CARDIOLOGY 2023

HEART TRANSPLANT MEDICATIONS

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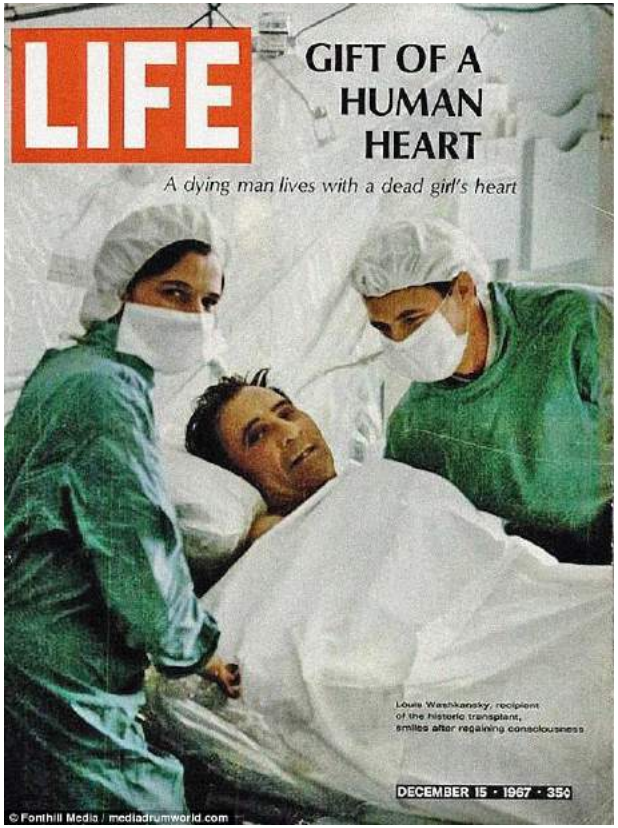
Cardiac Center

22CME0420/PPT/01-23

OBJECTIVES

- Review immune-suppression medications used in heart transplantation
- Describe mechanism of action and common side effects
- Provide practice clinical pearls for maintenance immune suppression medications
- Briefly review transplant rejection therapies and medications



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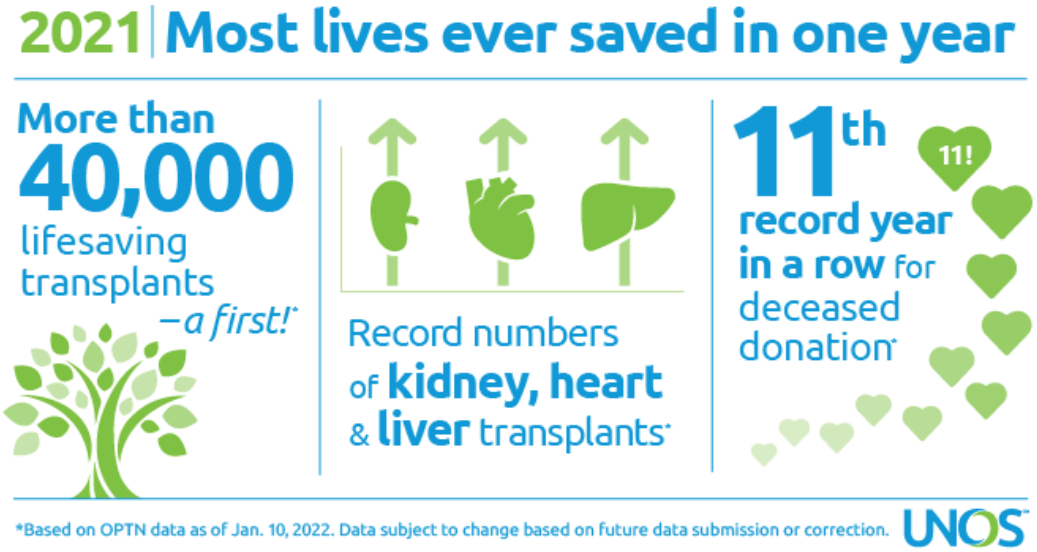
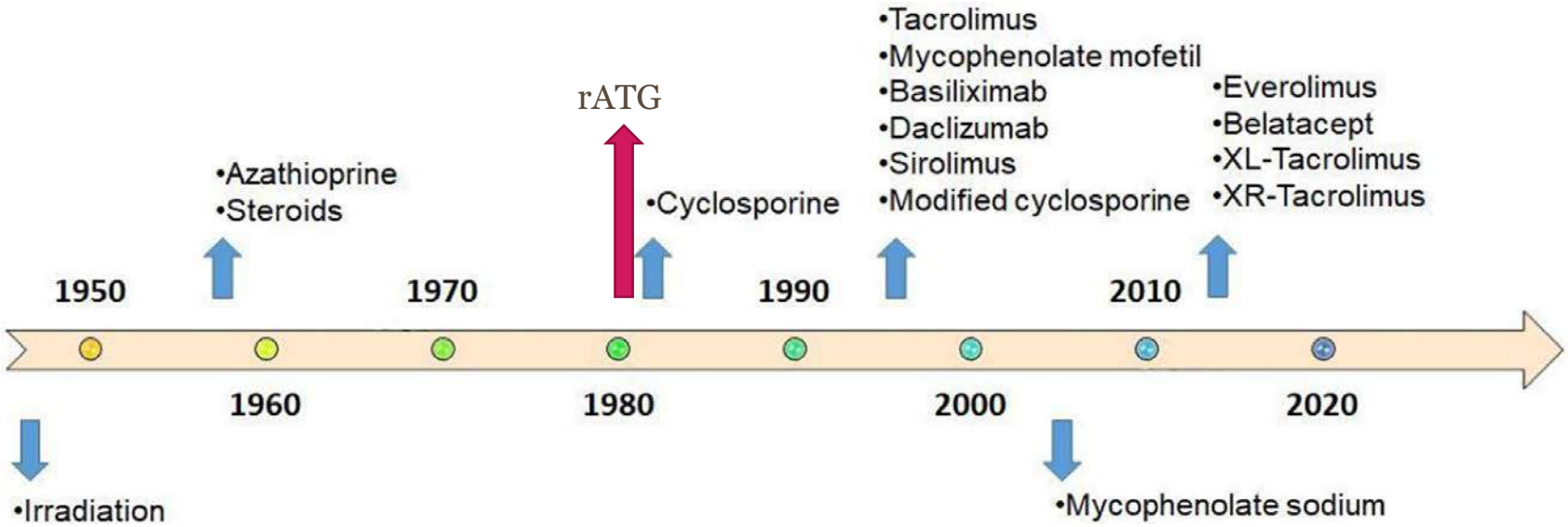


