European out-of-offices: "I'm away camping for the summer. Email again in September"

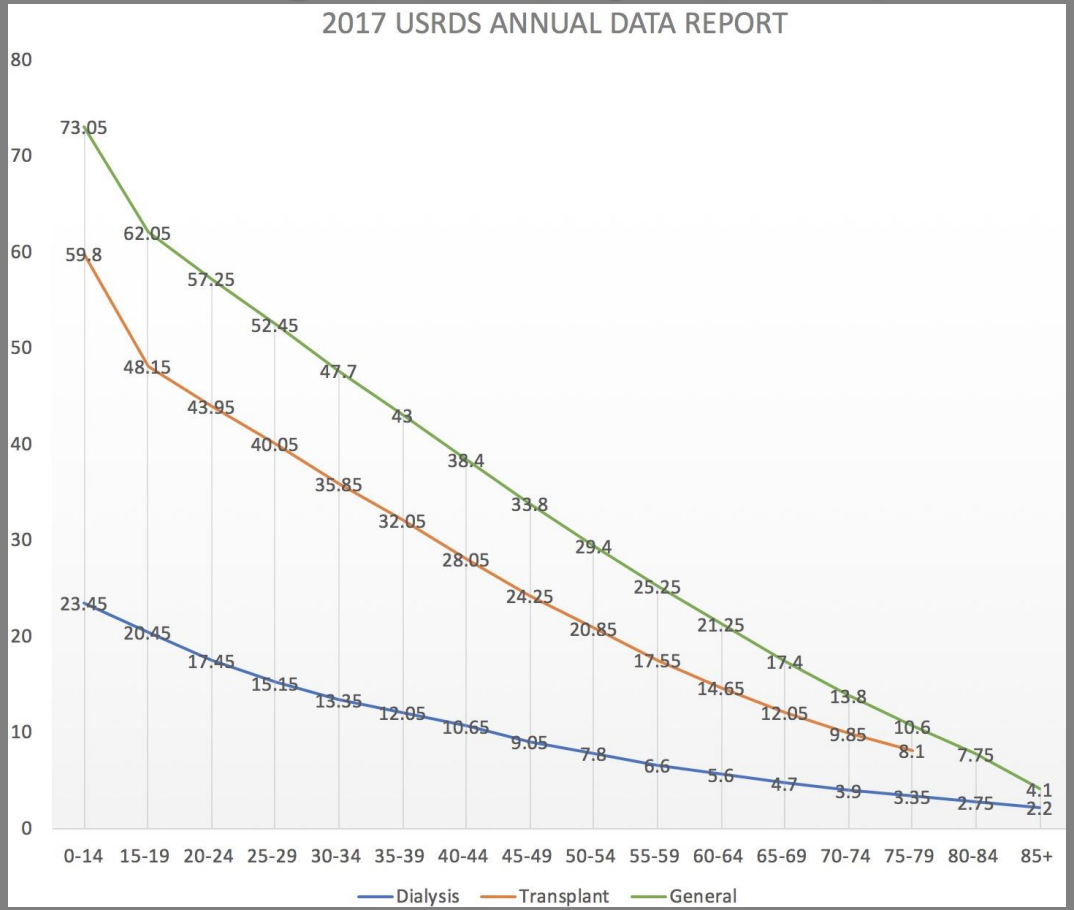
American out-of-offices: "I have left the office for two hours to undergo kidney surgery but you can reach me on my cell anytime"

Medications after kidney transplantation & improved treatment of infections

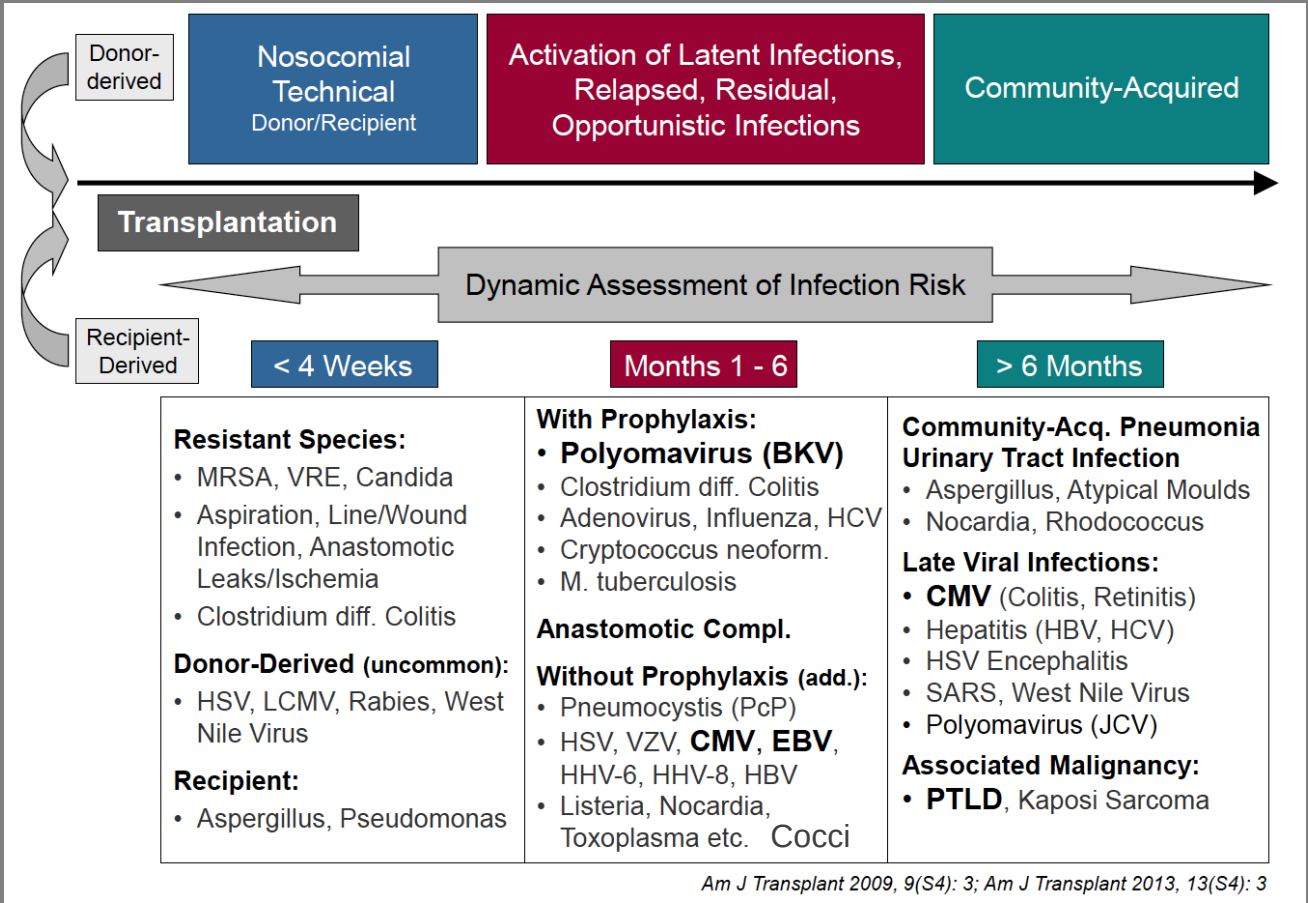
- Paul C. Grimm MD,
- Prof. Of Pediatrics
- Stanford University

Stanford Children's Health

Life gained by transplant



Timeline of Post-Transplant Infections



Am J Transplant 2009, 9(S4): 3; Am J Transplant 2013, 13(S4): 3

Viruses may be dangerous . . . .

"Uh-oh."

Infection Prevention

- Pre-Transplant
- Post Transplant- Prophylaxis and Surveillance
- Post Transplant- Living

Infection Prevention

- Pre-Transplant
  - Infection Risk Assessment
  - Immunizations

Infection Exposure History

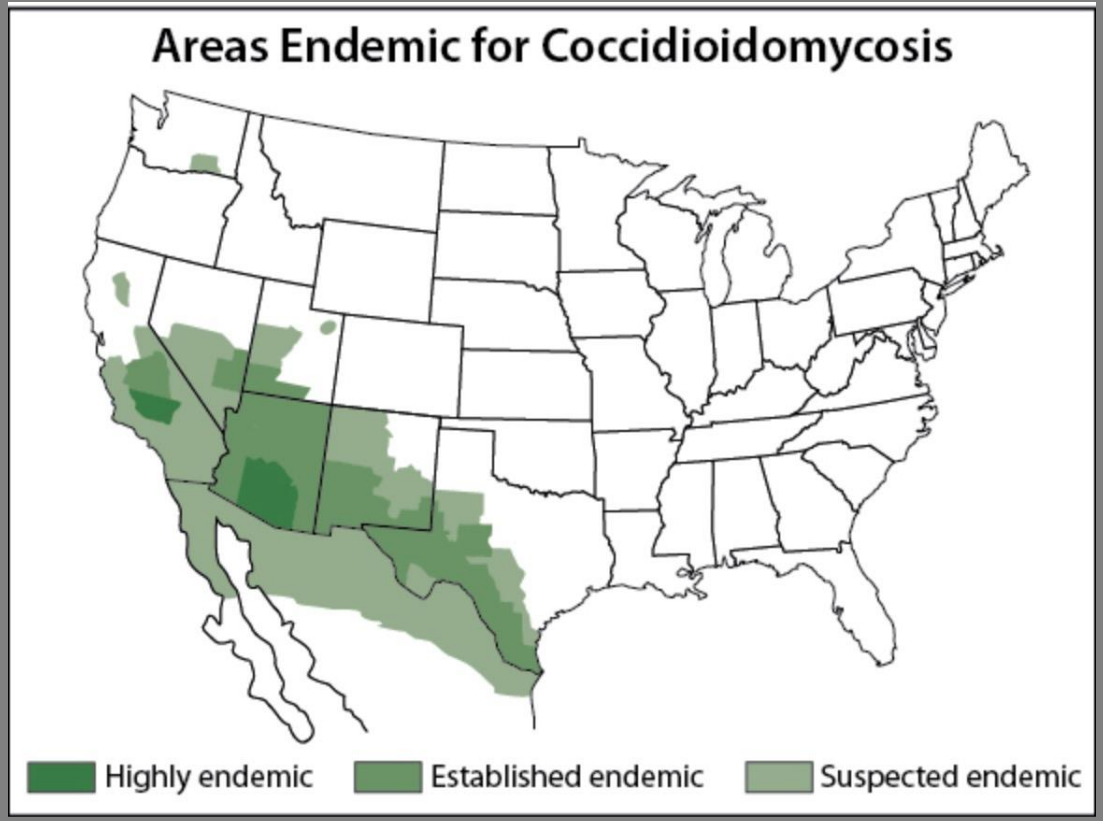
- Family members and household members:
  - Treatment for active/latent TB
- Vaccine history
- Animal exposure
  - Pets, farm animals, petting zoos
- Recent insect bites – ticks, mosquitoes
- Sexual activity
  - If sexually active, consider testing for: Syphilis, GC & Chlamydia
- Diet
  - High risk foods
  - Unpasteurized dairy products

