inflammatory Bowel Disease of the Elderly: A Wake-Up Call

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Abstract: As the baby-boomer generation enters the ranks of the elderly (defined as patients over 60 years of age), the increased burden of managing older inflammatory bowel disease (IBD) patients requires recognition of the impact of comorbid disease, polypharmacy, and surgical candidacy criteria. There is a surprisingly positive response to newer therapies and surgery, provided that a distinction is made between "fit elderly" and "frail elderly" patients. The former group should not be denied access to the newer biologics, clinical trials, or surgical alternatives on the basis of age alone. There is a need for clinicians caring for elderly IBD patients to be cognizant of the multiple and often disguised conditions contributing to disease management as well as the importance for careful allocation of health resources.

Keywords
Inflammatory bowel disease, elderly, drug interactions

The prognosis of elderly patients with inflammatory bowel disease (IBD) has consistently improved, discounting earlier reports that presumed more aggressive disease and higher mortality. The recognition of a growing elderly IBD population (defined as >60 years of age) mandates a critical overview of drug interactions, comorbid disease influence, varied disease presentations, and risks of interventions, both diagnostic and therapeutic.[1-4] The demands of the emerging baby-boomer population will require a comprehensive review of health-related resources. The prospects of reevaluating the elderly into "fit elderly," distinguished from "frail elderly," will better qualify patients for more aggressive therapy and/or entry into clinical trials, as opposed to classification based solely on age. Also required will be an increase in the attention given to training physicians in the biology of IBD in the elderly, the recognition of drug-drug interactions, and the coexistence of multiple comorbid diseases. The following clinical characteristics of elderly IBD patients are stated in comparison with the younger IBD population.

Demographics

The incidence of Crohn's disease (CD) in patients over 60 years of age is 4 of 100,000 patients per year, whereas the incidence of ulcerative colitis (UC) in patients over 60 years of age is 6–8 of 100,000.[1-3] In Europe, 8–10% of UC/CD patients are over 60 years of age (M>F).[2] Generally, one third of newly diagnosed cases of CD occur in elderly patients (F:M, 2:1).[4-6] Unfortunately, 60% of elderly patients with CD are initially misdiagnosed, as opposed to 15% of younger patients.[7,8] A greater delay usually exists in diagnosing the elderly: 6 years compared to only 2 years in younger patients,[9] though there are conflicting data regarding this observation.[8] Overall, clinicians have greater difficulty diagnosing IBD in the elderly.

Differences of Clinical Presentation in the Elderly

Elderly IBD patients are less likely to present with symptoms of abdominal pain, diarrhea, and anemia.[8-10] More frequent symptoms include weight loss, bleeding, fever, and paradoxical constipation (with distal UC, which is more common than pancolitis).[11] Colonic CD is more common than small-bowel or ileocolonic disease and has a lower incidence of fever and strictures than small-bowel disease.[9,12,13] Elderly patients have a lower incidence of IBD family history and, as expected, a greater incidence of osteoporosis, but their incidence of extraintestinal IBD manifestations is similar to that of younger patients.[8,10,12,14] However, a disparity exists in the literature, with some reports claiming that there is no difference in disease location.[8,10,14,15]

Differential Diagnoses in the Elderly

There is a greater percentage of infectious colitis and IBD (38% and 41%, respectively) when bloody diarrhea is the presenting symptom.[16] For example, *Giardia, Yersinia, Escherichia coli* 0157:H7, *Clostridium difficile, Salmonella, Shigella*, and *Campylobacter* are often suggested by a shorter duration of symptoms and are detectable within 1–2 weeks of fever.[17] *C. difficile* represents a significant threat to the elderly. Ischemia is a possibility in elderly patients with congestive heart failure (CHF), peripheral vascular disease, diabetes mellitus, arrhythmias (eg, atrial fibrillation), or hypovolemia. It is characterized by rapid onset and pain, but it is usually a self-limiting process. Diverticular disease with "segmental colitis" involves an active inflammation site adjacent to (sigmoid) diverticulae.[18] It is responsive to antibiotics/5-aminosalicylates (5-ASAs) and easily confused with CD and neoplasia (eg, carcinoma, lymphoma) of the bowel.[18] Radiation therapy (RT) for prostate cancer may present with an active, often-resistant proctitis. RT for ovarian or intra-abdominal neoplasia must always be considered in the differential of bloody diarrhea.[19] Neoplasia of the colon and rectum obviously plays a significant role in this age group. Drug-related colitis can involve nonsteroidal anti-inflammatory drugs (NSAIDs), estrogens, digitalis medicines, gold, sodium phosphate enemas, and methyldopa. Colonoscopic biopsy remains the most useful examination for distinguishing acute self-limited colitis from chronic idiopathic IBD. The diagnosis of microscopic colitis (collagenous/lymphocytic) requires more than 20 intra-epithelial lymphocytes/100 epithelial cells or a collagen band of greater than 10 micra, both of which occur predominately in males.[20]