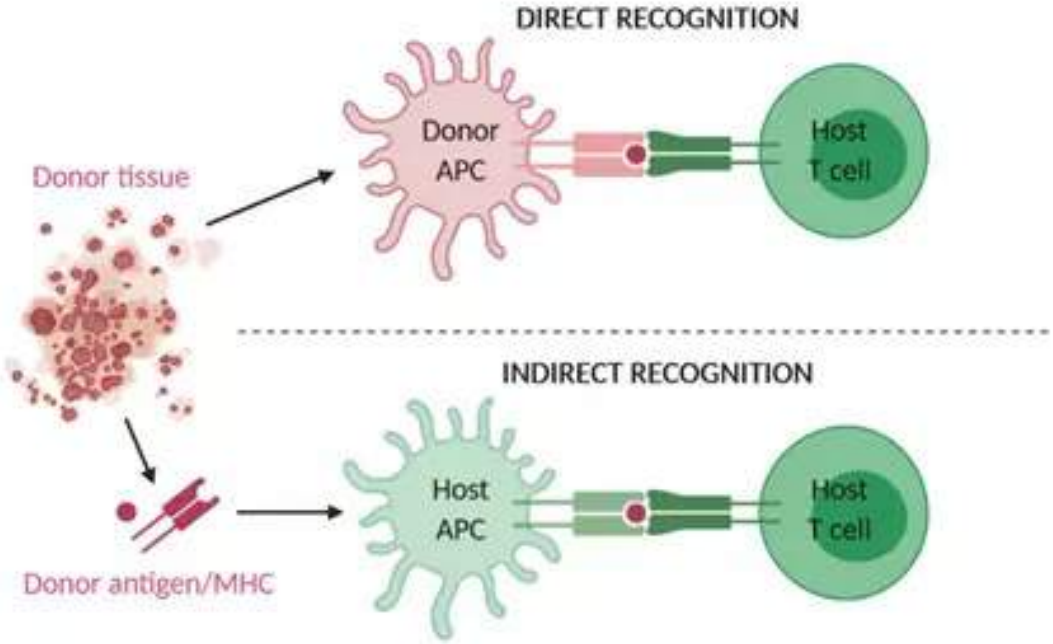
600-700

Heart transplants performed annually worldwide



Pharmacotherapy, Volume: 42, Issue: 8, Pages: 599-633, First published: 29 August 2022, DOI: (10.1002/phar.2716)

T CELLS



https://www.immunologyresearchjournal.com/articles/immunosuppressive-drugs-in-organ-transplantation-to-prevent-allograft-rejection-mode-of-action-and-side-effects.html

