25th Annual Southwestern Conference on Medicine

Pearls in Allergy & Immunology for Primary Care

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Goals and Objectives

- ASTHMA- Understand the basics of asthma and strategies to improve otucomes

- IMMUNODEFICIENCY- Identify potential warnings signs and the basics of immunodeficiency as a primary care provider

ON THE FRONT LINES OF ASTHMA

What is asthma?

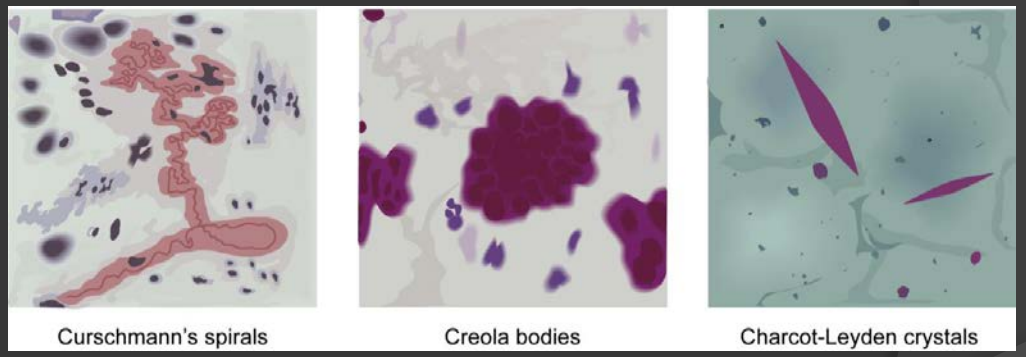
- A complex disorder characterized by:
- Underlying airway inflammation

Leading to:

- Variable and recurring symptoms
- Airway obstruction
- Bronchial hyper-responsiveness

What is asthma- pathophysiology?

- Chronic inflammatory disorder of the airways.
  - Infiltration of neutrophils, eosinophils, and lymphocytes.
  - Mast cell activation
  - Airway Remodeling
- Leads to:
  - epithelial cell injury
  - basement membrane fibrosis-remodeling
  - mucous hyper-secretion
  - airway hyper-responsiveness.



Symptoms of asthma?

- Recurrent episodes of:
  - Wheezing
  - Chest tightness
  - Cough
  - Breathlessness
- Symptoms occur after exercise, exposure to allergens or irritants, laughing or crying, and especially occur at night.

Diagnosis of Asthma

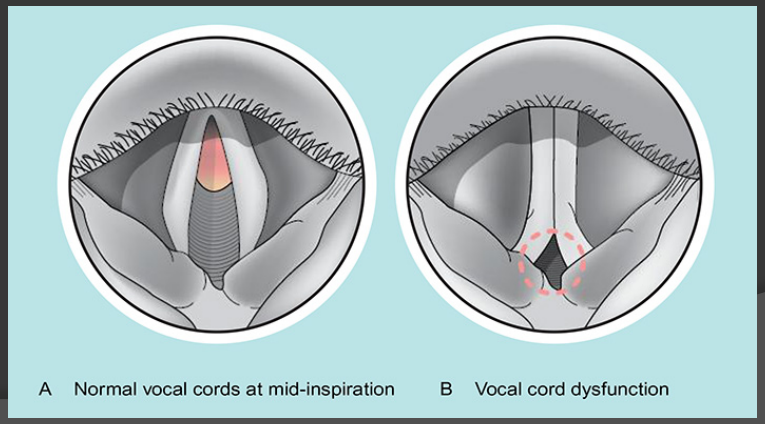
- Wheezing on lung exam
- Hyper-expansion of chest
- Allergic Rhinitis, Conjunctivitis, Eczema
- Objective measures
  - Reversible airway obstruction- ≥5 years old
  - Methacholine Challenge- High NPV
  - Mannitol Challenge High PPV

Differential Diagnosis

- VCD
- post nasal drip, upper airway obstruction (tonsils)
- foreign body aspiration
- Cystic Fibrosis
- GERD
- De-conditioning/out of shape
- Obesity
- Panic disorder/Anxiety

Paradoxical Vocal Fold Motion

- Inspiratory ADDuction of vocal cords with posterior chinking
- Symptoms intermittent and can be very severe- requiring ED treatment and intubation.
- Irritant triggers- Exercise, cold air, multiple chemicals cause symptoms.
- Show me- Can point to where the trouble is.



Paradoxical Vocal Fold Motion

- Gavin et al. found in small case control study that adolescents with VCD+asthma (n=12) have more anxiety and comorbid psychiatric illness than pts with severe asthma alone.
- Rundell and Spiering found 19 of 370 (5%) elite athletes had VCD (18 woman)
- Jain et al. found 5 out of 48 (10%) adult patients presenting to the emergency room with asthma had VCD on laryngoscopy.

How bad is my asthma?

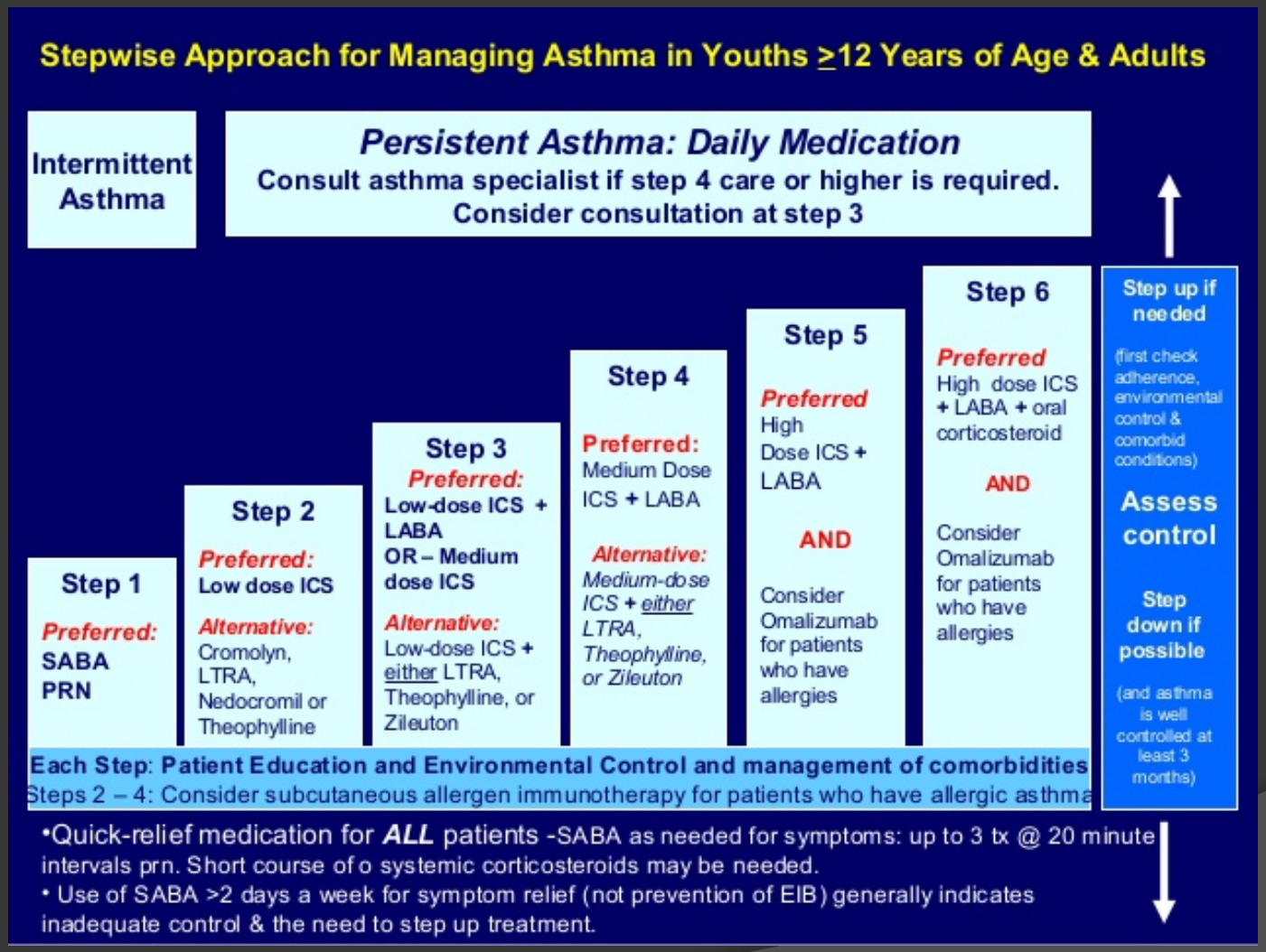
- Severity: the intrinsic intensity of the disease process.
  - Severity is most easily and directly measured in a patient who is not currently receiving long-term control treatment.
- Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.
- Goals of therapy: To have no impairment, lower risk.

