AUTOIMMUNE DISEASES

Guardian Pharmacy

1

OBJECTIVES

- Explore a general overview of autoimmune disease
- Review how autoimmune diseases affect system function
- Examine the signs/symptoms of several of the more common conditions, as well as touch on some less common manifestations of autoimmune disease
- Look at the evolution of treatments for these conditions
- Review several treatment options, their efficacy, and how they have impacted the treatment of autoimmune diseases

2

What is an Autoimmune Disease?

- Autoimmune = a disorder of the body's defense mechanism in which an immune response is generated against component or products of its OWN tissues; treating them as foreign material and attacking them.
- Disorder caused by inflammation and destruction of tissues by the body's immune response as a result of autoimmunity is known as autoimmune disease.
- A variety of mechanisms have been proposed to account for the T-cell mediated generation of autoimmune disease. It is likely that autoimmune disease does not develop from single event but rather from a number of different events.

3

Autoimmune Disease Risk Factors

- **Genetics**:
  - Certain disorders such as lupus and multiple sclerosis (MS) tend to run in families.
  - "Having a relative with autoimmune disease increases your risk, but it doesn't mean you will develop a disease for certain," says Orbai.
- **Weight**:
  - Being overweight or obese raises your risk of developing rheumatoid arthritis or psoriatic arthritis. This could be because more weight puts greater stress on the joints or because fat tissue makes substances that encourage inflammation.
- **Smoking**:
  - Research has linked smoking to a number of autoimmune diseases, including lupus, rheumatoid arthritis, hyperthyroidism and MS.
- **Certain medications:**
  - "Certain blood pressure medications or antibiotics can trigger drug-induced lupus, which is often a more benign form of lupus," Orbai says. "Our myositis center also discovered that specific medications used to lower cholesterol, called statins, can trigger statin-induced myopathy."
  - Myopathy is a rare autoimmune disease that causes muscle weakness.
  - Before starting or stopping any medications, however, make sure to talk to your doctor.

4

Systemic or Non-Organ Specific Autoimmune Diseases

- Type of autoimmune disease which is directed against an antigen that is present in many different sites and can include involvement of several organs and tissues.
- They are one of the leading causes of death and disability.
- With the use of glucocorticoids, immune suppression drugs and new developed biologics, the outcome of this group of diseases has greatly improved, but there is still no cure for them. Knowledge of the pathogenesis, diagnosis, and treatment of those diseases will lead to better understanding of the diseases and better care of patients.
- These disease reflect a general defect in immune regulation that result in hyperactive T-cells and B-cells.
  - **Examples**: Rheumatoid arthritis, Systemic Lupus Erythematosus (SLE), Multiple Sclerosis (MS)

5

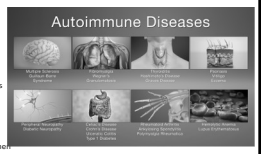
Organ Specific Autoimmune Diseases

- Autoimmune disease directed against a component of one particular type of organ.
- The organ specific autoimmune disease can further be divided into two groups:
  1. **Autoimmune disease mediated by direct cellular damage:**
     - This type of damage occur when lymphocytes or antibodies bind to cell membrane antigens, causing cellular lysis or inflammatory response in the affected organ.
     - The damaged cellular structure is then replaced by connective tissue (fibrous) & loses its function.
     - Examples: Hashimoto's thyroiditis, autoimmune anaemia, Goodpasture's syndrome, Insulin dependent diabetes mellitus.
  2. **Autoimmune disease mediated by stimulating or blocking auto antibodies:**
     - In some cases, antibodies act as antagonists & bind to hormone receptors stimulating inappropriate activity. This usually leads to overproduction of mediators or increase cell growth.
     - They also bind to hormone receptors and thereby block receptor function. This causes impaired secretion of mediators and gradual atrophy of the affected organ.

6

Prevalence of Common Autoimmune Diseases

- Thyroid diseases (includes Hashimoto's thyroiditis and Graves' disease):
  - More than 3% of adult women
- Rheumatoid arthritis:
  - 1% of general population, but female excess
- Primary Sjogren's syndrome:
  - 0.6% to 3% of adult women
- Systemic lupus erythematosus:
  - 0.12% of general population, but female excess
- Multiple sclerosis:
  - 0.1% of general population, but female excess
- Type 1 diabetes mellitus:
  - 0.1% of children
- Primary biliary cirrhosis:
  - 0.05% to 0.1% of middle-aged and elderly women
- Myasthenia gravis:
  - 0.01% of general population, but female excess



7

Disease	Self antigen	Immune response
ORGAN-SPECIFIC AUTOIMMUNE DISEASES		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_H1 cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_H1 cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
SYSTEMIC AUTOIMMUNE DISEASES		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjögren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