Infection Exposure History

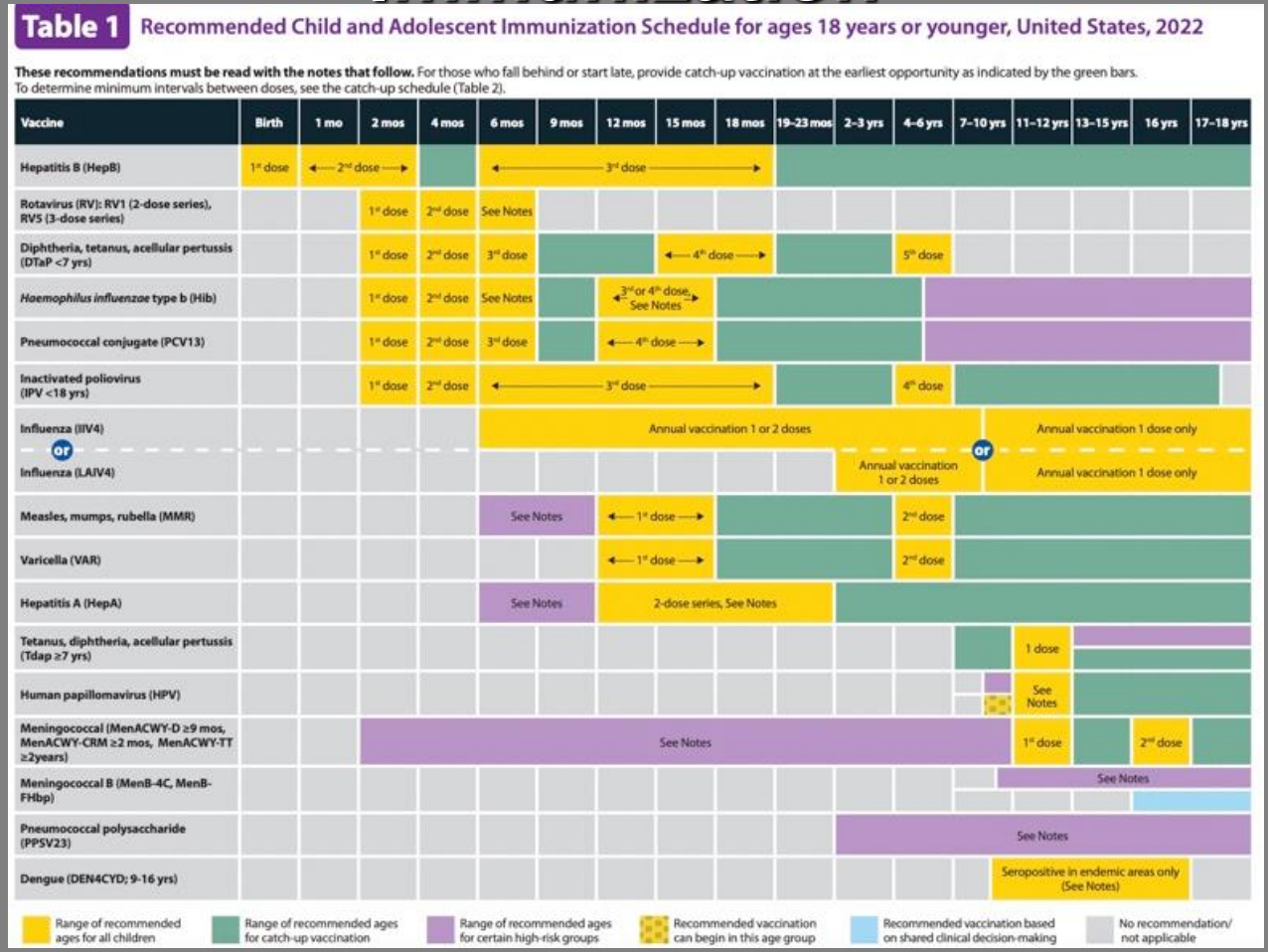
- Travel history, especially past 2 years
  - California Central Valley, Utah, Nevada, Arizona, and New Mexico consider Coccidioides.
  - Ohio River Valley consider: Histoplasma
  - Mexico consider: Coccidioides, Histoplasma, Strongyloides
  - South America consider: Coccidioides, Histoplasma, Toxoplasma and Trympanosoma cruzi (Chaga's)
  - Europe consider: Toxoplasma
  - Nile, Africa, Some parts of South America consider: Schistosoma

