Pharmacology Update: Gastroenterology, Pulmonary and Infectious Diseases

Wendy L. Wright,
DNP, ANP-BC, FNP-BC FAANP, FAAN, FNAP
Adult / Family Nurse Practitioner
Owner - Wright & Associates Family Healthcare
Amherst, New Hampshire
Owner- Wright & Associates Family Healthcare
Concord, NH
Owner – Partners in Healthcare Education, PLLC

1

Disclosures

- Speaker Bureau: Sanofi-Pasteur, Merck, Pfizer, AbbVie, Biohaven
- Consultant: Sanofi-Pasteur, Pfizer, Merck, GlaxoSmithKline

2

Objectives

Upon completion, the participant will be able to:

- Discuss latest statistics pertaining to asthma, COPD, GI disorders, and emerging infectious diseases
- Discuss pharmacologic treatment options for patients with the above conditions
- Compare and contrast various pharmacologic treatment options for patients with the above conditions

3

Asthma

Wright, 2021 4

4

Asthma is...

- Derived from the Greek word for panting or breathlessness
- Recurrent airflow obstruction caused by chronic airway inflammation with a superimposed bronchospasm
- Leads to… wheezing, breathlessness and a cough

Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. NIH, NHLBI. June 2002. NIH publication no. 02-5075.

Wright, 2021 5

5

Prevalence of Asthma

- Impacts approximately 19 million individuals in the United States (18 and older)
- Most common chronic disease of childhood affecting 5.5 million children
- Increasing incidence of this disease
  - 76% increase in the prevalence of asthma within the past decade

https://www.cdc.gov/nchs/fastats/asthma.htm accessed 04-01-2021

Wright, 2021 6

6

Impact of Asthma

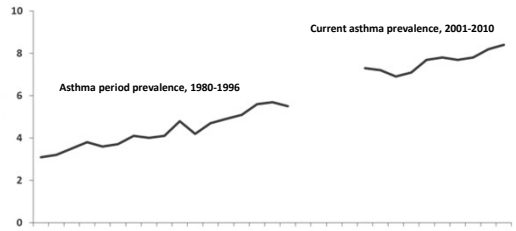
- 9.8 million visits to providers office annually
- 1.6 million ED visits annually
  - 189,000 hospitalizations
- 3524 deaths annually (2019)
  - Highest rates: adults (5x more likely than children to die)
- Children: boys > girls
- Adults: women > men

https://www.cdc.gov/nchs/fastats/asthma.htm accessed 04-01-2021

Wright, 2021 7

7

Asthma Period Prevalence and Current Asthma Prevalence: United States, 1980-2010



The percentage of the U.S. population with asthma increased from 3.1% in 1980 to 5.5% in 1996 and 7.3% in 2001 to 8.4% in 2010.

8

Pathophysiology of Asthma

- Likely genetic predisposition with environmental triggers
- Genetic predisposition
  - Chromosome: 5Q31-Q33
- Results from repeated exposure to allergens in the individual already equipped with the genetic predisposition
- Upon exposure to an allergen, there is a release of IgE antibodies
- IgE antibody binds with the antigen

Wright, 2021 9

9

Pathophysiology of Asthma

- IgE/allergen complex - then attaches itself to the mast cells on the nasal and bronchial mucosa
- Release of numerous chemical mediators

10

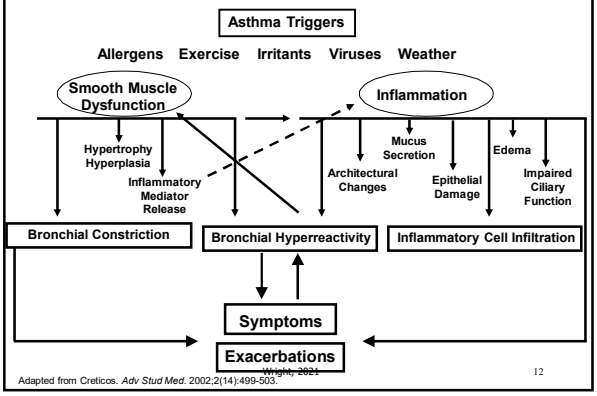
Histamine

- Histamine is stored mainly in the mast cell
  - Circulated in the blood via the basophil
- Causes an increase in blood flow to the affected area.
  - Responsible for the increased nasal discharge, edematous mucous membranes, sneezing, itchy nose and eyes, and hives
  - Also associated with airway inflammation and bronchoconstriction

Adapted from Creticos. *Adv Stud Med.* 2002;2(14):499-503.

11

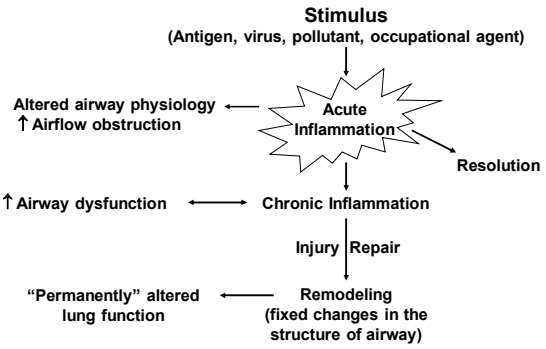
Components of Asthma



Adapted from Creticos. *Adv Stud Med.* 2002;2(14):499-503.

12

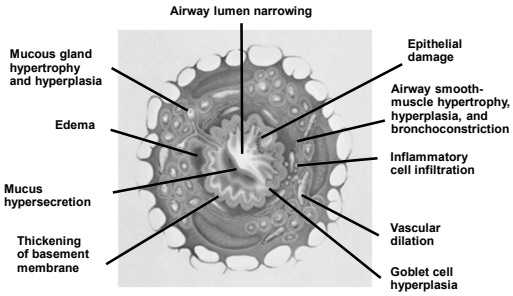
Consequences of Inflammation in Asthma



Adapted from Creticos. *Adv Stud Med.* 2002;2(14):499-503.

13

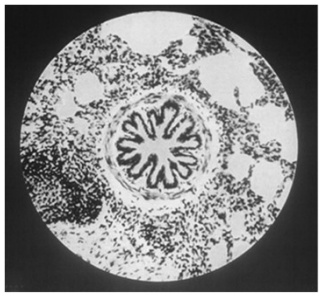
Asthma: Pathophysiologic Features and Changes in Airway Morphology



Adapted from *Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma.* NIH, NHLBI. 1991. NIH publication 91-3042.

14

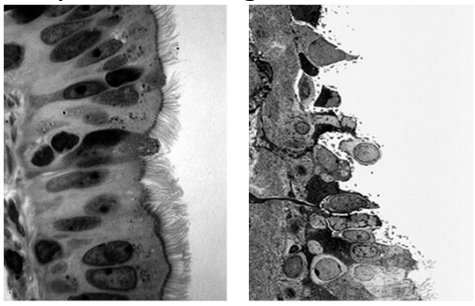
Cross Section of Bronchiole Showing Bronchospasm



Color Atlas of Respiratory Disease. Volume 2, 1995.

15

Epithelial Damage in Asthma



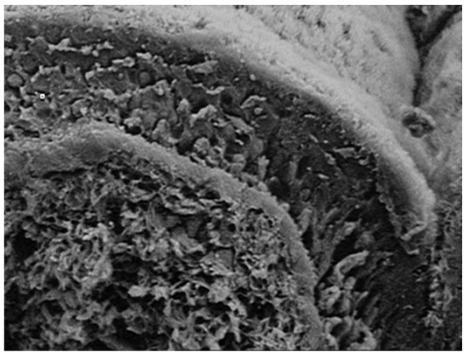
Normal

Asthmatic

Jeffery P. In: Asthma, Academic Press 1998

16

Basement Membrane Thickening



Jeffery P. In: Asthma, Academic Press 1998

17

Asthma is...

- A disease of:
  - Inflammation
    - Primary Process
  - Hyperresponsiveness
  - Airway bronchoconstriction
  - Excessive mucous production

18

Diagnosis of Asthma

19

M.E.

- 21-year-old female
  - C/o shortness of breath with running; present x months. Accompanied by coughing.
  - Denies CP, audible wheezing, runny nose, dizziness.
  - Has not been previously evaluated
  - Nonsmoker
  - Bronchiolitis: infancy

20

Diagnosis of Asthma

- History and Physical Examination
- Spirometry is needed to make diagnosis
- Monitoring:
  - Peak Flow Meters

21

Important:

2% of individuals who present with asthma symptoms have a significant cardiorespiratory condition (other than asthma)

https://www.aafp.org/afp/2020/0615/p762.html accessed 04-01-2021

22

Symptoms and Signs of Asthma in Children and Adults

- Coughing, particularly at night or after exercise
- Wheezing
- Chest tightness
- SOB
- Cold that lingers x months

23

Methods for Measuring Airway Caliber

24

M.E. (continued)

- VSS
- Lungs clear
- Heart: S1, S2, RRR; no S3 or S4; no murmurs
- Spirometry (Quality A)
  - FEV1: 72% predicted
  - FEV1/FVC ratio: 94% predicted

25

Diagnosis

- Diagnosis:
  - Improvement of 12% or more in FEV1 and 200 mL from baseline after bronchodilator OR
  - 20% improvement in PEFR post bronchodilator

https://www.aafp.org/afp/2020/0615/p762.html accessed 04-01-2021

26

M.E. (continued)

- Baseline spirometry (Quality A)
  - FEV1: 72% predicted
  - FEV1/FVC ratio: 94% predicted
- Post-bronchodilator
  - FEV1: 90% (up 18%)
  - FEV1/FVC ratio: 95%

27

Classification of Asthma Severity (Youths≥12 Years of Age and Adults)

Initial Diagnosis: Determine Severity and Treatment Needed					
Components of Severity			**Persistent**		
		Intermittent	**Mild**	**Moderate**	**Severe**
Impairment **Normal FEV_1/FVC:** **8-19 y 85%** **20-39 y 80%** **40-59 y 75%** **60-80 y 70%**	**Symptoms**	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1 >80% predicted	FEV_1 >80% predicted	FEV_1 >60% but <80% predicted	FEV_1 <60% predicted
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see note)		≥2/year (see note)	
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended Step for initiating Treatment		Step 1	Step 2	Step 3	Step 4
				and consider short course of oral systemic corticosteroids	
		In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Wright, 2021 28

28

M.E. (continued)

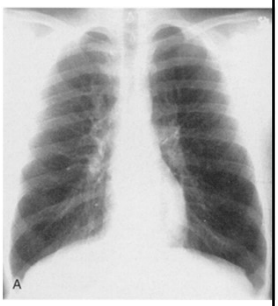
- Diagnosis:
  - –Moderate Persistent Asthma
- Plan: Step 3 Care

Wright, 2021 29

29

Asthma

- Hyperinflation
- Diaphragm is down to the 11th ribs
- Most patients with asthma have normal x-rays

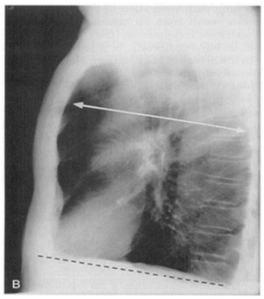


Wright, 2021 30

30

Chronic Asthma Changes

- Increased AP Lateral diameter
- The way you know that AP/Lat diameter is increased by this clear space between the sternum and the ascending aorta
- Flat diaphragms



31

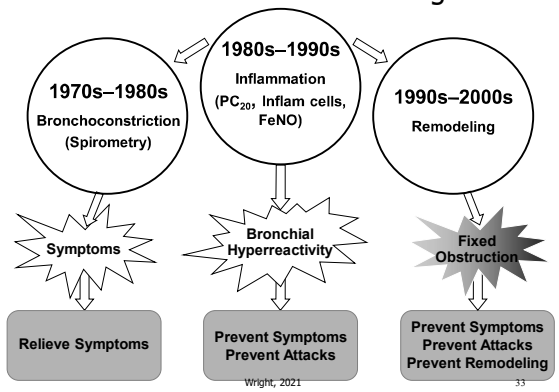
31

Treatment of Asthma

Wright, 2021 32

32

Evolution of Asthma Paradigms



Wright, 2021 33

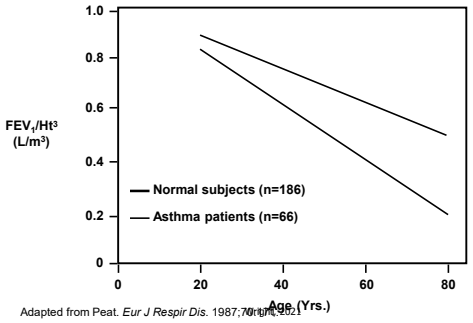
33

Childhood Asthma Control Can Predict Adult Lung Status

- Study of 119 asthmatic children during 1966 and 1969
- Ages: 5-14 were evaluated using FEV1
- Follow-up performed 17-18 years later and 27-28 years later
- Children who were well controlled during childhood had the smallest decline in total lung volume during adulthood

34

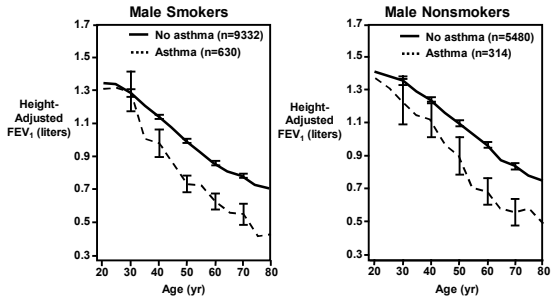
Rate of Decline in FEV_1



Adapted from Peat. *Eur J Respir Dis.* 1987;70:171-179.

35

Changes With Age in FEV_1 According to Smoking and Asthma Status



Lange et al. *N Engl J Med.* 1998;339:1194-1200.

36

Table 10-14: Classification of Asthma Severity (Youths≥12 Years of Age and Adults)

Initial Diagnosis: Determine Severity and Treatment Needed					
Components of Severity		**Persistent**			
		Intermittent	**Mild**	**Moderate**	**Severe**
Impairment **Normal FEV_1/FVC:** **8-19 y 85%** **20-39 y 80%** **40-59 y 75%** **60-80 y 70%**	**Symptoms**	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1 >80% predicted	FEV_1 >80% predicted	FEV_1 >60% but <80% predicted	FEV_1 <60% predicted
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see note)		≥2/year (see note)	
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended Step for initiating Treatment		Step 1	Step 2	Step 3	Step 4
				and consider short course of oral systemic corticosteroids	
		In 2 to 6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

37

https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

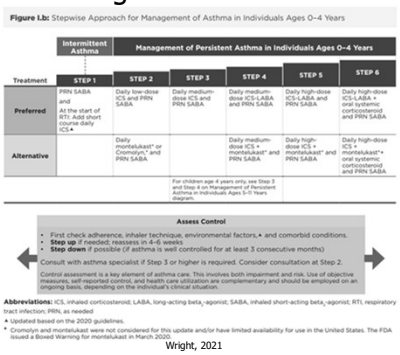
38

Indoor Allergen Mitigation

- Can be very helpful for individuals with allergic component
- Recommend air purifiers, mattress and pillow covers, HEPA filters

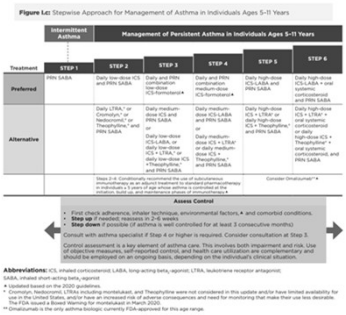
39

Stepwise Approach
Ages 0 – 4 Years



40

Stepwise Approach
Ages 5 – 11 Years



41

Stepwise Approach
Ages 12 Years and Older

42

M.E. (continued)

- Where do we go with her?
- Plan:
  - –ICS with LABA (formoterol)
  - –Return for f/u in 4 - 6 weeks
    - If well-controlled, continue x 3 months
    - If not well-controlled, step up care

43

Major Focus in EPR-3

- Controlling asthma is a major focus of the EPR-3 guidelines

44

Assessing Asthma Control (Youths ≥12 Years of Age and Adults)

Follow-up Visits: Determine Level of Control and Treatment Needed

Components of Control		Well-controlled	Not Well-controlled	Very Poorly Controlled
Impairment	**Symptoms**	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2 x/month	1-3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/personal best	60-80% predicted/personal best	<60% predicted/personal best
	Validated Questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1-2 ≥1.5 16-19	 3-4 N/A ≤15
	Exacerbations	0-1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
Risk	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

*ACQ values of 0.76-1.4 are indeterminate regarding well-controlled asthma. Wright, 2021 45

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second. See figure 3-8 for full name and source of ATAQ, ACQ, ACT.

45

Monitoring Control in Clinical Practice: Asthma Control Test™ for Patients Aged ≥12 Years[1]

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?
   All of the time ○ Most of the time ○ Some of the time ○ A little of the time ○ None of the time ○ ☐
2. During the past **4 weeks**, how often have you had shortness of breath?
   More than once a day ○ Once a day ○ 3 to 6 times a week ○ Once or twice a week ○ Not at all ○ ☐
3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
   4 or more nights a weeky ○ 2 or 3 nights a week ○ Once a week ○ Once or twice ○ Not at all ○ ☐
4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?
   3 or more times per day ○ 1 or 2 times per day ○ 2 or 3 times per week ○ Once a week or less ○ Not at all ○ ☐
5. How would you rate your **asthma** control during the **past 4 weeks**?
   Not controlled at all ○ Poorly controlled ○ Somewhat controlled ○ Well controlled ○ Completely controlled ○ ☐

Level of Control Based on Composite Score[2]
≥20 = Controlled
16-19 = Not Well Controlled
≤15 = Very Poorly Controlled
Regardless of patient's self assessment of control in Question 5

1. Asthma Control Test™ copyright, QualityMetric Incorporated 2002, 2004. All rights reserved.
2. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/epr3resource.pdf. Accessed February 5, 2007.

