

MY PATIENT WAS DIAGNOSED WITH A RHEUMATIC CONDITION! NOW WHAT?

Elisa Wershba, MD, MPH

Pediatric Rheumatologist

Phoenix Children's Hospital

Clinical Assistant Professor University of Arizona COM- Phoenix



DISCLOSURES

- I have participated in Advisory board for Silvergate pharmaceuticals for Xatmep
- I do not plan to discuss this medication or any unapproved or off-label use of this medication
- I will briefly discuss off-label use of FDA approved medications



OBJECTIVES

- Identify when vaccinations are contraindicated
- Understand role in managing common pediatric conditions in setting of rheumatologic diagnoses
- Recognize the uniqueness of adolescent management with chronic illness



What vaccinations does she need?

Recommended Immunizations from birth to 18 years old

Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-5 years	11-15 years	15-18 years
Hep B	Hep B				Hep B						
		Rota	Rota	Rota							
		DtaP	DtaP	Dtap		DtaP			DtaP	TdaP	TdaP
		Hib	Hib	Hib	Hib					HPV	HPV
		PCV	PCV	PCV	PCV					MCV-4	MCV-5
		IPV	IPV	IPV					IPV		
				Influenza Yearly							
					MMR				MMR		
					VZV				VZV		
					Hep A		Hep A				

<https://www.google.com/imgres?imgurl=http%3A%2F%2Fwww.abqhp.com%2FImages%2FShotChart.png&imgrefurl=http%3A%2F%2Fwww.ixora.pro%2Fchildhood-immunizations-2017&docid=hiS5L7sEQPvF9M&tbnid=aBFHeTyj3tvMEM%3A&vet=10ahUKEwiY3ZyFhLfiAhWIhIQKHd5fAwlQMwhqKAQwBA..i&w=1012&h=446&client=safari&bih=512&biw=800&q=immunization%20schedule&ved=0ahUKEwiY3ZyFhLfiAhWIhIQKHd5fAwlQMwhqKAQwBA&iact=mrc&uact=8>



CASE 1 – JIA

- 3 yr 11 month old female with polyarticular JIA on MTX and Humira for past 2 months
 - Disease difficult to control initially
 - Past month finally without limping or joint swelling
 - ESR and CRP have normalized once Humira added 2 months ago
 - She is scheduled for 4 y/o WCC during her birthday month October



WHAT VACCINATIONS ARE NEEDED?

- MMR
- Varicella
- DTaP
- IPV
- Flu shot



WHICH VACCINATIONS ARE CONTRAINDICATED?

- MMR and Varicella
- Household contacts can and should receive vaccinations

When can patient receive these vaccinations if on MTX or steroids?

- Defer live vaccine at least 1 month after immunosuppression stopped
- With anti TNF treatment – withhold live vaccine at least 3 months after medication stopped

When can patient restart medications?

- 4 weeks after live vaccination
- 2 weeks after for inactivated



WHAT ELSE DO YOU WANT TO CONSIDER?

- Ophthalmology referral
- PT referral/OT referral



CASE 2: 6 Y/O F WITH JIA PRESENTS WITH SORE THROAT

- On subcutaneous MTX weekly (15mg/m²)
- Naproxen PRN joint pain which has increased now that sick
- Presents to PCP with fever of 102 x 3 days, vomiting, decreased PO, headache
- On exam palatal petechiae
- Do you stop her MTX while starting abx?



METHOTREXATE

- Risk of infection increases with MTX (or any immunosuppressive medication)
 - Theoretical? – infections in children treated with MX similar course and response to therapy as children not on MTX
- Bacterial infection – MTX held until antibiotics stopped * - metabolism of MTX affected
- Ok to continue MTX for dental work
- Major surgery – hold MTX 1 week prior and 2 weeks after
- Contraindicated in pregnancy and w/in 3 months of planning pregnancy
- Rare cases of lymphoma reported (EBV related) but in JIA risk may due to disease itself, not only MTX
- Routine monitoring = cbc/diff, LFTs

-Hashkes PJ, Turner DL, Becker ML, Cabral DA, Laxer RM, Paller AS, Rabinovich CE, Zulian F. Dan L. Turner, Mara L. A. Becker, David A. M. Cabral, Ronald M. S. Laxer, Amy S. E. Paller, C. Eglia Rabinovich, and Francesco Zulian. Methotrexate: New Uses for an Old Drug. *Journal of Pediatrics* 164.2 (2014): 231-36. Web.

