WHEN MEDICATIONS COLLIDE: NAVIGATING DRUG-DRUG INTERACTIONS IN TRANSPLANT AND ONCOLOGY PATIENTS

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CONFLICT OF INTEREST

- No conflicts of interest to disclose

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LEARNING OBJECTIVES FOR TECHNICIANS

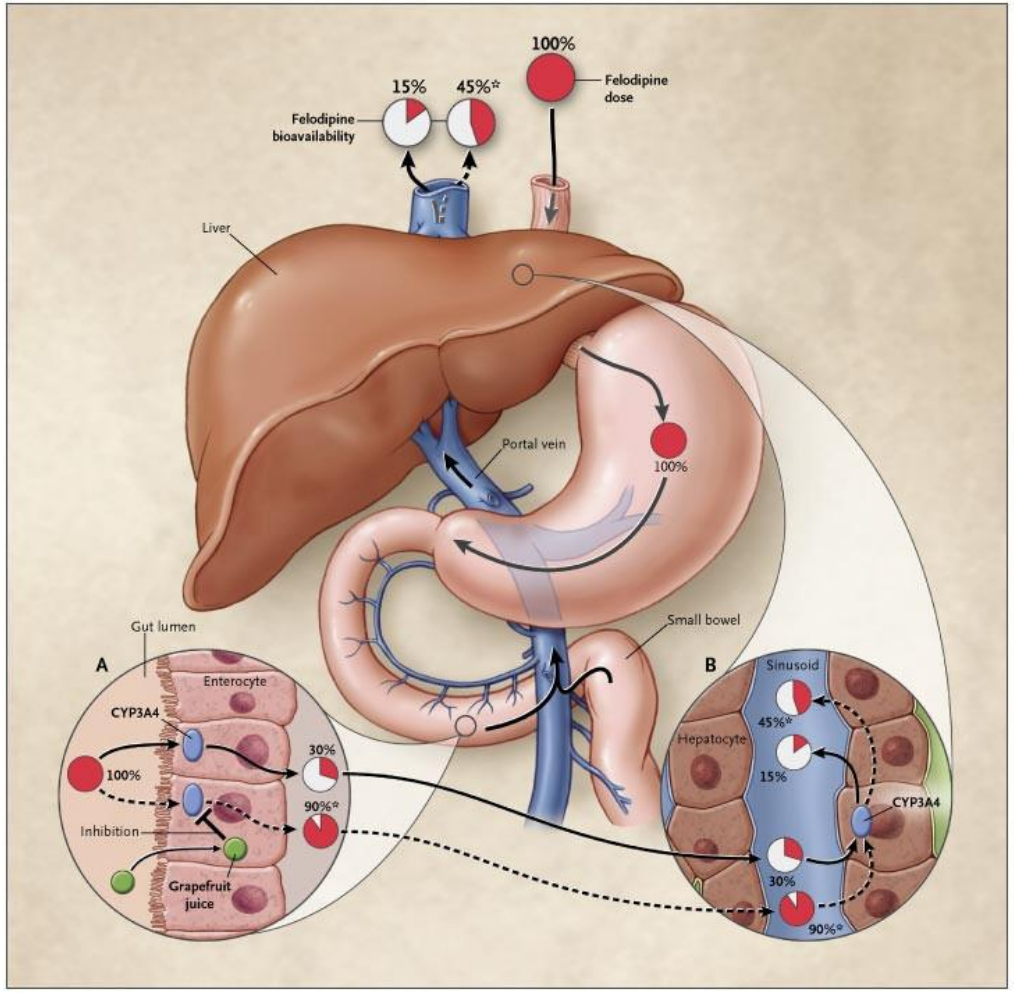
- Identify antimicrobial classes that commonly cause clinically significant drug interactions in transplant and oncology patients
- Recognize high-risk drug interaction combinations
- Describe why transplant and oncology patients frequently receive antimicrobials for prophylaxis, empiric therapy, and directed therapy
- Identify key toxicity stacking risks associated with antimicrobials in immunocompromised patients

LEARNING OBJECTIVES FOR PHARMACISTS

- Assess antimicrobial drug interactions and determine whether the main risk is toxicity or loss of efficacy
- Apply a structured drug interaction approach using avoidance, substitution, dose adjustment, and monitoring strategies
- Manage antimicrobial interactions with transplant and oncology therapies to prevent therapy interruption and clinically significant harm
- Identify and reduce additive toxicity from antimicrobial therapy in this high-risk population