46

Short -Acting Beta-2 Agonists

- Albuterol (Proventil HFA, Ventolin HFA, ProAir HFA, Xopenex HFA)
  - 90mcg/puff, 200 puffs
  - 1 - 2 puffs every 4-6 hours or 2 puffs 15 minutes before exercise
  - Onset: 5 minutes
- Generic albuterol HFA is now available

47

Short-Acting Beta-2 Agonists

- Usage of these medications more than 2 times/week is indicative of poor control
- 1 inhaler = 200 inhalations

48

Controller Medications

49

Maintenance or Prevention is the Key

- Good management is the key to preventing exacerbations and hospitalizations

50

Inhaled Corticosteroids

- Most potent and effective anti-inflammatory medication currently available

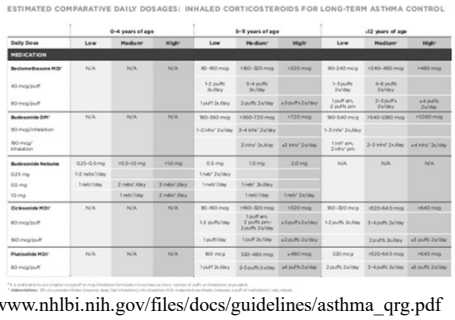
51

Inhaled Corticosteroids

- Examples
  - Beclomethasone (QVAR)
  - Budesonide (Pulmicort)
  - Fluticasone (Flovent, ArmonAir, Arnuity Ellipta)
  - Mometasone (Asmanex)
  - Ciclesonide (Alvesco)

52

Comparative Daily Doses: ICS



ESTIMATED COMPARATIVE DAILY DOSAGES: INHALED CORTICOSTEROIDS FOR LONG-TERM ASTHMA CONTROL

	0–4 years of age			5–11 years of age			≥12 years of age		
Daily Dose	Low	Medium*	High*	Low	Medium*	High*	Low	Medium*	High*
MEDICATION									
Beclomethasone HDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	80–240 mcg	>240–480 mcg	>480 mcg
40 mcg/puff				1–2 puffs 2x/day	3–4 puffs 2x/day		1–3 puffs 2x/day	4–6 puffs 2x/day	
80 mcg/puff				1 puff 2x/day	2 puffs 2x/day	>3 puffs 2x/day	1 puff am, 2 puffs pm	2–3 puffs 2x/day	>4 puffs 2x/day
Budesonide DPI†	N/A	N/A	N/A	180–360 mcg	>360–720 mcg	>720 mcg	180–540 mcg	>540–1080 mcg	>1080 mcg
90 mcg/inhalation				1–2 inhs† 2x/day	3–4 inhs† 2x/day		1–3 inhs† 2x/day		
180 mcg/inhalation					2 inhs† 2x/day	≥3 inhs† 2x/day	1 inh† am, 2 inhs† pm	2–3 inhs† 2x/day	>4 inhs† 2x/day
Budesonide Nebules	0.25–0.5 mg	>0.5–1.0 mg	>1.0 mg	0.5 mg	1.0 mg	2.0 mg	N/A	N/A	N/A
0.25 mg	1–2 neb's†/day			1 neb† 2x/day					
0.5 mg	1 neb†/day	2 neb's†/day	3 neb's†/day	1 neb†/day	1 neb† 2x/day				
1.0 mg		1 neb†/day	2 neb's†/day		1 neb†/day	1 neb† 2x/day			
Ciclesonide HDI†	N/A	N/A	N/A	80–160 mcg	>160–320 mcg	>320 mcg	160–320 mcg	>320–640 mcg	>640 mcg
80 mcg/puff				1–2 puffs/day	1 puff am, 2 puffs pm–2 puffs 2x/day	>2 puffs 2x/day	1–2 puffs 2x/day	3–4 puffs 2x/day	
160 mcg/puff				1 puff/day	1 puff 2x/day	>2 puffs 2x/day		2 puffs 2x/day	>4 puffs 2x/day
Fluticasone HDI†	N/A	N/A	N/A	100 mcg	220–440 mcg	>440 mcg	220 mcg	>220–440 mcg	>440 mcg
110 mcg/puff				1 puff 2x/day	2–3 puffs 2x/day	>4 puffs 2x/day	2 puffs 2x/day	3–4 puffs 2x/day	>6 puffs 2x/day

https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf

53

To Reduce Side Effects of Inhaled Corticosteroids

- Administer with spacers or holding chambers
- Rinse mouth after inhalation
- Use lowest possible dose to maintain control
- Children - monitor growth

54

Schenkel, E. et. al

- 98 patients randomized to either placebo or mometasone furoate aqueous nasal spray
- Ages: 3 - 9 years
- After 1 year, there was no suppression of height in the children using the nasal corticosteroid when compared with the child using placebo

Pediatrics Vol 105 No. 2 February 2000, p. 22

55

Remember...

- Poorly controlled asthma often delays growth
- In general, children with asthma tend to have longer periods of reduced growth rates prior to puberty

56

Leukotriene Receptor Antagonists

- Cysteinyl leukotriene production in the body has been associated with airway edema, smooth muscle constriction and the inflammatory process
- These medications block the leukotriene receptors which in turn is able to prevent inflammation and bronchoconstriction

57

Leukotriene Receptor Antagonists

(Zafirlukast) Accolate
- 10mg bid for ages 5-11
- 20mg bid for 12 and older
- Studied in children as young as 5
- Avoid food 1 hour before and 2 hours after taking: Food decreases the bioavailability of Accolate
- Metabolism: Metabolized through the CY P450 2C9 and 3A4 pathways
  - Major pathways in the body
  - Numerous other medications use this same pathway

58

Zafirlukast (Accolate)

- Drug/Drug Interactions
  - Aspirin: Increased zafirlukast levels by 40%
  - Erythromycin: 40% decrease in zafirlukast
  - Theophylline: Postmarketing reports of increased theophylline levels
  - Coumadin: 35% increase in PT/INR

59

Zafirlukast (Accolate)

- Side effects
  - Headache (12.9%)
  - Dizziness
  - Nausea
  - Churg Strauss syndrome
- Pregnancy: B
- Precautions
  - Not for an acute exacerbation

60

Montelukast (Singulair)

- (Montelukast) Singulair
  - 4 mg Granules once daily: 12 – 23 months
  - 4 mg tablet for children 2 - 5 years of age
  - 5mg qhs for ages 6-14
  - 10mg qhs for ages 15 and older

61

Montelukast (Singulair)

- Drug Interactions
  - Metabolized through CYP2A6 (minor pathway)
  - Phenobarbital: decreases montelukast but no dosage adjustment is required
- Side effects: headache, fatigue, dizziness, Churg-Strauss
- Precautions
  - Not for an acute exacerbation
- Category: B

62

Updates

- Montelukast (Singulair)
  - FDA strengthened warnings re: serious behavior changes and mood changes

63

Methylxanthines

- Theophylline
  - Theo-24, Theo-Dur, Uni-Dur, Slo-Bid
  - Bronchodilates and increases the force with which the diaphragm contracts
  - 6 years and older
  - Difficult to manage and as a result has not really gained wide spread acceptance
  - Indicated for individuals with moderate to severe asthma
  - Numerous drug interactions

64

Theophylline

- Numerous medications, foods and chemicals interact with theophylline
  - All of the following decrease theophylline levels
    - Smoking (cigarettes and marijuana)
    - High protein/low carbohydrate diet
    - Phenytoin
    - Phenobarbital
    - Carbamazepine
    - Ketoconazole
    - Diuretics

65

Theophylline

- Theophylline levels (normal 6-15mcg/dL)
  - 15-25: GI upset, N/V, diarrhea, abdominal pain
  - 25-35: Tachycardia, occasional PVC's
  - >35: Ventricular tachycardia, seizures
- Category: C

66

Long-Acting Beta-2 Agonists

- Salmeterol (Serevent)
  - Diskus
    - ≥4 years of age-1 puff po q 12 hours
  - No role for acute exacerbations
  - Seems to help children affected by the nocturnal cough and wheezing
  - Good for prevention of exercise induced asthma

67

Long-Acting Beta-2 Agonists

- Formoterol (Foradil, Perforomist)
  - ≥ 5 years of age: 1 inhalation every 12 hours
  - May be used for prevention of EIB
- Olodaterol (Striverdi Respimat)
  - Indicated for COPD only
- Indacaterol (Arcapta Neohaler)
  - Indicated for COPD only

68

LABA

- REMOVED: FDA warning regarding increased deaths in patients treated with LABA
- Should be used only with inhaled corticosteroid in the patient with asthma

www.fda.gov/CDER/Drug/infopage/LABA/default.htm accessed 07-20-2010

69

Combination Products

- Fluticasone/salmeterol (Advair, AirDuo, Wixela Inhub)
- Budesonide/formoterol (Symbicort)
- Mometasone/formoterol (Dulera)
- Fluticasone/vilanterol (Breo Ellipta)

70

Monoclonal Antibodies

71

Omalizumab (Xolair)

- Indicated for adults and adolescents (6 and older) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen
- And…whose symptoms are inadequately controlled with inhaled corticosteroids
- SC injection (weight and IGE based)
- Every 2 – 4 weeks
- Warning: anaphylaxis

72

Omalizumab (Xolair)

- Recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to human immunoglobulin E (IgE).
- Inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils
- Limits the degree of release of mediators of the allergic response.

73

Eosinophilic phenotypes

- Interleukin-4/13 antagonist
  - Dupilumab (Dupixent)
- Interleukin-5 antagonists
  - Mepolizumab (Nucala)
  - Reslizumab (Cinqair)
  - Benralizumab (Fasenra)

74

LAMA

- LAMA
  - Long acting bronchodilator
  - Increasing/emerging role in the management of asthma
  - Controller medication
  - LAMA are only added to patient with poorly controlled asthma after LABA/ICS is in place

75

LAMA

- Caution: urinary retention and glaucoma
- Approved LAMA
  - Tiotroprium bromide: approved 6 years of age and older - asthma

76

Triple Drug Therapy

- Fluticasone, umeclidinium, and vilanterol (Trelegy Ellipta)
  - 1 inhalation daily

77

Fractional Exhaled Nitric Oxide

- Nitric oxide can be measured in exhaled breath
- Measure of airway inflammation
- Used:
  - When diagnosis is uncertain
  - In children 4 years of age and younger with recurrent wheezing

https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

78

Fractional Exhaled Nitric Oxide

- FeNO > 50 ppb (or > 35 ppb in children ages 5 – 12 years) are consistent with elevated T2 (Type 2) inflammation and support diagnosis of asthma
- Allergic rhinitis can increase FeNO levels as well; interpret cautiously

https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

79

FeNO Testing

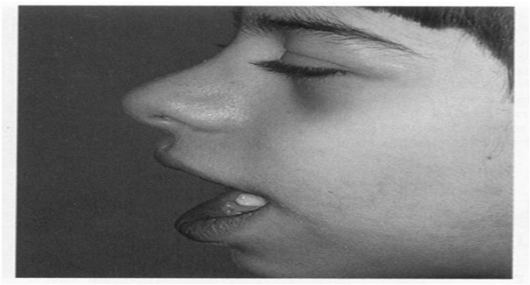
80

Last….

- Don't forget to treat the nose
- 85% of individuals with asthma have concomitant allergic rhinitis

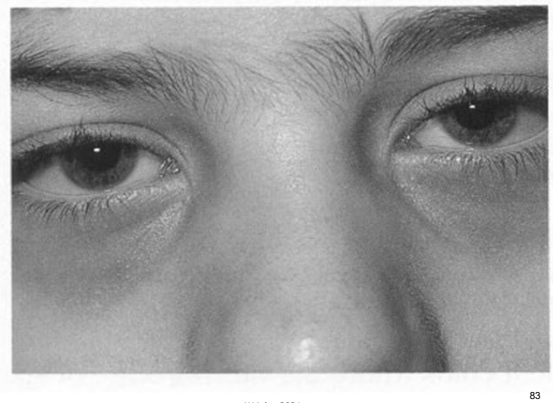
81

Allergic Facies



82

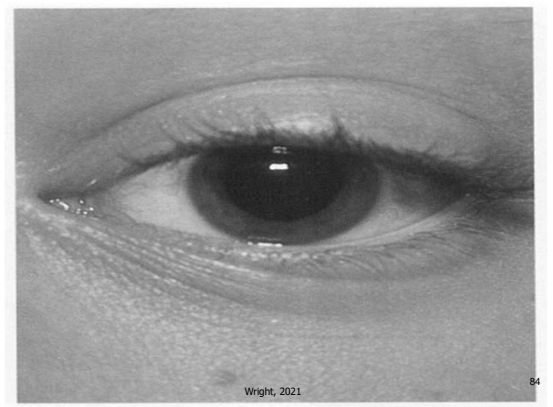
82



Wright, 2021

83

83



Wright, 2021

84

84

Consider Immunotherapy

- SCIT
- SLIT
- Consider as an adjunct for individuals with significant or unresponsive allergens/allergic rhinitis

85

Acute Asthma Exacerbation Management

86

Severity of Acute Exacerbations

FIGURE 5–1. CLASSIFYING SEVERITY OF ASTHMA EXACERBATIONS IN THE URGENT OR EMERGENCY CARE SETTING

Note: Patients are instructed to use quick-relief medications if symptoms occur or if PEF drops below 80 percent predicted or personal best. If PEF is 50–79 percent, the patient should monitor response to quick-relief medication carefully and consider contacting a clinician. If PEF is below 50 percent, immediate medical care is usually required. In the urgent or emergency care setting, the following parameters describe the severity and likely clinical course of an exacerbation.

	Symptoms and Signs	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF ≥70 percent predicted or personal best	▪ Usually cared for at home ▪ Prompt relief with inhaled SABA ▪ Possible short course of oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40–69 percent predicted or personal best	▪ Usually requires office or ED visit ▪ Relief from frequent inhaled SABA ▪ Oral systemic corticosteroids; some symptoms last for 1–2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40 percent predicted or personal best	▪ Usually requires ED visit and likely hospitalization ▪ Partial relief from frequent inhaled SABA ▪ Oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun ▪ Adjunctive therapies are helpful
Subset: Life threatening	Too dyspneic to speak; perspiring	PEF <25 percent predicted or personal best	▪ Requires ED/hospitalization; possible ICU ▪ Minimal or no relief from frequent inhaled SABA ▪ Intravenous corticosteroids ▪ Adjunctive therapies are helpful

Key: ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; PEF, peak expiratory flow; SABA, short-acting beta$_2$-agonist

http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf accessed 06-15-2019

87

Acute Asthma Exacerbation

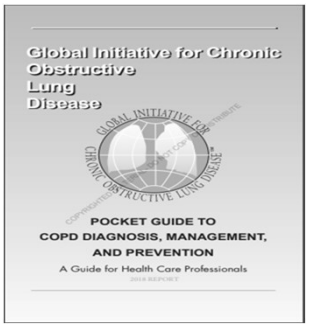
- Measure FEV1
- Inhaled short acting beta 2 agonist: Up to three treatments of 2-4 puffs by MDI at 20 minute intervals OR a single nebulizer
- Can repeat x 1 – 2 provided patient tolerates
- Prednisone
  - What dose and schedule??

88

COPD

89

Global Initiative for Chronic Obstructive Lung Disease, 2018



90

Case Study

- 55 year old male
- Presents with 3 year history of worsening sob on exertion
  - Denies chest pain, diaphoresis, palpitations, lightheadedness
- Smoker x 35 years; 1 ppd

91

Case Study

- PMH
  - Asthma in childhood
- ROS
  - Wheezing with exercise and URI's
  - Sputum production every morning

92

Case Study

- Physical examination
  - VS: 128/78, Pulse: 88, RR: 20, Temp: 97.2
  - HEENT: normal
  - Heart: S1, S2, RRR; no S3, S4, murmurs
  - Lungs: clear, but diminished
  - O2 sat – 97% on RA

93

COPD Definition

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

94

Definition and Overview

OVERALL KEY POINTS:

- The most common respiratory symptoms include dyspnea, cough and/or sputum production.
- The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute.

95

Chronic Obstructive Pulmonary Disease (COPD)

- COPD is currently the fourth leading cause of death in the world.[1]
- COPD is projected to be the 3rd leading cause of death by 2020.[2]
- More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380(9859): 2095-128.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; 3(11): e442.

96

Economic and Social Burden

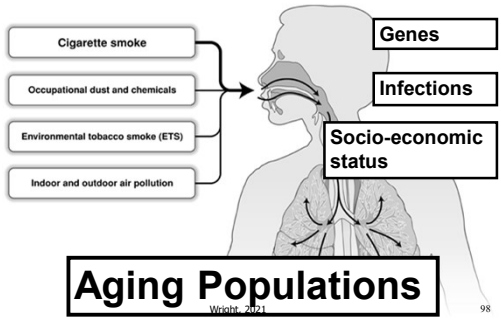
Economic burden of COPD

- ►COPD is associated with significant economic burden.
- ►COPD exacerbations account for the greatest proportion of the total COPD burden.
- ►USA:
  - ➢Direct costs of COPD are $32 billion
  - ➢Indirect costs $20.4 billion.