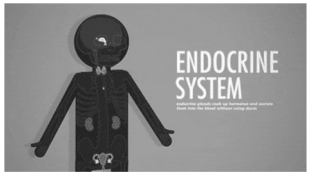
8

Organ Specific Autoimmune Diseases

- **Endocrinological**
  - Grave's Disease
  - Hashimoto's Thyroiditis
  - Type 1 Diabetes
  - Addison's Disease
  - Autoimmune Pancreatitis
- **Neurological**
  - Myasthenia Gravis
  - Guillain Barre Syndrome
- **Gastrointestinal**
  - Ulcerative Colitis
  - Pernicious Anemia
  - Celiac Disease
  - Primary Biliary Cirrhosis
- **Hematological**
  - Hemolytic Anemia
  - Immune Thrombocytopenic Purpura
- **Dermatological**
  - Scleroderma
  - Dermatomyositis
  - Psoriasis
  - Vitiligo
  - Alopecia Areata

9

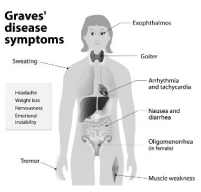
Endocrinological Autoimmune Diseases



10

Graves Disease

- The production of thyroid hormones is carefully regulated by thyroid stimulating hormone (TSH) produced by pituitary gland.
- The binding of TSH to receptors on thyroid cell activates adenylate cyclase enzyme → stimulating synthesis of thyroxine and tri-iodo thyroxine.
- A patient with Graves' disease produces autoantibody (LATS) that bind to receptor of TSH & mimics the normal action of TSH, activating adenylate cyclase & resulting in production of thyroid hormones.
- Unlike TSH, antibodies are not regulated and consequently, they overstimulate the thyroid gland.



11

Graves Disease Treatment

First-Line

- *β*-Blockers provide quick control of adrenergic symptoms; start while workup is in progress. Long-acting propranolol is used most commonly and titrated to symptom control (40 to 160 mg/day).
- Radioactive iodine (RAI)
  - Concentrates in the thyroid gland and destroys thyroid tissue
  - Radioiodine plus prednisone therapy has the least probability of leading to an exacerbation or new appearance of ophthalmopathy. Solo radioiodine therapy has the least probability of causing a recurrence.
  - Treatment of choice for definitive therapy of hyperthyroidism in the absence of moderate or severe orbitopathy
  - Risks:
    - Side effects (neck soreness, flushing, decreased taste); worsening ophthalmopathy (15% incidence, higher in smokers);
    - Posttreatment hypothyroidism (80% incidence, not dosage-dependent); radiation thyroiditis (1% incidence);

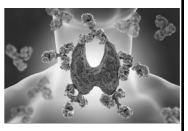
Pretreatment with antithyroid medication should be considered in patients with severe disease and the elderly, to reduce risk of posttreatment transient hyperthyroidism and posttreatment radiation thyroiditis as well as quicker return to normal thyroid function.

  - May be repeated in as soon as 3 months if minimal response or after 6 months if not euthyroid

12

Hashimoto's Thyroiditis

- In Hashimoto Thyroiditis, the individual produces antibodies & sensitized TH1 Cells specific for thyroid antigens.
- A delayed type hypersensitivity (DTH) response is characterized by an intense infiltration of the thyroid gland by lymphocytes, macrophages and plasma cells which form lymphocytic follicles and germinal centers.
- The following inflammatory response causes goiter (visible enlargement of the thyroid gland)
- Hypothyroidsm is caused when antibodies are formed against a number of thyroid proteins including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine.
- Binding of auto-antibodies to these proteins interferes with thyroid gland function



13

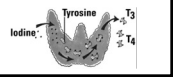
Hashimoto Disease Treatment

First-Line

- Levothyroxine (Synthroid, Levothroid)
  - 1.5 to 1.8 µg/kg/day (use ideal body weight); titrate by 12.5 to 25 µg/day every 4 to 8 weeks until TSH in normal range.
  - Dosage requirements may vary with age, gender, residual secretory capacity of thyroid gland, other drugs being taken by patient, and intestinal function.
  - Use caution when changing between capsule, tablet, and injection as dose conversions are not a 1:1 ratio.
  - Levothyroxine should be taken on an empty stomach, ideally an hour before breakfast. Administering at bedtime may result in higher levels than administering in the morning.
  - Medications that interfere with its absorption should be taken 4 hours after the dose: ferrous sulfate, PPIs, calcium carbonate, bile acid resins.

Second-Line

- No benefit to adding T3 to T4.
- Desiccated thyroid hormone is not recommended for the treatment of hypothyroidism.
- Liothyronine (T3) or desiccated thyroid hormone (T3 and T4) may be an alternative for patients who do not feel balanced on T4 alone.