DRUG METABOLISM

DRUG METABOLISM

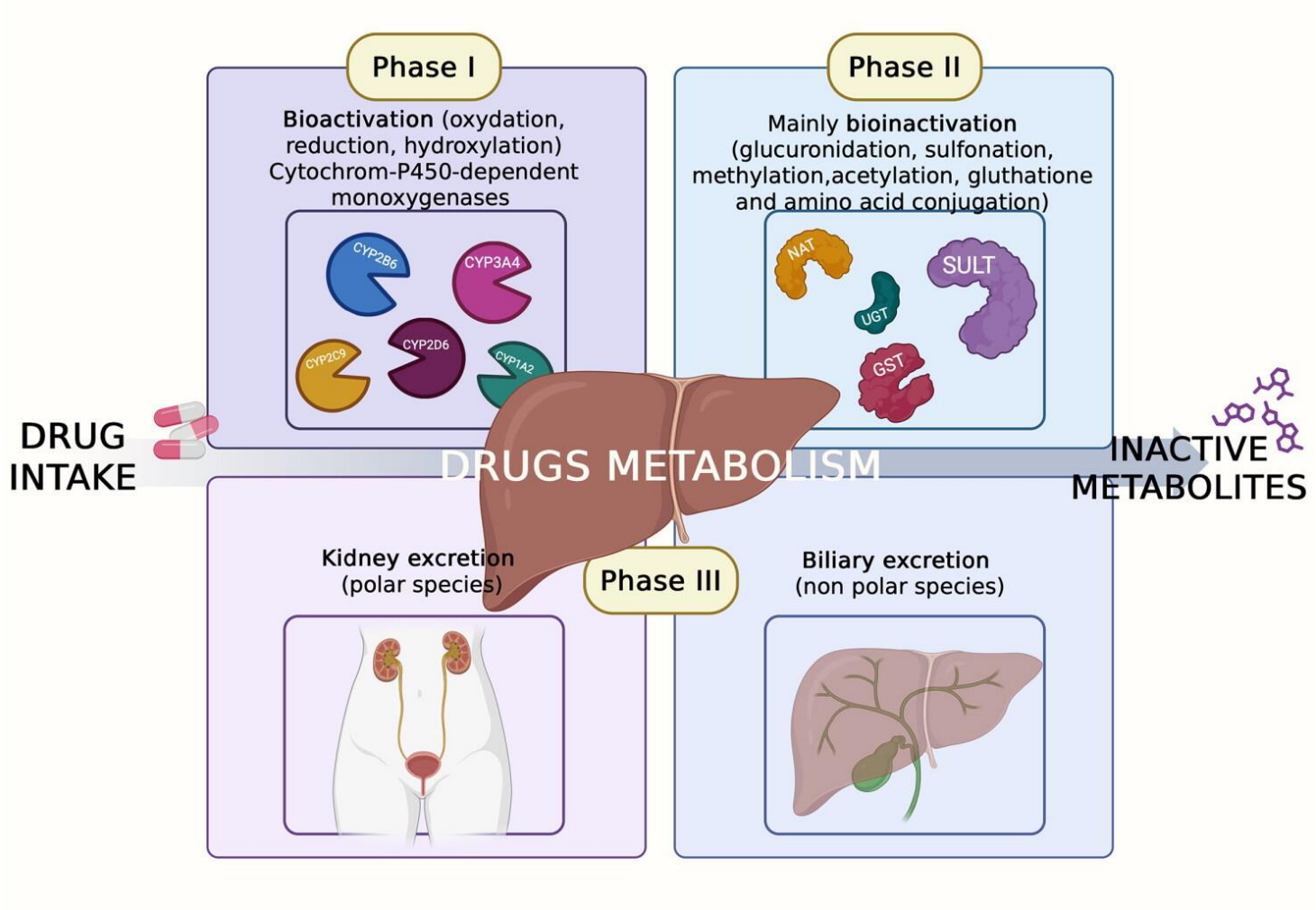


First-pass metabolism

- Oral medications must pass through the liver and/or other sites of major drug metabolism prior to reaching systemic circulation
- Cytochrome P450 (CYP) enzymes metabolize drugs during initial absorption
- Transporter P-glycoprotein (P-gp) pumps drug back into the intestinal lumen
- Drugs with more first-pass metabolism have lower oral bioavailability
- Inhibition or induction of CYP/P-gp can alter bioavailability before reaching systemic circulation

Susa ST, Hussain A, Preuss CV. First-Pass Effect. StatPearls, NCBI Bookshelf. 2023
Punnapuzha S. Febrile Neutropenia. StatPearls, NCBI Bookshelf. 2023
Wilkinson GR. Drug Metabolism and Variability Among Patients in Drug Response. N Engl J Med. 2005

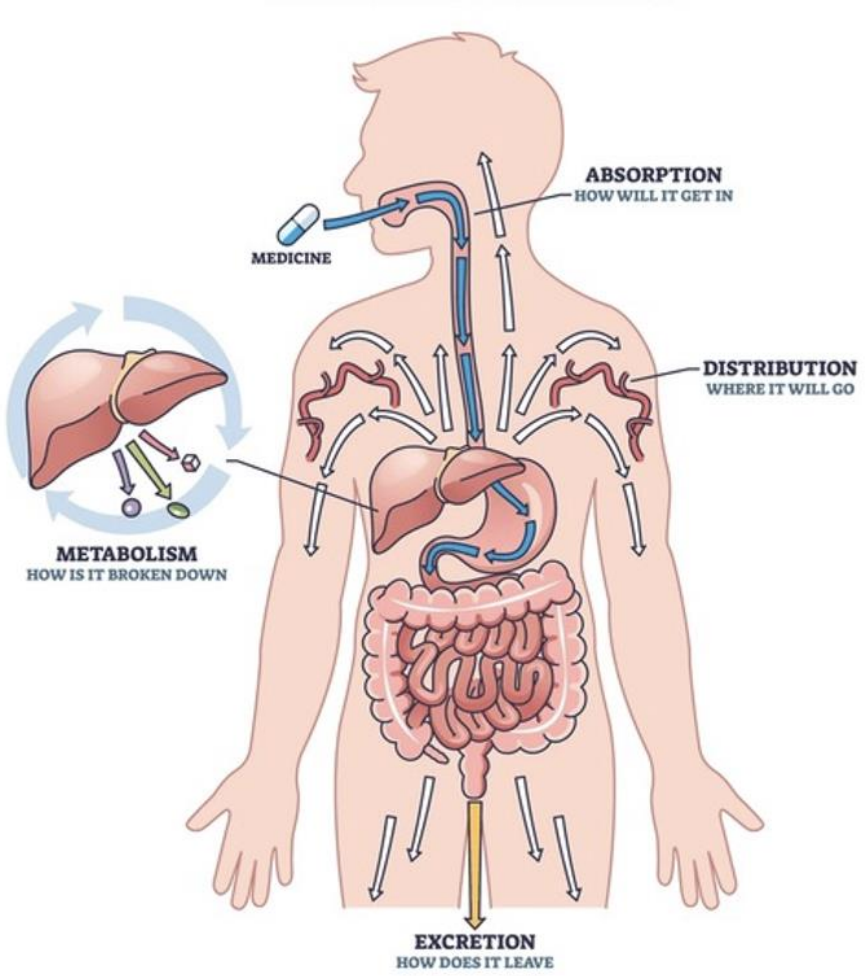
DRUG METABOLISM: PHASE I, II & III



Pietrzak A et al. Phase II metabolism in xenobiotic biotransformation. Drug Metab Rev. 2025.

MECHANISMS OF DRUG-DRUG INTERACTIONS

WHERE DRUG-DRUG INTERACTIONS (DDI) HAPPEN



- DDIs occur at multiple sites within the body
- Primarily in the gastrointestinal tract, liver, kidneys
- Through mechanisms involving absorption, metabolism, transport, and elimination
- Greatest harm with narrow therapeutic index medications

Liu X. Transporter-mediated drug-drug interactions. Springer. 2019.

PHARMACOKINETICS VS. PHARMACODYNAMICS

Pharmacokinetic interactions

- Absorption
- Metabolism
- Transporters
- Elimination

Pharmacodynamic interactions

- Additive toxicity
- Antagonistic effects
- Synergistic effects

Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007.
Niu J, Straubinger RM, Mager DE. Pharmacodynamic drug-drug interactions. Clin Pharmacol Ther. 2019.

