CROHN'S & COLITIS FOUNDATION OF AMERICA

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An Update in Inflammatory Bowel Disease Medications

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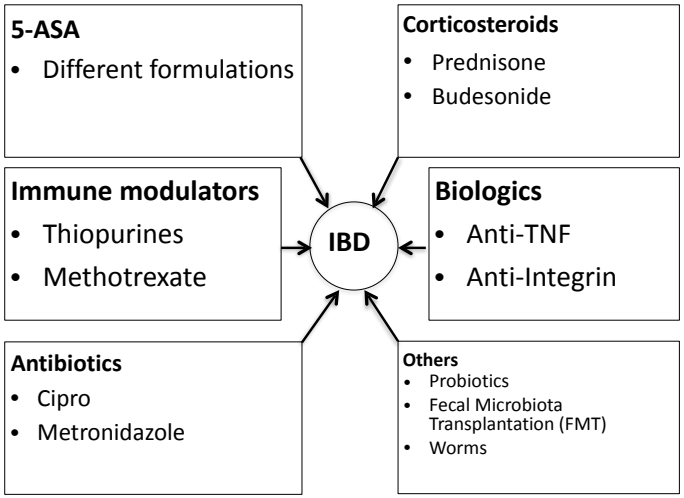
Inflammatory Bowel Disease (IBD)

is due to an
Inappropriate Inflammatory Response to
Intestinal Microbes in a
Genetically Susceptible Host

Abraham et al: NEJM 2009

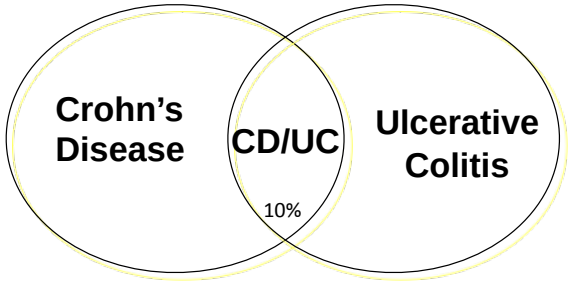
Medications in IBD



Targets and Effects

- Target at stopping inflammation
- Aminosalicylates (5-ASA) and/or Steroids are effective in ***Mild to Moderate Disease*** and ***Acute Flares***
- Biologics and combination with immunomodulators are more efficacious in ***Moderate and Severe Disease*** for
  - achieving mucosal healing
  - decreasing disease complications
  - needing surgery

Crohn's Disease and Ulcerative Colitis are part of a spectrum of Inflammatory Bowel Disease



Incidence: CD =7 in 100,000 ; UC = 10-15 in 100,000

	UC	CD
1950's	sulfasalazine steroids	
	New FDA Approved Medications	
1997	Asacol (mesalamine)	
1998		Remicade (inflixmab) *adult
2000	Colazal (basalazide)	
2001		Entocort (budesonide)
2006		Remicade (inflixmab) *peds
2007	Liada (mesalamine)	Humira (adalimumab)
2008	Apriso (mesalamine)	Tysabri (natalizumab) Cimzia (certolizumab pegol)
2011	Remicade (inflixmab) *adult	
2012	Humira (adalimumab)	
2013	Uceris (budesonide) Delzicol (mesalamine) Simponi (golimumab)	
2014	Entyvio (vedolizumab)	Entyvio (vedolizumab)

IBD Medications (Route of Delivery)

1	**Aminosalicylate (5-ASA)**	Oral Enema Suppository
2	**Corticosteroid/ Immunosuppressive**	Oral Rectal Intravenous
3	**Immunomodulator**	Oral Injection
4	**Biologic**	Injection Infusion
5	**Antibiotic**	Oral Intravenous
6	**Probiotic**	Oral Rectal
7	**Fecal Microbiota Transplant** (investigational)	Oral Rectal
8	**Worm** (small studies)	Oral