14

Type I Diabetes

- T1DM or Insulin Dependent Diabetes Mellitus (IDDM) is caused by an autoimmune attack on pancreas
- The attack is directed against specialized insulin producing Beta-cells that are located in islets of Langerhans, scattered throughout the pancreas
- The autoimmune attack destroys beta cells resulting in decreased production of insulin and subsequently increased levels of blood glucose.
- Several factors are important in destruction of beta cells:
  - Activated CTLs migrate into an islet and begin to attack the insulin producing cells.
  - The CTL infiltration & activation of macrophages, frequently referred to as insulitis, is followed by cytokine release and presence of autoantibodies. This leads to a cell mediated DTH.
- The autoantibodies to beta cells may contribute to cell distribution by facilitating either antibody-mediated complement lysis or antibody-dependent cell-mediated cytotoxicity (ADCC).

15

Type I Diabetes Pharmacological Treatment

- Most patients with T1DM will require insulin supplementation, either multiple-dose insulin (MDI) injections or continuous subcutaneous insulin infusion (CSII).
- Types of insulin:
  - Long-acting insulin analogues:
    - insulin glargine (Lantus/Toujeo)
    - insulin detemir (Levemir)
    - insulin degludec (Tresiba)
    - These should not be mixed with other insulins in the same syringe.
  - Intermediate-acting insulin (NPH):
    - Humulin N
    - Novolin N
    - can be mixed with other insulins.
  - Short-acting (regular) insulin:
    - Novolin R
    - Humulin R
  - Very rapid-acting insulin analogues:
    - insulin lispro (Humalog)
    - insulin aspart (Novolog)
    - insulin glulisine (Apidra)

16

Type I Diabetes Pharmacological Treatment cont.

First-Line

- Flexible intensive insulin therapy is the gold standard
- MDI or CSII have equal efficacy
- Total initial dose is 0.2 to 0.4 U/kg/day for insulin-naive patients (will often need 0.6 to 0.7 U/kg/day).
- 40–60% of total dose given as basal insulin, with the rest as bolus insulin
- MDI regimen:
  - Basal, long-acting insulin once or twice a day
  - Prandial, short-acting insulin based on number of carbohydrate portions (e.g., 1:10, meaning 1 U of insulin for every 10 g of carbohydrate to be eaten)
  - Correctional short-acting mealtime insulin based on premeal blood glucose level (subtract target blood glucose level and divided by sensitivity factor)
- CSII regimen:
  - May use regular insulin or rapid-acting insulin analogues
  - Insulin is infused continuously at a preset rate, and bolus doses are given with meals as above.

Second-Line

- Twice-daily injections with NPH along with regular or rapid-acting insulin
- Pramlintide- delays gastric emptying, increases satiety and weight loss; if used, adjustment of mealtime insulin dose required
- Pancreatic transplantation is usually reserved for patients with end-stage renal failure, who may receive kidney-pancreatic transplants at the same time.
- Oral hypoglycemics generally not indicated in type 1 diabetes
- Ongoing trials with tocilizumab to prevent beta cell loss in type 1 diabetes

17

Type I Diabetes Non-Pharmacological Treatment

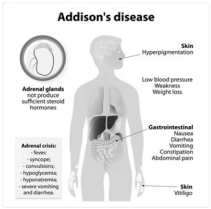
General Measures

- Education regarding matching of meal-time insulin dose to carbohydrate intake, premeal blood glucose level and anticipated activity
  - Before meals, strive for blood glucose levels in range of 80-130 mg/dL (5.0 to 7.2 mmol/L).
  - Bedtime/overnight: 90 to 150 mg/dL (5.0 to 8.3 mmol/L)
  - A1c goal: <7.5% across all pediatric age groups
    - Very tight control might be dangerous in young children due to risk of repeated hypoglycemia.
- Adult A1c goal: <7.0%
  - A1c <6.5% reasonable in select individuals
  - Less stringent A1c goals (such as <8%) may be appropriate for elderly patients and other special populations.
- Normal growth and development and overall good health (asymptomatic) :
  - Reach optimal height for genetic potential.
  - Appropriate and timely pubertal maturation
  - Coping psychosocial development: normal school or work attendance and performance; normal goals/career plans. Screen for depression.
- Prevent acute complications, including hypoglycemic insulin reactions and ketoacidosis, and delay or prevent chronic end-organ complications.

18

Addison's Disease

- An uncommon autoimmune disease characterized by chronic and insufficient functioning of the outer layer of the adrenal gland
- The adrenal glands are located atop each kidney and produce vital glucocorticoid hormones
- Because of this chronic under-functioning of the adrenal glands, persons with Addison's disease have a deficiency in the production of glucocorticoid hormones.
- Glucocorticoid hormones are involved in how the body utilizes and stores carbohydrates, protein, fat and blood sugar.