Classification of Asthma Severity ≥ 12

Impairment | Risk

Symptoms	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Daytime	<2 x/week	>2 x/Week but not daily	Daily	All day
Nighttime	<2 x/month	3-4x/month	>1x/week Not nightly	Nightly
SABA	<2 x/week	>2x/week Not daily	Daily	>1/Day daily
Activity	None	Minor	Some	Extreme
Spiro	-Normal -FEV1 >80% - Nl FEV1/FVC	-FEV1 >80% - Nl FEV1/FVC	-FEV1 60-80% -FEV1/FVC Reduced >5%	-FEV1 <60% -FEV1/FVC Reduced >5%
Oral Steroids	0-1 x per year	≥2 times per year		

Asthma Step Up Therapy



Control- Assess Q1-6 months

Components of Control	Well Controlled	Not Well controlled	Very Poorly Controlled
Symptoms	**≤2 days/week**	>2 days/week	Throughout the week
Nighttime Awakenings	**≤2 nights/month**	1-3x/week	**≥4x/week**
SABA Use	**≤2 days/week**	>2 days/week	Several x per day
Limitations	None	Some	Extremely
FEV1 or PEFR	>80% Pred/or personal best	60-80% Pred/or Personal best	<60% Pred/or Personal best
Validated ? ACT ACQ ATAQ	**≥20** **≤0.75** 0	16-19 >1.5 1-2	**≤15** N/A 3-4
Exacerbations-Steroids	0-1x/year	**≥2 x per year**	

Assessing Asthma Control

- In 10,428 UK primary care patients, 59% were considered uncontrolled. Physicians felt that only 42% were uncontrolled.
- We overestimate how many patients are well controlled.
- Because of this we are often under-treating asthma.

Chapman, 2008; Horne, 2007; Barnes, 2004

Asthma Control Test

- >12 years old- use the Adult ACT
- Validated questionnaire that the patient fills out.
- The questions reflect the components of impairment from the guidelines based on the past **4** weeks.

Asthma Control Test

1- In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school or at home?					Score
All of the time	Most of the time	Some of the time	A little of the time	None of the time	
1	2	3	4	5	
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	
1	2	3	4	5	
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 week	2 - 3 nights a week	Once a week	Once or twice	Not at all	
1	2	3	4	5	
4- During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as (salbutamol)?					
3 or more times per day	1 or 2 times per day	2 or 3 time per week	Once a week or less	Not at all	
1	2	3	4	5	
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	
1	2	3	4	5	
How to interpret ACT					Score
ACT Score ⩾ 20	*ACT Score = 16 – 19*		*ACT Score < 16*		
controlled asthma	*partially controlled*		*uncontrolled*		

Asthma Control Test

- A score of 20 or above is considered well controlled.
- 15-19 is considered not well controlled
- <15 the patient is very poorly controlled.
- A score of 20 or above with FEV1< 80% suggests the patient is a poor perceiver of symptoms.

Asthma Action Plan

- All asthma guidelines recommend the use of an asthma action plan
- Typically based on stoplight color coded categories- Green, Yellow, Red
- Can be symptom based or peak flow based.
- Depending on category, it recommends specific therapy or need for evaluation.

Asthma Action Plan

GREEN ZONE means no symptoms.
- Use prevention medicines to keep your lungs strong.

YELLOW ZONE means Caution. Asthma symptoms are starting.
-Use quick relief medicines in addition to prevention medicines to keep an asthma attack from becoming serious.

RED Zone means Danger. This is a serious asthma attack.
- Follow the emergency relief plan and get help from a doctor.

Asthma Action Plan

This is a tool we us for asthma that will be given to your child who has asthma

ASTHMA ACTION PLAN

Name:_____DOB:_____ Date:_____ Provider: _____

Green zone **"You're doing well!"** - breathing is good - no cough or wheeze - sleep well at night -can go to school and play	◻ Singulair ____ mg once each day ◻ Flovent ____ mcg ____ puffs ____ times a day ◻ Pulmicort ____ mg nebulized ___ times a day ◻ Advair ____/50 one puff ____ times/day ◻ No routine medicine is needed **If asthma occurs with exercise** give Albuterol 2 puffs with spacer for younger kids or 2 puffs w/o spacer for older children/adolescent 10-15 minutes *prior to exercise* _____ _____ _____
Yellow zone **"Caution"** - first signs of a cold - cough - mild wheeze - tight cough - coughing, wheezing, or trouble breathing at night	**(Continue Green Zone medications)** ◻ Albuterol 2 puffs with spacer for younger kids or w/o spacer for older children/adolescent every 4 hours as needed for wheezing, chest tightness or persistent cough ◻ Albuterol Nebulizer Solution nebulize 1 vial every 4 hours as needed for wheezing, chest tightness or persistent cough ◻ Increase Flovent ____ mcg ____ puff(s) twice a day thru cold ◻ Increase Pulmicort ____ mg nebulized twice a day thru cold Call office if you need to use Albuterol every 4 hours for longer than 24 hours, or using Albuterol for longer than 4 days in a row, or 2 times/week three times/month _____ _____ _____
Red zone **"Get Help!"** - medicine is not helping - breathing is hard and fast - nose opens wide - skin pulling in between ribs(retractions) _cannot talk well	Albuterol 4 puffs immediately or Albuterol Nebulizer solution nebulize 1 unit immediately followed by another unit immediately after the first unit is done. **Call the office immediately.** If after hours, asked that the doctor who is on be paged STAT. If you can not reach your doctor on call, **GO to ER** **Call 911 if your child is having extreme difficulty breathing** _____ _____ _____

Triggers:
◻ Colds ◻ Cigarette smoke ◻ Out door allergens
◻ Dogs / Cats ◻ Cold air ◻ Dust / mold
◻ Exercise ◻ Other_____

Follow up visit:_____
Please bring all your medicines with you.

Adapted from Westwood-Mansfield Pediatric Associates and Framingham Pediatrics asthma plans by WRisko MD, PPOC, March 2011

Asthma Action Plan- Evidence

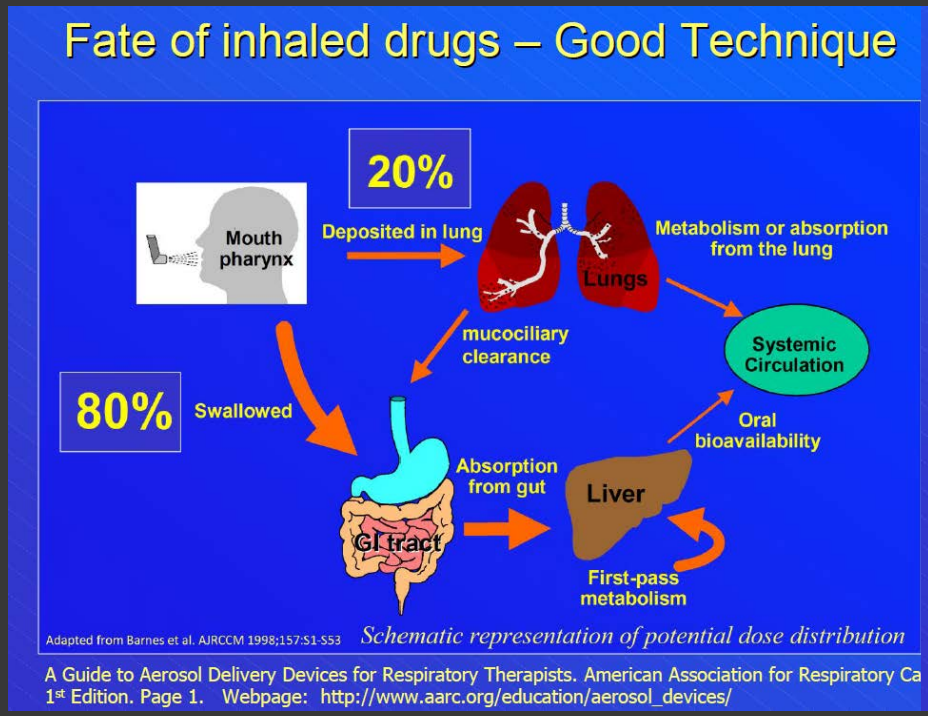
- In 2008, Zumek et al. performed a Cochrane analysis of action plans in children.
- Only one peak flow based study used placebo in comparison group. It showed a lower rate of acute care visits in action plan group. (Agrawal, 2005)
- Four studies compared symptom based plans to peak flow based plans and showed a NNT of 8 to prevent 1 acute care visit.

Asthma Action Plan- Evidence?