Aminosalicylate (5-ASA) Formulations

Sulfasalazine (AZULFADINE)	Drug linked to sulfapyridine - delayed released tablet
Basalazide (COLAZAL)	Drug linked to inert molecule - capsule
Osalazine (DIPENTUM)	Drug linked to drug (mesalamine-mesalamine) capsule
Mesalamine (PENTASA)	Time released (ethylcellulose-coated microgranule) capsule
Mesalamine (LIADA)	MMX drug released at pH ≥7 (gastro resistant polymer film-coated) tablet
Mesalamine (ASACOL HD)	Delayed release tablet
Mesalamine (APRISO)	Extended release capsule
Mesalamine (DELZICOL)	Delayed release capsule
Mesalamine enema (ROWASA)	Topical directly in the left distal colon
Mesalamine suppository (CANASA)	Topical mesalamine directly in rectum

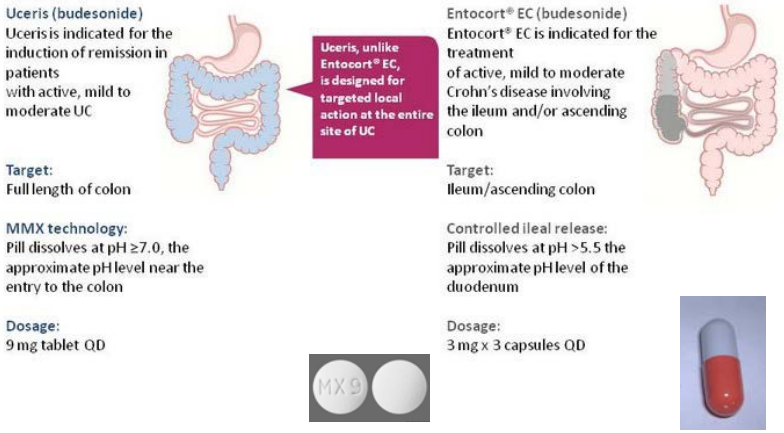
Side Effects of 5-ASA

sulfasalazine	headache, nausea, loss of appetite, rash, fever, low WBC count, pancreatitis
mesalamine	abdominal pain, cramps, diarrhea, gas, nausea, hair loss, headache, dizziness, decrease kidney function
olsalazine	diarrhea most common
balsalazide	headache, abdominal pain

Corticosteroid Preparations

prednisone	oral
budesonide	oral (EC, MMX), rectal foams
methyl-prednisone	intravenous, enemas
hydrocortisone	intravenous, enemas, rectal foams
cortisone	enemas

MMX technology vs Enteric Coated Delivery System



Side Effects of Corticosteroid

- high blood pressure
- high blood sugar levels
- increased risk of infection
- cataracts
- osteoporosis (weakened bones)
- osteonecrosis (avascular necrosis)
- rounding of the face "moon face"
- acne
- increased facial hair
- stretch marks
- weight gain
- mood swings
- psychosis and other psychiatric symptoms
- insomnia (difficulty sleeping)

Corticosteroid usage - Caveats

- Steroids cannot be stopped abruptly after prolonged use. Dose adjustments must be gradual reductions to zero over several weeks
- Half of patients treated with steroids become steroid dependent or steroid resistant
- 30% acute IBD may not respond to steroids

Corticosteroids in IBD

(Moderate to Severe Disease)

	UC (n=63)			CD (n=74)		
	Remission	Steroid dependent	No change	Remission	Steroid dependent	No change
1-month responses*	54% (34)		16% (19)	58% (43)		16% (10)
12- months responses	49% (31)	22% (14)	29% (18) Surgery	32% (24)	28% (21)	38% (28) Surgery

***30 days after initiating corticosteroid therapy**

>50% will fail steroids in 1 year

Faubion W et al. *Gastroenterology* 2001;121:225

Off Label Prescription

- Immunomodulators
  - Azathioprine (Imuran) is approved for rheumatoid arthritis and to prevent organ rejection after a transplant
  - Methotrexate is approved to treat cancer and severe cases of psoriasis and rheumatoid arthritis
- Immunosuppressives
  - Cyclosporine: approved for organ transplant; iv cyclosporine is effective in fulminant UC not CD
  - Tacrolimus (FK506): approved for organ transplant; effective in refractory UC & pyoderma gangrenosum
- Antibiotics
  - metronidazole (Flagyl) and ciprofloxacin (Cipro) in treating Crohn's disease absence of infection

Immunomodulators

Purines • Azathioprine (IMURAN) • 6-mercaptopurine (PURANTOL)	oral
Methotrexate (ABITREXATE, FOLEX, MEXATE)	oral (not effective), injection (sq or im 25mg/week for Crohn's)