19

Addison's Disease Treatment

Oral Corticosteroids:

- Hydrocortisone (Cortef), prednisone, or methylprednisolone → replace cortisol
  These hormones are given on a schedule to mimic the normal 24-hour fluctuation of cortisol levels.
- Fludrocortisone acetate → replaces aldosterone

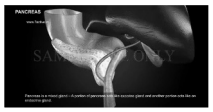
Non-pharmacological Treatment:

- Maintain adequate salt intake especially during times of physical activity and exercise

20

Autoimmune Pancreatitis

- Acute inflammatory process of the pancreas with variable involvement of regional tissue or remote organ systems
- Inflammatory episode with symptoms related to intrapancreatic activation of enzymes with pain, nausea and vomiting, and associated intestinal ileus
- Varies widely in severity, complications, and prognosis. Accounts for ~280,000 hospital admissions per year in the United States
- Complete structural and functional recovery expected if there is no necrosis or pancreatic ductal disruption



21

Autoimmune Pancreatitis Treatment

First-Line

- Analgesia: no consensus; guidelines vary.
  - Hydromorphone (Dilaudid) 0.5 to 1 mg IV q1–2h PRN
  - AVOID Demerol due to the potential of accumulation of a toxic metabolite.
- Antibiotics:
  - In the clear absence of infection, the use of prophylactic antibiotics is no longer recommended (even with necrotizing pancreatitis)
  - In patients with ascending cholangitis or necrotizing pancreatitis, if there is a strong suspicion of active infection, consider empiric β-lactam/β-lactamase inhibitor (e.g., piperacillin/tazobactam 4.5 g IV q8h) for initial treatment before cultures (especially aspirates) return.
  - Levofloxacin 500 mg QD IV if cholangitis and there is an allergy to penicillin
  - Be vigilant for fungal superinfections when giving prophylactic antibiotics.

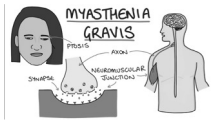
22

Neurological Autoimmune Diseases

23

Myasthenia Gravis

- An autoimmune disease mediated by blocking antibodies
- A patient with this disease produces auto-antibodies that bind the acetylcholine receptor on motor end plates of muscles→ blocking the normal binding of acetylcholine
- The result is progressive weakening of the skeletal muscles
- This disease also induces complement mediated lysis of cells and the antibodies cause the destruction of the cells bearing receptors



24

Myasthenia Gravis Treatment

- Treatment is based on age, gender, and disease severity/progression
- Three basic approaches: symptomatic, immunosuppressive, and supportive. Few should receive a single therapeutic modality.

1. Symptomatic treatments (anticholinesterase agents)
    - Pyridostigmine bromide (Mestinon):
        - *Most commonly prescribed because available in oral tablet*
        - Starting dose of 30 mg PO TID w/ food
        - Maximum dose: 120 mg PO Q3–4h
        - Long-acting available but effect not consistent
    - Neostigmine methylsulfate (Prostigmin):
        - Starting dose of 0.5 mg SC or IM Q3h
        - Titrate dosage to clinical need
    - Patients with anti-MuSK may not respond well to these meds.

25

Myasthenia Gravis Treatment cont.

2. Immunosuppressants: Oral corticosteroids are the first choice of drugs when immunosuppression is necessary.
    - Prednisone: Start as inpatient with a 60 mg/day PO; taper the dosage every 3 days; switch to alternate-day regimen within 2 weeks.
    - Cyclophosphamide: adults:1-5 mg/kg/day PO; children:2- 8 mg/kg/day PO
    - Cyclosporine: adults: 5 mg/kg/day PO (nephrotoxicity and drug interactions)
    - Mycophenolate: 1 g PO or IV BID
    - Azathioprine: 100 to 200 mg/day PO
        - *Most frequently used for long-term immunomodulation*, similar efficacy to steroids and IVIG
        - Benefit may not be apparent for up to 18 months after initiation of therapy.
        - Prednisolone + azathioprine may be effective when used as a corticosteroid-sparing agent.

3. Acute immunomodulating treatments:
    - Plasmapheresis: bulk removal of 2-3 L of plasma 3x per week
    - Immunoglobulin: 2 g/kg IV over 2 to 5 days
    - *Plasmapheresis and immunoglobulin have comparable efficacy in treating moderate to severe MG.*
        - Rapid onset of effect but short duration of action
        - Used for acute worsening of MG to improve strength prior to surgery, prevent acute exacerbations induced by corticosteroids, and as a chronic intermittent treatment to provide relief in refractory MG

Other immunosuppressive therapies:
    - Tacrolimus
    - Rituximab
    - Seronegative MuSK-antibody positive MG patients may have better response to rituximab than conventional therapies.

26

Guillain Barre Syndrome

- A group of acquired autoimmune disorders that cause acute peripheral neuropathy and ascending paralysis that progressively worsens for up to 4 weeks, followed by a slow spontaneous recovery of function
- Sometimes it is triggered by an infection, surgery, or a vaccination.
- In severe cases, the disease state is life-threatening. A ventilator may be required to breathe as symptoms worsen over a period of weeks and then eventually stabilize. Recovery can take a few weeks to a few years.