97

Global Strategy for Diagnosis, Management and Prevention of COPD

Risk Factors for COPD



98

Alpha-1 antitrypsin deficiency (AATD)

- Alpha-1 antitrypsin deficiency (AATD) screening
  - –Screen all individuals with COPD, particularly those who live in areas of high prevalence
  - –Levels < 20% may suggest familial homozygous deficiency and family members should be screened

https://goldcopd.org/wp-content/uploads/2018/02/WMS-GOLD-2018-Feb-Final-to-print-v2.pdf

99

Diagnosis and Initial Assessment

OVERALL KEY POINTS:

- COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease.
- Spirometry is required to make the diagnosis; the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation.
- The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.

100

Global Strategy for Diagnosis, Management and Prevention of COPD

Diagnosis of COPD

SYMPTOMS
shortness of breath
chronic cough
sputum

EXPOSURE TO RISK FACTORS
tobacco
occupation
indoor/outdoor pollution

SPIROMETRY: Required to establish diagnosis

101

Global Strategy for Diagnosis, Management and Prevention of COPD

Assessment of Airflow Limitation: Spirometry

- Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator to minimize variability.
- A post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of airflow limitation.
- Where possible, values should be compared to age-related normal values to avoid overdiagnosis of COPD in the elderly.

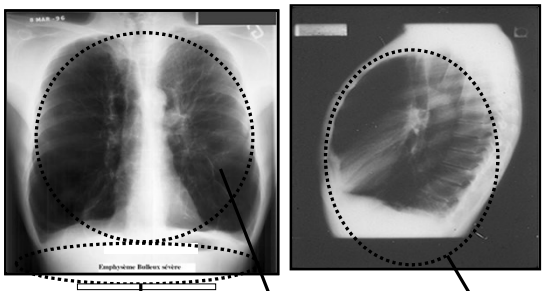
102

Spirometry Testing

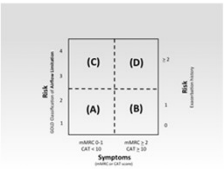
- CPT codes
  - 94010: $32.84 (FEV1/FVC)
  - 94060: $56.65 (spirometry before and after bronchodilator)
  - 94375: $36.81 (flow loop)
  - 94620: $64.59 (pulmonary stress test)

103

Utilized with permission from Fitzgerald Health Education Associates, 2007



104



Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

105

Global Strategy for Diagnosis, Management and Prevention of COPD

Assessment of COPD

- Assess symptoms

Use the COPD Assessment Test(CAT)

or

mMRC Breathlessness scale

106

Global Strategy for Diagnosis, Management and Prevention of COPD

Assessment of Symptoms

COPD Assessment Test (CAT): An 8-item measure of health status impairment in COPD (http://catestonline.org).

Breathlessness Measurement using the Modified British Medical Research Council (mMRC) Questionnaire: relates well to other measures of health status and predicts future mortality risk.

107

CAT: What are the questions?

Reproduced from: COPD Assessment Test Healthcare Professional User Guide

108

Global Strategy for Diagnosis, Management and Prevention of COPD

Classification of Severity of Airflow Limitation in COPD*

In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

**Based on Post-Bronchodilator FEV_1*

109

Case Study

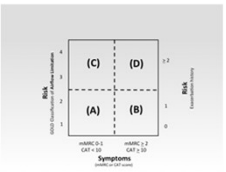
- Spirometry Test Results
  - FEV1
    - Pre-bronchodilator: 2.22 L (69%)
    - Postbronchodilator: 243 L (76%)
    - Change: 9%
  - FVC
    - Pre: 4.22 L (107%)
    - Post: 4.45 L (113%)
    - Change: 5%

110

Case Study

- Spirometry Test Results
  - FEV1/FVC
    - Pre: 53%
    - Post: 55%
  - CAT test: 12

111



Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

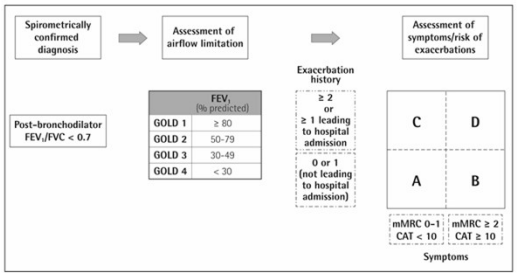
*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

112

ABCD Assessment Tool

Figure 2.4. The refined ABCD assessment tool



113

What Patient Type is Our Patient?

- A
- B
- C
- D

114

What Would You Initiate?

- What would you do?
- Which medication would you choose??

115

Evidence Supporting Prevention & Maintenance Therapy

OVERALL KEY POINTS (1 of 3):

- Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
  - The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present.
- Pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- Inhaler technique needs to be assessed regularly.

116

Evidence Supporting Prevention & Maintenance Therapy

OVERALL KEY POINTS (2 of 3):

- Influenza vaccination decreases the incidence of lower respiratory tract infections.
- Pneumococcal vaccination decreases lower respiratory tract infections.
- Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival.

117

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: COPD Medications

Beta$_2$-agonists
Short-acting beta$_2$-agonists
Long-acting beta$_2$-agonists
Anticholinergics
Short-acting anticholinergics
Long-acting anticholinergics
Combination short-acting beta$_2$-agonists + anticholinergic in one inhaler
Methylxanthines
Inhaled corticosteroids
Combination long-acting beta$_2$-agonists + corticosteroids in one inhaler
Systemic corticosteroids
Phosphodiesterase-4 inhibitors

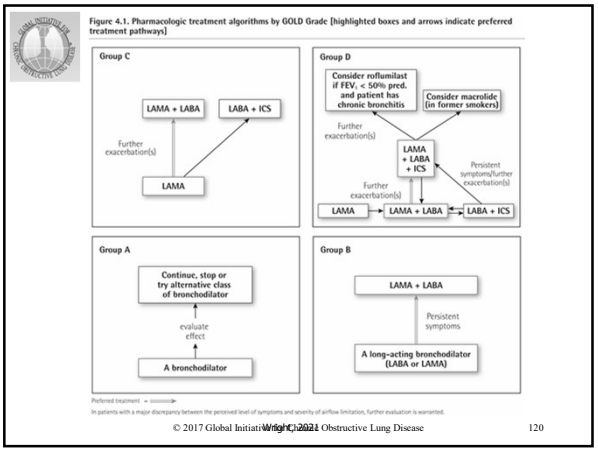
118

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Non-pharmacologic

Patient Group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Influenza vaccination Pneumococcal vaccination
B, C, D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Influenza vaccination Pneumococcal vaccination

119

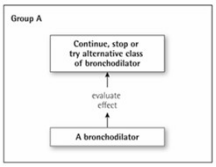


120

Pharmacologic treatment algorithms

Group A

- All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.
- This should be continued if symptomatic benefit is documented.

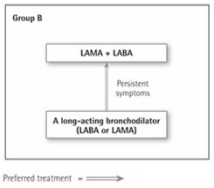


121

Pharmacologic treatment algorithms

Group B

- Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., *pro re nata* (prn) and are therefore recommended.
- There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.
- For patients with persistent breathlessness on monotherapy the use of two bronchodilators is recommended.

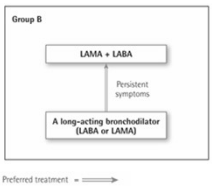


122

Pharmacologic treatment algorithms

Group B (continued)

- For patients with severe breathlessness initial therapy with two bronchodilators may be considered.
- If the addition of a second bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to a single bronchodilator.
- Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.

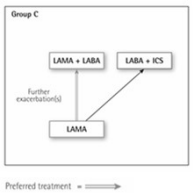


123

Pharmacologic treatment algorithms

Group C

- Initial therapy should consist of a single long acting bronchodilator. In two head-to head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.
- Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting $beta_2$-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.



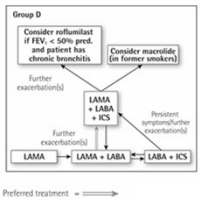
 Wright, 2021

124

Pharmacologic treatment algorithms

Group D

- We recommend starting therapy with a LABA/LAMA combination because:
  - In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs (for details see GOLD 2017 Chapter 3).
  - A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients (for details see GOLD 2017 Chapter 3).
  - Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.



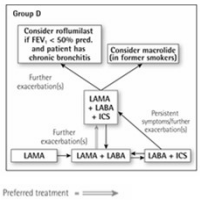
 Wright, 2021

125

Pharmacologic treatment algorithms

Group D (continued)

- In some patients initial therapy with LABA/ICS may be the first choice. These patients may have a history and/or findings suggestive of asthma-COPD overlap. High blood eosinophil counts may also be considered as a parameter to support the use of ICS, although this is still under debate
- In patients who develop further exacerbations on LABA/LAMA therapy we suggest two alternative pathways:
  - Escalation to LABA/LAMA/ICS. Studies are underway comparing the effects of LABA/LAMA vs. LABA/LAMA/ICS for exacerbation prevention.
  - Switch to LABA/ICS. However, there is no evidence that switching from LABA/LAMA to LABA/ICS results in better exacerbation prevention. If LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added.



 Wright, 2021

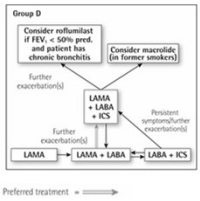
126

Pharmacologic treatment algorithms

Group D (continued)

If patients treated with LABA/LAMA/ICS still have exacerbations the following options may be considered:

- Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis,particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.
- Add a macrolide. The best available evidence exists for the use of azithromycin. Consideration to the development of resistant organisms should be factored into decision making.
- Stopping ICS. A reported lack of efficacy, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports this recommendation



127

Bronchodilators

- Important pharmacological treatment
  - Short (albuterol) and long acting (formoterol, salmeterol, aformoterol)
  - Improve emptying of lungs, exercise tolerance and reduce hyperinflation

128

Short Acting Inhaled Beta-2 Agonists

- Albuterol (Proventil HFA, Ventolin HFA, ProAir HFA)
  - 90mcg/puff, 200 puffs
  - 2 puffs q 4-6 hours or 2 puffs 15 minutes before exercise
  - Onset: 5 minutes

129

Short Acting Anticholinergics

- SAMA
  - –Ipratroprium bromide (inhaled and nebulized)
- SAMA/SABA
  - –Ipratroprium bromide/albuterol (inhaled or nebulized)

130

All Stages…

- SABA or SAMA should be available to individuals with all stages of COPD
- May be used as needed and with exacerbations

131

Long Acting Muscarinic Antagonists

- LAMAs
  - – Umeclidinium inhaled (Incruse Ellipta)
  - – Tiotroprium inhaled (Spiriva Respimat or Handihaler)
  - – Glycopyrrolate inhaled (Lonhala Magnair, Seebri Neohaler)
  - – Aclidinium bromide inhaled (Tudorza Pressair)
  - – Revefenacin inhaled (Yupelri nebulizer)

132

Long Acting Beta-2 Agonists

- LABAs
  - Salmeterol (Serevent)
  - Arformoterol inhaled (Brovana, Perforomist)
  - Indacaterol inhaled (Arcapta Neohaler)
  - Olodaterol inhaled (Striverdi Respimat)
  - Formoterol (Foradil Aerolizer)

133

Long Acting Muscarinic Antagonists/Long-Acting Beta-2 Agonists

- LAMA/LABA combination
  - Umeclidinium/vilanterol (Anoro Ellipta)
  - Glycopyrrolate/formoterol (Bevespi Aerosphere)
  - Tiotropium/olodaterol inhaled (Stiolto Respimat)
  - Indacaterol/glycopyrrolate inhaled (Utibron Neohaler)

134

Inhaled Corticosteroids

- ICSs
  - Beclomethasone (QVAR and QVAR Redihaler)
  - Budesonide (Pulmicort Flexhaler and Respules)
  - Flunisolide (AeroBid, Aerospan)
  - Fluticasone (Flovent, Arnuity Ellipta, ArmonAir)
  - Mometasone (Asmanex HFA and Twisthaler)
  - Ciclesonide (Alvesco)

135

Triple Drug Inhaler

- Fluticasone furoate/umeclidinium/ vilanterol inhaled (Trelegy Ellipta)

136

Methylxanthines

- Theophylline
  - Theo-24, Theo-Dur, Uni-Dur, Slo-Bid
  - Bronchodilates and increases the force with which the diaphragm contracts
  - 6 years and older
  - Difficult to manage and as a result has not really gained wide spread acceptance
  - Indicated for individuals with moderate to severe asthma
  - Numerous drug interactions

137

Phosphodiesterase-4 Inhibitors

- PDE-4s
  - Roflumilast (Daliresp)
    - 250 mcg once daily x 4 weeks then…
    - 500 mcg po once daily
    - Caution: liver disease, mood changes
    - Decreases acute exacerbations by approximately 20% - 25%

138

Antimicrobials

- Macrolide antimicrobial
  - Nonsmokers
  - Best evidence exists with azithromycin 250 mg daily
  - Macrolides have anti-inflammatory and immunoregulatory effects
  - Potential QT prolongation and temporary and permanent hearing deficits

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4203601/accessed 02-24-2019

139

Long-term oxygen therapy

- Goal
  - To ensure adequate oxygen delivery to the vital organs by increasing the baseline PaO_2 at rest to => 60 mm Hg at sea level and/ or producing a SaO_2=> 90%.

Utilized with permission from Fitzgerald Health Education Associates, 2008

140

Long-term oxygen therapy

- Indications to initiate long-term (> 15 hours/day) oxygen therapy
  - PaO2 < 55 mmHg or SaO2 < 88%
  - OR… PaO2 > 55 but < 60 mmHg with right heart failure or erythrocytosis
  - Goal: SaO2 $\geq$ 90%

- Source- www.goldcopd.org

141

Pulmonary Rehab

- Exercise training
- Nutrition counseling
- Education
- Conducted over 6 weeks
- Improves exercise performance and reduces dyspnea (no improvement on FEV1)

142

Surgery

- Bullectomy
- Lung Volume Reduction Surgery
- Lung transplant surgery

143

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations

An exacerbation of COPD is:

"*an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.*"

144

Management of Exacerbations

OVERALL KEY POINTS (1 of 3):

- An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.
- Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections.
- The goal for treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.

 Wright, 2021

145

Management of Exacerbations

OVERALL KEY POINTS (2 of 3):

- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.
- Systemic corticosteroids can improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days.
- Methylxanthines are not recommended due to increased side effect profiles.

 Wright, 2021

146

Management of Exacerbations

OVERALL KEY POINTS (3 of 3):

- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival.
- Following an exacerbation, appropriate measures for exacerbation prevention should be initiated

 Wright, 2021

147

Management of Exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

- They are classified as:
  - Mild (treated with short acting bronchodilators only, SABDs)
  - Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
  - Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

148

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations: Key Points

- The most common causes of COPD exacerbations are viral upper respiratory tract infections and infection of the tracheobronchial tree.
- Diagnosis relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms that is beyond normal day-to-day variation.
- The goal of treatment is to minimize the impact of the current exacerbation and to prevent the development of subsequent exacerbations.

149

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations: Key Points

- Short-acting inhaled beta$_2$-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.
- Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), and reduce the risk of early relapse, treatment failure, and length of hospital stay.
- COPD exacerbations can often be prevented.

150

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations: Treatment Options

Oxygen: titrate to improve the patient's hypoxemia with a target saturation of 88-92%.

Bronchodilators: Short-acting inhaled $beta_2$-agonists with or without short-acting anticholinergics are preferred.

Systemic Corticosteroids: Shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), and reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 30-40 mg prednisolone per day for 5 – 7 days is recommended.

151

New Information Emerging…

- 40 mg daily x 5 days may be all that is necessary for exacerbation of COPD
- Equal outcomes

152

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations: Treatment Options

Antibiotics should be considered and/or prescribed with moderate – severe exacerbations:

- Three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.
- Who require mechanical ventilation or hospitalization.

153

Antimicrobial Therapy

Mild to Moderate Exacerbations Antimicrobial therapy may not be indicated. If prescribed, consider spectrum of antimicrobial activity and side effects)	**If prescribed, use one of the following:** **1. Amoxicillin 875 mg 1 pill bid x 5 – 7 days** **2. TMP-SMX DS 1 pill bid x 5 – 7 days** **3. Doxycycline 100 mg 1 pill bid x 5 - 7 days** **4. Cephalosporin (cefdinir, cefpodoxime, cefuroxime)**
More Moderate - Severe Exacerbations **Severe: hospital admission**	Use one of the following: 1. Amoxicillin-clavulanate 875 mg 1 pill bid x 5 – 7 days 2. Cephalosporin: 2nd – 3rd generation 3. Azithromycin or clarithromycin 4. Respiratory fluoroquinolone (moxifloxacin or levofloxacin)

Source: Gilbert, D., Chambers, H., Saag, M., Pavia, A. (2017) The Sanford Guide to Antimicrobial Therapy (47th ed.). Sperryville, VA: Antimicrobial Therapy, Inc.