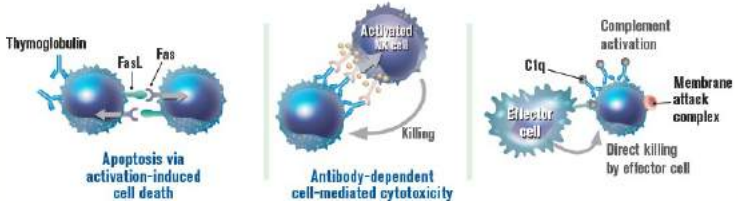
Induction

Maintenance

Treatment of Rejection

INDUCTION: ATG AND BASILIXIMAB

- Antithymocyte globulin (ATG, rabbit)
  - **Mechanism of Action**: T cell depletion, induction of apoptosis in B cell lineages, induction of regulatory and natural kill T cells
  - **Dosage**:
    - 1.5mg/kg x1 followed by CD3 based dosing
    - 1.5mg/kg/dose x5 in crossmatch positive or high risk transplants
  - Requires premedication with methylprednisone, acetaminophen, and benedryl
- Basiliximab
  - **Mechanism of action**: IL-2 receptor antagonist, prevents T cell proliferation
  - **Dosage**:
    - if <35kg, 10mg once in OR and again 4 days post transplant
    - If >35kg: 20mg once in OR and 20mg again 4 days later



Clinical Pearl:

- When drawing CD3 level to determine ATG dose, must also draw CBC
- If also giving steroids in the first 5 days, time daily steroid with ATG dosing
- ATG effect lasts about 3 months

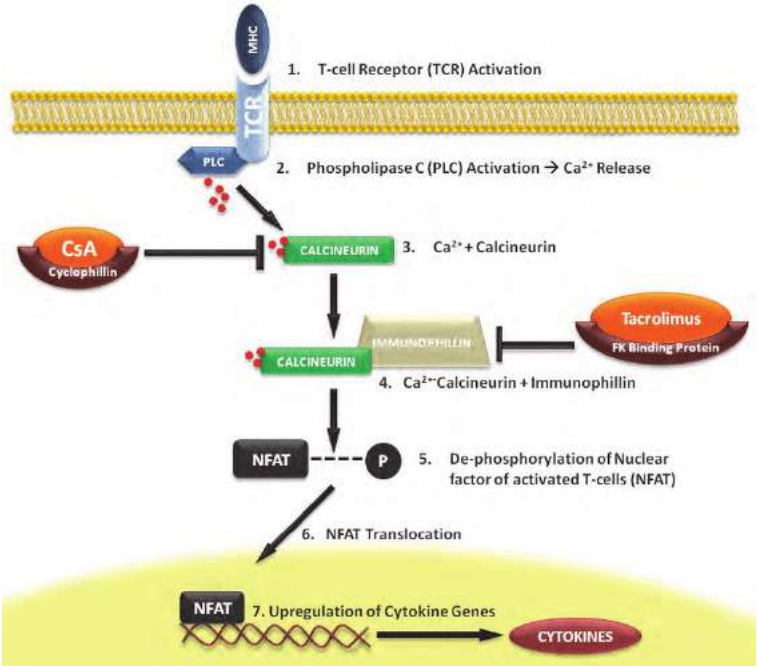
Induction

Maintenance

Treatment of Rejection

CALCINUERIN INHIBITORS

- **Mechanism of action**: Inhibits T cell activation, proliferation, and differentiation
- **Medications**: cyclosporine and tacrolimus
- Tacrolimus is more common in current immune suppression regimens
- **Many Drug-drug interactions**
  - **-Azole antifungals**
  - **Macrolides**
  - **Calcium channel blockers (diltiazem, verapamil)**
  - **Anti-seizure medications: phenytoin, carbamazepine, orlistat**
- Avoid grapefruit consumption
- Patients should avoid LIVE vaccines



Slattery, Craig & Cassidy, Hilary & Johnston, Olwyn & Ryan, Michael & Mcmorrow, Tara. (2012). Mechanisms of Calcineurin Inhibitor Nephrotoxicity in Chronic Allograft Injury. 10.5772/25778.

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CYCLOSPORINE

- **Mechanism of action**: Binds to cyclophilin to inhibit calcineurin phosphorylase
- Available formulations: oral, IV
- Therapeutic drug level range: 100-400 ng/mL.
- **Dosing**: 5-9 mg/kg/day in 2-3 divided doses; titrate dose according to goal levels
- **Common Side effects:** include **hirsutism**, **gum hyperplasia**, hypertension, renal toxicity, dyslipidemia, hepatotoxicity, malignancies

Clinical Pearl:

- Let transplant team know if STARTING or STOPPING any medications
- Stopping medications can result in in subtherapeutic drug levels/rejection

TACROLIMUS

- **Mechanism of action**: binds to FK to prevent T cell activation and proliferation
- **Dosage**: 0.05 mg/kg/dose every 12 hours, titrate to goal drug levels
- Therapeutic drug monitoring: typical 12 hour trough goals 6-12
- Available forms: oral, IV
  - Oral: liquid, capsules, tablets, sublingual
- **Common side effects**: acne, alopecia, anemia, headache, tremors, nephrotoxicity, osteoporosis, hypomagnesemia
- Rare but serious: PRES

Clinical Pearls

- Consistency is important
  - PO or NG/GT
  - With or without food
- Capsules can be opened up to add to food as patients transition to take pills
- Extended release formulation → DAILY med