-Beukelman T, Haynes K, Curtis JR, Xie F et al. on behalf of the Safety Assessment of Biological therapeutics (SABER) Collaboration. Rates of malignancy associated with juvenile idiopathic arthritis and its treatment. *Arthritis Rheum* 2012;64:1263-71.



CASE 3 – SLE

- 13 year old F diagnosed w/ SLE and lupus nephritis class IV-5m ago
- On IV cyclophosphamide, weaning prednisone, hydroxychloroquine and lisinopril
- Presents to PCP with sore throat, headache, *new* body aches
- Rapid Strep positive
- You decide to start Amoxicillin – is this contraindicated with her medications?



INFECTION AND SLE

- Infection – high morbidity and mortality in patients with SLE
 - Viral, bacterial, mycobacterial, fungal, parasitic
 - Sites– respiratory system, urinary tract, CNS
 - High dose of glucocorticoids & use of cyclophosphamid, azathioprine, mycophenolate mofetil etc.
- Infections can mimic SLE flare
 - Clues of infection: chills, leukocytosis or neutrophilia (esp. when not on steroids), increased bands on peripheral smear
 - Clues that SLE: leukopenia (not otherwise explained by medication), normal or slight increase in CRP, low C3/C4, elevated anti dsDNA antibody
 - fever not responding to higher doses of steroids--due to infection
 - Pending results of cultures – broad-spectrum anti-microbial therapy can reduce adverse outcomes

-Pasoto SG, Ribeiro AC, and Bonfa E: Update on infections and vaccinations in systemic lupus erythematosus and Sjogren's syndrome. *Curr Opin Rheumatol* 2014; 26: pp. 528-537

-Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, et al: Predictors of major infections in systemic lupus erythematosus. *Arthritis Res Ther* 2009; 11: pp. R109

-Rovin BH, Tang Y, Sun J, et al: Clinical significance of fever in the systemic lupus erythematosus patient receiving steroid therapy. *Kidney Int* 2005; 68: pp. 747-759

-Zhou WJ, and Yang CD: The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients. *Lupus* 2009; 18: pp. 807-812



ANTIBIOTICS AND SLE

- No absolute contraindication
- Often imperative in settings of bacterial infections
- Mom asks if she can take ibuprofen for her body aches?
 - Class IV LN – not recommended she take NSAIDs
 - Acetaminophen ok
- Bactrim associated with bone marrow suppression – consider other options if available

CASE 3

- Mom calls your office next day – ok for vacation in a week to beach -she will have 3 days of antibiotics left
- Besides discussing importance of finishing course antibiotics is there anything else you feel is important?
- Sunscreen!
 - UV, especially UVB known trigger of cutaneous and systemic lupus
 - UVB → systemic inflammatory response- chemokine released, recruitment of leukocytes → cutaneous lesions
 - UVB may decrease DNA methylation in peripheral cells and alter gene expression → pathogenesis of lupus

-Lehmann P, Homey B. Clinic and pathophysiology of photosensitivity in lupus erythematosus. *Autoimmune. Rev* 8(6). 2009:456-461

-Wang GS, Zhang M, Li XP, et al. Ultraviolet B exposure of peripheral blood mononuclear cells of patients with systemic lupus erythematosus inhibits DNA methylation. *Lupus.* 18:1037-1004 2009.



PHOTOSENSITIVITY AND SLE

- Photo on this slide



QUESTION

A 10-year-old girl presents with fevers, myalgias, rash and joint swelling of 4 weeks' duration. Physical examination reveals malar rash and erythematous lesions on the palate. The WBC is $3.5 \times 10^9/L$. Of the following, the MOST helpful laboratory finding to confirm the diagnosis is an elevated...

- A) anti-double stranded DNA titer
- B) antistreptolysin titer
- C) C3 complement titer
- D) C-reactive protein concentration
- E) proteinuria



QUESTION

A 14-year-old girl presents with joint pains, fever, & weight loss for 2 months. BP is 160/100 mmHg, and electrolytes are normal. UA reveals SG 1.015, pH 6.0, negative protein, moderate blood, 15-20 RBCs, and 5-10 WBCs. Lab tests reveal elevated antinuclear antibody (ANA) and anti-DNA levels and low serum complement levels (C3, C4). Therapy with oral steroids results in clinic improvement. Of the following, the laboratory test result that would BEST indicate response to therapy is...

- A) normalization of blood pressure
- B) normalization of C3 and C4 levels
- C) reduction of ANA levels
- D) reduction of red blood cells in urine
- E) reduction of white blood cells in urine



QUESTION

The most common skin manifestation in pSLE is:

- A) Alopecia
- B) Discoid lupus
- C) Gottron papules
- D) Malar rash
- E) Psoriasis



QUESTION

According to the ACR, which of the following is a diagnostic criterion for SLE?