- Significant time living in or born in TB endemic country & BCG

Climate Change is Changing Map



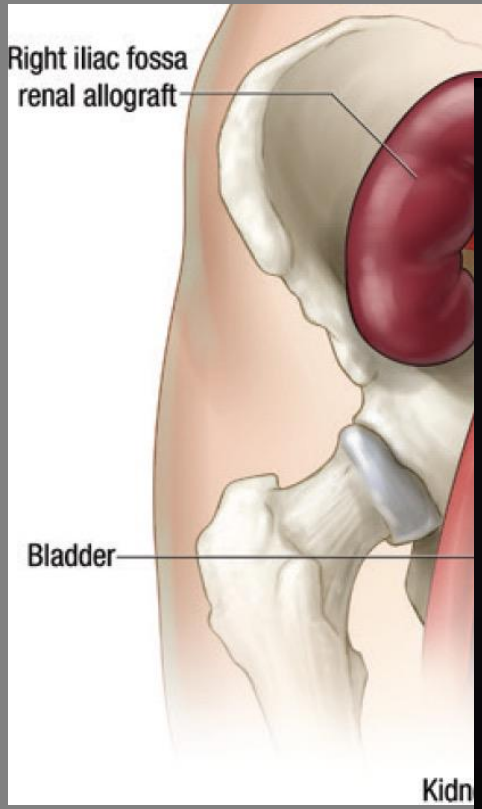
Immunization

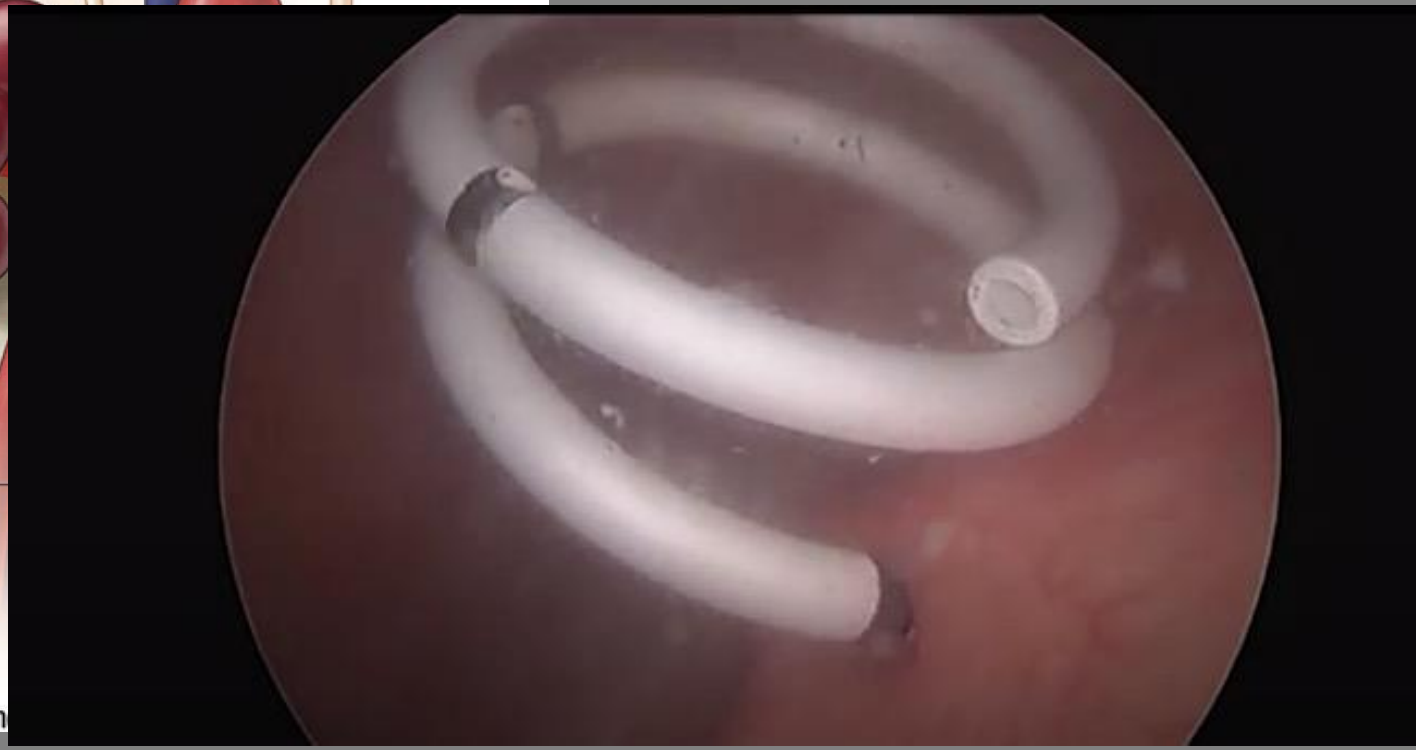
- 

Infection Prevention

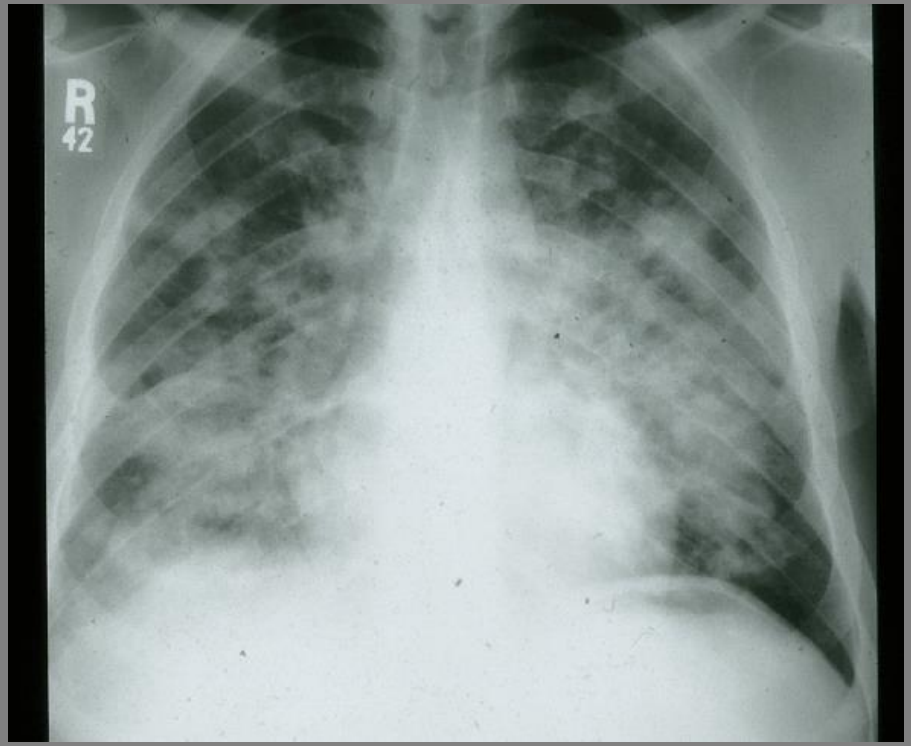
- Pre-Transplant
  - Infection Risk Assessment
  - Immunizations
- Post Transplant Prophylaxis and Surveillance
  - Antivirals, antimicrobials, antifungal

Urinary Tract Infection

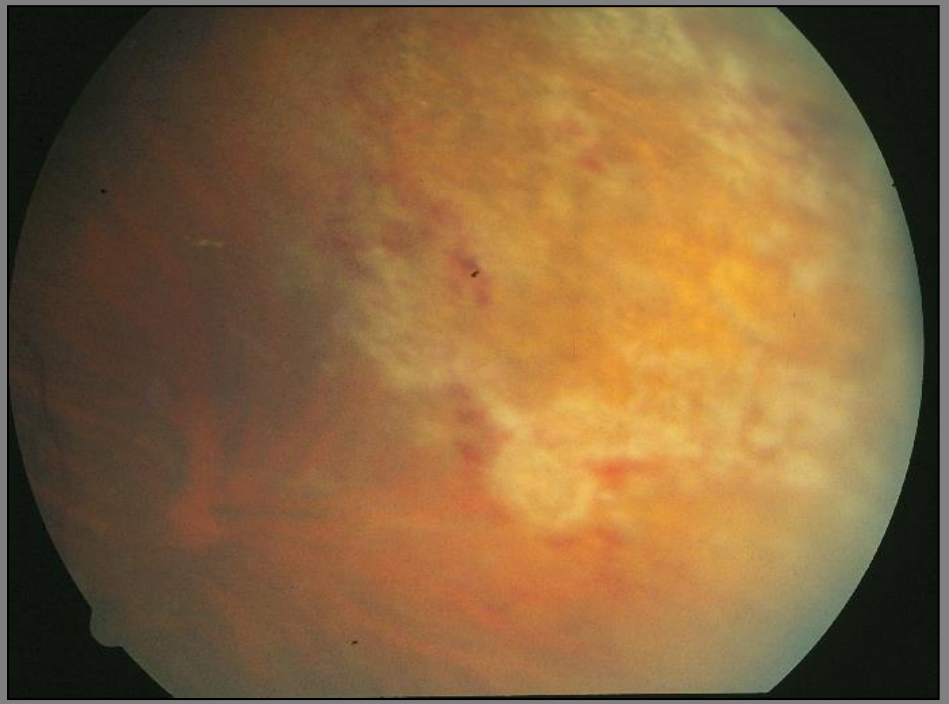




Three months after renal transplantation: Pneumocystis



CMV Retinitis



Surveillance ± Preventive Therapy

- Pneumocystis (PJP)
  - Trimethoprim-sulfa, pentamidine, atovaquone, dapsone
- EBV & CMV
  - Antiviral PCR Surveillance
  - Prophylactic/preemptive treatment with valacyclovir or valganciclovir
- BK Virus
  - Antiviral surveillance->Thoughtful immunosuppressive therapy reduction
- Coccidiodomycosis
  - Fluconazole (for life?)

Infection Prevention

- Pre-Transplant
  - Infection Risk Assessment
  - Immunizations
- Post Transplant Prophylaxis and Surveillance
  - Antivirals, antimicrobials, antifungal
- Post Transplant Living
  - Infection Risk
  - Immunizations

What's wrong with this picture?

VACCINATIONS

- SIMPLE RULE OF THUMB:

"Do NOT give patients LIVE or LIVE ATTENUATED VACCINES after transplantation"

BOARD STYLE QUESTION

A transplant patient on the same tacrolimus dose for 5 years started on a health food diet and OTC herbal products. His tacrolimus levels have abruptly decreased to unacceptably low levels, putting him at risk for rejection. The coordinator accused him of being noncompliant, but the patient insisted he was taking his medication as prescribed.

What is your assessment?

A. This patient is becoming noncompliant and is in denial; he needs an immediate psychiatry consult
B. This patient is taking grapefruit extracts.
C. This patient is taking St. John's Wort.
D. This patient is taking creatine supplements, which increase the activity of P-glycoprotein, leading to enhanced tacrolimus excretion
E. This patient is taking echinacea, which activates renal tubular excretion of tacrolimus.

CYP3A4 Inducers (Lower drug levels)

Class	Inducing Drug
Antiseizure Medications	Carbamazepine Fosphenytoin Oxcarbazepine Phenobarbital Phenytoin
Anittuberculosis	Rifabutin Rifampin
Antiviral	Efavirenz
Others	Bosentin Modafanil St. John Wort