ANTI-METABOLITES: MYCOPHENOLATE

- **Mechanism of action**: targets enzymes involved in de novo synthesis of purine which impairs DNA replication in both B and T cells
- Available formulations:
  - Mycophenolate mofetil (MMF, Cellcept®)
  - Mycophenolate sodium (MPS, Myfortic®)
    - Enteric coated
    - Can consider if patients experiencing GI symptoms with MMF
- **Common side effects**
  - GI symptoms: nausea, vomiting, diarrhea
  - Myelosuppression

Clinical Pearl: Teratogenic

- Capsules should never be opened and tablets should not be broken/crushed
- May require dose adjustments to help clear infections

ANTI-METABOLITES: AZATHIOPRINE

- Brand name: Imuran
- **Mechanism of action**: inhibits purine synthesis
- **Dosing**: 1-3mg/kg/day given daily
- **Common Side Effects**: nausea, vomiting, leukopenia, infections

Clinical Pearl:

- Antimetabolite of choice in patients who are pregnant or planning to become pregnant

MTOR INHIBITORS

- **Mechanism of Action**: inhibits IL-2 and other cytokine receptor-dependent signal transduction mechanisms, via action on mTOR, and thereby blocks activation of T and B cells.
- Available formulations:
  - Sirolimus and Everolimus
- **Common Side Effects**: diarrhea, anemia, rash**, mouth ulcers, stomatitis**, acne, infection, proteinuria, poor wound healing,
- **Main indications for use**
  - Worsening renal function
  - **New evidence of coronary vasculopathy**
  - Malignancy or infections
- Therapeutic drug goal: typically 4-6 if using in conjunction with tacrolimus

Clinical Pearl:

- Stop sirolimus prior to upcoming planned surgeries
  - consider stopping in patients listed for retransplant

CORTICOSTEROIDS

- **Mechanism of action**: inhibition of cytokine synthesis, anti-inflammatory effects, redirection of lymphocyte traffic
- Mainstay in preventing post transplant rejection for many years
- **Dose**:
  - Maintenance: 0.2mg/kg/dose
  - Pulse: up to 15mg/kg/day
- Side effects
  - Impaired bone health
  - Poor linear growth
  - Cushingoid appearance
  - Mood changes
  - Osteoprosis
  - hyperglycema and dyslipidemia

Clinical Pearl:

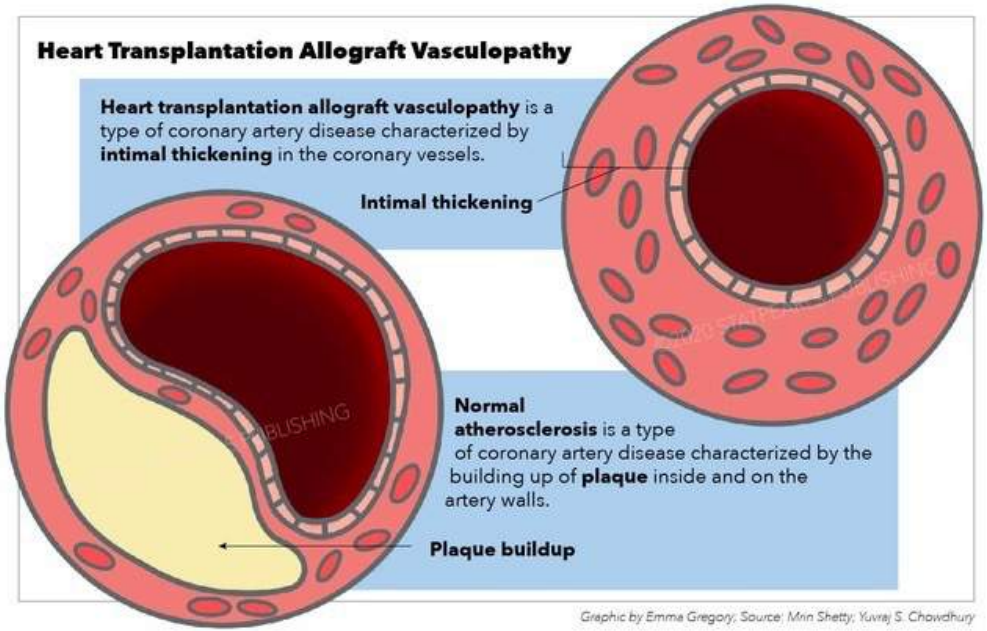
- Patients on chronic steroids should have routine bone health evaluation
- Try to use the lowest dose possible to minimize side effects