- A) Arthralgia
- B) Hemolytic anemia
- C) Interstitial pneumonitis
- D) Splenomegaly
- E) Vaginal ulcerations



QUESTION

The leading cause of morbidity and mortality in SLE is:

- A) Arthritis
- B) Nephritis
- C) Neuropsychiatric lupus
- D) Pericarditis
- E) Pneumonitis



CASE 4: FLU LIKE SYMPTOMS IN PATIENT WITH SLE

15 year old female--new diagnosis SLE 1 month ago: malar rash, fever, arthritis, LN class III, oral ulcers, +ANA, +dsDNA

- D/C from hospital 2-1/2 weeks ago s/p pulse IV Solumedrol x 3 doses
- Now presents to your office with new onset headaches
- Mom notes she seems “different” and at times confused
- Patient notes that headache is “horrible” worse than any she can remember
- She then states that she has to go to work – means school
- You look at her bp and see that it is w/nl

What would you like to do next?

- a. Call rheumatology
- b. Send to ER
- c. Reassure that likely just steroid induced psychosis and recommend f/up in 1 month
- d. A and B



CALL RHEUMATOLOGIST AND ER

- Call rheumatologist
- Recommend – send to ER
- In ER patient begins to act more confused and begins to lose her balance and stumble – admitted to floor
- On floor she begins to seize
- MRI brain w/ and w/o contrast + MRA = consistent with CNS lupus or embolic phenomenon – correlate clinically.



NEUROPSYCHIATRIC LUPUS

- CNS lupus usually involves small vessels – not apparent on vascular imaging
- No path findings specific for lupus but can see microscopic vasculopathy related to microinfarcts or antiphospholipid
- Brain volume loss – chronic steroids? Chronic inflammation?
- Hemorrhagic or thrombotic stroke occur
- Prevalence varies from 20-95%
- May present at any time in disease course
- Treatment - cyclophosphamide, high dose steroids including IV methylprednisolone, plasmapheresis

-No author. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndrome. *Arthritis Rheum.* 42:599-608 1999

-Ainiala H, Hietaharju A, Loukkola J, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. *Arthritis Rheum.* 45:419-423 2001.



Manifestations of NP pediatric SLE	
Headache (recurrent, migraine, intracranial HTN)	4-55%
Cognitive dysfunction - Acute confusional state	3-9%
Depression	5-9%
Mania	0-3%
Mixed (depression and mania)	0-1%
Seizure disorder (single episode or epilepsy)	4-20%
Anxiety disorder	1-10%
Cerebrovascular disease – TIA, stroke, venous thrombosis, vasculitis, hemorrhage, chronic multifocal disease	4-14%
psychosis	3-24%
Movement disorder (chorea, parkinsonian)	0-6%
Demyelinating syndrome	2-3%
Aseptic meningitis	0-2%
Myelopathy	1-2%
Peripheral: CIDP, autonomic disorder, mononeuropathy, MG, cranial neuropathy, plexopathy, polyneuropathy	0-4% and case reports

-Sibbitt WL, Brandt JR, Johnson CR, et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. *J. Rheumatol.* -29:1536-1542 2002.

-Spinosa MJ, Bandeira M, Liberalesso PBN, et al. Clinical, laboratory and neuroimage findings in juvenile systemic lupus erythematosus presenting involvement of the nervous system. *Arq. Neuropsiquiatr.* 65:433-439 2007



GOAL OF TREATMENT IN SLE

- Lupus presentation variable! Lifelong presentation and important to help patient take ownership of their disease to improve outcome
- EULAR – updated recommendations for management and treatment of SLE and aim:
 - remission of disease
 - prevention and minimization of long term damage on organs
 - minimize side effects of medications
 - Improvement of quality of life.



ADOLESCENT CASE

16 y/o female

- h/o asthma
- SLE and antiphospholipid ab syndrome
- lupus nephritis class IV
 - Recently transitioned from mycophenolate mofetil to cyclophosphamide (IV) for non-adherence
 - She presents to discuss birth control options since she is dating someone and wants to be safe



WHEN IS BIRTH CONTROL RECOMMENDED IN SLE?

- Rule of thumb: avoid estrogen containing contraception – lupus is a hypercoagulable state and baseline risk for clots
- Antiphospholipid Ab Positive - contraindication to use estrogen containing ocp
- Effective use of contraception in patients with rheumatic illness “underutilized”
 - Series of 97 SLE patients: 55% unprotected sex on occasion; 23% most of time
 - Series of 86 patients: 55% using less effective barrier methods when on teratogenic meds.