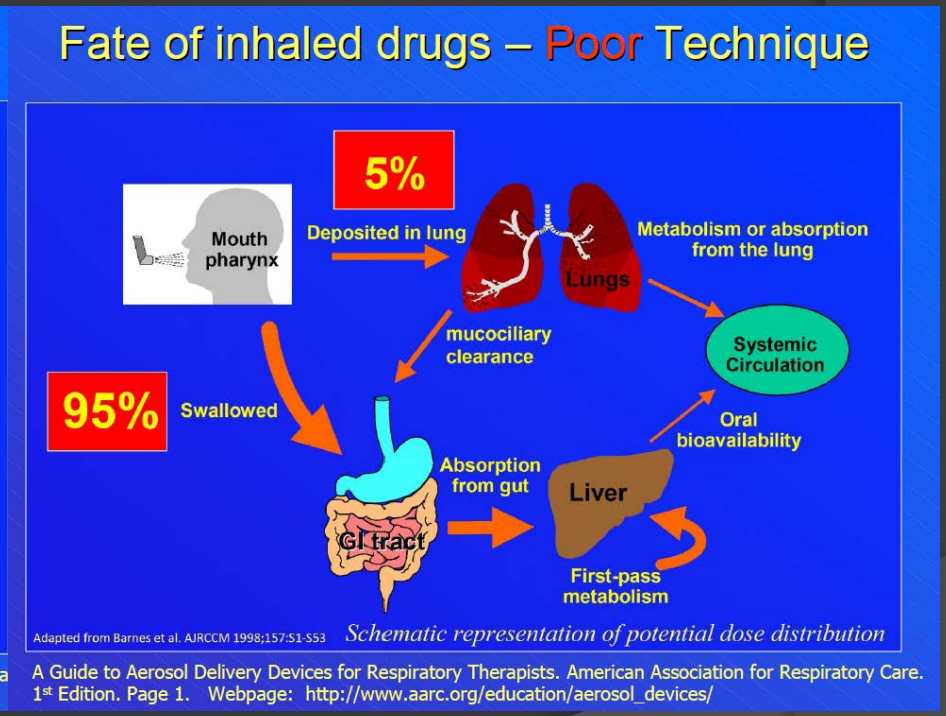
- Patients preferred symptom based plan.
- All plans studied recommended increase of ICS dose if having an exacerbation.
- Not sure what effect the action plan would have without the intervention.
- What was the mechanism leading to decreased acute care visits?

Step 1 – Do they know what their meds are for and how to use them? Proper technique

Step 1 – Proper Technique



A Guide to Aerosol Delivery Devices for Respiratory Therapists. American Association for Respiratory Ca
1st Edition. Page 1. Webpage: http://www.aarc.org/education/aerosol_devices/



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1st Edition. Page 1. Webpage: http://www.aarc.org/education/aerosol_devices/

Proper Technique—how bad is it?

- 2014 study of 105 asthmatics
  - 31 using dry powdered inhalers (DPI), 50 using metered dose inhalers (MDI), 24 using MDI with spacer
  - Proper use –6% DPI, 16% MDI, 21% MDI with spacer

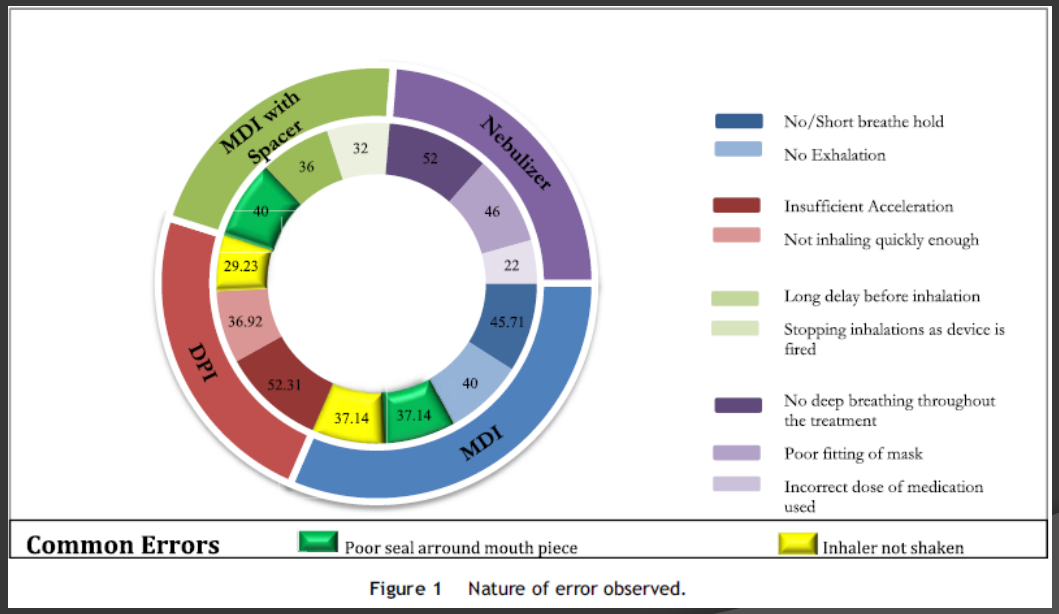


Figure 1 Nature of error observed.

Ganguly et al. J Clin Diag Res. 2014
Arora et. al. Resp Med 2014

Proper Technique—how bad is it?

- 2014 study of 300 patients
  - 82.3% made errors

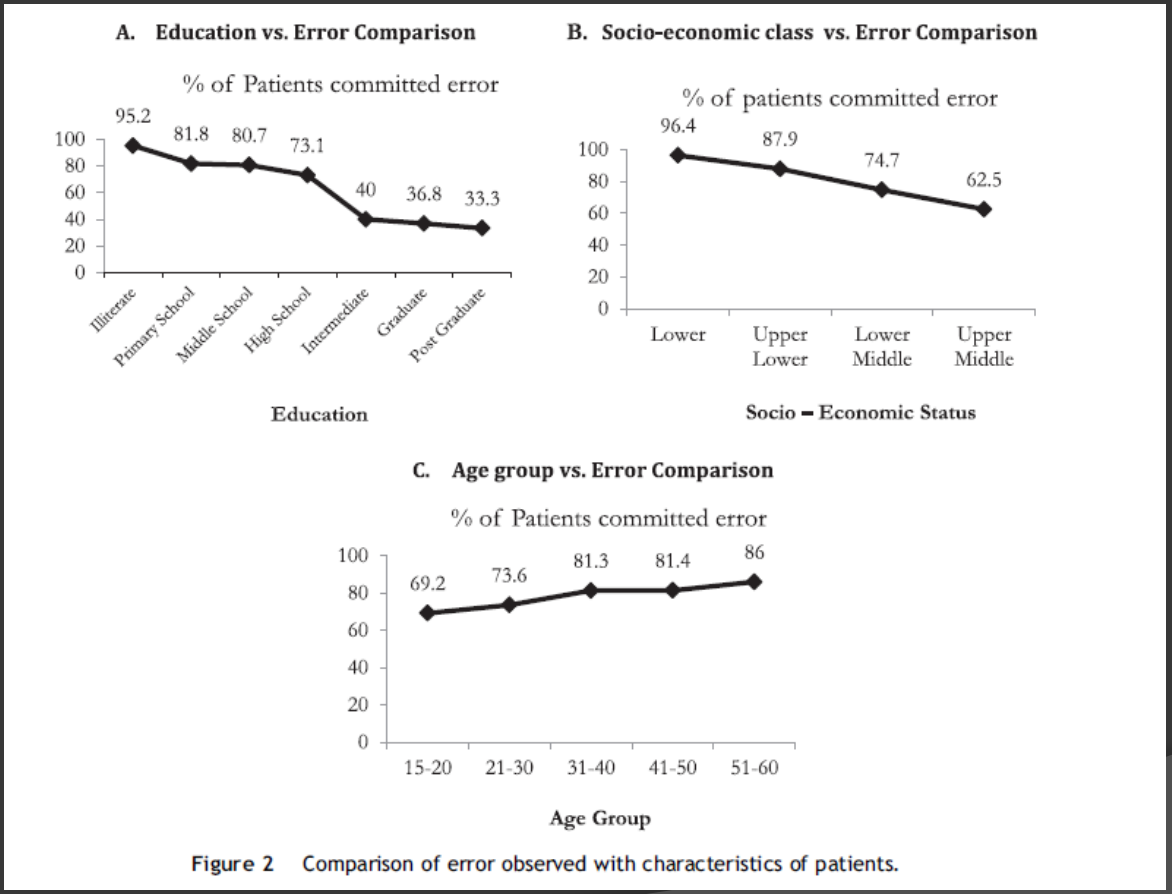


Figure 2 Comparison of error observed with characteristics of patients.

Arora et. al. Resp Med 2014

Why are there so many problems?