PRAVASTATIN

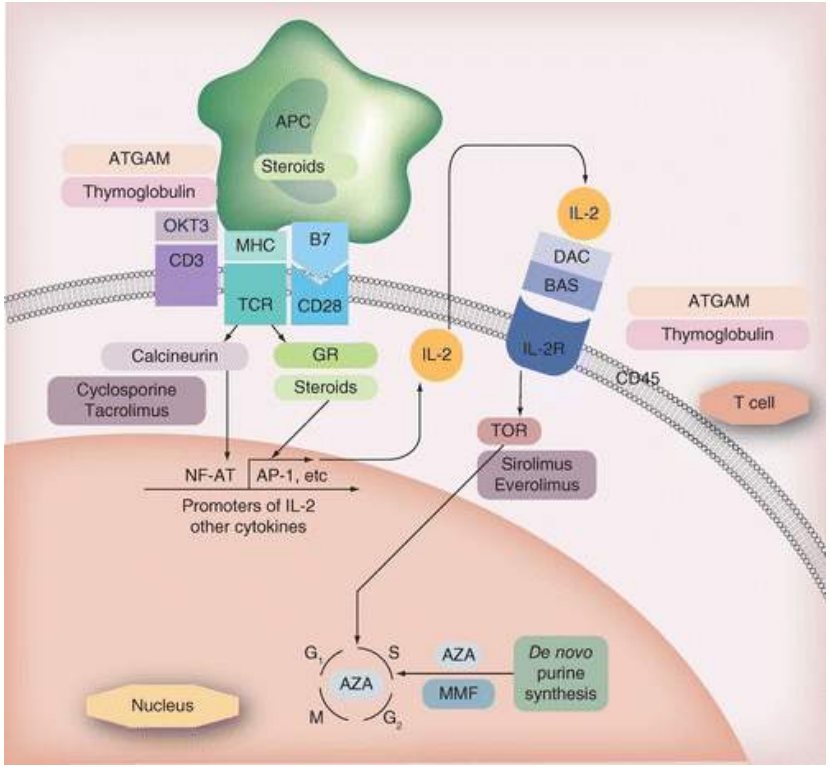
- **Mechanism of Action**: reducing cholesterol synthesis by acting on hydroxymethylglutaryl CoA reductase inhibitors
- Why we use it in transplant:
  - reduce the risk of developing coronary allograft vasculopathy
- **Dose**: 10mg daily when able to swallow pills
- Common side effects: muscle/leg pain, headache, nausea, dizziness, abnormal liver tests

Clinical Pearl:

- Check CMP at least annually
- Recommended to take at nighttime because that's when your body makes the most cholesterol!



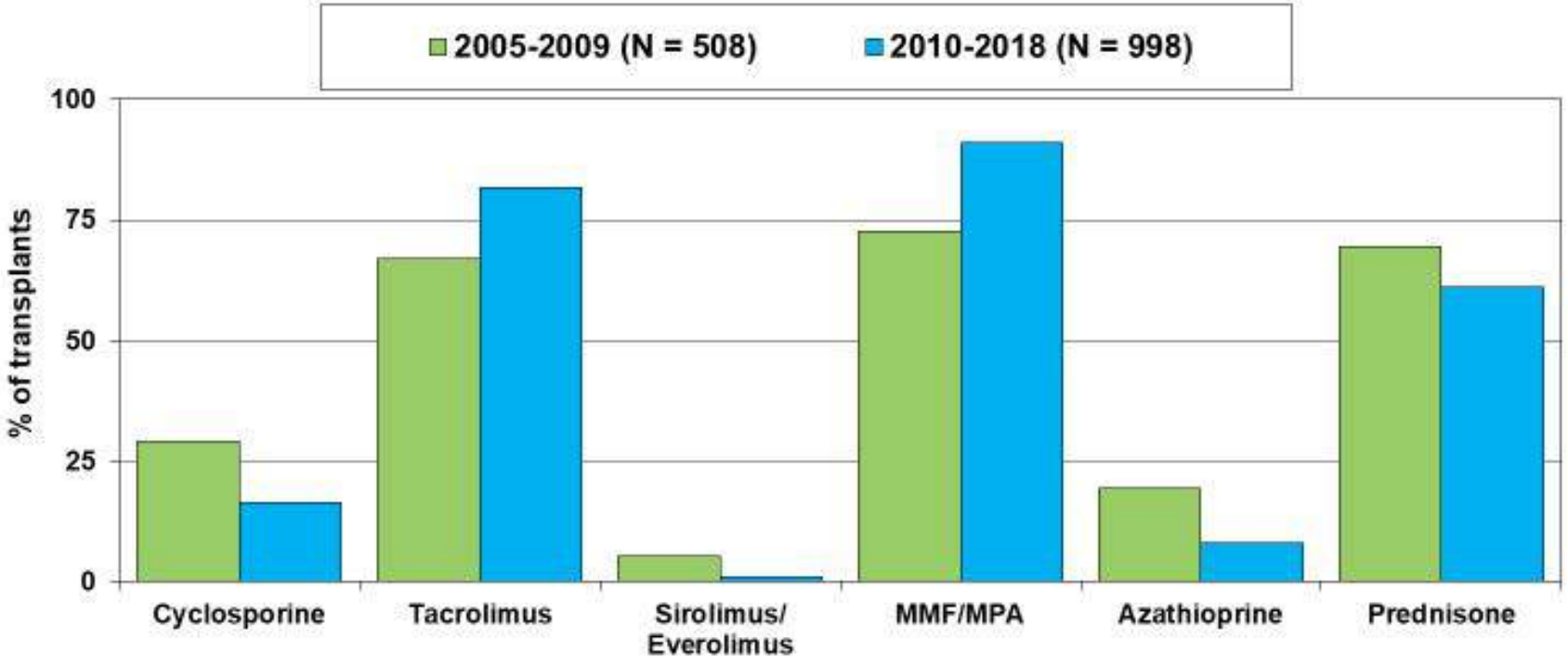
https://www.ncbi.nlm.nih.gov/books/NBK555999/bin/Heart_Transplantation_Allograft_Vasculopathy-01.jpg