BOARD STYLE QUESTION

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DRUG INTERACTIONS

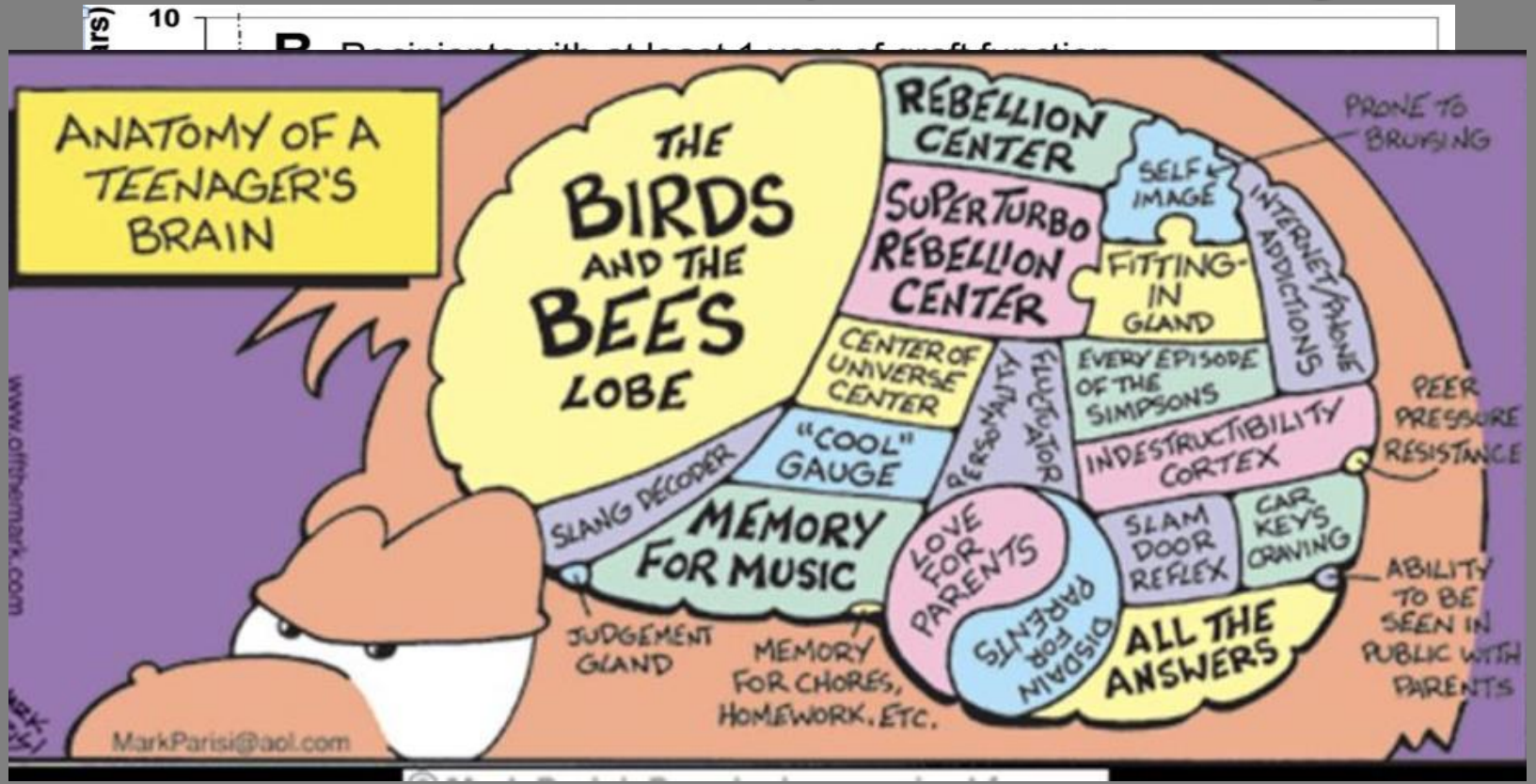
CYP3A4 Inhibitors (increase level)

Class	Inhibiting Drugs
Antibacterial (macrolide)	Clarithroymycin, Erythromycin
Antidepressants	Fluvoxamine, Nefazodone
Azole Antifungals	Fluconazole, Voriconazole, Itraconazole etc
Calcium Channel Blockers	Diltiazem, Verapamil
Foods	Grapefruit, pomegranate
Protease Inhibitors (Hep C)	Boceprevir, Telaprevir
Protease Inhibitors (HIV)	Atazanavir, darunavir Fosamprenavir, indinavir Nelfinavir, ritonavir, saquinavir
Others	Amiodarone, Dalfopristin, Statins
	Tacrolimus/Cyclosporine

COVID 19 Therapies (as of today)

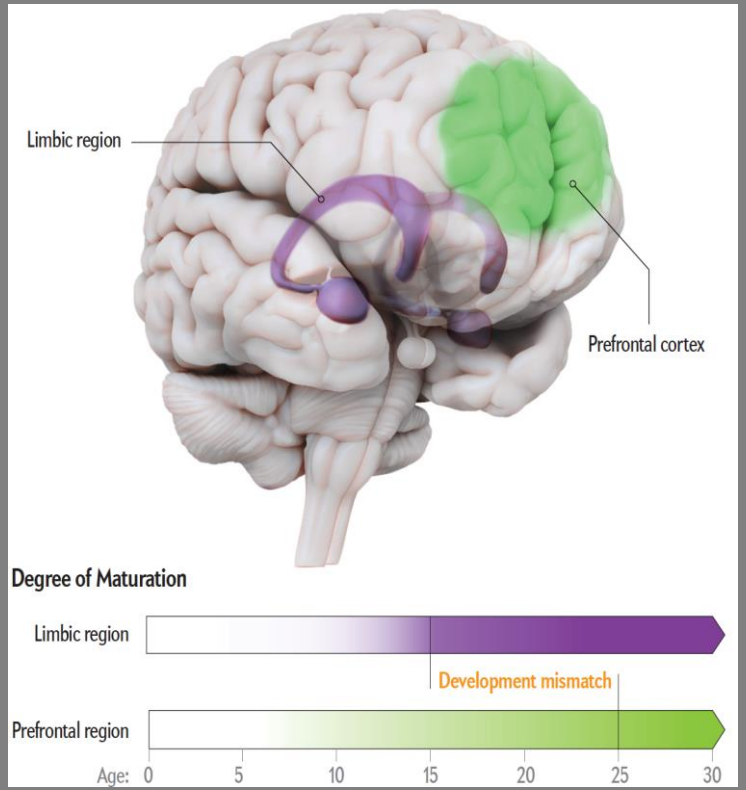
Patient age and weight requirement	First line	Second line	Third line	
Patients <12 years of age OR <40 kg	Remdesivir IV	N/A	N/A	N/A
Patients 12-17 years of age AND ≥40 kg	Paxlovid™ (nirmatrelvir with ritonavir)	Remdesivir IV *If Paxlovid™ is not available or is contraindicated*	N/A	Bebtelovimab IV *If both Paxlovid™ and remdesivir are not accessible or clinically appropriate*
Patients ≥18 years of age	Paxlovid™ (nirmatrelvir with ritonavir)	Remdesivir IV *If Paxlovid™ is not available or is contraindicated*	Molnupiravir *If both Paxlovid™ and remdesivir are not accessible or clinically appropriate*	Bebtelovimab IV *If both Paxlovid™ and remdesivir are not accessible or clinically appropriate*

Risk of Graft Loss by CURRENT Age



transplanted kidney at age 23… is <50%

The changing adolescent brain



Giedd, J. Scientific American 2015

timing of brain maturation

- ***Time gap may explain why adolescence is a period of heightened experimentation with risky behaviors.***
- Increased risk of
  - violence/criminal activity
    - kids under 18 years account for 25% of all violent crime in USA
  - drug & alcohol experimentation
  - unsafe sexual activities
  - medication noncompliance

Rumspringa

- is a term for a rite of passage during adolescence, translated in English as "running around", used in some Amish and Mennonite communities
- Lasts about 2 years

Adult Post-transplant nonadherence

- **Risk increases when medication regimen is:**
  - **Frequent dosing**
  - **Complicated regimen, multiple drugs and dosage frequencies**
  - **Drug side effects**

- **Forgetfulness is a powerful barrier**

1. *Laederach-Hofmann K, Bunzel B. Gen Hosp Psychiatry. 2000;22(6):412-424.*
2. *De Geest S, Moons P. Nephrol Dial Transplant. 2000;15(4):457-459.*
3. *Scmid-Mohler G et al (2010) Clin Transplant 2010: 24: 213–222*

Barriers to Adolescent Transplant Adherence

Pediatr Transplantation 2008: 12: 300–308

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Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2007.00886.x

Perceived barriers to adherence among adolescent renal transplant candidates

Zelikovsky N, Schast AP, Palmer JA, Meyers KEC. Perceived barriers to adherence among adolescent renal transplant candidates. Pediatr Transplantation 2008: 12: 300–308. © 2008 Blackwell Munksgaard

Nataliya Zelikovsky[1], Aileen P. Schast[2], JoAnn Palmer[3] and Kevin E.C. Meyers[1]

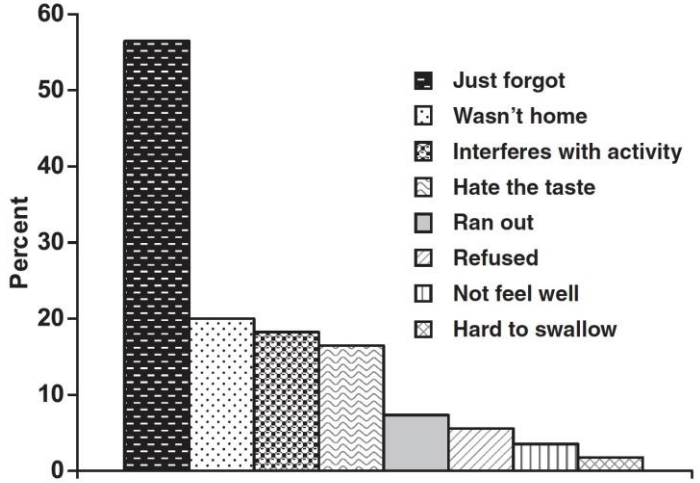


Fig. 1. Reasons reported by youth for non-adherence.