27

Guillain Barre Syndrome Treatment

General Measures

- Pain treatment: NSAIDs helpful but often insufficient. Gabapentin and carbamazepine decrease opioid requirements in patients with GBS.
- DVT prophylaxis recommended in nonambulatory patients
- Neostigmine or erythromycin may be effective for ileus, if present.

First-Line

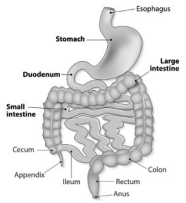
- IVIG 0.4 g/kg/day for 5 days or (less commonly) 1g/kg/day for 2 days
  - In severe disease, IVIG started within 2 weeks of onset hastens recovery as much as plasma exchange (PE)
  - In children, IVIG hastens recovery compared with supportive care alone
  - Combined treatment with IVIG and PE confers no clinically significant benefit.
- Plasma Exchange (PE):
  - Compared with supportive treatment alone, those treated with PE are quicker to recover walking (NNT 7), have less requirement and shorter duration for mechanical ventilation (NNT 8), recover full muscle strength more quickly (NNT 8), and have fewer severe sequelae at 1 year.
  - Higher risks of relapse found with PE versus supportive care with no difference in severe infection or mortality
  - In mild GBS, two sessions of PE are superior to none. In moderate GBS, four sessions are superior to two. In severe GBS, six sessions are not significantly better than four
  - PE is most beneficial if started within 7 days of disease onset. PE still helpful up to 30 days
  - Value of PE in children <12 is unknown

Second-Line

- Corticosteroids: not beneficial as monotherapy or as combined treatment. Low-quality evidence suggests steroids delay recovery

28

Gastrointestinal Autoimmune Diseases



29

Ulcerative Colitis

- Chronic relapsing and remitting inflammatory bowel disease causing recurrent episodes of diarrhea, that is often bloody and accompanied by abdominal pain, incontinence, fever, and weight loss
- Inflammation limited to the colonic mucosa
- Colonic involvement is universal but may be accompanied by large joint arthritis, ocular inflammation, skin lesions, biliary disease, liver disease, thromboembolic disease, and (rarely) pulmonary complications

30

Ulcerative Colitis Treatment

- First Line: Rectal treatment is usually tried first for mild disease limited to the rectum or left side of the colon. These often work faster than oral medications.
  - Mesalamine suppositories (*Canasa*) for rectal disease.
  - Enemas (*Rowasa*) for disease extending into the left-sided colon.
  - Hydrocortisone enema (*Cortenema*, etc) or a foam (*Cortifoam, Uceris,* etc) if patients can't retain a mesalamine enema. Save steroid suppositories for rectal symptoms.
- Oral 5-aminosalicylates (5-ASA)
- Oral steroids: should be saved for patients with *flares*.
- Biologics (*Remicade*, etc) and immunomodulators (azathioprine, etc) will be reserved for moderate to severe or refractory ulcerative colitis.
- *Xeljanz* (tofacitinib)

31

Pernicious Anemia

- A decrease in red blood cells when the body can't absorb enough vitamin B-12.
- Organ specific autoimmune disease in which the body's immune system attacks the lining of the stomach.
- Considered as a deadly disease due to the lack of available treatment.

Causes:

- Intrinsic factor (IF)- a glycoprotein made in the stomach that is necessary for the absorption of B12 →When the stomach does not make enough IF, the intestine cannot properly absorb vitamin B12 → permanent damage to nerves and other organs.
- Macrocytes
- Certain medications may lower vitamin B-12 (ex: Metformin)

Lab values:

- Serum B12 levels <200 pg/mL (150 pmol/L) are considered deficient

32

Pernicious Anemia Treatment

- Vitamin B12 is available as cyanocobalamin, hydroxocobalamin, or methylcobalamin in multiple formulations (oral tablets, sublingual tablets, lozenges, nasal spray, injection)
- For most patients → recommend **1000 to 2000** mcg/day of oral or sublingual cyanocobalamin for treatment and maintenance of B12 deficiency
- Consider IM vitamin B12 for patients with severe deficiencies or neurologic symptoms
  - If IM vitamin B12 is used, consider the following dosing options:
    - Cyanocobalamin: 1000 mcg IM daily for one week, followed by 1000 mcg weekly for one month, and then 1000 mcg monthly
    - Cyanocobalamin: 100 to 1000 mcg monthly
    - Hydroxocobalamin: 100 to 1000 mcg every two to three months
- Consider intranasal vitamin B12 (*Nascobal*; U.S. only) as an effective, alternative method of delivery (over $400 per month!)

33

Celiac Disease & Treatment

- An autoimmune disease in which people cannot eat gluten because it will damage their small intestine.
  - Gluten is a protein found in wheat, rye, and barley. Found mainly in foods but may also be in other products like medicines, vitamins and supplements, lip balm, and even the glue on stamps and envelopes.
- Symptoms may occur in the digestive system, or in other parts of the body. Symptoms include diarrhea and abdominal pain, irritability, depression, or patients may be asymptomatic.