APC
Steroids
ATGAM
Thymoglobulin
OKT3
CD3
MHC
B7
TCR
CD28
Calcineurin
GR
Steroids
Cyclosporine
Tacrolimus
IL-2
NF-AT
AP-1, etc
Promoters of IL-2
other cytokines
IL-2
DAC
BAS
IL-2R
ATGAM
Thymoglobulin
CD45
T cell
TOR
Sirolimus
Everolimus
G1
S
M
G2
AZA
AZA
MMF
De novo
purine
synthesis
Nucleus

WHAT'S NEW?

- **Belatacept**
  - Mechanism of action: co-stimulation inhibitor for rejection prophylaxis
    - Binds CD80 and CD86 receptors on APCS to block selective T cell co stimulation resulting in lack of response by T cell
  - IV medication given every 4 weeks
  - Can only be used in patients who are **EBV+** given increased risk of PTLD

Infant Heart Transplants (Age at Transplant <1 Year)
Maintenance Immunosuppression at Discharge by Era
(Transplants: January 2005 – June 2018)



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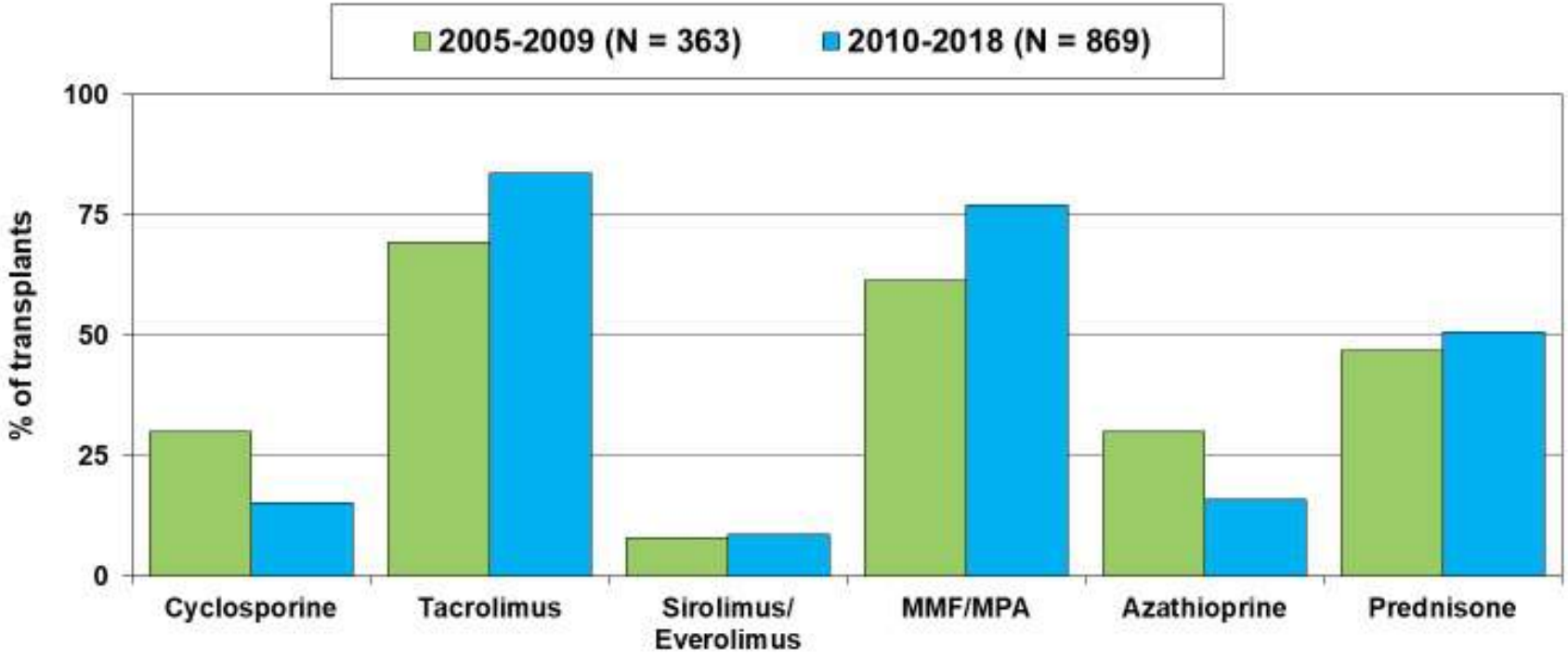
2022
JHLT. 2022 Oct; 41(10): 1335-1375

Analysis is limited to patients who were alive at discharge.