DRUG INTERACTIONS: ABSORPTION

pH-dependent solubility

- Acid suppression (PPI/H2RA/antacids) ↑ gastric pH and ↓ dissolution of weak bases with pH-dependent solubility
- Clinical impact: ↓ exposure and loss of efficacy (classically relevant for multiple oral oncolytics/azoles)
- Mitigation: alternative dosing schedules or avoidance of the combination

Chelation

- Polyvalent cations (Ca/Mg/Al/Fe) form non-absorbable complexes which ↓ bioavailability
- Highest risk with closer coadministration
- Mitigation: spacing strategy (often works well when feasible)

Budha NR, Frymoyer A, Smelick GS, et al. Drug absorption interactions between oral targeted anticancer agents. Clin Pharmacol Ther. 2012
Bauters T, Dadkhah A. Clinically relevant drug interactions in HCT. Hematopoietic Cell Transplantation and Cellular Therapies. Springer. 2024
Ogawa R, Echizen H. Clinically significant drug interactions with antacids. Drugs. 2011
Deng J, Zhu X, Chen Z, et al. A review of food-drug interactions on oral drug absorption. Drugs. 2017

DRUG INTERACTIONS: ABSORPTION CONTINUED

Food effects

- Food can change gastric emptying, bile secretion, splanchnic blood flow which alters rate and/or extent of absorption
- Effect depends on the drug (solubility-limited or permeability-limited; formulation-specific)
- Mitigation: follow labeled instructions

GI motility/mucositis/diarrhea

- Faster transit and inflamed mucosa can ↓ contact time, ↓ surface area, ↓ predictable permeability
- Mitigation: consider IV route, therapeutic drug monitoring when applicable, assess clinical response

Budha NR, Frymoyer A, Smelick GS, et al. Drug absorption interactions between oral targeted anticancer agents. Clin Pharmacol Ther. 2012
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Deng J, Zhu X, Chen Z, et al. A review of food-drug interactions on oral drug absorption. Drugs. 2017

DRUG INTERACTIONS: METABOLISM

Substrate

- Metabolized or transported by a specific pathway
- Exposure changes if the pathway is altered

Inhibitors

- ↓ activity of the pathway
  ↑ drug exposure
- Opposite effect for prodrugs requiring CYP-mediated activation

Inducers

- ↑ activity of the pathway
  ↓ drug exposure
- Opposite effect for prodrugs requiring CYP-mediated activation

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

COMMON CYP INHIBITORS/INDUCERS

GPACMAN = Major CYP inhibitors Inhibitors: ↓ metabolism → ↑ exposure (toxicity)	PSPORCS = Major CYP inducers Inducers: ↑ metabolism → ↓ exposure (failure)
G = Grapefruit	P = Phenytoin
P = Protease inhibitors (ritonavir-boosted regimens)	S = Smoking
A = Azole antifungals	P = Phenobarbital
C = Cimetidine/Cyclosporine/Cobicistat	O = Oxcarbazepine
M = Macrolides (erythromycin/clarithromycin)	R = Rifamycins (rifampin, rifabutin, rifapentine)
A = Amiodarone	C = Carbamazepine
N = Non-DHP CCBs (verapamil, diltiazem)	S = St. John's Wort

Gilani B, Cassagnol M. Biochemistry, cytochrome P450. StatPearls, NCBI Bookshelf. 2025.

DRUG INTERACTIONS: ELIMINATION

Elimination DDIs cause changes in clearance; ↑/↓ exposure (toxicity or failure)

Renal clearance (tubular secretion + glomerular filtration rate [GFR] changes)

- Transporter inhibition/competition ↓ tubular secretion and cause drug accumulation
- Acute kidney injury (AKI) as a functional interaction (nephrotoxins/volume depletion/tumor lysis syndrome/sepsis) ↓ GFR and cause accumulation of renally cleared drugs

Hepatic/biliary clearance (uptake + biliary excretion + liver injury)

- Hepatic uptake transporters inhibition (OATP) ↓ hepatocyte entry leading to ↑ plasma exposure
- Biliary efflux impairment (P-gp, MRP, BCRP pathways) ↓ biliary excretion and ↑ parent drug and/or metabolite exposure
- Cholestasis/hepatic injury as a functional interaction can ↓ clearance independent of CYP inhibition

Garza AZ, Park SB, Kocz R. Drug elimination. StatPearls, NCBI Bookshelf. 2025.

DRUG INTERACTIONS: TRANSPORTERS

Transporters are membrane proteins that move drugs across cell membranes

Change exposure through absorption and clearance

Efflux (pump OUT)

- Drug direction: cell → lumen/urine/bile
- Gut: ↓ absorption and ↓ systemic concentration
- Kidney/liver: ↑ excretion
- Examples: **P-gp (ABCB1), BCRP (ABCG2), MRPs (ABCC)**

Uptake (keep IN)

- Drug direction: blood → hepatocyte
- ↑ hepatic entry may ↑ clearance and ↓ systemic concentrations
- Examples: **OATP1B1/1B3**

Müller F, Fromm MF. Transporter-mediated drug-drug interactions. Pharmacogenomics. 2011.

POTENCY DEFINITIONS

CYP Inhibitors

- **Strong**: ≥ 5-fold ↑ AUC
- **Moderate**: ≥ 2- to <5-fold ↑ AUC
- **Weak**: ≥ 1.25- to <2-fold ↑ AUC

CYP Inducers

- **Strong**: ≥ 80% ↓ AUC
- **Moderate**: ≥ 50% to <80% ↓ AUC
- **Weak**: ≥ 20% to <50% ↓ AUC

Substrates

- **Sensitive substrate:** ≥5-fold ↑AUC with a strong inhibitor
- **Moderately sensitive substrate:** ≥2- to <5-fold ↑AUC with a strong inhibitor

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

COMMON ENZYME/TRANSPORT INHIBITORS

Drug	Inhibition
Posaconazole	• 3A4 strong inhibitor • P-gp inhibitor
Voriconazole	• 3A4 strong inhibitor
Itraconazole	• 3A4 strong inhibitor • P-gp inhibitor
Isavuconazole	• 3A4 moderate inhibitor • P-gp inhibitor
Fluconazole	• 3A4 moderate inhibitor

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

COMMON ENZYME/TRANSPORT INHIBITORS CONT.