Disease Course

Elderly IBD patients have indications for medical and surgical interventions similar to those of younger IBD patients.[8-10] Although the first IBD attack in elderly patients may be severe and require surgery, a study from Mayo Clinic showed lower surgical odds in CD patients with advancing age (odds ratio=0.86, 95% confidence interval, 0.75–0.91) but there was no association with disease distribution or smoking, unlike UC.[21] The surgical rate in UC was correlated to age, extent of disease, smoking, and comorbid conditions.[22-24] Two other studies demonstrated a lower surgical rate in elderly IBD patients.[13,25]

Overall, the elderly have a less severe disease course with fewer relapses and hospitalizations in UC, but not in CD.[8,12] Eighty percent of elderly patients ultimately respond to medical therapy.[15,26] Nevertheless, there is a higher mortality rate after a severe initial attack (in UC or CD), often related to multiple comorbidities.

There are data supporting a lower recurrence rate in CD.[8] Generally, the initial mortality rate in elderly CD patients is similar to that in younger patients. However, the elderly have a higher mortality rate after 10 years of CD, as would be expected with advancing age, and they indeed have a higher mortality rate (F>M) after 25 years of disease or if older than 40 years of age at diagnosis.[27-32]

Surgery

Ulcerative Colitis Surgery

Although a higher rate of earlier surgery occurs in the elderly with severe pancolitis, the rate of surgery late in disease course (>5 years) is greater in young IBD patients.[33] Predictors of poor outcome in the elderly include urgent surgery and hypoalbuminemia, although

age, sex, and disease extent do not appear to influence the outcome.[21] Surprisingly, ileal-anal pouch surgery has been successful in the elderly IBD population, provided that the patient retains good anal sphincter function. Ileal pouch-anal anastomosis pouch failure rates do not differ between young and old IBD patients,[34] though anal rectal incontinence contraindicates pouch surgery. Dysplasia is a more common indication for colectomy in the elderly UC patient. Toxic megacolon occurs much less commonly, and rates of overall morbidity/mortality are lower. The anastomotic leak rates are similar to those in younger IBD patients undergoing surgery.[35]

Crohn's Disease Surgery

The need for CD surgery occurs less frequently with disease onset late in life. The likelihood of requiring surgery is two times greater with ileocolitis than with disease limited to the ileum or colon, and ileocolitis is complicated by a greater postoperative recurrence rate.[36] Elderly CD patients have higher mortality rates and more perioperative problems.[37] Disparate reports in the literature have noted recurrence rates in the elderly after CD surgery ranging anywhere from five times greater to equal to the recurrence rates in younger patients.[38]

Overall, surgical rates are usually the same and may actually be lower in elderly IBD patients than in younger IBD patients.[12,13,25] The shorter time between onset of symptoms and the first abdominal surgery is presumed to be related to the need for excluding malignancy.[8,26,39-41]

Understanding the impact of making diet and lifestyle changes is crucial to the success of the elderly patient's IBD management. Elderly patients have a lower caloric requirement, often with restrictive diets (eg, low salt, sugar, fat) due to comorbidities. A low residue diet is often advised with active disease or fibrostenosis, but enteral nutrition is of limited use. Supplemental vitamin D and calcium are necessary but often overlooked. Total parenteral nutrition is not effective as a primary therapy for UC or fistulizing CD in this population, which often takes less than 50% of their calculated energy requirements when hospitalized.[42,43] Fish-oil supplements have not been successful in the maintenance of remission.[44] There have been little or no data on butyrate enema therapy in the elderly, but its malodorous smell and difficult administration would lessen any potential efficacy.