- Design of Inhalers differ
  - Formulation of Drug
  - Mechanical Activation (MDI vs DPI)
  - Internal resistances vary

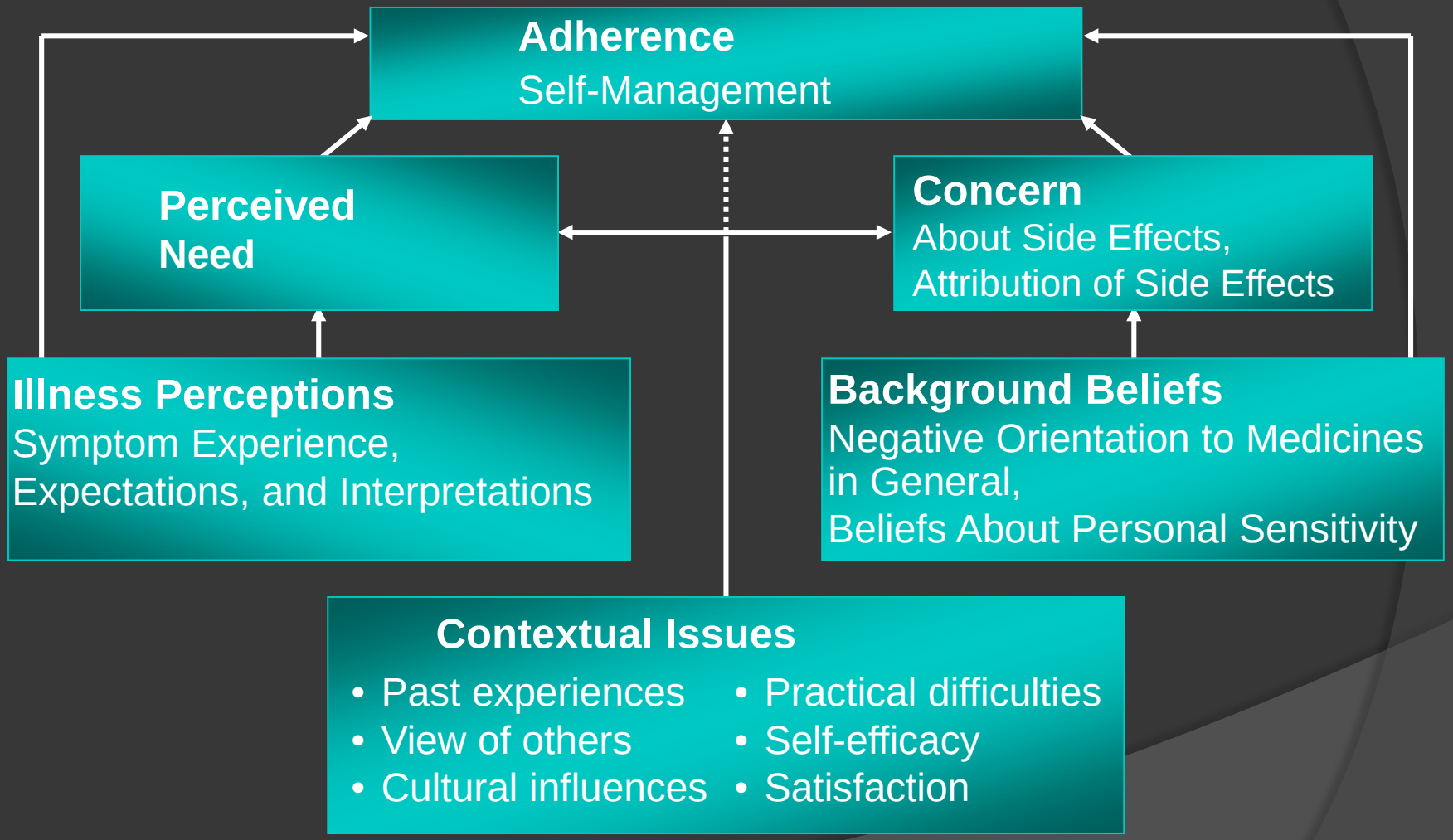
Patients Vary

-Ability to learn

-Physical size of lungs (adult vs peds)

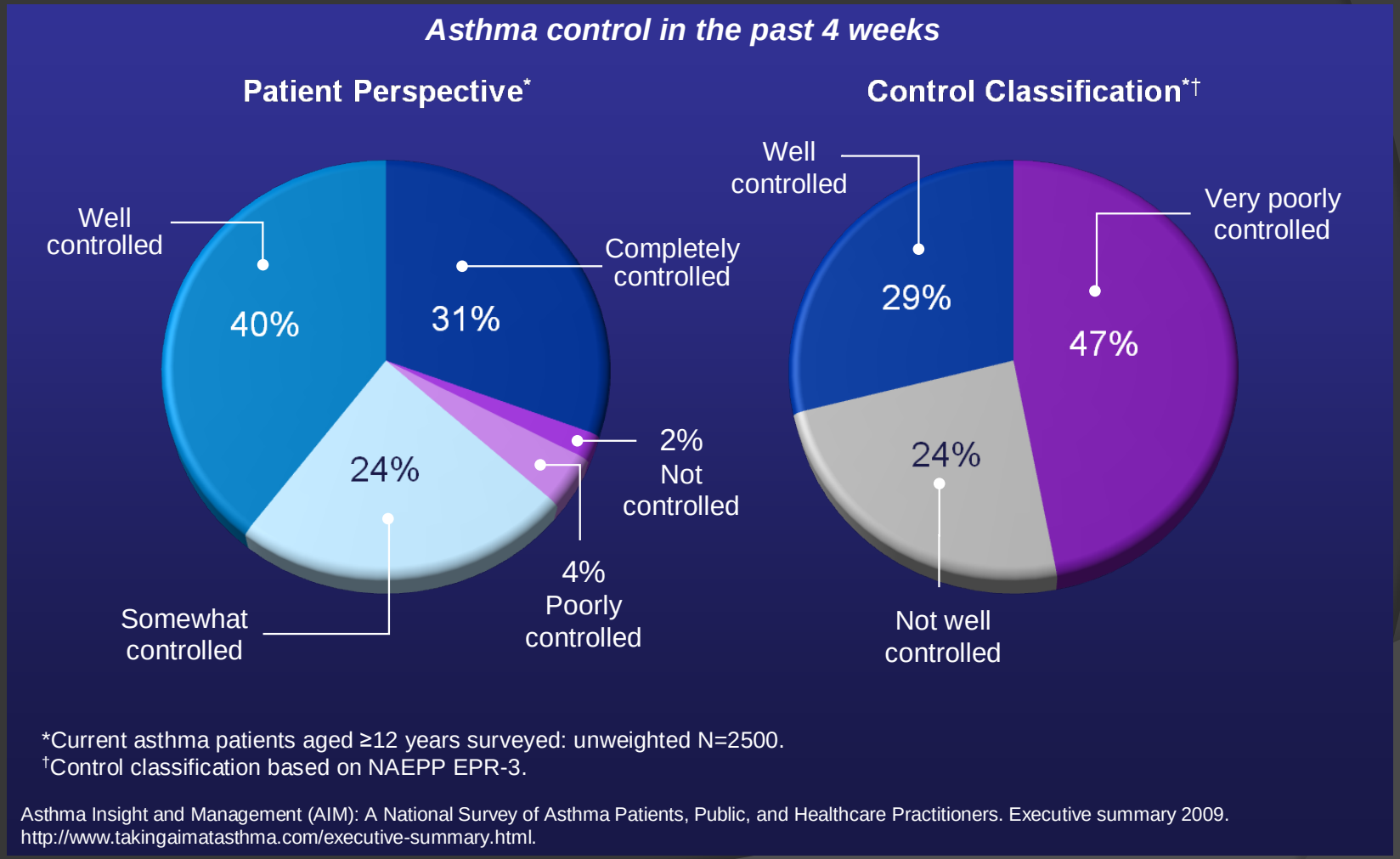
-Effort varies from dose to dose

Step 2 –They understand how to use their meds but do they take them?? Adherence in Asthma



Adapted from Horne R. *Chest*. 2006;130(suppl):65S-72S.

Step 2 –Adherence in Asthma-perceived need



*Current asthma patients aged ≥12 years surveyed: unweighted N=2500.
†Control classification based on NAEPP EPR-3.

Asthma Insight and Management (AIM): A National Survey of Asthma Patients, Public, and Healthcare Practitioners. Executive summary 2009. http://www.takingaimatasthma.com/executive-summary.html.

Risk Factors for Non-Adherence

- Positive correlation:
  - Race, Parental education, income.
- No consistent correlation:
  - smoking in home, large family size, parent marital status.