Treatment:

- First line: Follow a completely gluten-free diet and supplementation with vitamins
- Steroids to control inflammation
- Azathioprine (Azasan, Imuran) or budesonide (Entocort EC, Uceris)

34

Primary Biliary Cirrhosis

- Primary Biliary Cirrhosis (PBC) is a chronic cholestatic liver disease predominantly affecting middle-aged women
- Autoimmune mechanism→ leading to damage of biliary epithelial cells of small bile ducts
- Patients who are asymptomatic at presentation have a longer survival than those who are symptomatic
- It is most commonly diagnosed after the age of 40 years and 90% of patients with PBC are women
  - The prevalence is higher in northern European population groups

35

Primary Biliary Cirrhosis Treatment

General Measures

- Abstain from alcohol, drugs, hepatotoxic medications, and hepatotoxic herbs
- Pneumococcal, hepatitis A/B, and influenza vaccines
- NASH: weight reduction, exercise, optimal control of lipids/glucose

Medication:

- Ursodeoxycholic acid (ursodiol) 13 to 15 mg/kg PO divided BID–QID with food;
- Bile acid sequestrants (BAS) are first-line therapy for pruritus: cholestyramine 4 to 8 g PO BID
  - Antihistamines, rifampicin 150 to 300 mg PO BID, or opiate antagonists such as naltrexone 50 mg/day can be used for pruritus if ursodiol is ineffective.

36

Systemic or Non-Organ Specific Autoimmune Diseases

- Sjogren's Disease
- Scleroderma
- Rheumatoid arthritis (RA)
- Systemic Lupus erythematosus (SLE)
- Psoriasis
- Multiple Sclerosis (MS)

37

Sjörgen's Syndrome

- A late onset chronic systemic autoimmune disease characterized by:
  - lymphocytic infiltration and destruction of the salivary and lacrimal glands resulting in dry mouth (xerostomia)
  - dryness and atrophy of conjunctiva and cornea (keratoconjunctivits sicca)
- Immune-mediated inflammation of:
  - Salivary
  - Lacrimal
  - Sweat glands
    - Aka "Sicca syndrome"
- Female to male 9:1 ratio

38

Sjörgen's Syndrome Treatment

- Focused on symptomatic treatment
  - Keratoconjunctivitis sicca (dry eyes):
    - Methylcellulose eye drops 0.5% for dry eyes
    - Cyclosporine eye drops
  - Xerostomia (dry mouth)
    - Artificial saliva
    - Dental care

Oral Candidiasis common in this patient population:

- Nystatin topical (two to three times weekly)

39

Scleroderma

- Chronic disease of unknown cause characterized by diffuse fibrosis of skin and visceral organs and vascular abnormalities.
- Most manifestations have vascular features
- Can range from a mild disease, affecting the skin, to a systemic disease that can cause death in a few months
- The disease is categorized into two major clinical variants.
  - Diffuse: distal and proximal extremity and truncal skin thickening
  - Limited
    - Restricted to the fingers, hands, and face
    - CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia)
- Systems affected: include, but not limited to skin; renal; cardiovascular; pulmonary; musculoskeletal; gastrointestinal

40

Scleroderma Treatment

General Measures

- Treatment is symptomatic and supportive
- Esophageal dilation may be used for strictures
- Avoid cold; dress appropriately in layers for the weather; be wary of air conditioning
- Avoid smoking (crucial)
- Use softening lotions, ointments, and bath oils to help prevent dryness and cracking of skin

41

Scleroderma Treatment cont.

First-Line

- ACE inhibitors (ACEIs): for preservation of renal blood flow and for treatment of hypertensive renal crisis
- Corticosteroids: for disabling myositis, pulmonary alveolitis, or mixed connective tissue disease (not recommended in high doses due to increased incidence of renal failure)
- NSAIDs: for joint or tendon symptoms; caution with long-term concurrent use with ACEIs (potential renal complications)
- Antibiotics: for secondary infections in bowel and active skin infections
- Antacids, proton pump inhibitors: for gastric reflux
- Metoclopramide: for intestinal dysfunction
- Hydrophilic skin ointments: for skin therapy
- Topical clindamycin, erythromycin, or silver sulfadiazine: for prevention of recurrent infectious cutaneous ulcers
- Consider immunosuppressives for treatment of life-threatening or potentially crippling scleroderma or interstitial pneumonitis such as cyclophosphamide for ILD.
- Nitrates and dihydropyridine calcium-channel blockers for Raynaud phenomenon
- Avoidance of caffeine, nicotine, and sympathomimetics may ease Raynaud symptoms.
- PDE5 antagonists (e.g., sildenafil), prostanoids, and endothelin-1 antagonists are changing the management of pulmonary hypertension.
- Alveolitis: immunosuppressants and alkylating agents (e.g., cyclophosphamide)

42

Rheumatoid Arthritis (RA)

- Individuals with rheumatoid arthritis produce a group of auto-antibodies called rheumatoid factors that are reactive with determinants of Fc region of IgG antibody.
- The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM –IgG complexes that are deposited in the joints.
- The immune complexes can activate the complement cascade, resulting in type III hypersensitivity reaction which leads to chronic inflammation of the joints.