Uses of Immunomodulators

- not responsive to 5-ASA or corticosteroids
- steroid-dependent disease
- experienced side effects with corticosteroid treatment
- perineal disease that does not respond to antibiotics
- fistulas (abnormal channels between two loops of intestine, or between the intestine and another structure—such as the skin)
- to maintain remission
- Combine with biologics for moderate to severe disease for both UC, CD

Immunomodulators- Caveats

Purines

- Need to monitor for liver toxicity and bone marrow suppression and kidney damage
- Check for TPMT level
- Monitor 6-TG level
- Use folate supplement

MTX

- Monitor of liver toxicity and bone marrow suppression
- Use folate supplement

Rate of Non-Hodgkin Lymphoma associated with Immunomodulator and anti-tumor Necrosis Factor treatment

	Baseline US population*	Immunomodulator-treated†	Anti-TNF + immunomodulator-treated
Rate of lymphoma per 10,000 patient-years	1.9	3.6	6.1
Relative risk of anti-TNF + immunomodulator therapy			
Compared to baseline: SIR 3.23 (95% CI 1.5–6.9)			
Compared to immunomodulator alone: SIR 1.7 (95% CI 0.5–7.1)			

CI= confidence interval;
SIR= standardized incidence ratio.

*Based upon data from the Surveillance Epidemiology End Results registry.
†Immunomodulator=azathioprine or 6-mercaptopurine.

Imuran (azathioprine) Tablets and Injection

Serious Infections (***February 2014)***

Progressive Multifocal Leukoencephalopathy. ….Cases of JC virus-associated infection resulting in progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with immunosuppressants, including Imuran.

Malignancy (*May 2011)*

Lymphoma and Hepatosplenic T-cell lymphoma (HSTCL)

….Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease.

INCIDENCE is RARE

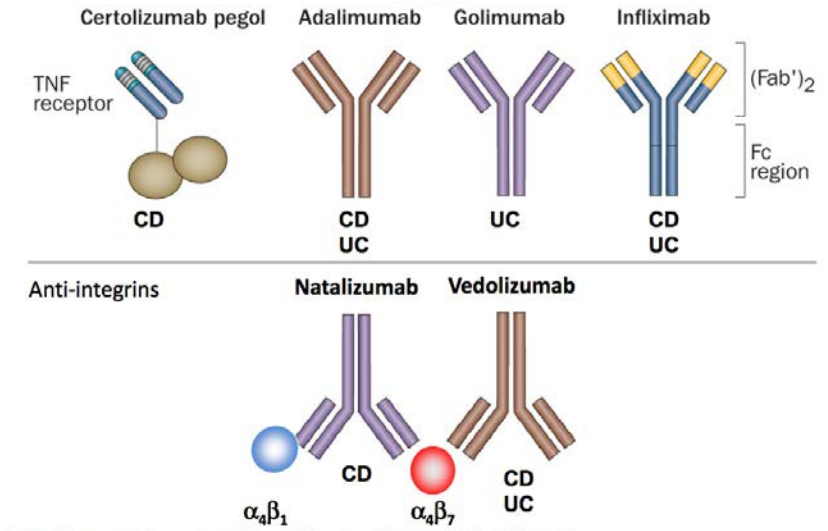
About 1 in 8 (12%) women in the US will develop invasive breast cancer during their lifetime.

discuss with your doctor; overall, thiopurines are safe to use

Biologic

- genetically engineered medications made from living organisms
- target at specific molecular players in the inflammatory process such as cytokines— specialized proteins that play a role in increasing or decreasing inflammation
- targets include tumor necrosis factor (TNF)-alpha, interleukins, adhesion molecules, colony-stimulating factors, and others

Biologic Medications for IBD



Modified from van Schouwenburg, P. A. *et al. Nat. Rev. Rheumatol.* 2013:;9(3):164-72.