Pharmacokinetics and Drug Interactions in Elderly Patients With Inflammatory Bowel Disease

Glucocorticosteroids

Although prednisone and prednisolone are metabolically interconvertible, prednisolone is the pharmacologically active form and has a 37% decrease in drug clearance (unbound) due to decreased renal and nonrenal functions (Table 1).[45] Budesonide (Rhinocort/Pulmicort, AstraZenca) undergoes systemic CYP3A4-mediated metabolism, which occurs in the intestinal wall and liver with a subsequent bioavailability reduction of 10–15%.[46] It is unknown whether the half-life (2.8 h) of the drug and its clearance is altered in elderly patients, but its high clearance, dependent upon hepatic blood flow, may provide greater bioavailability. Glucocorticosteroids (GCS) are associated with a greater number of adverse events, particularly osteoporosis and mental status changes, in elderly IBD patients.[47,48]

Coadministration of phenytoin, phenobarbital, ephedrine, or rifampin accelerates GCS clearance and lessens its activity.[3,49-51] The elderly are especially prone to hypertension, hypokalemia, hyperglycemia, and mental status changes, including depression.[47,48] Although recent literature regarding the herbal supplement St. John's Wort (inducer of the CYP3A4 enzyme) has shown a lack of pharmacokinetic interaction with prednisone, vigilance is still warranted with concurrent usage in the elderly.[52] Even when used as an enema, as much as 25% can be absorbed (eg, 60 mg hydrocortisone acetate in an enema corresponds to the absorption of 3 mg of prednisone).[3] In addition, when prescribing GCS, it is always important to have an exit strategy (eg, use of immunomodulators or retrial of high-dose 5-ASA).

5-Aminosalicylates

5-ASA has a half-life of 0.5–2 hours with a clearance range of 300–610 mL/min depending upon intestinal and hepatic acetylation (Table 2). In the elderly, sulfasalazine elimination is slower ($t_{1/2}$=13.7 h) and associated with a decreased glomerular filtration rate (GFR) and renal clearance of acetylated 5-ASA (an increase of 50% in inactive acetylated metabolites in steady-state plasma levels).[53] Potential nephrotoxicity (interstitial nephritis) may occur if there is decreased renal function.[54] 5-ASA formulations, particularly olsalazine, may increase the international normalized ratio (INR) and prothrombin time when administered with warfarin.[3,55] Elevated 6-thioguanine (6-TGN) metabolites of 6-mercaptopurine (6-MP)/azathioprine (AZA) may occur with 5-ASA, particularly in a dose-dependent manner (ie, increased 6-TGN levels of 40% with a 2.0-g dose and a 70% increase with a 4.0-g dose by a mechanism that is as yet unknown).[56] This combination of drugs may result in myelotoxicity in a small percentage of patients (7.7%). Paradoxically, IBD patients refractory to conventional doses of 6-MP/AZA may benefit from the elevated 6-TGN levels produced by the administration of 5-ASA.[56] Also noted are subtherapeutic levels of car-

Table 1. Glucocorticosteroid (GCS) Drug Interactions

Drug	Drug-Drug Interaction	Cytochrome Association	Renal Impairment	Hepatic Impairment
Prednisone Budesonide M-prednisolone Prednisolone Dexamethasone	**Aminoglutethimide:** decreases levels/therapeutic effects of GCS **Amphotericin:** increases hypokalemic effects of amphotericin B **Antacid:** may decrease the absorption of GCS **Anticholinesterase:** concurrent use can lead to profound weakness in myasthenia gravis patients **Antidiabetic agents:** may decrease hypoglycemic effects of diabetic medications **Aprepitant:** may increase serum levels/therapeutic effects of GCS **Antifungal agents:** may increase serum levels/therapeutic effects of GCS **Barbiturates:** may decrease levels/therapeutic effects of GCS **Bile acid sequestrants:** may reduce absorption of GCS **Calcium channel blockers:** may increase serum levels/therapeutic effects of GCS **Cyclosporine:** concurrent use may increase levels of cyclosporine **Diuretics:** hypokalemic effects may be increased **Estrogens:** may increase serum levels/therapeutic effects of GCS **Fluoroquinolones:** concurrent use can increase risk of tendinopathies (tendonitis, rupture), particularly in the elderly **Isoniazid:** decreased serum levels/therapeutic effects of GCS **Macrolides:** may increase serum levels/therapeutic effects of GCS **Neuromuscular-blocking agents:** concurrent use increases the risk of myopathy **NSAIDs:** concurrent use may lead to increased incidence of GI adverse effects **Rifamycin derivatives:** may decrease the levels/therapeutic effects of GCS **Salicylates:** concurrent use may increase GI adverse effects **Thalidomide:** concurrent use may increase the risk of toxic epidermal necrolysis and DVT **Vaccine (dead organism):** may decrease the effect of vaccines **Vaccine (live organism):** may increase the risk of infection. Usage of live vaccines is contraindicated in immunosuppressed patients **Warfarin:** concurrent use may increase anticoagulant effects **Note:** Corticosteroids interfere with calcium absorption. St. John's Wort may decrease corticosteroid levels.	Substrate of CYP3A4 Induces CYP2C19, 3A4	Use with caution—fluid retention may occur	Use with caution—fluid retention may occur