Drug	Inhibition
Clarithromycin	• 3A4 strong inhibitor • P-gp inhibitor
Erythromycin	• 3A4 moderate inhibitor • P-gp inhibitor
Ciprofloxacin	• 3A4 weak to moderate inhibitor
Protease inhibitors (Atazanavir, Darunavir, Ritonavir, etc.)	• 3A4 strong inhibitor
Cobicistat	• 3A4 strong inhibitor

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

COMMON ENZYME/TRANSPORT INDUCERS

Drug	Induction
Rifampin	• 3A4 strong inducer • P-gp inducer
Rifabutin	• 3A4 moderate inducer
Rifapentine	• 3A4 moderate inducer
Efavirenz	• 3A4 moderate inducer

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

QUESTION #1

For an oral drug with high first-pass metabolism, what happens to exposure if you add a strong CYP3A inhibitor?

A. Exposure decreases
B. Exposure increases
C. No change
D. Unpredictable change

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

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U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

QUESTION #2

Which interaction most commonly causes loss of efficacy by reducing oral drug absorption?

A. PPI increasing gastric pH for pH-dependent oral agents
B. Additive nephrotoxicity
C. CYP induction increasing metabolism
D. Increased renal tubular secretion of the drug

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

QUESTION #2

Which interaction most commonly causes loss of efficacy by reducing oral drug absorption?

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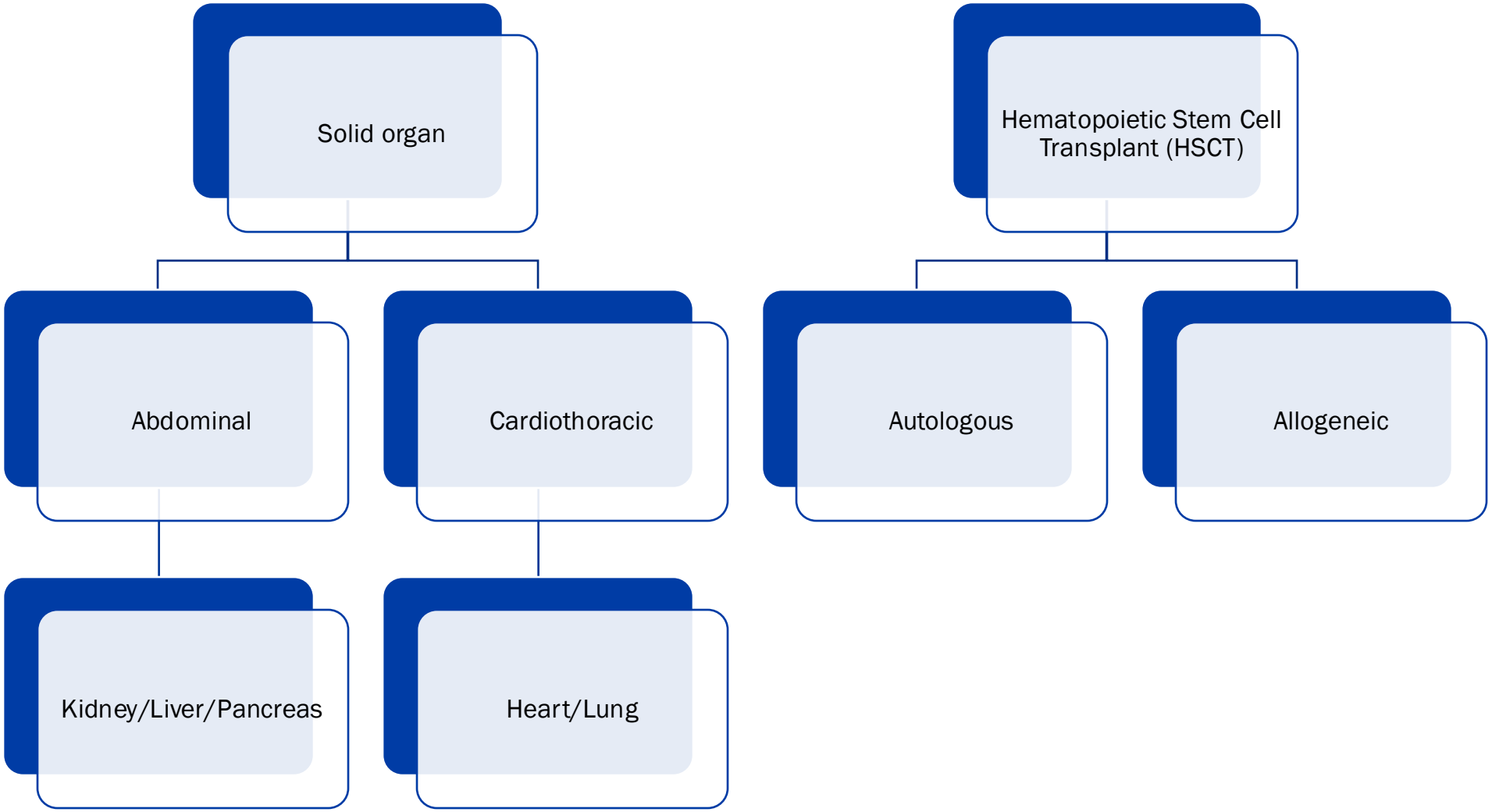
U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

DRUG INTERACTIONS IN THE TRANSPLANT POPULATION

TYPES OF TRANSPLANT



MEDICATION BURDEN: WHAT MAKES TRANSPLANT DIFFERENT

Polypharmacy (immunosuppression, prophylaxis, chronic disease medications)

Changes in organ function affecting clearance

Variable absorption (diarrhea, mucositis, gastric pH modifiers)

Frequent antimicrobial use (azoles, macrolides, rifamycins)

CORE IMMUNOSUPPRESSIVE REGIMENS

Typical maintenance (Triple therapy)

- Calcineurin inhibitors (tacrolimus/cyclosporine) OR mTOR inhibitors (sirolimus/everolimus)
- Antimetabolite (mycophenolate/azathioprine)
- Corticosteroids (prednisone)

Induction agents

- Antithymocyte globulin (ATG)
- Basiliximab
- Alemtuzumab
- Conditioning agents such as busulfan, cyclophosphamide, and fludarabine

Nelson J, Alvey N, Bowman L, et al. Consensus recommendations for maintenance immunosuppression. Pharmacotherapy. 2022.