Administration of Biologics

Intravenous Infusions

Infliximab, Vedolizumab

- Schedule
  - Induction: 0,2,6 weeks
  - Maintenance: q 8 weeks
- Dose
  - IFX (5mg/Kg)
  - Vedo (300mg @)

Subcutaneous Injections

Adalimumab
- Schedule: q2weeks
- Dose: 4,2,1 (40mg @)

Certolizumab
- Schedule:
  - Induction: 0,2,4 weeks
  - Maintenance q 4 weeks
- Dose: 1

Golimumab
- Schedule:
  - Induction q2 weeks 1st 2 shots
  - Maintenance q 4 weeks
- Dose: 2,1(100mg @)

Caveats of using Biologics

- TB skin testing prior to treatment
- Vaccination (inactivated influenza, tetanus, HPV, meningococcus, HAV, HBV); Live, attenuated influenza (intranasal vaccine)
- Contraindicated live vaccines:
  - Varicella zoster vaccine
  - Herpes zoster (live zoster vaccine)
  - Yellow fever vaccine
  - Measles-mumps-rubella vaccine
  - Typhoid live oral vaccine
  - Smallpox vaccine
  - Tuberculosis Bacillus Calmette-Guérin vaccine
  - Polio live oral vaccine
  - Anthrax vaccine
- Skin examination surveillance for skin cancer
- Trough drug level after loading dose prior to maintenance therapy
- Antibody testing if decreasing response
- Monitor for risk for infection

Adverse Effects of Anti-TNF Therapy

- Infusion-related reactions
- Infection and malignancy
  - Serous infection
  - Lymphoma and HSTCL (adalimumab, infliximab)
- Reactivation of HBV, TB
- Skin cancer
- Psoriasis
- Autoimmunity (lupus-like syndrome)
- Immunogenecity – antibodies to anti-TNF
- Demyelinating disorder, CHF, liver toxicity

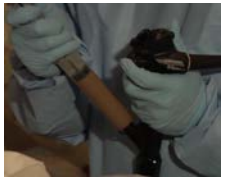
Adverse Effects of Anti-integrin Therapy

- Adverse effects of immunosuppression but less frequent than anti-TNF
- Progressive Multifocal Leukoencephalopathy (PML) a JC Virus infection in the brain was reported in natalizumab (anti-α4β1 integrin) not vedolizumab (anti-α4β7 integrin) use

Other Therapies in IBD

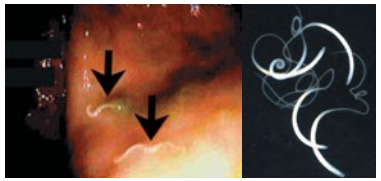
Bacteriotherapy

- Probiotics – effective in pouchitis
- FMT –
  - mixed results in UC ;
  - Larger studies are ongoing

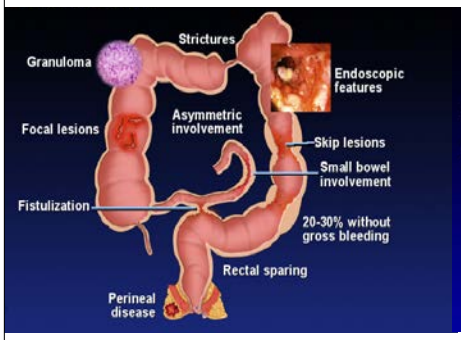


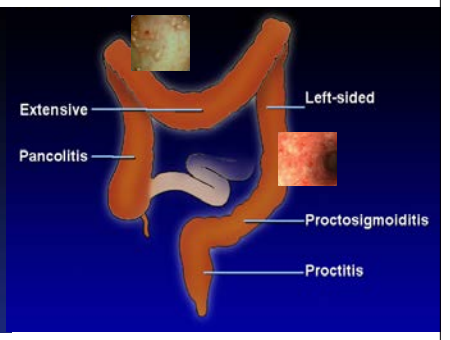
Worm (Trichuris Suis Ovum) Therapy

- CD trial (N=36): no response
- UC trial (n=54) 12 weeks:
  - positive response;
  - ↓UCDAI ≥ 4:
  - TSO:placebo = 43%:16.7% (p=0.04)