154

FDA Warning

- Fluoroquinolones:
  - –Spontaneous tendon rupture
  - –Tendonitis
  - –Peripheral neuropathy
  - –Aortic dissection
  - –Significant hypoglycemia

https://www.forbes.com/sites/brucelee/2018/12/21/fda-warns-about-what-fluoroquinolone-antibiotics-may-do-to-your-aorta/#121315605e7e

155

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Exacerbations: Indications for Hospital Admission

- Marked increase in intensity of symptoms
- Severe underlying COPD
- Onset of new physical signs
- Failure of an exacerbation to respond to initial medical management
- Presence of serious comorbidities
- Frequent exacerbations
- Older age
- Insufficient home support

156

Emerging Infectious Diseases

Wright, 2021 157

157

WHO in 2019:
What's Driving Infectious Diseases

- Antibiotic overuse and antimicrobial resistance
  - *Resistant C. difficile*
  - *Resistant candida strains*
  - *Resistant gram negative pathogens*
- Vaccine hesitancy and refusals
  - Measles
  - Influenza

Wright, 2021 158

158

Antibiotic overuse and antimicrobial resistance

Wright, 2021 159

159

Neisseria gonorrhoeae

- 2018 statistics
  - 580,000 cases; up 5% from 2017
  - Highest number reported since 1991
- Increasing antimicrobial resistance
  - 5,093 isolates
    - 25.3% resistant to tetracycline
    - 19.2% to ciprofloxacin
    - 16.2% to penicillin

www.cdc.gov accessed 01-19-2021

160

Updated 2020: Neisseria gonorrhoeae

- Treatment:
  - Single 500 mg IM dose of ceftriaxone for treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea.
    - If over 300 pounds (150kg or more) – 1 gram of ceftriaxone is recommended.
    - If chlamydial infection has not been excluded, concurrent treatment with doxycycline (100 mg orally twice a day for 7 days) is recommended.
- Changes are due to increased antimicrobial resistance to azithromycin

https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm?s_cid=mm6950a6_w accessed 12-30-2020

161

Updated 2020: Alternatives for *N. Gonorrhea Treatment*

- When ceftriaxone cannot be used for treating urogenital or rectal gonorrhea because of cephalosporin allergy, a single 240 mg IM dose of gentamicin plus a single 2 g oral dose of azithromycin is an option.

https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm?s_cid=mm6950a6_w accessed 12-30-2020

162

Test of Cure?

- A test-of-cure is unnecessary for persons with uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens

https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm?s_cid=mm6950a6_w accessed 12-30-2020

163

COVID – 19
Elephant in the Room

164

Information

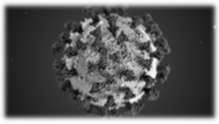
- SARS-CoV-2
- Disease Called: COVID-19
- The SARS-CoV-2 virus is a betacoronavirus, like MERS-CoV and SARS-CoV
- All three of these viruses have their origin in bats; believed to be mix of virus from bats and pangolin from a wet market in Wuhan, China. How it made its way to the people remains a topic of controversy

165

What is a Coronavirus?

- **Common human coronaviruses**

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)



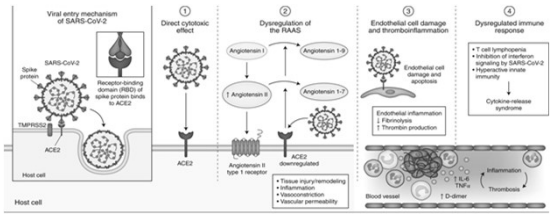
- **Other human coronaviruses**

5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

CDC. (2020, February 10). Human Coronavirus Types. Retrieved November 30, 2020, from https://www.cdc.gov/coronavirus/types.html#:~:text=People%20around%20the%20world%20commonly,and%20MERS%20CoV.

166

What Happens When Exposed?



Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., ... & Freedberg, D. E. (2020). Extrapulmonary manifestations of COVID-19. *Nature medicine*, *26*(7), 1017-1032.

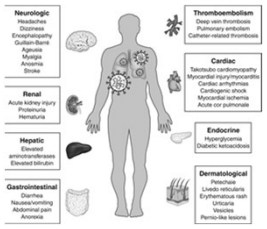
167

Symptoms

- 2-14 days after exposure
  - Cough
  - Fever
  - Shortness of breath
  - Loss of smell/taste
  - Headaches
  - Nasal congestion
- Some individuals can begin with nausea, vomiting, diarrhea

168

Extrapulmonary Side Effects



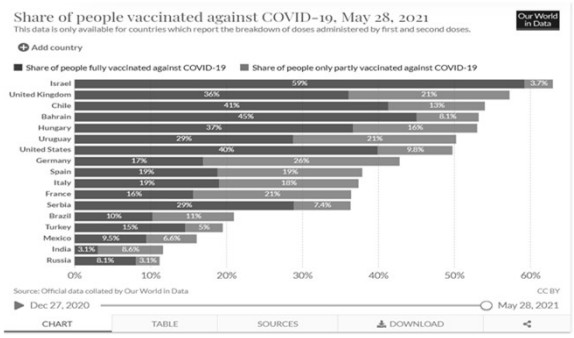
Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., ... & Freedberg, D. E. (2020). Extrapulmonary manifestations of COVID-19. *Nature medicine*, *26*(7), 1017-1032.

169

COVID 19 Vaccines

170

Vaccine Rollout



https://ourworldindata.org/covid-vaccinations accessed 05-29-2021

171

mRNA Technology

COVID-19 mRNA vaccines are given in the upper arm muscle. Once the instructions (mRNA) are inside the immune cells, the cells use them to make the protein piece. After the protein piece is made, the cell breaks down the instructions and gets rid of them.

Next, the cell displays the protein piece on its surface. Our immune systems recognize that the protein doesn't belong there and begin building an immune response and making antibodies, like what happens in natural infection against COVID-19.

At the end of the process, our bodies have learned how to protect against future infection. The benefit of mRNA vaccines, like all vaccines, is those vaccinated gain this protection without ever having to risk the serious consequences of getting sick with COVID-19.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mRNA.html?s_cid=10532:%2Bcovid%20%2Bvaccine%20%2Bchange%20%2Byour%20%2Bdna:sem.b:p:RG:GM:gen:PTN:FY21 accessed 02-01-2021

172

mRNA Vaccines

- Pfizer
  - Two dose series
  - Separated by 21 days
  - 52% efficacy 12 days after dose 1
  - 95% efficacy 7 days after dose 2
- Moderna
  - Two dose series
  - Separated by 28 days
  - 80.2% efficacy after 1 dose
  - 95.6% efficacy after dose 2 (18-65 years)
  - 86.4% for those over 65 years

www.bbc.com/future/article/202110114-covid-19 accessed 01-19-2021

173

Approved 2/27/2021

- Johnson & Johnson Vaccine
  - Adenovirus-based vaccine; uses weakened live adenovirus as the delivery method for transporting recombinant vaccine for COVID-19
    - Recombinant vaccines contain a small piece of genetic material from the virus to trigger an immune response
      - Examples of this type: pneumococcal
    - This type of vaccine is generally easy to make
    - Can be used in large number of people; including those who are immunocompromised
  - Single dose

https://whdh.com/news/johnson-johnsons-covid-19-vaccine-how-it-works-and-why-it-matters/ accessed 02-01-2021

174

Johnson & Johnson Vaccine

- 66% effective in preventing moderate and severe disease
- 85% effective overall at preventing hospitalization and death
- Efficacy against moderate and severe disease in the United States: 72%
- South African Variant B.1.351 efficacy against moderate to severe disease: 57%

https://whdh.com/news/johnson-johnsons-covid-19-vaccine-how-it-works-and-why-it-matters/ accessed 02-01-2021

175

Overview of Vaccines Currently Available or in Late-Stage Development

Vaccine	Pfizer	Moderna	Janssen	AstraZeneca-Oxford	Novavax
Type	mRNA	mRNA	Viral Vector DNA	Viral Vector DNA	Subunit Protein-Based
Doses	**2x doses** 21d apart	**2x doses** 28d apart	**1 dose**	**2x doses** ~4-12w apart	**2x doses** 21d apart
Storage	**Refrigeration** 2-8 ºC ≤ 5d **Ultra-Frozen** -80 to -60 ºC ≤ 6m	**Refrigeration** 2-8 ºC ≤ 30d **Frozen** -25 to -15 ºC ≤ 6m	**Refrigeration** 2-8 ºC ≤ 3m **Frozen** ≤ -20 ºC ≤ 2y	**Refrigeration** 2-8 ºC ≤ 6m	**Refrigeration** 2-8 ºC no time limit given
Availability	EUA for ≥**16YO** EUA in 12-15YOs filed 4/9/21	EUA for ≥**18YO**	EUA for ≥**18YO***	EUA filing ~Q1 2021	EUA filing ~Q1 2021
***Distribution resumed 4/23 following CVST concerns; Women < 50 YO should be informed of rare risk of blood clots with low platelets after vaccination**					

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Vaccine-candidate-tracking-table.ashx. Feb 8, 2021; https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/Pfizer-BioNTech-COVID-19-Vaccine/. Feb 4, 2021; https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/moderna-covid-19-vaccine/. Feb 4, 2021; https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines/#Phase3. Feb 9, 2021; https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astrazeneca-oxford-j-and-j-russia-s-sputnik-v/

176

Vaccines Currently Available or in Late-Stage Development: Efficacy Outcomes

Vaccine	Pfizer	Moderna	Janssen	AstraZeneca-Oxford	Novavax
Efficacy: Symptomatic COVID-19 (Primary Outcome), n	46,307	~30,000	43,783	32,449	~30,000
1st dose	52%	80%	66% (72% US trials)	76%	NR
2nd dose	91.3% (up to 6 months)	94%	Pending	76% (≥15d after 2 doses 4w apart) 85% (≥65YO)	96.4% 89.7% (Incl variants)
Secondary Efficacy Outcomes					
Severe Disease	100% (CDC definition) 95.3% (FDA definition)	100%	85%	100%	100%
Hospitalization/Death	100%	100%	100%	100%	100%

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Vaccine-candidate-tracking-table.ashx. Feb 8, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/Pfizer-BioNTech-COVID-19-Vaccine/. Feb 4, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/moderna-covid-19-vaccine/. Feb 4, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines/#Phase3. Feb 9, 2021. https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astrazeneca-oxford-j-and-j-russia-s-sputnik-v/. Voysey M, et al. Lancet. Feb 1 2021. https://www.wsj.com/articles/astrazeneca-vaccine-effective-against-u-k-covid-19-variant-in-study-11612530912. Feb 5, 2021.

177

Vaccines Currently Available or in Late-Stage Development: Efficacy Against Variants

Vaccine	Pfizer	Moderna	Janssen	AstraZeneca-Oxford	Novavax
Efficacy Against Variants	***In vitro neutralization potency (direct efficacy remains unknown)***				
UK (B.1.1.7)	Similar against B.1.1.7 & P.1, but lower against B.1.351	Not significantly changed for B.1.1.7, but reduced by 6-fold for B.1.351 & 2.8 fold for P.1	Data not available	70.4%	86.3%
South Africa (20H/501Y.V2 or B.1.351)			57%	10.4% (all severity)	48.6% (Overall) 55.4% (HIV-negative)
Brazil (P.1)			66% overall (Latin America; incl variant)	Data not available	No trial in Brazil

**Against mild to moderate infections only.*

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Vaccine-candidate-tracking-table.ashx. Feb 8, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/Pfizer-BioNTech-COVID-19-Vaccine/. Feb 4, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/moderna-covid-19-vaccine/. Feb 4, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines/#Phase3. Feb 9, 2021. https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astrazeneca-oxford-j-and-j-russia-s-sputnik-v/. Voysey M, et al. Lancet. Feb 1 2021. https://www.wsj.com/articles/astrazeneca-vaccine-effective-against-u-k-covid-19-variant-in-study-11612530912. Feb 5, 2021.

178

May Now Give Other Vaccines Concomitantly

179

CDC Meeting: Week of January 24, 2021

- AstraZeneca:
  - Enrollment has been completed in US
  - 32,459 people enrolled; as of January 21 – 26,327 have received 2nd dose
- V-safe data:
  - 2.08 million people participating (out of 21.8 million vaccinated)
  - 15,131 pregnancies reported to V-safe (they will be monitored for 3 months after babies born)

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

180

CDC Meeting: Week of January 24, 2021

- V-safe data:
  - Anaphylaxis:
    - Pfizer: 50 people out of 9.943 million doses
    - Moderna: 21 out of 7.581 million doses
    - 90% occurred within 30 minutes
    - 80 and 86% of these individuals (Pfizer/Moderna) had history of allergies
  - VAERS
    - 196 deaths reported after the vaccinations
    - None have been associated with the vaccine (monitoring and adjudication continues)

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

181

V-safe: No Surprises

Reactogenicity reported to v-safe

Local and systemic reactions, day 0-7*,†	All vaccines %	Pfizer- BioNTech dose 1 %	Pfizer-BioNTech dose 2 %	Moderna dose 1 %
Pain	70.7	67.7	74.8	70.1
Fatigue	33.4	28.6	50.0	29.7
Headache	29.4	25.6	41.9	26.0
Myalgia	22.8	17.2	41.6	19.6
Chills	11.5	7.0	26.7	9.3
Fever	11.4	7.4	25.2	9.1
Swelling	11.0	6.8	26.7	13.4
Joint pain	10.4	7.1	21.2	8.6
Nausea	8.9	7.0	13.9	7.7

* v-safe data lock point 1/14/2021, 5:00 AM ET
† Reported on at least one health check-in completed on days 0-7 after receipt of vaccine

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

182

VAERs: Reports of Deaths

Reports of deaths (due to any cause) following COVID-19 vaccination to VAERS* (N = 196)

Characteristics	Reports of death (N = 196)
Median age, years (range)	79 (25–104)
Age <65 years (%)	43 (22)
Female (%)	91 (46)
Long-term care facility (LTCF) resident (%)	129 (66)
Pfizer-BioNTech vaccine	113
Moderna vaccine	83

- These reports of death to VAERS involve temporally associated deaths following vaccination due to any cause; adverse event reports to VAERS, including deaths, should not be assumed to be causally related to vaccination

* Data through January 18, 2021

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

183

LTCF Residents

Reports of deaths in LTCF residents following COVID-19 vaccination to VAERS with death certificates available*(N = 18)

Cause of death from death certificate
Hypertension, leading to acute myocardial infarction, leading to anoxic brain injury
Atherosclerotic cardiovascular disease, acute myocardial infarction
Arteriosclerotic Disease
Cardiac arrest, cardiopulmonary arrest
Acute congestive heart failure, non-ischemic cardiomyopathy
Congestive heart failure, non-ischemic cardiomyopathy
Congestive heart failure
Congestive heart failure
Heart failure, hypertension
End stage chronic obstructive pulmonary disease
Acute kidney failure, resulting from acute liver failure, resulting from liver masses
Hypertension, hypothyroidism, bipolar disorder, peripheral vascular disease
Pneumonia, cardiac arrest and shock
Aspiration, frontotemporal dementia
Hypertension, mixed Alzheimer's and vascular dementia
Dementia
Chronic alcohol abuse and severe malnutrition, alcohol withdrawal, electrolyte derangement, ventricular arrhythmia, cardiogenic shock
Failure to thrive

* Data through January 18, 2021

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

184

Community Dwelling Adults

Reports of deaths following COVID-19 vaccination to VAERS in community dwelling adults aged <65 years with death certificate or autopsy report available* (N = 11)

Cause of death from death certificate or autopsy report
Atherosclerotic cardiovascular disease
Atherosclerotic cardiovascular heart disease, hypertension
Cardiac arrest, COVID-19
Cardiac arrest, hypertension, morbid obesity
Cardiopulmonary arrest, hypertensive heart disease, hypertension, DM type II
Hypertensive cardiovascular disease
Myocardial infarction, ventricular fibrillation
Drug overdose
Pulmonary hemorrhage from squamous cell cancer of the lung
Subarachnoid hemorrhage, intraparenchymal hemorrhage, intraventricular hemorrhage
COVID-19 stroke, COVID-19 acute respiratory failure

* Data through January 18, 2021

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf

185

Vaccine hesitancy and resistance

186

Measles

187

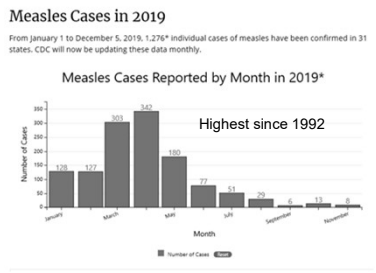
Measles

- Measles was declared eliminated (absence of continuous disease transmission for greater than 12 months) from the United States in 2000.

What happened?

188

Record Number: 2019



Worldwide 2019:
-869,770 Cases (556% increase from 2016)
-207K deaths (50% increase from 2016)
Highest number in 23 years

https://www.cdc.gov/measles/cases-outbreaks.html accessed 12-15-2020

189

Why is this occurring?

- In a given year, more measles cases can occur for any of the following reasons:
  - An increase in the number of travelers who get measles abroad and bring it into the U.S., and/or further spread of measles in U.S. communities with pockets of unvaccinated people

190

CDC Vaccine Recommendations

- All persons aged ≥6 months without evidence of measles immunity who travel outside the United States should be vaccinated before travel with 1 dose of MMR vaccine for infants aged 6–11 months and 2 doses for persons aged ≥12 months, at least 28 days apart
- Routine MMR vaccination is recommended for all children at age 12–15 months, with a second dose at age 4–6 years.