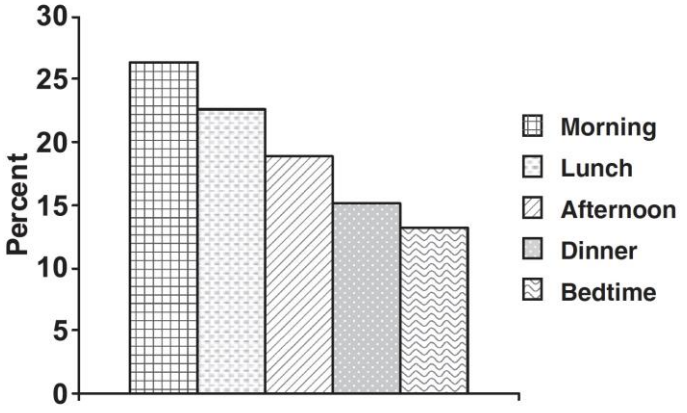
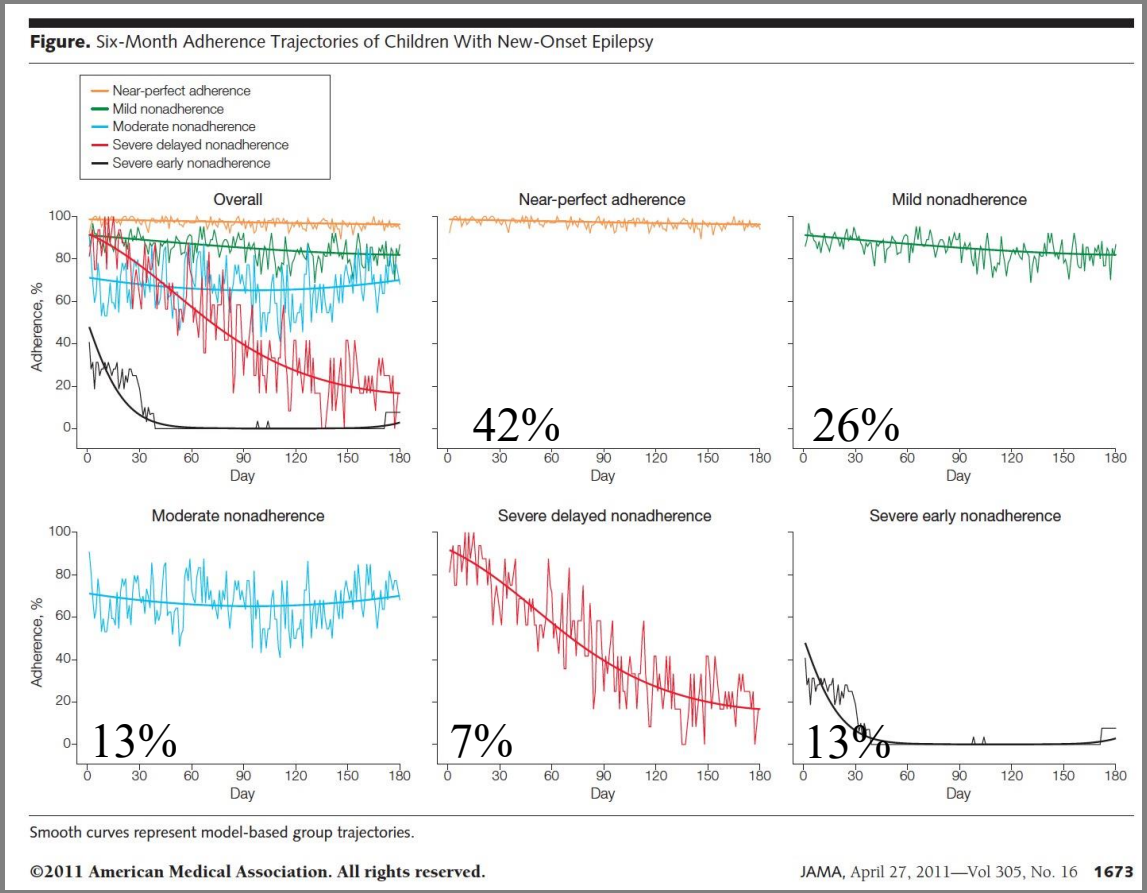


Fig. 2. Time of day youth reported to be most difficult for medication taking.

Adherence Patterns in Pediatric Epilepsy



Like Brushing your teeth

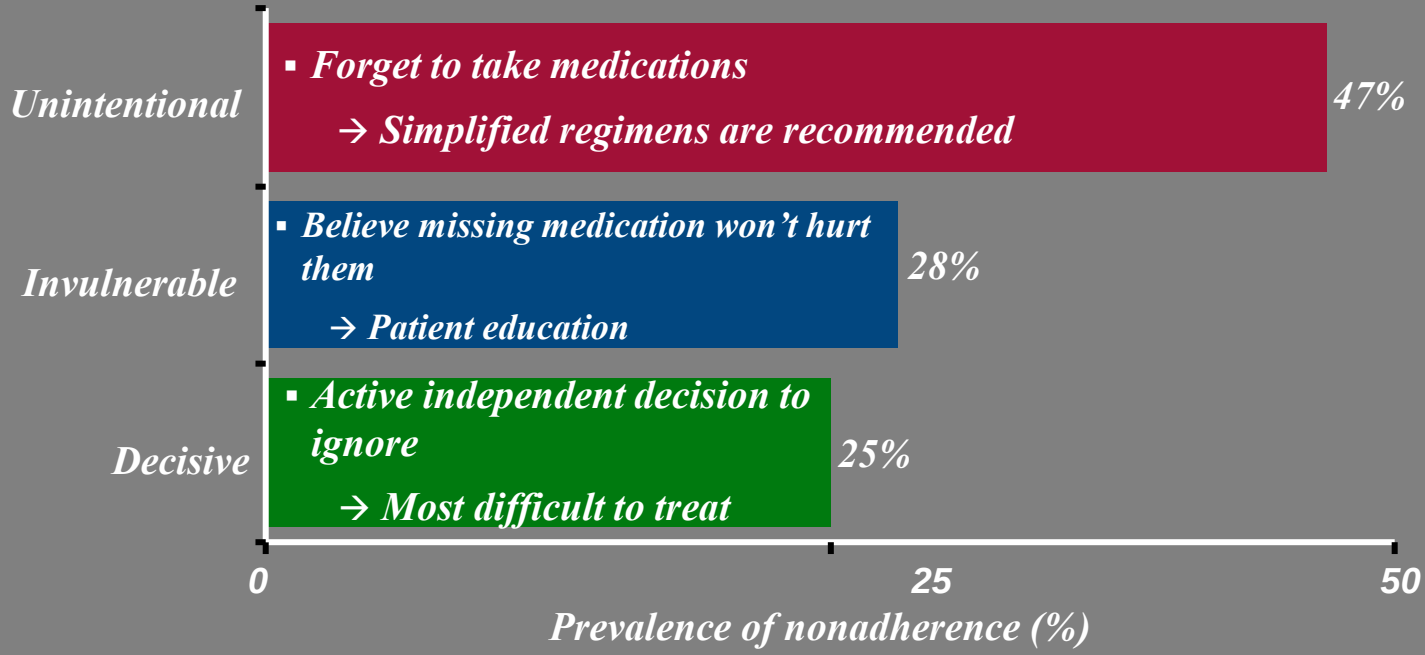
-Random, disorganized

-Benefit from problem solving and organizational strategies

-Occasionally miss doses with no consequence, so, believe meds are not important

-A decision

Patterns of post-transplant nonadherence



1. Greenstein S, et al. Transplantation 1998;66:1718–26
2. Rianthavorn P, et al. Pediatr Transplant 2005;9:398–407

Variation of Drug Levels

Within-patient variability in immunosuppressive drug exposure as a predictor for poor outcome after transplantation

Teun van Gelder[1,2]

Within-patient variability in immunosuppressive drug exposure is easily identified by measurement of drug concentrations at the outpatient clinic. Fluctuating levels despite a stable drug dose can be observed in a substantial proportion of patients. It has now been shown that this within-patient variability is a predictor for poor long-term outcome after transplantation. Nonadherence most likely is an important determinant of variability, and strategies to tackle nonadherence are being developed.

Kidney International (2014) **85,** 1267–1268. doi:10.1038/ki.2013.484

Following the study by Borra *et al.*,[2] we also suspected that nonadherence would be an important cause of within-patient variability. We decided to ask patients to come to the hospital to investigate whether self-reported medication adherence would be correlated with our pharmacokinetic assessment of variability. We invited patients from the lower quartile of variability, and patients from the highest quartile of variability. Almost all patients with low variability agreed to participate and arrived at their scheduled visits, whereas patients with high variability often claimed they were not available, or they canceled their appointments at a later point in time—obviously highly suggestive of nonadherence.

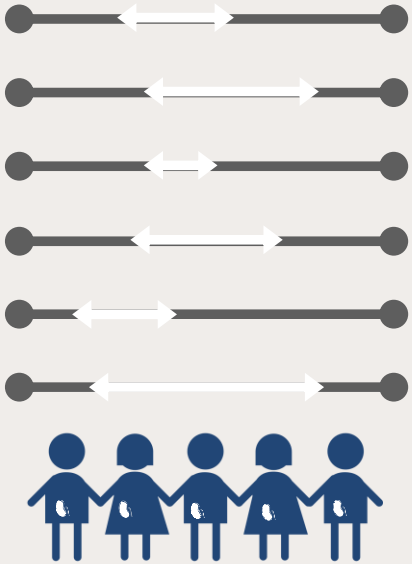
What are the implications for clin-

In pediatric kidney transplant recipients, is tacrolimus level variability associated with bad outcomes?