CALCINEURIN AND MTOR INHIBITORS

Cyclosporine, tacrolimus, sirolimus, and everolimus are metabolized through CYP3A and P-gp

Narrow therapeutic index medications = more susceptible to supra- or subtherapeutic levels

Drug	Substrate	Inhibition/Induction
Tacrolimus	• 3A4 sensitive substrate • P-gp major substrate (with inhibitors) • P-gp minor substrate (with inducers)	• N/A
Cyclosporine	• 3A4 sensitive substrate • P-gp major substrate (with inducers) • P-gp minor substrate (with inhibitors)	• 3A4 weak inhibitor • P-gp inhibitor
Sirolimus	• 3A4 sensitive substrate • P-gp major substrate	• N/A
Everolimus	• 3A4 sensitive substrate • P-gp major substrate	• N/A

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

MANAGING CO-ADMINISTRATION WITH INHIBITORS

Clarithromycin, erythromycin, posaconazole, voriconazole, itraconazole, protease inhibitors (CYP3A4 strong inhibitors): ⟶ ↑ CNI/mTOR levels	Fluconazole, Isavuconazole (CYP 3A4 moderate inhibitors): Moderate ↑ CNI/mTOR levels	Maribavir (Weak CYP3A4 and P-gp inhibitor): Low ↑ CNI/mTOR levels
• Management: avoid if possible OR pre-emptive dose reduction with rapid trough monitoring • Azithromycin preferred if a macrolide is needed	• Generally manageable with monitoring • Adjust therapy based on clinical response and toxicity	• Generally manageable with monitoring • Adjust therapy based on clinical response and toxicity

Sparkes T, Lemonovich TL, AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants. Clin Transplant. 2019.

MANAGING CO-ADMINISTRATION WITH INDUCERS

Rifampin (CYP3A4 strong inducer)

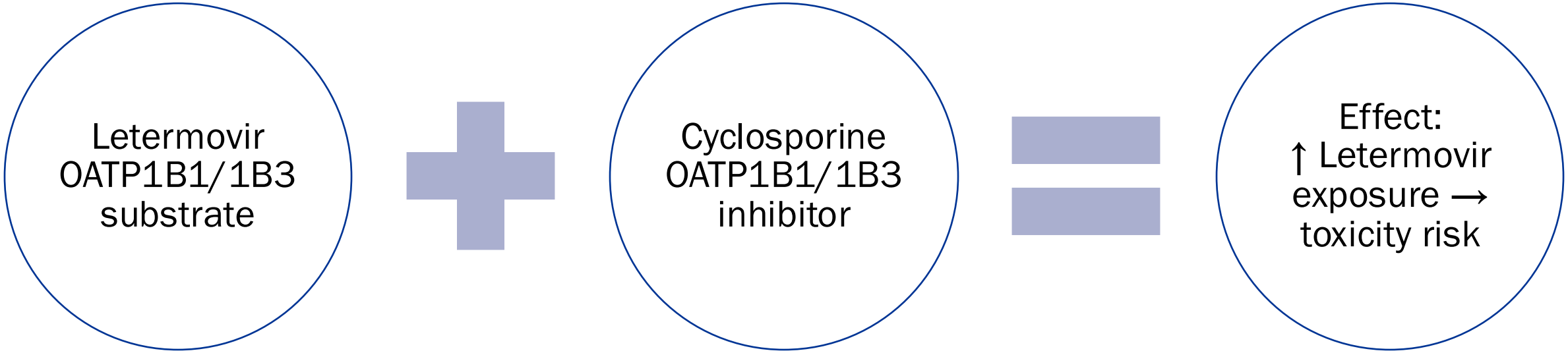
- Effect: ↓ CNI/mTOR inhibitor exposure → rejection risk
- Management: avoid when possible; if unavoidable, therapeutic drug monitoring, large dose increases often needed, and careful de-escalation when rifamycin stops

Efavirenz, rifabutin, and rifapentine (inducers; less than rifampin but still significant)

- Effect: ↓ CNI/mTOR inhibitor exposure → rejection risk
- Prefer alternatives when feasible; if required, can be used with close monitoring and dose adjustments

Sparkes T, Lemonovich TL, AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants. Clin Transplant. 2019.

CMV INTERACTION



Management for co-administration: reduce letermovir dose to 240 mg once daily

McCrea JB, Macha S, Adedoyin A, et al. Pharmacokinetic drug-drug interactions between letermovir and the immunosuppressants. J Clin Pharmacol. 2019.

CNI TOXICITIES

Nephrotoxicity

Neurotoxicity

Electrolytes (hyperkalemia, hypomagnesemia)

Hypertension

Hyperglycemia

QT prolongation (tacrolimus)

Tacrolimus [package insert]. Astellas Pharma US, Inc.; 2024
Cyclosporine [package insert]. Novartis Pharmaceuticals Corporation; 2025

MTOR INHIBITOR TOXICITIES

Mucositis/somatitis

Cytopenias

Delayed wound healing

Pneumonitis

Hyperlipidemia

Everolimus [package insert]. Novartis Pharmaceuticals Corporation; 2025
Sirolimus [package insert]. Pfizer Inc.; 2024

QUESTION #3

A transplant patient on tacrolimus starts posaconazole prophylaxis. What is the primary concern?

A. Tacrolimus levels drop causing kidney transplant rejection risk
B. Tacrolimus levels rise causing toxicity risk
C. No clinically meaningful change
D. Posaconazole levels drop causing fungal breakthrough

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

QUESTION #3

A transplant patient on tacrolimus starts posaconazole prophylaxis. What is the primary concern?

A. Tacrolimus levels drop causing kidney transplant rejection risk
B. Tacrolimus levels rise causing toxicity risk
C. No clinically meaningful change
D. Posaconazole levels drop causing fungal breakthrough

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

MYCOPHENOLATE: ABSORPTION INTERACTIONS

Two main formulations: mycophenolate mofetil (MMF) and mycophenolate acid (MPA)

Interactions are mainly through absorption binding and enterohepatic recirculation disruption

Antacids, proton pump inhibitors, bile acid sequestrants, and sevelamer may reduce serum concentrations of certain formulations

Antimicrobials including aminoglycosides, cephalosporins, fluoroquinolones, penicillins, and trimethoprim/sulfamethoxazole (TMP/SMX) can decrease MPA exposure

- These antimicrobials can interfere with enterohepatic recirculation leading to reduced systemic MPA levels and potentially decreased efficacy

Simoons M, Naipal KAT, de Jong H, et al. Oral antibiotics lower mycophenolate mofetil drug exposure. Pharmacology Research & Perspectives. 2023

MYCOPHENOLATE: GLUCURONIDATION

Mycophenolate mofetil (MMF) is rapidly hydrolyzed to mycophenolic acid

MPA is then metabolized predominantly by glucuronidation to MPA-glucuronide (MPAG)

Simoons M, Naipal KAT, de Jong H, et al. Oral antibiotics lower mycophenolate mofetil drug exposure. Pharmacology Research & Perspectives. 2023