43

Rheumatoid Arthritis Treatment

General Measures

- Goal is to achieve remission or minimize disease activity, prevent structural damage and prevent disability.
- Early, aggressive treatment prevents structural damage and disability.
- Periodic evaluation of disease activity and extent of synovitis can establish severity of disease.
- Disease activity measures include the DAS28 score and the RAPID 3 score.
- Treatment is based on severity of disease.

44

Rheumatoid Arthritis Treatment cont

- Early Disease-modifying antirheumatic drug (DMARD) therapy to slow disease progression and induce remission is standard of care.
- Nonbiologic DMARDs:
  - Start within 3 months of diagnosis.
  - Due to greater convenience, lower toxicity profiles, and quicker onset of action, initial therapy is a nonbiologic DMARD.
  - Methotrexate (MTX): is the first-line DMARD in patients with active RA; start with 7.5 to 25 mg/week PO. Titrate to optimal dosage within 4 to 8 weeks. DMARD with the most predictable benefit. Folic acid 1 mg PO daily reduces toxicity. Monitor CBC, renal and liver function every month for 3 months and then every 3 months; contraindicated in renal and hepatic diseases, pregnancy, and breastfeeding
  - Sulfasalazine (SSZ): 500 mg/day, increase to 2 g/day over 1 month; max: 2 to 3 g/day, 6-month trial. Monotherapy for low disease activity. Monitor CBC, liver enzymes every 2 weeks for 3 months, then every month for 3 months, and then every 3 months. Screen for G6PD deficiency.
  - Leflunomide (Arava): loading dose 100 mg/day × 3 days and then 10 to 20 mg/day, GI side effects and potentially teratogenic; contraindicated in pregnancy. Monitor CBC, LFTs, and phosphate monthly for the first 6 months. Stop use if ALT >3 × upper limit normal.
  - Hydroxychloroquine (Plaquenil) 400 mg QHS for 2 to 3 months and then 200 mg QHS; 6-month trial. Usually used to treat milder forms or in combination with other DMARDs. Ophthalmologic exam every 6 to 12 months due to potential maculopathy. Adjust dose in renal insufficiency.
  - Minocycline (100 mg BID), antibiotic with anti-inflammatory properties; used in mild disease

45

Rheumatoid Arthritis Treatment Cont.

- Biologic DMARDs:
  - TNF inhibitors: IV infliximab (Remicade), SC adalimumab (Humira), and SC etanercept (Enbrel). No evidence that one is superior; certolizumab pegol (Cimzia) and golimumab (Simponi), approved in moderate to severe disease
  - Janus kinase (JAK) inhibitor: tofacitinib citrate (Xeljanz), used for moderate to severe disease in adults that failed methotrexate
  - Interleukin-6 (IL-6) receptor antagonist: tocilizumab (Actemra) for moderate to severe active rheumatoid arthritis that failed DMARD therapy. Sarilumab (Kevzara), newly FDA approved in May 2017 for treatment of moderate to severe RA in patients who had an inadequate response or intolerance to anti-TNF therapy; need to monitor for neutropenia
  - Abatacept (Orencia) and anakinra (Kineret) no longer considered cost-effective or efficacious treatment for RA
  - Rituximab (Rituxan): A chimeric monoclonal antibody that targets CD20 on B cells. It is recommended with or without MTX for active moderate to severe RA with inadequate response to other DMARDs or failed anti-TNF agent.
- All biologics can be used in combination with a DMARD or steroids
- In patients with history of lymphoproliferative disorders, rituximab is preferred to TNF inhibitor
- In patients with skin cancer, DMARD are preferred to biologic agents
- In patients with CHF, combo DMARD therapy, a non-TNF biologic, or tofacitinib is recommended over a TNF inhibitor
- Check purified protein derivative (PPD) and screen for hepatitis prior to treatment.
- Ensure vaccinations (pneumococcal, HPV, hepatitis B, influenza, varicella zoster) are up-to-date prior to starting biologic agents.
- Treating flare-ups:
  - Intra-articular steroids: if disease is well controlled after ruling out intra-articular infection
  - Repository corticotropin injection, an ACTH analogue (Acthar gel)

46

Systemic Lupus Erythematosus (SLE)

- An individual affected by SLE may produce auto-antibodies to a vast array of tissues such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors.
- Interaction of these autoantibodies with their specific antigens produces various symptoms.
- Auto antibody specific for RBC and platelets for examples, can lead to complement mediated lysis resulting in hemolytic anemia and thrombocytopenia, respectively.
- When immune complex of autoantibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitivity reaction develops.
- The complexes activates the complement system and generate membrane- attack complexes and complement split products that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis.