Drotar D, Bonner MS. 2009

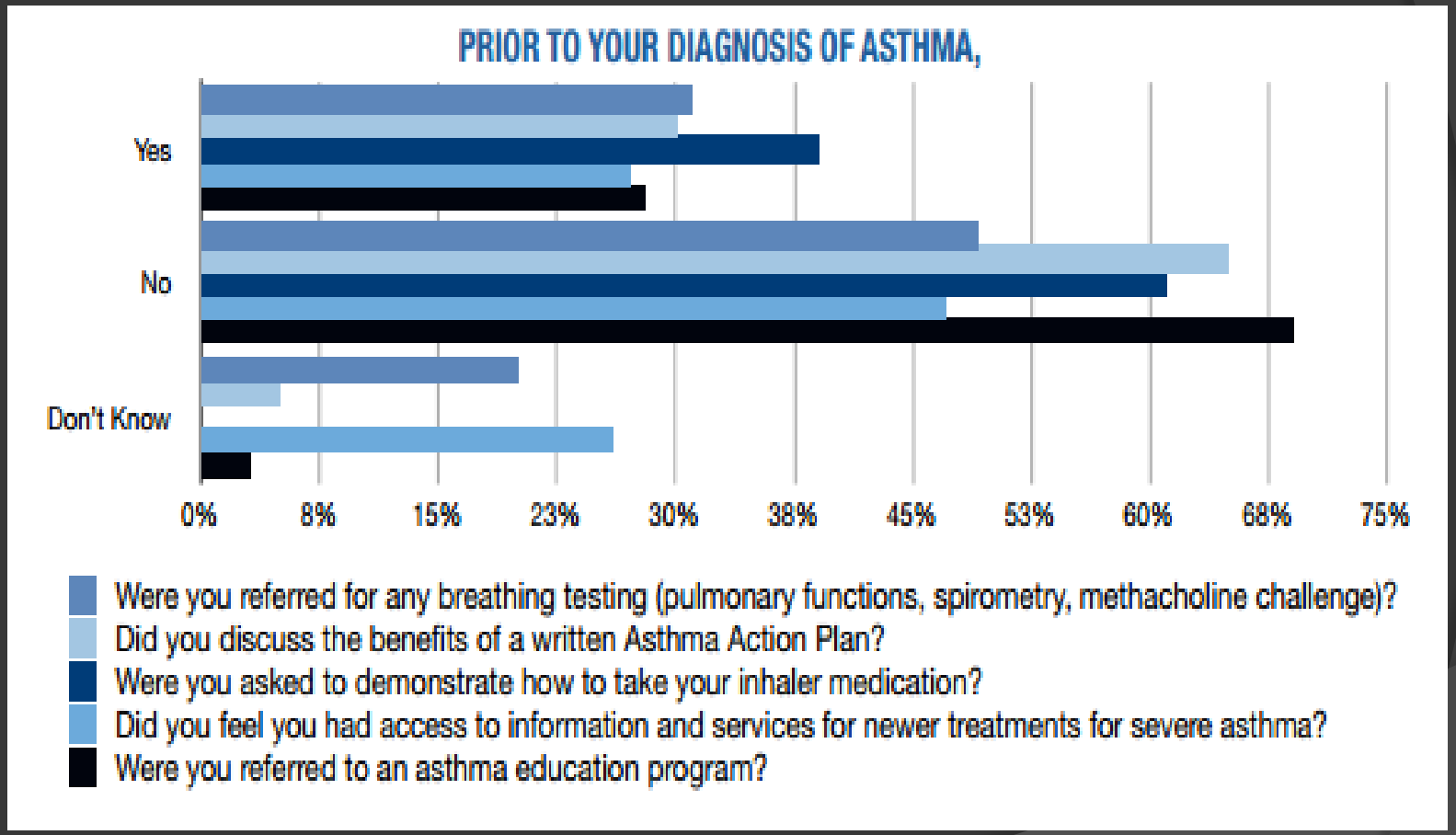
What should you do?

- Remind patients to monitor symptoms and medication use.
- Discuss consequences- short and long term.
- Ask about concerns about medication.
- Motivational interviewing techniques.

What should you do?

- Have them write their action plan/pick their medications.
- Try to use once a day regimens.
- Follow up with the same physician- build trust.
- Recommend audiovisual reminders- text message or daily alarms on cell phone.
- EDUCATE on proper technique-- reinforce

How Compliant are Physicians?



Asthma Summary

- Complex heterogeneous disease
- Follow severity and clinical course with ACT, spirometry
- Regimens can become confusing and difficult –set up and discuss an Asthma Action Plan
- Discuss compliance, technique, cost, side effects, etc on a REGULAR BASIS

Goals and Objectives

- ASTHMA- Understand the basics of asthma and strategies to improve otucomes

- IMMUNODEFICIENCY- Identify potential warnings signs and the basics of immunodeficiency as a primary care provider

INTRODUCTION TO PRIMARY IMMUNODEFICIENCY

Case

- 35 y/o F with 10-14 year hx of recurrent sinusitis, requiring oral antibiotics at least once a month.
- Courses of oral antibiotics have lasted as long as 2 months.
- Chronic sinus pain, sneezing, watery nose, shortness of breath, and coughing in the morning. She has significant purulent dark green-to-yellowish discharge – Abx help a bit.
- Sinus surgery few years ago to remove a bone spur and repair a deviated septum, electrocautery to remove excess mucosal tissue – no change in recurrent sinus infections.

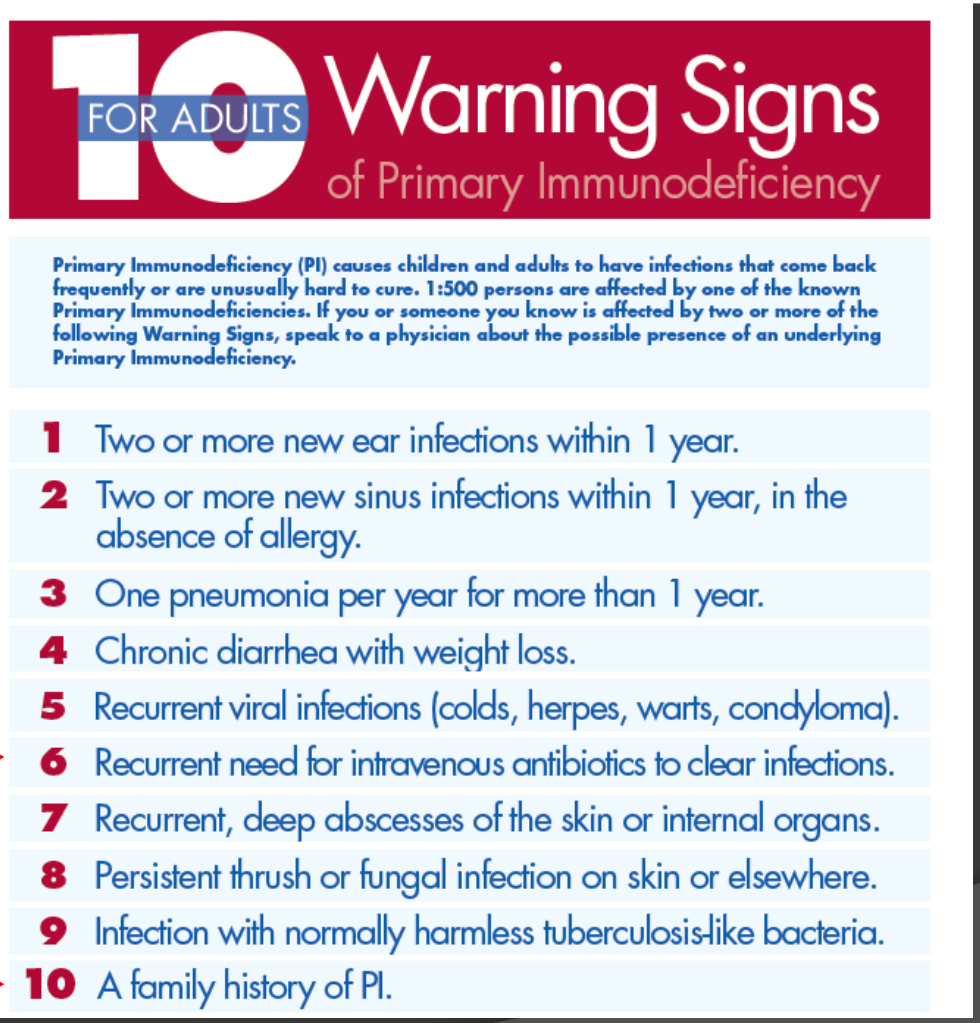
Infectious Hx –

- Bronchitis 3-4 times every winter.
- Multiple urinary tract infections, the last being two years ago.
- Multiple episodes of kidney infection with the most recent one being 1 year ago and requiring hospitalization and intravenous antibiotics.
- Denies pneumonia, meningitis, cellulitis, osteomyelitis, severe GI infection, bacteremia, sepsis, or endocarditis. She does have a history of chronic diarrhea.