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Mycophenolate mofetil (MMF) is rapidly hydrolyzed to mycophenolic acid

MPA is then metabolized predominantly by glucuronidation to MPA-glucuronide (MPAG)

Isavuconazole inhibits glucuronidation, increasing mycophenolic acid exposure and the risk of adverse reactions

Simoons M, Naipal KAT, de Jong H, et al. Oral antibiotics lower mycophenolate mofetil drug exposure. Pharmacology Research & Perspectives. 2023

MYCOPHENOLATE: RENAL COMPETITION

Mycophenolate + Acyclovir/Valacyclovir

- Compete for renal tubular secretion (OAT-mediated)
- ↑ MPAG, ↑ free MPA exposure, and ↑ acyclovir exposure
- Clinical effects: cytopenias, GI toxicity; acyclovir accumulation in CKD
- Management: renal dose antivirals, monitor serum creatinine (SCr) and CBC, hydration

Muller PY, Milton MN. The determination and interpretation of the therapeutic index in drug development. Nat Rev Drug Discov. 2006

MYCOPHENOLATE TOXICITIES

GI disturbances (Nausea/Vomiting/Diarrhea)

Cytopenias

Central nervous system (CNS) depression

Increased infection risk

Hyper/hypotension

Mycophenolate mofetil [package insert]. Genentech, Inc.; 2024

PHARMACODYNAMIC INTERACTIONS

Toxicity	Transplant Medication(s)	Antimicrobial(s) Involved
Nephrotoxicity	Tacrolimus, cyclosporine	Aminoglycosides, vancomycin, acyclovir, foscarnet, cidofovir, TMP/SMX, amphotericin B, tenofovir disoproxil fumarate (TDF)
QT prolongation	Tacrolimus, mTOR inhibitors	Macrolides, fluoroquinolones, foscarnet, azole antifungals (except isavuconazole)
Bone marrow suppression	Mycophenolate, azathioprine, mTOR inhibitors, ATG	Valganciclovir, ganciclovir, TMP/SMX, linezolid, flucytosine
Hyperkalemia	Tacrolimus, cyclosporine	TMP/SMX
Electrolyte disturbances (magnesium wasting)	Tacrolimus, cyclosporine	Amphotericin B, foscarnet

Sparkes T, Lemonovich TL, AST Infectious Diseases Community of Practice. Interactions between anti-infective agents and immunosuppressants. Clin Transplant. 2019.

DRUG INTERACTIONS IN THE ONCOLOGY POPULATION

ONCOLOGY PHARMACOTHERAPY

Traditional chemotherapy (“traditional chemo”)

- Kills rapidly dividing cells non-specifically

Targeted therapy

- Blocks specific cancer pathways (often oral “-nibs,” “-mabs,” etc.)

Immunotherapy

- Checkpoint inhibitors (PD-1/PD-L1, CTLA-4)
- Cellular therapies in select heme cancers

Hematopoietic stem cell transplant (HSCT)

- Autologous and allogeneic transplants require conditioning regimens
- Conditioning intensity varies by transplant type and patient factors
- Common highly immunosuppressive conditioning agents include cyclophosphamide, busulfan, and fludarabine

Rudd SG. Targeting pan-essential pathways in cancer with cytotoxic chemotherapy. Cancer Chemother Pharmacol. 2023.
Alard E, Butnariu A-B, Grillo M, et al. Advances in Anti-Cancer Immunotherapy. Cancers. 2020.
Khaddour K, Hana CK, Mewawalla P. Hematopoietic Stem Cell Transplantation. StatPearls, NCBI Bookshelf. 2023.

BRIDGE BETWEEN ID AND ONCOLOGY

Cancer care creates predictable immune deficits → heavy antimicrobial exposure

- Neutropenia (↓ risk of bacterial/fungal killing)
- Mucositis / barrier injury (↑ risk of bacteremia from translocation)
- Steroids / immune dysfunction (↑ risk of opportunistic infections)
- Central lines + procedures/devices (↑ risk of CLABSI/device infections)

Antimicrobials are used in 3 ways

- Prophylaxis during high-risk periods
- Empiric therapy (febrile neutropenia)
- Directed therapy once a pathogen/source is identified

Antimicrobial choices in oncology affect not just infection outcomes, but also the ability to stay on schedule with chemotherapy

Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression. J Clin Oncol. 2018.
Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2011.

COMMONLY AFFECTED MEDICATIONS

Drug	Substrate	Inhibition/Induction
Venetoclax	• 3A4 sensitive substrate • P-gp minor substrate • BCRP substrate	• N/A
Midostaurin	• 3A4 sensitive substrate	• BCRP inhibitor • OATP1A2 inhibitor • OATP1B1/1B3 inhibitor • 2B6 weak inducer • MRP2 inducer
Gilteritinib	• 3A4 sensitive substrate (with inhibitors) • 3A4 moderately sensitive substrate (with inducers) • P-gp minor substrate	• N/A
Ibrutinib	• 3A4 sensitive substrate • 2D6 minor substrate	• N/A

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

VENETOCLAX INTERACTIONS

Package insert recommended dosage modifications

Contraindicated with strong or moderate CYP3A inducers

Contraindicated with strong CYP3A inhibitors in CLL/SLL

Coadministered Drug	Ramp-Up Phase	Maintenance Daily Dose
Posaconazole	**Day 1**: 10 mg; **Day 2**: 20 mg; **Day 3**: 50 mg; **Day 4**: 70 mg	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor	**Day 1**: 10 mg; **Day 2**: 20 mg; **Day 3**: 50 mg; **Day 4**: 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce venetoclax dose by at least 50%	
P-gp inhibitor		

Venetoclax [package insert]. Genentech USA, Inc.; 2024

QUESTION #4

Posaconazole most affects venetoclax by:

A. Inducing CYP3A → decreased venetoclax exposure
B. Inhibiting CYP3A → increased venetoclax exposure
C. Chelating venetoclax in the gut → decreased absorption
D. Increasing renal clearance → decreased exposure

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

QUESTION #4

Posaconazole most affects venetoclax by:

A. Inducing CYP3A → decreased venetoclax exposure
B. Inhibiting CYP3A → increased venetoclax exposure
C. Chelating venetoclax in the gut → decreased absorption
D. Increasing renal clearance → decreased exposure

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

VINCRISTINE INTERACTIONS

CYP3A strong inhibitors

- Risk: ↑ vincristine exposure ⟶ severe neurotoxicity risk
- Peripheral neuropathy, ileus/constipation, motor dysfunction
- Coadministration is contraindicated
- If antifungal needed: consider weak/moderate CYP3A inhibitors or non-azole antifungal therapy

CYP3A strong inducers

- Risk: ↓ vincristine exposure ⟶ loss of efficacy risk
- Coadministration is contraindicated
- Consider alternative therapy (switching from rifampin to rifabutin/rifapentine)

Vincristine sulfate [package insert]. Fresenius Kabi USA, LLC; 2023.