Infant Heart Transplants (Age at Transplant <1 Year)
Maintenance Immunosuppression at 1 Year Follow-up by Era
(Follow-ups: January 2005 – June 2018)



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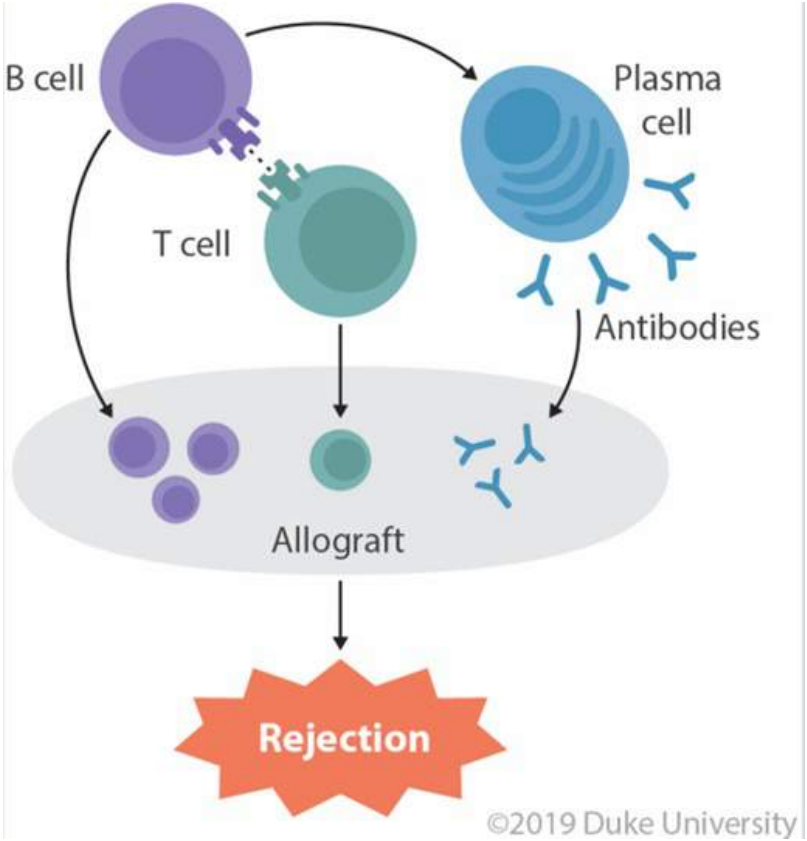
Induction