DVT=deep vein thrombosis; GI=gastrointestinal; NSAIDS=nonsteroidal anti-inflammatory drugs.

diac glycosides with concurrent 5-ASA derivatives. Olsalazine can cause new diarrhea due to excessive ileal-chloride secretion.[3] There is a small (<5%) incidence of mesalamine-induced exacerbation of UC, which may respond to a drug "holiday" (ie, discontinuing the 5-ASA and observing the effects).[57]

Immunomodulators

When given with allopurinol, 6-MP/AZA increases 6-TGN levels, potentially to the point of myelotoxicity[58] (Tables 3 and 4). If coadministered, the 6-MP dose must be reduced to one third or one quarter of the standard dose. However, at one center, allopurinol has also been

Table 2. Aminosalicylate Drug Interactions

Drug	Drug-Drug Interaction	Cytochrome Association	Renal Impairment	Hepatic Impairment
Aminosalicylates	5-ASA derivatives: may decrease the metabolism of thiopurine analogs (azathioprine, mercaptopurine, thioguanine) 5-ASA derivatives: may decrease the absorption of cardiac glycosides (digitoxin, digoxin)	None	Use with caution—minimal change nephropathy and acute/chronic interstitial nephritis have been reported	Use with caution

5-ASA=5-aminosalicylic acid.

Table 3. 6-Mercaptopurine (6-MP) Drug Interactions

Drug	Drug-Drug Interaction	Renal Impairment	Hepatic Impairment
6-MP	**Allopurinol:** may cause increased levels of mercaptopurine by inhibition of xanthine oxidase; may potentiate effect of bone marrow suppression. **Aminosalicylates (olsalazine, mesalamine, sulfasalazine):** may inhibit thiopurine methyltransferase, increasing toxicity and causing leukopenia/myelosuppression **Azathioprine:** metabolized to mercaptopurine; concomitant use may result in profound myelosuppression **Doxorubicin:** synergistic liver toxicity with mercaptopurine in more than 50% of patients **Hepatotoxic drugs:** any agent that could potentially alter the metabolic function of the liver could produce higher drug levels and greater toxicities from either mercaptopurine or 6-thioguanine **Warfarin:** mercaptopurine inhibits the anticoagulation effect of warfarin by an unknown mechanism	Dose should be reduced to avoid accumulation, but specific guidelines are not available Hemodialysis removed; supplemental dosing is usually required	Dose should be reduced to avoid accumulation, but specific guidelines are not available

Table 4. Azathioprine Drug Interactions

Drug	Drug-Drug Interaction	Renal Impairment	Hepatic Impairment
Azathioprine	**Angiotensin-converting enzyme inhibitors:** concomitant therapy may induce anemia and severe leukopenia **Allopurinol:** may increase serum levels of active metabolite (mercaptopurine) **Aminosalicylates (olsalazine, mesalamine, sulfasalazine):** may inhibit thiopurine methyltransferase, increasing toxicity and causing leukopenia/myelosuppression **Mercaptopurine:** azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression **Warfarin:** anticoagulant effect may be decreased	CrCl 10–50 mL/minute: administer 75% of normal dose CrCl <10 mL/minute: administer 50% of normal dose Hemodialysis: dialyzable (~45% removed in 8 hours) Administer dose posthemodialysis: CAPD effects are unknown; CAVH effects are unknown	Use with caution in patients with hepatic impairment

CAPD=continuous ambulatory peritoneal dialysis; CAVH=continuous arteriovenous hemofiltration; CrCl=creatinine clearance.