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6236a2.htm accessed 12-27-2013

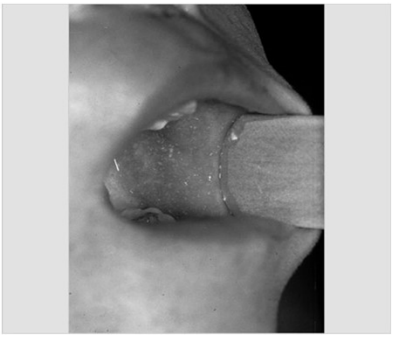
191

Need to Consider: The Three C's

- Cough
- Coryza
- Conjunctivitis
- Fever (up to 105)
- Koplick spots
- Photophobia
- Erythematous, disseminated, coalescing rash

192

Koplik Spots



http://www.immunize.org/photos/measles-photos.asp

Wright, 2021 193

193

What about contagion?

- Patients are considered to be contagious from 4 days before to 4 days after the rash appears
- Rash appears about 14 days after the illness begins
- It is the most contagious of all of the infectious diseases
  - 9 out of 10 exposed will develop the disease if not protected
  - Measles remains in the air for 2 hours after person has left the area

https://www.cdc.gov/measles/hcp/index.html

Wright, 2021 194

194

Complications

- Otitis media, pneumonia, laryngotracheobronchitis, and diarrhea
- One out of every 1,000 measles cases will develop acute encephalitis, which often results in permanent brain damage
- One or two out of every 1,000 children who become infected with measles will die from respiratory and neurologic complications
- Subacute sclerosing panencephalitis (SSPE) is a rare, but fatal degenerative disease of the central nervous system characterized by behavioral and intellectual deterioration and seizures that generally develop 7 to 10 years after measles infection.

https://www.cdc.gov/measles/hcp/index.html

Wright, 2021 195

195

Diagnosis

- Detection of measles-specific IgM antibody in serum and measles RNA by real-time polymerase chain reaction (RT-PCR) in a respiratory specimen
- Healthcare providers should obtain both a serum sample and a throat swab (or nasopharyngeal swab) from patients suspected to have measles
- Urine samples may also contain virus, and when feasible to do so, collecting both respiratory and urine samples can increase the likelihood of detecting measles virus

https://www.cdc.gov/measles/hcp/index.html accessed 12-15-2020

196

Recommendation

- People who are born during or after 1957 who do not have evidence of immunity against measles should get at least one dose of MMR vaccine.
- Exposed individuals
  - Either administer MMR vaccine within 72 hours of initial measles exposure, **or** immunoglobulin (IG) within six days of exposure. Do **not** administer MMR vaccine and IG simultaneously, as this practice invalidates the vaccine

197

Polio: September 2019

- Philippines:
  - Two cases of polio – 19 years after it was declared eradicated

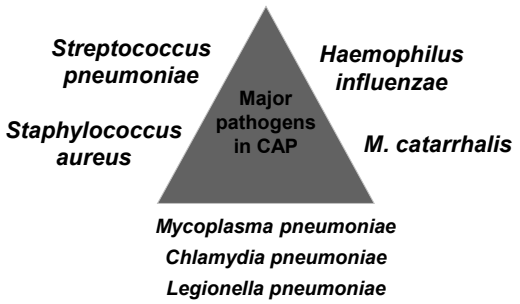
198

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

https://www.atsjournals.org/doi/10.1164/rccm.201908-1581ST
accessed 10-06-2019

199

Causative Pathogens in CAP



200

Microbial Etiology of CAP

- Microbial causes of CAP are changing
- Due in part to the introduction of the pneumococcal conjugate vaccines
- Increased recognition of the role of viral etiology

201

IDSA/ATS CAP Outpatient Treatment

- For healthy outpatient adults without comorbidities or risk factors for antibiotic resistant pathogens:
  - Amoxicillin 1 g three times daily (strong recommendation) or
  - Doxycycline 100 mg twice daily (conditional recommendation), or
  - A macrolide (azithromycin 500 mg on first day then 250 mg daily or clarithromycin 500 mg twice daily or clarithromycin extended release 1,000 mg daily) only in areas with pneumococcal resistance to macrolides <25% (conditional recommendation)

https://www.atsjournals.org/doi/10.1164/rccm.201908-1581ST accessed 10-06-2019

202

IDSA/ATS CAP classification for outpatient treatment

- For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia:
  - Combination therapy is now the recommendation

203

Higher Risk Individuals

- Combination therapy:
  - Amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily);
  - AND
  - Macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation),
  - OR doxycycline 100 mg twice daily (conditional recommendation); OR
- • Monotherapy:
  - Respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) (strong recommendation).

204

What Agent to Use?

- Recent therapy or a repeated course of therapy with beta-lactams, macrolides, or fluoroquinolones are risk factors for pneumococcal resistance to the same class of antibiotic.
- An antimicrobial agent from an alternative class is preferred for a patient who has recently received one of these agents

205

Opioid epidemic

206

Hepatitis B

207

Hepatitis B Vaccination

- Hepatitis B vaccination should be administered to:
  - Unvaccinated adults with diabetes mellitus who are aged 19 through 59 years
  - Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years
  - Administration of the hepatitis B vaccine series should be completed as soon as feasible after diabetes is diagnosed

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a4.htm?s_cid=mm6050a4_w accessed 12-20-2012

208

Hepatitis B Vaccination

- Reasons for vaccination:
  - Risk posed by an increased need for assisted blood-glucose monitoring in LTC facilities, the likelihood of experiencing chronic sequelae if infected with HBV, and the declining immunologic responses to vaccines that are associated with frailty, a geriatric syndrome characterized by decreased physiologic reserve and increased vulnerability, leading to early mortality in older adults

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a4.htm?s_cid=mm6050a4_w accessed 12-20-2012

209

Additional Recommendations

- Hepatitis B series
  - –All individuals with liver disease
  - –Including fatty liver, cirrhosis, alcoholic liver disease
  - –All individuals with ALT or AST > 2 x upper limits of normal

http://www.aafp.org/news/health-of-the-public/20161026acipoctmtg.html accessed 03-01-2017

210

Hepatitis C

- 2016: 41,200 acute hepatitis C cases
- 2016: 2.4 million people in the United States are living with hepatitis C virus infection
- HCV infection becomes chronic in approximately 75%–85% of cases
  - All individuals born between 1945 – 1965 should be screened
  - All injection drug users or those with history

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#a2

211

Hepatitis C

- All 18 years – 79 years should be screened for hepatitis C

https://www.hhs.gov/hepatitis/blog/2020/03/04/uspstf-issues-updated-hepatitis-c-screening-recommendation.html accessed 10-1-2020

212

Hepatitis A: October 2018

- All persons aged 1 year and older who experience homelessness should be routinely immunized against Hepatitis A

213

Tick Borne Illnesses

214

Two Sets of Guidelines

- IDSA
  - https://onlinelibrary.wiley.com/doi/10.1002/art.41562 (Updated 2020)
- ILADS
  - http://www.ilads.org/files/ILADS_Guidelines.pdf

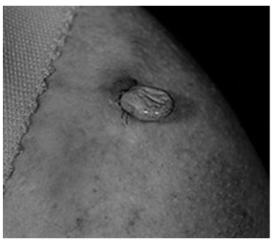
215

Lyme Disease

- Etiology
  - Caused by a spirochete called Borrelia Borgdorferi
  - Transmitted by the bite of certain ticks (deer, white-footed mouse)
  - 1st cases were in 1975 in Lyme, Connecticut
  - Affects many systems
  - Children more often affected than adults

216

This is NOT a Lyme Bearing Tick



Wright, 2021 217

217

Lyme Bearing Tick

Wright, 2021 218

218

Erythema Chronicum Migrans

- Symptoms
  - 3-21 days after bite
  - Rash (present in 72-80% of cases)-slightly itchy
  - Lasts 3-4 weeks
  - Mild flu like symptoms (50% of time)
  - Migratory joint pain
  - Neurological and cardiac symptoms
  - Arthritis, chronic neurological symptoms

Wright, 2021 219

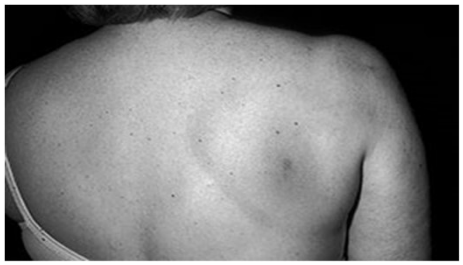
219

Erythema Chronicum Migrans

- Signs
  - Rash:
    - Begins as a papule at the site of the bite
    - Flat, blanches with pressure
    - Expands to form a ring of central clearing
    - No scaling
    - Slightly tender
  - Arthralgias:
    - Asymmetric joint erythema, warmth, edema
    - Knee is most common location

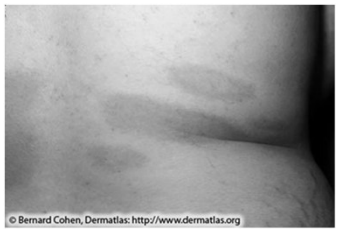
220

Erythema Migrans



221

Disseminated Erythema Migrans



222

Erythema Chronicum Migrans

- Signs
  - Systemic symptoms
    - Facial palsy
    - Meningitis
    - Carditis

223

Erythema Chronicum Migrans

- Plan
  - Diagnostic:
    - CDC and IDSA
      - EIA or immunofluorescence assay — followed by a supplemental immunoblot assay if the first test resulted in a positive or equivocal result.
    - Lyme Western Blot

224

Per ILADS

- "Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection"
- "The Centers for Disease Control and Prevention (CDC) considers a western blot positive if at least 5 of 10 immunoglobulin G (IgG) bands or 2 of 3 immunoglobulin M (IgM) bands are positive. However, other definitions for western blot confirmation have been proposed to improve the test sensitivity. In fact, several studies showed that sensitivity and specificity for both the IgM and IgG western blot range from 92 to 96% when only two specific bands are positive"
  - Lyme specific bands: 31, 34, and 39

http://www.ilads.org/lyme_disease/treatment_guidelines_clearing_ilads.html
Accessed 12-20-2013

225

Erythema Migrans: IDSA 2020

- 10 days of doxycycline is sufficient
- For children or those unable to tolerate doxycycline, 14 days of amoxicillin or cefuroxime is recommended

https://www.healio.com/news/infectious-disease/20201204/qa-lyme-disease-guidelines-updated-for-first-time-in-14-years accessed 01-19-2021

226

Prophylactic Treatment

- Prophylactic antibiotic therapy should be given only to adults and children within 72 hours of removal of an identified high-risk tick bite
  - If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended.
  - A tick bite is considered to be high-risk only if it meets the following 3 criteria: the tick bite was from (a) an identified *Ixodes* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours

https://onlinelibrary.wiley.com/doi/10.1002/art.41562

227

Erythema Chronicum Migrans

- Plan
  - Prophylactic: Doxycycline 200 mg single dose
  - Therapeutic: IDSA
    - Doxycycline 100 mg bid x 10 days
    - Amoxicillin 500 mg three times daily x 14 days
    - Cefuroxime 500 mg bid x 14 days
    - Alternative Azithromycin 500 mg once daily x 7 days

228

ILADS

- Believe in Chronic Lyme Disease
- Treatment may be continued as long as needed to treat symptoms
- Alternative recommendations are made:
  - Doxycycline 100-200 mg bid or TCN 500 mg 1 bid
  - Clarithromycin 500 mg 1 po bid along with hydroxychloroquine 200 mg 1 two times daily
  - Azithromycin 500 mg once daily

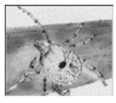
229

Additional Tick Borne Illnesses

230

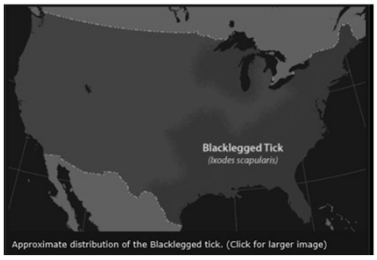
Anaplasmosis

- Formerly referred to as ehrlichiosis
- Transmitted by blacklegged tick or Lonestar tick



231

Locations of Blacklegged Tick



http://www.cdc.gov/ticks/geographic_distribution.html#blacklegg

232

Anaplasmosis (Ehrlichiosis)

- **Clinical picture**
  - Fever, chills, headaches, muscle aches
  - Occurs 1-2 weeks after a tick bite
  - Additional clues: thrombocytopenia, leukopenia, or elevated liver enzyme levels are helpful predictors of anaplasmosis, but may not be present in all patients
  - Testing: may be negative for first 7-10 days; PCR assay test
  - Treatment: doxycycline 100 mg 1 pill two times daily x 7-14 days (continue for minimum of 3 days after fever subsides)
    - Alternative: rifampin

http://www.cdc.gov/anaplasmosis/symptoms/index.html accesse

233

Babesiosis

- **Babesiosis**
  - Parasite which invades, infects, and kills the red blood cells (***Babesia microti)***
  - *Babesia microti* is spread in nature by *Ixodes scapularis* ticks (also called blacklegged ticks)
  - Symptoms: flu-like symptoms, such as fever, chills, sweats, headache, body aches, loss of appetite, nausea, or fatigue. Babesiosis can cause hemolytic anemia (from destruction of red blood cells)

234

Babesiosis

- **Babesiosis**
  - Treatment:
    - atovaquone (Mepron) PLUS azithromycin; OR
    - clindamycin PLUS quinine (this combination is the standard of care for severely ill patients)
  - Length: 7-10 days

235

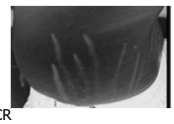
CDC: Babesiosis

Age Category	Drug		Dosage	Maximum	Duration (Days)
Adults	Prescribe together	Atovaquone	750 mg orally every 12 hours	N/A	7-10
		Azithromycin	On the first day, give a total dose in the range of 500–1000 mg orally; on subsequent days, give a total daily dose in the range of 250–1000 mg*	1000 mg per day	7-10
	OR				
	Prescribe together	Clindamycin**	300–600 mg IV every 6 hours OR 600 mg orally every 8 hours**	N/A	7-10
		Quinine**	650 mg orally every 6–8 hours	N/A	7-10

https://www.cdc.gov/ticks/tickbornediseases/babesiosis.html#:~:text=Babesiosis%20Treatment%20Regimen%20%20%20%20Age%20Category.%20%20N/A%20%203%20more%20rows accessed 01-19-2021

236

Bartonella



- **Bartonella** (cat-scratch)
  - Explanation: Bartonella spp. Bacterium
  - Diagnosis: *B. henselae* DNA may be detected by PCR
  - Symptoms: Fever, chills, headache, lymphadenopathy, and severe pain in the tibia, weight loss, sore throat, rash
  - Treatment:
    - Azithromycin:
      - For adults and children > 45.5 kg: 500 mg on day 1, followed by 250 mg for 4 days
      - For children ≤ 45.5 kg: 10 mg/kg on day 1, followed by 5 mg/kg for 4 days
    - ILADS – consider Levofloxacin

http://www.lymedisease.org/lyme101/coinfections/bartonella.html accessed 12-20-2013

237

STARI

- A rash similar to the rash of Lyme disease has been described in humans following bites of the lone star tick, *Amblyomma americanum*
  - Transmitted via the lone-star tick
- The rash may be accompanied by fatigue, fever, headache, muscle and joint pains.
- This condition has been named southern tick-associated rash illness (STARI)
- Treated with doxycycline

238

Alpha-Gal Meat Allergy

- May be linked to the lone star tick
  - Significant evidence that the lone star tick can inject the alpha-gal carbohydrate molecule into the human upon tick bite, thereby leading to an excessive production of IgE antibodies
- Alpha-gal allergy is a syndrome that was first described in 2009 as a delayed anaphylaxis to red meat
- Occurs about three to eight hours after eating red meat
  - Can resolve over 1 – 5 years

https://www.columbia-lyme.org/alpha-gal-meat-allergy

239

Rocky Mountain Spotted Fever

- Rapidly progressing disease
- Can be fatal within days if not diagnosed
- Generally within 1-5 days after tick bite
- Symptoms:
  - Early: fever, headache, n/v, abdominal pain, hand edema
  - Later symptoms – pink macular rash which spreads and can involve palms/soles, confusion, organ failure, petechial rash

240

Rocky Mountain Spotted Fever

- Diagnosis:
  - IFA for immunoglobulin IgG R. rickettsia antigen; acute and convalescent sample separated by 2-4 weeks
- Treatment:
  - Begin treatment immediately, even if no testing able to be completed
  - Doxycycline: AAP says able to use this in children of all ages for RMSF
    - 100 mg bid for adults until 3 days after fever subsides
    - Children < 45 kg – 2.2 mg/kg to a max of 100 mg bid
    - Pregnant women: must discuss benefits and risks

241

Enterovirus D-68

- Enterovirus:
  - Associated with common cold
  - Common in summer and fall
  - Started appearing August 2014 when children presented with more severe respiratory infections, many of whom were hospitalized
  - Not a new virus, but seems to be more common and more severe

www.cdc.gov accessed 10-13-2014

242

Enterovirus – D68

- From mid-August to October 10, 2014, CDC or state public health laboratories have confirmed a total of 691 people in 46 states and the District of Columbia with respiratory illness caused by EV-D68
- Testing:
  - nasopharyngeal and oropharyngeal swabs are preferred
- Treatment: aggressive asthma treatment
  - Prednisone and albuterol

www.cdc.gov accessed 10-13-2014

243

Acute Flaccid Myelitis

244

Acute Flaccid Myelitis

- Since 2014, most patients with AFM (more than 90%) had a mild respiratory illness or fever consistent with a viral infection before they developed AFM (CDC started tracking in 2014)
- Coxsackievirus A16, EV-A71, and EV-D68 found in the spinal fluid of four of 542 confirmed cases
- In 2014, 120 children in the US developed flaccid myelitis

245

Acute Flaccid Myelitis

- Incubation period: 6 – 20 days
- Paralysis: 11 – 17 days; but depending upon etiology can be as soon as 2 days and as long as 12 weeks
- Diagnosis: MRI – spinal cord lesions in the gray matter; pleocytosis of 5 cells/mm3
- Treatment: admission, antivirals and supportive care
  - Corticosteroids, IVIG – little evidence to support

246

Enterovirus D68

- Recent increase in Netherlands (June – July 2016)
  - –8 adults and 17 children
  - –Severe respiratory symptoms
  - –13 children required ICU management
  - –1 acute flaccid myelitis
  - –No specific treatment

https://wwwnc.cdc.gov/eid/article/23/1/16-1313_article accessed 12/17/2016

247

Rotavirus Vaccine

- **Rotavirus vaccine**
  - –Linked to lower rates of type 1 diabetes
  - –33% less likely to develop type 1 diabetes later in life than those who weren't vaccinated
  - –Studied looked at 1.5 million infants in the US between 2001 and 2017

https://www.nature.com/articles/s41598-019-44193-4 accessed 06-29-2019

248

Necrotizing Fasciitis

- Severe, deep, necrotizing infection
- Involves subcutaneous tissue down into the muscles
- Spreads rapidly
- Caused by Group A Beta Hemolytic Strep, Staph, Pseudomonas, E Coli
- Mortality: 8-70% depending upon organism and rapidity of treatment
- Disfigurement common

- Bolognia, Jean, Joseph L. Jorizzo, and Ronald P. Rapini. *Dermatology.* 2nd ed. St. Louis, Mo.: Mosby/Elsevier, 2008. Print.
- Habif, Thomas P.. *Skin disease: diagnosis and treatment.* 2nd ed. Philadelphia: Elsevier Mosby, 2005. Print.
- Hunter, J. A. A., John Savin, and Mark V. Dahl. *Clinical dermatology.* 3rd ed. Malden, Mass.: Blackwell Science, 2002. Print.