Objectives

- Recognize warning signs of PID
- Review initial laboratory tests in the evaluation of PID
- Understand the basic treatment options for humoral deficiency

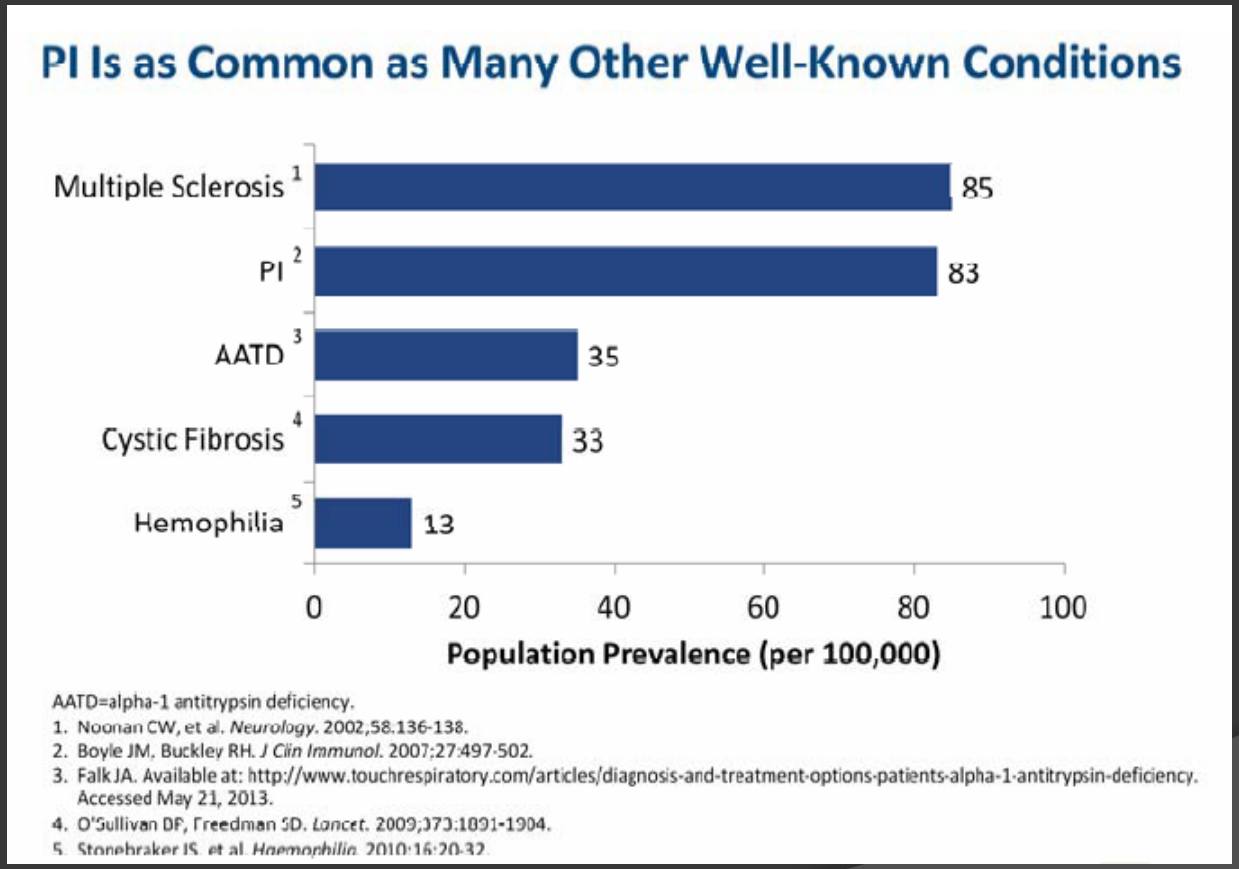
10 Warning Signs of Primary Immunodeficiency



The Jeffrey Modell Foundation: 1-866-INFO-4-PI • www.jmfworld.org

How Common is Primary Immunodeficiency?

- Probably more common than previously thought: earlier estimates were 1 in 10,000 to 50,000.



Boyle, JM, and Buckley, RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol Sept 2007 27(5): 497-810.

Basic immunology

	Cellular	Humoral
Innate	Phagocytic cells NK cells	Complement
Adaptive	T cells	Antibody (B cells)

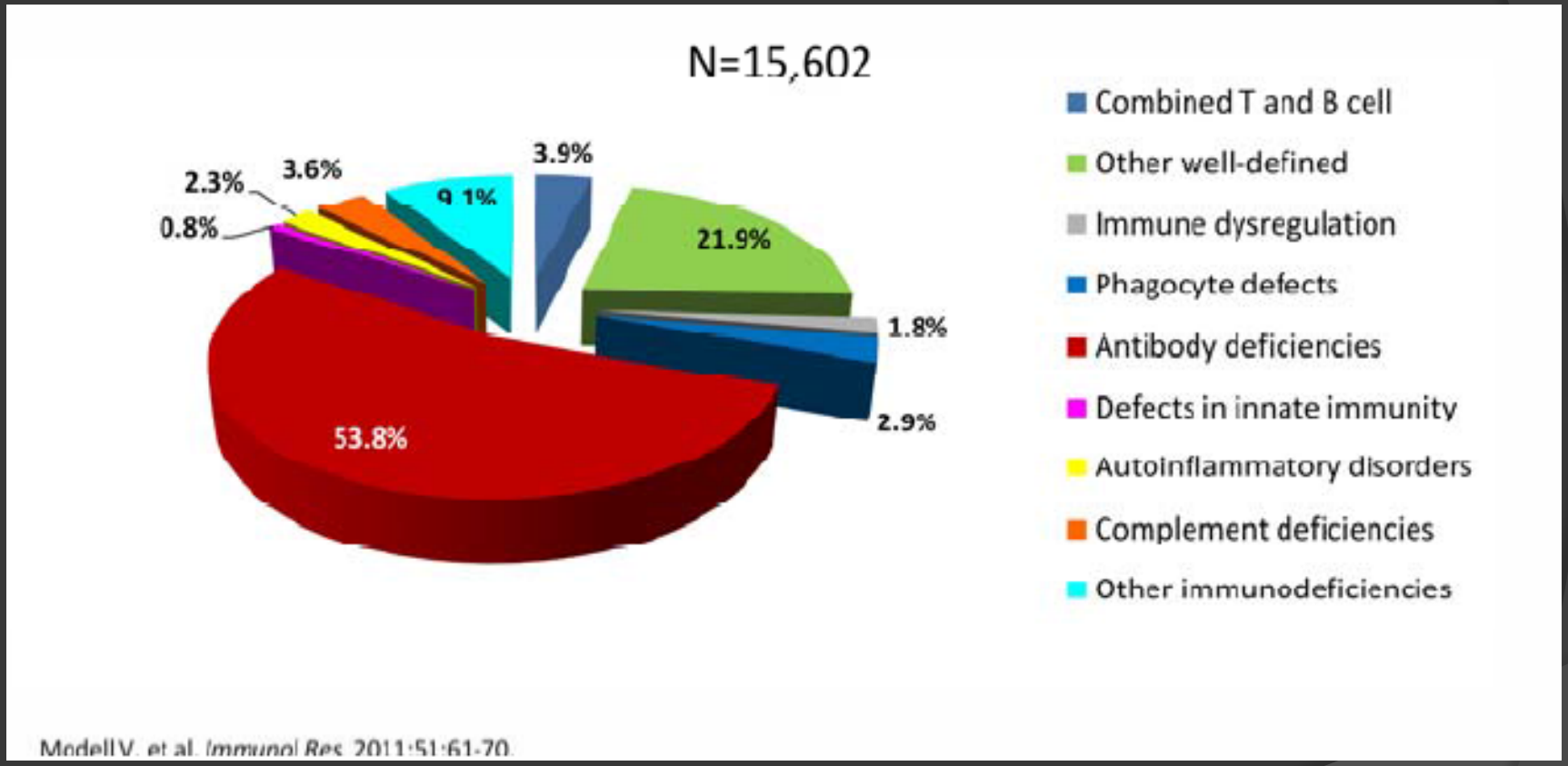
Humoral Deficiency (B-Cell)

- Unable to make specific antibodies
- Persistent upper respiratory tract infections
  - Streptococcus, haemophilis
- Many times symptoms blamed on allergies, asthma, other
- Multiple / severe bacterial infections

Cellular Deficiency (T-Cell)

- T-Cells directly attack foreign antigens
- Persistent thrush
- Diarrhea/malabsorption
- Opportunistic infections
  - *Candida infections, PCP pneumonia*
- Secondary more common than primary (HIV, corticosteroids, infections)

Primary Immunodeficiency Breakdown



Modell V. et al. *Immunol Res.* 2011;51:61-70.

Stage 1: History & Exam

- History
  - Infection history
  - History of miscarriage/ early unexplained death in infants
  - Primary Immune Deficiency in family
  - History of autoimmune/connective tissue d/o
  - Environment (smoke, allergies)

Taking a History of Infections: Features of Immunodeficiency

- Increased prevalence of common infections (URIs, sinusitis, otitis media, bronchitis)
- Recurrent bacterial infection (retrieve culture data if possible, different anatomic sites more c/w PID vs repeated infections at one site)
- Severe infections (pneumonia, sepsis, meningitis, osteomyelitis)
- Infections that present in unusual ways, do not respond to normal treatment, become chronic, or are more severe than would be anticipated
- Abscesses of internal organs, recurrent subcutaneous abscesses (different sites more c/w PID)
- Infections with unusual or opportunistic pathogens
- Prolonged or recurrent diarrhea

BEWARE: Immunodeficiency Doesn't Always Present With Recurrent Infections:

- Autoimmune disease (ex. autoimmune hemolytic anemia or thrombocytopenia in CVID, SLE-like syndrome in complement def.)
- Unusual lymphoid and granulomatous diseases (ex. Sarcoid-like lung disease in patients with CVID)
- Malignancies- myeloma, leukemia, etc.