Table 5. Methotrexate (MTX) Drug Interactions

Drug	Drug-Drug Interaction	Renal Impairment	Hepatic Impairment
MTX	**Acitretin:** may enhance hepatotoxic effects **Cholestyramine:** decreases levels of MTX **Corticosteroids:** decrease MTX uptake into leukemic cells **Cyclosporine:** concomitant administration may increase toxicity of both **Hepatotoxic agents:** may increase the risk of hepatotoxic reactions (retinoids, sulfasalazine) **Mercaptopurine:** concomitant administration may increase levels **NSAIDs:** BM suppression, aplastic anemia, gastrointestinal toxicity with concomitant therapy **Penicillins:** increase MTX concentrations (due to ↓ renal tubular secretion) **Probenecid:** increases MTX concentrations (due to ↓ in renal tubular secretion) **Salicylates:** may increase serum concentration of MTX **Sulfonamides:** may increase MTX concentrations (due to ↓ in renal tubular secretion); may ↓ folate levels increasing the risk/severity of BM suppression **Tetracyclines:** may increase MTX toxicity **Theophylline:** MTX may increase theophylline levels	Elimination ↓ with renal impairment; may require dose reduction/ discontinuation CrCl 61–80 mL/minute: reduce dose to 75% CrCl 51–60 mL/minute: reduce dose to 70% CrCl 10–50 mL/minute: reduce dose to 30–50% CrCl <10 mL/minute: avoid use Hemodialysis: Not dialyzable (0–5%)	Use caution with preexisting liver impairment Bilirubin 3.1–5 mg/dL or AST >180 units: administer 75% of dose Bilirubin >5 mg/dL: Do not use

AST=aspartate aminotransferase; BM=bone marrow; CrCl=creatinine clearance; NSAIDS=nonsteroidal anti-inflammatory drugs.

used in patients with high thiopurine methyltransferase activity and nonresponse to thiopurines by increasing 6-TGN levels with improved liver function tests.[58,59]

It should be emphasized that the combination of 6-MP and clotrimazole worsens leukopenia, angiotensin-converting enzyme inhibitors with 6-MP can induce anemia and leukopenia, and 6-MP/AZA decreases the anticoagulant effect of warfarin.[3]

Methotrexate

As methotrexate (MTX) is dependant on renal excretion, decreased GFR impacts drug clearance (Table 5).[3,60,61] NSAIDs/5-ASA inhibit renal tubular MTX excretion with the expected increase in toxicity.[3,61-64] Tetracycline inhibits intestinal absorption of MTX, and penicillin decreases its renal clearance.[3,61,64,65] MTX alters theophylline clearance and has the potential for bone marrow suppression and hepatic fibrosis.[3] Folate deficiency worsens MTX toxicity, therefore requiring supplemental folic acid.[3]

Cyclosporine

Cyclosporine (CSA) is metabolized by CYP3A4 (Table 6). No age differences in peak plasma concentration or half-life (10.7–12.7 h) have been known to be reported.[66] CSA may induce nephrotoxicity when given with antibiotics (eg, gentamicin, tobramycin, vancomycin, ketoconazole, trimethoprim/sulfamethoxazole, ciprofloxacin), histamine-2-receptor antagonists (eg, cimetidine), NSAIDs (eg, diclofenac), or melphalan (Alkeran, GlaxoSmithKline).[3,64,66,67] P-450 cytochrome inhibitors decrease CSA metabolism with the increase of CSA levels accompanied by the use of diltiazem, nicardipine, verapamil, metoclopramide, allopurinol, amiodarone, and macrolide antibiotics (eg, erythromycin, azithromycin, clarithromycin), particularly in the elderly.[3,64,66-70] Rifampin, phenytoin, phenobarbital, and carbamazepine are P-450 accelerants that reduce CSA serum levels via increased hepatic metabolism.[3,66,67]

Metronidazole

Metronidazole (MTZ) is a moderate inhibitor of CYP3A4 substrates that can increase levels of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (eg, simvastatin), sildenafil (Viagra, Pfizer), and calcium channel blockers (Table 7).[71] MTZ also potentiates warfarin, thereby prolonging INR.[3,55] Increased metabolism of MTZ (ie, elimination) occurs with coadministration of phenytoin and phenobarbital; cimetidine increases the half-life, thereby reducing MTZ clearance; and MTZ induces lithium toxicity even if a previous lithium level was stable. Alcohol induces an antabuse[71] (disulfiram) reaction; neuropathy is common and worsened in the elderly.[3,71]