249

Necrotizing Fasciitis

- Symptoms
  - Usually occurs after surgery, traumatic wounds, injection sites, cutaneous sores
  - Generalized body aches, fever, irritability
  - Key: Red area of skin that is severely painful (It is out of proportion to findings)
  - Leg is most common location
- Physical Examination Findings
  - 1st appears as local area of redness that looks like cellulitis

- Bolognia, Jean, Joseph L. Jorizzo, and Ronald P. Rapini. *Dermatology.* 2nd ed. St. Louis, Mo.: Mosby/Elsevier, 2008. Print.
- Habif, Thomas P.. *Skin disease: diagnosis and treatment.* 2nd ed. Philadelphia: Elsevier Mosby, 2005. Print.
- Hunter, J. A. A., John Savin, and Mark V. Dahl. *Clinical dermatology.* 3rd ed. Malden, Mass.: Blackwell Science, 2002. Print.

250

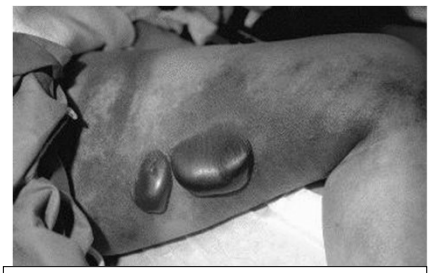
Necrotizing Fasciitis

- Physical Examination Findings
  - Tender
  - Bullae with purulent center which ruptures quickly
  - Black eschar appears and the pain decreases
  - Systemic symptoms begin

- Bolognia, Jean, Joseph L. Jorizzo, and Ronald P. Rapini. *Dermatology.* 2nd ed. St. Louis, Mo.: Mosby/Elsevier, 2008. Print.
- Habif, Thomas P.. *Skin disease: diagnosis and treatment.* 2nd ed. Philadelphia: Elsevier Mosby, 2005. Print.
- Hunter, J. A. A., John Savin, and Mark V. Dahl. *Clinical dermatology.* 3rd ed. Malden, Mass.: Blackwell Science, 2002. Print.

251

Necrotizing Fasciitis



Bullae: Below these lesions is necrotic tissue

252

Necrotizing Fasciitis

- Plan
  - –Diagnosis: Culture of wounds, blood cultures, biopsy of area, CBC with differential, urinalysis
  - –Therapeutic: HOSPITAL ADMISSION
  - –Educational: Good wound hygiene

- Bolognia, Jean, Joseph L. Jorizzo, and Ronald P. Rapini. *Dermatology.* 2nd ed. St. Louis, Mo.: Mosby/Elsevier, 2008. Print.
- Habif, Thomas P.. *Skin disease: diagnosis and treatment.* 2nd ed. Philadelphia: Elsevier Mosby, 2005. Print.
- Hunter, J. A. A., John Savin, and Mark V. Dahl. *Clinical dermatology.* 3rd ed. Malden, Mass.: Blackwell Science, 2002. Print.

253

Fifth's Disease (Erythema Infectiosum)

- Human Parvovirus B19
  - Occurs in epidemics
  - Occurs year round: Peak incidence is late winter and early spring
- Most common in individuals between 5-15years of age
  - Period of communicability believed to be from exposure to outbreak of rash
  - Incubation period: 5-10 days
  - Can cause harm to pregnant women and individuals who are immunocompromised

254

Fifth's Disease (Erythema Infectiosum)

- Low grade temp, malaise, sore throat
  - May occur but are less common
- 3 distinct phases
  - Facial redness for up to 4 days
  - Fishnet like rash within 2 days after facial redness
  - Fever, itching, and petechiae
  - –Petechiae stop abruptly at the wrists and ankles
    - –Hands and feet only

255

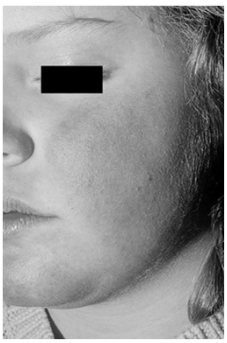
Fifth's Disease (Erythema Infectiosum)

- Physical Examination Findings
  - Low grade temperature
  - Erythematous cheeks
    - Nontender and well-defined borders
  - Netlike rash
    - Erythematous lesions with peripheral white rims
    - Rash-remits and recurs over 2 week period
  - Petechiae on hands and feet

Wright, 2021 256

256

Fifth's Disease



Wright, 2021 257

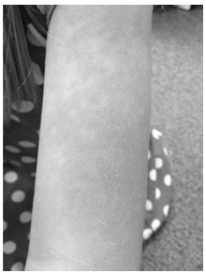
257

Classic

Wright, 2021 258

258

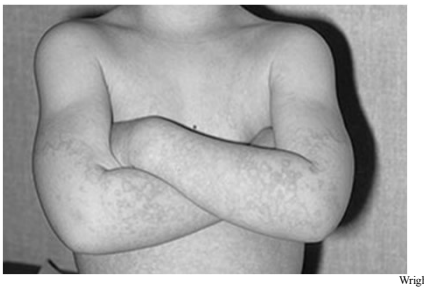
Fifth's Disease



Wright, 2021 259

259

Fifth's Disease



Wright, 2021 260

260

Fifth's Disease (Erythema Infectiosum)

- Diagnosis/Plan
  - Parvovirus IgM and IgG
  - IgM=Miserable and is present in the blood from the onset up to 6 months
  - IgG=Gone and is present beginning at day 8 of infection and lasts for a lifetime
  - CBC-May show a decreased wbc count

Wright, 2021 261

261

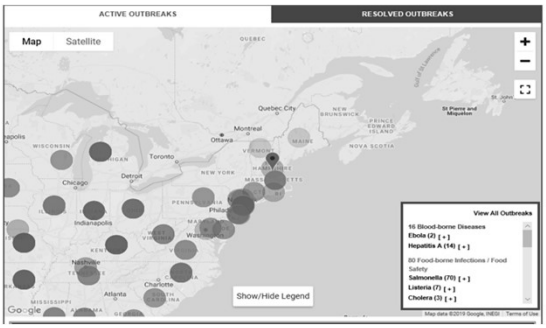
Fifth's Disease (Erythema Infectiosum)

- Diagnosis/Plan
  - Was contagious before rash appeared therefore, no isolation needed
    - Spread via respiratory droplets
  - Symptomatic treatment
  - Patient education-I.e. contagion, handwashing
  - Can cause aplastic crisis in individuals with hemolytic anemias
  - Concern regarding: miscarriage, fetal hydrops
  - Adults: arthralgias

Wright, 2021 262

262

Great Resource



https://www.contagionlive.com/outbreak-monitor

Wright, 2021 263

263

Great Resource

Category	Disease	Outbreak Name	Location	Total Cases	Total Deaths	Source
Skin & Soft Tissue Diseases	Acute Flaccid Myelitis	Acute Flaccid Myelitis 2018	Tennessee	2	0	Enterovirus A71 and Acute Flaccid Myelitis
Skin & Soft Tissue Diseases	Measles	Illinois Measles Outbreak	Illinois	4	0	More Exemptions and Less Vaccination: The 2 Factors Driving US Measles Outbreaks
Skin & Soft Tissue Diseases	Measles	Texas Measles Outbreak	Texas	8	0	More Exemptions and Less Vaccination: The 2 Factors Driving US Measles Outbreaks
Skin & Soft Tissue Diseases	Measles	Washington State Measles Outbreak	Multnomah County, Oregon	4	0	Travel-Associated Measles Outbreaks On the Rise in US
Skin & Soft Tissue Diseases	Measles	Rockland County, NY Measles Outbreak	Rockland County, NY	138	0	More Exemptions and Less Vaccination: The 2 Factors Driving US Measles Outbreaks
Zoonotic & Vector-		Hedgehog				CDC Announces Salmonella Outbreak

https://www.contagionlive.com/outbreak-monitor

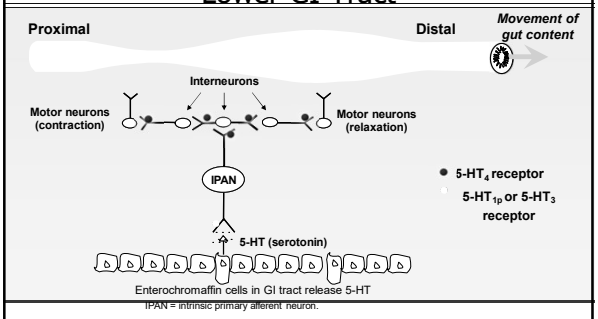
Wright, 2021 264

264

GI Disorders

265

Serotonin and Motor Activity in the Lower GI Tract

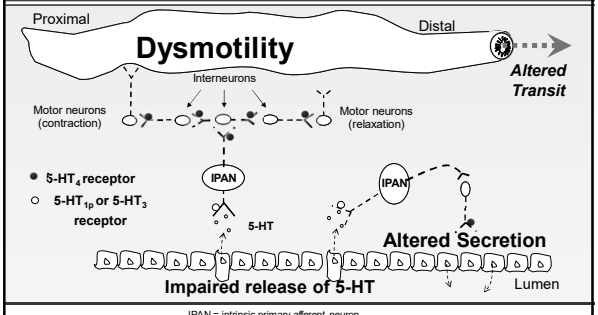


IPAN = intrinsic primary afferent neuron.

Adapted from Grider JR et al. *Gastroenterology.* 1998;115:370-380.
Adapted from Gershon MD. *Rev Gastroenterol Dis.* 2003;3:S25-S34.

266

Impaired 5-HT Release Leads to Impaired Enteric Reflexes, Dysmotility, and Altered Secretion



IPAN = intrinsic primary afferent neuron.
Adapted from Grider JR et al. *Gastroenterology.* 1998;115:370-380.
Adapted from Gershon MD. *Rev Gastroenterol Dis.* 2003;3:S25-S34.

267

5-HT (5 Hydroxytryptamine) What Role Does Serotonin Play in Functional Bowel Disorders?

268

Role of 5-HT (5-hydroxytryptamine)

- 5-HT is a neurotransmitter within the enteric nervous system
- Gut contains 95% of all 5-HT in the body
- 14 sub-types of 5-HT
  - 5-HT(3) and 5-HT (4) receptors are proving to be very important in the patient with IBS

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

269

Role of 5-HT(3) Receptors (5-hydroxytryptamine)

- 5-HT(3) receptors are extensively distributed within the gastrointestinal tract
- These receptors have been implicated in the mechanisms controlling colonic motility/ transit time, gastrointestinal secretions and pain.

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

270

Role of 5-HT(3) Receptors (5-hydroxytryptamine)

- Blockade of these receptors has been shown to reduce intestinal distension, reduce bowel frequency, slows colonic transit/motility, and increases jejunal water and sodium absorption.
- Alosetron - works on the 5-HT (3) receptors
  - Is now available

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

271

Role of 5-HT(4) Receptors (5-hydroxytryptamine)

- Blockade of these receptors has been shown to increase motility.
- New medication approved in 2018
  - Prucalopride (Motegrity)

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

272

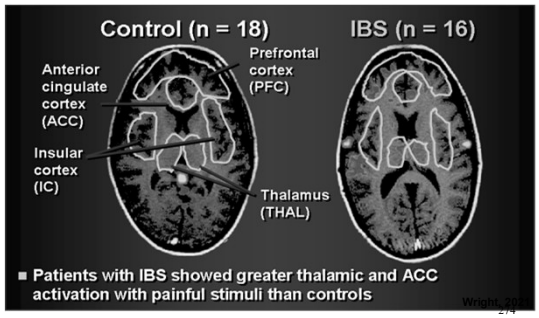
Pathophysiology

- Diarrhea and constipation are explained by the alteration in motor function.
- Abnormal pain experienced by patients with IBS is believed to be caused by excessive sensitivity to colonic distension.
  - Smaller amounts of distension causes more abdominal distress

Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology. 2000;118:842-848.

273

fMRI Imaging with Rectal Distension in IBS



- Patients with IBS showed greater thalamic and ACC activation with painful stimuli than controls

Wright, 2021
274

- Adapted from Mertz, GUT 2002 51, Suppl i29

274

The Role of Stress in IBS

- Stress is widely believed to play a significant role in the pathophysiology and clinical presentation of IBS.
- Genetically predisposed individual.
- Sustained stress can result in a permanent increased stress response in the central stress circuits/pathways.

Drossman DA. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? Am J Med 1999;107:41S-50S.
Drossman DA. Irritable bowel syndrome and sexual/physical abuse history. Eur J Gastroenterol Hepatol 1997;9:327-30.

Wright, 2021
275

275

Irritable Bowel Syndrome (PI-IBS) Four Years After The Outbreak Of Waterborne Gastroenteritis (GE)

- Purpose: Determine the incidence and natural history of Post Infectious-IBS (PI-IBS) in a population exposed to a municipal water contamination in Canada in 2000
- Methods/ Results:
  - Bowel Disease Questionnaire employed to identify IBS via Rome I criteria (n=1587)
  - 1,012 (63.8%) reported GE in '00, and of those, 273 (17.2%) fulfilled Rome I IBS criteria in '04
    - **Marshall J et al, DDW 2006 abstract 344**

Wright, 2021
276

276

Irritable Bowel Syndrome (PI-IBS) Four Years After The Outbreak Of Waterborne Gastroenteritis (GE)

- Conclusions:
  - The prognosis of PI-IBS appears favorable, with spontaneous resolution in half of patients.
  - Independent predictors of IBS in '04 were: female gender, weight loss, abdominal pain, and duration of diarrhea at outbreak

• **Marshall J et al, DDW 2006 abstract 344**

277

What About SIBO? (Small Intestinal Bacterial Overgrowth)

- Increasing attention to the role of small intestinal bacterial overgrowth in IBS
  - 84% of patients diagnosed with IBS had SIBO compared with 20% of control group
  - 35% of IBS group treated with neomycin had improvement in symptoms vs. 11.4% of placebo group
    - Further research is clearly needed
  - Now available: hydrogen breath test

Pimentel, M, Chow, EJ, Lin HC. Eradication of small intestinal bacterial Overgrowth reduces symptoms of irritable bowel syndrome: a double Blind, randomized controlled study. Am J Gastroenterol. 2003;98:412-19.

278

Pathophysiology of Functional Bowel Disorders

Altered Serotonin Signaling
SERT, TpH1, 5-HT release, EC cells

⇩

Altered GI Physiology
Motility, sensitivity, secretion

⇩

Clinical Symptoms and Disorders
Chronic Constipation
IBS- D, C and M

Coates MD et al. *Gastroenterology*. 2004;126:1657-1664.
Crowell M et al. *Curr Opin Investig Drugs*. 2004;5:55-60.
Baig MK et al. *Colorectal Dis*. 2002;4:348-354.

279

Diagnosis of Functional Bowel Disorders

280

Rome III Diagnostic Criteria for Irritable Bowel Syndrome (all subtypes)

- At least 3 months, with onset at least 6 months previously of recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) associated with 2 or more of the following:
  - Improvement with defecation; and/or
  - Onset associated with a change in frequency or stool; and/or
  - Onset associated with a change in form (appearance) of stool

ROME III *Gastroenterology* 2006:130:1377-1390.