Crohn's Disease Ulcerative Colitis

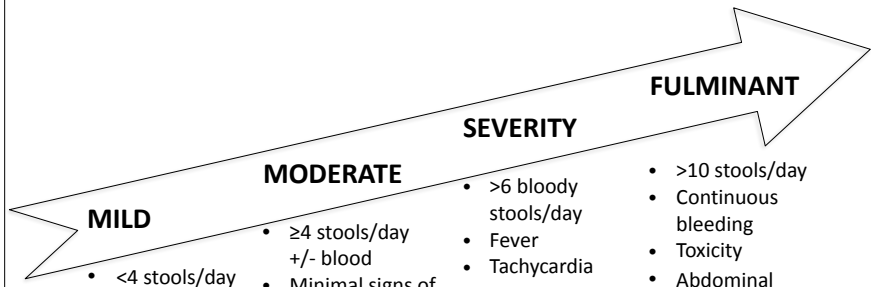




Features of CD:
Penetrating
Stricturing
Inflammatory

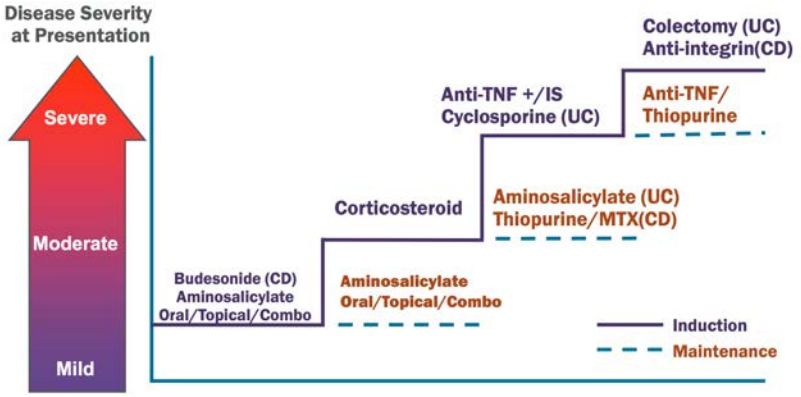
Features of UC:
Inflammatory

Severity of UC



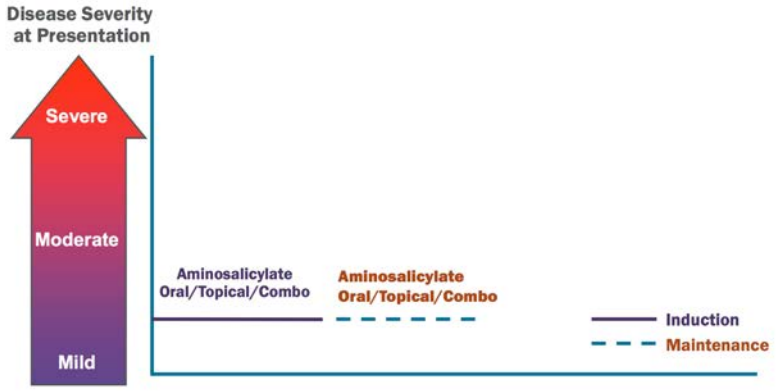
- **MILD**
  - <4 stools/day +/- blood
  - Normal ESR
  - No signs of toxicity
- **MODERATE**
  - ≥4 stools/day +/- blood
  - Minimal signs of toxicity
- **SEVERITY**
  - >6 bloody stools/day
  - Fever
  - Tachycardia
  - ↑ ESR
- **FULMINANT**
  - >10 stools/day
  - Continuous bleeding
  - Toxicity
  - Abdominal tenderness/ distension
  - Transfusion requirment
  - Colonic dilation on X-ray