ANTIFUNGAL ALTERNATIVES

Echinocandins (micafungin, caspofungin)

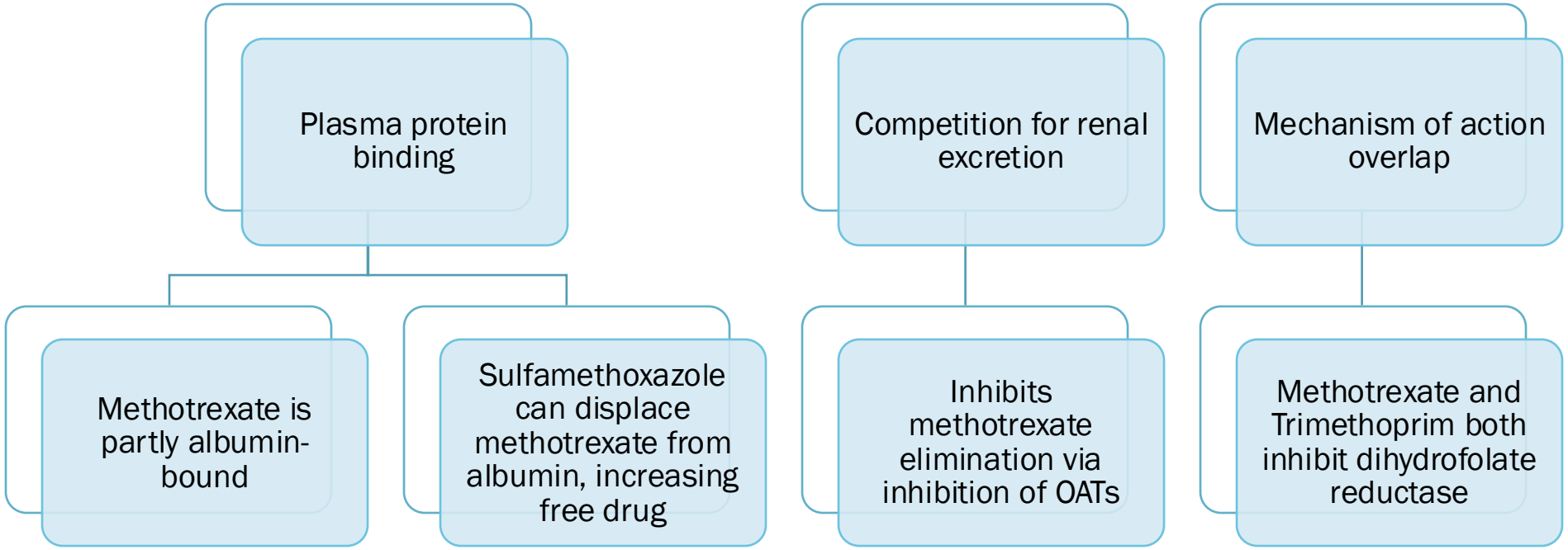
- Fewer CYP3A interactions than azoles
- Useful as prophylaxis/treatment when DDIs are clinically significant
- Trade-off: different spectrum of activity, routes of administration

Amphotericin B

- Minimal CYP-mediated interactions
- But major nephrotoxicity/electrolyte overlap with oncology regimens & supportive care

Lewis R, Niazi-Ali S, McIvor A, et al. Triazole antifungal drug interactions-practical considerations. J Antimicrob Chemother. 2024.

TMP/SMX AND METHOTREXATE



Bone marrow ⟶ myelosuppression (neutropenia, thrombocytopenia, anemia)

GI mucosa ⟶ mucositis/stomatitis/diarrhea

Cudmore J, Seftel M, Sisler J, et al. Methotrexate and trimethoprim-sulfamethoxazole. Can Fam Physician. 2014.

PD INTERACTIONS: QT PROLONGATION

Antimicrobial contributors

- Macrolides: clarithromycin, erythromycin (azithromycin least)
- Fluoroquinolones: levofloxacin, moxifloxacin, ciprofloxacin (moxifloxacin most, ciprofloxacin least)
- Azole antifungals: voriconazole, posaconazole, fluconazole (isavuconazole is QT-shortening)
- Pentamidine (IV especially) can prolong QT

Oncology-related contributors

- Arsenic trioxide
- Many tyrosine kinase inhibitors (TKIs) → agent-dependent; some more QT-prolonging than others

Supportive care that stacks QT:

- Antiemetics: ondansetron (and related 5-HT3 antagonists), sometimes dopamine antagonists
- Electrolyte abnormalities: hypokalemia/hypomagnesemia from diarrhea/vomiting, poor intake

Owens RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation. Clin Infect Dis. 2006.
Ondansetron [package insert]. Pfizer Inc.; 2024.
Arsenic trioxide [package insert]. Teva Pharmaceuticals USA, Inc.; 2024.

PD INTERACTIONS: MYELOSUPPRESSION

Antimicrobial contributors

- TMP-SMX
- Linezolid
- Ganciclovir/valganciclovir
- Flucytosine

Oncology-related contributors

- Cytotoxic chemotherapy: neutropenia, thrombocytopenia, anemia
- Marrow infiltration by malignancy (leukemia) → baseline cytopenias
- Hematopoietic stem cell transplantation (HSCT)
- Radiation involving marrow (pelvis/spine, other sites)
- Targeted/immune therapies that can suppress counts (agent-dependent)

Tverdek F, Kassamali Escobar Z, Liu C, et al. Antimicrobials in patients with hematologic malignancies. Transpl Infect Dis. 2023.
Carey PJ. Drug-induced myelosuppression: diagnosis and management. Drug Saf. 2003.

PD INTERACTIONS: NEPHROTOXICITY

Antimicrobial contributors

- Amphotericin B (esp deoxycholate; lipid forms still nephrotoxic)
- Aminoglycosides: gentamicin, tobramycin, amikacin
- Vancomycin
- IV acyclovir (crystal nephropathy risk)
- Foscarnet, cidofovir
- TMP-SMX (clinically significant or pseudo-AKI)

Oncology-related contributors

- Nephrotoxic chemo: platinum agents (cisplatin), ifosfamide
- Tumor lysis syndrome
- Contrast exposure
- Volume depletion: vomiting/diarrhea, poor PO intake, mucositis
- Obstructive uropathy from malignancy or stents/tubes

Malyszko J, Tesarova P, Capasso G, Capasso A. The link between kidney disease and cancer. Lancet. 2020.
Campbell RE, Chen CH, Edelstein CL. Overview of antibiotic-induced nephrotoxicity. Kidney Int Rep. 2023.