281

Diagnostic Criteria: Chronic Constipation

- Characterized by unsatisfactory defecation that results from:
  - Infrequent stools or
  - Difficult stool passage
    - Characterized by: straining, sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool
  - Or, a combination of both

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100:S1-4

282

Chronic Constipation and IBS-C Share GI Dysmotility Symptoms

Symptoms >3 months	Chronic Constipation	IBS-C
Straining	+++	+++
Hard/lumpy stools	+++	+++
<3 BM/wk	+++	+++
Feeling of incomplete evacuation	+++	+++
Bloating/abdominal distension	++	+++
Abdominal pain/discomfort	+	+++

IBS-C = irritable bowel syndrome with constipation.

Thompson WG et al. *Gut*. 1999;45(suppl 2):II43-II47.
Drossman DA et al. *Gastroenterology*. 1997;112:2120-2137.

283

Red Flags

- Evaluate for alarm features
  - Reported weight loss
  - Nocturnal symptoms
  - Recent travel history
  - Family history of colon cancer or inflammatory bowel disease
  - Family history of Celiac disease
  - Onset in older patients (> 50)
  - Fevers
  - Oral ulcers
  - **B**loody stools

284

Red Flags

- Evaluate for alarm features
  - Abnormal exam (weight loss, arthritis, rashes)
  - Fever, oral ulcers
  - Anemia
  - Leukocytosis
  - Abnormal chemistry – abnormal LFT's, Creatinine
  - Elevated sed rate
  - Abnormal TSH
  - Positive fecal occult blood test

285

ACG Evidence-Based Guideline: Diagnostic Testing

Chronic Constipation

- Among CC patient without alarm features, there are inadequate data to make a recommendation about the *routine* use of diagnostic tests

Irritable Bowel Syndrome

- Among IBS patients without alarm features, the *routine* use of colonoscopy (<50 years old), flexible sigmoidoscopy, thyroid function tests, etc is not recommended.
- Routine testing for celiac disease may be considered.
- Individuals ≥ 50 years should undergo colorectal cancer screening

ACG Functional GI Disorder Task Force. *Am J Gastroenterol.* 2005;100:S1-S21.
ACG Functional GI Disorder Task Force. *Am J Gastroenterol.* 2002;97:S1-S5.

286

Biochemical Assays for IBS

- Anti-Cdtb
- Anti-Vinculin
  - Antibodies in serum; present in IBS
  - Approximately 90% accuracy
  - Trial performed in 3000 individuals

287

Laboratory Evaluation

- Fecal wbc's
- Fecal lactoferrin[1]
  - During intestinal inflammation, activated leukocytes infiltrate the mucosa and lumen, increasing the level of fecal lactoferrin[1]
  - Lactoferrin is a glycoprotein secreted by mucosal membranes
  - Fecal lactoferrin is elevated in patients suffering from active inflammatory bowel disease (IBD) but not in those with irritable bowel syndrome (IBS)

[1]http://www.techlabinc.com/presentations/lactoferrin.pps Accessed September 13, 2006

288

Possible Additional Tests

- Celiac Disease Testing
  - 4.6% of individuals with IBS are likely to have this present; Compared with 0.25-0.5% of general population
  - Celiac Panel: Immunoglobin A (IgA), anti-tissue transglutaminase (tTGA), and IgA anti-endomysial antibodies (AEA)
- Sigmoidoscopy vs. Colonoscopy
  - Positive occult blood test
  - Nocturnal awakenings
  - Colon cancer

289

Consider Pelvic Floor Dysfunction and Colonic Inertia

- Rectal manometry
  - Catheter inserted into rectum to assess muscle pressure and nerve function
- Defecography
  - Done on individuals who have had an inconclusive result on rectal manometry or individuals suspected of a structural abnormality of the rectum
  - Barium is instilled into rectum. Patient then sits on radiolucent commode and pictures are taken as the patient defecates
- Sitz Marker Study
  - Procedure to assess colonic motility
  - Ingest Sitz Marker capsule; brought back in for abdominal x-ray on day 1, day 3 and day 5
  - Normal: complete evacuation by day 5

http://www.medscape.com/viewarticle/501075_4
Accessed on September 13, 2006.

290

Case Study

- **45 year old woman presents with a 30+ year history of straining, hard/lumpy stools, and a sense of incomplete evacuation. She passes stool approximately 2 times per week.**
- **Upon further questioning, she also notes frequent bloating, minimal abdominal discomfort, and partial relief with defecation.**

What is her diagnosis?

291

Treatment Options for Functional Bowel Disorders

292

Non-pharmacologic Treatments

- Dietary modification
  - Given high incidence of concomitant lactose intolerance, dairy avoidance may be helpful
  - 2 week trial of a lactose free diet can be helpful
  - Lactaid or similar as an adjunct to dairy products

ROME III *Gastroenterology* 2006:130:1377-1390.

293

Non-pharmacologic Treatments

- Dietary modification
  - Avoid potential triggers: caffeine, alcohol, sorbitol, citrus fruits, high fiber foods, high fructose corn syrup
    - Gas producing foods (beer, cauliflower, grapes, onions, beans, brussel sprouts, plums, raisins, red wine)
  - High fiber foods may occasionally help some individuals but need to tailor to individual patient

ROME III *Gastroenterology* 2006:130:1377-1390.

294

Pharmacologic Options

295

Bulking Agents

- Bulking agents
  - Psyllium (Metamucil): 15-25 grams per day
    - 1 teaspoon or packet 1 – 3 times/day
  - Methylcellulose (Citrucel): 19 – 57 grams per day
    - 1 heaping tablespoon 1 – 3 times/day
  - Polycarbophil (Fibercon)
    - 625 mg tablet
    - 2 tablets 1 – 4 times daily

Bijerk CJ, Muris JWM, Knottnerus JA et al. Systematic review: the role of different types of fiber in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:245-251.

296

Bulking Agents

- Begin these agents very slowly
  - Bloating, flatulence and abdominal pain are the side effects frequently encountered
- Advance dosage every 2 – 4 weeks
- Each patient will respond differently to each agent
  - Try various products

Bijerk CJ, Muris JWM, Knottnerus JA et al. Systematic review: the role of different types of fiber in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:245-251.

297

Summary of Trials on Bulking Agents

- 13 trials; 7 met high quality criteria
  - 3 trials showed a statistically significant benefit
- Supplemental fiber
  - Accelerates colonic and oro-anal transit
  - Improves constipation with sufficient supplementation (20-30g per day)
  - May worsen some IBS symptoms
    - Bloating and pain
  - Limited data suggest equivocal benefits in IBS

Muller-Lissner, *BMJ* 1988;296:615
Cann et al, *Gut* 1984; 25:168
Cook et al, *Gastroenterology* 1990; 998:66
Lucey et al, *Gut* 1987;28:221

298

Polyethylene Glycol

- Polyethylene glycol (Miralax)
  - Osmotic agent
- Indication: Constipation
- Adult dosage: 17 g in 8 ounces of water
  - FDA indication: once daily for up to 2 weeks
- Precautions
  - Nausea and vomiting
- Contraindications
  - Bowel obstruction

Am J Gastroenterol 2002;97: Suppl Nov. S18-25.

299

Anticholinergic Agents

- Anticholinergic agents (Antispasmodic)
  - Reduce sigmoid motility in response to fat
  - Decrease postprandial pain and distension by inhibiting postprandial colonic contractions

ROME III *Gastroenterology* 2006:130:1377-1390.

300

Anticholinergic Agents

- Dicyclomine (Bentyl)
  - –20mg-40mg ac
- Hyoscyamine sulfate (Levsin)
  - –0.125mg 1-2 tabs po q 4 hours prn
  - –Levsin SL, LevBid (0.375mg 1 – 2 tablets po bid)

ROME III *Gastroenterology* 2006:130:1377-1390.

301

Prescribing Information

- Precautions:
  - –Cardiovascular disease, Hypertension, Elders
- Side Effects
  - –Drowsiness
  - –Anticholinergic side effects
- Contraindications
  - –Glaucoma
  - –Unstable CV status

Hyoscyamine Product Insert

302

Lactulose

- Lactulose:
  - – Constulose; Enulose; Generla; Kristalose
- Dosage:
  - – 10-20 g/day; increased to bid as needed
- Indication: Chronic Constipation
- Mechanism of Action: Osmotic (draws fluid into colon)
- Precautions: use with caution in those with diabetes; monitor electrolytes
- Adverse Reactions: flatulence, diarrhea, abdominal discomfort, nausea, vomiting

Product insert

303

Lubiprostone

- Amitiza (lubiprostone)
- Class:
  - Locally acting chloride channel activator
- Indications:
  - IBS-C in women 18 years of age and older
  - Chronic idiopathic constipation in the adult population
    - Men and women
    - All adults, including 65 and older

Gastroenterology 2006;130:5.
Amitiza Product Insert

304

Lubiprostone

- Dosage:
  - 8 mcg bid with food
  - 24 mcg bid with food
- Mechanism of Action:
  - Activates CIC-2 (found in the human intestine)
  - By increasing intestinal fluid secretion and increases motility in the intestine
- Efficacy
  - Increases BM's by 3 per week on average
  - Significant increase over placebo of spontaneous bowel movements within first 24 hours after taking medication

Gastroenterology 2006;130:5
Amitiza Product Insert

305

Lubiprostone

- Side effects:
  - Nausea - 30%
  - Diarrhea – 13%
- Contraindications
  - History of mechanical GI obstruction
  - Diarrhea
- Precautions:
  - Not studied in individuals with moderate - severe hepatic or renal impairment
  - Pregnancy – C

Gastroenterology 2006;130:5
Amitiza Product Insert

306

New Approval

- Lubiprostone
  - Opioid-induced constipation
  - Not effective for those on diphenylheptane opioids (e.g., methadone) has not been established
  - 24 mcg two times daily with food

307

Linaclotide

- Brand name: Linzess
- Class:
  - Guanylate cyclase-C agonist
  - Activation of the GC-C – results in an increased in intra and extracellular concentrations of cGMP.
  - This stimulates secretion of chloride and bicarbonate into the intestinal lumen; resulting in increased intestinal fluid and accelerated transit
  - Also reduces intestinal visceral pain
- Indications:
  - Irritable bowel syndrome with constipation (IBS-C)
  - Chronic idiopathic constipation (CIC)
- Dosage:
  - IBS –C: 290 mcg once daily
  - CIC: 145 mcg once daily
  - Take on empty stomach; 30 minutes before first meal of the day
  - Taking it WITH foods – increases risk of loose stools/diarrhea
  - *** NOW available in 72 mcg dosage

http://www.frx.com/pi/linzess_pi.pdf accessed 12-20-2012

308

Linaclotide

- Boxed warning:
  - Contraindicated in pediatric patients up to 6 years of age
  - Avoid use in children 6 – 17 years of age
  - Linaclotide caused deaths in young juvenile mice
  - Another contraindication: suspected or known mechanical gastrointestinal obstruction

http://www.frx.com/pi/linzess_pi.pdf accessed 12-20-2012

309

Linaclotide

- Precautions:
  - Pregnancy category C
  - Nursing mothers (unknown if excreted in breast milk)
- Adverse reactions:
  - Diarrhea: 16% - 20% (depending upon indication)
  - Abdominal pain: 7%
  - Approximately 8% - 9%% of patients treated with linaclotide and 3%-4% with placebo discontinued due to adverse reactions
- Drug/drug interactions:
  - NONE; does not use P450 system; nor is it an inhibitor or substrate of the P-gp (P-glycoprotein)

http://www.frx.com/pi/linzess_pi.pdf accessed 12-20-2012

310

Plecanatide (Trulance)

- Class:
  - Guanylate cyclase-C agonist
- Indication:
  - Adults for treatment of chronic idiopathic constipation
- Dosage:
  - 3 mg taken orally once daily
  - With or without food; may be crushed and put in applesauce but not cut in 1/2

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208745lbl.pdf
Accessed 12-30-2017

311

Other options

- Methylnatrexone bromide (Relistor)
  - Indicated for the treatment of opioid-induced constipation when other therapies are ineffective
  - Subcutaneous injection
  - Used a lot in individuals receiving palliative care
  - One dose every other day
  - Dosage is weight based

312

Prucalopride (Motegrity)

- Indication:
  - Treatment of chronic idiopathic constipation (CIC) in adults
- Class:
  - Serotonin-4 (5-HT4) receptor agonist
  - Gastrointestinal prokinetic agent that stimulates colonic peristalsis and increases bowel motility

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

313

Prucalopride

- Dosage:
  - 2 mg once daily
  - With or without food
- Warnings and precautions:
  - Renal dosing (CCl < 30 mL/min) : 1 mg once daily
  - Monitor patients for persistent worsening of depression and emergence of suicidal thoughts and behavior
  - Pregnancy, Lactation, and Children
- Contraindications:
  - Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

314

Prucalopride

- Efficacy:
  - 2530 patients enrolled in clinical trials
    - 1251 received drug/1279 placebo
  - Responder was defined as a patient with an average of 3 or more CSBMs per week, over the 12-week treatment period
    - 33% vs. 10% and 38% vs. 18% (5 of 6 studies stat. significant)
- Drug – Drug Interactions:
  - No significant drug-drug interactions

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

315

Prucalopride

- Side effects (Drug/placebo):
  - Headache (19% vs. 9%)
  - Abdominal pain (16% vs. 11%)
  - Nausea (14% vs. 7%)
  - Diarrhea (13% vs. 5%)
  - Dizziness (4% vs. 2%)
  - Vomiting (3% vs. 2%)
- Advantages:
  - Another option to the market
  - No QT prolongation

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

316

Prucalopride

- Competition:
  - No direct competition
  - Tegaserod (Zelnorm) – 5-HT4 receptor agonist withdrawn from the market in 2007
  - Cisapride (also withdrawn from the market)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210166s000lbl.pdf
Accessed 01-04-2019

317

Summary: Traditional Treatment Options for IBS-D

Agent	GI Indication
Anti Diarrheal	IBS-D
Bile Acid Sequestrant	IBS-D
Selective 5 HT3 Receptor Antagonist	IBS -D
Discussion of possible psychological factors. Symptom resolution and reassurance	

Gastroenterology 2006;130:5.

318

IBS - D

- Loperamide HCl (Imodium)
  - Initially: 4 mg followed by 2 mg, as needed
  - Maximum: 16 mg daily
  - Mechanism of action: slows colonic motility
  - Side effects: abdominal pain, dry mouth, nausea

Loperamide HCL Product Insert

319

IBS-D

- Diphenoxylate hydrochloride and atropine (Lomotil)
  - Initially: 2.5mg
  - 1-2 pills up to 4x/day until control achieved
  - Maximum: 8 mg daily
  - Mechanism of Action: inhibits excessive GI motility and decreases GI propulsion
  - Side Effects: tachycardia, dry mouth, nausea

Lomotil Product Insert

320

IBS - D

- Cholestyramine (Questran); Colesevelam (Welchol); Colestipol (Colestid)
  - Off-label usage
  - Bile acid sequestrant
  - Cholestyramine - Dosage: 1 packet or scoop in fluid bid
    - Maximum: 6 scoops daily
  - Colesevelam: 4 – 7 capsules daily; titrate as needed
  - Side effects:
    - Constipation
    - Impaction
    - Inhibits absorption of other medications

Gastroenterology 2006;130:5.

Product Inserts

321

Alosetron

- Alosetron (Lotronex)
  - Withdrawn from the market in December of 2000
- Reintroduced in 2002
- Available under promethius prescribing program
- Indication: IBS – D
- Dosage: 0.5 – 2 mg daily

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

Alosetron Product Insert

Wright, 2021 322

322

Alosetron Post-Marketing Information

- Ischemic colitis
  - Of 275,000 patients given alosetron, ischemic colitis occurred in 80 patients
  - 74% of the cases occurred in the 1st month of alosetron use
  - Of the 80 cases, 48 hospitalizations, 6 surgeries, no deaths

An Evidence Based Approach to the Management of Chronic Constipation In North America. *American J of Gastroenterology* 2005:100;S1.