Physical Findings in Humoral PID

- Most patients will have a normal PE with appropriate growth and development, if they are treated before permanent structural damage has occurred.
- Signs may include evidence of chronic otitis media, sinusitis, skin abscesses, tooth loss, splenomegaly or persistent lymphadenopathy.

Stage 1 screening Labs: CBC, Immunoglobulins

- WBC count; absolute lymphocytes
- IgG, IgM, IgA, IgE
- Lab Variations
- Undetectable IgA
  - Symptomatic patient?
- High Levels IgM + Absence of other Ig
  - Hyper IgM
- IgE
  - Atopic Disease or Parasitic Illness, Hyper IgE

Excluding Other Causes of Secondary Immunodeficiency (usually low IgG)

Decreased Production

- **Medications**
- Malignancy
- Infections

Increased Losses

- Protein-losing enteropathies
- Nephrotic syndrome
- Burns

Other Secondary Causes of Impaired Immunity:

- **Immunosuppressive therapy:**
- Cytotoxic chemotherapy for malignancy
- Treatment of autoimmune disease
- Bone marrow ablation prior to transplantation
- Treatment or prophylaxis of graft vs. host disease following bone marrow transplantation
- Treatment of rejection following solid organ transplantation
- **Microbial infection**
- Viral infection (HIV, Measles,Herpes viruses)
- Bacterial infection (superantigens)
- Mycobacterial infection
- Parasitic infestation
- **Malignancy**
- Hodgkin's disease
- Chronic lymphocytic leukemia
- Multiple myeloma
- Solid tumors
- **Disorders of biochemical homeostasis**
- Diabetes mellitus
- Renal insufficiency/dialysis
- Hepatic insufficiency/cirrhosis
- Malnutrition

- **Autoimmune disease**
- SLE
- Rheumatoid arthritis
- **Trauma**
- Burns
- **Environmental exposure**
- Radiation, Ionizing
- Ultraviolet
- Toxic chemicals
- **Other**
- Pregnancy
- Stress
- Asplenia/hyposplenism
- Allogeneic blood transfusion
- Aging

UpToDate

A Common Question: What is the Effect of Oral or IV Steroids on Ig Levels?

Acutely (i.e., a few days of prednisone or solumedrol): very little change

Over Weeks:

J Allergy Clin Immunol Sep;62(3):162-6

- 9 asthmatics given 15 days of prednisone for asthma (avg. dose = 17 mg daily)
- While on the steroids, IgG decreased 22%, IgA decreased 10%, IgM unchanged, IgE increased slightly, persisted for a few weeks after therapy.

Prevalence of hypogammaglobulinemia - 12 to 17%.

Therefore, patients should be off steroids for 4-6 weeks before assessing Igs and vaccine response, if possible. If not possible, check anyway but interpret with caution.

How to Assess Vaccine Responses: First, Measure the Patient's Baseline Immunity

- Protein vaccine: obtain titers for tetanus and/or diphtheria

Adult patients are assumed to be vaccinated, but most have not stayed current on Q10 year boosters, so many will not have protective levels.

- Polysaccharide vaccine: see if patient ever received Pneumovax and check baseline titers, using 14 or 23 serotype panel (not the 7 serotype panel designed for the conjugate vaccine)

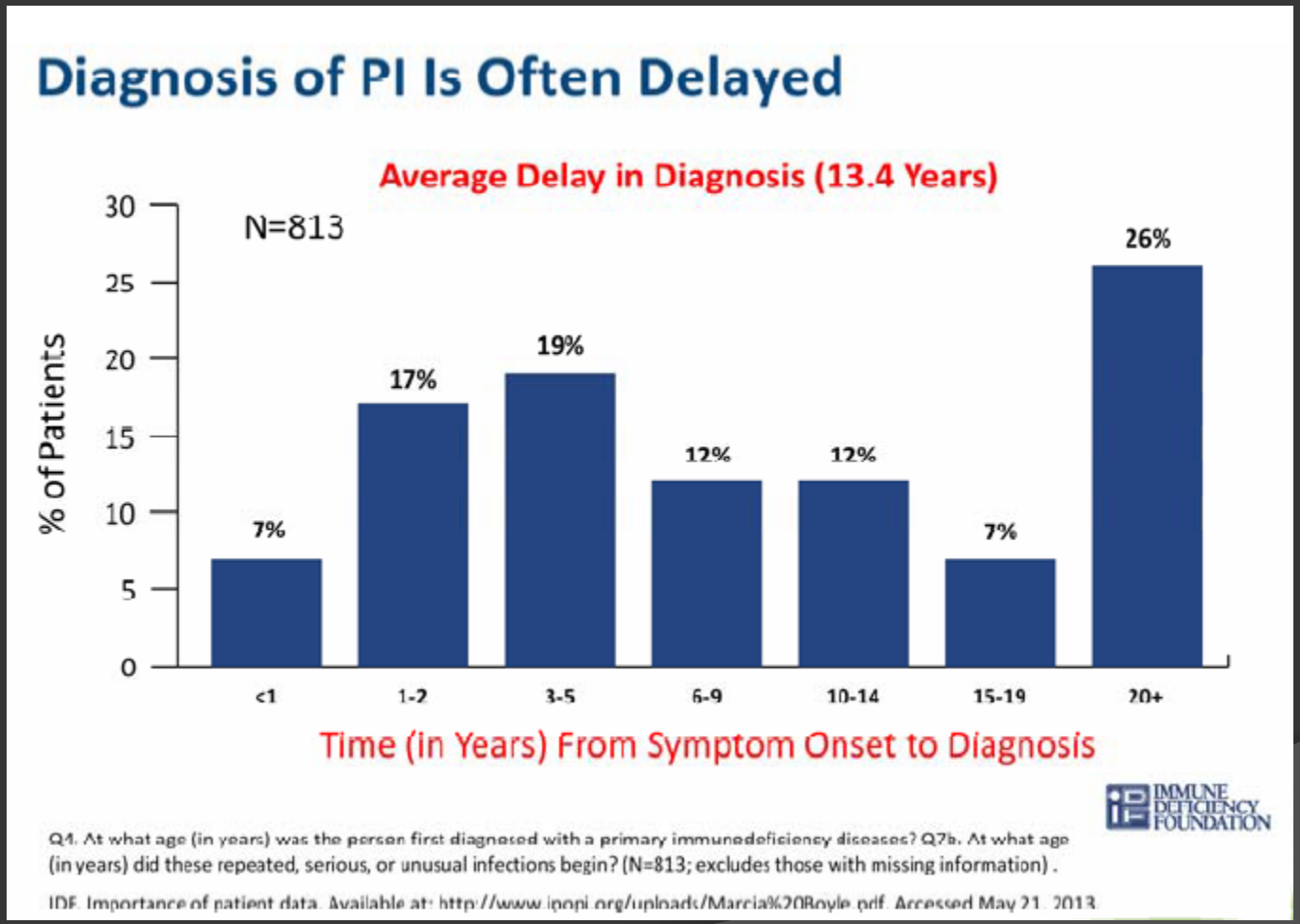
Interpreting Baseline Titers:

- Titers are considered protective if they are:
- Tetanus and diphtheria: at or above the laboratory reference ranges. >1.00 IU/mL (D) as protective
- Pneumococcal: Some never-immunized adults will have protective levels to most serotypes, and some will not. Immunized patients with normal immune systems would be expected to have protective levels to 70+ % for at least 5 years after.
- However, if they do not have baseline protective titers and weren't vaccinated in past 5 years, it does not mean they have poor vaccine response. Must vaccinate and look again in a month to determine non-response.