Ciprofloxacin

Ciprofloxacin[72] decreases theophylline clearance with the potential for a central nervous system adverse reaction

Table 6. Cyclosporine Drug Interactions

Drug	Potentiate Renal Dysfunction	↑ Cyclosporine Levels	↓ Cyclosporine Levels	Other Interactions
Cyclosporine	**Antibiotics:** ciprofloxacin gentamicin tobramycin vancomycin trimethoprim/ sulfamethoxazole **Antineoplastic:** melphalan **Antifungals:** amphotericin B ketoconazole **Anti-inflammatory drugs:** azapropazone colchicine diclofenac naproxen sulindac **Histamine-2 blockers:** cimetidine ranitidine **Immunosuppressant:** tacrolimus **Fibric acid derivative:** fenofibrate	**Calcium channel blockers:** diltiazem nicardipine verapamil **Antifungals:** fluconazole itraconazole ketoconazole **Antibiotics:** azithromycin clarithromycin erythromycin quinupristin/ dalfopristin **Glucocorticosteroid:** methylprednisolone **Protease inhibitors:** indinavir nelfinavir ritonavir saquinavir **Other drugs:** allopurinol amiodarone bromocriptine colchicine danazol imatinib metoclopramide oral contraceptives **Food:** grapefruit juice increases absorption	**Antibiotics:** nafcillin rifampin **Anticonvulsants:** carbamazepine phenobarbital phenytoin **St. John's Wort:** decreases serum concentrations of cyclosporine, resulting in subtherapeutic levels **Other drugs:** octreotide orlistat sulfinpyrazone terbinafine ticlopidine	**Rifabutin:** increases the metabolism of drugs metabolized by the cytochrome P-450 system **Diclofenac:** doubling of blood levels and (reversible) decrease in renal function **Methotrexate:** concentrations were increased 30% and the concentrations of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance is not known. **Decreased clearance of:** digoxin colchicines prednisolone 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (eg, simvastatin, lovastatin) **Potentiate hyperkalemia with:** potassium-sparing diuretics angiotensin-converting enzyme inhibitors angiotensin II receptor blockers

(Table 8).[73] Ciprofloxacin also reduces caffeine clearance,[74] alters phenytoin concentrations in serum,[3] and enhances warfarin sodium levels, requiring meticulous coagulation surveillance.[74,75]

Biologic Therapy

Anti-tumor necrosis factor antibodies[76] are distributed in the vascular compartment with a very slow half-life of 9–14 days (Table 9). Age is not known to have an effect, but a larger number of adverse effects are expected with comorbidities such as CHF, hepatitis, bone marrow depression, and/or infection. Concurrent usage with anakinra (Kineret, Amgen) and etanercept (Enbrel, Immunex) may increase the risk of serious infections, and potassium-sparing diuretics, live vaccines, and steroids should be avoided. Related hypocholesterolemic seizures are additional concerns.[76-78]

Caveats

The basic principles when prescribing for elderly patients involve recognition of the drug type, elimination patterns,

Table 7. Metronidazole Drug Interactions

Drug	Cytochrome Association	↑ Levels of CYP3A4 Substrates	Other Drug-Drug Interaction	Renal Impairment
Metronidazole	**Inhibits CYP:** 3A4 (moderate) 2C9 (weak)	benzodiazepines calcium channel blockers cyclosporine mirtazapine nateglinide nefazodone sildenafil (and other phosphodiesterase type 5 inhibitors) tacrolimus venlafaxine cisapride ergot alkaloids 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (lovastatin, simvastatin) pimozide	**Cimetidine:** increase levels of metronidazole **Cisapride:** proarrhythmic due to inhibition of metabolism **Ethanol:** disulfiram-like reactions **Lithium:** may increase lithium levels/toxicity **Phenytoin, phenobarbital:** may increase metabolism of metronidazole **Warfarin:** increases prothrombin time prolongation	Inconsistent recommendations; consider dosage reduction in longer-term therapy with severe renal failure (CrCl <10 mL/minute)

CrCl=creatinine clearance.