Sequential Therapies for IBD



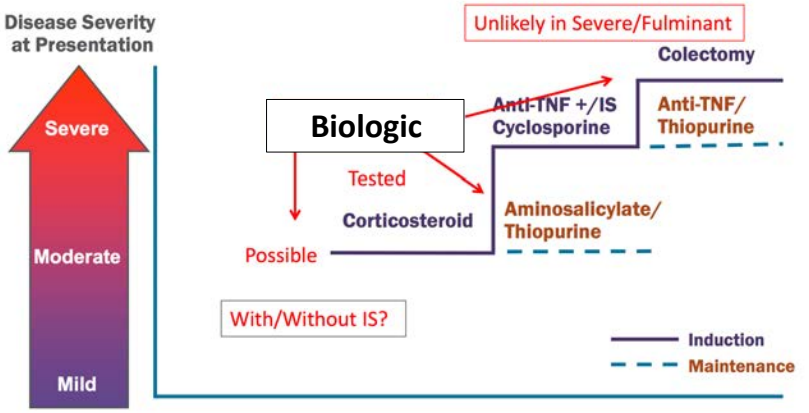
Hanauer

Mild to Moderate UC



Hanauer

Role of Biologics Rx in Moderate to Severe UC

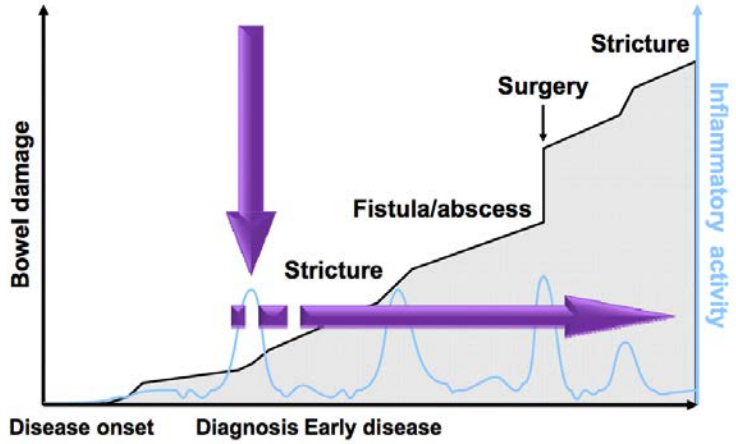


Hanauer

Clinical Remission Rates in CD Patients with Conventional Therapies

- Aminosalicylates
  - *Mild-Moderate Disease ~45-55%*
- Antibiotics
  - *Few controlled trials*
  - *Mild-Moderate Disease ~50%*
- Budesonide
  - Mild-Moderate Disease ~65-75%
- Corticosteroids
  - *Moderate to Severe Disease~70-80%*

Early initiation of Biologic Rx to Prevent Progression of CD



Pariente B, *et al. Inflamm Bowel Dis* 2011;17:1415–22

Risk Factors for Progression of CD

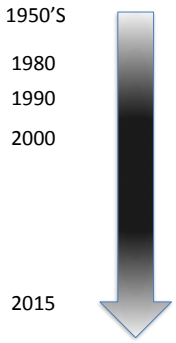
- Age of onset <40
- Elevated CRP
- Initial requirement of steroids
- Perianal fistulizing disease
- Genetic markers
  - NOD2/IBD5
- Smoking
- Severe endoscopic lesions
- Stricturing, penetrating behaviour
- Terminal ileum locaion
- Serological markers
  - ASCA/ANCA

Vargas et al Gastro DDW 2013 Abs 557
Danese S Aliment Pharmacol Ther 2011;33;857
Beaugerie L et al Gastroenterology 2006;130:650-6

Reasons for Medications Failure

- Non-adherence
- Inadequate dose
- Antibodies formation to biologics
- Other causes e.g. coexisting infection
- Misdiagnosis
- Allergic/sensitive/intolerance to drug

Goals of Medical Treatment



- Symptoms control
- Improve quality of life
- Mucosal healing
- Decrease hospitalization
- Avoid surgery

SUSTAINED DISEASE CONTROL

Take Home Message (I)

- Medications don't work if you don't take them.
- Maintenance therapy is needed in the majority of patients.
- Improvement of symptoms may not reflect mucosal healing.
- Cohn's Disease can run a more complicated course than ulcerative colitis. It can progress to fibrostenotic or fistulizing disease. Biologic therapies can decrease progression when use in the early phase of the disease in high risk patients.

Hsu

Take Home Message (II)

- 5-ASAs are effective in mild to moderate disease.
- Corticosteroids and immunosuppressive drugs can control flares but should not be used for long term maintenance.
- Immunomodulators are used in maintenance therapy for moderate to severe disease. They are also used in combination with biologics to decrease immunogenicity and potentiate effectiveness.

Hsu

Take Home Message (III)

- Biologics are very effective in stopping inflammation. Special measures and monitoring are necessary to avoid infection and enhance drug responsiveness.
- More biologics are being developed. Update the advances in IBD treatments from reliable resources.
- Work with your doctor to achieve our common **Goals of Medical Treatment.**

Hsu