PD INTERACTIONS: NEUROTOXICITY

Antimicrobial contributors

- Cefepime ⟶ Encephalopathy/seizures risk especially with renal dysfunction
- Carbapenems ⟶ Seizure risk, highest with imipenem
- Fluoroquinolones ⟶ Delirium, agitation, seizure
- Metronidazole ⟶ Neuropathy/encephalopathy with prolonged exposure
- Linezolid ⟶ Peripheral/optic neuropathy with prolonged exposure

Oncology-related contributors

- Neurotoxic chemo agents ⟶ ifosfamide
- CNS primary malignancy or metastases
- Opioids/benzodiazepines/antiemetics (delirium contributors)

Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use. Br J Clin Pharmacol. 2011.
Was H, Borkowska A, Bagues A, et al. Mechanisms of chemotherapy-induced neurotoxicity. Front Pharmacol. 2022

PREVENTING DDIS

Identify high risk interaction medications

- **High-risk antimicrobials:** azole antifungals, macrolides, fluoroquinolones, rifamycins
- **High-risk patient medications:** tacrolimus/cyclosporine, sirolimus/everolimus, oral oncolytics, QT prolonging medications

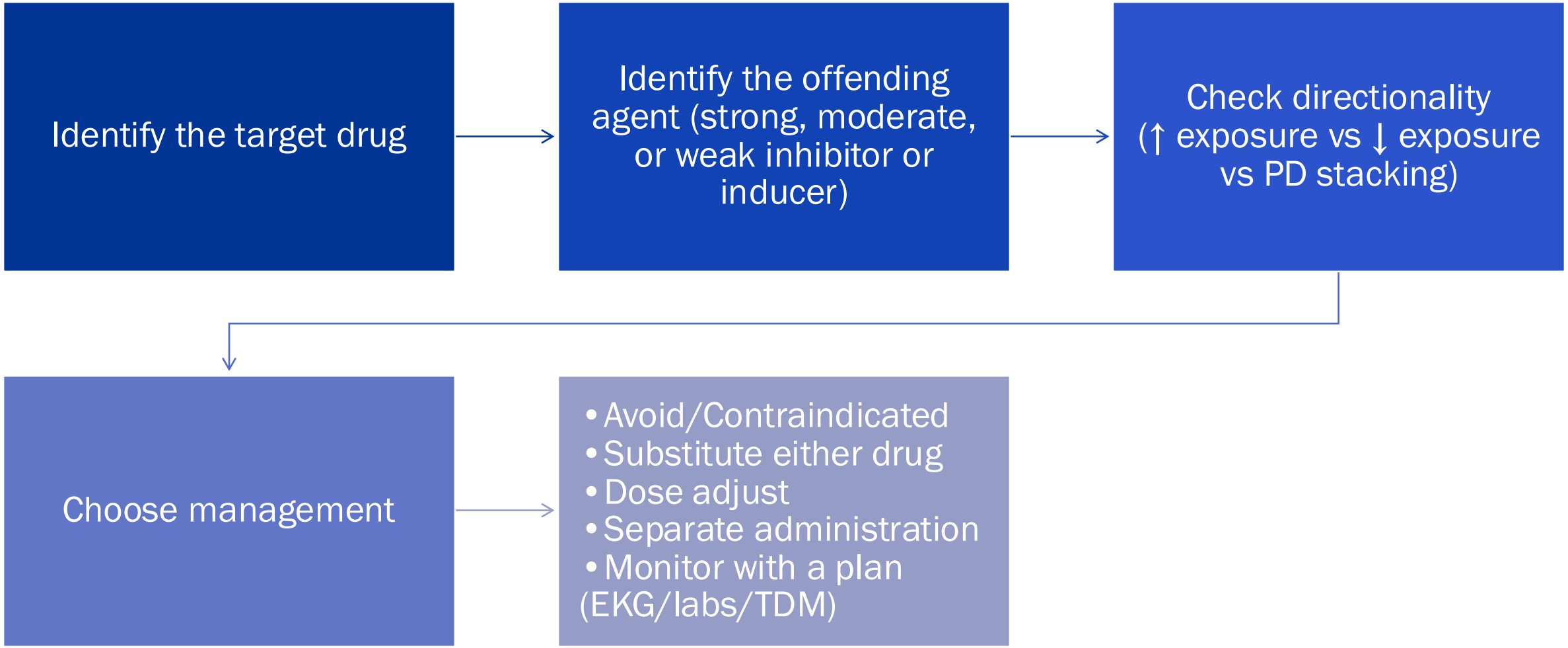
Catch potential interactions early

- If nursing/provider requests a fill urgently, pause assess for DDIs before filling
- Inform a pharmacist of the potential interaction

Prevent avoidable administration/dispensing issues

- Verify correct formulations & route of administration

APPROACHING DDIS



QUESTION #5

In a patient already at QT risk from oncology therapy and supportive care, which antimicrobial class should raise the most immediate QT-stacking concern?

A. Macrolides
B. Beta-lactams
C. Echinocandins
D. Tetracyclines

U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

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U.S. Food and Drug Administration. Examples of drugs interacting with CYP enzymes and transporters. FDA. 2025

KEY TAKEAWAYS

Care for transplant/oncology patients create predictable immune deficits due to heavy immunosuppressant/chemotherapy exposure

Strong inhibitors (azole antifungals, macrolides, protease inhibitors) → ↑ exposure of subtrates → toxicity risk

Strong inducers (rifampin >> rifabutin/rifapentine) → ↓ exposure → treatment failure risk

Population-specific consequences:

- Solid organ transplant: CNI/mTOR exposure changes → rejection risk (too low) vs toxicity/infection risk (too high)
- Oncology: oral targeted therapy exposure changes → toxicity/dose holds or loss of efficacy and delayed chemo schedules

PD stacking is similar in both populations: QT prolongation, nephrotoxicity, myelosuppression, neurotoxicity, hepatotoxicity

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WHEN MEDICATIONS COLLIDE: NAVIGATING DRUG-DRUG INTERACTIONS IN ONCOLOGY AND TRANSPLANT PATIENTS

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