Table 8. Ciprofloxacin Drug Interactions

Drug	Cytochrome Association	↑ Levels/Effects of CYP1A2 Substrates	Drug-Drug Interaction	Renal Impairment
Ciprofloxacin	**Inhibits CYP:** 1A2 (strong) 3A4 (weak)	aminophylline fluvoxamine mexiletine mirtazapine ropinirole tizanidine trifluoperazine	**Caffeine:** may decrease caffeine metabolism **Foscarnet:** associated with an increased risk of seizures **Glyburide:** may increase therapeutic effects **Methotrexate:** may decrease renal secretion **NSAIDs:** risk of seizures may be increased **Phenytoin:** may decrease levels **Probenecid:** concurrent usage may decrease renal excretion **Sevelamer:** may decrease oral absorption **Theophylline:** levels may increase **Tizanidine:** levels may increase—contraindicated **Warfarin:** anticoagulant effect may be enhanced **Metal cautions (aluminum, calcium, iron, magnesium, and zinc):** bind quinolones in the gastrointestinal tract and inhibit absorption	Caution warranted with renal impairment—dosage adjustment required

NSAIDS=nonsteroidal anti-inflammatory drugs.

Table 9. Biologic Drug Interactions

Drug	Drug-Drug Interaction	Cytochrome Association	Renal Impairment	Hepatic Impairment
Infliximab	**Abciximab:** increases potential for hypersensitivity reaction; may increase risk of thrombocytopenia and/or reduced therapeutic efficacy **Anakinra:** may increase risk of serious infection when used in combination **Etanercept:** may increase risk of serious infection when used in combination **Vaccine (dead organism):** infliximab may decrease the effect of vaccines **Vaccine (live organism):** immunosuppressants may enhance the adverse/toxic effects of vaccines	No	No	No
Adalimumab	**Anakinra:** increases risk of serious infection and neutropenia **Methotrexate:** reduces adalimumab clearance **Vaccine (live organism):** immunosuppressants may enhance the adverse/toxic effects of vaccines	No	No	No
Natalizumab	Caution with concurrent immunomodulator therapy/immunosuppression/antineoplastic therapy, as they may be risk factors for the development of PML, opportunistic infections, and neoplasms Interferon beta-1a: may increase the levels of natalizumab; no dosage adjustment necessary Caution advised in patients with history of depression Caution advised with hepatotoxic drugs, as they can increase bilirubin and transaminases	No	Not studied	Postmarketing reports of hepatotoxicity

PML=progressive multifocal leukoencephalopathy.

drug metabolism enzymes, and GFR effects. Most drugs require metabolic processing prior to elimination, as with hepatic elimination in the younger IBD patient and in the "fit elderly" population. An age-dependent decline occurs in GFR, but to a lesser degree in the latter population.

Caution is required when using antidiarrheals, analgesics, or opioids, as these agents may be less effective due to higher endogenous opioid levels.[79] Therefore, there is an inherent but faulty tendency to push dosage with adverse events such as confusion, ileus, or impaction. Anticholinergics should be avoided because of side effects associated with urinary retention, glaucoma, confusion, or arrhythmias, which are particularly problematic in the elderly.

Frailty may be more important than age in drug elimination. Therefore, a safe principle is "start low; go slow" when initiating any drug in this population.

Osteoporosis

The fracture rate is higher in the elderly population and associated with an additive drug effect (GCS, MTX, CSA) to the disease impact with an increase of inflammatory cytokines. Coexistent malabsorption (vitamin D, calcium) is often overlooked (85% of hospitalized elderly patients are "protein malnourished").[43] Twenty-one percent of hospitalized seniors take in less than 50% of their calculated maintenance nutritional requirements.[42]

Summary

In conclusion, it is important to recognize the impending burden of baby boomers on healthcare, which will create new standards for the allocation of available resources. The present concepts of the immutability of genetic

predisposition to disease by the aging effect should be challenged. Physicians should examine questions such as, "Does the diagnosis or the character of the disease change with time?" This change is seen in UC conversion to CD and altered severity with aging. It is essential to distinguish between the "fit elderly" and "frail elderly" when designing clinical trials, studying pharmacokinetics, and evaluating data. Another important issue is to establish a cadre of clinician-investigators skilled in the biology of aging (ie, drug interactions and comorbid disease impact), with the goal of saving lives in addition to saving money. One current approach to drug therapy in the elderly is to "start low; go slow" and then reassess their candidacy for more aggressive therapy (biologics, apheresis, surgery) and not treat or exclude patients on the basis of age alone.

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