Maintenance

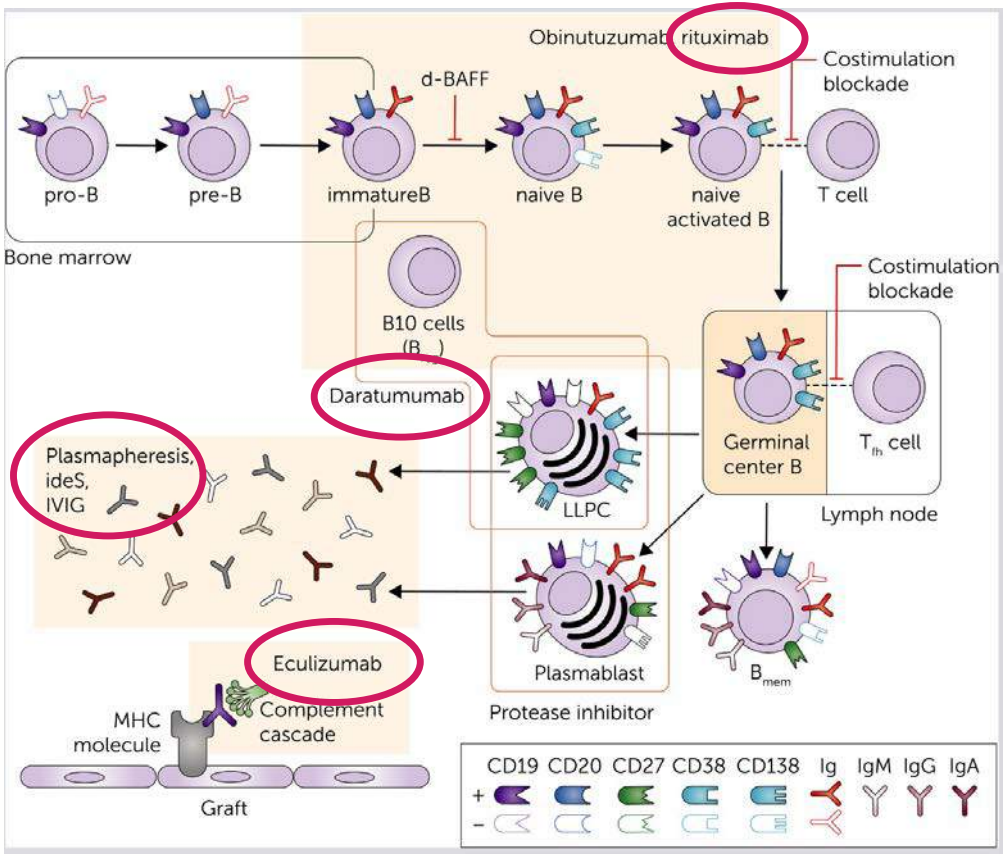
Treatment of Rejection



https://onlinelibrary.wiley.com/doi/epdf/10.1111/tri.13549

MEDICATIONS/THERAPIES REJECTION

1. Get rid of T cells!
   - ATG
   - Alemtuzumab (Campath®)
2. Antibody removal
   - Plasmapheresis
   - IVIG
3. Stop antibody production
   - Daratumumab
   - Bortezomib
4. Stop complement cascade
   - Eculizumab



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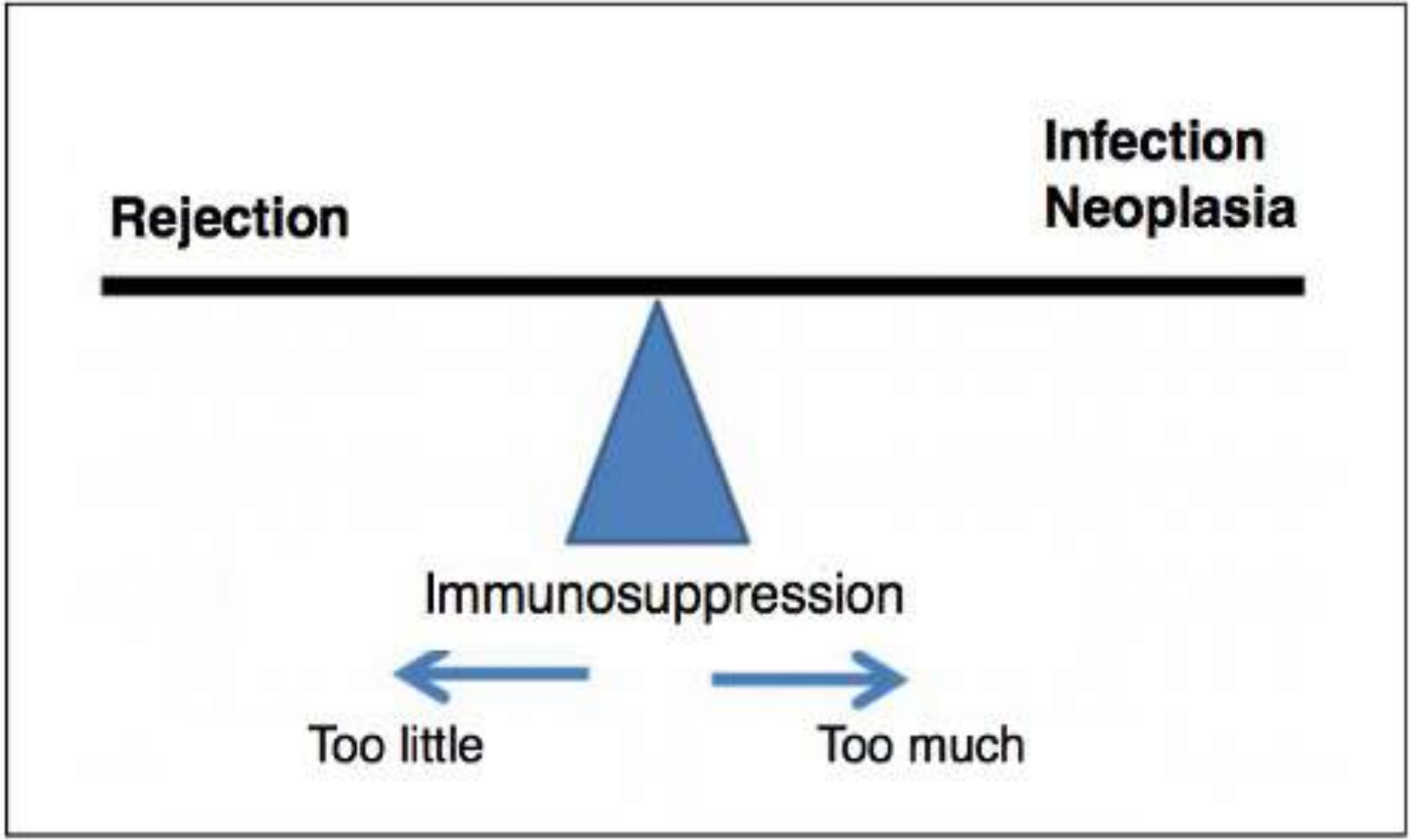
Infection
Neoplasia
Rejection
Immunosuppression
Too little
Too much

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