Options reviewed and started on depo-provera



1 YEAR LATER...

- presents to your office for SOB--started in middle of night ; + right calf pain
- She is requesting refill of albuterol inhaler--she lost her old inhaler – hasn't needed in years
- You don't refill but instead → ER
- While arranging transfer to ER you ask her about current meds specifically lupus related medications
- She says she has been “fine” and has not been taking her meds – IV cyclophosphamide stopped 6 months ago and restarted on mycophenolate mofetil. Other meds not taking: Lisinopril, hydroxychloroquine



ER COURSE

- CTA done consistent with your suspicion of PE
- Patient admitted and started on anticoagulation. Found to have HTN, arthritis, malar rash, oral ulcers, worsening proteinuria
- admits that she stopped all her medications about 6 months ago since she was doing well and was busy with other stuff

You can't help but think



Yet another non-adherent adolescent patient with chronic illness



NON-ADHERENCE

- = Extent to which a person's behavior (taking meds, following diet, or lifestyle changes) varies from medical advice
- Compliance implies passivity vs. adherence implies agreement
- Defined as $80\% = \frac{\# \text{ pills absent in given time period}}{\# \text{ of pills prescribed by physician in that time period}} \times 100$
- Effects: disease exacerbation → morbidity and mortality and increased cost to healthcare system

-Rapoff MA. Adherence to Pediatric Medical Regimens. 2nd edition. Springer, New York, NY. 2010

-Osterberg L, Blaschke T. Adherence to Medication. *The New Engl J Med.* 2005;353:487-497.

-Salema N-E M, Elliott RA, Glazebrook C. A Systematic Review of Adherence-Enhancing Interventions in Adolescents Taking Long-term Medicines. *Journal of Adolescent Health.* 2011;(49)455-466.



NONADHERENCE IN SLE

- Intentional vs. Unintentional
- Consequences in SLE not well studied: poor-prognosis, increased costs in ER utilization and hospitalizations
- LOS study: 834 subjects with SLE provided information on med adherence:
 - 46% reported forgetting to take meds sometimes⁷
 - Depression severity was strongly associated with decreased adherence (SS)
 - Decreased adherence associated with increased health care utilization

Duvdevany I, Cohen M, Minsker-Valtzer A, Lorber M. Psychological correlates of adherence to self-care, disease activity and functioning in persons with systemic lupus erythematosus. *Lupus*. 2011;20:14-22.

Julian LJ, Yelin E, Yazdany J, Panopalis P, Trupin L, Criswell LA, Katz P. Depression, Medication Adherence, and Service Utilization in Systemic Lupus Erythematosus. *Arthritis and Rheumatism (Arthritis Care and Research)*. 2009;61:240-246.



NON-ADHERENCE IN ADOLESCENTS AND YOUNG ADULTS

Background

- Interest in AYA with SLE → how illness shapes identity, affects daily life and how that creates barriers to adherence
- Behavior associated with medication taking is complex, individual → multifactorial strategies needed
- Adherence averages ~ 50-55% for chronic illness



WHAT ABOUT THE ADOLESCENTS AND YOUNG ADULTS (AYA)?

- Multiple studies show rate of med adherence in children with rheumatic diseases 38-96% (not specific for SLE) and adolescents 50-55%
- Questionnaire administered in clinic Brazil included 99 patients with JIA, SLE, JDM, scleroderma (ages 2-18)
 - Causes of poor adherence: refusal, suspension for AE, forgetfulness, wrong dose, lack of meds
 - MTX, HCQ and azathioprine had lowest adherence rates



WHAT ABOUT AYA WITH SLE?

New ideas needed about barriers to adherence in this populations in order to devise practical solutions

- Scant evidence examines experience of chronic illness through others *BUT...*
- Best information of experience in chronic illness (SLE) from individual diagnosed
- Need for insight from patients
- Complex issue concerning behavior: what are the contributing factors in teens with SLE?