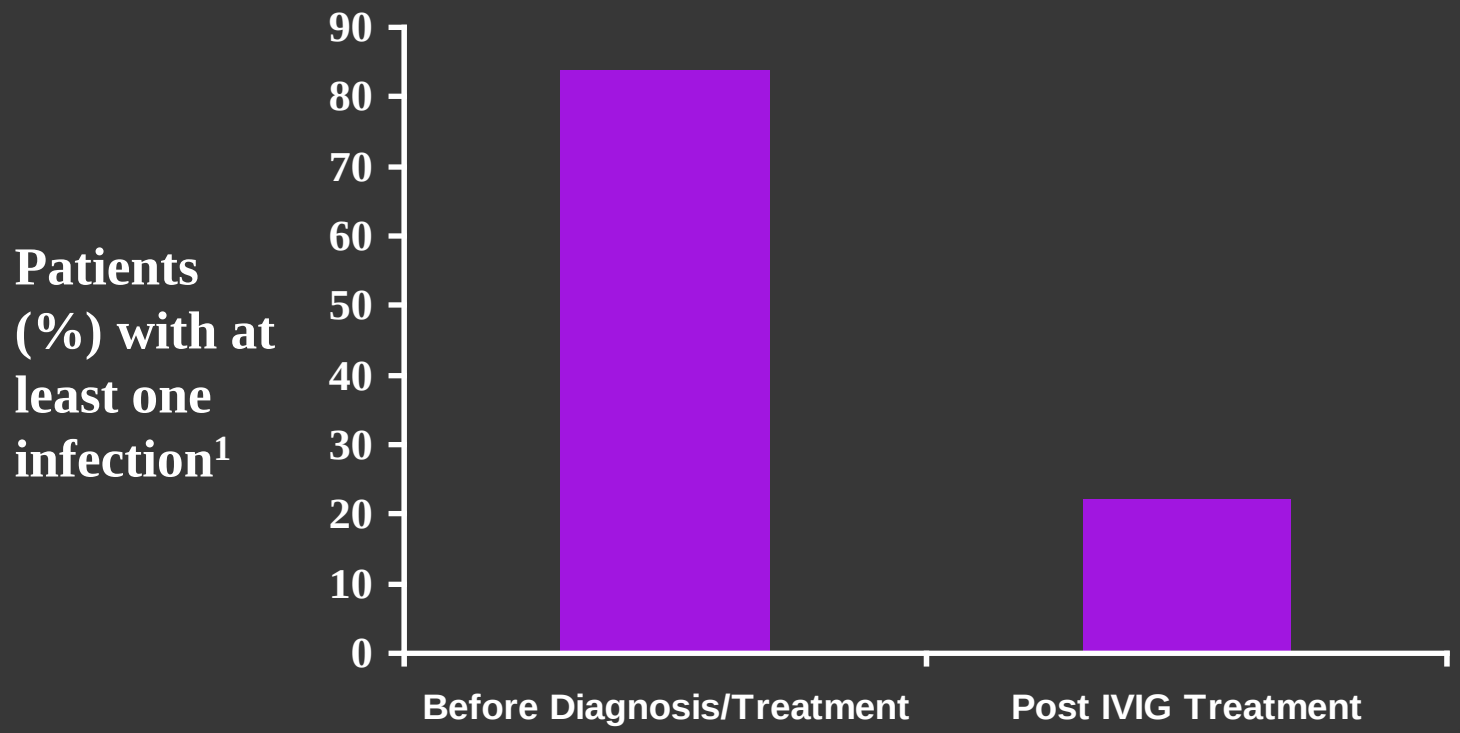
What Defines an Adequate Pneumovax Response in Adults?

- A post-immunization antibody concentration measured 4-6 weeks after vaccination (NOT sooner) ≥1.3 mg/mL is considered protective (or double from baseline).
- ≥70% (10 of 14, or 16 of 23) serotypes should be protective.
- This has been proposed as an adequate response based on limited epidemiological studies, but the response of the normal population to vaccines has not been exhaustively studied. Vaccine response must be supported by an appropriate clinical history to be meaningful.

Diagnosis of PID



Infection Frequency Is Reduced by Immunoglobulin Replacement



Busse PJ, et al. J Allergy Clin Immunol. 2002;109:1001-1004.
Skull S, Kemp A. Arch Dis Child. 1996;74:527-530.

Economic Impact Summary

Summary

Economic Consequences of the Most Frequent Conditions Affecting Patients with Primary Immunodeficiencies Pre-Period Compared to Post-Period

Condition	Cost per episode/ per day	# of episodes pre-period	Cost prior to diagnosis	# of episodes post-period	Costs After diagnosis	Annual Savings
-Acute Infections	$2,950 (per episode)	6.4	$18,880	1.8	$5,310	$13,570
-Severe Infections	$5,708 (per episode)	4.3	$24,544	0.6	$3,424	$21,119
-Bacterial Pneumonia	$7,529 (per episode)	2.8	$21,081	0.6	$4,517	$16,564
-Chronic Infection	$36.33 (per day)	44.7	$1,623	12.6	$457	$1,166
-Physician/Hospital/ ER Visits	$125 (per visit)	70.9	$8,862	11.8	$1,475	$7,387
-Hospitalizations	$1,158 (per day)	19.2	$22,233	5.1	$5,905	$16,328
-Antibiotics	$4.25 (per day)	166.2	$706	72.9	$309	$397
-School/Work Days missed	$136.40 (per day)	33.9	$4,623	8.9	$1,213	$3,410
Totals per patient:			**$102,552**		**$22, 610**	**$79,942**

April 2007

Global Impact

1) **Each undiagnosed patient with an underlying Primary Immunodeficiency disease costs the healthcare system an average of $102,736 annually.**

2) Each diagnosed patient with a recognized Primary Immunodeficiency disease costs the healthcare system an average of $22,696 annually.

3) The economic impact to the healthcare system of diagnosing a patient with an underlying Primary Immunodeficiency disease in contrast to not diagnosing patients, **represents average savings of $79,942 per patient per year**.

4) The U.S. National Institutes of Health (NIH) estimates that **at least 500,000 cases of Primary Immunodeficiency remain undiagnosed in the United States.**

5) **The economic impact of undiagnosed Primary Immunodeficiency patients to the healthcare system in the United States totals over $40 billion annually.**

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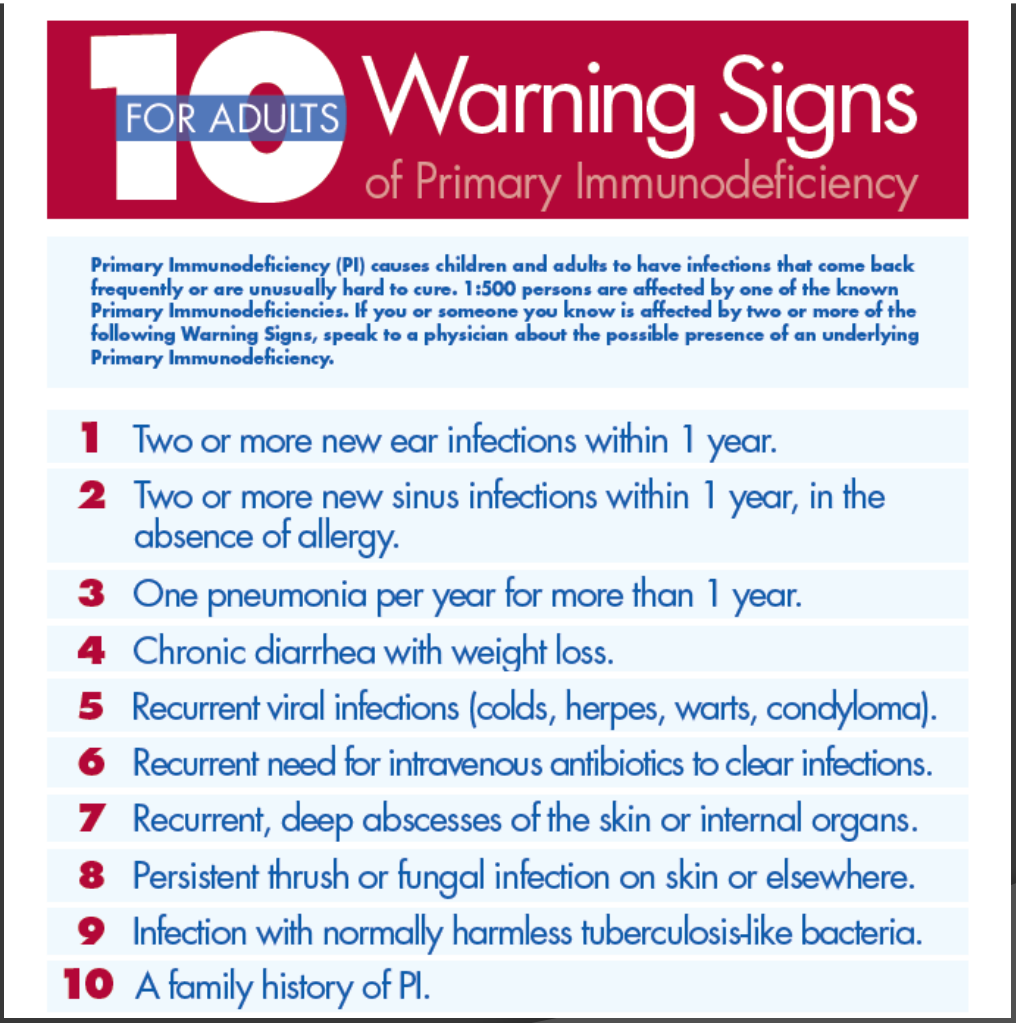
Jeffrey Modell Foundation. Economic Impact Study April 2007

Summary:

- Immunodeficiency usually presents as frequent, severe, or recurrent infections
- Can present with autoimmunity, GI complications, lymphoid or granulomatous disease
- Recurrent sinopulmonary infections are the most common presentation of primary ID in adults
- Take a detailed history, retrieve culture data if possible
- Consider secondary immunodeficiency
- Check immunoglobulin levels
- Get immunology consult

10 Warning Signs of Primary Immunodeficiency



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THANK YOU!