Alosetron Product Insert

Wright, 2021 323

323

Eluxadoline (Viberzi)

- Eluxadoline
- Class: mu-opioid receptor agonist
- Indications: IBS-diarrhea predominant
- Dosage: 100 mg two times daily with food
  - Start lower dosage (75 mg two time daily) in the following individuals
    - Concomitant OATP1B1 inhibitor (Organic Anion Transporting Polypeptide1B1) inhibitor
    - Mild-moderate hepatic impairment

www.viberzi.com accessed 01-02-2016

Wright, 2021 324

324

Eluxadoline Efficacy

- 1700 patients with IBS-D have been exposed to eluxadoline
- Length of exposure: 3 months – 12 months
- ROME III criteria for IBS-D
- Efficacy in Study 1 (improvement in worst abdominal pain by 30% AND reduction in the BSS to < 5 on at least 50% of days):
  - 12 weeks: 24% – 25% vs. 17% placebo
  - 26 weeks: 23% – 29% vs. 19%
  - Abdominal pain improvement ≥ 30%: 42% – 43% vs. 40%

www.viberzi.com accessed 01-02-2016

325

Eluxadoline Efficacy

- Study 2:
  - Same criteria as study 1
  - Response over 12 weeks:
    - 29% - 30% vs. 16%
  - Response over 26 weeks:
    - 30% - 33% vs. 20%
  - Abdominal pain response improved by ≥ 30% over 12 weeks
    - 48% - 51% vs. 45%

www.viberzi.com accessed 01-02-2016

326

Eluxadoline

- Contraindications:
  - Biliary duct obstruction
  - Alcoholism or individuals drinking more than 3 drinks per day
  - History of pancreatitis
  - Severe hepatic impairment
  - Severe constipation

www.viberzi.com accessed 01-02-2016

327

Eluxadoline Precautions

- NOW contraindicated in individuals without a gallbladder

www.viberzi.com accessed 01-02-2016

328

Eluxadoline

- Side effects:
  - Constipation (8% vs. 2%)
  - Nausea (7% vs. 5%)
  - Abdominal pain (7% vs. 4%)
  - Vomiting (4% vs. 1%)
- Drug/drug interactions
  - OATP1B1 Inhibitors: cyclosporine, gemfibrozil, antiretrovirals, rifampin
    - Use 75 mg two times daily

www.viberzi.com accessed 01-02-2016

329

Additional drug/drug interactions

- Strong CYP inhibitors
  - Ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine and bupropion
  - Use 75 mg two times daily
- Rosuvastatin
  - Increase exposure to rosuvastatin
  - Use lowest dosages of rosuvastatin
- Caution in drugs with narrow therapeutic index
  - www.viberzi.com accessed 01-02-2016

330

Eluxadoline

- Avoid in pregnancy and lactation
- Do not use in children < 18 years of age
- Do not take other medications such as alosetron (Lotronex) or loperamide (Imodium) on a regular basis while using this medication

www.viberzi.com accessed 01-02-2016

331

Rifaximin (Xifaxan)

- Indication: IBS-D; targeting SIBO
- Dosage: 550 mg three times daily x 2 weeks
  - May repeat dose up to 2 times if helpful or patient has recurrent symptoms
- With or without food

www.xifaxan.com accessed 01-03-2016

332

Rifaximin (Xifaxan)

- Precautions/Contraindications:
  - Avoid use in 1st trimester (increased risk of congenital abnormalities based upon animal data)
- Side effects:
  - Diarrhea
  - Peripheral edema
  - Nausea
  - Risks of *C. difficile*
- Drug/drug interactions:
  - P-glycoprotein inhibitors (cyclosporine): increased rifaximin exposure

www.xifaxan.com accessed 01-03-2016

333

TCA's

- Numerous products:
  - Examples: Amitryptyline and nortriptyline
- Mechanism of action
  - Low dose at bedtime may reduce abdominal pain
  - May decrease diarrhea, therefore helping those with IBS-D
  - May worsen IBS-C
- Side effects:
  - Sedation
  - Anticholinergic effects

334

SSRI's

- Although no conclusive evidence exists to document efficacy…
  - SSRI's work on the 5-HT (2) receptors in the body
  - Majority are in the brain but some are in the bowels
  - Some patients report significant improvement in anxiety, frequency, and urgency of stools

Gastroenterology 2006;130:5.

335

Studies to Date on SSRI's

- Broekaert and colleagues reported that Citalopram (Celexa) reduced the number of abdominal pain days as well as the severity of the pain
  - Also reduced bloating and severity
  - Only 14 patients studied
- Paroxetine (Paxil) has also been looked at in patients with ibs
  - 257 patients; 78% women; randomized to 1 or 3 treatment arms: routine care by GI provider; 8 weeks of psychotherapy or 20 mg of paroxetine
  - Paroxetine: lower number of pain days at 3 months; not statistically significant at 1 year

Gastroenterology 2006;130:5.

336

Probiotics

- Bifidobacterium infantis
  - Only one shown in multiple clinical trials to be effective
  - Has been shown to reduce gas, bloating, abdominal pain
  - ? May help to reduce inflammatory cytokines in IBD
  - Decreased straining and hard stools
  - Note: symptoms may worsen before better

337

Case Study

338

Case Study

- **45-year old woman presents with a 30+-year history of straining, hard/lumpy stools, and a sense of incomplete evacuation. She passes stool approximately 3 times per week**

- **Previously, she tried bulking agents and anticholinergic agents with minimal improvement in her symptoms, and she experienced bloating with lactulose**

What treatment would you consider?

339

What Would You Recommend?

- Nonpharmacologic therapies??
- Pharmacologic therapies??

340

GERD

341

EE

- 52 year old female presents with anterior chest pain; non-radiating and not associated with any exertion. Occurs daily unless she avoids most foods. Has tried OTC antacids without much effect.
- Aggravating factors:
  - Foods – fatty meals, spicy meals
- Alleviating factors:
  - None
- Medications:
  - Lexapro 5 mg one daily

342

EE (Continued)

- PMH
  - Anxiety disorder
  - Postmenopausal
  - Overweight
  - L5-S1 disc surgery
- No previous work-up for symptoms
- Physical Examination
  - Unremarkable except for 1+ tenderness epigastric region
  - 12-lead ECG: No abnormalities
  - Hemocult: negative

343

What is GERD?

- Heartburn is one symptom of GERD
- This is characterized by:
  - Reflux of food and acid from stomach into esophagus
  - Often associated with esophageal inflammation
  - May be associated with mucosal injury or even cancer
    - Erosive esophagitis and/or Barrett's

344

Symptoms of GERD

- Burning, substernal pain
- Radiates up into the throat
- Acid taste in mouth
- Chest pain
- Nausea
- Hoarseness of voice
- Wheezing
- Cough
- Dysphagia

345

Frequency of Heartburn

- Frequency and severity of heartburn does not necessarily correlate with development of esophageal damage or erosions
- Individuals with severe and frequent heartburn may have no esophageal damage whereas individuals with little heartburn may have significant damage
- Therefore…response to standard OTC medications by the patient is likely to be a predictor of more serious or less serious pathology

346

EE (Continued)

- Most likely diagnosis is:
  - GERD
  - Consider cardiac etiology given age; Negative nuclear stress test

347

Etiology of Heartburn and GERD

- Heartburn and GERD occurs when:
  - The lower esophageal sphincter (LES) temporarily relaxes
  - Allows reflux of stomach acid into the esophagus
  - Normally, gravity and peristalsis clear material from the esophagus and the saliva that we swallow neutralizes the remaining esophageal acid
  - Heartburn occurs when any one of these mechanisms are impaired

348

Cause of Lower Esophageal Sphincter Relaxation

- Relaxation or weakening of the LES can be caused by:
  - Eating certain foods
    - Onions, garlic, black pepper
  - Pressure on the stomach because of an individual's weight
  - Frequent bending and lifting, particularly after eating
  - Vigorous exercise

Wright, 2021
349

349

Cause of Lower Esophageal Sphincter Relaxation

- Relaxation or weakening of the LES can be caused by:
  - Pregnancy
    - Progesterone relaxes LES; slows peristalsis and increases retention of partially digested food and acid
  - Medications also can decrease LES pressure
    - CCB's, hormone replacement therapy, muscle relaxants, beta blockers
    - Alpha-blockers
    - Nitrates
  - Pathophysiologic mechanisms
    - Hiatal hernia and gastric acid hypersecretion
    - Zenker's diverticulum

Wright, 2021
350

350

Etiology

- Several other defects thought to contribute to heartburn and GERD
  - Abnormal esophageal epithelial resistance
  - Abnormalities of gastric emptying
  - Gastric distention
  - Abnormal acid production

Wright, 2021
351

351

Diagnosis of Heartburn and GERD

- Diagnosis of heartburn is usually made with history and physical examination
  - Usually, this is all that is needed
- Many clinicians will try routine treatments first and assess for response prior to ordering a variety of tests
- EGD – is not needed to make diagnosis

352

Diagnosis

- Multiple tests available to make this diagnosis
  - Often times, patient is treated with medication 1st to see how he/she responds
  - If inadequate response, testing performed or…if any worrisome signs present
    - UGI: easiest, least expensive test
      - Hiatal hernia: present in 40-60% of population
      - Mild reflux seen in 30% of general population
      - Looking for esophageal irregularities, ulcers
      - Normal barium swallow may be seen in 40-60% of all individuals with GERD

353

Endoscopy

- Endoscopy (Esophagoscopy)
  - Best study for the evaluation and treatment of GERD
  - Allows for direct visualization of the mucosa of the esophagus and the lining of the stomach
  - Essential when suspecting Barrett's esophagitis
  - If abnormalities are seen, biopsy is conducted

354

Intraesophageal Acid Perfusion

- Also called Bernstein test
- This is a test where the patients symptoms are reproduced or eliminated with this procedure
- NG tube placed 30-35 cm from the tip of the nares into the esophagus
  - Saline is infused followed by HCL
  - Looking for reproduction of symptoms with HCL and relief of symptoms with saline infusion

Wright, 2021
355

355

24-hour pH Monitoring

- 2 mm flexible probe is placed transnasally to about 5 cm above the LES
- Probe is connected to a box similar to a Holter monitor
- Wireless: transmits signals to box regarding pH
- Monitoring of pH is conducted in addition to the patients symptoms

Wright, 2021
356

356

Esophageal Motility Studies

- Conducted to measure the pressure of the LES
- Thin, pressure sensitive tube is passed through mouth or nose and into stomach
- Once in place, the tube is pulled back slowly into the esophagus while the patient is asked to swallow
- The pressure of the muscle contractions is then measured along several sections of the tube

Wright, 2021
357

357

H. Pylori

- Role of *H. pylori* in heartburn is subject of frequent debate
- *H. pylori* – water supplies
- First identified in countries where water supply is poor
- Transmitted via saliva
- Bacteria may help erode protective layer of esophagus
- *H. pylori* breath test or stool tests – most accurate tests to be performed in primary care
  - Biopsy – gold standard

358

H. Pylori

- ***H. pylori*** is associated with significant morbidity
- Causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers
- Linked to 60% of gastric cancer (adenocarcinoma and primary ß-cell lymphoma [MALT lymphoma]) cases
  - The World Health Organization has classified *H. pylori* as a Group 1 carcinogen

359

H. Pylori Breath Test or Stool Test

Sensitivity and Specificity of Tests for *H. pylori* Infection[2,3]

	Sensitivity	Specificity
UBT	95%[a]	96%[a]
Stool (antigen test)	93%[a]	93%[a]
Serology (ELISA)	N/A[c]	N/A[c]
Endoscopic biopsy (Routine histology)	93%[b]	90%[b]

- Used to detect urease
- By measureing the ratio of CO_2 to CO_2 in the patient's breath samples, UBT accurately detects active *H. pylori*-associated urease
- No PPI's x 2 weeks, No peptobismol; no food x 1 hour
- Okay to use H2RA's

360

ACG

- Routine testing for *H. Pylori* is not necessary for GERD

361

Barrett's Esophagitis

- Occurs in < 1% of heartburn sufferers
- Occurs when the esophageal lining is replaced by tissue normally found in the intestines (metaplasia)
- Increased risk of adenocarcinoma of the esophagus
  - 30 – 125 times higher in the patient with Barrett's
- Treatment:
  - PPI
  - Halo procedure: thermal ablation of tissue

362

The Good News IS…

- 53 – 71% of all heartburn sufferers have endoscopically normal esophageal mucosa

363

Treatments

- Lifestyle Modification
- Elimination of medications
- PPI (Proton pump inhibitors)
  - Have become first line therapy
- Surgery
  - For recalcitrant cases

364

EE

- History and physical examination were consistent with GERD
- No additional testing performed
- Cardiac pathology ruled-out
- No additional red flags
- Patient started on lifestyle modification and a proton pump inhibitor given frequency and severity of symptoms

365

Treatment Options

366

AGA Guidelines

- PPI therapy is now first line
- No role for H. pylori
- No diagnostic testing needed
- No need for repeat endoscopy

367

Nonpharmacologic Treatment Options

- Dietary Modification
  - Bland diet
  - Smaller meals
  - Less acidic foods
  - Avoidance of chocolate/mint

368

Nonpharmacologic Treatment Options

- Dietary Modification
  - Avoidance of alcohol
  - Decrease fat in diet
  - Weight loss
  - Lifestyle changes
    - Elevate head of bed

369

Medications

370

ACG

- It is appropriate to start with PPI for patients with GERD
- Two week trial may be all that is needed
- 8 weeks necessary to heal erosive esophagitis unless patient has Barrett's

371

Antacids

372

Antacids

- Examples:
  - Maalox
    - Aluminum hydroxide, magnesium hydroxide
  - Mylanta
    - Same as above
  - Rolaids
    - Calcium carbonate, magnesium hydroxide
  - Surpass
    - Calcium carbonate
  - Tums
    - Calcium carbonate

373

Antacids

- Although antacids have long been thought to work in the gastric lumen to decrease gastric acidity, they actually work in the esophageal lumen
- Rapidly increase esophageal pH
- Neutralize esophageal acid for 90 minutes after dosing
- Little change in gastric pH
- Indication: intermittent or episodic heartburn

374

Antacids

- Advantages
  - Multiple products available
  - Many different preparations: liquid, swallowable tablets, chewable tablets, effervescent solutions and gum
  - Gum and chewed tablet antacids seem to be more effective (per patients) than liquid products
  - Fast onset of action
  - Ease of dosing – take when patient has symptoms

375

Disadvantages of Antacids

- Frequent dosing required
  - Short duration of action
- Few studies done with antacids
- No role with prevention

Wright, 2021
376

376

H2RA's

Wright, 2021
377

377

H2RA's

- Axid
  - 75 mg nizatidine
- Pepcid AC
  - 10 mg famotidine
- Maximum Strength Pepcid AC
  - 20 mg famotidine
- Pepcid Complete
  - 10 mg famotidine, 800 mg of $CaCO_3$ (Tums) and 165 mg of MG $(OH)_2$
- Tagamet HB
  - 200 mg cimetidine
- Zantac 75/150
  - 75 mg ranitidine

Wright, 2021
378

378

Mechanism of Action

- Drugs bind to histamine-2 receptors on parietal cells to decrease gastric acid secretion
- Begin to work by decreasing gastric acid secretion within 1 – 2 hours of dosing
- Seem to work best on nocturnal acid secretion vs. daytime (i.e. after meal secretion)
- Antacids vs. H2RA
  - Antacids: Onset: 30 minutes, Last: 60 minutes
  - H2RA: Onset: 90 minutes, Last: 9 hours

Wright, 2021
379

379

H2RA's

- Numerous studies conducted at both OTC and prescription strength dosages
- Clearly surpass placebo in onset of action and sustained efficacy

Wright, 2021
380

380

H2RA's

- Indication: episodic heartburn
- All products can be taken daily
- Not indicated for frequent heartburn

Wright, 2021
381

381

Combination of Antacid and H2RA

382

Low Dose H2RA and Antacid

- H2RA and antacid combination
- Speed of an antacid + duration of H2RA
- Indication: intermittent or episodic heartburn
  - Not cost effective or indicated for individuals with frequent heartburn

383

Proton Pump Inhibitors

384

Mechanism of Action

- PPIs
  - Suppress gastric acid production by blocking parietal cell hydrogen/potassium ion adenosine triphosphatase
  - Known as the proton pump
  - This is the final pathway involved in acid secretion
  - Remember…PPI's affect only those pumps which are active
    - Not all pumps are active at the same time
  - 25% of new proton pumps are synthesized daily

385

Proton Pump Inhibitors

- Omeprazole (Prilosec)
- Lansoprazole (Prevacid)
- Esomeprazole (Nexium)
- Rabeprazole (AcipHex)
- Pantoprazole (Protonix)
- Deslansoprazole (Dexilant)

386

Proton Pump Inhibitors

- Recent studies have shown an increased risk of:
  - Osteoporosis
    - Should take calcium citrate NOT carbonate
    - Carbonate – i.e. Tums needs an acidic environment
  - Pneumonia
    - Diminished acid protection
  - B12 deficiency
  - C. difficile related infections
  - ? Link with dementia

387

Combination Therapy

- Omeprazole/sodium bicarbonate (Zegerid)
  - Indications
    - Gastric and duodenal ulcer
    - Erosive esophagitis
    - Symptomatic GERD

388

Interaction with Clopidigrel

- Interaction is well documented
- Does not necessarily seem to be a class effect
- Most interaction to least interaction
  - Omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid)
  - Lowest interaction: pantoprazole (Protonix) and deslansoprazole (Dexilant)

389

Surgical Options

- Nissen fundoplication
  - The upper curve of the stomach (the fundus) is wrapped around the esophagus and sewn into place so that the lower portion of the esophagus passes through a small tunnel of stomach muscle
  - This surgery strengthens the LES between the esophagus and stomach
  - In one study, 62% of people who had surgery were still taking medications to control GERD symptoms.
    - However, they were less likely to need to take medications regularly; and, when they did not take medications, their remaining symptoms were likely to be less severe.

390

Additional Surgical Option

- EsophyX
  - Transoral Incisionless Fundoplication
  - Treatment of GERD
    - Reconstruction of the antireflux barrier
    - Restores GE junction back to normal anatomy
    - Same concept as the Nissen without incisions
    - Now FDA approved and cleared for US market

391

EE

- Patient returns 1 month after initiating treatment with a PPI; no improvement in symptoms
- Referred for endoscopy given lack of response to traditional methods
  - Endoscopy shows mild esophagitis; negative biopsy
- PPI – increased by GI to 2 daily
  - No improvement at 1 month

392

What Now??

- 24 hour pH probe
- Esophageal motility studies
- Bernstein test

393

EE

- 24 hour probe shows NO significant correlation between pH and symptoms
- Esophageal motility studies showed decreased motility
  - Started on metoclopramide (reglan) 5 mg 1 po tid – 30 minutes prior to meals with significant improvement in symptoms
  - Black box warning re: tardive dyskinesia

394

Thank You For Your Time and Attention!!!

Wendyarnp@aol.com

395