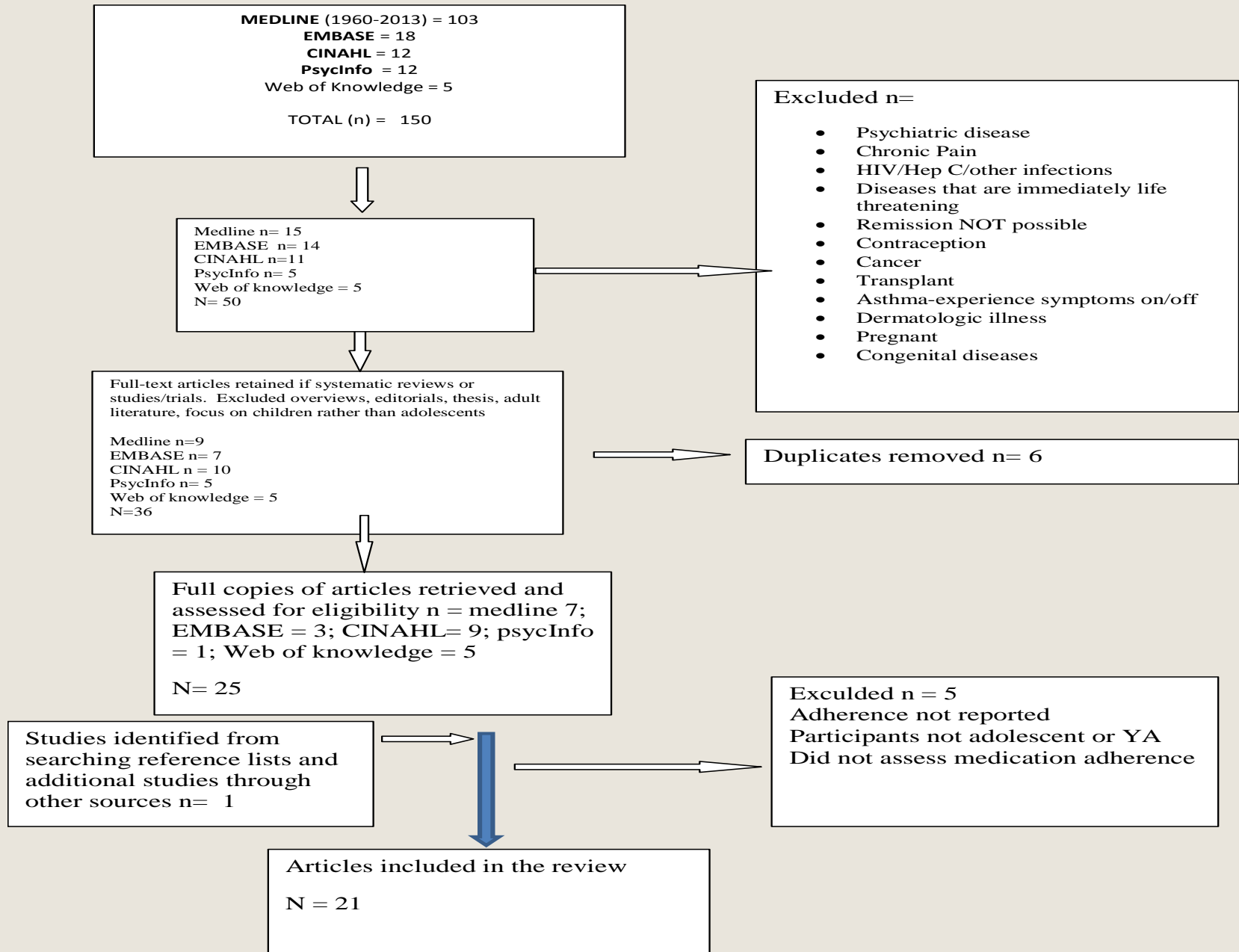
WHAT DOES THE RESEARCH SAY?

- Literature search performed on medication adherence OR barriers to medication adherence in (adolescents OR teens OR young adults) with (SLE OR chronic illness OR IBD)...or derivations of this...
- Quantitative literature available
- Qualitative literature not specific for SLE and adolescents



LITERATURE REVIEW--QUALITATIVE STUDIES

Records identified through database searching
Keywords: adolescents, lupus, medication, adherence



- Conclusion difficult: studies varied based on diseases, design, populations and definitions
- Limitations: patient interviews or questionnaires overestimate adherence; pill counts can overestimate if patients aware; lab assays variable
- Many evaluated adherence to 1 med over short time
- Increasing number of meds decreasing adherence

- **Summary:**
 - non-adherence problematic,
 - not well studied in chronic rheumatic conditions,
 - should be addressed at visits,
 - negotiate with patients to tailor therapy accordingly,
 - more research needed to assess, predict, improve adherence.





“Until we understand a child’s experience of growing up with chronic illness, we will never know how to design successful strategies for their adjustment.”

-Christian and D’Auria 1997