47

Systemic Lupus Erythematosus (SLE) Treatment

- Many patients with lupus will end up taking multiple medications to control inflammation, minimize organ damage, and manage symptoms.
  - Hydroxychloroquine
    - Advise max doses of 5 mg/kg per day to limit med-induced retinopathy.
  - Immunosuppressants (azathioprine, methotrexate)
  - Biologics
  - NSAIDs for joint pain or topical steroids for skin rashes.
  - Recommend sun exposure protection→ sun exposure can worsen lesions
    - Discourage against the use of skin sensitizing drugs such as quinolones

48

Psoriasis

- A chronic, inflammatory disorder most commonly characterized by cutaneous erythematous plaques with silvery scale.
- It is a complex immune-mediated disorder that results from a polygenic predisposition in the setting of environmental triggers.
- It is associated with flares related to systemic, psychological, infectious, and environmental factors; skin disease with multiple different phenotypic variations and degrees of severity

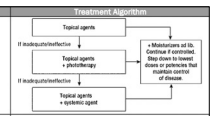
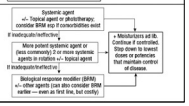
49

Psoriasis

- Most common inflammatory disease in the U.S. and Canada, especially among Caucasians
- Affects 2% population
- Affects males and females *equally*
- Onset before 40 YO, most common between 20-30 and 50-60 YO
- Genes: PSOR1 accounts for 50% of disease heritability, HLA, TNFα, IL23, and more
- Risk factors:
  - Skin trauma, disorders, and infection
  - Alcohol
  - Smoking
  - Obesity
  - Psychological stress
  - Medications (NSAIDs, ACEIs, β blockers, lithium, steroids, antimalarials, tetracyclines, interferons)
- Triggers: cold dry weather, skin injury, stress or infection, alcohol, smoking, medications
- Pathophysiology:
  - Psoriasis involves both adaptive and innate immunity
  - Epidermal hyperplasia and dermal inflammation caused by T cells, cytokines, growth factors, and dermal dendritic cells
  - Dendritic cells (DC) are antigen-presenting cells that activate and recruit T cells to induce immune response

50

Psoriasis Treatment

	1st LINE	2nd LINE	Treatment Algorithm
MILD-MODERATE	• Emollients • Keratolytics • Tazarotene • Topical steroids • Vitamin D analogues	• Coal tar • Anthralin • Immunomodulators	
MODERATE-SEVERE	• Acitretin • Cyclosporine • Methotrexate • Biologics	• Tacrolimus • Mycophenolate mofetil • Pimecrolimus • Sulfasalazine • 6-Thioguanine • Hydroxyurea	

51

Psoriasis Treatment

- Do NOT use high potency steroids for >3 weeks and avoid in areas of thin skin
- Steroids are susceptible to tachyphylaxis (less effective the more you use it)
- Be very cautious with children, elderly, or liver impaired
- Cutaneous side effects: skin atrophy or hyperproliferation, telangiectasia, hypopigmentation, steroid acne, hair growth, rosacea, easy bruising, striae
- Systemic side effects: HPA suppression, growth retardation, glaucoma, cataracts, mycotic infections, Cushing's syndrome

Potency	Generic Name	Formulations
Very high potency	Halobetasol propionate	Cream, ointment
	Betamethasone dipropionate	Ointment
High potency	Betamethasone dipropionate	Cream
	Fluocinonide	Cream
	Triamcinolone	Ointment Cream
Medium potency	Betamethasone valerate	Cream
	Hydrocortisone valerate	Cream
	Triamcinolone acetonide	Ointment, cream, lotion
Low potency	Hydrocortisone	Cream, ointment

52

Multiple Sclerosis (MS)

- Multiple sclerosis (MS) is the most common cause of neurologic disability associated with autoimmune disease.
- Production of auto-reactive T-cells that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers.
- The cerebrospinal fluid of patient with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin.
- Since myelin function to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions.

53

Multiple Sclerosis Treatment

Subcutaneous and Intramuscular Injections:

- Glatiramer (Copaxone) * *first line therapy*
- Interferon beta-1a (Avonex, Rebif) **first line therapy*
- Interferon beta-1b (Betaseron, Extavia) **first line therapy*
- Ofatumumab (Kesimpta)
- Peginterferon beta-1a (Plegridy)

Oral medications:

- Cladribine (Mavenclad)
- Diroximel Fumarate (Vimerity)
- Dimethyl futamate (Tecfidera)
- Fingolimod (*Gilenya)*
- Natalizumab **(***Tysabri)*


54

Questions or Concerns?

55