CJASN
Clinical Journal of the American Society of Nephrology

Single center
All children with kidney transplant, 2004-2018
n = 426 patients

Tacrolimus coefficient of variation 30% (IQR 21-41%)



Outcome cohort

220 patients with data on *de novo* C1q-binding donor-specific antibody (DSA)

Formed *de novo* DSA

38%

(IQR 28-48)

Median coefficient of variation

No *de novo* DSA

28%

(IQR 20-38)

Loci 3
SORL1

Median coefficient of variation over

30%

Loci 6
PLCL2

HR **5.0**

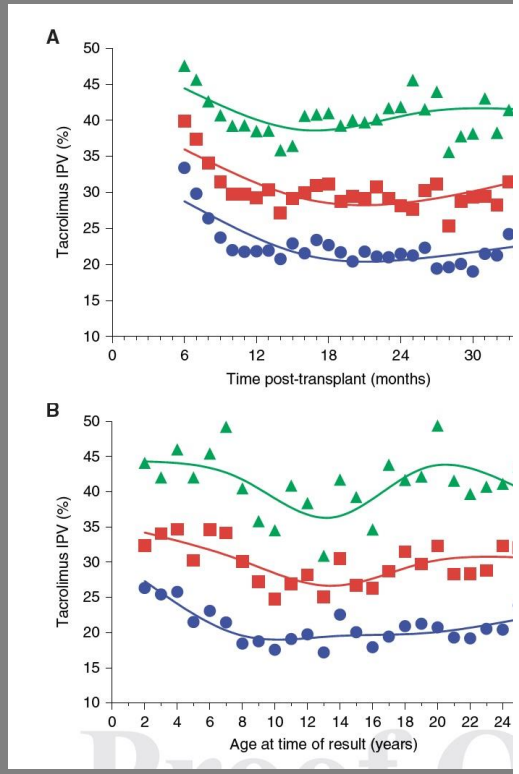
de novo DSA

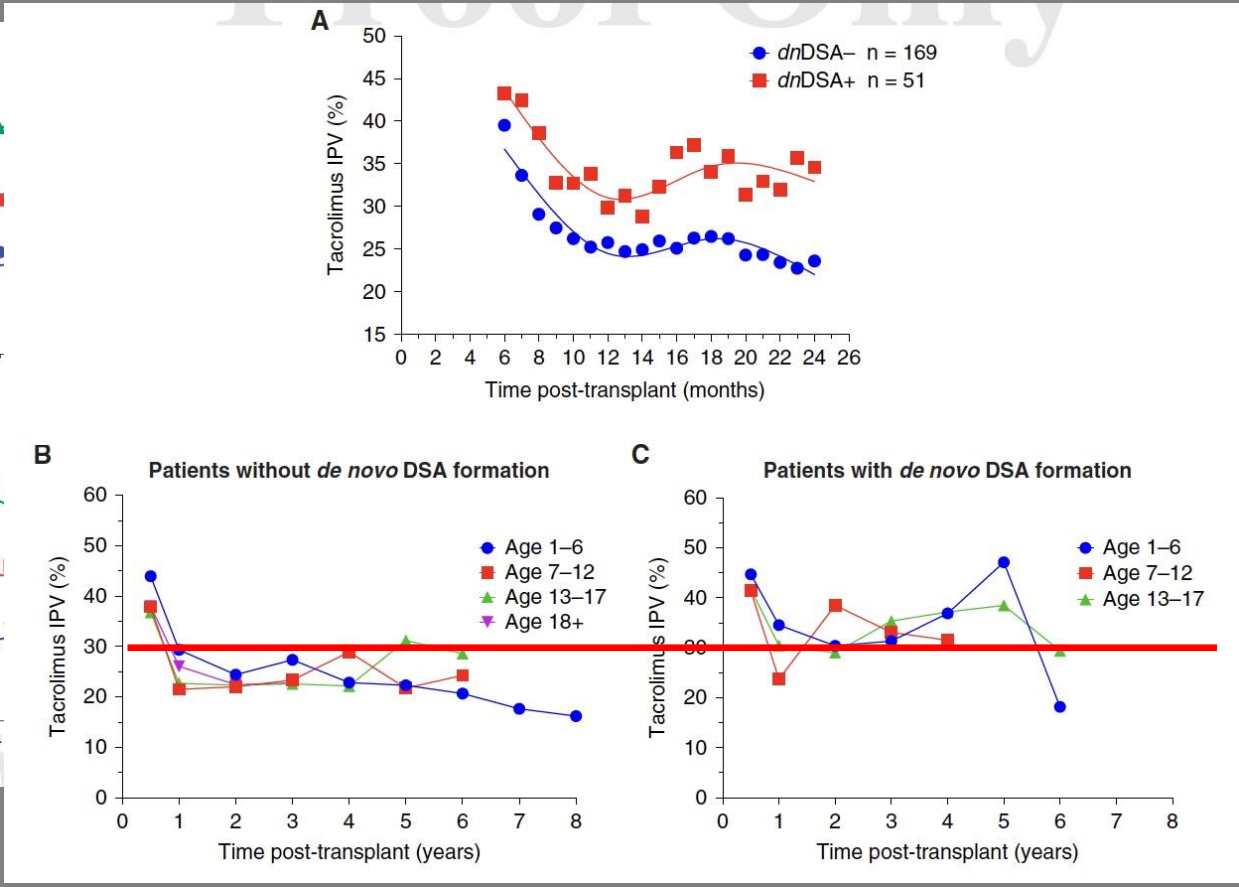
Conclusion: In pediatric kidney transplant recipients, high tacrolimus intrapatient variability was associated with *de novo* DSA formation.

Kim H. Piburn, Vaka K. Sigurjonsdottir, Olafur S. Indridason, et al. ***Patterns in Tacrolimus Variability and Association with De Novo Donor-Specific Antibody Formation in Pediatric Kidney Transplant Recipients***. CJASN doi: 10.2215/CJN.16421221.

Visual Abstract by Joel Topf @Kidney_Boy

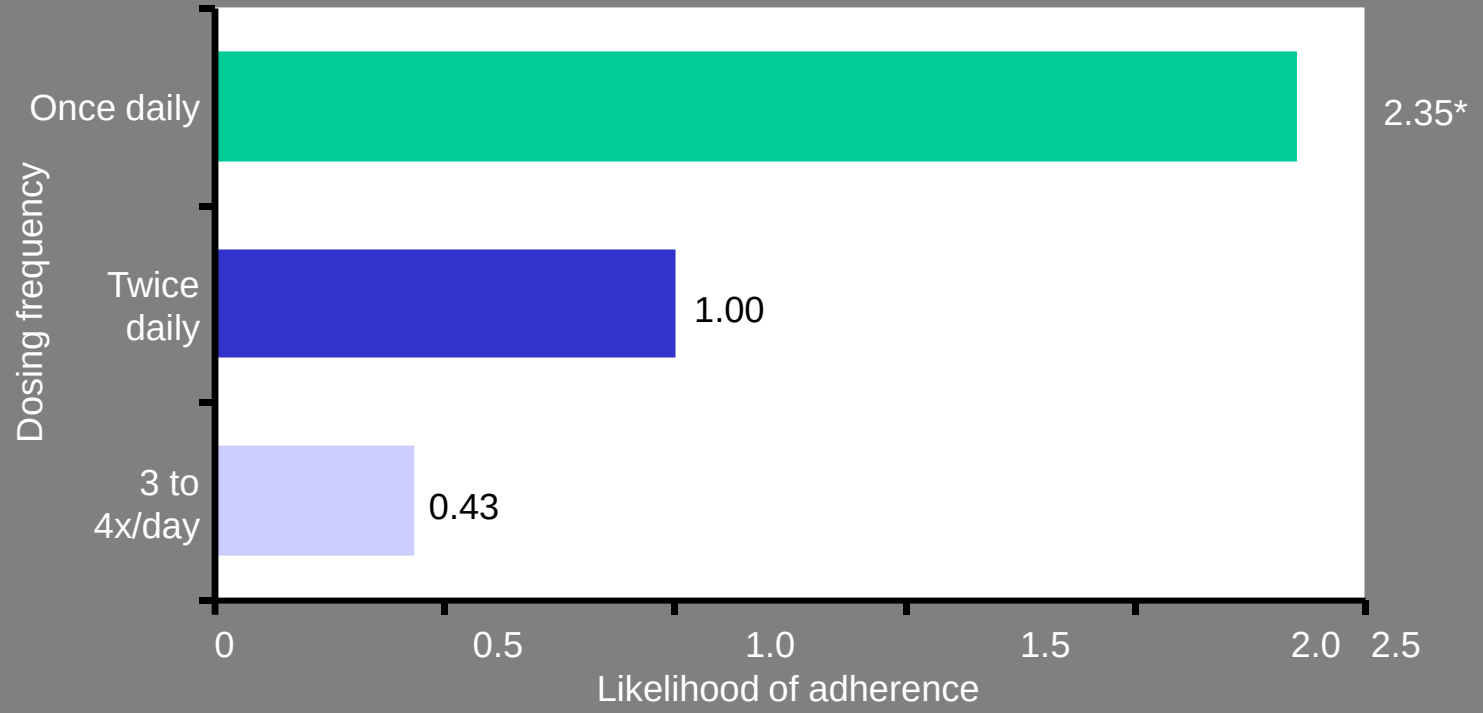
Tacrolimus Variability & Outcome





Influence of dosing frequency on adherence

Prospective multicentre cohort study in 278 renal transplant recipients



*p=0.003 vs twice-daily dosing

1. Weng FL, et al. J Am Soc Nephrol 2005;16:1839–48

Immediate release tacrolimus vs Envarsus

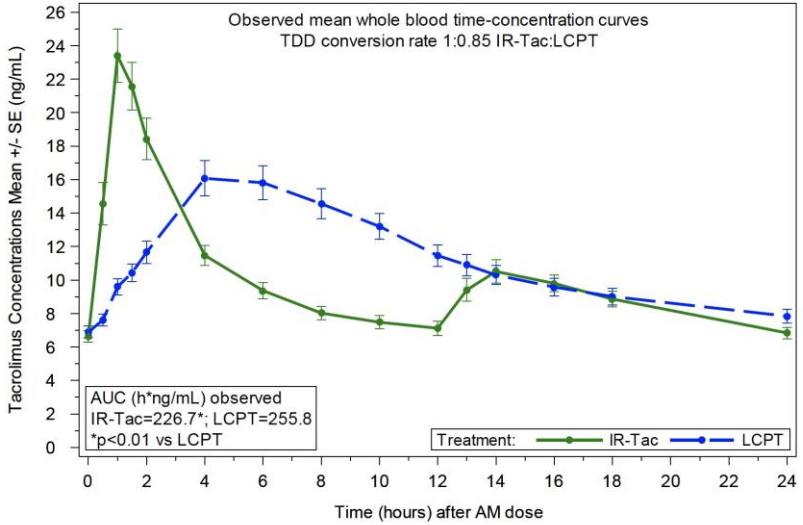


Figure 3. Observed mean tacrolimus whole blood time-concentration curves for immediate-release tacrolimus (IR-Tac) and LCPT (extended-release tacrolimus; originally LifeCycle Pharma Tacrolimus). Abbreviations: AUC, area under the curve; SE, standard error; TDD, total daily dose.

Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients

Jennifer Trofe-Clark, Daniel C. Brennan, Patricia West-Thielke, Michael C. Milone, Mary Ann Lim, Robin Neubauer, Vincenza Nigro, and Roy D. Bloom

Evaluating the Risk and Benefit of Once Daily Mycophenolate Acid in Pediatric Kidney Transplant Recipients

L. Maestretti[1], A. McGrath[1], A. Fong[1], A. Brubaker[2], A. Gallo[2], P. Grimm[2], A. Chaudhuri[2]
Lucile Packard Children's Hospital Stanford[1], Stanford University[2]

Objectives/Aims

- *The main objective is to demonstrate that once daily dosing of Mycophenolate Acid (Myfortic) ® is well tolerated, mounts a good blood MMF level, improves adherence and does not increase the risk to the allograft.*
- *Risk defined as the development of acute cellular rejection (ACR), antibody mediated rejection (AMR), donor specific antibodies (DSAs), and graft loss.*

CONTACT

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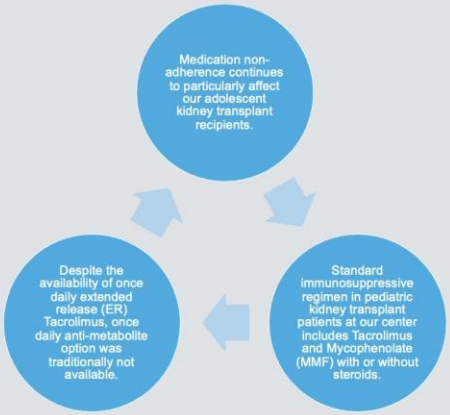
INTRODUCTION



METHODS AND MATERIALS

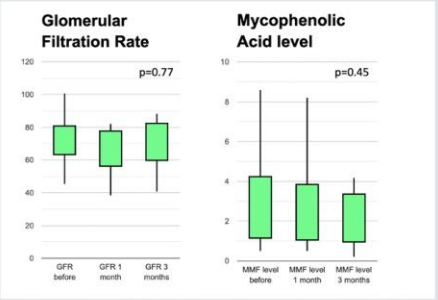
Retrospective chart review of all patients placed on once daily regimen as described above.

Evaluated the cohort for ACR, AMR, DSAs, graft function, Mycophenolate toxicity, infection, and graft loss.

RESULTS

- 16 patients were included who had history suggestive of immunosuppression non-adherence and were converted from a twice daily to a once daily regimen:
  - 37.5% were steroid-based
  - 50% presented with biopsy proven ACR
  - 25% patients had AMR and de novo DSAs
- Age range was 14-22 years, 62.5% patients were female.
- Regimen initiated in January 2019.
- Follow up period for all patients was at least 3 months.
- **No new ACR with new regimen.**
  - 2 patients had incomplete resolution of previous ACR requiring further anti-rejection therapy.
- One patient developed de-novo DSA within a month.
- GFR (estimated by the CKiD Under 25 GFR equation) remained unchanged.
- **No graft loss.**
- Trough tacrolimus level and MMF level did not change (Figure).
- **Median MMF trough level at 3 months remained >3 µg/ml.**
- There were no infections nor evidence of neutropenia.
- The regimen was well tolerated with no report of gastrointestinal or other side effects.

Mycophenolic Acid levels and kidney function remained stable following the change to once daily dosing of Mycophenolic Acid.



DISCUSSION

Smaller patient population.

Once daily Mycophenolate Acid is well tolerated, mounts a good MMF level and offers patients the ability for once-a-day immunosuppression regimen improving adherence and not increasing the risk of graft loss.

The safety and efficacy of this regimen should be studied in a large scale randomized controlled study.

Once a day observed therapy

- Any time that works!
- A single reliable person
- Parent, Grandparent, older sib or relative, neighbor
- School or school teacher, coach or nurse during school days

Belatacept

- Costimulation blockaid
- Every 4 weeks IV
- Low doses of oral meds necessary

New onset Diabetes Mellitus after transplant (NODAT)

- African genetic background or Hispanic
- Family History
- Obesity
- Hepatitis C Virus infection
- Pre-existing glucose intolerance
- High steroid dose
- Cystinosis

Incidence of Pediatric NODAT

- 20-35% for TAC
- 2-9% for Cyclosporine
- Reviewed by Garro et al. Ped. Neph 2015;30:405-416

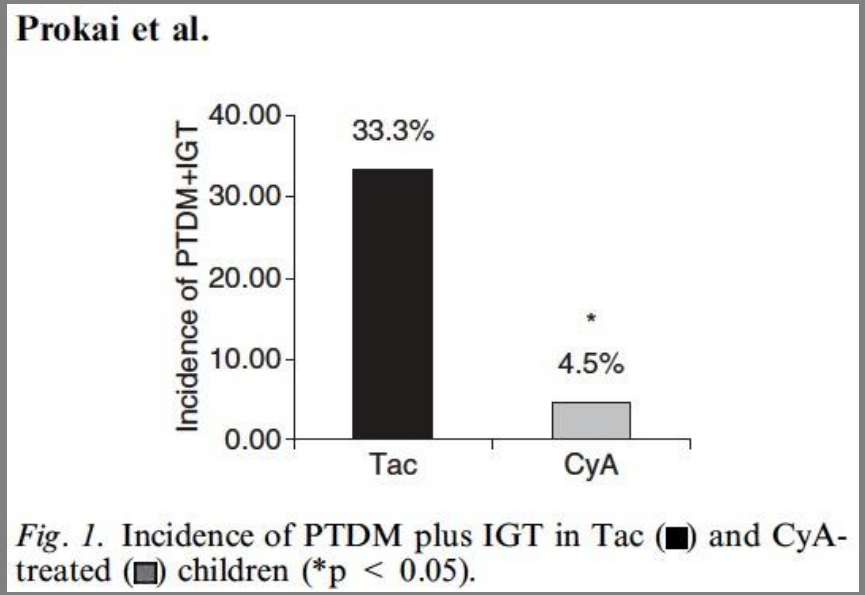
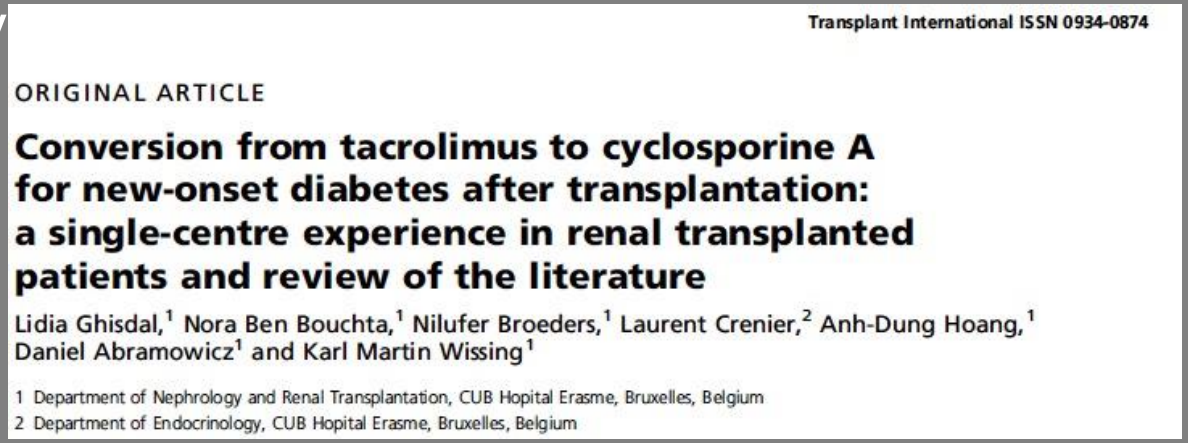


Fig. 1. Incidence of PTDM plus IGT in Tac (■) and CyA-treated (■) children (*p < 0.05).

IGT = Impaired Glucose Tolerance

Adult NODAT

- Retrospective review of 54 adult renal allograft recipients with NODAT on TAC/MMF/Pred
- 34 patients switched to cyclosporine
  - 42% (14) recovered from NODAT
- 20 patients stayed on tacrolimus
  - No recovery



Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

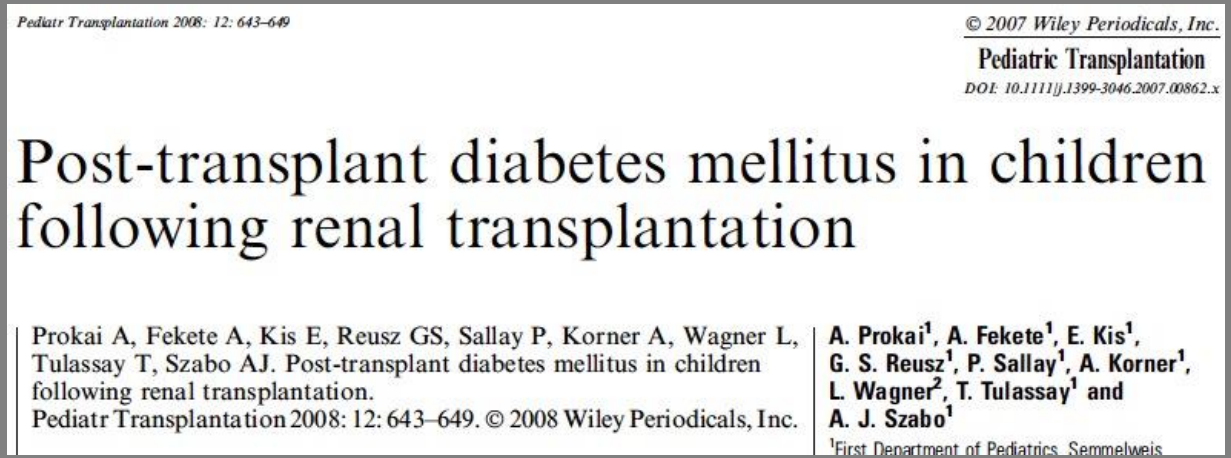
Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature

Lidia Ghisdal,[1] Nora Ben Bouchta,[1] Nilufer Broeders,[1] Laurent Crenier,[2] Anh-Dung Hoang,[1] Daniel Abramowicz[1] and Karl Martin Wissing[1]

1 Department of Nephrology and Renal Transplantation, CUB Hopital Erasme, Bruxelles, Belgium
2 Department of Endocrinology, CUB Hopital Erasme, Bruxelles, Belgium

Pediatric NODAT

- Retrospective study of 45 pediatric and young adult cases of NODAT
- In 6 cases, TAC was switched to cyclosporine
  - 3 of those (50%) recovered from NODAT



Pediatr Transplantation 2008: 12: 643–649

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Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2007.00862.x

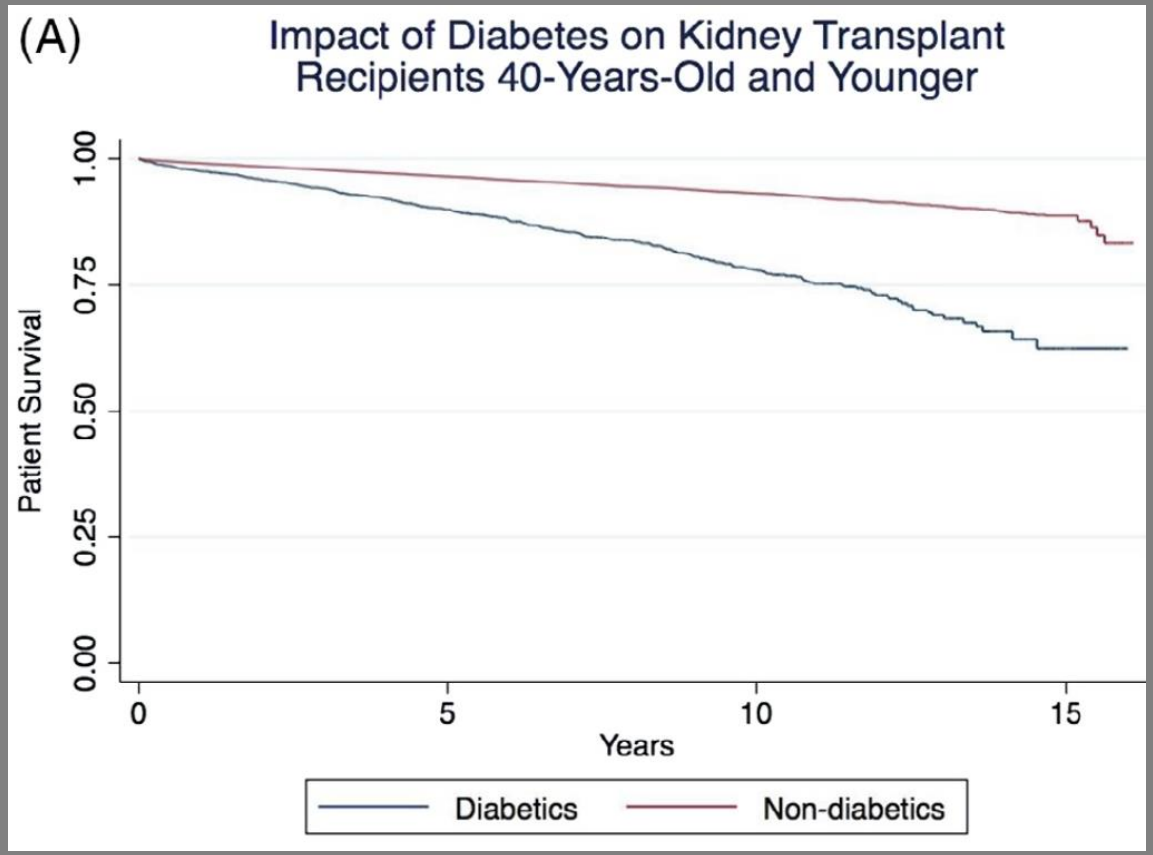
Post-transplant diabetes mellitus in children following renal transplantation

Prokai A, Fekete A, Kis E, Reusz GS, Sallay P, Korner A, Wagner L, Tulassay T, Szabo AJ. Post-transplant diabetes mellitus in children following renal transplantation.
Pediatr Transplantation 2008: 12: 643–649. © 2008 Wiley Periodicals, Inc.

A. Prokai[1], A. Fekete[1], E. Kis[1], G. S. Reusz[1], P. Sallay[1], A. Korner[1], L. Wagner[2], T. Tulassay[1] and A. J. Szabo[1]

[1]First Department of Pediatrics, Semmelweis

Diabetes is bad for young kidney transplant patients



Received: 7 July 2021 | Revised: 9 November 2021 | Accepted: 31 December 2021
DOI: 10.1111/nep.14019

ORIGINAL ARTICLE

NEPHROLOGY WILEY

The impact of diabetes on young transplant recipients: An American perspective

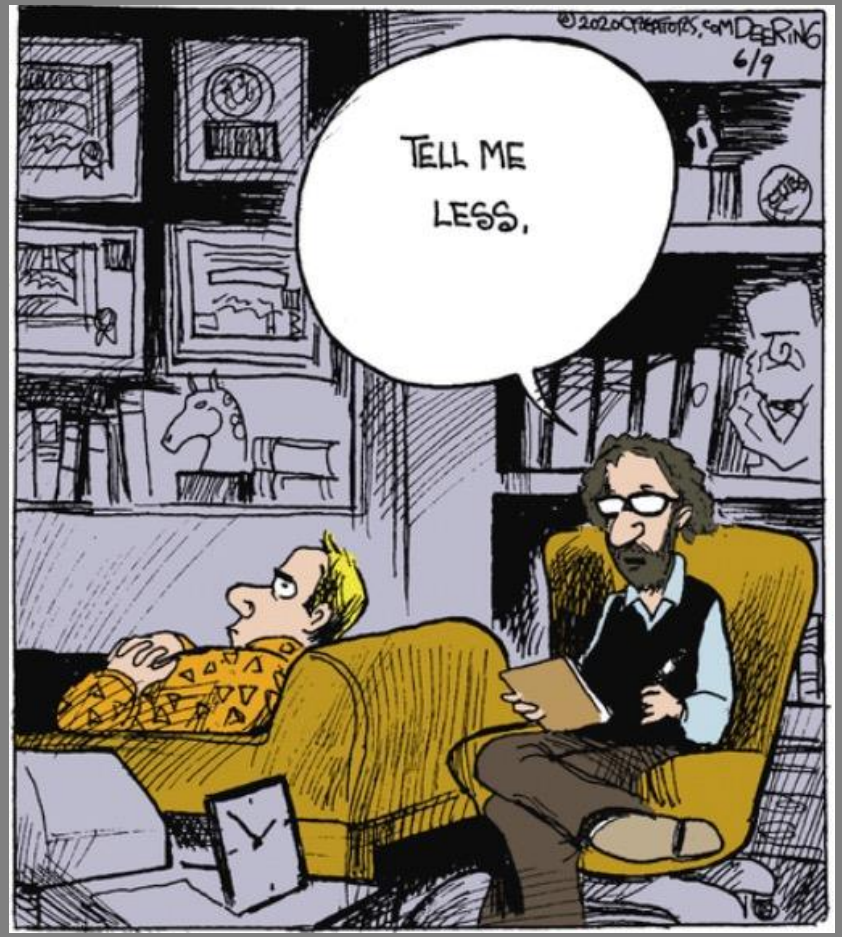
Jackquelin M. Loera[1] | Spencer C. Barrett[1] | Theodore S. Zhang[1] | Adrish Anand[1] | Ahmed A. Y. Awan[2] | Bhamidipati V. R. Murthy[2] | Christine A. O'Mahony[1,2] | John A. Goss[1,2] | Abbas A. Rana[1,2]

Nephrology. 2022;27:450–457.

FIGURE 1 (A) Kaplan–Meier curve comparing diabetic and non-diabetic transplant recipient survival over time.

NODAT

- Consider rapid switch to belatacept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Costimulation Story